CONTEMPORARY OB/GYN JULY 2013, Vol. 58, No. 7

OBESITY AND WEIGHT GAIN IN PREGNANCY ■ GROUP B STREP SCREENING GUIDELINES ■ AN EHR PRIMER

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OBESITY IN PREGNANCY

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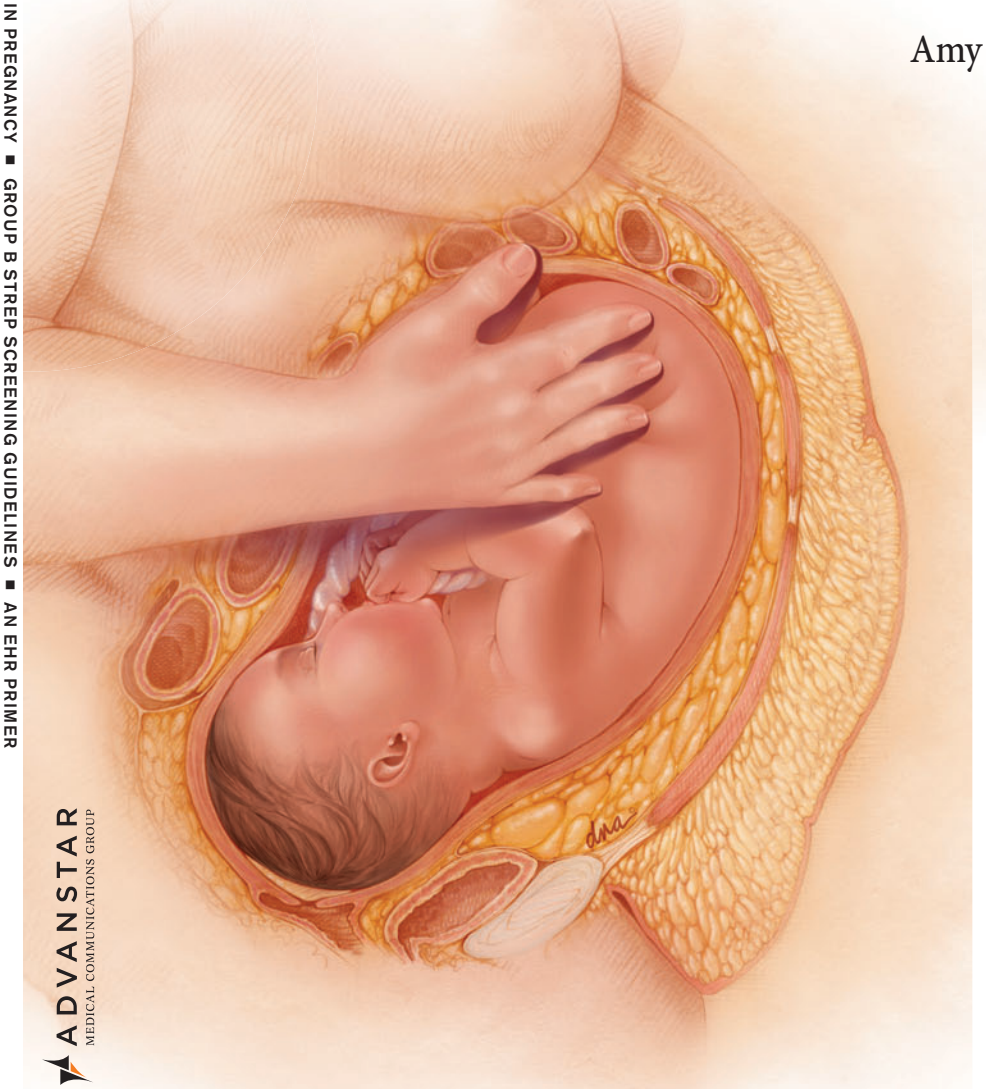
Amy Flick, MD, and Raul Artal, MD



GBS screening

What ob/gyns need to know

JULY IS GBS AWARENESS MONTH

Homa K. Ahmadzia, MD, MPH,
R. Phillips Heine, MD, & Haywood L. Brown, MD

POINT/COUNTERPOINT

The ethics of prebirth sex selection

TECH TOOLS

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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.

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

Please see accompanying Brief Summary of the full Prescribing Information.

