CONTEMPORARY OB/GYN NOVEMBER 2014, Vol. 59, No. 11

SICKLE CELL DISEASE IN PREGNANCY ■ PERIVIABLE PROM ■ HPV TESTING DEBATE ■ CFDNA IN ONCOLOGY

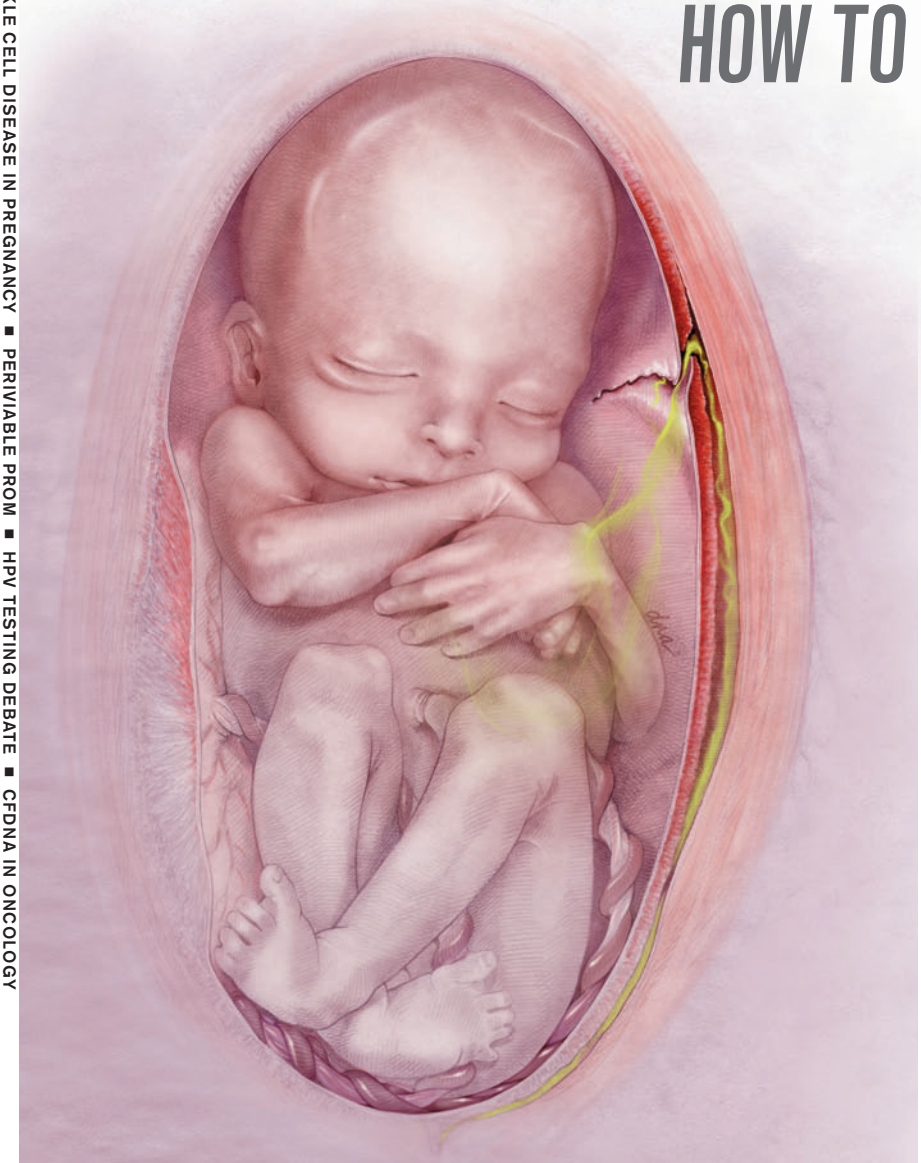
Contemporary OB/GYN®

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

SOCIETY FOR MATERNAL-FETAL MEDICINE

Periviable PROM

HOW TO COUNSEL PATIENTS



Sickle cell disease in pregnancy

POINT/COUNTERPOINT

Will HPV testing replace the Pap?

cfDNA screening in oncology

NOVEMBER 2014 | VOLUME 59, NUMBER 11

ADVANSTAR MEDICAL COMMUNICATIONS GROUP

CONTEMPORARY OB/GYN NOVEMBER 2014, Vol. 59,

Contemporary OB/GYN®

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

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

Lo Loestrin Fe

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

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

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

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

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

SELECTED SAFETY INFORMATION about Lo Loestrin Fe, including Boxed Warning

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

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

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

BRIEF SUMMARY: Consult the Package Insert for Complete Prescribing Information

WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS

Cigarette smoking increases the risk of serious cardiovascular events from combination oral contraceptive (COC) use. This risk increases with age, particularly in women over 35 years of age, and with the number of cigarettes smoked. For this reason, COCs should not be used by women who are over 35 years of age and smoke *[see Contraindications (4)]*.

1 INDICATIONS AND USAGE

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

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

4 CONTRAINDICATIONS

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

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

5 WARNINGS AND PRECAUTIONS

5.1 Thrombotic and Other Vascular Events

Stop Lo Loestrin Fe if an arterial or deep venous thrombotic event occurs. Although use of COCs increases the risk of venous thromboembolism, pregnancy increases the risk of venous thromboembolism as much or more than the use of COCs. The risk of venous thromboembolism in women using COCs is 3 to 9 per 10,000 woman-years. The risk is highest during the first year of use of a COC. Use of COCs also increases the risk of arterial thromboses such as strokes and myocardial infarctions, especially in women with other risk factors for these events. The risk of thromboembolic disease due to oral contraceptives gradually disappears after COC use is discontinued.

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

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

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

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

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

5.2 Carcinoma of the Breast and Cervix

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

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

5.9 COC Use Before or During Early Pregnancy

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

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

5.10 Depression

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

5.11 Interference with Laboratory Tests

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

5.12 Monitoring

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

5.13 Other Conditions

In women with hereditary angioedema, exogenous estrogens may induce or exacerbate symptoms of angioedema. Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation while taking COCs.

6 ADVERSE REACTIONS

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

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

Adverse reactions commonly reported by COC users are:

- Irregular uterine bleeding
- Breast tenderness
- Nausea
- Headache

6.1 Clinical Trial Experience

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

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

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

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

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

7 DRUG INTERACTIONS

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

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

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

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

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

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

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

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

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

7.3 Changes in Plasma Levels of Co-Administered Drugs

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

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

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

8.3 Nursing Mothers

When possible, advise the nursing mother to use other forms of contraception until she has weaned her child. Estrogen-containing OCs can reduce milk production in breastfeeding mothers. This is less likely to occur once breastfeeding is well-established; however, it can occur at any time in some women. Small amounts of oral contraceptive steroids and/or metabolites are present in breast milk.

8.4 Pediatric Use

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

8.5 Geriatric Use

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

8.6 Renal Impairment

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

8.7 Hepatic Impairment

No studies have been conducted to evaluate the effect of hepatic impairment on the disposition of Lo Loestrin Fe. However, steroid hormones may be poorly metabolized in patients with impaired liver function. Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal and COC causation has been excluded *[see Contraindications (4)* and *Warnings and Precautions (5.3)]*.

8.8 Body Mass Index

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

10 OVERDOSAGE

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

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling.

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

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

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

© 2014, Actavis Pharma, Inc. All rights reserved. 05/14

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

5.3 Liver Disease
Discontinue Lo Loestrin Fe if jaundice develops. Steroid hormones may be poorly metabolized in patients with impaired liver function. Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal and COC causation has been excluded.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Women who are not pregnant and use Lo Loestrin Fe may experience amenorrhea (absence of scheduled and unscheduled bleeding/spotting). In the clinical trial with Lo Loestrin Fe, the incidence of amenorrhea increased from 32 percent in Cycle 1 to 49 percent by Cycle 13. If scheduled (withdrawal) bleeding does not occur, consider the possibility of pregnancy. If the patient has not adhered to the prescribed dosing schedule (missed one or more active tablets or started taking them on a day later than she should have), consider the possibility of pregnancy at the time of the first missed period and take appropriate diagnostic measures. If the patient has adhered to the prescribed regimen and misses two consecutive periods, rule out pregnancy.

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

INDICATION AND USAGE for Lo Loestrin® Fe

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

SELECTED SAFETY INFORMATION about Lo Loestrin Fe, including Boxed Warning

WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS

Cigarette smoking increases the risk of serious cardiovascular events from combination oral contraceptive (COC) use. This risk increases with age, particularly in women over 35 years of age, and with the number of cigarettes smoked. For this reason, Lo Loestrin Fe should not be used by women who are over 35 years of age and smoke.

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

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

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

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

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

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

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

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

Actavis

© 2014 Actavis Pharma, Inc. Parsippany, NJ 07054 All rights reserved. 10860 6/14

From the creators of biotène®

Women no longer need to ignore Vaginal Dryness...

a major cause of feminine discomfort and odor

For more information and office samples:
call 1-877-522-5333 or visit www.luvenacare.com

Finally,

A PROACTIVE VAGINAL MOISTURIZER

our proactive philosophy includes incorporating natural and safe ingredients

COMMON SENSE

Unlike many moisturizers, **LUVENA® Proactive Vaginal Moisturizer** does **NOT** contain parabens that can kill beneficial bacteria and glycerin that can increase yeast infections.

SOOTHES

LUVENA® Proactive Vaginal Moisturizer contains unique blend of moisturizers, humectants and lipids.

pH BALANCED

LUVENA® Proactive Vaginal Moisturizer utilizes lactic acid, normally found in the vagina, for pH balance.

Because vaginal dryness has many causes, most females may experience dryness at some point and can will benefit from the "natural care" of LUVENA® Proactive Vaginal Moisturizer.

Benefits include:

- ☑ Dry discomfort relief
- ☑ Eliminates unpleasant odors
- ☑ Lactic acid to maintain optimal pH
- ☑ Contains natural enzymes instead of parabens and chlorhexidine.

LUVENA®

The Closest You Can Get to Natural Moisture

Get the freshness you want with the *feminine health you need*

- Silk amino acids, lanolin and vitamin E
- Optimum pH for all skin types
- Odor protection formula
- Formula contains natural enzymes instead of parabens and chlorhexidine
- Helps maintain freshness longer

SLS FREE | PARABEN FREE | LOW FOAMING FORMULA

Biotene® is a trademark owned by GlaxoSmithKline and Companies

Contemporary OB/GYN

EDITOR IN CHIEF

Charles J Lockwood, MD, MHCM
Senior Vice President, USF Health
Dean, Morsani College of Medicine
University of South Florida
TAMPA, FL

DEPUTY EDITOR

Jon I Einarsson, MD, PhD, MPH
Associate Professor of Obstetrics and Gynecology
Harvard Medical School
Director, Division of Minimally Invasive Gynecologic Surgery
Brigham and Women's Hospital
BOSTON, MA

YOUR EDITORIAL BOARD

Haywood L Brown, MD
Roy T. Parker Professor and Chair, Division of Maternal Fetal Medicine
Duke University Medical Center
DURHAM, NC

Paula J Adams Hillard, MD
Professor, Department of Obstetrics and Gynecology, Chief, Division of Gynecologic Specialties
Stanford University School of Medicine
STANFORD, CA

Sharon T Phelan, MD
Professor, Department of Obstetrics and Gynecology
University of New Mexico
ALBUQUERQUE, NM

Ilana Cass, MD
Vice Chair, Associate Clinical Professor, Department of Obstetrics and Gynecology
Cedars-Sinai Medical Center
LOS ANGELES, CA

Sarah J Kilpatrick, MD, PhD
Helping Hand Endowed Chair, Department of Obstetrics and Gynecology
Cedars-Sinai Medical Center
LOS ANGELES, CA

Joe Leigh Simpson, MD
Executive Associate Dean for Academic Affairs, Professor of Obstetrics and Gynecology, and Human and Molecular Genetics
Florida International University College of Medicine
MIAMI, FL

Joshua A Copel, MD
Professor, Obstetrics, Gynecology, and Reproductive Sciences, and Pediatrics
Yale University School of Medicine
NEW HAVEN, CT

Elliott K Main, MD
Director, California Maternal Quality Care Collaborative, Chair and Chief, Department of Obstetrics and Gynecology
California Pacific Medical Center
SAN FRANCISCO, CA

FOUNDING EDITOR
John T Queenan, MD
Professor of Obstetrics and Gynecology
Georgetown University School of Medicine
WASHINGTON, DC

John O DeLancey, MD
Norman F Miller Professor of Gynecology, Director, Pelvic Floor Research, Group Director, Fellowship in Female Pelvic Medicine and Reconstructive Surgery
University of Michigan Medical School
ANN ARBOR, MI

Laurie J McKenzie, MD
Director of Oncofertility, Houston IVF, Director
Houston Oncofertility Preservation and Education (H.O.P.E.)
HOUSTON, TX

OUR MISSION For nearly a half century, busy practitioners have trusted *Contemporary OB/GYN* to translate the latest research into outstanding patient care. We are dedicated to providing them with evidence-based information on scientific advances in a clinically useful format.

CONTENT

Judith Orvos
Editorial Consultant

Susan C Olmstead
Content Channel Director
solmstead@advanstar.com

Miranda Hester
Content Specialist
mhester@advanstar.com

Robert McGarr
Group Art Director

Nicole Davis-Slocum
Art Director

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

SALES & MARKETING

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

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

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

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

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

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

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

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

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

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

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

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

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

Reprint Services
877-652-5295 ext. 121/
bkolb@wrightsmedia.com
Outside US, UK, direct dial:
281-419-5725. Ext. 121

AUDIENCE DEVELOPMENT

Joy Puzzo
Corporate Director
jpuzzo@advanstar.com

Christine Shappell
Director
cshappell@advanstar.com

Joe Martin
Manager
jmartin@advanstar.com

ADVANSTAR

Chief Executive Officer
Joe Loggia

Executive Vice-President, Chief Administrative Officer & Chief Financial Officer
Tom Ehardt

Executive Vice-President
Georgiann DeCenzo

Executive Vice-President
Chris DeMoulin

Executive Vice-President, Business Systems
Rebecca Evangelou

Executive Vice-President, Human Resources
Julie Molleston

Sr Vice-President
Tracy Harris

Vice-President, General Manager Pharm/Science Group
Dave Esola

Vice-President, Legal
Michael Bernstein

Vice-President, Media Operations
Francis Heid

Vice-President, Treasurer & Controller
Adele Hartwick

AmniSure®

Rapid, Reliable, Non-Invasive Test for ROM

(Rupture Of [fetal] Membranes)

When she's relying on you, rely on AmniSure.

- **99% CORRELATION WITH INDIGO CARMINE DYE TEST[1]**
- **NO GESTATIONAL AGE LIMITATION**
- **RESULTS IN MINUTES**
- **MOST WIDELY USED ROM IMMUNOASSAY**

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

©2014 AmniSure® International LLC, all rights reserved.

QIAGEN®

Now a QIAGEN company

Contemporary OB/GYN

CONTEMPORARYOBGYN.NET
VOL. 59, NO. 11
NOVEMBER 2014

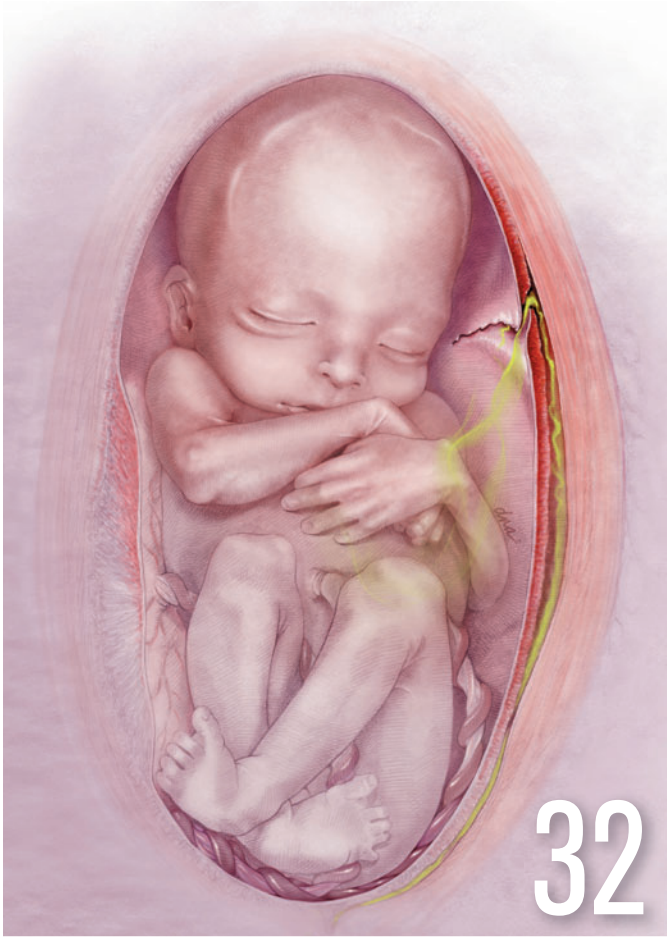


ILLUSTRATION BY ALEX BAKER, DNA ILLUSTRATIONS, INC.

CONTEMPORARY OB/GYN (Print ISSN#0090-3159, DIGITAL ISSN#2150-6264), is published monthly by Advanstar Communications, Inc, 131 West First St, Duluth, MN 55806-2065. One-year subscription rates: $110.00 per year (USA and Possessions); $140.00 per year (elsewhere). Single copies (prepaid only) $12.00 in the USA; $18.00 per copy elsewhere. Include $6.50 per order plus $2.00 for US postage and handling. **Periodicals postage paid** at Duluth, MN 55806 and additional mailing offices. **POSTMASTER:** Please send address changes to *Contemporary OB/GYN*, PO Box 6084, Duluth, MN 55806-6084. Return Undeliverable Canadian Addresses to: IMEX Global Solutions, PO Box 25542, London, ON N6C 6B2, CANADA. Canadian GST number: R-124213133RT001. Publications Mail Agreement Number 40612608. Printed in USA. Subscription inquiries/address changes: toll-free 888-527-7008, or dial direct 218-740-6477.
©2014 Advanstar Communications Inc. All rights reserved. No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including by photocopy, recording, or information storage and retrieval without permission in writing from the publisher. Authorization to photocopy items for internal/educational or personal use, or the internal/educational or personal use of specific clients is granted by Advanstar Communications Inc for libraries and other users registered with the Copyright Clearance Center, 222 Rosewood Dr, Danvers, MA 01923, 978-750-8400 fax 978-646-8700 or visit http://www.copyright.com online. For uses beyond those listed above, please direct your written request to Permission Dept, fax 440-756-5255 or email: mcannon@advanstar.com.

Introducing

informaSeq℠

non-invasive prenatal test

Integrated GENETICS

LabCorp Specialty Testing Group

Integrated Genetics now offers informaSeq℠ Prenatal Test – an advanced, non-invasive, next generation prenatal screening for T21, T18, and T13 chromosomal aneuploidies that can be administered as early as 10 weeks gestation.

A test your patients can trust. A company you know and trust.

You have the opportunity to select the test that best meets the needs of your patients.

informaSeq	Appropriate for high-risk patients. Provides only risk assessment for the most common autosomal trisomies.
informaSeq with Y analysis	Appropriate for high-risk patients. Provides risk assessment for the most common autosomal trisomies and fetal gender, but not sex chromosome aneuploidies.
informaSeq with XY analysis	Appropriate for high-risk patients with singleton pregnancies. Provides risk assessment for the most common autosomal trisomies, sex chromosome aneuploidies, and fetal gender.

Integrated Genetics is committed to providing comprehensive care to you and your patients. We offer:

- The largest commercial genetic counseling team with unparalleled services
- Extensive managed care contracts helping patients maximize their benefits
- A network of more than 1,700 patient service centers

To learn more about our informaSeq test offerings,
please visit **www.integratedgenetics.com** or call **800-848-4436**.

informaSeq℠ Prenatal Test is
Powered by Illumina® sequencing technology.

informaSeq℠ is a service mark of Laboratory Corporation of America® Holdings.
Powered by Illumina® is a trademark of Illumina, Inc. in the U.S. and/or other countries.
©2014 Laboratory Corporation of America® Holdings. All rights reserved.
rep-901-v1-0814

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

Updates on neonatal encephalopathy and CP

A new report shows that monitoring and early intervention may help reduce adverse outcomes and malpractice claims.

To get a sense of the magnitude of the medicolegal threat and economic drain posed by the plaintiff's bar from cerebral palsy (CP) lawsuits, just google "cerebral palsy lawsuits." You will be astonished by the misinformation and recklessness contained in many of the 350,000-plus sites that come up. Into this sea of misinformation sails the second edition of ACOG's *Neonatal Encephalopathy and Neurologic Outcome*.[1]

ACOG's Task Force on Neonatal Encephalopathy was commissioned by President Richard Waldman, MD, and chaired by Mary D'Alton, MD. At more than 230 pages, the report is not for the faint of heart, but it is crammed with the latest findings on the etiology, diagnosis, prevention, and treatment of neonatal encephalopathy (NNE) and CP.

I encourage all ob/gyns to read it carefully, and it is a must-read for department chairs, residency program directors, and those involved in hospital patient safety efforts.

Background

First, definitions: NNE is defined as the clinical syndrome of "disturbed neurological function in the earliest days of life in an infant born at or beyond 35 weeks of gestation, manifested by a subnormal level of consciousness or seizures and often accompanied by difficulty with initiating and maintaining respiration and depression of tone and reflexes."[1]

> Hypoxic-ischemic encephalopathy (HIE) is **but one of many causes** of both NNE and CP.

