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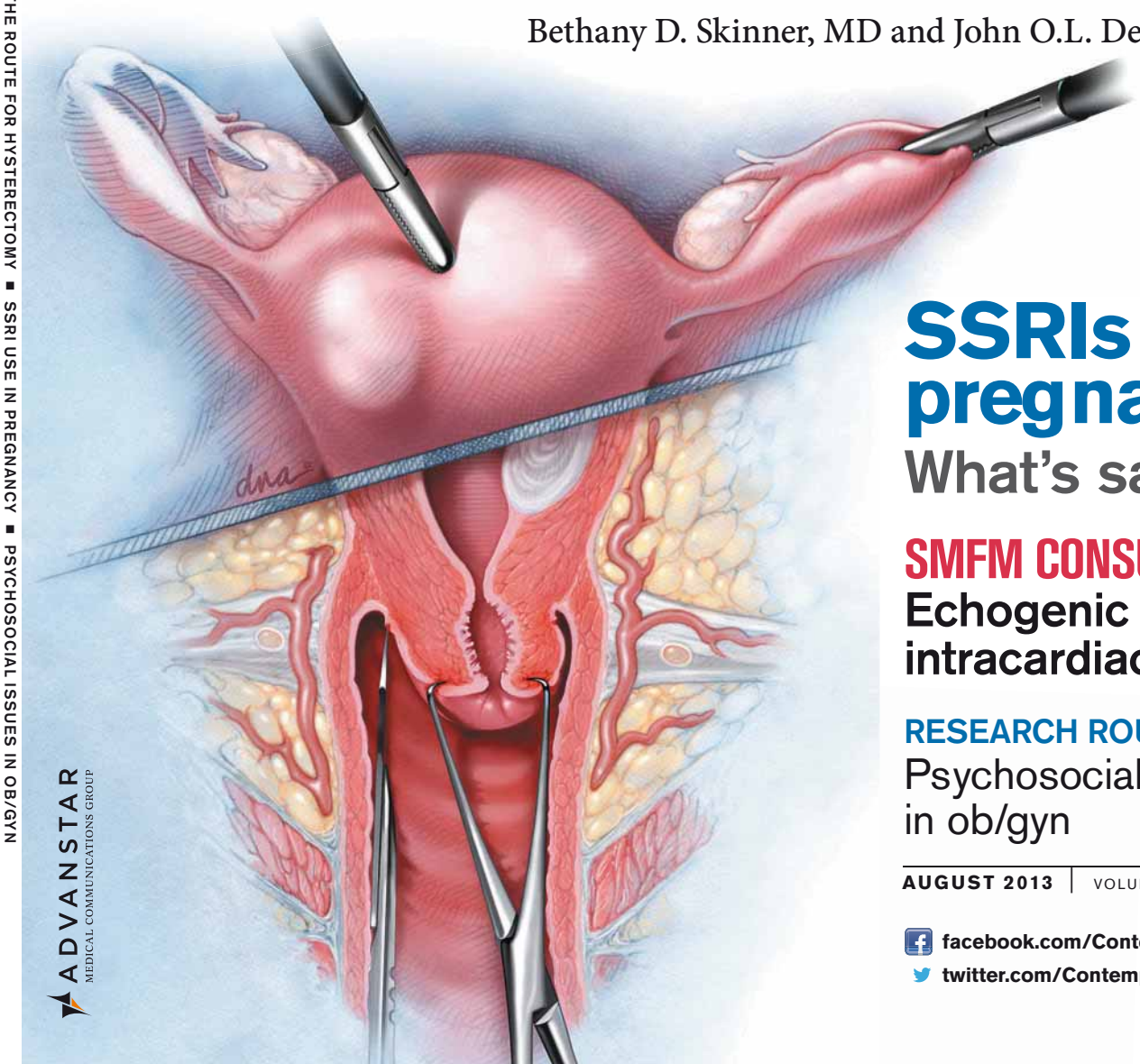
A MAP FOR HYSTERECTOMY SUCCESS

Bethany D. Skinner, MD and John O.L. Delancey, MD



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

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

INDICATIONS AND USAGE

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

Limitations of Use

DICLEGIS has not been studied in women with hyperemesis gravidarum.

DOSAGE AND ADMINISTRATION

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

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

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

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

DOSAGE FORMS AND STRENGTHS

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

CONTRAINDICATIONS

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

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

WARNINGS AND PRECAUTIONS

Activities Requiring Mental Alertness

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

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

Concomitant Medical Conditions

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

Drug Interactions

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

Drug-Food Interactions

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

ADVERSE REACTIONS

The following adverse reactions are discussed elsewhere in labelling:

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

Clinical Trial Experience

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

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

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

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

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

Postmarketing Experience

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

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category A

DICLEGIS is intended for use in pregnant women.

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

Nursing Mothers

Women should not breastfeed while using DICLEGIS.

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

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

Pediatric Use

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

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

OVERDOSAGE

Signs and Symptoms of Overdose

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

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

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

Management of Overdose

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

PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information)

Somnolence and Severe Drowsiness

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

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

Storage and Handling

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

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Indication

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

Limitations of Use

Diclegis has not been studied in women with hyperemesis gravidarum.

Important Safety Information

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

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

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

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

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

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

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

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

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

Please see accompanying Brief Summary of the full Prescribing Information.

Tablet(s) shown are not actual size.

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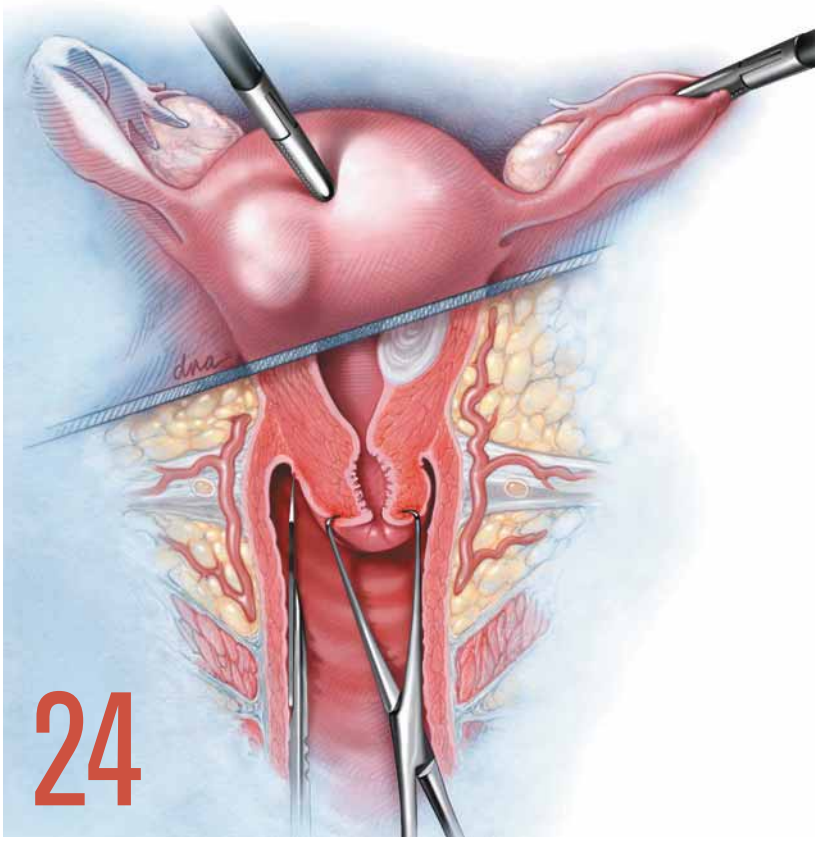

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BY CHARLES J. LOCKWOOD, MD, MHCM

Spontaneous preterm birth

Preconceptional nutrition matters

During a recent trip, I couldn't help observing the bulging waistlines of even the fairly well-to-do in Newport, Martha's Vineyard, and Nantucket. It was a stark reminder that although the obesity epidemic in the United States has leveled off, nearly 36% of adults have a body mass index (BMI) ≥30 and thus are considered obese.[1] Seeing several rather large pregnant women also reinforced the importance of a recent *JAMA* article that establishes a clear association between obesity and extremely early spontaneous preterm birth (PTB).[2]

Scope of the problem

We are all very familiar with the general health risks attendant obesity, including an increased prevalence of cardiovascular diseases such as hypertension, myocardial infarction, and stroke; and increased rates of diabetes, osteoarthritis, and certain cancers. Indeed, the Framingham Heart Study suggests that nonsmoking women who are obese at age 40 have a shorter life expectancy by 7 years.[3]

We are also increasingly aware of the reproductive sequelae of obesity. Obese women have significantly higher rates of preeclampsia, gestational hypertension, and gestational diabetes, which increase with increasing BMI.[4] The fetuses of obese women are also at increased risk of congenital anomalies, death, and macrosomia, and, when there is maternal hypertension, intrauterine growth restriction.[5,6]

A recently published study confirms increased rates of labor induction accruing obesity, from 25.3% in women with normal BMI to 42.9% in women with BMI ≥40, odds ratio (OR) 1.67 (95% CI, 1.43–1.93).[7] Similarly, rates of primary cesarean delivery rise with increasing BMI and are highest among morbidly obese women (36.2% vs. 22.1% in women with normal BMI, OR 1.46 [95% CI, 1.23–1.73]).[8]

Obesity and spontaneous PTB

About the only major obstetrical outcome that seemed immune from the obesity epidemic was spontaneous PTB, although it has been appreciated for some time that obesity increases rates of indicated prematurity in women with hypertension and diabetes. Indeed, underweight women seemed at greater risk of spontaneous PTB. Well, this illusion also has recently been shattered.

Cnattingius and associates analyzed the association between early pregnancy BMI and risk of PTB in 1.6 million women with live singleton births.[2] Preterm births were stratified as extremely preterm (22–27 weeks), very preterm (28–31 weeks) and moderately preterm (32–36 weeks). Outcomes were further analyzed based on spontaneous and medically indicated PTBs. In the latter, obesity was associated with all 3 PTB categories but only in women with pre-existing hypertension or diabetes. In contrast, after adjusting for confounding, obesity was most closely linked to spontaneous extremely PTBs.

Compared with normal-weight women, therefore, those with BMI values of 25–30 had an OR for spontaneous extremely PTB of 1.26 (95% CI, 1.15–1.37), while those with BMI values of 30–35 had an OR of 1.58 (95% CI, 1.39–1.79). Moreover, women with BMIs of 35–40 and ≥40 had ORs for extremely PTB of 2.01 (95% CI, 1.66–2.45) and 2.99 (95% CI, 2.28–3.92), respectively.

Thus, there is a clear "dose-response" effect of obesity, suggesting strong biological plausibility. The authors also allude to potential obesity-related pathogenic mechanisms, including exaggerated inflammatory response to subclinical genital tract infections. They found that the strongest links between obesity and spontaneous PTB were for preterm premature rupture of membranes. This study also confirmed the long-held observation that underweight women (BMI <18.5) have a modestly increased risk of very and moderately PTB. In this setting fetal stress may play the dominant pathogenic role.

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Many prior studies and meta-analyses link obesity with indicated PTB.[9] One prior study also links increasing levels of obesity with increasing risk of very and extremely PTBs, especially in African Americans, but the report did not differentiate between spontaneous and indicated PTBs.[10] Thus, the Cnattingius et al. report suggests an additional powerful tool to prevent precisely those spontaneous PTBs most likely to result in perinatal mortality and severe morbidity: weight loss.

Prevention strategies

Clearly weight loss is most easily accomplished before conception. Because indicated PTBs among obese patients are almost exclusively limited to those with hypertension and diabetes, and given that weight loss reduces the prevalence and/or severity of both conditions,[11,12] we can be reasonably confident that preconceptional weight loss will reduce the occurrence of medically indicated prematurity. Based on the Cnattingius et al. study, we can now also be reasonably confident that reduction in BMI from >40 to normal before conception will reduce the risk of spontaneous extremely PTB, perhaps 3-fold!

Unfortunately, however, most of us see obese patients once they are pregnant and only inconsistently in the preconceptional period. So, what's to be gained by achieving gestational weight loss in obese patients? At least from a prematurity perspective, the answer seems to be not much. Beyerlein et al. found that gestational weight loss in obese patients was associated with an increased risk of PTB.[13]

Another recent study suggests that while weight gain above the Institute of Medicine (IOM) recommendations is indeed harmful, reduced weight gain in obese patients has no discernible impact on spontaneous PTB rates.[14] The authors analyzed 8293 pregnancies, of which 9.5% had weight gain below, 17.5% within, and 73% above IOM guidelines. Not surprisingly, across all BMI categories, excess gestational weight gain led to an increased risk of complications such as hypertension, diabetes, cesarean delivery, and macrosomia. However, after adjusting for confounders, obese women who gained less than the IOM recommendations were found not to have reduced rates of either indicated or spontaneous PTBs.

Take-home message

Beyond the myriad adverse long-term health effects triggered by obesity, it has now been clearly linked to virtually all the major adverse maternal and fetal outcomes of pregnancy, including gestational diabetes, preeclampsia, macrosomia, excess cesarean delivery rates, congenital anomalies, fetal death, indicated PTB, and now spontaneous extremely PTB. Furthermore, waiting until an obese patient is pregnant to attempt to ameliorate the effects of obesity is probably too late. Aggressive preconceptional weight loss is needed.

Lastly, attainment of a normal preconceptional BMI will also likely prevent obesity and related long-term health effects in the developing child.[15] In short, preconceptional nutrition matters. COG

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

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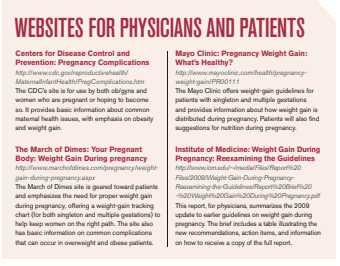
It's sweltering in the Northeast this week. Dehydration can pose a risk to expectant mothers and their babies, says Editorial Board Member Joshua Copel of Yale-New Haven Hospital in this interview with News Channel 8. Moms-to-be, stay cool and drink lots of water!

Heat risks for pregnant woman | WTNH.com Connecticut
www.wtnh.com
The 90 plus degree weather is affecting all of us but women who are pregnant are especially feeling the heat.

Contemporary OB/GYN
July 5

Looking for expert information on weight gain in pregnancy? A table of resources featured in our July issue is available online.



WEBSITES FOR PHYSICIANS AND PATIENTS

Centers for Disease Control and Prevention: Pregnancy Complications
http://www.cdc.gov/reproductivehealth/MaternalInfantHealth/PregComplications.htm
The CDC's site is for use by both ob/gyns and women who are pregnant or hoping to become so. It provides basic information about common maternal health issues, with emphasis on obesity and weight gain.

Mayo Clinic: Pregnancy Weight Gain: What's Healthy?
http://www.mayoclinic.com/health/pregnancy-weight-gain/PR00111
The Mayo Clinic offers weight-gain guidelines for patients with singleton and multiple gestations and provides information about how weight gain is distributed during pregnancy. Patients will also find suggestions for nutrition during pregnancy.

The March of Dimes: Your Pregnant Body: Weight Gain During pregnancy
http://www.marchofdimes.com/pregnancy/weight-gain-during-pregnancy.aspx
The March of Dimes site is geared toward patients and emphasizes the need for proper weight gain during pregnancy, offering a weight-gain tracking chart (for both singleton and multiple gestations) to help keep women on the right path. The site also has basic information on common complications that can occur in overweight and obese patients.

Institute of Medicine: Weight Gain During Pregnancy: Reexamining the Guidelines
http://www.iom.edu/~/media/Files/Report%20Files/2009/Weight-Gain-During-Pregnancy-Reexamining-the-Guidelines/Report%20Brief%20-%20Weight%20Gain%20During%20Pregnancy.pdf
This report, for physicians, summarizes the 2009 update to earlier guidelines on weight gain during pregnancy. The brief includes a table illustrating the new recommendations, action items, and information on how to receive a copy of the full report.