Tablet(s) shown are not actual size.

DUCHESNAY USA

2013-0040-01-041213 Apr 2013 Printed in the USA.

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 DIGLEGIS than Placebo are shown)

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

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

Postmarketing Experience

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

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category A

DICLEGIS is intended for use in pregnant women.

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

Nursing Mothers

Women should not breastfeed while using DICLEGIS.

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

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

Pediatric Use

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

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

OVERDOSAGE

Signs and Symptoms of Overdose

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

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

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

Management of Overdose

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

PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information)

Somnolence and Severe Drowsiness

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

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

Storage and Handling

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

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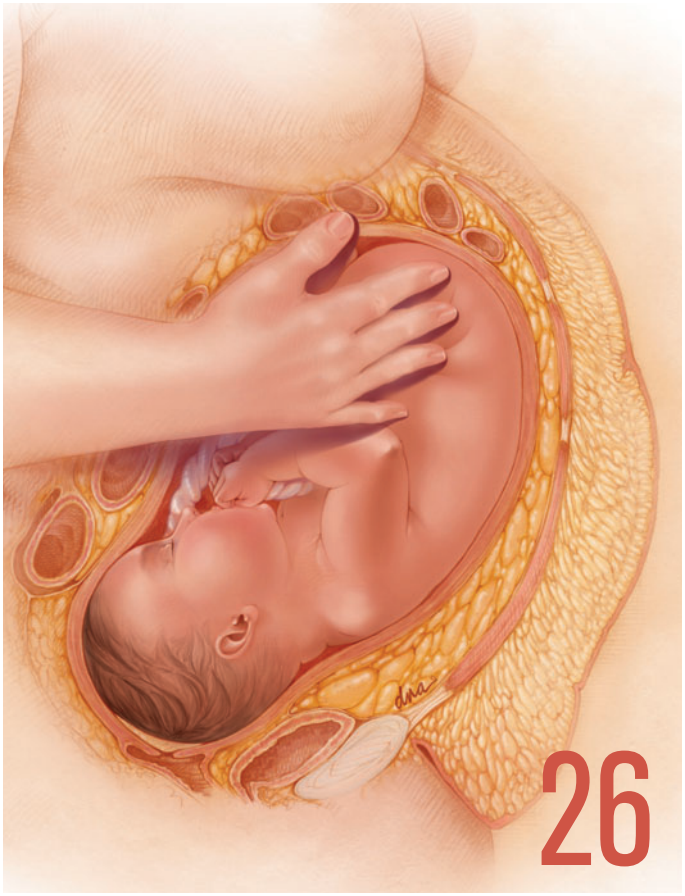

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BY **CHARLES J. LOCKWOOD, MD, MHCM**

Do genetic factors explain recurrent pregnancy loss?

We're at the dawn of a new age in identification of etiologies for pregnancy loss

For the better part of the past 20 years I have consulted on or cared for well over 1000 patients with recurrent pregnancy loss (RPL) due to either stillbirths or miscarriages. So this is an area of obstetrics I have thought about quite a bit and it is fair to say that I have been very frustrated by my frequent inability to identify the cause of this tragic condition or to offer effective treatments.

A rough classification scheme for RPL

To grossly simplify this disorder based on 2 decades of personal observations, I would argue that there are 3 major patient populations affected by RPL. The first are older nulliparous patients who have delayed childbearing until their late 30s or early 40s and present with recurrent preembryonic (<5 weeks) or embryonic (<10 weeks) miscarriages with or without infertility. In rare cases, they also will have interspersed second- and third-trimester fetal deaths. When the products of conception (POCs) from these patients are accessible and can be karyotyped, they most often display aneuploidy (eg, trisomies, triploidy, or less commonly, deletions and insertions). We really do not understand the pathogenesis of maternal age-associated chromosomal instability and there is not much that we can offer to these patients beyond encouragement, and ultimately donor egg in vitro fertilization.