CP describes a cluster of disorders manifest by nonprogressive motor disabilities (spasticity, dyskinesis, and ataxia) that can occur to infants born at any gestational age. Not all cases of NNE result in CP and not all cases of CP are associated with prodromal NNE. The risk of CP increases with earlier gestational ages at delivery, with very preterm delivery (<32 weeks' gestation) being the single-greatest risk factor. Hypoxic-ischemic encephalopathy (HIE) is but one of many causes of both NNE and CP. Neonatal encephalopathy complicates 2.7 to 3.3 per 1000 live births, CP 2 to 2.5/1000 live births, and HIE 1.3 to 1.7/1000 live births.[1] The rates of CP among term infants have remained remarkably stable over time at 1.4 to 1.8 per 1000, despite a significantly increased cesarean delivery rate.[1] The occurrence of CP without antecedent NNE excludes HIE as a cause.

Prior epidemiologic studies suggested that 69% of NNE cases were the result of factors occurring prior to the onset of labor, whereas only 29% were associated with intrapartum events and only 5% could be exclusively linked to intrapartum factors.[2] Major risk factors for NNE include preterm and postterm birth, fetal growth restriction, preeclampsia, perinatal infections, chorioamnionitis, maternal thyroid disease, placental abnormalities, infertility treatment with resultant multiple gestations, and prematurity.

WE WANT TO HEAR FROM YOU

Send your feedback to:
DrLockwood@advanstar.com.

Using MRI to reassess intrapartum factors

Our ability to determine timing and etiology of NNE/CP has vastly improved with the introduction of early (24 to 96 hours of birth) and sophisticated magnetic resonance imaging (MRI) technologies. While the focus of the first edition of ACOG's *Neonatal Encephalopathy and Neurologic Outcome* monograph was on the apparent low prevalence of intrapartum hypoxic-ischemic events in the genesis of NNE/CP, recent MRI data suggest a far more common role for peripartum and intrapartum factors.

Advances in MRI include use of diffusion-weighted imaging, which measures random self-diffusion of water through neural tissue, and MR spectroscopy, in which the presence and relative abundance of specific molecular markers of neural injury (eg, lactate-to-N-acetylaspartate ratios) can be discerned over specific locations in the brain (eg, the thalamus). While early MRI assists in timing insults, repeat MRI at 10 days (7–21 days) can more precisely characterize the extent of lesions and provide crucial prognostic information.

These studies suggest that up to 80% of term NNE cases are in fact acute, although such studies cannot differentiate insults occurring in labor from those occurring within 24 hours or a few days of birth. Two primary patterns of acute neural injury have been observed that are associated with CP: 1) basal-ganglia-thalamus injury; and 2) watershed or borderline cortical white-matter injury. Animal studies suggest that the former pattern is associated with acute, near-total "asphyxia" and the latter with a less severe but more prolonged asphyxial process. If either of these 2 pathologic processes becomes extreme, a more global pattern of brain injury develops, resulting in death.

Early MRI assists in timing insults, and repeat MRI at 10 days can more precisely characterize the extent of lesions and provide crucial prognostic information.

The pathophysiology of neural injury

The impact of hypoxic-ischemic insults on the fetal and neonatal brain is dependent on not only the severity and duration of oxygen deprivation but also gestational age. Older fetuses have greater neural vulnerability, as well as concomitant fever and hypoglycemia, which greatly exacerbate hypoxic-ischemic injuries.

Different neural structures have different intrinsic metabolic rates, and thus, varying vulnerability to hypoxia. For example, the higher metabolic rates of the thalamus, basal ganglia, and other subcortical nuclei render these structures more vulnerable than the cerebral cortex. In addition, prior chronic hypoxia and nutrient deprivation due to uteroplacental vascular insufficiency exacerbate acute hypoxic-ischemic effects, accounting for the strong link between CP and fetal growth restriction.

A birth weight below the third percentile is associated with an odds ratio for NNE of 38.2 (95% CI: 9.4–154.8) and an odds ratio for CP of 6.4 (95% CI: 4.2–10.1).[3] This finding helps to reconcile apparently disparate epidemiologic and MRI data, suggesting that antepartum factors greatly increase the potency of intrapartum factors that drive CP. This phenomenon also accounts for the link between postdate (>42 weeks) pregnancies and NNE, with an adjusted relative risk of 13.2.[4]

Genetic susceptibility factors such as polymorphisms for cytokine genes may also exacerbate or attenuate inflammation-associated neural damage, helping to explain why the same insult can have such different consequences in different fetuses and why low Apgar scores and umbilical artery pH values are such poor predictors of eventual outcome.

Moreover, most of the damage to neonatal brain cells accruing from in utero hypoxic-ischemic events actually occurs following reperfusion due to the detrimental effects of excitatory amino acids, reactive oxygen species, and inflammation, which collectively trigger apoptosis. This helps explain the remarkable therapeutic benefit of hypothermia when started within 8 hours of birth. Hypothermia therapy blunts all these secondary adverse effects and significantly reduces the risk of CP in at-risk neonates with a risk ratio of 0.64 (95% CI: 0.5–0.82).[1]

Finally, changes in circulation in response to hypoxic-ischemic events tend to maximize cerebral blood flow while reducing blood flow to the kidneys, the gastrointestinal tract, and striated muscle. The resistance of these organs to hypoxia helps explain why mul-

tiorgan failure is not a universal feature of NNE due to HIE.

Other causes of NNE and fetal brain injury

The use of MRI can also better define non-hypoxic-ischemic causes of NNE. Malformations (eg, lissencephaly) and perinatal stroke are easily detected by such imaging. The latter occurs in about 1/3000 live births and often presents with seizures and focal deficits including hemiplegic but not quadriplegic CP. The etiologies of most strokes are unknown, although fetal thrombophilia, infection, and maternal cocaine use are major risk factors.

Fortunately, the recurrence risk for both fetal cerebral arterial and venous thrombi is low. Conversely, absence of discrete findings on early MRI in an infant with apparent NNE should suggest genetic causes (eg, chromosomal microdeletions and inborn errors of metabolism) and can trigger timely and potentially lifesaving interventions.

Criteria for establishing HIE as a cause of NNE/CP

While it is still very difficult to confirm that a hypoxic-ischemic event was the cause of NNE, the following criteria are suggestive:

- Apgar score <5 at 10 minutes in association with an umbilical artery pH ≤7.0 and a base deficit of ≥12 mmol/L.
- Suggestive MR neuroimaging obtained within 24 to 96 hours of birth and read by a radiologist with expertise in pediatric neuroradiology, or suggestive MR spectroscopic findings. Repeat imaging at 10 days is more predictive of the full extent of the injury.
- Presence of multisystem organ failure (although, as noted, this is not an invariable correlate to HIE-induced NNE/CP).
- Suggestive intrapartum findings:
  - **a** Sentinel hypoxic-ischemic event occurring immediately before or during labor and delivery, including uterine rupture, severe abruption, umbilical cord prolapse, amniotic fluid embolism or other causes of maternal hemodynamic collapse, and fetal exsanguination (eg, associated with vasa previa, fetal-to-maternal hemorrhage, twin demise with monochorionic placentation).
  - **b** Suggestive fetal heart rate pattern (eg, conversion of a Category 1 to Category III tracing). The observation of a Category III tracing upon admission is strong evidence of pre-existent insult and NNE with or without the subsequent diagnosis of CP may occur despite appropriate management and expeditious delivery within 30 minutes.
- Spastic quadriplegic or dyskinetic CP.

Take-home message

The advent of improved neonatal MR neuroimaging and MR spectroscopy suggests that a significant number of infants with NNE and subsequent CP suffered causative intrapartum or peripartum events. Although the precise timing of such insults within 24 to 48 hours of delivery cannot be established from such contemporary imaging data, increased attention must be placed on optimizing intrapartum monitoring. Detection of HIE should prompt expeditious hypothermia therapy.

Moreover, because evidence is strong that a focused patient safety program can reduce the occurrence of such adverse obstetrical outcomes and reduce malpractice claims,[5,6] every obstetric unit in the United States should adopt such a program. COG

DR LOCKWOOD, Editor-in-Chief, is Dean of the Morsani College of Medicine and Senior Vice President of USF Health, Universit yof South Florida, Tampa. He can be reached at DrLockwood@advanstar.com.

REFERENCES

1. The American College of Obstetricians and Gynecologists and the American Academy of Pediatrics. *Neonatal Encephalopathy and Neurologic Outcome*, second edition. American College of Obstetricians and Gynecologists (ACOG). Washington, DC, 2014.

2. Badawi N, Kurinczuk JJ, Keogh JM, et al. Intrapartum risk factors for newborn encephalopathy: the Western Australian case-control study. *BMJ*. 1998;317(7172):1554–1558.

3. Blair E, Stanley F. Intrauterine growth and spastic cerebral palsy. I. Association with birth weight for gestational age. *Am J Obstet Gynecol*. 1990;162(1):229–237.

4. Badawi N, Kurinczuk JJ, Keogh JM, et al. Antepartum risk factors for newborn encephalopathy: the Western Australian case-control study. *BMJ*. 1998;317(7172):1549–1553.

5. Pettker CM, Thung SF, Norwitz ER, et al. Impact of a comprehensive patient safety strategy on obstetric adverse events. *Am J Obstet Gynecol*. 2009;200(5):492.e1-8. doi:10.1016/j.ajog.2009.01.022.

6. Pettker CM, Thung SF, Lipkind HS, et al. A comprehensive obstetric patient safety program reduces liability claims and payments. *Am J Obstet Gynecol*. 2014;211(4):319–325. doi:10.1016/j.ajog.2014.04.038.

HOLOGIC®
The Science of Sure

It's Coming...

Proven technology just got better

New NovaSure® 6mm endometrial ablation device

- Smaller dilation
- Same market leading ablation

Smaller is better!

Contact your rep to pre-order today.

Hologic.com | NovaSure.com

ADS-01086-001 Rev. 001 ©Hologic 2014. All rights reserved. Printed in USA. Specifications are subject to change without prior notice. Hologic, NovaSure and associated logos are trademarks and/or registered trademarks of Hologic, Inc. and/or its subsidiaries, in the United States and/or other countries. This information is intended for medical professionals in the U.S. and other markets and is not intended as a product solicitation or promotion where such activities are prohibited. Because Hologic materials are distributed through websites, eBroadcasts and tradeshows, it is not always possible to control where such materials appear. For specific information on what products are available for sale in a particular country, please contact your local Hologic representative or write to **womenshealth@hologic.com**.

READER RESPONSE TO

'Technologies for laparoscopic contained tissue extraction'

TO THE EDITOR:

I thank Dr. Greenberg and Dr. Ajao for the great review article on technologies for laparoscopic contained tissue extraction [*Contemporary OB/GYN*, October 2014]. But in my opinion, the laparoscopic approach to the fibroid uterus and specifically the tissue extraction controversy is currently a puzzle. The very non-scientific but highly passionate debate on this topic is getting interesting.

After a 2-day meeting held by the Obstetrics and Gynecology Devices Advisory Panel of the FDA to analyze risks, benefits, and the overall clinical role of laparoscopic power morcellators in gynecology, one of the recommended conclusions was to include in the informed consent a disclosure of the risk of disseminating the disease and upstaging uterine malignancy if present. I salute the effort of the panel and agree on the necessity of a comprehensive consent process that includes the risk of occult uterine malignancy that if morcellated will worsen the patient's prognosis. But how will having the patient sign a consent form change the risk of this unfortunate event? How will it protect the surgeon from the subsequent liability? Who will be responsible for worsening the patient's survival?

Soon after the aforementioned FDA meeting, the largest morcellator manufacturing company (following what I speculate was a business decision in anticipation of the possible liability, among other reasons) initiated a worldwide withdrawal of the company's morcellation devices. Some hospitals banned its use. With no scientific evidence to support it, the gynecologists were left without morcellators, which makes the energy, effort, and great creativity shown by Dr. Greenberg and Dr. Ajao along with a large group of smart physicians working on contained tissue extraction in a bag a moot point because we will have no morcellators to do it with. Perhaps the last morcellator remaining in the market should be used to morcellate the tort system and finally build a system based on solid scientific evidence that will protect patients and physicians.

For better or for worse, the morcellator almost certainly will no longer be available. Use of open laparotomy will increase. Unless we keep the morcellator available, we will see increased morbidity and mortality as a result of going back to open surgery, with the subsequent cost to society. This is a real complex dilemma that, in my opinion, could be best answered only using an evidence-based, non-passionate, scientific approach.

Jose Carugno, MD, FACOG
Zephyrhills, Florida

IN REPLY:

We very much appreciate Dr. Carugno's impassioned letter and share his frustration with the apparent absence of "a system based on solid scientific evidence that will protect patients and physicians." That said, we have used the current morcellator controversy as an opportunity to reflect on our practices in this surgical niche and ask ourselves, "Can we do better?"

After months of collaborative reflection, interchange of ideas, and clinical experience, we have come to the conclusion that there *may* be a better way of extracting excised tissues during minimally invasive procedures using insufflated bags. Have our early techniques been perfected? No. Have they been proven to be safer for patients based on "solid scientific evidence"? No. But to claim that the current standard methods of open power morcellation are perfect is also somewhat less than forthcoming.

We are encouraged by our early experience and excited by the progress in this space. Rather than bemoan the process by which this controversy has developed, we choose to look forward. To expect perfection is unrealistic; to not seek perfection is unacceptable.

Jim Greenberg, MD
Mobolagi Ajao, MD

For your patients with varicose and spider veins...

IF THESE LEGS COULD TALK℠

They'd say:
"You have been dedicated to her health throughout the most important nine months of her life—So don't forget to talk to her about treating varicose veins after pregnancy."

Don't let vein disease stand in her way.

Our phlebologists will treat your patients with the same care and expertise you have provided them to ensure healthy, strong legs after pregnancy. Refer your patients to the largest network of highly trained vein specialists who have been helping patients since 1981.

veinclinics of America®

Our physicians provide free consultations* for your patients.

To speak to a representative, please call **(855) 953-VEIN (8346)** or visit **veinclinics.com/foryourpatients**

*Due to legal constraints, this offer cannot be extended to licensed healthcare providers, Medicare or Medicaid beneficiaries, or other recipients of federal or state healthcare benefit programs. Offer expires December 31, 2014. Consultation must occur on or before December 31, 2014. This offer valid at all participating VCA network locations. New patients only. One free consultation per person during promotional period. Not redeemable for cash.

© 2014 Vein Clinics of America, Inc. All rights reserved. VCA-0306

Do women understand mammograms?

A new report finds that many women are unaware that health insurers are required to cover yearly mammograms. A high rate of "false alarms" contributes to women's mixed feelings about mammography screening.

How do women feel about mammograms? What prevents some women from receiving the screening?

A newly published report from the Society for Women's Health Research, which surveyed more than 3000 women aged 18 years or older, provides some key insights. One of the most important was that a sizeable majority of the women (68%) did not know or believe that the Affordable Care Act requires health insurance companies to cover the screenings, with no financial burden on the patient.

While most of the women (78%) responded that they strongly believe that mammograms are important, more than half of them (64%) indicated that they lack an adequate understanding of the benefit of undergoing the screening. The recommendation of a healthcare provider was the most significant reason for scheduling a mammogram for 56% of the women. Meanwhile, roughly 46% of the women reported that they did not schedule annual mammogram screenings.

The cost of screening and a lack of insurance were considered to be the biggest barriers to annual screening. Sixty percent of women with a household income of more than $50,000 reported that they had an "annual or better" rate of mammogram screening, while just 49% of women with an income of less than $50,000 reported an annual or better rate of mammogram screening. Just 23% of women who were uninsured reported an annual or better rate of mammography screening, while 57% of insured women reported the same rate. Non-medical costs, such as the cost to travel for screening, were also considered to be a factor in whether a woman had a mammogram.

> Nearly half of the women said that they had been asked to come back for further testing, **causing stress and alarm**.

Nearly half of the women (47%) said that they had been asked to come back for further testing, causing stress and alarm. Of those called back, the initial abnormal results were determined to be a "false alarm" in 89% of cases. So it's no surprise that 81% of women want mammograms that provide better detection and 82% want screenings that reduce the chance of being called back.

SOME SURVEY RESPONSES

- "My primary care doctor and the imaging center where I have my mammograms motivate me. Otherwise, I would not think of it."
- "I have not gone since the initial screening, I check regularly, and have no plans to schedule a mammogram anytime soon."
- "Nothing. I don't go because I have no insurance. The only one I've had was because my doctor had concerns."
- "Nothing prevents me from getting a mammography every year. I do what my doctors recommend and that's what they recommend."

A sizeable majority (88%) said that 3D mammography should be covered by insurance companies. Two-thirds of the women said that they might consider switching insurance companies if the new company offered coverage for the technology. COG

Society for Women's Health Research. What women want: Expectations and experiences in breast cancer screening. http://swhr.org/wp-content/uploads/2014/05/FINAL-SWHR-Exec-Sum-.pdf. Accessed October 28, 2014.

OLYMPUS®

Your Vision, Our Future

The World's Only Complete Portfolio of Products to Perform LESS* Hysterectomy

ENDOEYE FLEX

Autoclavable 5 mm HD
Deflectable-Tip Video Laparoscope

THUNDERBEAT

Fully-Integrated Ultrasonic and
Advanced Bipolar Technology

Triport+ and Triport15

Up to Four 5 mm Instruments
Through a 15 mm Incision

Discover Where Innovation Can Take You

For more information, call 800-848-9024 to speak
to your local Olympus sales representative

*Laparo-Endoscopic Single-Site Surgery

medical.olympusamerica.com/less

© 2014 Olympus America Inc. Trademark or Registered Trademark of Olympus or its affiliated entities in the U.S. and/or other countries of the world. All patents apply. AD624-0913

TRENDING NOW

The top ob/gyn clinical and practice management resources from ContemporaryOBGYN.net

ONLINE EXCLUSIVE

New look for website

The new ContemporaryOBGYN.net features a fresh design and more tools to help you quickly navigate to the information you need. Part of the Modern Medicine Network, it also allows for knowledge-sharing among medical professionals in other specialties.

POLL **Visit Contemporaryobgyn.net to weigh in:** Would you be comfortable using a black box (a complete audio and video recording) during surgery or office procedures? Cast your vote and see how others are responding.

on twitter

A few recent tweets and retweets from and about ContempOBGYN

Tamara
@SoUtHeRnCuTiE66
@muwhk RT @ContempOBGYN: Healthy pre-#pregnancy lifestyle may reduce risk of gestational #diabetes. ... http://tmi.me/1eOgTO

Brian A. Levine
@DrBrianLevine
Heavier #Babies Do Better in School http://ow.ly/CLRHt #BirthWeight @ACOGnews @ContempOBGYN

DocnetUSA
@DocnetUSA
Vaginal reconstructive surgery: A case for and against mesh use http://ow.ly/CHKtw (via @ContempOBGYN) #OBGYN #physicians #healthcare

Alfredo Levy
@EndometriosisAL
International consensus statement outlines endometriosis care http://shar.es/1mbYo3 vía @ContempOBGYN

on facebook

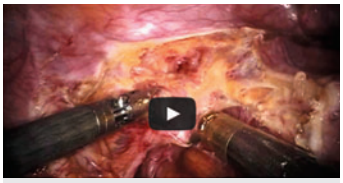
See news, make your opinion known, and read what your colleagues are saying.

Contemporary OB/GYN
October 16

Attending the The American Congress of Obstetricians and Gynecologists (ACOG National) District II meeting? Talk technology with our Tech Tools Editor, Dr. Brian Levine, first thing tomorrow morning.

Contemporary OB/GYN
October 4

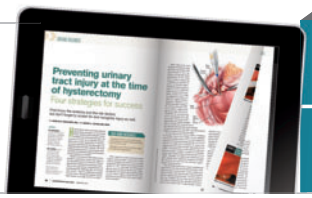
New Video On Our Website: Surgeon Javier Magrina shows step by step how to protect the ureter during endoscopic hysterectomy.



VIDEO: Prevention of ureteral injury in endoscopic hysterectomy
Javier F Magrina, MD, demonstates the prevention of ureteral injury while performing an endoscopic hysterectomy.

digital app

Introducing the *Contemporary OB/GYN* app for iPad and iPhone. Download it for free today at **www.ContemporaryOBGYN.net/ContemporaryOBGYNapp**



Follow us on Twitter
twitter.com/ContempOBGYN

Like us on Facebook
facebook.com/ContempOBGYN

Part of the ModernMedicine NETWORK

Contemporary OB/GYN is part of the ModernMedicine Network, a Web-based portal for health professionals offering best-in-class content and tools in a rewarding and easy-to-use environment for knowledge-sharing among members of our community.

What would you call a breakthrough technology that detects 41%[1] more invasive breast cancers?

If you're a woman whose breast cancer might have been missed, you'd call it genius.

Genius 3D mammography™ is the first and only FDA approved 3D mammography clinically proven to be superior to 2D.

It is a major breakthrough in the early detection of breast cancer and the best mammogram for all breast densities. What's more, it reduces false positives by up to 40%.[1,2]

Talk to your patients about the benefits of Genius 3D mammography™ and the importance of having an annual mammogram.