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Committee on Practice Bulletins—Obstetrics
ACOG Practice Bulletin No. 132: *Antiphospholipid Syndrome*, December 2012 (Replaces Practice Bulletin No. 118, January 2011). *Obstet Gynecol.* 2012;120(6):1514-1521. Full text of ACOG Practice Bulletin available to ACOG members at http://www.acog.org/Resources_And_Publications/Practice_Bulletins/Committee_on_Practice_Bulletins_--_Obstetrics/Antiphospholipid_Syndrome.

Antiphospholipid Syndrome

Antiphospholipid syndrome (APS) is an autoimmune disorder defined by the presence of characteristic clinical features and specified levels of circulating antiphospholipid antibodies. Diagnosis requires that at least one clinical and one laboratory criterion are met. Because approximately 70% of individuals with APS are female (1), it is reasonably prevalent among women of reproductive age. Antiphospholipid antibodies are a diverse group of antibodies with specificity for binding to negatively charged phospholipids on cell surfaces. Despite the prevalence and clinical significance of APS, there is controversy about the indications for and types of antiphospholipid tests that should be performed in order to diagnose the condition. Much of the debate results from a lack of well-designed and controlled studies on the diagnosis and management of APS. The purpose of this document is to evaluate the data for diagnosis and treatment of APS.

COMMENTARY

The Mystery of the Antibodies Still Awaits a Solution

By **Charles J. Lockwood, MD, MHCM**
Dr. Lockwood is Dean of the College of Medicine and Vice President for Health Sciences, The Ohio State University, Columbus, and Editor in Chief of *Contemporary OB/GYN*.

The American College of Obstetricians and Gynecologists' Practice Bulletin *Antiphospholipid Syndrome* (No. 132, December 2012) replaces the original bulletin from November 2005.[1] That there is little difference between these 2 documents should not be surprising, since there has been little progress in research into this still-quite-mysterious disorder during that interval.

The new Practice Bulletin reviews the association of antiphospholipid syndrome (APS) with thrombosis, noting that most thrombotic events are venous and that among untreated APS patients, risk of recurrent venous thromboembolism (VTE) may be as high as 25% per year.[1] Pregnancy poses a particular risk of clotting (5% to 12%). Other hemostatic sequelae of the disorder include the presence of antiphospholipid antibodies (APA) in around 5% of stroke victims younger than 50 and the 40% to 50% prevalence of thrombocytopenia among APS patients.

To test or not to test?

Obstetrical sequelae include fetal loss after 10 weeks, recurrent (>2) embryonic losses, and an association with preeclampsia and uteroplacental insufficiency.[1] The Bulletin recommends testing women for APS only if they have had an unexplained fetal loss (>10 weeks) or 3 or more unexplained embryonic losses. Testing is also indicated in previously untested patients with current or prior venous or arterial thrombosis.

The tests to be employed have not changed—they are a lupus anticoagulant assay and a screen for anticardiolipin and anti-beta-2-glycoprotein I antibodies. These tests must be positive on 2 occasions 12 weeks apart.

> We still do not know how these **antibodies arise, how they trigger losses,** or **how heparin prevents such losses.**

Complexities of treatment

According to ACOG, therapy with prophylactic anticoagulation is indicated in women with APS and prior thrombosis during pregnancy and for 6 weeks postpartum.[1] Similar therapy is warranted for women with APS associated with fetal loss or recurrent embryonic loss. Low-dose aspirin may be added in both cases.

ACOG also opines that, "For women with APS who have not had a thrombotic event, expert consensus suggests that clinical surveillance or prophylactic heparin use antepartum in addition to 6 weeks of postpartum anticoagulation may be warranted." This recommendation would apply if the diagnosis of APS was made based on the occurrence of 1 or more preterm births associated with eclampsia, severe preeclampsia, or features consistent with placental insufficiency, since ACOG does not recommend treatment for these indications.

Looking back—and forward

This unusual condition fascinated me as a young maternal-fetal medicine fellow and led to my career-long interest in the study of uterine hemostasis.

However, it is frustrating to realize what little progress has been made in understanding APS in the ensuing 25 years. We still do not know how these antibodies arise, how they trigger losses, or how heparin prevents such losses. Pregnancy loss was long assumed to be due to uteroplacental thrombosis. However, thrombosis is rarely observed with embryonic losses, and whether it is a cause or consequence of later losses is unclear.[2] There is even recent evidence that inflammation and complement activation, not clotting, may be at the heart of the disease process.[3,4] Thus, there is much left to be discovered about these mysterious antibodies. COG

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Practice Bulletin No. 133: Benefits and Risks of Sterilization
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Practice Bulletin No. 134: Fetal Growth Restriction
A review of the topic with a focus on terminology, etiology, diagnostic and surveillance tools, and guidance for management and timing of delivery.

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The Supreme Court rules on gene patenting

BY **REBECCA NAGY, MS, CGC**, **BRITTON D. RINK, MD, MS**, AND **RAY HERSHBERGER, MD**

On June 13, the United States Supreme Court unanimously ruled that naturally occurring DNA cannot be subject to patent.[1] The landmark decision was the end of a 4-year court battle between the petitioners in the case, the Association for Molecular Pathology and the molecular genetic testing company Myriad Genetics Laboratories, Inc. For the past 17 years, Myriad Genetics was the sole laboratory offering clinical genetic testing for the breast- and ovarian cancer-predisposing BRCA1 and BRCA2 genes, having obtained several patents after discovering the location and sequence of these genes. The petitioners argued that genes are a product of nature and thus, patents held by Myriad Genetics on the BRCA1 and BRCA2 sequence were invalid. The Court agreed.

Numerous professional organizations and advocacy groups praised the decision, claiming it would likely result in increased access to testing with reduced costs.[2] Researchers and laboratory directors predicted more open and unfettered access to genetic testing data that previously would have been considered proprietary, as well as use of new and improved methods of BRCA1/BRCA2 mutation detection. But what will be the impact on clinicians and their patients who are considering genetic testing, and on the biotechnology industry?

Lower cost for cancer genetic studies

Without question, this ruling is a win for individuals with hereditary breast and ovarian cancer and their families. Within hours of the decision, 3 separate genetic testing laboratories announced that they would begin offering BRCA1 and BRCA2 genetic testing, all at significantly lower cost than previously available. With testing costs dropping, more insurers may be willing to cover the service, which will result in increased access to testing.

Testing may also be more comprehensive and provide a more complete risk profile. Importantly, BRCA1 and BRCA2 can now be included in multi-gene panel testing, in which multiple genes known to contribute to a specific disease phenotype are tested at the same time. Panel testing for hereditary breast cancer has been problematic, because the Myriad patents prevented inclusion of the 2 genes most commonly responsible for the disease. As a result, women who qualified for screening were forced to have it done in steps, with testing for BRCA1 and BRCA2 first, followed by additional panel testing only if BRCA1 and BRCA2 results were negative. The total cost of that approach is about $6,000.

Since the Supreme Court ruling, 2 laboratories have already added BRCA1 and BRCA2 to their panels, offering testing for up to 25 genes at a cost equivalent to testing only for the 2 genes. More companies likely will follow.

What providers need to know about the ruling

For healthcare providers caring for patients at potential risk of cancer, the decision analysis surrounding molecular genetic testing now offers more options and greater flexibility. However, a free market also brings greater complexity. Providers ordering genetic testing now must be familiar with the various laboratories and the types of tests they

continued on **PAGE 16**

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continued from **PAGE 14**

offer and understand each test's mutation detection rate, the quality and cost of the interpretation, and the options for insurance reimbursement.

When considering a multi-gene panel for hereditary cancer conditions that includes BRCA1 and BRCA2, the provider will also need to consider and review with the patient other cancer syndromes that the testing may identify, such as Cowden or Li Fraumeni syndrome.

Li Fraumeni syndrome is caused by heritable mutations in TP53 and includes family clustering of premenopausal breast cancer, sarcoma, osteosarcoma, and leukemia, as well as brain, adrenal, and other cancers.[3] Cowden syndrome is a rare multiple hamartoma syndrome from mutations in PTEN associated with breast, endometrial, and thyroid cancer.[4]

The same principles apply to the many phenotypes that result from several genes, including some no longer subject to patent protection, such as the genes for Long QT syndrome. With larger gene panels, delivering effective pre- and post-test genetic counseling and accurately interpreting results are critical.

Although larger gene panels expand the scope of testing for the cancer phenotype of interest, many such panels include genes for which we have little clinical correlation. For most, there are no published practice guidelines to assist clinicians in acting on positive or negative results.

For physicians already feeling the strain in today's managed healthcare environment, staying current with best practices and spending additional time with patients to explain the purpose of larger panels before and after testing may be challenging. However, it is critical that the boon of increased access resulting from this ruling not be diminished by an increase in inappropriately ordered genetic testing or misinterpreted results.

Limitations

Though the Supreme Court ruled that naturally occurring human DNA could not be patented, it did affirm that complementary DNA (cDNA) may be patented.[2,5,6] cDNA is artificially synthesized in the laboratory from naturally occurring genomic DNA. Many existing patents on human DNA sequences include claims on cDNA, and these patents will stand even after this ruling.

The extent to which this will allow biotechnology companies to benefit from and protect their discoveries remains to be seen. For example, as a result of the Supreme Court ruling, 24 patents by Myriad containing more than 500 valid claims will remain in effect. The reaction to this seemingly ambiguous ruling within the biotechnology and patent law fields has been mixed. Some experts criticized the ruling as undermining the long-standing history of innovation and discovery, while others disagreed, saying that methods claims and use of modified DNA such as cDNA remain patent-eligible.[2,5,6]

Conclusion

Early signs indicate that the Supreme Court ruling in the Myriad case buttresses patient rights, increases access to genetic information, and enhances free market competition, which should reduce costs. We strongly support this ruling and these outcomes, even though we recognize that such a major decision may also adversely impact some of the many interested parties in unexpected ways.

In the wake of this decision, at least for BRCA1 and BRCA2 testing in at-risk women, physicians and other healthcare providers will have more genetic testing options to assess risk of breast and ovarian cancer. Armed with up-to-date knowledge about cancer genetics, physicians and genetic counselors will have more tools to address their patients' questions. That is progress!

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Dr. Rink is a clinical geneticist and holds an appointment in the Division of Molecular & Human Genetics, Nationwide Children's Hospital, Columbus, Ohio. She is also a maternal-fetal medicine specialist and the director of Genetics, Prenatal Diagnosis & Ultrasound in the Division of Maternal Fetal Medicine, The Ohio State University Wexner Medical Center, Columbus.

Dr. Hershberger is a cardiologist specializing in the genetic causes of cardiomyopathy and director of the Division of Human Genetics within the Department of Internal Medicine of The Ohio State University Wexner Medical Center, Columbus. His research is based at the Dorothy M. Davis Heart and Lung Research Institute at OSU.

This commentary originally appeared in the June 27, 2013, *Contemporary OB/GYN* email newsletter.

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Regarding 'Medical costs: incomprehensible and unsustainable'

TO THE EDITOR:

A recent editorial was dedicated to the incomprehensible and unsustainable medical costs prevalent throughout the nation today.[1]

For the first time, the government is publically revealing how much hospitals charge, and the differences are astounding: some bill tens of thousands of dollars more than others for the same treatment, even within the same city.[2] These massive pricing differentials are too large to be explained by obvious differences among hospitals, such as a more expensive regional economy, older or sicker patients, or the extra costs of running a teaching hospital.

This is particularly evident when we consider that hospitals in the same city as well as hospitals with similar levels of prestige charge profoundly divergent rates. At the Beth Israel Medical Center in New York, the average charge to treat a blood clot in a lung is $51,580. Down the street at the NYU Hospitals Center, the charge for the same care would be $29,869. At the Mayo Clinic in Minnesota, the list price is $16,861.

Medicare pays hospitals on its own fee schedule that isn't based on these charges, and the insurance companies routinely negotiate discount rates. But patients who are uninsured are billed the full amount. The Obama administration hopes that releasing the information, at the website www.cms.gov, will pressure some hospitals to lower their charges.

The Dartmouth Institute for Health Policy has long found wide geographic variation in Medicare payments for the similarly ill, yet people who receive more expensive care don't necessarily receive better care.[3] Besides the regional variations, the application of unnecessary testing and treatments can dramatically and unnecessarily increase medical costs.

In all hospitals [. . .] a patient's bill of rights is proudly displayed. It generally recounts a patient's right to equal medical care independent of the patient's race, gender, religion, and sexual preferences. However, patients, as consumers, are entering into a mystifying system that too often leaves them with little way of knowing what a hospital will charge or what their insurance companies are paying for their treatments.

Thus, patients are deprived of the knowledge [. . .] of the price of tests, procedures, and consulting fees. Patients should be fully aware of the costs of tests, procedures, and consultative services and have the right to decline them after proper counseling.

Furthermore, protecting the patient's rights as a consumer of medical products and services is particularly important because [. . .] patients, due to the nature of medical treatment, generally do not have the ability to compare prices with those of other institutions offering the same services. While a customer looking for a car might go to 3 or 4 stores to get the best price, the patient seeking treatment will often not have this same opportunity for obtaining medical care.

At very least, patients should have the opportunity to be fully informed of the pricing and cost effectiveness of their different treatment options to be able to make a fully informed decision.

A hospital's charges are akin to a car dealership's "list price." Hospitals say they frequently give discounts to the uninsured: $41 billion in financial aid in 2011. But some people pay full price because they don't know they can seek a discount and even for those who do bargain, the listed charge "is the opening bid in the hospital's attempt to get as much money as possible out of [the patient and his/her family]."[2]

Boris Petrikovsky, MD, PhD
Chief, Maternal-Fetal Medicine,
New York Downtown Hospital
New York, New York

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to read **DR. LOCKWOOD'S RESPONSE**, please see **PAGE 43**

Selecting the route for hysterectomy
A structured approach

A practical 'roadmap' to an appropriate route for hysterectomy for benign conditions focuses on patient evaluation and answers to key questions.

BY **BETHANY D. SKINNER, MD** AND **JOHN O. L. DELANCEY, MD**

DR. SKINNER is Clinical Assistant Professor in the Division of Minimally Invasive Gynecologic Surgery in the Department of Obstetrics and Gynecology at the University of Michigan Health System, Ann Arbor.

DR. DELANCEY is Norman F. Miller Professor of Obstetrics and Gynecology, Director of Pelvic Floor Research, and Group Director of the Fellowship in Female Pelvic Medicine and Reconstructive Surgery in the Department of Obstetrics and Gynecology at the University of Michigan Health System, Ann Arbor. He is also a member of the *Contemporary OB/GYN* Editorial Board. Neither author has a conflict of interest to disclose with respect to the content of this article.