The second RPL population consists of patients with recurrent severe fetal growth restriction and stillbirths, which generally occur at progressively earlier gestational ages. These patients have a heterogeneous set of etiologies that ultimately involve severe uteroplacental vascular insufficiency. Some are due to antiphospholipid antibody (APA) syndrome, others are associated with severe chronic hypertension with associated decidual vasculopathy, and a few are associated with poorly understood alloimmune etiologies like chronic intervillositis.[1] Treatment options are also limited in this population, except for APA syndrome patients, who often benefit from heparin and low-dose aspirin therapy.[2]

The greatest riddle to me is the third population of RPL patients. These women are generally younger, often multiparous, and prone to intermittent fetal loss at or after 10 weeks, although the occasional patient also presents with recurrent intermittent embryonic loss. As a general rule of thumb, these losses tend to occur around the same gestational age, or at least in the same trimester. Given the intermittent pattern of occurrence, genetic causes can be suspected. Indeed, in about 3% of RPL cases, usually involving early losses, a parental-derived unbalanced chromosomal translocation will be found.[3]

However, I have long suspected that most cases of intermittent RPL result from Mendelian disorders. For example, intermittent early losses may rarely be caused by homozygosity for the adult-onset polycystic kidney disease gene.[4] In rare cases, later losses are caused by autosomal and X-linked recessive lethal multiple pterygium syndromes (aka fetal akinesia deformation sequence) that present as mid-pregnancy fetal death associated with hydrops, cystic hygroma, contractures of the extremities,

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> Future discoveries concerning RPL are unlikely to come out of relatively crude genome-wide association studies.

and other anomalies triggered by mutations in neuromuscular junction genes.[5]

Of course, a number of other mutations associated with obvious congenital anomalies also can cause stillbirth, but the precise genetic etiology of the vast majority of cases of intermittent RPL, particularly in anatomically normal fetuses, has remained undiscovered.

Lethal fetal arrhythmias caused by ion channel mutations

Recently Crotti and associates tested the hypothesis that mutations leading to long QT syndrome (LQTS)—a cause of unexpected death in infants, children, and young adults—might also cause fetal death after 13 weeks.[6] They conducted postmortem anatomic studies and karyotype, toxicological, microbiologic, and biochemical analyses on a series of fetuses that died in utero, followed by an analysis for genes causing (or strongly associated with) LQTS. A total of 91 cases were evaluated (51 females, 40 males) with an average gestational age of 26.3 weeks (range, 14-41 weeks) at demise.

The investigators identified 8 cases (8.8% [95% CI, 3.9%-16.6%]) where there were mutations associated with dysfunctional LQTS-associated ion channels (2 in losses at <20 weeks and 6 in losses at ≥20 weeks). This high frequency stands in stark contrast to the reported frequency of LQTS in adults (1/5,500 to 1/10,000)[7] suggesting that lethality might be greatly enhanced during fetal life.

The authors theorize that high levels of circulating progesterone, a hormone that prolongs the QT interval, may contribute to higher lethality of these mutations in affected fetuses.[6] Other factors that may contribute to lethality in an affected fetus include immaturity of the cardiac conduction system, volatility of the fetal autonomic nervous system with large physiological swings in sympathetic tone, and cord compression leading to sequential parasympathetic and sympathetic stimulation. Perhaps some losses associated with nuchal cords may have this underlying disorder.

Of note, the prevalence of LQTS mutations is also greatly increased in infants who die of SIDS (10%) compared with adults.[8]

Clearly, additional studies are needed to confirm these observations. Moreover, because more than 300 mutations contribute to LQTS,[9] expanded genetic surveys are needed. It will also be important to learn what percent of such mutations occur de novo and what percent reflect cryptic parental disease. Confirmation of inheritance also presents the opportunity for prevention in future pregnancies through maternal beta-adrenergic blockade therapy and detection of adults at risk for sudden death.[9]

Take-home message

You may suspect that I am obsessed with genetics and you may be wondering why I have not mentioned the role of other putative causes of RPL, including luteal-phase defects, infections, uterine anomalies, and inherited thrombophilias.

The bottom line is that I think that, with rare exceptions, these conditions are either unrelated to RPL or they are serendipitous findings. Indeed, we are at the dawn of a new age in the identification of etiologies for both isolated and recurrent pregnancy loss. However, future discoveries concerning RPL are unlikely to come out of relatively crude genome-wide association studies, which, as in the case of many common diseases, have led to only modest correlations with single nucleotide polymorphisms (SNPs).[10]

Rather, breakthroughs will likely require examination of whole exome and/or genomic sequences of affected POCs with subsequent targeted studies of parental DNA. This approach should lead to identification of a host of autosomal and X-linked recessive causes of intermittent losses, as well as autosomal-dominant disorders of variable penetrance.