What woman wouldn't want a more accurate mammogram?

genius™ 3D MAMMOGRAPHY

HOLOGIC®

Brought to you by Hologic, a leader in women's health.

Aptima® HPV test | Genius 3D mammography™ | f FN test | Horizon™ DXA system | MyoSure® tissue removal system | NovaSure® endometrial ablation system | ThinPrep® Pap test

For more information - Physicians: breasttomo.com/ja Patients: genius3Dmammography.com CME: icpme.us

1 Friedewald S, Rafferty E, Rose S, et al. "Breast Cancer Screening using Tomosynthesis in Combination with Digital Mammography." Journal of the American Medical Association. 2014 July;311(24):2499-2507. Epub 2014 June 24.
2 Rose S, Tidwell A, Bujnock L, et al. "Implementation of Breast Tomosynthesis in a Routine Screening Practice: An Observational Study." American Journal of Roentengenology. 2013 Jun; 200(6): 1401-1408. Epub 2013 May 22.

ADS-01083 ©2014 Hologic, Inc. All rights reserved. Printed in the USA. Specifications subject to change without notice. Hologic, Dimensions, Genius 3D mammography, Aptima,fFN, Horizon, MyoSure, NovaSure, Selenia and ThinPrep and associated logos are trademarks and/or registered trademarks of Hologic, Inc. and/or its subsidiaries in the United States and/or other countries. All other trademarks, registered trademarks, and product names are the property of their respective owners.

BY ANDREW I KAPLAN, ESQ

Case hinges on use of off-label tocolytics

Facts

A WOMAN CARRYING MONOCHORIONIC-DIAMNIOTIC TWINS IN 2008 began seeing perinatologists Drs. A, B, and C on referral from her ob/gyn, Dr. D. She had had one previous live cesarean delivery.

On June 5th, cervical shortening was noted by Dr. C. On June 9th, when the patient had reached 23 weeks' gestation, Dr. B recommended that the patient be admitted to the defendant hospital for cerclage, which was performed by Dr. D. The patient was then placed on indocin for 48 hours by Dr. D but began having premature contractions thereafter, for which she was begun on terbutaline at the recommendation of Dr. A on June 14th.

On June 16th, the patient had some moderate contractions documented by the nursing staff, consisting of 4 contractions anywhere from 2 to 22 minutes apart, lasting 60 seconds. As a result of discussions between Drs. D and A, the patient was discharged on terbutaline via pump with home care from Group E. Dr. D signed the order for the home infusion and was to receive reports from Group E.

The patient was on home therapy for a month and had daily monitoring, although there was no clear-cut and documented daily monitoring of her heart rate. On June 21st, the patient was spiking a pulse of 117, and on June 24th it reached 122. The Group E notes show that a nurse suspended the automatic bolus and asked the patient to retake her pulse, which was recorded 3 hours later as 103. On the 25th, the patient spiked another pulse of 114; it went up to 115 the next day, and on the 27th, it went up to 120.

A 1:16 PM note on June 27th by Group E indicates that the patient's pulse went up to 130 on that date, and that at 3:25 PM, with a pulse of 127, the patient was complaining of shortness of breath and "feeling a little strange," so the pump was stopped and Dr. D's office was alerted. The terbutaline dosage was decreased, as was the frequency, and a 4:46 PM note indicates that the patient's pulse went up to 133, but the pump was recommenced by 5:54 PM. The pulses thereafter ranged from 103 to 115.

> The plaintiffs alleged that **the defendants were negligent** in prescribing a terbutaline pump for outpatient therapy.

On June 26th, the patient was seen by Dr. C, who noted she was stable other than having a pulse of 124, although she had just received her bolus of terbutaline and the rate came down thereafter. On July 10th, Dr. B documented a positive fetal fibronectin (FFN) test performed by Dr. D on July 8th. The patient's pulse was stable at 96 at that time. Dr. B saw the patient for a final visit on July 17, 2008, when she presented with a pulse of 100. Dr. B placed her on glyburide for gestational diabetes.

On July 19th, the patient's husband found her unresponsive and in cardiac arrest. An ambulance was called and the patient was resuscitated and taken to a nonparty medical center. Her pupils were noted to be fixed and dilated but she had a blood pressure. She was placed on life support and had an emergency cesarean delivery. One infant was delivered stillborn and the second was born alive. That infant lived for 1 month but eventually died as a result of injuries including Grades III and IV intraventricular hemorrhages.

The mother was declared brain dead on July 24th. No autopsy was performed on the infant, but an autopsy on the mother revealed small atherosclerotic vessel disease. The coronary arteries appeared essentially unremarkable. The cause of death was listed as "anoxic ischemic encephalopathy post cardiac arrest secondary to small vessel arteriosclerotic heart disease."

Allegations

The plaintiffs alleged that the defendants were negligent in prescribing a terbutaline pump for outpatient therapy, because that use was off-label

and both the FDA and ACOG at that time proscribed utilization of tocolytics and, particularly terbutaline, for longer than 72 hours. The plaintiff asserted that the science showed that the utilization of terbutaline for off-label purposes came with an increased risk of severe tachycardia and cardiac arrhythmia and that defendants D and A, in prescribing a terbutaline pump to be utilized on an outpatient, were negligent in failing to evaluate the patient's cardiac status by EKG, electrolytes, or consultation with a cardiologist prior to hospital discharge.

Furthermore, the plaintiff asserted that the patient was not properly monitored despite bouts of significant tachycardia at home after discharge from the defendant hospital and also that in the absence of any contractility in the weeks after the commencement of terbutaline, it would have been appropriate for a trial off the terbutaline to see if the patient's preterm labor would recur, and that Drs. B and C were in the best position to take the patient off the terbutaline when they saw her in the office after discharge from the defendant hospital.

The plaintiff contended that the patient should have been given a trial off the terbutaline as an outpatient, and that the failure to do so resulted in cardiac arrhythmia and sudden cardiac death.

Discovery

Dr. C stated that the terbutaline in and of itself was not the cause of this patient's death. Rather, he felt that Group E, the non-party home healthcare agency that was monitoring the patient's terbutaline administration via pump at home, was responsible for failing to appropriately give "hypotensive precautions" to the patient, and their failure to do so resulted in a vasovagal response, wherein the patient fell or fainted in the shower and hit her head. Thus, a subdural hematoma in conjunction with the twin fetuses compressing her aorta resulted in diminished blood flow to the brain and heart, putting the patient into cardiac arrest and brain death.

The private ob, codefendant Dr. D, proposed the same theory at his deposition, but the medical examiner called it a death secondary to cardiac arrest.

Dr. C was also of the opinion that when he saw the patient on June 26th after her discharge and she had a pulse of 124 within an hour of receiving a bolus of terbutaline, it came down during the course of her presentation, and thus he felt there was no need to alter her dosage or discontinue the drug. It was the position of all the physicians that in this particular patient, with a prior cesarean scar, twin gestation, cerclage, and positive FFN test, it would have been improper to discontinue terbutaline because she likely would have gone into immediate preterm labor.

The risk of uterine rupture given the prior cesarean scar was very real, and the doctors felt that the potential benefit of prolonging the pregnancy mitigated the risks, as long as the patient was being appropriately monitored. As to the theory that there was no pre-terbutaline EKG, Dr. C argued that the anesthesiologist performed one before the cerclage surgery, but he had to concede this was not a standard 12-lead EKG, and it could not rule out ventricular tachycardia.

The defendant perinatologists (Drs. A, B, and C) took the position that home care Group E was reporting directly to private ob codefendant Dr. D, which was the case, but the plaintiff argued that as the perinatologists, they still had an obligation to avail themselves of that information.

> The expert evaluation was mixed. One local perinatologist **was opposed to long-term maintenance on tocolysis**.

The expert evaluation was mixed. One local perinatologist was opposed to long-term maintenance on tocolysis. He believed that the proper methodology was to put the patient on bed rest, to monitor her, and to let nature run its course. He did not believe that cerclage was warranted in a twin gestation in that there was no evidence that it would truly prolong the pregnancy. He felt this patient should have had a cardiology consult before she was put on long-term terbutaline and, at minimum, should have had an EKG and electrolytes performed.

A second perinatologist, however, felt the care was appropriate, warranted under the circumstances, and could not be said to any reasonable degree of medical certainty to have caused or contributed to the patient's demise.

A pathology expert reviewed the autopsy slides and stated his opinion that the diagnosis of "small vessel arteriosclerotic heart disease" was inaccurate. He saw no evidence of small vessel disease. However, he could not rule out acute arrhythmia as a possible cause of death.

Analysis

This was a difficult case to settle. From a medical perspective, the care and

continued on **PAGE 22**

A NOVEL TREATMENT WITH AN ALTERNATIVE TO A PROGESTIN

FOR YOUR POSTMENOPAUSAL PATIENTS WITH A UTERUS[1]

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

The first and only treatment of its kind[1]

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

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

Purposeful pairing of
CONJUGATED ESTROGENS

with the SERM
BAZEDOXIFENE
instead of a progestin

IMPORTANT SAFETY INFORMATION

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

There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens. DUAVEE contains bazedoxifene, an estrogen agonist/antagonist that reduces the risk of endometrial hyperplasia that can occur with estrogens and which may be a precursor to endometrial cancer. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding.

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

The Women's Health Initiative (WHI) estrogen-alone substudy reported increased risks of stroke and deep vein thrombosis (DVT). Should either of these occur or be suspected, DUAVEE should be discontinued immediately.

The WHI Memory Study (WHIMS) estrogen-alone ancillary study of WHI reported an increased risk of probable dementia in postmenopausal women 65 years of age and older.

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

DUAVEE™

CONJUGATED ESTROGENS/
BAZEDOXIFENE 0.45 MG/20 MG TABLETS

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

Use DUAVEE for the shortest duration consistent with treatment goals and risks for the individual woman. Postmenopausal women should be re-evaluated periodically, as clinically appropriate, to determine if treatment is still necessary.

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

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

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

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

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

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

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

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

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

© 2014 Pfizer Inc. All rights reserved.

Printed in USA/July 2014 APC660613-01

Pfizer U.S. Pharmaceuticals

DUAVEE™

CONJUGATED ESTROGENS/
BAZEDOXIFENE 0.45 MG/20 MG TABLETS

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

WARNING: ENDOMETRIAL CANCER, CARDIOVASCULAR DISORDERS, AND PROBABLE DEMENTIA

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

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

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

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

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

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

Estrogens should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

INDICATIONS AND USAGE

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

Important Limitations of Use

Use DUAVEE for the shortest duration consistent with treatment goals and risks for the individual woman. Postmenopausal women should be re-evaluated periodically as clinically appropriate to determine if treatment is still necessary. When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and non-estrogen medication should be carefully considered.

CONTRAINDICATIONS

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

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

WARNINGS AND PRECAUTIONS

Drugs Containing Progestins, Estrogens or Estrogen Agonist/Antagonists

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

Cardiovascular Disorders

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

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

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

Stroke

In the WHI estrogen-alone substudy, a statistically significant increased risk of stroke was reported in women 50 to 79 years of age receiving daily CE (0.625 mg)-alone compared to women in the same age group receiving placebo (45 versus 33 per 10,000 women-years). The increase in risk was demonstrated in year 1 and persisted.

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

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

Coronary Heart Disease

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

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

Venous Thromboembolism (VTE)

In the WHI estrogen-alone substudy, the risk of VTE [DVT and PE] was increased for women receiving daily CE (0.625 mg)-alone compared to placebo (30 versus 22 per 10,000 women-years), although only the increased risk of DVT reached statistical significance (23 versus 15 per 10,000 women-years). The increase in VTE risk was demonstrated during the first 2 years.

If feasible, DUAVEE should be discontinued at least 4 to 6 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization. Because immobilization increases the risk for venous thromboembolic events independent of therapy, DUAVEE should be discontinued prior to and during prolonged immobilization (e.g., post-surgical recovery, prolonged bed rest) and DUAVEE therapy should be resumed only after the patient is fully ambulatory. In addition, women taking DUAVEE should be advised to move about periodically during travel involving prolonged immobilization.

Malignant Neoplasms

Endometrial Cancer

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

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

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

Breast Cancer

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

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

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

Ovarian Cancer

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

Probable Dementia

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

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

Gallbladder Disease

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

Visual Abnormalities

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

Elevated Blood Pressure

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

Hypertriglyceridemia

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

Hepatic Impairment and Past History of Cholestatic Jaundice

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

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

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

For women with a history of cholestatic jaundice associated with past estrogen use or with pregnancy, caution should be exercised; and in the case of recurrence, DUAVEE should be discontinued. Use of DUAVEE in patients with hepatic impairment is contraindicated *[see Contraindications]*.

Hypothyroidism

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

Fluid Retention

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

Hypocalcemia

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

Hereditary Angioedema

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

Exacerbation of Other Conditions

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

Premenopausal Women

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

Laboratory Tests

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

Drug-Laboratory Test Interactions

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

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

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

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

Impaired glucose tolerance.

ADVERSE REACTIONS
The following adverse reactions are discussed in greater detail in other sections of the label:
- Cardiovascular Disorders *[see Warnings and Precautions]*
- Malignant Neoplasms *[see Warnings and Precautions]*
- Gallbladder Disease *[see Warnings and Precautions]*
- Hypertriglyceridemia *[see Warnings and Precautions]*

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

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

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

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

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

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

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

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

Cytochrome P450 (CYP)
In vitro and *in vivo* studies have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4, such as St. John's Wort (*Hypericum perforatum*) preparations, phenobarbital, carbamazepine, and rifampin, may reduce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effects and/or changes in the uterine bleeding profile.

Inhibitors of CYP3A4, such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir and grapefruit juice, may increase the exposure of CE resulting in an increased risk of endometrial hyperplasia. Therefore, for chronically administered CYP3A4 inhibitors (>30 days) concurrently administered with DUAVEE, adequate diagnostic measures, including directed or random endometrial sampling when indicated by signs and symptoms of endometrial hyperplasia, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding.

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

Uridine Diphosphate Glucuronosyltransferase (UGT)
Bazedoxifene undergoes metabolism by UGT enzymes in the intestinal tract and liver. The metabolism of bazedoxifene may be increased by concomitant use of substances known to induce UGTs, such as rifampin, phenobarbital, carbamazepine, and phenytoin. A reduction in bazedoxifene exposure may be associated with an increased risk of endometrial hyperplasia. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Use in Women with Body Mass Index (BMI) > 27 kg/m^2
A 17% reduction in bazedoxifene exposure was predicted in women with BMI > 27 kg/m^2 (N=144) compared to those with BMI ≤ 27 kg/m^2 (N=93) after administration of DUAVEE, based on a population pharmacokinetic model using data from four Phase 1 studies. A reduction in bazedoxifene exposure may be associated with an increased risk of endometrial hyperplasia. Regardless of BMI, adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding.

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

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

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

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

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

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

© 2014 Pfizer Inc. All rights reserved.
Printed in USA/July 2014 APC660613-02
Pfizer U.S. Pharmaceuticals

continued from **PAGE 17**

treatment appeared to be appropriate, and the patient's cause of death was speculative. However, from a litigation perspective, the perinatologists were fighting an uphill battle.

Despite the fact that terbutaline was used by many obstetricians and perinatologists in just this manner—to prevent premature delivery secondary to cervical incompetence—the fact of the matter was that it was "off label." Both the FDA and ACOG warned against the use of tocolytics beyond 48 to 72 hours, but particularly terbutaline, in light of its propensity to cause tachycardia, pulmonary edema, hypoglycemia, shortness of breath, and chest pain.

While there is significant literature to support the proposition that the administration of terbutaline via pump is appropriate if the patient is adequately monitored, there were questions regarding the monitoring in this case and whether the patient was appropriately evaluated from a cardiac perspective before being placed on long-term tocolytics.

There was also the question of whether, once the patient's contractility diminished or ceased, the tocolytics should have been discontinued, particularly given her spikes of tachycardia.

Ultimately, because the case portended significant sympathy for the loss of a mother and wife and her twin babies, and because communicating the treatment decisions to a lay jury would have been difficult, it was settled before trial.

The verdict

The 3 defendant perinatologists resolved the case before trial, with Dr. A and Dr. B paying 90% of the settlement and Dr. C paying 10%, for a total of $1.5 million. Co-defendant Dr. D ultimately obtained discontinuance. COG

ANDREW I. KAPLAN, ESQ, is a partner at Aaronson, Rappaport, Feinstein & Deutsch, LLP in New York City, specializing in medical malpractice defense and healthcare litigation. He welcomes feedback on this column via email to aikaplan@arfdlaw.com.

BEST HOSPITALS
U.S.News & WORLD REPORT
NATIONAL
GYNECOLOGY
2014-15

WE'RE CHANGING THE WAY

OVARIAN CANCER PATIENTS FEEL ABOUT THE FUTURE

Intraperitoneal (IP) chemotherapy was introduced as a way to treat ovarian cancer by administering chemotherapy directly to the abdomen rather than through a vein. While this treatment extended median survival for women, the side effects were harsh and many women were unable to complete treatment. Our faculty at **Magee-Womens Hospital of UPMC** and **UPMC CancerCenter** played a major role in the adaptation of IP to a modern outpatient regimen, reducing side effects and improving outcomes by adjusting dosing and anticipating and controlling symptoms. Oncologists at Magee and throughout UPMC were also among the first to use hyperthermic IP chemotherapy for the treatment of ovarian cancer. Learn more at **UPMCPhysicianResources.com/OvarianCancer.**

Magee-Womens Hospital of UPMC

UPMC is affiliated with the University of Pittsburgh School of Medicine.

Sickle cell disease in pregnancy

A pregnancy complicated by SCD is high-risk for both mother and fetus. Surveillance helps manage problems such as vaso-occlusive crises and alloimmunization.

BY **ANDRA H. JAMES, MD, MPH**

DR. JAMES is Consulting Professor, Department of Obstetrics & Gynecology, Duke University, Durham, North Carolina.
She has no conflicts of interest to report with respect to the content of this article.

Sickle cell disease (SCD) is a devastating abnormality of red blood cells (RBCs) that results in circulatory impairment, tissue damage, infarctions, severe anemia, and life-threatening infections. SCD affects between 70,000 and 100,000 Americans, mostly of African descent, with a minority of Hispanic, southern European, Middle Eastern, and Asian Indian descent. Today, SCD is most often discovered during routine newborn screening.

Although SCD is associated with major morbidity, more than 90% of children with SCD in the United States survive into adulthood. Compared to the general population, however, their lifespans are 2 or 3 decades shorter and limited by both acute and chronic morbidity.

Acute complications of SCD include ischemic, vaso-occlusive (pain) crises, acute chest syndrome (which most closely resembles pneumonia, but may also result from fat embolism from bone marrow, intrapulmonary aggregates of sickled cells, atelectasis, or pulmonary edema), stroke, splenic sequestration, acute renal failure, and cholecystitis. Chronic complications include chronic pain, cholelithiasis, renal dysfunction, hypertension, pulmonary hypertension, and retinal problems.[1]

By the time they reach childbearing age, young women with SCD may have suffered many severe complications. Clinically apparent stroke occurs in 11% of those with SCD by age 20 and in 24% by age 45.[2] Although the condition is not usually regarded as a thrombophilia, 25% of adults with SCD have experienced venous thromboembolism (VTE) by a median age of 30, which is comparable to the rate in adults with high-risk thrombophilias.[3]

Available therapies

The only established disease-modifying therapies are chronic transfusion and hydroxyurea. The latter is strongly recommended for adults with 3 or more severe vaso-occlusive crises per year, pain or chronic anemia interfering with daily activities, or severe or recurrent episodes of acute chest syndrome. Hydroxyurea therapy is also suggested for adolescents without regard to symptoms.

Long-term transfusion therapy is used to prevent stroke in children with abnormal transcranial Doppler velocity. Potential conse-

quences of long-term transfusion therapy are alloimmunization and iron overload. Because transfused blood contains iron that circumvents the normal pathways of iron regulation, excess iron can accumulate in tissues and can become pathological. Chelation therapy can be used to remove excess iron in patients with evidence of iron overload.[1]

Issues during pregnancy

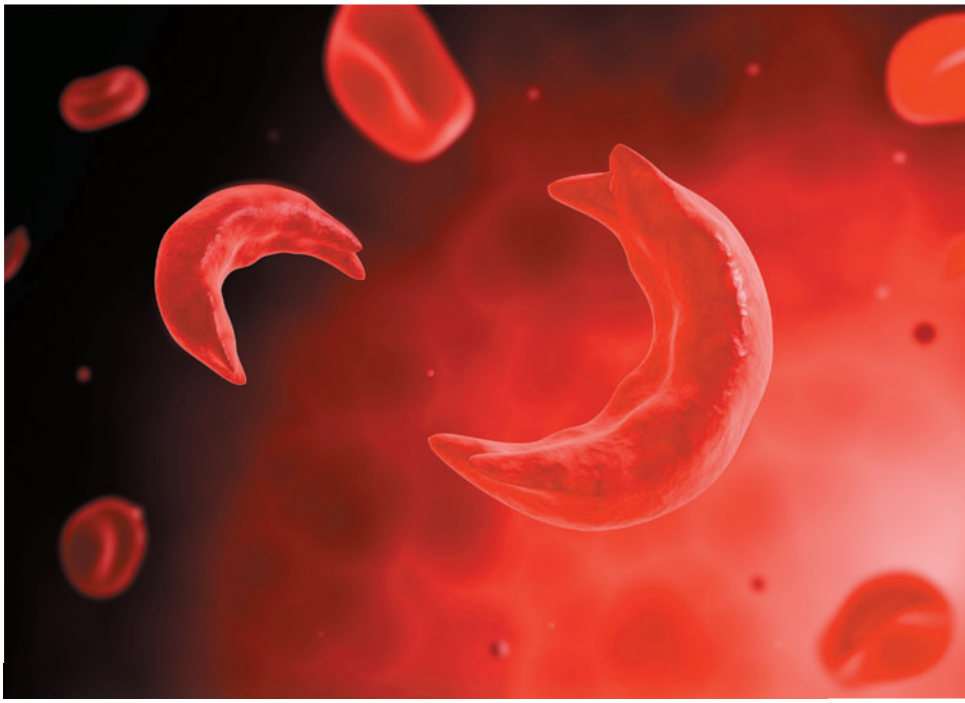
Maternal

During pregnancy, SCD poses problems to both mother and fetus. Maternal problems can arise from chronic underlying organ dysfunction such as renal disease or pulmonary hypertension, from acute complications of SCD such as vaso-occlusive crises and acute chest syndrome, and from pregnancy-related complications.