More than 600,000 hysterectomies are performed in the United States each year.[1] Although recent data have shown an increase in rates of minimally invasive hysterectomy, the majority of hysterectomies continue to be performed through abdominal routes.[1-3] This is in spite of a large body of evidence supporting that vaginal and laparoscopic hysterectomy are associated with less infectious morbidity, shorter hospital stay, and faster return to normal activity than abdominal hysterectomy.[4-13] Vaginal hysterectomy is also the most cost-effective type of hysterectomy.[14]

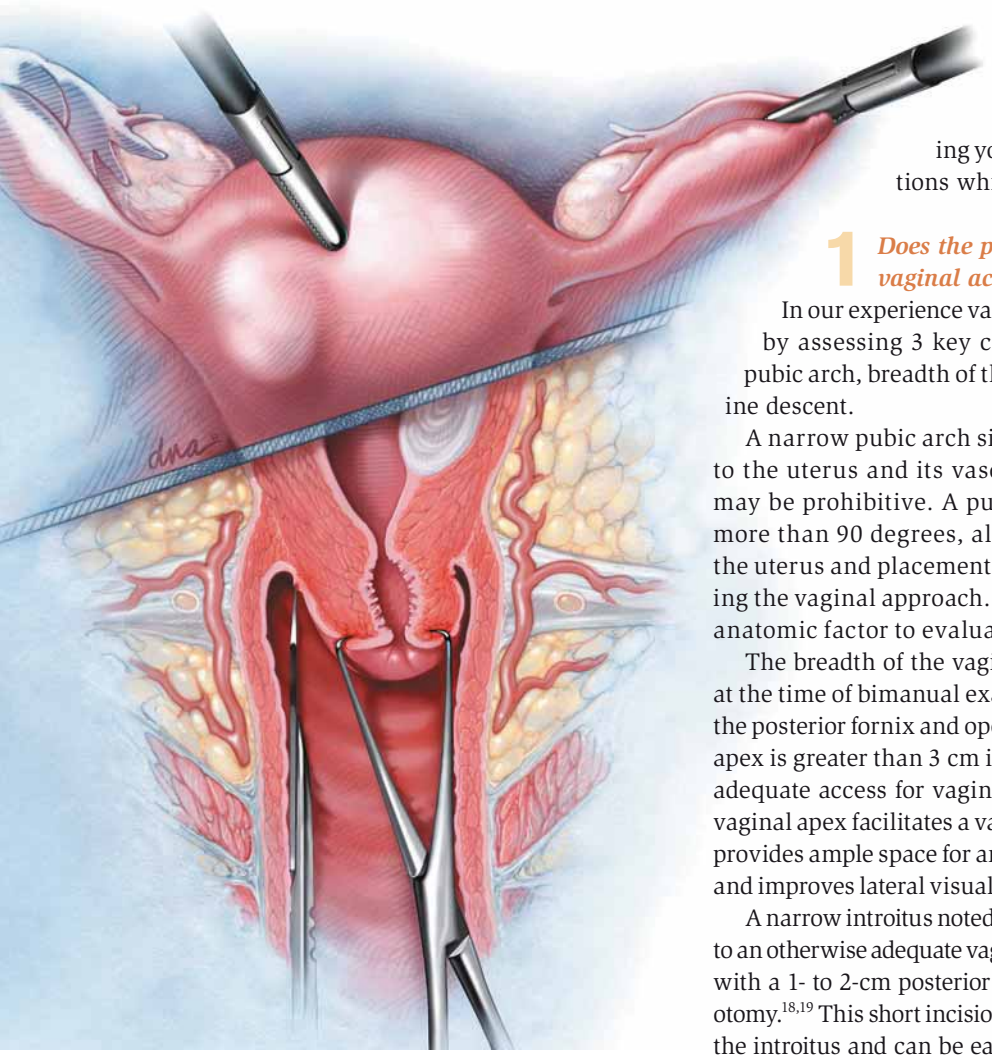
Based on these findings, vaginal and laparoscopic hysterectomy should be recommended over the abdominal route when possible.[15,16]

Determining surgical candidacy and selecting the appropriate route of hysterectomy are decisions made at the time of patient evaluation in the office and can be limiting factors to offering a minimally invasive approach. The algorithm in Figure 1 is provided to help guide the surgeon through this decision-making process.[17] The structured approach presented here presumes that the patient has been counseled regarding alternatives to hysterectomy and that gynecologic malignancy has been ruled out to the best of the surgeon's ability using endometrial biopsy, imaging studies, and tumor markers as indicated based on the patient's risk factors and the surgeon's index of suspicion.

In addition, robotic surgery is not considered separately, but rather is grouped as a subset of the laparoscopic approach. Several case studies are presented to highlight important factors in choosing the best route of hysterectomy.

TAKE-HOME MESSAGES

- The patient's anatomy and history as well as the surgeon's expertise must be considered when determining the most appropriate route.
- A structured approach to selecting the most appropriate route will lead to the best outcomes for the patient.



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Case 1: Above or below

A 42-year-old obese G2P2 presents with heavy menses failing medical management. She has no significant past medical or surgical history and has had 2 spontaneous vaginal deliveries of 7-lb infants. Ultrasound showed a 12.5-cm uterus with evidence of adenomyosis and normal ovaries. On exam she has a 12-week size mobile uterus located high in the pelvis with descent to 5 cm above the hymen on valsalva, and her pubic arch is wide. She desires hysterectomy.

Q How would you counsel this patient regarding route of hysterectomy?

A An orderly approach is necessary to determine the least invasive route of hysterectomy, including detailed history and physical exam to assess this woman's candidacy for surgery. Consider asking yourself the following questions while performing the exam:

1 *Does the patient have adequate vaginal access?*

In our experience vaginal access is determined by assessing 3 key components: angle of the pubic arch, breadth of the vaginal apex, and uterine descent.

A narrow pubic arch significantly limits access to the uterus and its vasculature, and if present, may be prohibitive. A pubic arch that is wide, or more than 90 degrees, allows for easier access to the uterus and placement of instruments, facilitating the vaginal approach. Therefore this is the first anatomic factor to evaluate on exam in the office.

The breadth of the vaginal apex is best assessed at the time of bimanual exam by placing 2 fingers in the posterior fornix and opening them laterally. If the apex is greater than 3 cm in width there is generally adequate access for vaginal hysterectomy. A wider vaginal apex facilitates a vaginal approach because it provides ample space for anterior and posterior entry and improves lateral visualization of the vasculature.

A narrow introitus noted on exam that limits access to an otherwise adequate vaginal apex can be overcome with a 1- to 2-cm posterior midline first-degree episiotomy.[18,19] This short incision can increase the width of the introitus and can be easily repaired with delayed absorbable suture at the conclusion of the procedure.

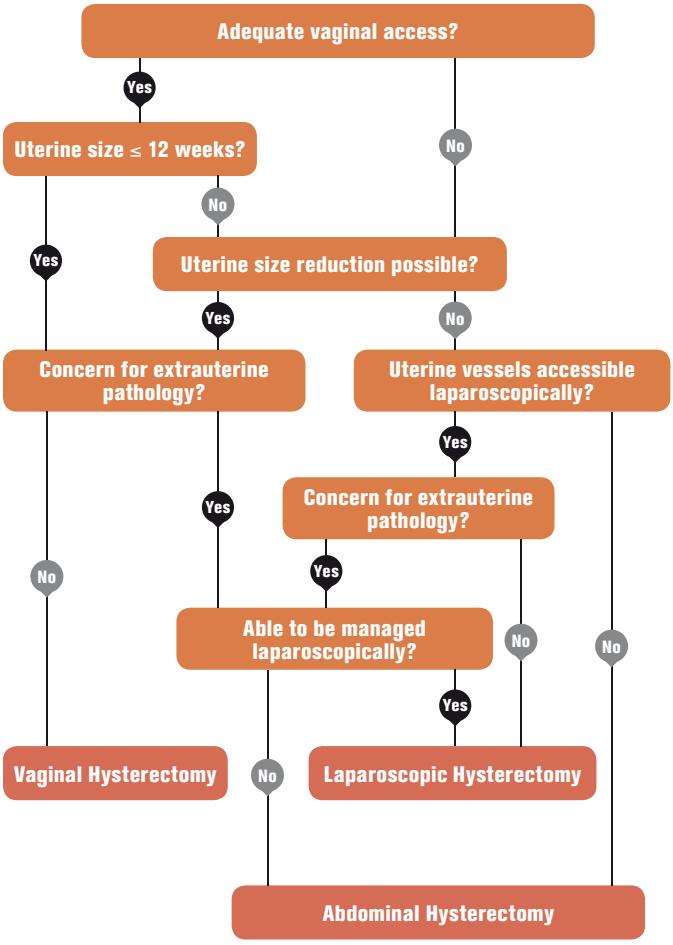
Uterine descent is the final component of vaginal access and can be evaluated by asking the patient to perform a valsalva maneuver and observing the movement of the uterus. Descent is measured relative to the ischial spines, as on an obstetric exam. In general, descent to at least 1 cm below the level of the ischial spines is adequate. Although this is often given heavy weight in determining a patient's candidacy for vaginal hysterectomy, lack of descent need not rule out the option of a vaginal approach.[20-22]

If the patient otherwise has good vaginal access but lacks descent, that factor can be reassessed preoperatively under anesthesia with paralysis.

2 *What is the size and shape of the uterus?*

Uterine size is assessed on bimanual exam or by ultrasound imaging if exam is limited by body habitus. A measurement of approximately 12 cm or less usually allows for a vaginal approach, but that cutoff is

FIGURE 1 Hysterectomy for benign gynecologic conditions: an algorithm



loose and can increase with time and experience.[22,23]

Equally important is the evaluation of uterine shape and mobility. The presence of bulky fibroids in the cervix or lower uterine segment can make colpotomy difficult. Large lateral fibroids can limit the ability to safely secure the uterine vasculature and reach the cornua to complete vaginal hysterectomy. In addition, presence of a fibroid that obstructs uterine descent is unlikely to improve under anesthesia and can preclude a vaginal approach. Limited mobility can also be an indication of extrauterine pathology, as discussed herein.

3 *Is uterine size reduction possible?*

Uterine size can be preoperatively reduced with gonadotropin-releasing hormone (GnRH) agonists. Administration for 3 months results in an average uterine size reduction of 25% to 50%. If the patient complains of abnormal uterine bleeding and is found to be anemic, this pharmacologic cycle suppression allows for improvement in hemoglobin before surgery.[24,25] Patients should be counseled regarding the menopausal side effects of this medication. They should also be warned of the flare associated with initiation of GnRH agonist therapy, which can result in a short period of increased bleeding.

Uterine size can be intraoperatively reduced by performing transvaginal uterine morcellation (Figure 2). Many morcellation techniques have been described, and all can be performed only after the uterine vessels are secured.[23,26] It is useful to begin with uterine bivalving, wherein the cervix and lower uterine segment are sharply divided into right and left halves using a scalpel (Figure 2, A and B). Once this step is complete the central portion of the uterine body is accessible, including any submucosal and/or intramural fibroids. This centrally located tissue can then be grasped with a toothed clamp, and serial wedges of tissue can be sharply resected (Figure 2, C and D).

Alternatively, coring can be performed by making a circumferential incision at the level of the internal cervical os and then sharply removing cores of myometrium. With either method the uterine body is decompressed, which permits further uterine descent, lateral mobility, and eventual access to the uterine cornua.

4 *Is extrauterine pathology present?*

A final consideration in determining a patient's candidacy for vaginal hysterectomy is the possible presence of extrauterine pathology, such as pelvic adhesive disease, endometriosis, or large adnexal cysts. If extrauterine pathology is suspected based on history, exam, or ultrasound findings, but the patient is otherwise a good candidate for a vaginal approach, diagnostic laparoscopy can be performed immediately prior to hysterectomy to quickly visualize pelvic anatomy and determine if vaginal hysterectomy is feasible.

Additional laparoscopic procedures can also be performed if needed to allow for vaginal hysterectomy.

Case 2: Open or laparoscopic

A 46-year-old G3P3 presents with symptomatic uterine fibroids and heavy menstrual bleeding. She previously controlled her bleeding with oral contraceptive pills, but now her bleeding is increasing and she has become mildly anemic. She is also bothered

continued on **PAGE 30**

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Generess® Fe is an estrogen/progestin combined oral contraceptive indicated for use by women to prevent pregnancy.

IMPORTANT SAFETY INFORMATION

Women who are over 35 years old and smoke should not use Generess® Fe. Cigarette smoking increases the risk of serious cardiovascular events from combination oral contraceptive use. Generess® Fe is contraindicated in pregnant patients, and those with a high risk of arterial or venous thrombotic disease, undiagnosed abnormal uterine bleeding, breast cancer or other estrogen- or progestin-sensitive cancer, liver tumors, or liver disease. Use of Generess® Fe should be stopped if a thrombotic event occurs, and at least 4 weeks before and through 2 weeks after major surgery. Generess® Fe should not be started any earlier than 4 weeks after delivery, in women who are not breastfeeding. If jaundice occurs, Generess® Fe treatment should be discontinued. 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 Generess® Fe. Alternate contraceptive methods should be considered for women with uncontrolled dyslipidemia. Patients using Generess® Fe who have a significant change in headaches or irregular bleeding or amenorrhea should be evaluated. The most commonly reported adverse events associated with the use of Generess® Fe included nausea/vomiting, headaches/migraine, depression/mood complaints, dysmenorrhea, acne, increased weight, breast pain/tenderness and anxiety. **Generess® Fe will not protect against HIV infection (AIDS) or other sexually transmitted diseases.**

Generess® Fe
(norethindrone and ethinyl estradiol chewable tablets and ferrous fumarate chewable tablets) 0.8 mg/25 mcg

Brief Summary

For full prescribing information, see package insert. Rx only

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

GENERESS Fe is indicated for use by women to prevent pregnancy.

The efficacy of GENERESS Fe in women with a body mass index (BMI) of > 35 kg/m² has not been evaluated.

4 CONTRAINDICATIONS

Do not prescribe GENERESS Fe to women who are known to have the following:

- 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 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), Use in Specific Populations (8.7),* and *Clinical Pharmacology (12.3)]*
- Undiagnosed abnormal uterine bleeding *[see Warnings and Precautions (5.8)]*
- Pregnancy, because there is no reason to use COCs during pregnancy *[see Warnings and Precautions (5.9)* and *Use in Specific Populations (8.1)]*

5 WARNINGS AND PRECAUTIONS

5.1 Thrombotic and Other Vascular Events

Stop GENERESS Fe if an arterial or deep venous thrombotic (VTE) event occurs. Although the 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 excess 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 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 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 among older (> 35 years of age), hypertensive women who also smoke. COCs also increase the risk for stroke in women with other underlying risk factors.

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

Stop 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 Breasts and Reproductive Organs

Women who currently have or have had breast cancer should not use 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 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/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 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 and with extended duration of use. The incidence of hypertension increases with increasing concentration of progestin.

5.5 Gallbladder Disease

Studies suggest the relative risk of developing gallbladder disease may be increased among COC users.

5.6 Carbohydrate and Lipid Metabolic Effects

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

Consider alternative contraception for women with uncontrolled dyslipidemia. 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 GENERESS Fe develops new headaches that are recurrent, persistent, or severe, evaluate the cause and discontinue 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

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 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. GENERESS Fe use should be discontinued if pregnancy is confirmed.

The 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 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

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 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 with 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 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.

7.3 Changes in Plasma Levels of Co-Administered Drugs

COCs containing some synthetic estrogens (e.g., 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 may start COCs no earlier than four 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 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

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

8.6 Renal Impairment

The pharmacokinetics of 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 disease on the disposition of 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 *[see Contraindications (4),* and *Warnings and Precautions (5.3)]*.

8.8 Body Mass Index

The safety and efficacy of GENERESS Fe in women with a 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 nausea, and withdrawal bleeding may occur in females.

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Medical Communications Parsippany, NJ 07054 USA
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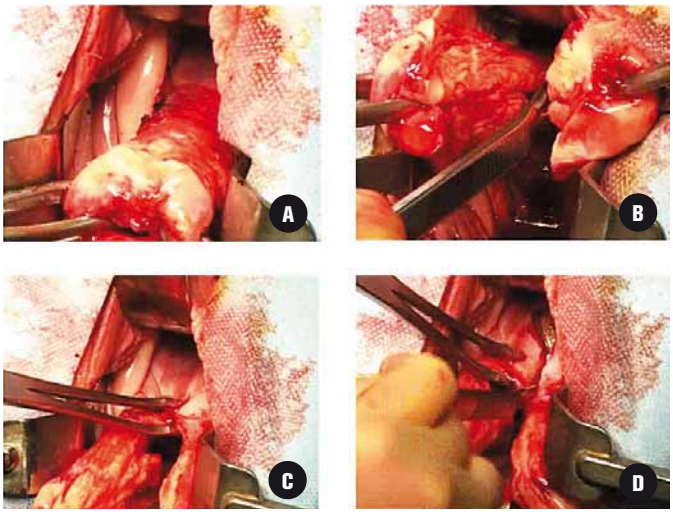
FIGURE 2 Transvaginal uterine morcellation



Uterine bivalving (A,B) and toothed clamp allowing resection of serial wedges of tissue from uterus (C,D)

by increasing pelvic pressure and is interested in definitive surgical management. She has no other past medical history, and her past surgical history is significant for 3 prior cesarean sections.