Whole exome and/or genomic sequencing may also commonly detect de novo germ line mutations and copy number variants in the POCs of women with maternal-age-associated recurrent losses found to be "euploid" by karyotype analysis. This would be analogous to the observation of increased rates of genetic abnormalities detected in stillborn specimens using chromosomal microarray studies, which detect far smaller (50 to 100 kb) deletions or duplications, compared with traditional karyotype analysis.[11]

Exome and genomic sequencing would increase this resolution down to the base pair level. In fact, I would argue that such women have age-induced genetic instability in their oocytes of which karyotype-detected aneuploidy is just the tip of the "genetic" iceberg.

continued on **PAGE 48**

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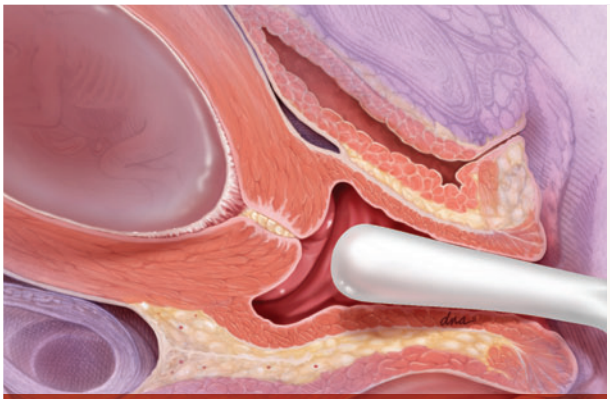

Cervical length

Who should we screen?

contemporaryobgyn.net/cervical_length_screening

Doing nothing is no longer an option, say the authors. Cervical length assessment should be provided to a larger population of women to identify and treat those with cervical shortening.

on twitter

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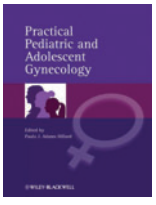
Contemporary OB/GYN
June 10

Contemporary OB/GYN Editorial Board member Sharon T. Phelan, MD (center), participates in a meeting of new ACOG Fellow Section Officers.

Contemporary OB/GYN
June 1

Congratulations to Editorial Board member Paula Hillard, MD, on her new textbook. According to Dr. Hillard, "It's written for primary clinicians: pediatricians, general ob/gyns, internists, family physicians, nurse practitioners, nurses, midwives, and others who provide care for girls and adolescents/young women whose gynecologic needs deserve attention and care."



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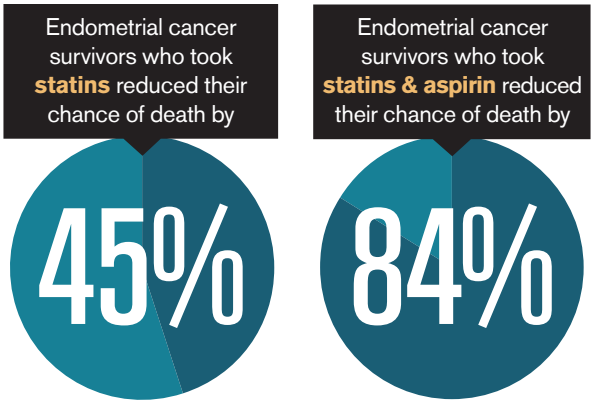
Lipid-lowering agents linked to improved survival in women with endometrial Ca

Endometrial cancer patients reduced their chance of death by 84% with the use of statins and aspirin, according to a new study by researchers at Montefiore Einstein Center for Cancer Care (MECCC) that was presented at the 2013 annual meeting of the American Society of Clinical Oncology (ASCO) in Chicago. In addition, women in the study who used only statins saw their risk of dying decline by 45%.



A retrospective cohort study evaluated overall survival of 554 patients who had been diagnosed and treated for endometrial cancer at Montefiore Medical Center between January 2005 and December 2009. Among them, 333 were not hyperlipidemic, 165 had hyperlipidemia treated with statins, and 56 were hyperlipidemic and had not received statin therapy. In the study, women who received statin therapy had hypertension, diabetes, and were older than those who did not.