In normal, iron-replete women, RBC mass should increase by 400–450 mL during pregnancy to support the 40%–50% increase in blood volume.[4] This increase in RBC mass is not achievable in women with SCD. During pregnancy 50%–70% of women with SCD require at least one hospitalization and 30%–40% require transfusion.[5-7] In one cohort, women with SCD were hospitalized an average of 6 days during pregnancy.[5]

Women with SCD not only require transfusion, but also have frequently been transfused previously and, according to published reports, 20% to 50% of SCD patients are alloimmunized.[8] Limited blood products are available to women who are alloimmunized and need transfusion, but the most serious consequence is the maternal risk of developing a delayed hemolytic transfusion reaction, which can be life-threatening.

Another potentially life-threatening problem is pulmonary hypertension. It affects 6%–11% of SCD patients[9] and is especially morbid in pregnancy due to the increased cardiopulmonary demands of gestation. Although maternal mortality from pulmonary hypertension was previously reported to be 30%–50%, mortality remains in the range of 16%.[10]



A microscopic view of sickled red blood cells, which can trap leukocytes and block circulation.

GETTY IMAGES/STOCKTREK IMAGES

Perhaps because of underlying renal disease, hypertension, or placental ischemia, women with SCD are more likely to experience preeclampsia and eclampsia.[11-14] They are also more likely to experience VTE, infections (urinary tract infections, pneumonia, sepsis, and postpartum infections), acute renal failure, and death.[5,11-16]

In the United States, the maternal mortality rate is approximately 10 times higher than it is for women without SCD.[11,13] Similarly increased rates are seen in other countries.

Fetal

Fetal concerns for women with SCD include the consequences of uteroplacental insufficiency, alloimmunization, and opioid exposure. Studies from multiple cohorts, including large population studies, have documented the increased risk of fetal growth restriction, preterm delivery, and stillbirth.[5,11-21] Fetal growth appears to start normally, then lag after 25 weeks' gestation.[18] When fetal growth restriction occurs, it has been described as asymmetric.[22]

Women with SCD who have formed antibodies to fetal RBC antigens that are associated with hemolytic disease in the fetus or newborn and who are alloimmunized are at risk of having an anemic fetus or a stillbirth.[23] Although there are no data specifically for infants born to mothers with SCD, in a retrospective cohort study of infants born at Mayo Clinic between

SICKLE CELL DISEASE: AN OVERVIEW

Sickle cell disease (SCD) was first linked to an abnormality of red blood cells (RBCs) by Dr. Ernest Irons and Dr. James Herrick in 1910. By the 1920s, enough experience had accumulated about the disease to call it sickle cell anemia, due to the abnormally shaped RBCs that resemble the classic "sickle" or crescent shape found on peripheral blood smears. By the 1940s, sufficient biochemical and genetic data had accumulated for Linus Pauling to call it the first molecular disease.[1]

Genotypes include homozygous hemoglobin SS (HbSS) and compound heterozygous conditions, such as hemoglobin SC (HbSC), hemoglobin Sβ^0-thalassemia (HbSβ^0-thal), hemoglobin Sβ^+-thalassemia (HbSβ^+-thal), and several rare genotypes. The most prevalent phenotype is HbSS, which accounts for about 70% of cases and is identified as sickle cell anemia. The HbSC variant accounts for most of the remaining cases. Sβthal^0, due to its similar phenotype, is also identified as sickle cell anemia. These 2 genotypes are associated with the most severe manifestations of SCD.

The gene defect in HbS causes hemoglobin to form long chains or polymers that deform RBCs, damage their membranes, and alter the configuration of their cell surface molecules. These deformed RBCs are stiff and angular and can be trapped with leukocytes to block circulation, causing inflammation, tissue damage, and infarctions in vital organs including the eyes, brain, heart, lungs, liver, spleen, kidneys, bones, and, during pregnancy, the placenta. Early removal from the circulation and hemolysis lead to a very short life span of the sickled RBCs (16 to 20 days, compared with 120 days in normal RBCs). Hemolysis results in release of free hemoglobin that damages the endothelium, causing further RBC adhesiveness and blockage of small blood vessels.[2-4]

REFERENCES

1. Steensma DP, Kyle RA, Shampo MA. Walter Clement Noel-first patient described with sickle cell disease. *Mayo Clinic proceedings.* 2010;85:e74–75.

2. Rees DC, Williams TN, Gladwin MT. Sickle-cell disease. *Lancet.* 2010;376:2018-2031.

3. Hematopoietic and Lymphoid Systems: Hemolytic anemias: Sickle cell anemia. In: Kumar V, Abbas AK, Aster JC, eds. *Robbins Basic Pathology.* 9th ed. Bridgewater, NJ: Elsevier; 2012:411–412.

4. Trampont P, Roudier M, Andrea AM, et al. The placental-umbilical unit in sickle cell disease pregnancy: a model for studying in vivo functional adjustments to hypoxia in humans. *Hum Pathol.* 2004;35:1353–1359.

1998 and 2009, neonatal withdrawal syndrome occurred in 5.6% of infants exposed to chronic narcotic use in utero.[24]

Preconception counseling

Couples contemplating pregnancy should be aware of the increased risks to a woman's health of SCD during pregnancy.

Prior to pregnancy, the physician should assess a woman's overall health and her potential risks during pregnancy. She and her partner should be counseled accordingly. Some studies have found poorer outcomes in women with sickle cell anemia as opposed to other SCD genotypes, but other studies have found no differences.

It is the experience of the author and her colleagues that a history of frequent hospitalizations and/or episodes of acute chest syndrome correlates with poorer overall health and increased risks during pregnancy. An assessment of urine protein and a retinal examination should be performed.[1] Hypertension should be treated to lower systolic blood pressure to ≤140 mmHg and diastolic blood pressure to ≤90 mmHg.[1]

Some experts recommend that all SCD patients be screened for pulmonary hypertension with Doppler echocardiography.[9] At a minimum, any woman with signs of pulmonary hypertension should undergo Doppler echocardiography.[1] Women with significant pulmonary hypertension should be counseled that pregnancy is contraindicated and that if it occurs, termination should be considered.[10]

All patients with SCD should receive immunizations according to the Advisory Committee on Immunization Practices, but with particular attention to the immunizations recommended for people who have functional asplenia. These include pneumococcal, haemophilus influenza type b, and meningococcal vaccinations.

A ferritin level should be checked before prescribing any iron. (A serum ferritin level >1000 ng/mL is suggestive of iron overload.) The American College of Obstetricians and Gynecologists recommends 4 mg of folate per day during pregnancy.[25]

Women with SCD who have been transfused should be tested for RBC alloantibodies. If a woman has RBC alloantibodies and the antibodies are known to cause hemolytic disease

True Fact 6:

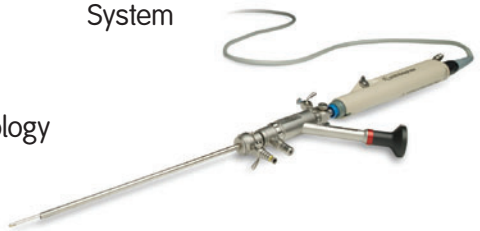
The TRUCLEAR System is designed to **capture all** resected tissue.

Adhesiolysis • RPOC Evacuation • Diagnostic Visual D&C and Endometrial Biopsy • Myomectomy • Polypectomy • Hysteroscopic Adhesiolysis • RPOC Evacuation

The truth is clear. TRUCLEAR◇

smith&nephew

TRUCLEAR◇ System



The TRUCLEAR System allows for the targeted removal of intrauterine pathology under continuous visualization. Efficient tissue capture allows evaluation of the entire pathology for histological confirmation.

Get the true facts. Make the clear choice. **Visit us at the annual AAGL Global Congress, booth #621 to learn what's new at Smith and Nephew.**

Smith & Nephew, Inc.
150 Minuteman Road
Andover, MA 01810
USA

www.sntruclear.com
T +1 978 749 1000
US Customer Service: +1 800 343 5717
International Customer Service: +1 978 749 1140

◇Trademark of Smith & Nephew.
Registered US Patent and Trademark Office.
©2014 Smith & Nephew. All rights reserved.
Printed in USA. 02677-6 09/14

sntruclear.com/TRU

STEM-CELL TRANSPLANTATION FOR SICKLE CELL DISEASE

The only curative therapy for SCD is allogeneic hematopoietic stem-cell transplantation. Several hundred patients with SCD, almost exclusively children, have received transplants with bone marrow cells from HLA-identical siblings. Reported overall survival after transplantation is 92%–94% and event-free survival is 82%–86%.[1] Besides complications from bone marrow-suppressive chemotherapy and from transplantation-related mortality, there is the possibility of graft failure and chronic graft-versus-host disease. The chronic organ damage that was sustained prior to the transplantation also may not be reversible.

The risk of toxicities and complications from transplantation is so high in adults that the procedure is not usually considered for them. Despite rare anecdotal reports of successful pregnancies in women after stem-cell transplantation, the vast majority lose fertility as a consequence of the chemotherapy.

REFERENCE

1. Locatelli F, Pagliara D. Allogeneic hematopoietic stem cell transplantation in children with sickle cell disease. *Pediatr Blood Cancer.* 2012;59:372–376.

in the fetus or newborn, her partner should also be tested for the corresponding RBC antigen(s). If the partner tests positive, the couple should be counseled about the risks of hemolytic disease, how it is monitored, and how it is treated.

Couples should also be counseled about the potential fetal and neonatal effects of maternal medications, including chronic opioids. Angiotensin-converting enzyme (ACE) inhibitors, which are used to treat microalbuminuria in adults with SCD, should be discontinued.

Hydroxyurea, which has caused birth defects in experimental animals who were given very high doses, has not been associated with an increased risk of birth defects in infants with in utero exposure.[26] Nonetheless, it is generally not prescribed to pregnant women. Women who are trying to become pregnant or who become pregnant while on hydroxyurea therapy are generally advised to discontinue it.[27]

Women with SCD are at risk of having a child affected with SCD if their partners have SCD, HbS, β-thalassemia trait, or are carriers of another abnormal hemoglobin such as HbC. Women with SCD whose partners' sickle cell or thalassemia status is unknown should be referred for hemoglobin electrophoresis.

Women whose partners carry one of the traits listed above can avoid an affected pregnancy by undergoing preimplantation genetic diagnosis. Alternatively, after spontaneous conception, prenatal diagnosis of SCD is possible by chorionic villus sampling in the first trimester or by amniocentesis in the second trimester. Couples who are at risk of having a child affected with SCD should be referred for genetic counseling.

Care during pregnancy

During pregnancy, evaluation should include consultation with a hematologist and a maternal-fetal medicine specialist. Pertinent history includes the patient's genotype, history of transfusions, hospitalizations, episodes of acute chest syndrome, vaso-occlusive crises, Doppler echocardiography, stroke, VTE, cholecystectomy, status of spleen, renal evaluations, and immunizations.

Issues not addressed before conception should be addressed early in pregnancy. An assessment of iron stores is usually made with the initial complete blood count (CBC). Most patients with SCD have elevated serum ferritin levels and should not receive additional iron supplementation, but should continue to receive folic acid. Hydroxyurea therapy, chelating agents, and ACE inhibitors should be discontinued, although only ACE inhibitors have been associated with congenital anomalies.

Women with SCD are at high risk of preeclampsia and both arterial thromboembolism and VTE. Therefore, it is reasonable to initiate low-dose aspirin after the first trimester.[28] Women with a history of VTE should receive anticoagulation with low-molecular-weight heparin (LMWH) during pregnancy and the postpartum period.

Care during pregnancy includes maternal and fetal surveillance. Monthly CBCs are typically performed to monitor for severe anemia. In the only randomized controlled trial published to date, prophylactic transfusion was associated with a decreased risk of pain crises and severe anemia, but no difference was observed in pregnancy outcomes.[29]

Other therapies that have shown promise in reducing vaso-occlusive crises and would potentially be safe in pregnancy (such as propranolol and LMWH) have not been confirmed in multicenter trials and have not been studied in pregnancy.[30]

Risks of adverse fetal outcomes are reduced, but not eliminated, with fetal surveillance, which may

lead to planned early delivery. Fetal surveillance should include, at a minimum, serial ultrasonography for fetal growth every 3–4 weeks starting in the third trimester with initiation of antepartum fetal testing at 32 weeks' gestation or sooner if indicated.

A contributing factor to the increased incidence of stillbirth is utero-placental insufficiency, but sudden and unpredictable stillbirths do occur. Some experts recommend induction of labor after 37 weeks' gestation.[5] Plans for the mode of delivery should be according to obstetric indications while recognizing that the rate of cesarean delivery is higher in women with SCD.[5,11,12,15,20] An anesthesiologist should be consulted in the third trimester or during any hospitalization.

Although prophylactic transfusion was not shown to improve pregnancy outcomes in patients with SCD, preoperative transfusion therapy to increase hemoglobin levels to 10 g/dL is strongly recommended in patients with sickle cell anemia (HbSS and HbSβ^0-thal), and should be considered in patients with other genotypes.[1] When a transfusion is clinically indicated in the patient with SCD, the objective is to lower the percentage of HbS to approximately 40% while simultaneously raising the total hemoglobin concentration to about 10 g/dL.[25]

Since the need for cesarean delivery cannot be predicted, and women with SCD are at high risk of cesarean delivery, it may be reasonable to aim for this total hemoglobin concentration in the last month of pregnancy.

Women with SCD have a risk of thrombosis comparable to that in patients with high-risk thrombophilia. Women with SCD should have pneumatic compression devices during antepartum hospitalizations, during labor, and at the time of cesarean delivery. For women who are not already receiving anticoagulation for a history of VTE, some consideration should be given to prophylactic or low-dose anticoagulation during pregnancy and for 6 weeks postpartum.

> Women with SCD have a risk of thrombosis comparable to that in patients with **high-risk thrombophilia.**

The rare pregnant patient with SCD who has undergone stem-cell transplantation (see sidebar on page 28) should be evaluated and managed as are other women with SCD. This patient may be at reduced risk of vaso-occlusive crises, but will likely have been selected for transplantation due to some chronic organ damage and may have suffered additional tissue damage from bone marrow-suppressive chemotherapy. Regimens typically include busulfan, which should prompt an evaluation of pulmonary function.[31]

Management of vaso-occlusive crises

There are no randomized trials on the safety and efficacy of interventions (transfusion, oxygen therapy, fluid replacement analgesia, and/or steroids) for treating pain crises during pregnancy.[32]

A pregnant woman with SCD who presents with pain should be evaluated for other complications, and pain should be treated promptly and aggressively.[1] Nonsteroidal drugs are contraindicated, so opioids should be used. Many women with SCD have a high tolerance for opioids, but they still need adequate and appropriate medication to control pain during vaso-occlusive crises in pregnancy. Opioids should not be withheld due to concerns for addiction.

Transfusion should be administered only if there are other indications.[1] Oxygen should be given if saturation is less than 95% by pulse oximetry.[1,25] Incentive spirometry should be initiated for patients who are hospitalized for a vaso-occlusive crisis.[1]

Postpartum contraception

Hormonal contraception may provide women with SCD with decreased menstrual blood flow and improved hemoglobin levels. VTE is the primary risk associated with combined hormonal methods containing estrogen.

Intrauterine devices (IUDs) and implants carry risks associated with the insertion procedure, and sterilization carries risks associated with the surgical procedure. Nonetheless, these risks are trivial compared to the risks associated with pregnancy. Copper IUDs (as opposed to progestin IUDs) may increase bleeding, which is a more significant problem for women with SCD. Systematic reviews of the literature have demonstrated the safety of progestin-only contraception for patients with SCD.[33,34]

Summary

During pregnancy, SCD poses problems to both mother and fetus. Maternal problems can arise from chronic underlying organ dysfunction such as renal disease or pulmonary hypertension, from acute complications of SCD such as vaso-occlusive crises and acute chest syndrome, and/or from pregnancy-related complications.

Fetal problems include alloimmunization, opioid exposure, growth restriction, preterm delivery, and stillbirth.

Couples should be counseled that a pregnancy with SCD is high risk for both fetus and mother and be made aware of the increased risks of adverse pregnancy outcome. Risks of adverse fetal outcomes are reduced but not eliminated with fetal surveillance. COG

REFERENCES

1. Yawn BP, Buchanan GR, Afenyi-Annan AN, et al. Management of sickle cell disease: summary of the 2014 evidence-based report by expert panel members. *JAMA.* 2014;312:1033–1048.

2. Ohene-Frempong K, Weiner SJ, Sleeper LA, et al. Cerebrovascular accidents in sickle cell disease: rates and risk factors. *Blood.* 1998;91:288–294.

3. Naik RP, Streiff MB, Haywood C, Jr., Nelson JA, Lanzkron S. Venous thromboembolism in adults with sickle cell disease: a serious and under-recognized complication. *Am J Med.* 2013;126:443–449.

4. Hytten F. Blood volume changes in normal pregnancy. *Clin Haematol.* 1985;14:601-612.

5. Ngo C, Kayem G, Habibi A, et al. Pregnancy in sickle cell disease: maternal and fetal outcomes in a population receiving prophylactic partial exchange transfusions. *Eur J Obstet Gnecol Reprod Biol.* 2010;152:138–142.

6. Yu CK, Stasiowska E, Stephens A, Awogbade M, Davies A. Outcome of pregnancy in sickle cell disease patients attending a combined obstetric and haematology clinic. *J Obstet Gynaecol.* 2009;29:512–516.

7. Al Jama FE, Gasem T, Burshaid S, Rahman J, Al Suleiman SA, Rahman MS. Pregnancy outcome in patients with homozygous sickle cell disease in a university hospital, Eastern Saudi Arabia. *Arch Gynecol Obstet.* 2009;280:793–797.

8. Yazdanbakhsh K, Ware RE, Noizat-Pirenne F. Red blood cell alloimmunization in sickle cell disease: pathophysiology, risk factors, and transfusion management. *Blood.* 2012;120:528–537.

9. Klings ES, Machado RF, Barst RJ, et al. An official American Thoracic Society clinical practice guideline: diagnosis, risk stratification, and management of pulmonary hypertension of sickle cell disease. *Am J Respir Crit Care Med.* 2014;189:727–740.

10. Pieper PG, Lameijer H, Hoendermis ES. Pregnancy and pulmonary hypertension. *Best Pract Res Cl Ob.* 2014;28:579–591.

11. Villers MS, Jamison MG, De Castro LM, James AH. Morbidity associated with sickle cell disease in pregnancy. *Am J Obstet Gynecol.* 2008;199:125 e121–125.

12. Barfield WD, Barradas DT, Manning SE, Kotelchuck M, Shapiro-Mendoza CK. Sickle cell disease and pregnancy outcomes: women of African descent. *Am J Prev Med.* 2010;38:S542–549.

13. Alayed N, Kezouh A, Oddy L, Abenhaim HA. Sickle cell disease and pregnancy outcomes: population-based study on 8.8 million births. *J Perinat Med.* 2014;42:487–492.

14. Boulet SL, Okoroh EM, Azonobi I, Grant A, Craig Hooper W. Sickle cell disease in pregnancy: maternal complications in a Medicaid-enrolled population. *Matern Child Health J.* 2013;17:200–207.

15. Howard RJ, Tuck SM, Pearson TC. Pregnancy in sickle cell disease in the UK: results of a multicentre survey of the effect of prophylactic blood transfusion on maternal and fetal outcome. *BJOG.* 1995;102:947–951.

16. Costa VM, Viana MB, Aguiar RA. Pregnancy in patients with sickle cell disease: maternal and perinatal outcomes. *J Matern Fetal Neonatal Med ISO.* 2014:1–5.

17. Brown AK, Sleeper LA, Pegelow CH, Miller ST, Gill FM, Waclawiw MA. The influence of infant and maternal sickle cell disease on birth outcome and neonatal course. *Arch Pediatr Adolesc Med.* 1994;148:1156–1162.

18. Thame MM, Osmond C, Serjeant GR. Fetal growth in women with homozygous sickle cell disease: an observational study. *Eur J Obstet Gnecol Reprod Biol.* 2013;170:62–66.

19. Serjeant GR, Loy LL, Crowther M, Hambleton IR, Thame M. Outcome of pregnancy in homozygous sickle cell disease. *Obstet Gynecol.* 2004;103:1278–1285.