Ultrasound showed a dominant fundal fibroid with likely submucosal component measuring 8 cm and normal ovaries. On exam she has a 16-week size mobile uterus with a narrow lower uterine segment. Her pubic arch is narrow and there is no descent on valsalva.

Q How would you counsel this patient regarding route of hysterectomy?

A The combination of large uterine size, prior uterine surgeries, narrow pubic arch, and lack of uterine descent in this patient makes vaginal hysterectomy difficult for all but the most experienced vaginal surgeons. Thus the decision is between laparoscopic and open hysterectomy. In contrast, consider Case 3.

Case 3: Open or laparoscopic

A 48-year-old G3P2012 presents with increasing pelvic pressure and a visible abdominal mass. She requests surgical management. She has no other past medical or surgical history, and she has had 2 vaginal deliveries of 8- to 9-lb infants. Ultrasound showed a 25-cm multifibroid uterus. On exam the uterus has limited mobility, fills the pelvis laterally, and projects to 5 cm above the umbilicus.

Q What are the key factors you would use to determine route of hysterectomy in Cases 2 and 3? Uterine size is certainly larger in Case 3, but what is it about the size and shape of each uterus that makes one patient a good candidate for laparoscopic hysterectomy and the other a poor candidate?

A In Case 3, the decision also lies between laparoscopic and open hysterectomy, because vaginal hysterectomy is not feasible for most surgeons. As with the evaluation for vaginal hysterectomy, it is useful to take a stepwise approach to determine if laparoscopic or abdominal hysterectomy is most appropriate. Asking the following questions may be helpful:

1 *Is laparoscopy contraindicated?*

There are very few contraindications to laparoscopic surgery, which usually arise from inability to tolerate pneumoperitoneum and/or Trendelenburg positioning, such as in patients with severe cardiopulmonary disease. For women with these conditions who need hysterectomy, an open approach may be indicated for patient safety.

Obesity may make a laparoscopic approach to hysterectomy more challenging due to comorbid diseases, the impact of obesity on respiratory mechanics, and the impact of abdominal body fat distribution on patient positioning, trocar placement, and intraoperative visualization.[27] Obesity, particularly morbid obesity, is associated with increased operative time, estimated blood loss, and perioperative morbidity when compared with patients of normal weight.[28,29] When compared to obese women having abdominal hysterectomy, however, those undergoing minimally invasive routes of hysterectomy benefit from lower estimated blood loss and shorter hospital stay.[6,30]

Obesity alone should not be considered a contraindication to vaginal or laparoscopic approaches.

2 *Are the uterine vessels accessible laparoscopically?*

The next important factor in determining if laparoscopic hysterectomy is possible is access to the uterine vasculature. The upper pedicles can typically be secured regardless of uterine size. Access to the uterine vessels deeper in the pelvis can be limited, however, by the confines of the bony pelvis, particularly if the lower uterine segment is wide.

Compare the narrow lower uterine segment in Figure 3A to the bulky lower uterine segment seen in Figure 3B. Despite the fact that the first uterus projects higher above the sacral promontory and may be palpably larger on exam, the uterine vessels are likely more accessible because there is more space between the uterus and pelvic side wall. Uterine manipulation can also be impaired in cases in which significant uterine bulk is present. Access to the vasculature can be evaluated on bimanual exam by palpating the width of the lower uterine segment at its junction with the cervix, and by moving this segment of the uterus toward the contralateral pelvic side wall. A lateral mobility of more than 2 cm on each side usually provides adequate access to the uterine vessels.

Obstructing fibroids or pelvic adhesive disease limiting uterine mobility should also be considered. Placing cephalad pressure on the lower uterus and evaluating if it can be elevated out of the pelvis is also helpful, as lateral space and therefore access to uterine vessels increases higher in the pelvis. In Case 2 there is adequate access to the uterine vasculature, but access is inadequate in Case 3.

3 *Can extrauterine pathology be addressed laparoscopically?*

The presence of pelvic adhesive disease, endometriosis, adnexal cysts, or other benign pelvic pathology can impact successful completion of laparoscopic hysterectomy. The ability to address these issues laparoscopically is dependent on the experience, skill, and comfort of the surgeon. Diagnostic laparoscopy can also be useful in these cases, adding minimal time and risk in the event that abdominal hysterectomy is ultimately required.

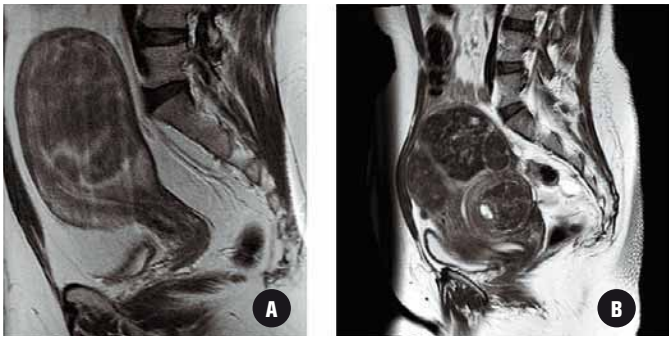
Consultation with surgeons who have additional training and/or expertise in minimally invasive gynecologic surgery can also be of benefit to the patient.

Other considerations

When adding new surgical skills or increasing the difficulty of procedures performed using a less invasive approach, it is best to select patients with presentations that optimize the likelihood of successful completion of the planned surgery and then gradually move toward more challenging cases.

One way to safely achieve this gradual acquisition of skill is to think of factors that may inhibit your ability to safely complete the surgery as "strikes." For example, strikes against successful vaginal hysterectomy may include a narrow vaginal apex, limited uterine descent, uterine size greater than 12 weeks, or history of cesarean section. Beginning with cases that have no strikes and then gradually adding cases that have 1, 2, or 3 strikes will allow you to progress along your learning curve and perform less invasive surgeries in more complex patients over time.

FIGURE 3 Lower uterine segment



Narrow lower uterine segment (A) versus bulky lower uterine segment (B)

It is also helpful to view conversion (from vaginal to laparoscopic surgery or from laparoscopic to open surgery) as a decision made to safely complete hysterectomy rather than as a failure to perform the intended approach.

Practical considerations such as the hospital environment, availability of surgical mentorship from senior partners, and availability of skilled surgical assistants can impact a surgeon's ability to acquire or improve on existing minimally invasive surgical skills. It is helpful to reflect on which portion of the procedure is the most challenging. Is it entering anteriorly or securing the upper pedicles during vaginal hysterectomy, or creating the colpotomy or closing the vaginal cuff during laparoscopic hysterectomy? Are you comfortable with vaginal or laparoscopic morcellation techniques needed for removal of large uterine specimens?

Thinking about the steps that are difficult for you can help you to define your strikes and allow you to seek additional training or assistance with those portions of the procedure. National courses and simulation training are available to who want to add new surgical skills or refine existing techniques.

It is notable that surgical volume has been found to affect route of hysterectomy and postoperative morbidity and mortality, with high-volume surgeons (those who perform more than 10 hysterectomies per year) performing significantly fewer abdominal hysterectomies and having significantly lower rates of postoperative complications and death.[31] Surgical complications and procedure costs associated with laparoscopic hysterectomy have also been found to be lower for

high-volume surgeons (those who perform more than 14 hysterectomies per year) at high-volume centers.[32]

In light of these findings, lower-volume surgeons early in their learning curves should consider consulting more experienced surgeons or referring patients with multiple strikes to surgeons with advanced training in minimally invasive gynecologic surgery.

Summary

Given the considerable data supporting an association between less-invasive routes of hysterectomy and lower morbidity and faster recovery, vaginal and laparoscopic routes should be considered for every patient in need of hysterectomy. Structured evaluation in clinic and the operating room can help the surgeon chose the appropriate type of hysterectomy by clarifying factors that hinder or facilitate a given route.

Choosing cases with no strikes against success and gradually adding more difficult cases allows gynecologic surgeons to improve surgical skill while maintaining patient safety. Most women are candidates for vaginal or laparoscopic hysterectomy, and minimally invasive routes should be considered the standard of care.

Use of the structured approach described here to determine route of hysterectomy will help a surgeon maximize minimally invasive routes in women undergoing hysterectomy. CDG

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Indication

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

Select Important Safety Information

Boxed 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.

Please see additional Important Safety Information and Brief Summary of the Full Prescribing Information, including Boxed WARNING, on the following pages.

Select 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 following page.

The first and only NON-ESTROGEN ORAL treatment for moderate to severe dyspareunia, due to menopause

- **REVERSES** key physiological signs of vulvar and vaginal atrophy (VVA), which include increasing superficial cells, decreasing parabasal cells, and decreasing vaginal pH
- Significantly **IMPROVED** the most bothersome symptom (MBS)* of VVA, which was moderate to severe dyspareunia
- Available in a 60-mg **ORAL** tablet taken once daily with food
- Most common adverse reactions include hot flush, vaginal discharge, muscle spasms, hyperhidrosis, and genital discharge

NLY The **FIRST** FDA-approved estrogen agonist/antagonist for moderate to severe dyspareunia, due to menopause.

New Osphena™
(ospemifene) tablets
60 mg

STUDY DESIGN: Two 12-week, randomized, double-blind, placebo-controlled, parallel-group efficacy studies in 1745 generally healthy postmenopausal women. The first clinical study included 3 treatment groups: Osphena 30 mg (n=282), Osphena 60 mg (n=276), and placebo (n=268). The second clinical study included 2 treatment groups: Osphena 60 mg (n=463) and placebo (n=456). Clinical endpoints for both clinical studies included: a mean change from baseline to Week 12 for percentage of superficial cells on a vaginal smear, percentage of parabasal cells on a vaginal smear, vaginal pH, and most bothersome symptom of VVA (dyspareunia) self-reported by the patient.* A 52-week, randomized, double-blind, placebo-controlled, long-term safety study was also conducted with 2 treatment groups: Osphena 60 mg (n=363) and placebo (n=63).

*MBS was defined as the most bothersome moderate to severe symptom at baseline.

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.

SHIONOGI INC.

Isolated echogenic intracardiac focus

A 31-year-old G2P1 Caucasian patient presents for a routine fetal anatomic survey at 19 weeks' gestation. Her current pregnancy has been uncomplicated. An isolated echogenic intracardiac focus (EIF) is identified during her ultrasound. No other anomalies are detected.

What is an EIF and how commonly do they occur?

An EIF is a small echogenic area appearing within the fetal cardiac ventricle that has a sonographic brightness equivalent to that of bone (Figure). It was first described in 1987 and is most commonly left-sided, although it may be present in either or both ventricles.[1] EIF is believed to represent a microcalcification of the papillary muscle. Other specular reflections in the heart may mimic an EIF.[2] To avoid this, it is important to image the suspected EIF in multiple planes.

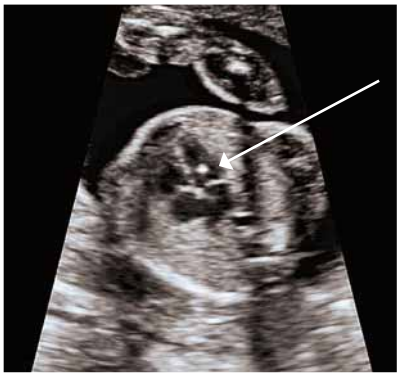
An EIF is a common finding during a routine second-trimester fetal anatomic survey and is identified in 3% to 5% of normal fetuses. The prevalence of EIF may vary according to maternal ethnicity.[3-5] Specifically, one study found that the frequency of EIF was as high as 30% in fetuses of Asian mothers.[6] Other studies have supported an increased prevalence of EIF in individuals of Asian, African-American, and Middle-Eastern descent.[7]

What are the clinical implications of an isolated EIF?

An EIF is not considered a structural or functional cardiac abnormality. It has not been associated with cardiac malformations in the fetus or newborn.[8,9] The only reported clinical implication is an increased risk of trisomy 21.[3]

When an EIF is identified, an experienced provider should perform a detailed fetal anatomic survey to assess for the presence of structural malformations and other sonographic markers of aneuploidy. In addition, the physician should perform an assessment of other risk factors, including maternal age, results of other screening or diagnostic tests, and family history. Most EIFs are isolated and occur in otherwise low-risk pregnancies.

FIGURE **Echogenic intracardiac focus**



Four-chamber view of the fetal heart with an echogenic focus in the left ventricle

When an isolated EIF is detected, how does counseling differ for women at increased risk for fetal aneuploidy and for women with normal aneuploidy screening results?

All patients, regardless of ultrasound findings, should be offered prenatal screening for aneuploidy and should have the option of invasive diagnostic testing.[10,11] Counseling for a woman after prenatal iden-

continued on **PAGE 42**

Indications and Usage

Vagifem® (estradiol vaginal tablets) is an estrogen indicated for the treatment of atrophic vaginitis due to menopause.

Important Safety Information

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

Estrogen-Alone Therapy

Endometrial Cancer

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

Cardiovascular Disorders and Probable Dementia

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) 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.

The WHI Memory Study (WHIMS) estrogen-alone ancillary study of WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 5.2 years of treatment with daily CE (0.625 mg) alone, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women.

In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and other dosage forms of estrogens. Estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

Estrogen Plus Progestin Therapy

Cardiovascular Disorders and Probable Dementia

Estrogen plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia.

The WHI estrogen plus progestin substudy reported increased risks of DVT, pulmonary embolism, stroke and myocardial infarction 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.

Breast Cancer

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.

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

The use of Vagifem® is contraindicated in women who exhibit one or more of the following: undiagnosed abnormal genital bleeding; known, suspected, or history of breast cancer; known or suspected estrogen-dependent neoplasia; active deep vein thrombosis, pulmonary embolism or history of these conditions; active arterial thromboembolic disease or a history of these conditions; known anaphylactic reaction or angioedema to Vagifem®; known liver impairment or disease; known protein C, protein S, or antithrombin deficiency, or other known thrombophilia disorders, or known or suspected pregnancy.

Vagifem® is intended only for vaginal administration. Systemic absorption occurs with the use of Vagifem®. The warnings, precautions, and adverse reactions associated with the use of systemic estrogen therapy should be taken into account.

The WHI estrogen plus progestin substudy reported a statistically non-significant increased risk of ovarian cancer.

Other warnings include: gallbladder disease, severe hypercalcemia, loss of vision, severe hypertriglyceridemia, cholestatic jaundice, and vaginal abrasion caused by the Vagifem® applicator. Women on thyroid replacement therapy should have their thyroid function monitored.

In a randomized, double-blind, parallel group, placebo-controlled study for Vagifem® 10 mcg, adverse events with an incidence of ≥5% included vulvovaginal mycotic infection, vulvovaginal pruritus, back pain and diarrhea.

Please see Brief Summary of the Prescribing Information on adjacent pages.

novo nordisk®

Reference: 1. Vagifem [package insert]. Princeton, NJ: Novo Nordisk Inc; 2012.

For your postmenopausal patients experiencing atrophic vaginitis

Low-dose Vagifem® (estradiol vaginal tablets) 10 mcg

- **The lowest dose* of local vaginal estrogen commercially available**

*Based on a 12-week dosing schedule according to Vagifem® Prescribing Information.[1]

Convenient applicator

- **Pre-loaded[1]**
- **Precise dosing[1]**
- **Single use[1]**

Start your patients today!

Call **1-855-NOVO-V10** (668-6810) to order samples and co-pay cards† today.

Mention the code "HCP 123" when you call.

†Some restrictions apply.

Please see Important Safety Information and Brief Summary of the Prescribing Information on adjacent pages.

VAGIFEM® 10 mcg
estradiol vaginal tablets

Vagifem® (estradiol vaginal tablets)

Rx only

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

WARNING: ENDOMETRIAL CANCER, CARDIOVASCULAR DISORDERS, BREAST CANCER and PROBABLE DEMENTIA: Estrogen-Alone Therapy: Endometrial Cancer: There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding *[see Warnings and Precautions]*. Cardiovascular Disorders and Probable Dementia: Estrogen-alone 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 developing probable dementia in postmenopausal women 65 years of age or older during 5.2 years of treatment with daily CE (0.625 mg)-alone, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women *[see Warnings and Precautions]*. In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and other dosage forms of estrogens. Estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman. Estrogen Plus Progestin Therapy: Cardiovascular Disorders and Probable Dementia: Estrogen plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia *[see Warnings and Precautions]*. The WHI estrogen plus progestin substudy reported increased risks of DVT, pulmonary embolism (PE), stroke and myocardial infarction (MI) in postmenopausal women (50 to 79 years of age) during 5.6 years of treatment with daily oral CE (0.625 mg) combined with medroxyprogesterone acetate (MPA) [2.5 mg], relative to placebo *[see Warnings and Precautions]*. 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 *[see Warnings and Precautions]*. Breast Cancer: The WHI estrogen plus progestin substudy also demonstrated an increased risk of invasive breast cancer *[see Warnings and Precautions]*. In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and MPA, and other combinations and dosage forms of estrogens and progestins. Estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

INDICATIONS AND USAGE: Treatment of Atrophic Vaginitis due to Menopause

CONTRAINDICATIONS: Vagifem® should not be used in women with any of the following conditions: Undiagnosed abnormal genital bleeding; Known, suspected, or history of breast cancer; Known or suspected estrogen-dependent neoplasia; Active DVT, PE, or history of these conditions; Active arterial thromboembolic disease (for example, stroke, and myocardial infarction), or a history of these conditions; Known anaphylactic reaction or angioedema to Vagifem®; Known liver impairment or disease; Known protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders; Known or suspected pregnancy

WARNINGS AND PRECAUTIONS: Risks from Systemic Absorption: Vagifem® is intended only for vaginal administration. Systemic absorption occurs with the use of Vagifem®. The warnings, precautions, and adverse reactions associated with the use of systemic estrogen-alone therapy should be taken into account. **Cardiovascular Disorders:** An increased risk of stroke and DVT has been reported with estrogen-alone therapy. An increased risk of PE, DVT, stroke, and MI has been reported with estrogen plus progestin therapy. Should 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. Subgroup analysis of women 50 to 59 years of age suggests a statistically non-significant reduction in CHD events (CE [0.625 mg]-alone compared to placebo) in women with less than 10 years since menopause (8 versus 16 per 10,000 women-years). 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). 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 the original HERS, HERS II. Average follow-up in HERS II was an additional 2.7 years, for a total of 6.8 years overall. Rates of CHD events were comparable among women in the CE plus MPA group and the placebo group in HERS, HERS II, and overall. *Venous Thromboembolism:* In the WHI estrogen-alone substudy, the risk of VTE (DVT and PE) was increased for women receiving daily CE (0.625 mg)-alone compared to placebo (30 versus 22 per 10,000 women-years), although only the increased risk of DVT reached statistical significance (23 versus 15 per 10,000 women-years). The increase in VTE risk was demonstrated during the first 2 years. 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. Should a VTE occur or be suspected, estrogen plus progestin therapy should be discontinued immediately. If feasible, estrogens should be discontinued at least 4 to 6 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization. **Malignant Neoplasms:** *Endometrial Cancer:* An increased risk of endometrial cancer has been reported with the use of unopposed estrogen therapy in a woman with a uterus. The reported endometrial cancer risk among unopposed estrogen users is about 2 to 12 times greater than in non-users, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with use of estrogens for less than 1 year. The greatest risk appears associated with prolonged use, with an increased risk of 15- to 24-fold for 5 to 10 years or more and this risk has been shown to persist for at least 8 to 15 years after estrogen therapy is discontinued. Clinical surveillance of all women using estrogen-alone or estrogen plus progestin therapy is important. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding. There is no evidence that the use of natural estrogens results in a different endometrial risk profile than synthetic estrogens of equivalent estrogen dose. Adding a progestin to estrogen therapy in postmenopausal women has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. *Breast Cancer:* The most important randomized clinical trial providing information about breast cancer in estrogen-alone users is the WHI substudy of daily CE (0.625 mg)-alone. In the WHI estrogen-alone substudy, after an average follow-up of 7.1 years, daily CE-alone was not associated with an increased risk of invasive breast cancer *[relative risk (RR) 0.80]*. 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. Consistent with the WHI clinical trial, observational studies have also reported an increased risk of breast cancer for estrogen plus progestin therapy, and a smaller increased risk for estrogen-alone therapy, after several years of use. The risk increased with duration of use, and appeared to return to baseline over about 5 years after stopping treatment (only the observational studies have substantial data on risk after stopping). Observational studies also suggest that the risk of breast cancer was greater, and became apparent earlier, with estrogen plus progestin therapy as compared to estrogen-alone therapy. However, these studies have not generally found significant variation in the risk of breast cancer among different estrogen plus progestin combinations, doses, or routes of administration. The use of estrogen-alone and estrogen plus progestin therapy has been reported to result in an increase in abnormal mammograms requiring further evaluation. All women should receive yearly breast examinations by a healthcare provider and perform monthly breast self-examinations. In addition, mammography examinations should be scheduled based on patient age, risk factors, and prior mammogram results. *Ovarian Cancer:* The WHI estrogen plus progestin substudy reported a statistically non-significant increased risk of ovarian cancer. After an average follow-up of 5.6 years, the relative risk for ovarian cancer for

CE plus MPA versus placebo was 1.58 (95 percent CI, 0.77-3.24). The absolute risk for CE plus MPA versus placebo was 4 versus 3 cases per 10,000 women-years. 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. In the WHIMS estrogen plus progestin ancillary study of WHI, a population of 4,532 postmenopausal women 65 to 79 years of age was randomized to daily CE (0.625 mg) plus MPA (2.5 mg) or placebo. After an average follow-up of 4 years, 40 women in the CE plus MPA group and 21 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE plus MPA versus placebo was 2.05 (95 percent CI, 1.21-3.48). The absolute risk of probable dementia for CE plus MPA versus placebo was 45 versus 22 cases per 10,000 women-years. 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. **Gallbladder Disease:** A 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in postmenopausal women receiving estrogens has been reported. **Hypercalcemia:** Estrogen administration may lead to severe hypercalcemia in women with breast cancer and bone metastases. If hypercalcemia occurs, use of the drug should be stopped and appropriate measures taken to reduce the serum calcium level. **Visual Abnormalities:** Retinal vascular thrombosis has been reported in women receiving estrogens. Discontinue medication pending examination if there is a sudden partial or complete loss of vision, or a sudden onset of proptosis, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, estrogens should be permanently discontinued. **Addition of a Progestin When a Woman Has Not Had a Hysterectomy:** Studies of the addition of a progestin for 10 or more days of a cycle of estrogen administration, or daily with estrogen in a continuous regimen, have reported a lowered incidence of endometrial hyperplasia than would be induced by estrogen treatment alone. Endometrial hyperplasia may be a precursor to endometrial cancer. There are, however, possible risks that may be associated with the use of progestins with estrogens compared to estrogen-alone regimens. These include an increased risk of breast cancer. **Elevated Blood Pressure:** In a small number of case reports, substantial increases in blood pressure have been attributed to idiosyncratic reactions to estrogens. In a large, randomized, placebo-controlled clinical trial, a generalized effect of estrogens on blood pressure was not seen. **Hypertriglyceridemia:** In women with pre-existing hypertriglyceridemia, estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis. Consider discontinuation of treatment if pancreatitis occurs. **Hepatic Impairment and/or Past History of Cholestatic Jaundice:** Estrogens may be poorly metabolized in women with impaired liver function. For women with a history of cholestatic jaundice associated with past estrogen use or with pregnancy, caution should be exercised, and in the case of recurrence, medication should be discontinued. **Hypothyroidism:** Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Women with normal thyroid function can compensate for the increased TBG by making more thyroid hormone, thus maintaining free T_4 and T_3 serum concentrations in the normal range. Women dependent on thyroid hormone replacement therapy who are also receiving estrogens may require increased doses of their thyroid replacement therapy. These women should have their thyroid function monitored in order to maintain their free thyroid hormone levels in an acceptable range. **Fluid Retention:** Estrogens may cause some degree of fluid retention. Women with conditions that might be influenced by this factor, such as a cardiac or renal dysfunction, warrant careful observation when estrogen-alone is prescribed. **Hypocalcemia:** Estrogen therapy should be used with caution in women with hypoparathyroidism as estrogen-induced hypocalcemia may occur. **Exacerbation of Endometriosis:** 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. **Local Abrasion:** A few cases of local abrasion induced by the Vagifem® applicator have been reported, especially in women with severely atrophic vaginal mucosa. **Laboratory Tests:** Serum follicle stimulating hormone (FSH) and estradiol levels have not been shown to be useful in the management of moderate to severe symptoms of vulvar and vaginal atrophy. **Drug-Laboratory Test Interactions:** Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, II-VII-X complex, and beta-thromboglobulin; decreased levels of antifactor Xa and antithrombin III, decreased antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity. Increased thyroid-binding globulin (TBG) levels leading to increased circulating total thyroid hormone as measured by protein-bound iodine (PBI), T_4 levels (by column or by radioimmunoassay) or T_3 levels by radioimmunoassay. T_3 resin uptake is decreased, reflecting the elevated TBG. Free T_4 and free T_3 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 HDL_2 cholesterol subfraction concentrations, reduced low-density lipoprotein (LDL) cholesterol concentrations, increased triglyceride levels. Impaired glucose tolerance.

ADVERSE REACTIONS: The following serious adverse reactions are discussed elsewhere in the labeling: Cardiovascular Disorders *[see Boxed Warning, Warnings and Precautions]*; Malignant Neoplasms *[see Boxed Warning, 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 practice. In a 12-month randomized, double-blind, parallel group, placebo-controlled study, a total of 309 postmenopausal women were randomized to receive either placebo or Vagifem® 10 mcg tablets. Adverse reactions with an incidence of ≥ 5 percent in the Vagifem® 10 mcg group and greater than those reported in the placebo group are listed in Table 1.

Table 1: Treatment-Emergent Adverse Reactions Reported at a Frequency of ≥ 5 Percent in Women Receiving Vagifem® 10 mcg

Body System Adverse Reaction	**Treatment** Number (%) of Women	
	Placebo N = 103, n (%)	**Vagifem®** N = 205, n (%)
Body As A Whole		
Back Pain	2 (2)	14 (7)
Digestive System		
Diarrhea	0	11 (5)
Urogenital System		
Vulvovaginal Mycotic Infection	3 (3)	17 (8)
Vulvovaginal Pruritus	2 (2)	16 (8)

N = Total number of women in study.
n = Number of women who experienced adverse reactions.

In a 12-week, randomized, double-blind, placebo-controlled study, 138 postmenopausal women were randomized to receive either placebo or Vagifem® 25 mcg tablets. Adverse reactions with an incidence of ≥ 5 percent in the Vagifem® 25 mcg group and greater than those reported in the placebo group are listed in Table 2.

Table 2: Treatment-Emergent Adverse Reactions Reported at a Frequency of ≥ 5 Percent in Women Receiving Vagifem® 25 mcg

Body System Adverse Reaction	**Treatment** Number (%) of Women	
	Placebo N = 47, n (%)	**Vagifem®** N = 91, n (%)
Body As A Whole		
Headache	3 (6)	8 (9)
Abdominal Pain	2 (4)	6 (7)
Back Pain	3 (6)	6 (7)
Respiratory System		
Upper Respiratory Tract Infection	2 (4)	5 (5)
Urogenital System		
Moniliasis Genital	1 (2)	5 (5)

N = Total number of women in study.
n = Number of women who experienced adverse reactions.

Postmarketing Experience: The following adverse reactions have been identified during post-approval use of Vagifem® 25 mcg. 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. *Genitourinary System:* Endometrial cancer, endometrial hyperplasia, vaginal irritation, vaginal pain, vaginismus, vaginal ulceration. *Breast:* Breast cancer. *Cardiovascular:* Deep vein thrombosis. *Gastrointestinal:* Diarrhea. *Skin:* Urticaria, erythematous or pruritic rash, genital pruritus. *Central Nervous System:* Aggravated migraine, depression, insomnia. *Miscellaneous:* Fluid retention, weight increase, drug ineffectiveness, hypersensitivity, blood estrogen increase. Additional postmarketing adverse reactions have been reported in patients receiving other forms of hormone therapy.

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

More detailed information is available upon request.

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> If noninvasive prenatal testing is negative, **an isolated EIF may be considered a normal variant** because of the extremely low residual risk of trisomy 21.

continued from **PAGE 37**

tification of EIF should be guided by presence of other sonographic markers or structural abnormalities, maternal serum screening for risk of Down syndrome (if performed), and maternal age. If an isolated EIF is detected in a woman who has already had an invasive diagnostic test—and the fetal karyotype is known—she can be reassured that the finding is considered a normal variant.

Numerous studies have described the association between EIF and aneuploidy, specifically Down syndrome.[12] Meta-analyses of studies conducted primarily in high-risk pregnancies reported that the risk of trisomy 21 was increased 1.8- to 5.4-fold by the finding of an isolated EIF.[3,12,13] Recently, another meta-analysis similarly identified a 2.9 likelihood ratio (LR) for isolated EIF, when defined as no major abnormalities and no evidence of ventriculomegaly, increased nuchal skinfold thickness, echogenic bowel, pyelectasis, short humerus, or short femur.[14]

A suggested method of risk assessment is to multiply the patient's a priori risk (based on maternal age or screening) by a published likelihood ratio such as 2.9 as indicated above to generate a modified risk. In women with serum screening indicating an increased risk for trisomy 21 following risk modification, genetic counseling may be helpful. Noninvasive prenatal testing (NIPT) may be a reasonable option for women who are concerned about the procedure-related risk of pregnancy loss.[15,16] If the NIPT result is negative, an isolated EIF may be considered a normal variant because of the extremely low residual risk of trisomy 21. These women, however, should still have the option of an invasive diagnostic test.

Despite the many studies performed to date, there is controversy regarding the significance of EIF in pregnancies at low risk of Down syndrome. With the considerable improvements in imaging technology and aneuploidy screening in recent years, the current risk of trisomy 21 in the setting of isolated EIF is considered low.

Therefore in a woman with a negative aneuploidy screen for Down syndrome (either first- or second-trimester screening) and no visualized fetal structural abnormalities or other aneuploidy markers on a detailed ultrasound, the provider has options. One option is to use the approach highlighted previously, using the LR for risk assessment. For these women at low risk of trisomy 21 pregnancies, other practitioners may consider an EIF a normal variant, and as a result of this perspective, provide no additional counseling or testing.[17]

How should a woman with an isolated EIF be followed throughout pregnancy?

Because an isolated EIF does not represent a cardiac abnormality, fetal echocardiography is not needed and no specific follow-up is recommended. Follow-up should be performed based on the presence of other clinical indications or the results of the patient's prenatal screening and/or diagnostic testing. COG

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Disclaimer: The practice of medicine continues to evolve and individual circumstances will vary. Clinical practice also may vary. This opinion reflects information available at the time of acceptance for publication and is not designed nor intended to establish an exclusive standard of perinatal care. This publication is not expected to reflect the opinions of all members of the Society for Maternal-Fetal Medicine.

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Letters to the editor CONTINUED from PAGE 17

IN REPLY:

I thank Dr. Petrikovsky for his passionate commentary on my recent editorial. Clearly the Accountable Care Act (ACA) embodies his call for a hospital pricing "Bill of Rights" by requiring transparent pricing information.[1]

However, while I am sympathetic to his arguments, in the absence of high deductibles and copays, it is unlikely that most consumers will avail themselves of this information. Moreover, while the intent of this ACA provision is to create market discipline and curb healthcare price inflation, our more libertarian readers might contend that it is the consumer's job to look out for himself or herself (caveat emptor) and that such price comparisons are one of the reasons for purchasing health insurance in the first place. That is because insurance companies actively negotiate with providers for discounted prices and would rarely tolerate such extremes in the price they paid to comparable providers in the same area for treating similar patients in similar fashions.