20. Costa S, Rocha G, Leit OA, Guimar Es HL. Transient tachypnea of the newborn and congenital pneumonia: a comparative study. *J Matern Fetal Neonatal Med ISO.* 2011.

21. Muganyizi PS, Kidanto H. Sickle cell disease in pregnancy: trend and pregnancy outcomes at a tertiary hospital in Tanzania. *PloS one.* 2013;8:e56541.

22. Thame M, Lewis J, Trotman H, Hambleton I, Serjeant G. The mechanisms of low birth weight in infants of mothers with homozygous sickle cell disease. *Pediatrics.* 2007;120:e686–693.

23. Moise KJ, Jr., Argoti PS. Management and prevention of red cell alloimmunization in pregnancy: a systematic review. *Obstet Gynecol.* 2012;120:1132–1139.

24. Kellogg A, Rose CH, Harms RH, Watson WJ. Current trends in narcotic use in pregnancy and neonatal outcomes. *Am J Obstet Gynecol.* 2011;204:259 e251-254.

25. ACOG Practice Bulletin No. 78: Hemoglobinopathies in pregnancy. *Obstet Gynecol.* 2007;109:229–237.

26. Ballas SK, McCarthy WF, Guo N, et al. Exposure to hydroxyurea and pregnancy outcomes in patients with sickle cell anemia. *J Natl Med Assoc.* 2009;101:1046–1051.

27. Brawley OW, Cornelius LJ, Edwards LR, et al. NIH Consensus Development Statement on Hydroxyurea Treatment for Sickle Cell Disease. *NIH Consens State Sci Statements.* 2008;25:1–30.

28. Duley L, Henderson-Smart DJ, Meher S, King JF. Antiplatelet agents for preventing pre-eclampsia and its complications. *Cochrane Database Syst Rev.* 2007:CD004659.

29. Koshy M, Burd L, Wallace D, Moawad A, Baron J. Prophylactic red-cell transfusions in pregnant patients with sickle cell disease. A randomized cooperative study. *New England J Med.* 1988;319:1447–1452.

30. Manwani D, Frenette PS. Vaso-occlusion in sickle cell disease: pathophysiology and novel targeted therapies. *Blood.* 2013;122:3892–3898.

31. Locatelli F, Pagliara D. Allogeneic hematopoietic stem cell transplantation in children with sickle cell disease. *Pediatr Blood Cancer.* 2012;59:372–376.

32. Marti-Carvajal AJ, Pena-Marti GE, Comunian-Carrasco G, Marti-Pena AJ. Interventions for treating painful sickle cell crisis during pregnancy. *Cochrane Database Syst Rev.* 2009:CD006786.

33. Legardy JK, Curtis KM. Progestogen-only contraceptive use among women with sickle cell anemia: a systematic review. *Contraception.* 2006;73:195–204.

34. Manchikanti A, Grimes DA, Lopez LM, Schulz KF. Steroid hormones for contraception in women with sickle cell disease. *Cochrane Database Syst Rev.* 2007:CD006261.

“My income more than tripled after adding aesthetic laser treatments.”

DR. MICHAEL SINCLAIR, MD
FAMILY PRACTITIONER

Add revenue. Improve patient care.

Aesthetic treatments for skin revitalization and hair removal make the perfect complement to your practice. Your patients will love it because it builds their confidence. You'll love it because it builds your business. And it couldn't be easier. We can have you trained and up in running faster than you think. Stop worrying about your practice and start growing it. With Cynosure.

CYNOSURE®

Learn more at startwithaesthetics.com

© 2014 Cynosure, Inc. All rights reserved. Cynosure is a registered trademark

Patient counseling following periviable PROM

Understanding the usual clinical course of periviable PROM helps physicians guide families who are making difficult decisions.

Society for Maternal-Fetal Medicine

BY THE SOCIETY FOR MATERNAL-FETAL MEDICINE (SMFM) WITH THE ASSISTANCE OF
ANTHONY SCISCIONE, DO, AND GWENDOLYN GRANT, DO

DR. SCISCIONE is director of the Delaware Center for Maternal and Fetal Medicine and program director of the Christiana Care ob/gyn residency program, Newark, Delaware.

DR. GRANT is a resident in the Department of Obstetrics and Gynecology at Christiana Care, Newark, Delaware.

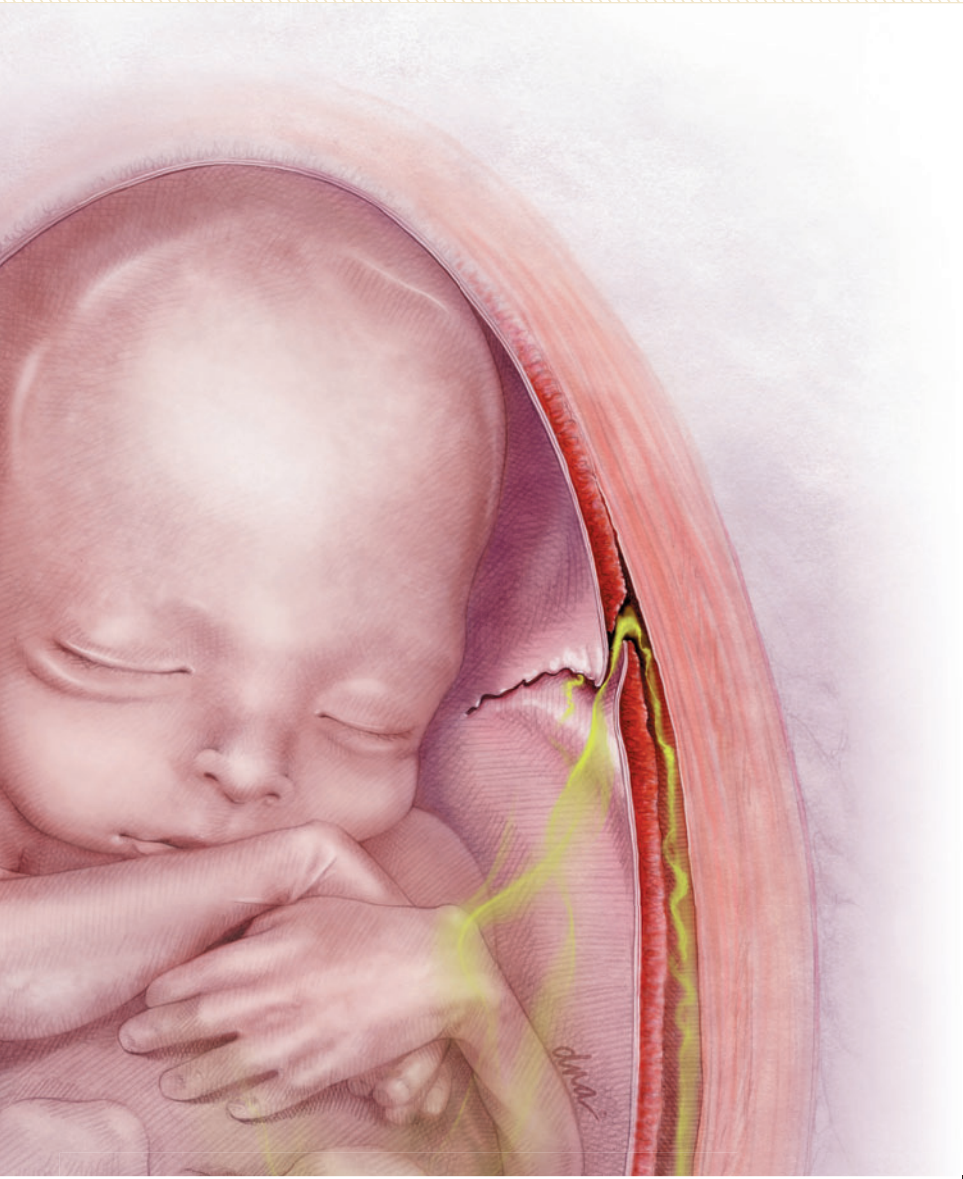
The authors have no conflicts of interest to report with respect to the content of this article.

A 24-year-old G1P0 at 22 4/7 weeks' gestation presents to labor and delivery after feeling a "pop" and experiencing a gush of fluid from her vagina. On sterile speculum exam, pooling of fluid is noted in the vaginal vault, with nitrazine and ferning tests both positive. On speculum exam the cervix appears closed and long. Transabdominal ultrasound reveals decreased amniotic fluid. You make the diagnosis of periviable rupture of the membranes. How do you counsel the patient regarding the likely clinical course, as well as potential maternal and neonatal risks and outcomes?

Premature rupture of membranes (PROM) is a condition characterized by rupture of the amniochorionic membranes prior to the onset of labor. Periviable PROM refers to instances of PROM occurring between 20 0/7 and 25 6/7 weeks' gestation.[1] Although less than 1% (approximately 0.4%)[2] of pregnancies are affected by this complication, the neonatal and maternal outcomes, along with the psychological and socioeconomic impacts, can be devastating.

Periviable PROM refers to instances of PROM occurring **between 20 0/7 and 25 6/7 weeks'** gestation.

Understanding the usual clinical course of periviable PROM not only allows physicians to appropriately counsel families, it also provides a basis from which to guide families in making difficult decisions. The median latency period until delivery varies greatly depending upon the gestational age at which PROM occurs (Table 1).[3-7] Development of intrauterine infection is the primary cause leading to delivery, with placental abruption and nonreassuring fetal testing the next-most-common indications.[5,7-10] The duration of the latency period appears to be inversely related to the gestational age at which PROM occurs, with longer latency periods reported in pregnancies affected by PROM at earlier gestational ages.[11] When counseling families, it is important to note that because most of the published studies are retrospective and exclude patients ineligi-



Consequences of perviable PROM may include oligohyramnios, umbilical cord compression, bacterial infection, and pulmonary hypoplasia. The neonatal mortality rate for pregnancies complicated by pulmonary hypoplasia is very high.

ILLUSTRATION BY ALEX BAKER, DNA ILLUSTRATIONS, INC.

ble for expectant management (eg, pregnancies with chorioamnionitis or with a fetal demise). As a result, the latency period for pregnancies complicated by periviable PROM is likely overestimated, with maternal and neonatal morbidity likely being underreported.

Obstetric providers should carefully review the potential maternal and neonatal outcomes with the woman and any involved family members before either active or expectant management is chosen. Consultative input from maternal-fetal medicine and neonatology subspecialists, if available, helps expand understanding and facilitate a more fully informed decision by the family. If the patient is not at a Level III hospital or medical center, transfer to one with resources to care for a periviable neonate should be considered.

Are any treatment options available to correct periviable PROM?

The fetal amniochorionic membranes are not innervated and are poorly vascularized, making physiologic wound healing, which involves local inflammation and scar formation, unlikely in the setting of spontaneous rupture.[12] The rate of resealing of the amniochorionic membranes after rupture has been reported to be as high as 8%. This number, however, is likely an overestimate and more reflective of membrane resealing after an invasive event such as amniocentesis or fetoscopy rather than to spontaneous rupture.[13,14] Although favorable outcomes have been reported in the literature, limited data exist describing outcomes of pregnancies that continue after membrane resealing.

There is currently no accepted definitive treatment to attempt correction of periviable PROM. In recent years, research has focused on the development of amniochorionic membrane plugs and sealants, which may patch tears in the membranes and allow for fluid reaccumulation. Various sealants have been studied, including platelets, fibrin, and gelatin.[14-16] The results of some of these studies have demonstrated increased latency and improvement in neonatal survival but they are likely biased by small sample sizes and lack of comparative data.

Transabdominal amnioinfusion has similarly been reported as a potential intervention in the "treatment" of preterm PROM. A recent meta-analysis of the available data from observational studies (4 studies, N=147 total patients) and randomized controlled trials (RCTs) (3 studies, N=165 total patients) indicated a potential improvement in latency to

TABLE 1 Summary of studies assessing latency period following periviable PROM

Reference	Patients (N)	Range GA at PROM (wks)	GA at PROM (wks)	GA at delivery (wks)	Latency (d)
Xiao (2000)[3]	28	14–24	21.6	27.1 (2.1)	39.4 (23.9)
Grisaru-Granvosky (2003)[4]	25	16–24	22.7	-	15.6
Falk (2004)[5]	57	14–24	20.3	-	6.0*
Dinsmoor (2004)[6]	43	16–24	22.0*	25.8 (3.4)	13.0*
Muris (2007)[7]	29	18–24	21.1	23.2	14.1

Abbreviation: GA, gestational age
Data expressed as mean (standard deviation)
*Median

delivery and survival when intramniotic amnioinfusion was initiated.[17] Although this and other interventions may appear promising, they should still be viewed as experimental and not be performed outside of research protocols, given the limited evidence.

What fetal/neonatal and maternal risks are associated with periviable PROM?

Rates of perinatal and neonatal morbidity and mortality are high in pregnancies complicated by periviable PROM. Antenatally, stillbirth is a significant risk from cord compression due to oligohydramnios and cord prolapse. In addition, although the live birth rate for pregnancies affected by periviable PPROM is approximately 50% (mean 47%–56%) the survival to discharge rate is only 26.3%.[5,7-10]

Respiratory distress syndrome, neonatal sepsis, and severe intraventricular hemorrhage are the most common contributors to neonatal mortality. These causes are not specific to periviable PROM, but rather, to delivery at the extremes of prematurity. Adverse neonatal outcomes specific to periviable PPROM most commonly result from chronic oligohydramnios, and include pulmonary hypoplasia, limb deformities (eg, clubbed feet) and other components of fetal compression syndrome. When present, the neonatal mortality rate for pregnancies complicated by pulmonary hypoplasia is very high.

Few studies have specifically evaluated the long-term morbidity associated with expectant management of periviable PROM. This is likely a result of the small population of neonates surviving this condition. In a secondary analysis of a multicenter RCT conducted by the Maternal-Fetal Medicine Units Network and Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), Manuck et al. reported that neonates born following pregnancies complicated by PROM at <25 weeks gestational age suffered severe early childhood morbidity (defined as mild or severe cerebral palsy, Bayley MDI/PDI scores >2 SD below mean, or death) in 51.5% of cases.[9]

One tool that can also be of assistance in counseling regarding neonatal prognosis, although not specifically designed for PROM, is the use of the NICHD Neonatal Research Network (NRN) Extremely Preterm Birth Outcome Data estimator (**www.nichd.nih.gov/about/org/der/branches/ppb/programs/epbo/pages/epbo_case.aspx?start=10:43:23**). Based on 5 patient characteristics (gestational age, fetal plurality, birth weight, fetal gender, and exposure to antenatal corticosteroids), this tool provides estimates for overall survival and intact survival.[18]

Although the focus of many studies has been on neonatal outcomes, it is important to consider that expectant management of periviable PROM pregnancies can also pose a significant risk to the mother. Intrauterine infection is the most common complication affecting periviable PPROM; chorioamnionitis has been reported to occur in 31.6% to 54% of these pregnancies, placing the pregnant women at significant risk of sepsis.[5,7-10] In addition, delivery by cesarean (34%), venous thromboembolism (4%), and in very rare instances, maternal death, have also been described in the literature.[5,7-10]

Adverse neonatal outcomes **specific to periviable PPROM** most commonly result from chronic oligohydramnios.

TABLE 2 General guidance regarding obstetric interventions for threatened and imminent periviable birth

	Gestational age (weeks)		
Intervention	< 22 0/7	22 0/7–22 6/7	> 23 0/7
Antenatal corticosteroids	Not recommended	Consider if delivery at >23 0/7 wks is anticipated	Recommended
Magnesium sulfate for neuroprotection	Not recommended	Not recommended	Recommended
Antibiotics for PPROM to enhance latency	Consider if delivery not imminent	Consider if delivery not imminent	Recommended if delivery not imminent
Intrapartum antibiotics for GBS prophylaxis	Not recommended	Not recommended	Recommended

Abbreviations: GBS, Group B *Streptococcus*; PPROM, preterm premature rupture of membranes
Source: Raju et al., AJOG 2013 (reference 1).

What risk factors can predispose a patient to periviable PROM, and how can they affect outcomes?

Retrospective studies have identified risk factors for periviable PROM that include intrauterine infection, history of cervical insufficiency, cerclage, antepartum bleeding, multifetal gestation, history of prior pregnancy affected by PROM or preterm labor, smoking, and both amniocentesis and fetoscopy.[5,7-10]

The risks and outcomes associated with periviable PROM following invasive procedures, such as genetic amniocentesis and fetoscopy, are quite different than those seen with spontaneous PROM. The incidence of PROM following midtrimester genetic amniocentesis has been reported as 1% to 2%.[19, 20] Pregnancies complicated by PROM after midtrimester genetic amniocentesis, however, have much better perinatal outcomes than pregnancies complicated by spontaneous PROM at comparable gestational ages. In a retrospective study by Borgida et al., pregnancies complicated by PROM following genetic amniocentesis achieved both longer latencies from the time of membrane rupture to delivery (124 days compared to 28 days) and higher gestational ages at delivery (34 weeks compared to 21.6 weeks), when compared to pregnancies with spontaneous periviable PROM.[19] In addition, the perinatal survival rate was 91% after periviable PROM following genetic amniocentesis versus 9% when the PROM was spontaneous. Rates of periviable PROM following fetal surgical procedures varies greatly based on the type and indication for surgery, but is in the range of 20% to 30%. The type of surgery, indication, and size of ports used in fetoscopy directly influence both the gestational age at PROM and neonatal outcomes.[19,20]

What are the management options and routine interventions for pregnancies complicated by periviable PROM?

Patients are most often presented with three management options following periviable PROM: pregnancy termination, indicated delivery, or expectant management. Pregnancy termination in the setting of PROM prior to viability should be discussed as an option given the neonatal prognosis and maternal risks. This management is selected in approximately one of three pregnancies in which PROM occurred prior to viability.[5,7-10] For patients who elect to continue the pregnancy, the potential need for medically indicated delivery regardless of gestational age must still be assessed and discussed. Expectant management is therefore reserved for those without indications for delivery (and would exclude patients with chorioamnionitis, placental abruption, active hemorrhage, or labor).

The primary goals of expectant management are to prolong latency and improve neonatal outcomes while limiting maternal risk. Multiple antenatal interventions that have been shown to improve outcomes for pregnancies >24 weeks (antenatal corticosteroids, antibiotics, and magnesium sulfate for neuroprotection) have unknown effectiveness for those <24 wks since most clinical trials testing these interventions have not included pregnancies <24 wks.[19,21-26]

In February 2014, a joint workshop held by the NICHD, the Society for Maternal-Fetal Medicine, American Academy of Pediatrics, and American College of Obstetricians and Gynecologists addressed management of periviable pregnancies.[1] At this workshop, general guidance for management was categorized based on GA <22 weeks 0 days, 22 weeks to 22 weeks 6 days, and ≥23 weeks 0 days (Table 2).

How should this patient be counseled regarding risks in future pregnancies?

Patients with prior periviable PROM

TABLE 3 Clinical recommendations

Recommendation	Grade
In women who develop periviable PROM, consultation with maternal-fetal medicine and neonatology should be considered.	1B
In women who develop periviable PROM, transfer to a Level III center should be considered.	1B
In counseling women and families with periviable PROM, the NICHD Neonatal Research Network: Extremely Preterm Birth Outcome Data estimator tool should be utilized.	Best practice
Following periviable PTB complicated by PROM, use of 17OHPC and cervical length screening in subsequent pregnancies is recommended.	1A

are at increased risk of recurrent premature PROM and preterm birth, but most women who present with periviable PROM have no prior history. A detailed evaluation focusing on the potentially modifiable causes of periviable PROM is of particular importance (eg, smoking or cervical insufficiency). A discussion regarding the potential benefits and risks of progestogens supplementation (17 OHPC 250 mg IM weekly starting at 16 weeks) and sonographic cervical length screening for future pregnancies is appropriate.[22]

Table 3 lists clinical recommendations for periviable PROM and the strength of evidence for those recommendations. COG

REFERENCES

1. Raju TN, Mercer BM, Burchfield DJ, Joseph GF Jr. Periviable birth: executive summary of a joint workshop by Eunice Kennedy Shriver National Institute of Child Health and Human Development, Society for Maternal-Fetal Medicine, American Academy of Pediatrics, and American College of Obstetricians and Gynecologists. *Am J Obstet Gynecol.* 2014; 210(5):406–417.

2. Waters TP, Mercer BM. The management of preterm premature rupture of the membranes near the limit of fetal viability. *Am J Obstet Gynecol.* 2009; 201(3):230–240.

3. Xiao ZH, Andre P, Lacaze-Masmonteil T, Audibert F, Zupan V, Dehan M. Outcome of premature infants delivered after prolonged premature rupture of membranes before 25 weeks of gestation. *Eur J Obstet Gynecol Reprod Biol.* 2000;90(1):67–71.

4. Grisaru-Granovsky S, Eitan R, Kaplan M, Samueloff A. Expectant management of midtrimester premature rupture of membranes: a plea for limits. *J Perinatol.* 2003; 23(3):235–239.

5. Falk SJ, Campbell LJ, Lee-Parritz A, Cohen AP, Ecker J, Wilkins-Haug L, Lieberman E. Expectant management in spontaneous preterm premature rupture of membranes between 14 and 24 weeks' gestation. *J Perinatol.* 2004;24(10):611–616.

6. Dinsmoor MJ, Bachman R, Haney EI, Goldstein M, Mackendrick W. Outcomes after expectant management of extremely preterm premature rupture of membranes. Am J Obstet Gynecol. 2004;190(1):183–187.

7. Muris C, Girard B, Creveuil C, Durin L, Herlicoviez M, Dreyfus M. Management of premature rupture of membranes before 25 weeks. *Eur J Obstet Genecol Reprod Biol.* 2007;131(2):163–168.

8. Gonzales-Mesa E, Herrera JA, Urgal A, Lazarraga C, Benitez MJ, Gomez C. Temporal trends of latency period and perinatal survival after very early preterm premature rupture of fetal membranes. *Arch Gynecol Obstet.* 2012;286(2): 347-52.

9. Manuck TA, Eller AG, Esplin MS, Stoddard GJ, Varner MW, Silver RM. Outcomes of expectantly managed preterm premature rupture of membranes occurring before 24 weeks of gestation. *Obstet Gynecol.* 2009;114(1):29–37.

10. Al Riyami N, Al-Ruheili I, Al-Shezaw F, Al-Khabori M. Extreme preterm premature rupture of membranes: risk factors and feto maternal outcomes. *Oman Med J.* 2013;28(2):108–111.

11. Melamed N, Hadar E, Ben-Haroush A, Kaplan B,Yogev Y. Factors affecting the duration of the latency period in preterm premature rupture of membranes. *Matern Fetal and Neonatal Med.* 2009;22(11):1051–1056.

12. Jain VD, Sciscione A. Considerations in membrane resealing after preterm PROM. *Clin Obstet Gynecol.* 2011;54(2):351–357.

13. French JI, McGregor JA. The pathobiology of premature rupture of membranes. *Semin Perinatol.*1996;20(5): 344–368.

14. Sciscione AC, Manley JS, Pollock M, et al. Intracervical fibrin sealants: a potential treatment for early preterm premature rupture of the membranes. Am J Obstet Gynecol. 2001;184(3):368–373.

15. O'Brien JM, Barton JR, Milligan DA. An aggressive interventional protocol for early midtrimester premature rupture of the membranes using gelatin sponge for cervical plugging. *Am J Obstet Gynecol.* 2002;187(5):1143–1146.

16. Reddy UM, Shah SS, Nemiroff RL, et al. In vitro sealing of punctured fetal membranes: potential treatment for midtrimester premature rupture of membranes. *Am J Obstet Gynecol.* 2001;185(5):1090–1093.

17. Porat S, Amsalem H, Shah PS, Murphy KE. Transabdominal amnioinfusion for preterm premature rupture of membranes: a systematic review and metaanalysis of randomized and observational studies. *Am J Obstet Gynecol.* 2012;207(5): 393.e1–11.

18. Tyson JE, Parikh NA, Langer J, Green C, Higgins RD; National Institute of Child Health and Human Development Neonatal Research Network. Intensive care for extreme prematurity—moving beyond gestational age. *N Engl J Med.* 2008;358(16):1672–1681.

19. Borgida AF, Mills AA, Feldman DM, Rodis JF, Egan JF. Outcome of pregnancies complicated by rupture of membranes after genetic amniocentesis. *Am J Obstet Gynecol.* 2000;183(4):937–939.

20 . Beck V, Lewi P, Gucciardo L, Devlieger R. Preterm prelabor rupture of membranes and fetal survival after minimally invasive fetal surgery: a systematic review of the literature. *Fetal Diagn Ther.* 2012;31(1):1–9.

21. Carlo WA, McDonald SA, Fanaroff AA, et al. Eunice Kennedy Shriver National Institute of Child Health and Neonatal Research Network. Association of antenatal corticosteroids with mortality and neurodevelopmental outcomes among infants born at 22 to 25 weeks' gestation. *JAMA.* 2011;306(21):2348–2358.

22. Society for Maternal-Fetal Medicine Publications Committee, with assistance of Vincenzo Berghella. Progesterone and preterm birth prevention: translating clinical trials data into clinical practice. *Am J Obstet Gynecol.* 2012;206(5):376–386.

vitaPearl™

Complete prenatal in one tiny pearl

40% MORE FOLIC ACID than the leading prescription prenatal vitamin.

Request samples from your sales representative or online at www.vitaMedMDRx.com/sample

Unique, proprietary combination featuring

FOLMAX™

1.4 mg of folic acid as FOLMAX
Proprietary, immediate and modified release folic acid

pur-DHA

200 mg of DHA as pur-DHA
Patented, advanced supercritical CO_2 extraction and purification process

FePlus

30 mg of iron as FePlus
Proprietary, blended chelate containing iron

Plus key vitamins and minerals

Gluten, Lactose, and Sugar-Free

www.vitaMedMDRx.com

vitaMedMD, vitaPearl, FOLMAX, FePlus, and pur-DHA are trademarks of TherapeuticsMD.

© 2014 TherapeuticsMD®

vitaMedMD®

VITP-0031V.C 9/14

PATIENT HANDOUT

What is PROM?

Society for Maternal-Fetal Medicine

For the Society for Maternal-Fetal Medicine (SMFM) with the assistance of Andrea Edlow, MD, MSc, of Tufts Medical Center Maternal-Fetal Medicine, and Stephen Bacak, DO, MPH, of University of Rochester Maternal-Fetal Medicine.

What is Periviable Premature Rupture of Membranes (PROM)?

Premature rupture of membranes (PROM) occurs when there is a rupture in the sac that contains the baby and the amniotic fluid, prior to the onset of labor. This event is commonly referred to as "breaking the water." "Viable" refers to the age at which it is possible for the baby to survive outside the mother's body. The Society for Maternal-Fetal Medicine (SMFM) defines periviable PROM as rupture of membranes that occurs between 20 0/7 and 25 6/7 weeks' gestation. Fewer than 1% of pregnancies are affected by this complication, but the consequences for both the mother and the baby can be devastating.

How long can a woman stay pregnant after PROM occurs?

The amount of time a woman stays pregnant after PROM is called the "latency period." This period varies significantly from person to person. Usually, the earlier in the pregnancy that PROM occurs, the longer the latency period. When periviable PROM occurs, the average latency period ranges from 6 to 39 days.

Many women wonder if the rupture can heal on its own. Resealing of the sac may occur in as many as 8% of pregnancies. This is less common if the sac ruptures on its own, and more common if PROM occurs as a result of a procedure such as amniocentesis. Currently, there is very little information available about pregnancy outcomes in women with PROM when the sac reseals.

What are the risks to mother and baby when periviable PROM occurs?

The most common complication of periviable PROM is infection affecting both mother and baby. There is a high rate of significant illness or death of the baby in pregnancies complicated by periviable PROM. Although approximately 50% of babies will be born alive after periviable PROM, the survival of the baby to discharge from the hospital is only 26%. The baby may die in utero ("stillbirth") due to compression of the umbilical cord from the low level of amniotic fluid, or if the cord passes out of the cervix into the vagina and is compressed ("cord prolapse").

After the baby is born, the most common complications are usually due to extreme prematurity, and not necessarily to PROM itself. These include breathing problems, severe infection (sepsis), and bleeding in the brain. Other complications are due to the lack of fluid around the baby, including undeveloped or underdeveloped lungs, and compression of the limbs and face, which can result in contractures or flattened facial features. If the lungs are unable to fully develop due to the lack of fluid (also called pulmonary hypoplasia), the baby is at higher risk of death after delivery. There is little information about long-term developmental outcomes in children born after periviable PROM. The best available study shows that nearly 52% of these children have mild or severe cerebral palsy, poor performance on cognitive and motor testing, or death.

It is also important to consider that periviable PROM poses a significant risk to the mother. Intrauterine infection is already present at the time of PROM in many women, and serious infection occurs in up to 54% of pregnancies complicated by periviable PROM. This infection may spread from the uterus to the bloodstream (sepsis) and even to other organs, which can in rare circumstances result in maternal death or other severe complications. If an infection develops, delivery is indicated and the woman can no longer stay pregnant. Another common complication that may require delivery is placental separation (also

called placental abruption). Women with PROM are also at increased risk of cesarean delivery and blood clots (due to inactivity). It may be helpful to consult with a high-risk obstetrician and a neonatologist to better understand these risks, if such specialists are available.

What are risk factors for having periviable PROM and how can these risk factors impact outcomes?

Risk factors for periviable PROM include infection in the uterus, history of premature cervical shortening or dilation, stitch in the cervix (cerclage), bleeding in pregnancy, twins or triplets, smoking, or a prior pregnancy with PROM, and preterm labor. Amniocentesis and fetal surgery during pregnancy are also risk factors.

What are the options for managing pregnancies complicated by periviable PROM?

In general there are three management options when periviable PROM occurs:

1) Terminating the pregnancy (depending on state rules regarding viability).
2) Delivery if medically indicated by either mother's or baby's status.
3) Continuing the pregnancy (also called "expectant management").

The primary goals of expectant management are to prolong pregnancy and improve the baby's outcome, while limiting maternal risk. Women are eligible for expectant management if there is no evidence of infection, placental separation, heavy bleeding, or active labor. Steroid injections between 22 and 25 weeks of pregnancy may help to mature the baby's lungs and decrease other complications of prematurity, and may improve the baby's outcome. Maternal steroid injections are not recommended prior to 22 weeks. Administering magnesium sulfate during delivery before 32 weeks' gestation may decrease the rate of cerebral palsy and other long-term neurologic complications for the baby, but magnesium should only be given if delivery in the near future is likely and the fetus is viable. The use of magnesium sulfate under 24 weeks remains controversial. The risks and benefits of steroids, magnesium sulfate, antibiotics, and tocolytics should be discussed with each patient's unique clinical situation in mind.

Hospitalization of the mother to allow for close observation of the mother and baby is usually initiated at 23 to 24 weeks. Delivery is recommended if there is suspicion of maternal infection or illness, regardless of the weeks of pregnancy. After 23 to 24 weeks, if there is a suspicion that the baby's condition is worsening based on monitoring, delivery is recommended.

There is no accepted standard treatment to reseal the membranes in the setting of periviable PROM, although certain sealants to patch the tears and allow for fluid re-accumulation have been tested. Injection of fluid back into the sac via a needle that travels through the maternal abdomen into the amniotic sac has also been reported. There is currently not enough information to recommend either of these experimental treatments, which also carry risk. SMFM does not suggest their use unless the patient is in a research study.

What is the risk in future pregnancies?

Patients with a history of periviable PROM are at increased risk of recurrent early rupture of membranes and preterm birth in a subsequent pregnancy. Maternal smoking is a modifiable risk factor for periviable PROM. Women whose periviable PROM is thought to be due to preterm cervical shortening, softening, or dilation before contractions occur (also called cervical insufficiency) may have a decreased risk of recurrence if a stitch is placed in the cervix (cerclage) in future pregnancies. If cervical insufficiency is not the suspected cause of the prior periviable PROM, patients should be offered progesterone injections starting at 16 weeks, with repeated evaluations of cervical length by ultrasound.

COG **To download a PDF of this patient education handout, go to wwww.contemporaryobgyn.net/periviablePROM.pdf**

LAURIE J. MCKENZIE, MD
SECTION EDITOR

Is HPV testing ready for 'prime' time in cervical cancer detection?

Two experts discuss whether the cobas test can replace the Pap.

PRO

Primary HPV testing is a potentially exciting new approach to cervical cancer screening

Sarah Feldman, MD, MPH

On April 24, the United States Food and Drug Administration (FDA) approved the cobas human papillomavirus (HPV) DNA test for use as primary cervical cancer screening among women aged 25 years and older. This is the first time that an HPV test has been approved in the United States for use independent of a Pap test, although there are 4 FDA-approved tests for use as a reflex (ie, after an abnormal Pap test) or as a cotest (at the same time as a Pap test).[1]

The FDA approval is limited to the cobas test within the screening framework presented to them, and the agency stated that it is the only test that is safe and effective as an alternative to cytology testing. This means that the FDA does not recommend the cobas test but has indicated that it is safe and no worse than the standard of care, ie, cytology/Pap screening or cotesting after age 30. National guideline committees so far have not issued recommendations about how to use the test, and we do not yet know whether the data presented to the FDA concerning the cobas test can be extrapolated to other HPV tests (which may not have been as rigorously studied), nor do we know the costs and benefits of different screening alternatives in different settings.

So what is known about primary HPV screening? Several prospective European studies have shown the improved sensitivity of HPV as compared to Pap in detecting high-grade dysplasia earlier, with improved long-term detection of cancer, although increased rates of colposcopy were noted, as compared to the use of cytology alone for primary screening.[2]

The recent FDA approval is based on a well-designed prospective study set in multiple US clinics (known as the ATHENA trial, funded by ROCHE and studying the cobas HPV test and ThinPrep cytology) and comparison of 4 screening strategies in women 25 and older who were managed under a specific study protocol.[3] Only 3 years of data are available to date, and they

continued on **PAGE 42**

CON

More data are needed before the HPV test can stand alone

Aparna Kamat, MD

The United States Food and Drug Administration (FDA) recently approved a DNA-based human papillomavirus (HPV) test as a primary screening option for cervical cancer in women 25 years and older. The cobas HPV test provides high-risk pooled HPV DNA results and individual detection of HPV 16 and HPV 18, both responsible for about 70% of invasive cervical cancer. While the cobas test is currently recommended for use alongside the traditional Pap smear, the FDA's new approval permits the HPV test to be used on its own as a screening tool.

Current guidelines based on recommendations by the American Cancer Society and the US Preventive Services Task Force recommend that doctors screen women ages 21 to 65 every 3 years using a Pap smear.[1] Alternatively, the groups recommend a screening procedure called "cotesting," which combines the Pap smear and HPV testing for screening of women ages 30 to 65 for cervical cancer every 5 years. With the newly approved algorithm, women would be screened using the cobas HPV test. Those who test positive for HPV 16 and HPV 18 would be triaged directly to colposcopy and directed biopsies and only those who were positive for the other 14 HPV types would undergo cytology. Patients who are HPV-negative would undergo routine screening with further DNA testing, thus eliminating the Pap smear in the majority of cases.

While current screening guidelines remain unchanged, patients and physicians will now have the ability to choose the cobas HPV test over current screening methods. I believe that this will add confusion to an already complicated screening process, may result in unnecessary procedures in women between ages 25 and 30, and may miss detection of non-HPV cervical cancers.

These recommendations were largely based on the results of the ATHENA trial that tested 47,000 women and compared HPV testing to cytology as a screening option.[2] The trial has several weaknesses. First, CIN2/3 was used as a surrogate for invasive cervical cancer in the trial. Based on different studies, the rate of spontaneous regression of these lesions varies from 6% to 50%. Thus, using CIN2/3 as a surrogate for invasive cervical cancer is likely overestimating the rate of detection. In addition, the quality of the cytology used in the trial varied widely with below-average abnormal cytology rates reported among the patients tested. Sensitivity for >CIN3 was only 58% in the trial,[3] whereas the reported rate in our laboratory and others for significant cervical neoplastic disease approaches 93%; this is a quality control issue that was not addressed in the trial. More importantly, about 4% of cervical cancer cases are not HPV-related at all and about 10% of patients with invasive cervical cancer will test negative for HPV.[3] These data underscore the importance of using HPV typing as an adjunct and not as a replacement for screening cytology.

In fact, data from Kaiser Permanente show that 5-year cumulative cervical cancer incidence is lowest with conventional Pap and HPV cotesting as compared to either method used alone.[4] Using data from the largest laboratory pathology database in the United States, Quest Diagnostics issued a statement to the FDA that primary screening with HPV testing alone could miss 13.5% of cervical cancers that would normally be identified with cotesting. Finally, the FDA approval allows HPV testing in women ages 25 to 30, a group not covered under current screening guidelines. There are currently no data to support routine HPV testing in women in this age group, given their high rate of spontaneous clearance of the virus.

In addition, more women, especially in this age group, are likely to be referred to colposcopy and for unnecessary biopsies. The recent FDA approval will allow direct marketing of the cobas HPV test to patients and physicians as a screening test, a move that may be premature given the limited data concerning its efficacy as a primary screening tool for cervical cancer.

In summary, while HPV typing plays a key role in screening women for invasive cervical cancer, I believe longer follow-up and more data are needed before replacing the current screening guidelines with the cobas HPV test as a stand-alone screening tool for cervical cancer. COG

continued on **PAGE 42**

PRO CONTINUED

have not yet been published (although they were presented to the FDA). Of note, current guidelines in women older than age 30 recommend cotesting at 5-year intervals; thus the comparison to standard of care is not yet available.

So far, the data presented show a notably improved rate of detection of high-grade dysplasia among women aged 25–30, especially those who test positive for HPV 16/18.[4] Cytology is a particularly poor test in this age group, although HPV is particularly common, and the best balance of testing and increasing rates of colposcopy with actual cancer prevention is not yet clear. More data need to be accrued to understand the relative costs and benefits. The relative benefits for women age 30 and older are less clear, given that dysplasia is less common and cytology or cotesting at currently recommended intervals are reliable approaches in this age group.

Summary

Promising data from a well-designed study in US women, with limited long-term data, a very specific set of comparison algorithms, and using only one type of HPV test suggest that use of primary HPV testing for some women (especially in the 25–30 age group) may enable us to detect high-grade dysplasia earlier and more effectively than Pap testing. This might allow us to identify and treat precancers sooner, and thus perhaps focus our resources on greater surveillance of higher-risk women or screening of women who were previously unscreened.

It is important to note, however, that improved detection of precancerous changes of the cervix may not automatically translate into fewer cancers, as the ability to prevent cancer is related not just to the screening test used, but also to the management and resources used to intervene to prevent cancer. As greater numbers of young women receive HPV vaccination before the onset of sexual activity, a test that could better differentiate women at higher risk of developing cervical cancer may enable us to better focus our resources for cervical cancer prevention on those at higher risk. So, although we need longer-term data, as well as data about other tests in both vaccinated and unvaccinated women, HPV testing is promising and likely to have a role in the future in cervical cancer screening in the United States. COG

REFERENCES

1. U.S. Food and Drug Administration. FDA News Release: FDA approves first human papillomavirus test for primary cervical cancer screening. http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm394773.htm. Accessed October 23, 2014.

2. Ronco G, Dillner J, Elfstrom KM, et al. Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials. *Lancet.* 2014;383(9916):524–532.

3. Wright TC, Stoler MH, Behrens CM et al. The ATHENA human papillomavirus study: design, methods, and baseline results. *Am J Obstet Gynecol.* 2012;206(1):46,e1-46.e11.

4. Roche Molecular Systems, Inc. Cobas HPV Test Medical Devices Advisory Committee Microbiology Panel Meeting: Sponsor Executive Summary. http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/medicaldevices/medicaldevicesadvisorycommittee/microbiologydevicespanel/ucm388565.pdf. Accessed July 1, 2014.

DR. FELDMAN is Associate Professor of Obstetrics, Gynecology and Reproductive Biology at Harvard Medical School, Director of Ambulatory Gynecologic Oncology, and Director of the Center for Pre-Invasive Disease of the Lower Genital Tract, Brigham and Women's Hospital/Dana Farber Cancer Institute, Boston, Massachusetts.

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

CON CONTINUED

REFERENCES

1. Saslow D, Solomon D, Lawson HW, et al. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. *Am J Clin Pathol.* 2012;137(4):516-542.

2. Stoler MH, Wright TC Jr, Sharma A, et al. High-risk human papillomavirus testing in women with ASC-US cytology.: results from the ATHENA HPV study. *Am J Clin Pathol.* 2011;135(3):468–475.

3. Park Y, Lee E, Choi J, Jeong S, Kim HS. Comparison of the Abbott RealTime high-risk human papillomavirus (HPV), Roche Cobas HPV, and Hybrid Capture 2 assays to direct sequencing and genotyping of HPV DNA. *J Clin Microbiol.* 2012;50(7):2359–2365.

4. Katki HA, Kinney WK, Fetterman B, et al. Cervical cancer risk for women undergoing concurrent testing for human papillomavirus and cervical cytology: a population-based study in routine clinical practice. *Lancet Oncol.* 2011;12(7):663–672.

DR. KAMAT is the Director of Gynecologic Oncology in the Department of Obstetrics and Gynecology at the Methodist Hospital, Houston, Texas.

She reports receiving service fees from Myriad Genetics.

DR. MCKENZIE is Director of Oncofertility, Houston IVF, and Director, Houston Oncofertility Preservation and Education (H.O.P.E.), Texas.

More consistent delivery of prescibed dose helps you achieve more predictable results

FIRST®
UNIT-OF-USE PRESCRIPTION COMPOUNDING KITS

Make it easier for your patients to accurately follow your prescription.

Specify FIRST®- Kits, allowing no substitutions, and our innovative Kits will do the rest.

- Each Kit contains everything needed to precisely and accurately compound one prescription from one prescriber for one patient
- Pre-weighed and pre-measured components support consistent, accurate dosage no matter how long the treatment period
- More convenient for patient to fill and eases third-party reimbursement

FIRST®-PROGESTERONE VGS VAGINAL SUPPOSITORY USP COMPOUNDING KIT

Progesterone VGS 25 mg	NDC # 65628-060-01
Progesterone VGS 50 mg	NDC # 65628-061-01
Progesterone VGS 100 mg	NDC # 65628-062-01
Progesterone VGS 200 mg	NDC # 65628-063-01
Progesterone VGS 400 mg	NDC # 65628-064-01

To learn more, call
1-800-461-7449
www.cutispharma.com

BY **BRIAN A. LEVINE, MD, MS,**
AND **DAN GOLDSCHLAG, MD, FACOG**

Cell-free DNA and oncology

cfDNA gives insight into the pathogenesis of serious disease and early information about benign conditions

In September's installment of Tech Tools, *Noninvasive prenatal testing: A new standard of care?* we discussed the utility of cell-free fetal DNA in prenatal diagnosis and the capabilities of the 4 commercially available noninvasive prenatal testing technologies. In this continuation of our cell-free DNA series, we discuss the role of cell-free nucleic acids as noninvasive biomarkers in oncology.