Finally, while the Dartmouth Institute for Health Policy's findings on regional variations in pricing are oft touted, it must be pointed out that at least some of this cost variability, if not all of it, is due to regional variations in population health (ie, sicker patients cost more to care for).[2]

Thanks again for your comments.

Charles J. Lockwood, MD, MHCM
Editor in Chief, *Contemporary OB/GYN*

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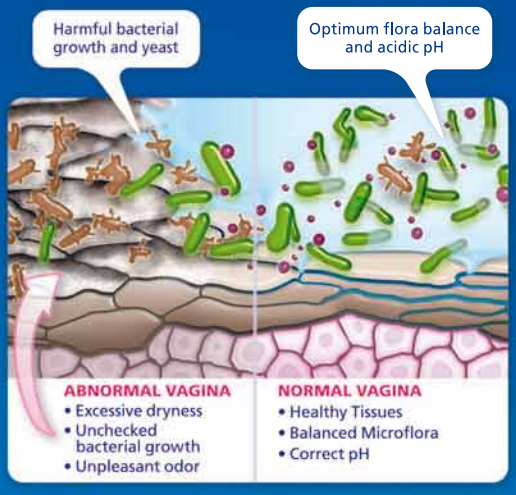

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SSRIs in pregnancy
Weighing benefits and risks

Use of selective serotonin reuptake inhibitor therapy is common for depression in pregnancy, but not without risk. An assessment of the latest scientific evidence and a tailored treatment approach are necessary to ensure the best outcome for both mother and infant.

BY **DAVID E. ABEL, MD**

DR. ABEL is a maternal-fetal medicine specialist at Prenatal Diagnosis of Northern California, Sacramento.

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

Obstetricians often see pregnant patients with psychiatric disorders, the most common being depression. Treatment includes both nonpharmacologic and pharmacologic options. This article focuses on use of selective serotonin reputake inhibitors (SSRIs), the drugs most often used to treat depression in pregnancy.[1]

Scope of the issue

A woman has a 10% to 25% risk of being diagnosed with major depressive disorder at some point in her life, with the greatest risk occurring during the childbearing years.[2] It is estimated that 14% to 23% of pregnant women will experience a depressive episode while pregnant.[3]

The number of pregnant women in the United States using antidepressants during pregnancy ranges from 7% to 13%.[4] As the number of pregnant women taking antidepressants has increased over the past 10 to 15 years, so has the body of literature investigating the safety and effects of these medications during pregnancy. Most of the studies are nonrandomized, increasing the risk of confounding and as-

TAKE-HOME MESSAGES

- Absolute risks of adverse effects of maternal SSRI use on neonatal health are small.
- Only recently have studies begun to take into account the effects of depression itself, rather than merely medication use, on adverse outcomes.

certainment bias. Results from many studies are conflicting, in part because past studies did not take into account the effect of depression or its severity.[5] More recent studies, however, have incorporated propensity score matching, which attempts to equalize the variables among treated and untreated depressed women.[3]

The potential effects of SSRI exposure on the newborn are discussed here.

TABLE 1 Signs and symptoms of poor neonatal adaptation

- Poor muscle tone
- Jitteriness
- Weak or absent cry
- Increased motor activity
- Seizures
- Hypoglycemia
- Heightened startle reflex
- Jaundice
- Respiratory failure (rare)

Poor neonatal adaptation

If SSRIs are abruptly stopped, neonates may demonstrate a constellation of symptoms similar to the withdrawal-type phenomenon seen in adults. Exposure in late pregnancy to SSRIs confers a 10% to 30% risk of poor neonatal adaptation (PNA) syndrome, although the true risk is not known.[6] In most cases symptoms are mild and self-limiting. Some infants will require observation for a few days postnatally. It should also be noted that PNA may not be related to medication withdrawal at all. It could also reflect medication side effects (toxicity), nicotine withdrawal, or other factors common to women who take antidepressants.

To reduce the risk of PNA, or to possibly ameliorate neonatal symptoms, some have suggested stopping SSRIs near term. This can have deleterious consequences for the mother and neonate, particularly in the vulnerable postpartum period. One recent study looked at the neonatal effects of continuing SSRIs until delivery compared to stopping them 14 days prior to delivery.[7] Stopping SSRIs prior to term did not appear to improve neonatal outcomes. Importantly, these researchers used propensity score matching in an attempt to control for disease severity, although they did acknowledge limitations such as not controlling for maternal race and alcohol or tobacco use.

Most studies in the past did not take into account the possible effects of depression or control for the severity of it. Thus establishing causal relationships between medication use and adverse outcomes proved difficult. Only recently has the focus shifted to also taking into account the effects of the disease itself.

Table 1 lists some of the features suggestive of PNA. This cluster of findings has also been called neonatal withdrawal or neonatal abstinence syndrome. It is unclear whether PNA is a withdrawal phenomenon or possibly reflects serotonin toxicity. It is important to alert a patient's pediatrician about maternal SSRI use and to counsel the patient about the possibility of PNA. As noted in a recent review examining risks versus benefits, if pharmacotherapy is indicated the potential benefits outweigh the possible risks of PNA.[8]

Persistent pulmonary hypertension of the newborn

Also known as persistent fetal circulation, persistent pulmonary hypertension of the newborn (PPHN) is a serious condition in which the pulmonary vascular resistance does not decrease after birth. As a result, pulmonary blood flow is decreased and right-to-left shunting of deoxygenated blood occurs across the foramen ovale and ductus arteriosus to the systemic circulation.

PPHN occurs primarily in term or post-term infants, with a reported incidence of 2 per 1000 live births. Mortality ranges from 5% to 10% and is often associated with the presence of congenital anomalies such as heart disease and congenital diaphragmatic hernia.

A possible link between late SSRI exposure (>20 weeks' gestation) and PPHN was suggested in a case-controlled study and another study using data from the Swedish Medical Birth Register.[9,10] Neither study contolled for mode of delivery. In one of these studies, there were only 14 SSRI exposures and a 6-fold risk of PPHN with SSRI exposure was demonstrated.[9] The absolute risk of PPHN, however, remained extremely small (3–12/1000 live births). Since these studies, several others have failed to demonstrate an association between SSRI exposure and PPHN. Two studies—a multicenter retrospective cohort of 1104 exposures and a case-controlled study looking at all births over a 6-year period—did not observe an association.[11,12] A strength of these 2 studies was the elimination of any recall bias because data ascertainment was based on a prospectively collected database.

Most recently a large multinational cohort that looked at 1.6 million births over an 11-year period in 5 countries suggested an association between SSRI exposure after 20 weeks' gestation and PPHN.[13] The absolute risk, however, remained very small (3/1000). In a review of this study certain weaknesses were noted.[14] In particular are the inherent confounders when analyzing data from a registry and the failure to control for untreated depression, the latter a concern in many studies attempting to link SSRIs with adverse perinatal outcomes. The reviewer goes on to state that clinicians should not change their practice of prescribing SSRIs if indicated based on the findings of this study.

The biologic mechanisms by which SSRI exposure might cause PPHN are unknown. Serotonin's vasoconstrictive properties and mitogenic effects on pulmonary smooth muscle have been postulated. Still, if there is a risk of PPHN with SSRI use, in my opinion, the absolute risk is very small and the benefits likely outweigh this marginal risk.[8]

Congenital anomalies

Despite the limitations of a small sample size, most studies have failed to demonstrate a link between SSRI exposure and fetal malformations. In 2005, a report by the drug manufacturer of paroxetine noted a 1.5-fold risk of cardiac defects (primarily atrial and ventricular septal defects) in children exposed in utero to paroxetine. This prompted the FDA to change the pregnancy category of paroxetine from C to D and issue an advisory for clinicians to consider discontinuation of this medication, or to reduce the dose to decrease the risk of PNA and PPHN.[15] The data in this report were not published in a peer-reviewed journal and were derived from a Swedish registry and a US insurance-claims database, sources with inherent bias and methodologic limitations.

A December 2006 Committee Opinion from the American College of Obstetricians and Gynecologists did not specifically state that paroxetine is absolutely contraindicated during pregnancy but advised that its use preconceptionally or during gestation should be avoided if possible.[16] The opinion added that "the benefits of paroxetine therapy in a given pregnant patient may outweigh the potential risks" and "fetal echocardiography should be considered for women who were exposed to paroxetine in early pregnancy."[16]

Subsequently, prospectively ascertained data from teratology information services worldwide with the largest number of paroxetine exposures (1174) to date did not show an association between paroxetine exposure in early pregnancy and cardiac malformations.[17]

Two large case-controlled studies examining the relationship between first-trimester SSRI exposure and congenital anomalies were published in the same issue of *The New England Journal of Medicine*.[18,19] The results were conflicting. In the National Birth Defects Prevention (NBDP) Study, data from 9622 infants with congenital anomalies over a 6-year period were compared with over 4000 controls.[18] No significant association was found between maternal use of SSRIs overall and congenital heart defects or most other birth defects.

There was an increased odds ratio with maternal SSRI use, however, for anencephaly, craniosynostosis, and omphalocele. The use of paroxetine significantly increased the risk of this latter pooled group. Prior to this study, paroxetine was not linked to any of these anomalies. Importantly, the numbers were extremely small. From a total of 214 infants with anencephaly, only 9 were exposed to SSRIs. Data from the Slone Epidemiology Center Birth Defects Study investigating exposures in 9849 infants compared to 5860 controls over a 12-year period did not demonstrate the association noted in the NBDP study.[19] An editorial in the same issue addressing these conflicting results concluded that specific defects (if any) are rare and absolute risks are small.[20]

A recent retrospective cohort study was published analyzing data over a 10-year period obtained from national population-based registers in Finland.[21] An association between fluoxetine and paroxetine with isolated ventricular septal defects and right ventricular outflow tract defects, respectively, was noted. In addition, citalopram use was found to be associated with neural tube defects. Again the absolute risks were small. Importantly, despite the high prevalence of fetal alcohol spectrum disorders this study has been criticized for not controlling for alcohol use and other confounders.[22]

Data from the first prospective study to examine the effects of escitalopram, a relatively new SSRI, were recently analyzed and no association with major congenital anomalies was found.[23] Further, a large retrospective cohort study used birth data obtained from the Danish Medical Birth Register to analyze more than 4000 first-trimester SSRI exposures. Only

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a small 2-fold increase in the risk of cardiac septal defects was noted.[24] Once more, the absolute risks remained small.

In summary, evidence that SSRI exposure increases the risk of congenital anomalies is conflicting, but reassuring overall. If there is indeed an increased risk, the question of biologic plausibility remains. All SSRIs are rated pregnancy category C, with the exception of paroxetine, which is a category D as previously discussed (Table 2).

Adverse perinatal outcomes

Many studies have looked at the association between SSRI use and preterm birth (PTB), low birth weight (LBW), and small for gestational age (SGA). Results are conflicting, and many studies were underpowered to detect a difference.[3] When propensity score matching is used to control for maternal disease, there appears to be a statistically significant association between these adverse perinatal outcomes and SSRI use during pregnancy. Still, whether these are clinically significant associations that would warrant a change in practice is a key question.

A meta-analysis of 23 studies published earlier this year looked at exposure to various antidepressants and the relationship with adverse perinatal outcomes.[25] Most of the antidepressants were SSRIs. No association was noted between exposure and spontaneous abortions. A significant association was noted between antidepressant exposure and preterm birth, SGA, lower birth weight, and lower Apgar scores. For preterm birth and length of gestation, the statistically significant association remained when compared only to untreated depressed mothers. For birth weight, when compared to the infants of untreated depressed mothers, the association with antidepressant exposure was no longer significant.

The take-home message from this important study is that even if certain associations persist after considering the effect of depression itself, the differences are small and unlikely to be clinically significant.

In a recent prospective, population-based study performed in the Netherlands, birth outcomes included preterm birth, LBW, and SGA.[26] Among the 7696 patients included in this study, 99 were exposed to SSRIs and 570 had untreated depression. The SSRI-exposed group showed a reduced fetal head circumference but not reduced body growth.

TABLE 2 Pregnancy classification of SSRIs

Generic name	Trade name	Pregnancy classification
Citalopram	Celexa	C
Escitalopram	Lexapro	C
Fluoxetine	Prozac	C
Fluvoxamine	Luvox	C
Paroxetine	Paxil	D*
Sertraline	Zoloft	B
Venlaxifine	Effexor	C

* Changed from C to D after FDA advisory.

In addition, SSRI exposure was associated with preterm birth, even when compared to untreated depressed mothers. However, the untreated depressed group showed reduced fetal head and body growth. The researchers acknowledge that more data are needed to assess medication effect versus the effect of untreated depression.

Developmental effects

Few studies have examined the long-term developmental effects of SSRI exposure in utero. Earlier studies did not reveal any differences in IQ, language, behavior, or temperament when a fluoxetine-exposed group was compared to an unexposed, nondepressed group.[27] This study was one of the first to assess the effect of depression itself on outcomes. Despite the lack of an unexposed group with depression, with the use of multiple regression analysis, the authors were able to demonstrate an adverse effect on child development as it relates to the duration of depression and the number of depressive episodes. This adverse effect was not associated with fluoxetine exposure.

A recent prospective cohort did include a group of untreated depressed women.[28] Children's intelligence and behavior outcomes were evaluated once between ages 3 years and 7 years. Both groups with depression showed a higher but nonsignificant rate of behavioral issues. The investigators concluded that factors other than antidepressant exposure predicted children's intellect and behavior.

A possible association between autism spectrum disorder (ASD) and SSRI exposure during pregnancy was suggested in a recent study that received considerable media attention.[29] The sample in this population-based, case-controlled study was drawn from the

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[1]IMS Health, NDTI, December 2011

TABLE 3 SSRI discussion checklist

- ☐ Discuss small risk of PNA; infant may require observation
- ☐ Discuss possible but small absolute risk of PPHN
- ☐ Risk of congenital anomalies not greater than baseline risk
- ☐ Stopping SSRIs during pregnancy can have serious consequences
- ☐ Stopping SSRIs prior to delivery not recommended
- ☐ Continue medication during breastfeeding
- ☐ Alert pediatrician to maternal SSRI use
- ☐ Consider not using paroxetine as a first-choice SSRI
- ☐ If using paroxetine, consider a fetal echocardiogram at 22-24 weeks
- ☐ Watch for postpartum depression
- ☐ Schedule a postpartum visit soon after delivery

Abbreviations: PNA, poor neonatal adaptation; PPHN, persistent pulmonary hypertension of the newborn

Childhood Autism Perinatal Study, and it included 298 children with ASD and 1507 unaffected controls matched for age, sex, and area of residence within Northern California.

The study found a correlation between a prescription filled for an SSRI and a diagnostic code for ASD. Maternal use of an SSRI during the year before delivery was associated with a 2-fold increased risk of ASD, although this finding was not statistically significant. The strongest effect was associated with treatment during the first trimester (adjusted OR, 3.8 [95% CI, 1.8-7.8]). Among the children whose mothers had a history of mental health treatment but did not take SSRIs, the risk of ASD was not increased.

This study was limited by a small number of SSRI exposures in both the ASD and control groups. In addition, ASD as a variable was not taken into account.

It would be prudent for clinicians to await prospectively ascertained data before more firm conclusions can be drawn regarding the link between SSRI exposure and ASD.

TABLE 4 Commonly used SSRIs and suggested doses

Generic name	Trade name	Dose range (mg/day)	Titration increment (mg)
Citalopram	Celexa	20-40	10
Escitalopram	Lexapro	10-20	5
Fluoxetine	Prozac	20-60	10
Paroxetine	Paxil	20-60	10
Sertraline	Zoloft	50-200	25

Breastfeeding

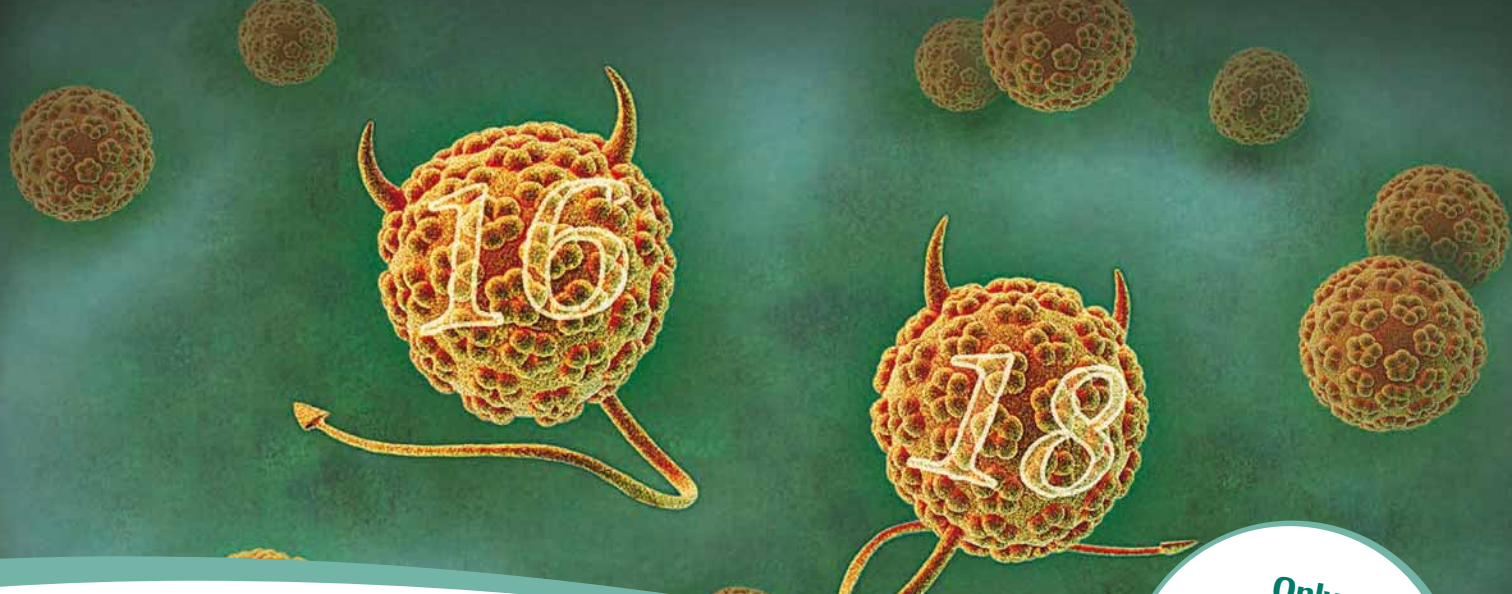
The American Academy of Pediatrics considers all SSRIs compatible with lactation.[30] SSRI molecules do pass into the mother's milk due to their low molecular weight, but the infant dose remains minimal. In a review of antidepressant use during lactation, the researchers prefer sertraline and paroxetine due to their low infant dose as compared with other SSRIs.[31]

Some have suggested that continuing SSRIs in the postpartum period may reduce the risk of PNA if it is a withdrawal phenomenon. There are no adequate studies looking at this. Women with depression are particularly at risk of postpartum depression, which can have grave consequences if untreated. At this time, irrespective of the specific SSRI, it is reasonable for women to continue their SSRI in the vulnerable postpartum period and to be encouraged to breastfeed.

Summary

A history of depression is a strong risk factor for developing postpartum depression, and depression late in pregnancy is the strongest predictor.[8] Other concerns associated with maternal depression during pregnancy include increased use of other pharmacologic agents such as hypnotics, opiates, and tobacco, and poorer compliance with prenatal care. When discontinuing medication during pregnancy, the relapse rate can be significant, with an increased risk of suicidal ideations.[32] As noted previously, the risk of adverse outcomes may also be increased in untreated depressed mothers.

The clinician must individualize treatment, informing patients of both the possible risks and benefits of continuing (or in some cases, initiating) medication. It is also important to document these discussions. Table 3 provides a guide to aid in this discussion.



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Patients should know that their SSRI doses may have to be increased during pregnancy, although symptoms are often controlled with the same dose that was used prior to pregnancy. There are no recommendations regarding dose adjustments once a patient becomes pregnant. Table 4 lists some commonly used SSRIs and their suggested doses. COG

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Dr. Copel is well known world-wide as an expert in maternal and fetal medicine and in high-risk pregnancy. His passion for working in medical ultrasound derives from his excitement for the possibilities in obstetrics. His time is generously spent on advancing the ultrasound profession, for which he has received numerous awards, ranging from the Nathan Kase Award for Excellence in Clinical Teaching at Yale University to the Dru Carlson Memorial Award for Best Research in Ultrasound and Genetics from SMFM. He received the William Fry lectureship award from the American Institute of Ultrasound in Medicine in 2012.

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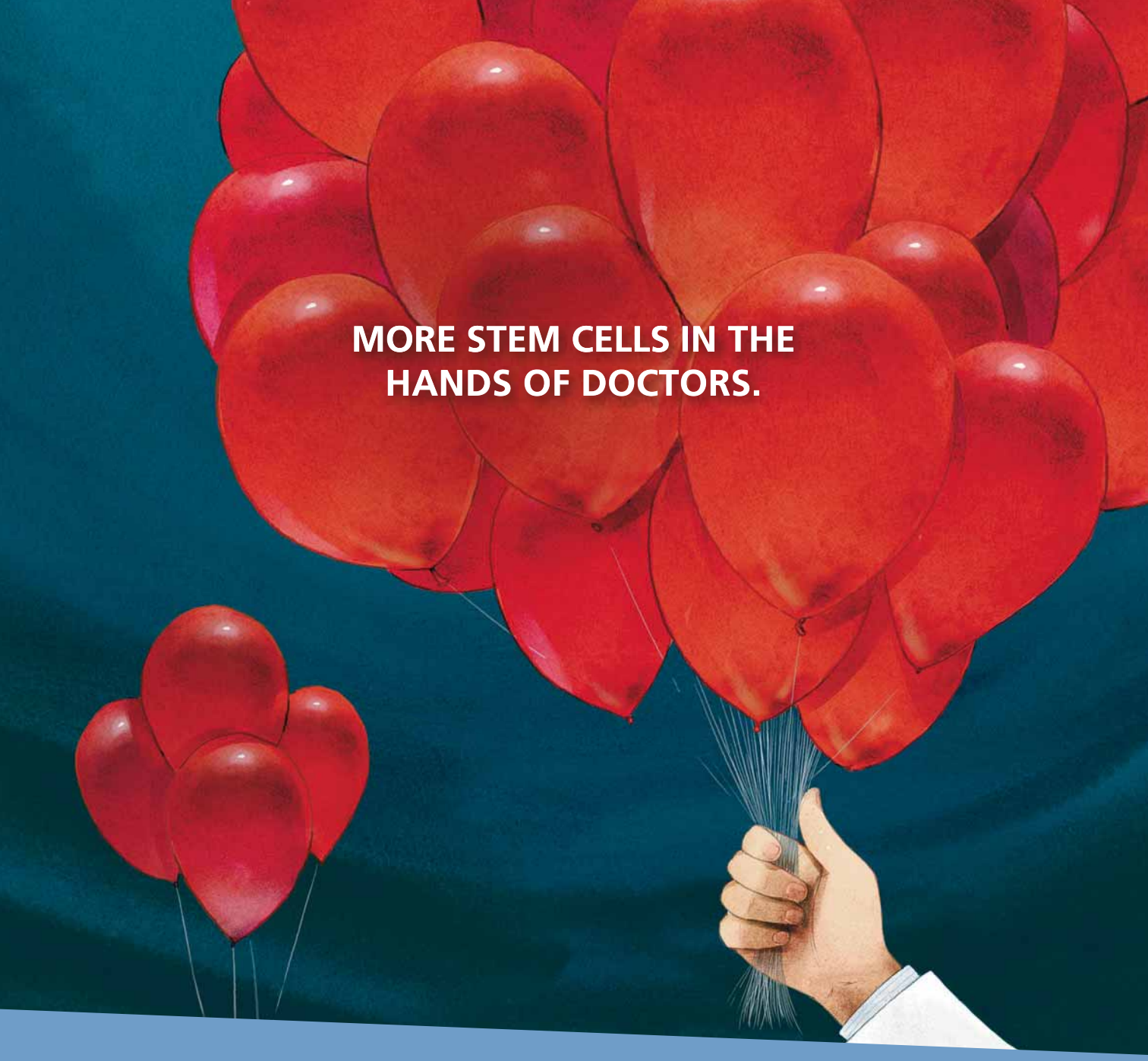

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A 21-YEAR-OLD Maryland woman went to an ob/gyn in 2008 for an examination and was diagnosed with a molar pregnancy. She was instructed to obtain 3 consecutive beta-human chorionic gonadotropin (hCG) tests and a chest x-ray before a follow-up appointment in 2 weeks. The chest x-ray was normal, and the beta-hCG tests revealed elevated levels that decreased with each test. When the patient returned to the physician's office, she was told that she needed 1 more beta-hCG test to complete her treatment. She had the test 3 days later but was not notified of the results.

Three months later the woman suddenly had massive vaginal bleeding. She went to an emergency room, where a beta-hCG test was performed. The level was more than 200,000 mIU/mL. A dilation and curettage (D&C) was performed, but the patient continued to have uterine hemorrhaging and low blood counts. She was emergently transferred to another hospital and was seen by a gynecologic oncologist. She was taken to the operating room, but her bleeding could not be stopped and a hysterectomy was performed. The molar pregnancy had developed into cancer, which had spread to the lungs.

The patient underwent several months of chemotherapy. She required multiple hospitalizations and experienced nausea, vomiting, fatigue, and hair loss. She also had depression related to her inability to bear children.

Legal perspective

In this case the patient was not notified of the results of the final beta hCG test, which showed an increasing level, indicating the ongoing presence of a molar pregnancy, which if untreated can become malignant and metastasize.

The patient filed a lawsuit against the original ob/gyn and claimed that the doctor should have notified her of the test results and sent her to a gynecologic oncologist for immediate treatment. At that time, the patient alleged, the treatment would have consisted of only a short course of chemotherapy. The claim of not following the molar pregnancy to its conclusion, of course, would be difficult to defend. The claim of injury from prolonged treatment and hysterectomy would be subject to expert medical opinions. The jury in this case returned a verdict for the patient in the amount of $1.07 million.

Premature delivery results in cerebral palsy

In 2001 a Maryland woman was admitted to a hospital for hypertension at 31 2/7 weeks' gestation. She was placed on a fetal heart rate (FHR) monitor and evaluated by a maternal-fetal medicine specialist, who determined that delivery was necessary and that a vaginal route was reasonable as long as the patient and fetus were stable, otherwise cesarean delivery would be required. The patient was managed by an ob/gyn and a nurse midwife. She was given Cervidil and was started on oxytocin the next morning. In the afternoon, some late and variable decelerations of the FHR were noted.

A nuchal cord was found when the woman delivered vaginally a few hours later. Apgar scores were 4 and 7, and the infant initially required positive pressure ventilation due to bradycardia and poor respiratory effort. He was subsequently diagnosed with cerebral palsy and is not cognitively impaired, but is severely physically handicapped. He underwent multiple operations to correct uneven leg lengths, and has only 65% use of his arms, making him unable to comb his hair, brush his teeth, or dress himself.

The patient sued those involved with her care, claiming that a cesarean delivery should have been performed 3 hours earlier than the vaginal delivery. She claimed that the late and variable decelerations were severe and prolonged, that the fetus required delivery just after noon, and that allowing the labor to continue caused the brain injury.

The defense maintained that the FHR tracing was normal up to the delivery, the Apgar score of 7 at 5 minutes

was normal, cord blood gases showed a pH of 7.3, and the ultrasound (U/S) of the infant's head did not show any abnormality. The first abnormal U/S of the head was performed when the infant was 2 weeks old, and the defense pointed to prematurity as the cause of the child's handicaps. A $21 million verdict was returned, including $1 million in non-economic damages, which was to be reduced to $650,000 under the state cap. An appeal is pending.

Obstruction of ureter after cystoscopy

A 59-year-old New York woman underwent gynecological surgery, which included a cystoscopy, in 2006. The ob/gyn who performed the surgery found normally functioning ureters. During the following month, the patient was seen for several follow-up examinations. A year later the patient was diagnosed with a complete obstruction of the right ureter. The problem was repaired but the patient lost all function in her right kidney. She will require medication to improve the function of her left kidney for the rest of her life.

The woman sued the ob/gyn and claimed that the obstruction was due to the original operation, alleging that the ureter was ligated and should have been diagnosed in the weeks following surgery.

The physician claimed the cystoscopy was properly performed and that the patient did not report any symptoms after the procedure that would have suggested the presence of a ureteral obstruction. He claimed the obstruction was a gradual development that could not be diagnosed any sooner than it was. A defense verdict was returned.

Uterine artery laceration during cesarean delivery

A 29-year-old Texas woman underwent a scheduled cesarean delivery in 2008, performed by her ob/gyn. After the delivery the patient had low pressures and an altered state of consciousness. She was returned to the operating room and her abdomen was reopened.

A uterine artery hematoma and lacerations were found and repaired, but uterine atony continued and an emergency hysterectomy was performed.

The patient sued those involved with the cesarean, alleging negligence in lacerating the uterine artery, failure to recognize it during the surgery, and failure to properly monitor her after surgery and repair the artery in a more timely manner.

She also claimed the hospital nurses failed to properly check her vital signs postoperatively and failed to report abnormalities in her blood pressure and alertness to the physician earlier.

The hospital and physician claimed that a uterine laceration can occur in the absence of negligence and is a known risk of cesarean delivery. A defense verdict was returned.

Perforation following drain placement results in sepsis

A 50-year-old Rhode Island woman underwent a total abdominal hysterectomy performed by her ob/gyn. After the surgery the patient developed an abdominal cyst. A Jackson-Pratt drain was placed. The patient was subsequently diagnosed with a perforated colon. She developed overwhelming sepsis and died. An autopsy was inconclusive for the cause of death.

A lawsuit was filed on the patient's behalf and alleged that the colon was perforated when the drain was placed and the physician failed to recognized and treat the injury, leading to the patient's death.

The physician denied perforating the colon during placement of the drain. He claimed that the patient suffered from diverticulosis, which was revealed by radiologic tests 3 months prior to the surgery, and that complications from the diverticulosis caused the perforation. A defense verdict was returned.

Misplaced forceps delay delivery of twin

In 2007, a woman gave birth to twins in a North Carolina hospital. The first twin, a boy, was delivered without complications. The patient labored over the next hour with the second twin, a girl, monitored by a second-year resident and an attending physician. When the FHR tracing became concerning, a third physician was called to review the FHR strip. He recommended immediate delivery.

The attending physician decided to perform a forceps delivery rather than a cesarean delivery. It took 15 minutes to locate forceps and the infant was born with severe brain damage and was subsequently diagnosed with cerebral palsy. She has a tracheostomy and is at home but requires 24-hour nursing care for life.

A lawsuit was filed against those involved with the delivery and a $10 million settlement was reached for past and future care. COG

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

What's new in psychosocial obstetrics and gynecology

A commentary on some of the best research in this field published in the past year

BY **JONATHAN SCHAFFIR, MD**

By its very nature, the field of obstetrics and gynecology is steeped in psychosocial issues. Because of the complex interplay of hormones and behavior, as well as the many instances in our field when social behaviors affect medical outcomes, psychosocial issues affect nearly all aspects of women's health.

To provide optimal care for women, ob/gyn physicians should be comfortable dealing with such issues and should be knowledgeable about new developments in psychological and social topics that pertain to obstetrics and gynecology. The following highlights of research published within the past year reflect the breadth of issues in the field.

Editor's note: Portions of this article originally appeared on NASPOG.org in the Winter 2013 newsletter. They are reprinted with the permission of the North American Society for Psychosocial Obstetrics and Gynecology.