Colorectal screening

In August 2014, the FDA approved Cologuard, the first stool-based colorectal screening test. Cologuard assesses the presence of colorectal neoplasia-associated DNA markers and occult hemoglobin in stool.[1] The test takes advantage of the fact that the gastrointestinal tract is constantly regenerating and shedding epithelial cells. As these cells are sloughed, they release their DNA and are removed through the stool stream, making them an ideal noninvasive target.[2]

A recently published study found that the multi-target stool DNA testing (targeting methylation and mutation biomarkers that are associated with cancer and precancer) detected significantly more cancers than the American College of Gastroenterology-recommended fecal immunochemical test (FIT), although there were more false-positive results (Cologuard detected 86.6% true negatives for a false-positive rate of 13.4%, whereas FIT detected 94.9% of true-negative patients, for a false-positive rate of 5.1%).[3] While many may be concerned about this relatively high risk of false-positives, others may argue that it is more desirable for a screening test to catch as many affected cases as possible (ie, to have high sensitivity) even if it means that some unaffected individuals may be misclassified as at-risk (lower specificity).

> Cell-free DNA is sometimes referred to as **a "liquid biopsy"** because it can be a serum surrogate for tumor sampling.

The US Preventive Services Task Force (USPSTF) recommends screening for colorectal cancer using fecal occult blood testing, sigmoidoscopy, or colonoscopy in adults, beginning at age 50 and continuing until age 75.[4] According to the Centers for Disease Control and Prevention (CDC), if everyone age 50 years or older had regular screening tests as recommended, at least 60% of colorectal cancer deaths could be avoided.[1] However, barriers to adherence with these screening recommendations include lack of access to a provider, the cumbersome nature of the sigmoidoscopy/colonoscopy's required bowel prep, and incomplete adherence to the pretest dietary restrictions. Cologuard eliminates all those barriers: it only requires the patient to collect a stool sample at home and mail it to the Exact Sciences laboratory.

'Liquid biopsy'

While mailing a stool sample is a prime example of noninvasive testing, blood-based cancer screening and monitoring takes this even further. Quite frequently cell-free DNA is referred to as a "liquid biopsy" because it can be a serum surrogate for tumor sampling. As opposed to cell-free fetal DNA, the source of cell-free tumor DNA in cancer patients is unclear. It has been hypothesized that a large proportion originates from malignant cells that are constantly going through growth/remodeling/

One of the most **promising uses of cell-free DNA** is in the identification of early-stage epithelial ovarian cancer.

apoptosis/necrosis and subsequently releasing digested or possibly metastatic/pathogenic nucleic acids into the blood.[5] Although its etiology is not clear, we have known for more than 30 years that circulating serum cell-free DNA concentration is markedly elevated in malignancy (nearly 4 times), and moderately elevated in benign disease, as compared to controls.[6]

In May 2012 the USPSTF updated its position and recommended against prostate-specific antigen (PSA)-based screening for prostate cancer, stating that there is inadequate evidence of the benefit of PSA screening and early treatment.[7] While it may seem that serum prostate cancer screening is a thing of the past, it is important to recognize that prostate cancer is the most commonly diagnosed non-skin cancer in men in the United States, with a lifetime risk for diagnosis currently estimated at 15.9%.[5]

When the plasma-based DNA integrity assay, which measures cell-free DNA of a length characteristic of that shed by necrotic malignant cells, was employed as a screening tool for the detection of prostate cancer, it achieved a sensitivity of nearly 70% while maintaining an overall specificity of 68.2% to 92%, which is far superior to the PSA 60%–70% range of specificity.[8]

The advent of better tests using new technology in molecular medicine may result in the revision of current screening guidelines.

Ovarian cancer detection

One of the most promising uses of cell-free DNA is in the identification of early-stage epithelial ovarian cancer, the deadliest of gynecologic cancers, with a lifetime risk of approximately 1 in 80. A recent study demonstrated that after choosing a handful of candidate genes that are associated with gynecologic malignancies and have a high frequency of methylation, a PCR-based assay achieved a sensitivity of 85.3% and a specificity of 90.5% for stage I epithelial ovarian cancer.[9] This is much higher than the sensitivity and specificity rates of a single CA125 (56.1% sensitivity and 64.15% specificity).[9]

Furthermore, cell-free DNA has been shown to be a potential marker of not only tumor treatment response, but also prognosis. A paper published in October 2014 reported a significant and independent association between elevated cell-free DNA and outcome in multiresistant ovarian cancer patients undergoing last-line treatment with a specific chemotherapy regimen.[10]

It seems undeniable that cell-free DNA testing will play an important role in the future of medicine: The technology is becoming increasingly affordable and constantly improving in both sensitivity and specificity. Regardless of your practice area, it is only a matter of time until you will be counseling your patients about the benefits of cell-free DNA testing and its ability to offer unique insight into the pathogenesis of serious disease as well as critical early information about benign conditions. COG

DR. LEVINE is Clinical Fellow, Reproductive Endocrinology & Infertility, Ronald O. Perelman and Claudia Cohen Center for Reproductive Medicine, Weill Cornell Medical College, New York.

DR. GOLDSCHLAG is Assistant Professor of Clinical Obstetrics and Gynecology and Assistant Professor of Clinical Reproductive Medicine, Ronald O. Perelman and Claudia Cohen Center for Reproductive Medicine, Weill Cornell Medical College, New York.

REFERENCES

1. FDA approves first non-invasive DNA screening test for colorectal cancer. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm409021.htm

2. Ahlquist DA, Skoletsky JE, Boynton KA et al. Colorectal cancer screening by detection of altered human DNA in stool: feasibility of a multitarget assay panel. *Gastroenterology.* 2000;119(5):1219-1227.

3. Imperiale TF, Ransohoff DF, Itzkowitz SH, et al. Multitarget stool DNA testing for colorectal-cancer screening. *N Engl J Med.* 2014;370(14):1987-1997.

4. U.S. Preventive Services Task Force-Colorectal Cancer: Screening http://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/colorectal-cancer-screening

5. Stroun M, Maurice P, Vasioukhin V et al. The origin and mechanism of circulating DNA. *Ann N Y Acad Sci.* 2000;906:161-168.

6. Shapiro B, Chakrabarty M, Cohn EM, Leon SA. Determination of circulating DNA levels in patients with benign or malignant gastrointestinal disease. *Cancer.* 1983;51(11):2116-2120.

7. U.S. Preventive Services Task Force-Prostate Cancer: Screening http://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/prostate-cancer-screening

8. Hanley R, Rieger-Christ KM, Canes D et al. DNA integrity assay: a plasma-based screening tool for the detection of prostate cancer. *Clin Cancer Res.* 2006;12(15):4569-4574.

9. Zhang Q, Hu G, Yang Q, Dong R, Xie X, Ma D, Shen K, Kong B. A multiplex methylation-specific PCR assay for the detection of early-stage ovarian cancer using cell-free serum DNA. *Gynecol Oncol.* 2013;130(1):132-139.

10. Steffensen KD, Madsen CV, Andersen RF et al. Prognostic importance of cell-free DNA in chemotherapy resistant ovarian cancer treated with bevacizumab. *Eur J Cancer.* 2014;50(15):2611-8. doi: 10.1016/j.ejca.2014.06.022. Epub 2014 Jul 30.

Pediatricians on adolescent contraception

The AAP weighs in on best contraceptives for teens

The American Academy of Pediatrics (AAP) Committee on Adolescence issued a new policy statement in September that recommends the safest and most effective contraceptive options for teenagers.

The policy statement, an update of the AAP's 2007 statement, advises pediatricians counseling adolescents to recommend single-rod progestin implants and intrauterine devices (IUDs) as the first and second-best birth control options, followed, in order, by progestin-only injections every 13 to 15 weeks; combined oral contraceptive pills (COCs); and condoms, the most frequently used birth control method in this age group.

The recommendation for the first-line use of long-acting reversible contraception (LARC) mirrors the recommendation by the American College of Obstetricians and Gynecologists (ACOG) published in 2012.

LARC has the advantage of equal or almost equal efficacy (failure rate of less than 1%) with both typical use and perfect use; injection, COCs, and condoms are less effective as typically used. LARC also has the highest percentages of continued use by women at 1 year after initiation. Both implants and IUDs are considered safe for adolescent girls. Combined oral contraceptive pills and condoms aren't the best options because teenagers don't always use them consistently.

Abstinence, the only completely sure way to prevent pregnancy and sexually transmitted infections, remains an important part of contraceptive counseling, and pediatricians should encourage adolescents to postpone sex until they're ready, the statement notes. Data indicate that adherence is low, however.

A statement from the AAP recommends LARCs but also counsels pediatricians **to encourage teens to postpone sex** until they're ready.

The policy statement—which also includes advice on contraception counseling for obese teenagers and adolescents with disabilities and complex medical conditions (eg, chronic disease, HIV, solid organ transplants)—is supported by an accompanying technical report.

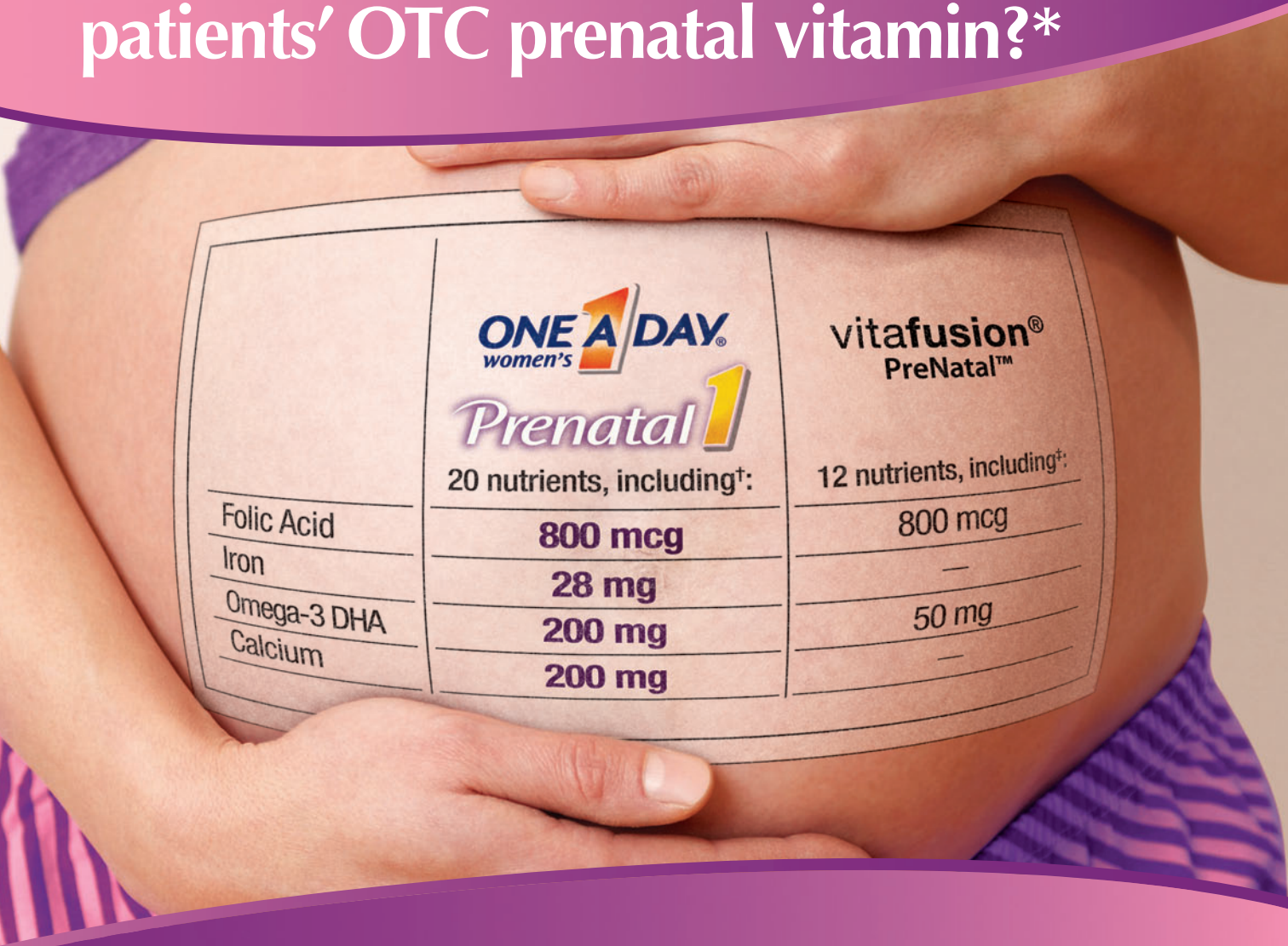
In an October 12 session at the AAP National Conference and Exhibition in San Diego titled "What's new in adolescent reproductive health: long-acting reversible contraception and Pap smear guidelines," Paula J. Adams Hillard, MD, professor, Department of Obstetrics and Gynecology, Stanford University School of Medicine, California, and a member of the *Contemporary OB/GYN* Editorial Board, updated practicing pediatricians on the effectiveness, safety, mechanism of action, and indications for the use of LARC in adolescent girls.

"Talk to teens about the LARC options as the top tier of methods," she urged. "These are the most effective methods, they are safe, and very easy to use."

Additional recommendations by the AAP on contraception use in adolescents urge clinicians to get more involved in educating adolescents about contraception use and, in particular, to recommend the use of LARCs as the first-line contraceptive choice.

Dr. Hillard also discussed the barriers to clinicians and adolescents regarding use of LARCs. The main barrier for clinicians is the lack of up-to-date information on the safety of intrauterine devices for adolescent girls who have never been pregnant. For teens, the biggest barrier is that they do not know about LARCs as a contraceptive option, so they also do not have any information on their efficacy and safety. COG

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



One A Day® Women's Prenatal 1 contains folic acid, calcium, iron, and has omega-3 DHA — all recommended by ACOG during pregnancy[1]

- Provides key nutrients for women before, during, and after pregnancy
- Ensure your patients aren't missing key nutrients they may need

Learn more at oneadaypro.com.

*Among leading brands.
†20 nutrients per One A Day Women's Prenatal 1 label. Serving size is 1 softgel daily, with food.
‡12 nutrients per vita**fusion** PreNatal label. Serving size is 2 gummy vitamins daily.
‖Contains 200 mg of calcium compared to 300 mg in One A Day Women's Prenatal 2-pill formula.

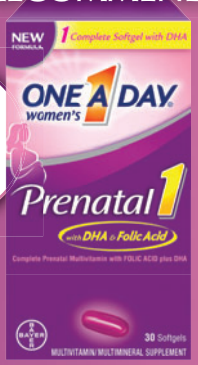
vita**fusion** is a registered trademark of Church & Dwight Co., Inc.

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

© 2014 Bayer HealthCare LLC March 2014 53135-PP-OAD-PRNTL-US-0039

RECOMMEND

#1 OTC prenatal vitamin brand*



BAYER

A BRAND WOMEN TRUST

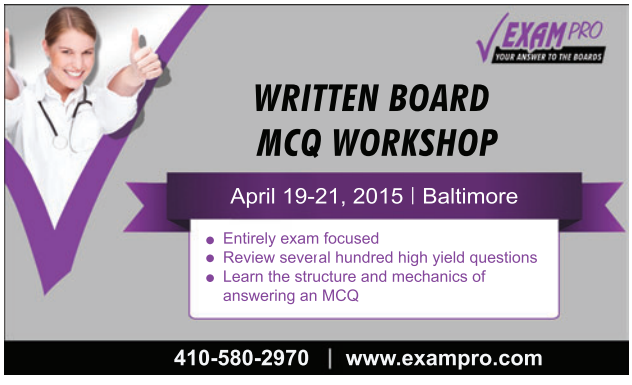
NEW formula‖ — one complete softgel

FEMININE HYGIENE

- Offers 12 hours of leak-free protection.
- Is clean, easy-to-use and comfortable.
- Empowers women with new cycle knowledge.
- Is better for women's health and the environment.

divacup.com

SEMINARS



Wonder what these are?

COMPANY NAME Search

Go to products.modernmedicine.com and enter names of companies with products and services you need.

marketers, find out more at:
advanstar.info/searchbar

Contemporary OB/GYN
Expert Advice for Today's Ob/Gyn

Search for the company name you see in each of the ads in this section for **FREE INFORMATION!**

CONTINUING MEDICAL EDUCATION

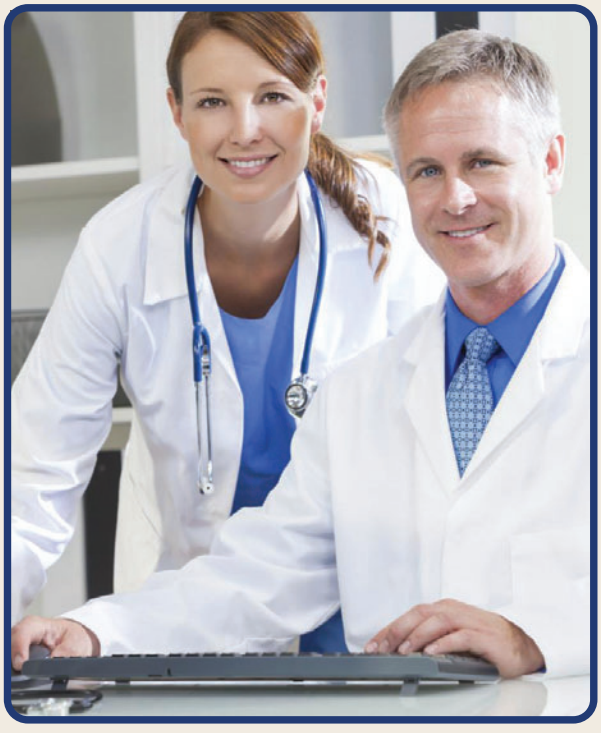
NERVOUS About the MOC Year 6 Written Exam? DON'T BE!

RAPID RECERT™ Has You Covered

- **Compendium Review**
  - Our professionally prepared 300 page summary of ACOG's 2000 page compendium
- **QuizWhiz**
  - Unlimited online access to Rapid Recert's high-yield Board-level questions
- **Reading List Highlights**
  - Summaries of the board's best assigned articles

New Exclusive

- Up to **100 CME's** are now available for less than $6.00 a credit hour



Don't Listen To Us, Listen To Our Subscribers:

"…this is the first time I ever completed an exam early. These resources condensed the material into a manageable volume for someone with a busy practice. I felt totally prepared and did great on the exam." DC

"I just wanted to pass along that the combination of the QuizWhiz and Compendium Review was excellent. I could go on, but this was well worth the money." RP

"I used your service to prepare for the OB recertification exam. Your summaries are complete and concise. The practice quizzes are a great tool....Thanks." MP

RAPID RECERT
THE RECERTIFICATION EXPERTS™

rapidrecert.com **1-877-273-2378**

Still Haven't Taken the MOC Written Exam?

IT'S NOT TOO LATE!