Klevens J, Kee R, Trick W, et al.

Effect of screening for partner violence on women's quality of life: a randomized controlled trial.

Journal of the American Medical Association.
2012;308(7):681-689.

Summary

While domestic violence is widely viewed as a public health issue with diverse adverse effects on health, the utility of universal screening has not yet been proven to improve outcomes.

The authors of this study sought to demonstrate whether a computerized screening tool and routine distribution of information on partner violence improved quality of life (QOL) for a primary care pop-

ulation. They enrolled 2708 women who were attending one of 10 primary health clinics in Cook County, Illinois. The women were randomized into 3 groups: one that was screened for partner violence and given a list of resources if screening was positive, one that received only the list of resources, and a control group that received neither. One year later, participants were asked to complete a series of questionnaires describing QOL issues and mental health.

There was no difference among the 3 groups in any QOL measures or mental health components. There were also no differences among the groups in missed work days, hospital or emergency department visits, contact with partner violence agencies, or recurrence of partner violence.

Commentary

At face value, the results of this study are discouraging in demonstrating a lack of improved health among women screened for intimate partner violence. It may be that a single intervention is insufficient to spur women to seek help for this problem, or that such intervention would be better received from a provider with whom a woman has multiple visits and develops a rapport and trust.

The study also suggests that providing a list of resources may not be an effective means of communicating options for intervention.

Universal screening may still have some benefit. Encouraging clinicians to screen all patients for domestic violence keeps the topic in mind so they remain aware of the possibility that this exposure can occur in any social stratum. It also signals to patients that it is an issue that the medical community considers important and worthy of intervention.

In any case, it would behoove the medical community to find effective ways to screen for and treat domestic violence rather than giving up on routine screening entirely.

Straub H, Adams M, Kim JJ, Silver RK.

Antenatal depressive symptoms increase the likelihood of preterm birth.

American Journal of Obstetrics and Gynecology.
2012;207(4):329.e1-4.

Summary

Psychosocial stress has been identified as a risk factor for preterm delivery in the past, but the degree to which maternal depression may contribute to preterm labor is unclear.

This study aimed to clarify whether such an association exists. The study examined the pregnancy outcomes of 14,175 women who were administered the Edinburgh Postnatal Depression Scale as a routine screening test between weeks 24 and 28 of pregnancy.

Women who screened positive were significantly more likely to deliver before 37 weeks (13.9%) than their asymptomatic counterparts (10.3%), with an adjusted odds ratio of 1.3 (95% CI, 1.09-1.35). Significant differences were demonstrated at each gestational age breakpoint (<28, <32, and <34 weeks), and there was also an increased risk in screen-positive women among the 1019 with prior preterm birth.

Commentary

It is unclear whether the differences demonstrated in this study reflect a causal effect or simply association. There is a biologically plausible mechanism to explain earlier delivery in depressed women, in that depression may be associated with derangements of the hypothalamic-pituitary axis and elevated levels of corticotropin-releasing hormone (CRH). Studies have linked excessive CRH levels to preterm birth.

On the other hand, a number of other factors may be involved, including other stressors in the home environment, sleep hygiene, nutrition, and access to and use of health care. Nevertheless, this study contributes to the growing body of evidence that depression adversely affects pregnancy, and that treatment for symptomatic women should not be withheld during pregnancy.

Whether intervention with antidepressants or psychotherapy can reduce the risk of preterm delivery in this group remains to be seen.

Baller EB, Wei SM, Kohn PD, et al.

Abnormalities of dorsolateral prefrontal function in women with premenstrual dysphoric disorder: a multimodal neuroimaging study.

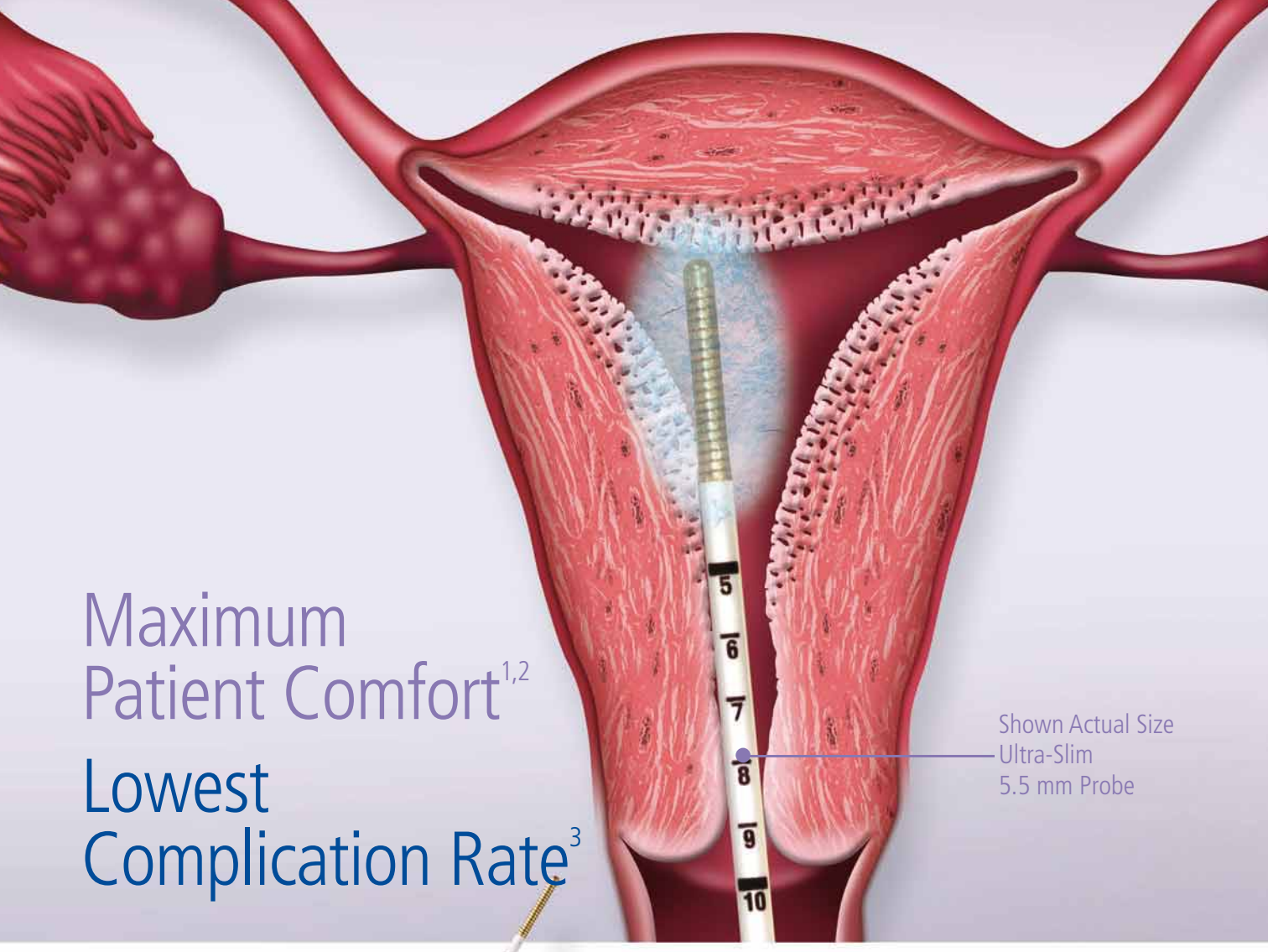
American Journal of Psychiatry. 013;170(3):305-314.

Summary

Premenstrual dysphoric disorder (PMDD) is a condition marked by profound changes in affect, cognition, and behavior in the luteal phase, yet there are no hormonal markers to differentiate women with this disorder from healthy controls.

This study was done to determine how brain function differs in women with PMDD by using neuroimaging of brain areas that are likely to be affected during luteal phase symptoms. The authors compared the functional magnetic resonance imaging (fMRI) scans of 14 women with prospectively documented PMDD and 14 controls during each of 3 hormonal conditions: leuprolide-induced ovarian suppression, leuprolide with estradiol, and leuprolide with progesterone. Positron emission tomography (PET) scans were also performed on 15 women in each category.

Women were given a memory task to perform during the scan to assess prefrontal function. In both PET and fMRI scans, a greater prefrontal activation was observed in women with a diagnosis of PMDD, indicating dysregulation in the working memory neural circuitry. Furthermore, these changes appeared



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> **Women suffering from PMDD are often frustrated** by the common perception that it is not a legitimate disease, or that it is merely an exaggeration of normal premenstrual symptoms.

to be more pronounced in women with greater degrees of PMDD-related symptomatology.

Commentary

Women suffering from PMDD are often frustrated by the common perception that it is not a legitimate disease, or that it is merely an exaggeration of normal premenstrual symptoms. The lack of measurable hormonal changes that identify susceptible women has not helped their case, and has frustrated researchers seeking to identify novel treatments for refractory cases.

By identifying a reproducible, biological phenomenon that differentiates women with PMDD from normal controls, this study legitimizes PMDD as a condition based in changes of brain physiology. It may also help to direct future research that will improve function and QOL for women who struggle with this condition.

Toffol E, Heikinheimo O, Koponen P, et al.

Further evidence for lack of negative associations between hormonal contraception and mental health.

Contraception.
2012;86(5):470-480.

Summary

Although hormonal contraception (HC) is generally well-tolerated and has few adverse effects, concern remains among segments of the public that its use will have an adverse effect on mood.

The authors of this study aimed to clarify whether there is a difference in affect and psychological symptoms between HC users and nonusers. The study analyzed data obtained as part of a large cross-sectional population study carried out every 5 years in Finland. Information was analyzed from 8586 women of reproductive age who were asked about various aspects of reproductive health and screened with a modified Beck Depression Inventory (BDI) as well as a questionnaire on somatic and psychological symptoms.

Women using combined oral contraceptives were compared to women using the levonorgestrel intrauterine device (IUD) and to women who were not using HC. Although the group using oral contraceptives tended to be younger, more educated, and single, there was an association between oral contraceptive use and lower BDI score (indicating better mood) that persisted after controlling for these confounding factors.

No noteworthy associations were apparent between IUD use and any of the items of interest.

Commentary

Literature on the mental health side effects of HC has been inconsistent. Studies examining the reasons for discontinuation of effective contraception often list changes in mood or well-being as contributing factors.

This population-based study suggests that not only do oral contraceptives not have a negative impact on mood, but they might actually improve it. Certainly, it would be unreasonable to suggest that oral contraceptives should be prescribed with the intention of mood elevation, and there will no doubt be idiosyncratic reactions among subgroups of women vulnerable to depressed mood.

Still, prescribers can remain confident that HCs should not be expected to contribute to depressed mood, and women considering starting these methods should know that such an effect is unlikely.

Erekson EA, Martin DK, Zhu K, et al.

Sexual function in older women after oophorectomy.

Obstetrics and Gynecology.
2012;120(4):833-842.

Summary

Perimenopausal women undergoing hysterectomy are often counseled

that surgical menopause may have a detrimental effect on postoperative sexual function, although the literature examining sexual function following oophorectomy is conflicting.

The authors of this study compared sexual function in older women who had undergone bilateral oophorectomy with those who had not. They analyzed data from 1352 women between the ages of 57 and 85 who were part of the National Social Life, Health and Aging Project. Because sexual ideation would not be affected by the presence of a partner or physical limitations, this was made the primary outcome of interest.

The 26% of women who had undergone oophorectomy were not significantly different in measures of sexual ideation or function from the women whose ovaries remained intact.

Commentary

Women who are deciding whether or not to retain their ovaries at the time of hysterectomy are often counseled about sexual side effects that may result from their surgery.

Oophorectomy, according to conventional wisdom, may have a detrimental effect on sexual function, presumably by eliminating the small amount of testosterone still secreted by the postmenopausal ovary, the clinical significance of which is unclear.

This study adds to the growing body of evidence that sexual function in older women is multifactorial and not likely to be influenced in the long term by small changes in androgen concentration.

Women faced with the decision of whether to remove their ovaries can base their decisions on other medical issues, and need not feel that the surgery will doom them to less-fulfilling sex lives.

Mozurkewich EL, Clinton CM, Chilimigras JL, et al.

The Mothers, Omega-3, and Mental Health Study: a double-blind, randomized controlled trial.

American Journal of Obstetrics and Gynecology.
2013;208(4):313.e1-9.

Summary

Fish oils are being increasingly used as food supplements for a variety of medical indications, including depressed mood. Women with low levels of omega-3 fatty acids, found in these oils, are more likely to develop perinatal depression.

In this study, the authors explore the hypothesis that supplementation with docosahexaenoic acid (DHA) or eicosapentaenoic acid (EPA) may prevent depression in women at risk. They enrolled 126 pregnant women with either a history of depression or a moderately elevated score on the Edinburgh Postnatal Depression Scale. The women were randomized to receive either a fish oil rich in DHA, a fish oil rich in EPA, or a soy oil placebo.

Although serum levels of fatty acids rose appropriately in the groups receiving supplements, there were no significant differences among the groups in measures of depressed mood at 26-28 weeks, 34-36 weeks, and 6-8 weeks postpartum.

Those who had used the DHA supplement delivered at later gestational age and their infants had higher birth weights on average.

Commentary

Depression in pregnancy and the postpartum period may be associated with significant morbidity, and medications to treat or prevent this condition may improve both maternal and fetal well-being.

Rather than use antidepressants that are proven effective but carry a small risk of adverse effect, many patients are drawn to so-called natural remedies that are perceived to be safe.

While fish oils have been demonstrated to have some use in preventing depression in the general population, this study shows no benefit in using them for this purpose in pregnancy.

For now, it would appear that antidepressants such as selective serotonin reuptake inhibitors remain a better choice for patients at risk of significant morbidity associated with peripartum depression. COG

DR. SCHAFFIR is the president of the North American Society for Psychosocial Obstetrics and Gynecology (NASPOG) and Associate Professor in the Department of Obstetrics & Gynecology, The Ohio State University College of Medicine, Columbus.

NASPOG is a multidisciplinary group comprised of gynecologists, psychiatrists, social workers, and psychologists whose goal is to encourage scientific study and clinical discourse on psychosocial issues in women's health.

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18-21: American Gynecological and Obstetrical Society Annual Meeting
Chicago, Illinois
www.agosonline.org/meetings.html

19-21: Reproductive Health 2013 Association of Reproductive Health Professionals (ARHP)
Denver, Colorado
www.arhp.org/RH13

19-21: 3rd Annual Meeting of the Society of OB/GYN Hospitalists
Denver, Colorado
http://societyofobgynhospitalists.com

OCTOBER

2-4: International Society for the Study of Vulvovaginal Disease International Postgraduate Course
Tel Aviv, Israel
www.issvd.org/wordpress

2-6: Pacific Coast Obstetrical and Gynecological Society 80th Annual Meeting
Walla Walla, Washington
www.pcogs.org/meetings.cfm

4-6: Women's and Pediatric Dermatology Seminar
Newport Beach, CA
www.globalacademycme.com/conferences/women-s-and-pediatric-dermatology-seminar-2013/conference-overview.html

9-12: 24th Annual Meeting of the North American Menopause Society
Dallas, Texas
www.menopause.org/annual-meetings/2013-meeting/general-information

12-17: 69th Annual Meeting of the American Society for Reproductive Medicine/International Federation of Fertility Societies (ASRM/IFFS)
Boston, Massachusetts
www.asrm.org/IFFS-ASRM2013

NOVEMBER

6-8: Perinatal Mental Health: Optimizing Maternal Treatment to Improve Infant Outcomes Conference
Chicago, Illinois
http://perinatalmentalhealthmeeting.com/

10-14: 42nd American Association of Gynecologic Laparoscopists Global Congress of Minimally Invasive Gynecology
National Harbor, Maryland
www.aagl.com/annual-meeting

14-15: OB/GYN Clinical Reviews
Rochester, Minnesota
www.mayo.edu/cme/women-s-health-2013r040

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