Rapid Recert™ has you covered

Look no further than our suite of AMAZING products:

Compendium Review
- Our professionally prepared summaries of ACOG's 2000 page Compendium

QuizWhiz
- Unlimited online access to Rapid Recert's high-yield Board-level questions

Reading List Highlights
- Summaries of the Board's best assigned readings

(Use coupon code "suitedeal" and receive $100 off when you order all three)

rapidrecert.com RAPID RECERT THE RECERTIFICATION EXPERTS™ **1-877-273-2378**

CONTINUING MEDICAL EDUCATION

INCREASE PRACTICE REVENUES
HANDS-ON-CME

AESTHETIC MEDICINE SYMPOSIUM

Scottsdale, Arizona

Learn the Top 5:
- BOTOX®
- FILLERS
- LASERS
- CHEMICAL PEELS
- MEDICAL MICRODERM

Add Additional Classes!
- Business Training

Dec 6-7
Jan 24-25
Mar 7-8

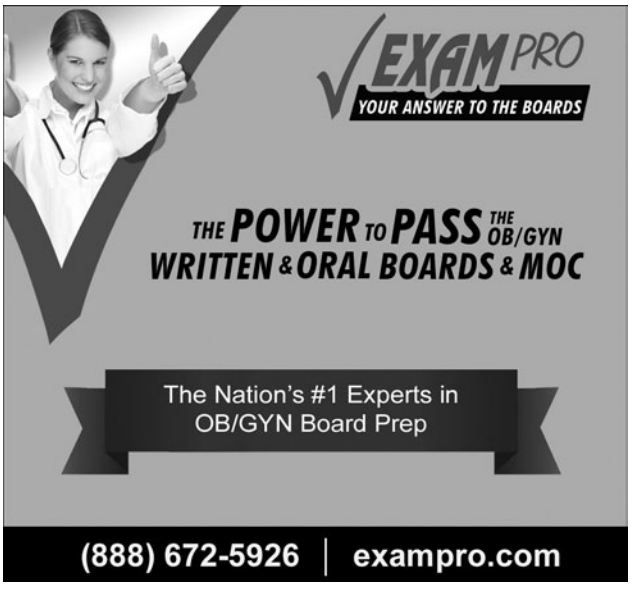
SAVE $1100 Register Today

Medically Supervised Weight Loss
Dec 5 • Jan 23 • Mar 6

IAPAM
INTERNATIONAL ASSOCIATION FOR PHYSICIANS IN AESTHETIC MEDICINE

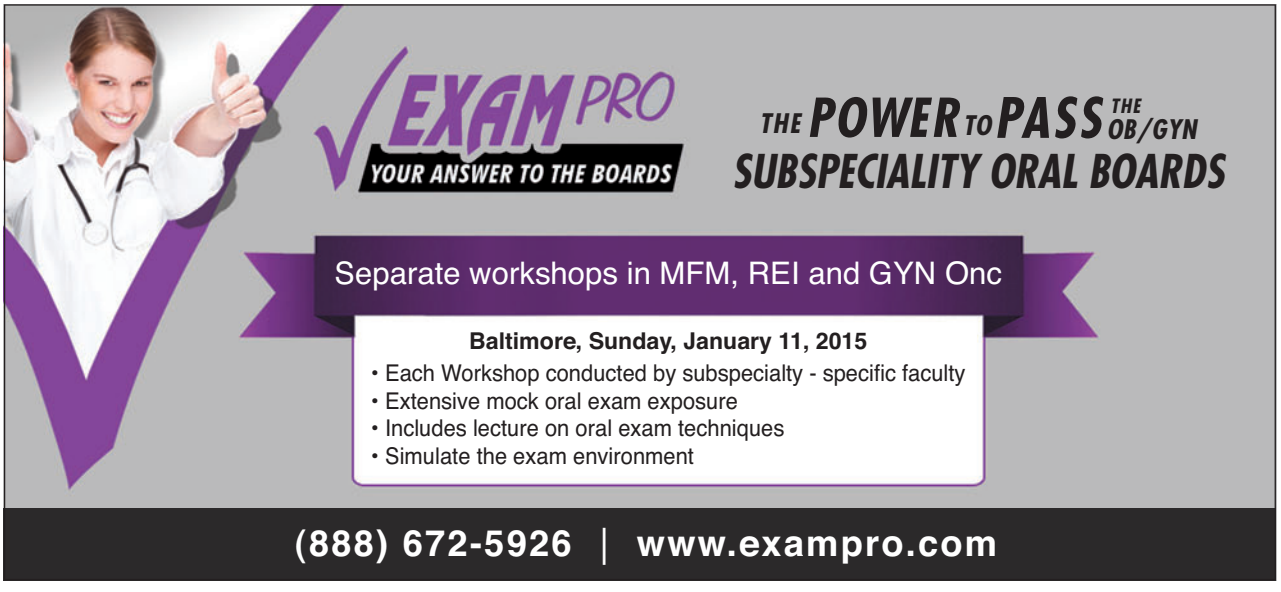
800-219-5108 x704
www.AestheticMedicineSymposium.com
NON-INSURANCE PROCEDURES: THE KEY TO A PROFITABLE PRACTICE

SEMINARS



MARKETPLACE ADVERTISING WORKS FOR YOU !

SEMINARS



FOR PRODUCTS & SERVICES ADVERTISING
Contact: Joan Maley (800) 225-4569 ext. 2722 • jmaley@advanstar.com

MARKETPLACE

SEMINARS

EXAMPRO ADVANCED
THE RESOURCE FOR THE CERTIFIED OB/GYN

Take the
ExamPro Advanced Standard of Care/ MOC Review Course

Don't Let
MOC
Stand in Your Way

- Designed for the MOC Part 3 Exam and all Board Certified OB/GYNs
- Learn recent changes in Standard of Care
- The shortest and only totally MOC-focused course available
- Curriculum Based on Expected Exam-Relevant Information

February 15-17, 2015 • Orlando, Florida

Register at examproadvanced.com or by calling (888) 672-5926

Contemporary OB/GYN
Expert Advice for Today's Ob/Gyn

FOR PRODUCTS & SERVICES ADVERTISING

Contact: Joan Maley

(800) 225-4569 ext. 2722

jmaley@advanstar.com

RECRUITMENT

For Recruitment Advertising, contact: **Joanna Shippoli**
(800) 225-4569 ext. 2615, jshippoli@advanstar.com

NATIONAL

PORTLAND/SEATTLE AREA OBGYN POSITIONS

Two hospital employed obgyn positions 45 minutes to downtown Portland/Seattle associated with 454/135 bed hospitals with Level III NICU and DaVinci Robotics including OB-Laborist programs. 1-4/1-6 call. Excellent salary ($304K) signing and production bonus and benefits. OBGYN Search, 800-831-5475, obgynsrch@aol.com, www.obgynpractices.com

ARKANSAS

SE ARKANSAS LAKE COMMUNITY (VISA WAIVER SITE)

Hospital employed joining one obgyn provider in either full or part time position and optional gyn position in family oriented community with large recreational lake and associated with modern 25 bed critical access hospital with beautiful L/D in low volume practice setting. 1-2 call. J-1 and H1B Visa sponsor. Excellent salary,signing and production bonus and benefits. OBGYN Search, 800-831-5475, obgynsrch@aol.com, www.obgynpractices.com

CALIFORNIA

SOUTHERN CALIFORNIA

Join Well-Established OB-Gyn private Practice
in the Los Angeles area.
College Town 1-5 Call or No Calls Option
Excellent Salary With Benefits New Grads Welcome!

E-mail : jcvck@yahoo.com · Call : 951-220-1478 · Fax : 909-623-5505

FLORIDA

ORLANDO AREA

45 Minutes From The Beach!

Seeking BC/BE OB/GYN physician and Urogynecologist to join 9 physician group

Level 3 hospital ~ No emergency room call
Income potential unlimited

Send CV to e-mail: dgearity@wcorlando.com
or fax: 407-209-3575
Check out our website @ www.wcorlando.com
For more information, please call 407-857-2502 ext. 1404

KENTUCKY

SE KENTUCKY (VISA WAIVER AND NHS SITE)

Hospital employed general obgyn position replacing relocating obgyn and joining one obgyn provider in low volume obgyn position in family oriented community 90 minutes to Lexington and Knoxville associated with a 63 bed hospital. 1-2 call. Excellent salary,signing and production bonus and benefits. J-1 and H1B Visa sponsor and NHS Scholar Loan Repayment Site. OBGYN Search, 800-831-5475, obgynsrch@aol.com, obgynpractices.com

MASSACHUSETTS

Join Harvard Vanguard Medical Associates - an employer of choice !

We are a physician-led non-profit, multispecialty group practice with 20 plus locations in the greater Boston area that is recognized nationally for clinical quality and an innovator in healthcare delivery.

Our collegial practices are seeking dynamic OB/GYN generalists to provide high quality care to our patients. Our full-service Department includes specialists in REI, MFM, MIGS, SPU, Urogynecology, Menopause, and Vulvovaginal disorders. Excellent call schedules. Onsite and remote access to electronic medical records. Strong clinical and administrative practice management support to include nurse practitioners and certified nurse midwives.

Competitive compensation with comprehensive benefits including a 401(k) employer-match contribution. Boston is home to top ranking academic schools, international airport, four-season living, fine arts, multicultural activities, and winning sports teams!

All interested candidates, please send your confidential CV to
Lin Fong, Harvard Vanguard Medical Associates
Email: lin_fong@vmed.org | Fax: 617-559-8255
Mail: 275 Grove Street, Suite 3-300, Newton, MA 02466
Phone: 800-222-4606 | EOE/AA | www.harvardvanguard.org
No third party agency.

MICHIGAN

LAKE HURON PART-TIME OBGYN POSITION

Hospital employed part-time obgyn position working 2-3 days per week with 1-4 call joining two full time obgyn physicians and one part-time obgyn in family oriented Lake Huron community associated with a progressive 60 bed hospital with 400 annual deliveries with modern L/D and DaVinci Robot. $210K (part-time salary), signing and production bonus and full benefits. OBGYN Search, 800-831-5475, obgynsrch@aol.com, www.obgynpractices.com

FOR RECRUITMENT ADVERTISING

Contact

Joanna Shippoli

800.225.4569 ext. 2615

jshippoli@advanstar.com

NEW JERSEY

Southern New Jersey

Seeking an experienced OB/GYN. Hospital-based practice with 1:4 call. Moderate volume with on-call via telephone. The hospital has recently renovated its OB department and has all appropriate equipment (colposcopy, ultrasound, etc.). This three-hospital system has a General Surgery residency, an OB/GYN residency, and other residencies, in addition to third and fourth year medical students. Service area of 370,000. Area is noted for lower cost of living and a variety of attractive housing. Two hours to New York City and less than 35 minutes to historic Philadelphia or the Jersey shoreline. New Jersey is noted for its 130 miles of coastline and white-sand beaches, barrier islands, light houses and the Boardwalk.

Wanda Parker, The HealthField Alliance
866-232-2333 or 203-778-3333
healthfield@mindspring.com

SOUTHERN NEW JERSEY

Employed general obgyn positions joining well established FQHC in Atlantic City area and other southern New Jersey locations associated with a 494 bed Level III NICU hospital with DaVinci Robotics with 1-5 call. Flexible hours. Excellent salary, signing and production bonus, benefits, relocation and loan repayment. OBGYN Search, 800-831-5475, obgynsrch@aol.com, www.obgynpractices.com

NEW MEXICO

Excellent Opportunity in Obstetrics and Gynecology

- Join an established thriving group in the fastest growing city in New Mexico
- 70-90 deliveries per month
- 250-bed hospital with 7 state of the art OB/GYN L&D suites and 16 Postpartum and GYN rooms
- Two dedicated OR suites for C-Sections on L&D floor.
- Level 1 nursery with HUGS infant protection system and 24/7 dedicated respiratory team and anesthesiology.
- All Board Certified OBYN providers. One in three call schedule. Supportive medical staff.

Comprehensive recruitment package may include:

CME allowance, Relocation expense, Medical education debt assistance, Commencement bonus, Major Medical insurance, Dental, Vision, Life insurance, 401K Plan, Profit sharing plan, 4 weeks paid vacation, $325,000.00 starting salary, Partnership in one year, Production bonus, Profit sharing plan.

New office with superb staff. Moderate four season climate, country club and brand new golf course, strong public school system, two colleges in town, Airport with two flights daily to and from Houston.

Contact: Kathleen Callaghan, MD, FACOG at
575-318-3962 (cell) or 575-392-6600
Email: businessoffice@valornet.com

NEW YORK

CENTRAL NEW YORK

Private practice OB/GYN practice looking for an additional ob-gyn to join a busy practice of 3 ob-gyns and a P.A. We are in beautiful Central NY at the foothills of the Adirondack Park. Call will be 1:7. Starting Salary and benefits are competitive and we plan to offer partnership in 1-2 years.

Please email: lbearse@medcareadmin.com
www.medicalarts.com

CONNECT

with qualified leads and career professionals

Post a job today

Medical Economics Careers
www.modernmedicine.com/physician-careers

Joanna Shippoli
RECRUITMENT MARKETING ADVISOR
(800) 225-4569, ext. 2615
jshippoli@advanstar.com

UTAH

Intermountain Healthcare is widely recognized as a leader in transforming healthcare through high quality and sustainable costs. We are seeking BC/BE OB/GYN physicians to practice with our medical groups in American Fork, Logan, Mount Pleasant & Ogden, Utah. Contact Intermountain Healthcare, Physician Recruiting, 800-888-3134. Physicianrecruit@imail.org, http://physicianjobsintermountain.org

Contemporary OB/GYN
Expert Advice for Today's Ob/Gyn

Content Licensing for Every Marketing Strategy

Marketing solutions fit for:
Outdoor | Direct Mail
Print Advertising
Tradeshow/POP Displays
Social Media | Radio & TV

Leverage branded content from *Contemporary OB/GYN* to create a more powerful and sophisticated statement about your product, service, or company in your next marketing campaign. Contact Wright's Media to find out more about how we can customize your acknowledgements and recognitions to enhance your marketing strategies.

For information, call
Wright's Media at 877.652.5295
or visit our website at
www.wrightsmedia.com

CALENDAR

FEBRUARY 2015

2–7: The Society for Maternal-Fetal Medicine 35th Annual Pregnancy Meeting
San Diego, California
https://www.smfm.org/the-pregnancy-meeting

MARCH

4–7: Council on Resident Education in Obstetrics and Gynecology and Association of Professors of Gynecology and Obstetrics
San Antonio, Texas
https://www.apgo.org/meetings/creog-a-apgo-annual-meeting.html

22–25: Society of Gynecologic Surgeons 41st Annual Scientific Meeting
Orlando, Florida
http://www.sgsonline.org/scientific-meeting

25–28: Society for Reproductive Investigation Annual Meeting
San Francisco, California
http://www.sgionline.org/sri-meetings

28–31: Society of Gynecologic Oncology Annual Meeting on Women's Cancer
Chicago, Illinois
https://www.sgo.org/education/annual-meeting-on-womens-cancer/

MAY

2–6: American College of Obstetricians and Gynecologists Annual Clinical Meeting
San Francisco, California
http://www.acog.org/About-ACOG/ACOG-Departments/Annual-Meeting

JUNE

6-10: American Medical Association Annual Meeting
Chicago, Illinois
http://www.ama-assn.org/ama/pub/about-ama/our-people/house-delegates/meeting-dates.page?

9-12: The Society of Obstetricians and Gynaecologists of Canada Annual Clinical and Scientific Conference
Quebec City, Quebec, Canada
http://sogc.org/events/annual-clinical-scientific-conference/

SEPTEMBER

2-5: Society of Laparoendoscopic Surgeons Minimally Invasive Surgery Week / Annual Meeting and Endo Expo
New York City, New York
http://sls.org/mis2015/

17-19: American Gynecological and Obstetrical Society Annual Meeting
Half Moon Bay, California
http://agosonline.org/event-2015-annual-meeting.html

30- OCT 3: North American Menopause Society Annual Meeting
Las Vegas, Nevada
http://www.menopause.org/annual-meetings

OCTOBER

4-9: International Federation of Gynecology and Obstetrics World Congress
Vancouver, British Columbia, Canada
http://figo2015.org/

10-15: International Society of Ultrasound in Obstetrics and Gynecology World Congress
Montreal, Quebec, Canada
http://www.isuog.org/WorldCongress/2015/

13-17: American Urogynecologic Society Annual Scientific Meeting
Seattle, Washington
http://www.augs.org/p/cm/ld/fid=52

17-21: American Society for Reproductive Medicine Annual Meeting
Baltimore, Maryland
http://www.asrm.org/awards/detail.aspx?id=5802

HAVE AN EVENT?

E-MAIL your event to:
solmstead@advanstar.com
Please type "Event" in the subject line.

ADVERTISER INDEX Companies featured in this issue

To obtain additional information about products and services advertised in this issue, use the contact information below.
This index is provided as an additional service. The publisher does not assume any liability for errors or omissions.

PAULA J. ADAMS HILLARD, MD
SECTION EDITOR

SEXUAL AND INTIMATE PARTNER VIOLENCE

The Ray Rice case put domestic violence in the headlines. The prevalence of sexual and intimate partner violence against women in this country is spotlighted by new findings from a Centers for Disease Control and Prevention (CDC) survey of nearly 13,000 adults.

WOMEN

19.3% of women have been raped during their lifetimes

8.8% have been raped by an intimate partner

The majority of the rapes in women (78.7%) occurred when the victims were younger than age 25.

MEN

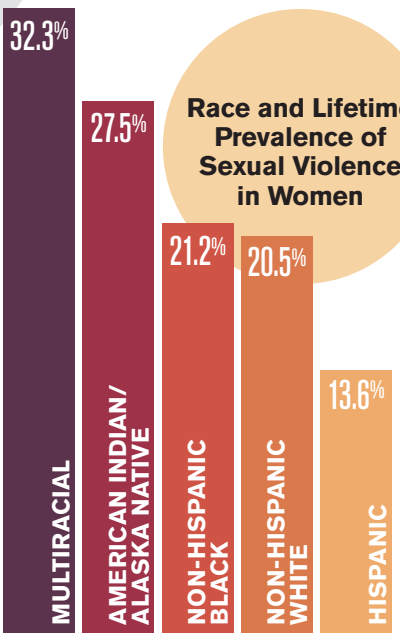
1.7% of men have been raped during their lifetimes

0.8% have been raped by an intimate partner

Lifetime prevalence of sexual violence other than rape

Women **43.9%**

Race and Lifetime Prevalence of Sexual Violence in Women



Perpetrators of Sexual Violence

Almost half of all victims of sexual violence knew their perpetrators

Female rape victims who knew their perpetrators **46.7%**

Female victims who were raped by an intimate partner **45.4%**

From a public health perspective, the CDC says, these statistics suggest that primary prevention of sexual and intimate partner violence must begin early and address changing social norms and behaviors with bystander and other prevention. Ob/gyns have a role to play in primary prevention by educating adolescent patients about healthy relationship behaviors so that they can avoid violence in their relationships.

Breiding MJ, Smith SG, Basile KC, et al. Prevalence and characteristics of sexual violence, stalking, and intimate partner violence victimization—national intimate partner and sexual violence survey, United States, 2011. MMWR. 2014;63(8):1-18.

Rx only

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

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

INDICATIONS AND USAGE

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

Limitations of Use

DICLEGIS has not been studied in women with hyperemesis gravidarum.

DOSAGE AND ADMINISTRATION

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

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

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

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

DOSAGE FORMS AND STRENGTHS

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

CONTRAINDICATIONS

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

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

WARNINGS AND PRECAUTIONS

Activities Requiring Mental Alertness

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

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

Concomitant Medical Conditions

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

Drug Interactions

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

Drug-Food Interactions

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

ADVERSE REACTIONS

The following adverse reactions are discussed elsewhere in labelling:

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

Clinical Trial Experience

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

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

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

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

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

Postmarketing Experience

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

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category A

DICLEGIS is intended for use in pregnant women.

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

Nursing Mothers

Women should not breastfeed while using DICLEGIS.

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

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

Pediatric Use

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

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

OVERDOSAGE

Signs and Symptoms of Overdose

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

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

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

Management of Overdose

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

PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information)

Somnolence and Severe Drowsiness

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

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

Storage and Handling

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

Distributed by:

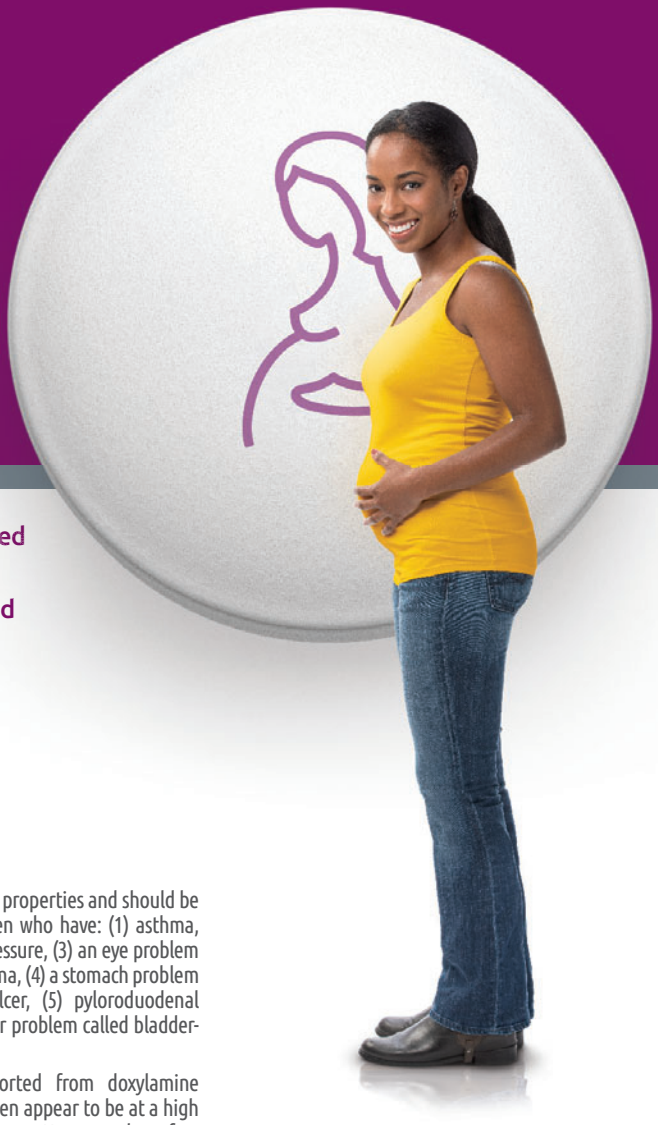
Duchesnay USA, Inc.
Bryn Mawr, PA, 19010
www.Diclegis.com
©2013, Duchesnay Inc. All rights reserved.

DUCHESNAY

2013-0002-01 Apr 2013

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

…Now You Can.



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

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

Visit www.Diclegis.com for more information.

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

NVP | NAUSEA AND VOMITING OF PREGNANCY

Indication

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

Limitations of Use

Diclegis has not been studied in women with hyperemesis gravidarum.

Important Safety Information

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

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

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

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

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

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

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

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

Diclegis®

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

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

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

Tablet(s) shown are not actual size.

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

DUCHESNAY USA

©2013 Duchesnay USA. All rights reserved. 2013-0040-02 Sep 2013 Printed in the USA.