"Antihyperlipidemic medications are extremely common medications taken by women with obesity and cardiovascular risk factors," said lead author Nicole Nevadunsky, MD, a gynecologic oncologist at MECCC and an assistant professor in the department of obstetrics & gynecology and women's health of Albert Einstein College of Medicine of Yeshiva University, Bronx, New York.

Multivariate analysis showed that endometrial cancer survivors who received statin therapy had a 45% decreased hazard of death compared with women who did not have hyperlipidemia (HR=0.55; 95% CI, 0.35-0.87). There was an 84% decreased hazard of death for survivors taking both statins and aspirin compared with other subgroups (HR=0.16; 95% CI, 0.07-0.38).

"Statin therapy may represent a low-cost, low-side-effect adjuvant therapy to prevent death after diagnosis of endometrial cancer," Dr. Nevadunsky told *Formulary*, a sister publication to *Contemporary OB/GYN*. "Furthermore, study of the mechanisms of action of statin therapy may help development of therapies targeted at the molecular level as well as nontraditional interventions such as dietary and exercise lifestyle modifications."

There is a close association between the development of endometrial cancer and obesity, according to Dr. Nevadunsky. "Hyperlipidemia and heart disease are common comorbidities of obesity for which statin therapy is used," she said. "Antihyperlipidemic agents have been reported to improve survival in other cancer types and decrease cancer occurrences. The investigative team was interested in assessing the effect of statin therapy on overall survival of women diagnosed and treated for endometrial cancer."

Spoozak LA, Girda E, Van Arsdale A, Einstein MH, Goldberg GL, Nevadunsky N. Statin use in uterine malignancies. *J Clin Oncol.* 2013;31 (suppl; abstr 5592).

The importance of 'the fertility talk'

Making patients aware of how fertility decreases with age can be difficult, because for many patients, it is a touchy subject. Today's ob/gyns are saying they are working to make the conversation as routine as the talk about contraception, according to a recent *Wall Street Journal* article titled "More doctors broach delicate topic of women's age and fertility."

According to Laurie McKenzie, MD, a reproductive endocrinologist and director of oncofertility at Houston IVF in Texas, as well as a member of the *Contemporary OB/GYN* editorial board, the article is timely. "For ob/gyns, family practitioners, or internal medicine physicians, this is a valuable discussion to initiate when female patients are seen in their reproductive years," she said. "But it's important to make it spontaneous and nonjudgmental in tone."

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LETTERS TO THE EDITOR

REGARDING "AUTISM AND THE OBSTETRICIAN"

TO THE EDITOR:

[Regarding your editorial "Autism and the obstetrician" that appeared in the June 2013 issue of *Contemporary OB/GYN*:]

Is it possible that individually or in combination, prenatal sonography, fetal heart rate Doppler in the office, and fetal monitoring in the labor room are contributing to the cause of autism? This did not occur with such frequency in the age of the fetoscope.

Martin S. Dubner, MD
Suffern, New York

IN REPLY:

My short answer is: probably not. Abramowicz recently reviewed this topic and concluded that no independently confirmed peer-reviewed published evidence has established a cause-effect relationship between prenatal exposure to clinical ultrasound and subsequent development of autism spectrum disorders (ASDs).[1] There is a mouse study suggesting that fairly prolonged (30-minute) exposure to diagnostic ultrasound can affect neuronal migration.[2] However, this experimental design is unlikely to be relevant to clinical exposures in humans.

The timing of the sudden surge in ASD diagnoses does overlap with the rise of prenatal ultrasound. However, most observers believe the bulk of the additional diagnoses reflect improved surveillance.

I hope that helps. Thank you for your interest.

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

References

1. Abramowicz JS. Ultrasound and autism: association, link, or coincidence? *J Ultrasound Med.* 2012;31(8):1261-1269.

2. Ang ES Jr, Gluncic V, Duque A, Schafer ME, Rakic P. Prenatal exposure to ultrasound waves impacts neuronal migration in mice. *Proc Natl Acad Sci U S A.* 2006;103(34):12903-12910.

continued from **PAGE 14**

Dr. McKenzie notes the significance of not making assumptions when planning to discuss reproductive issues. "We have to be sensitive when approaching the subject, and we don't want to make the assumption all women want to have children. There are many different ways to have children and build [a] family, such as embryo adoption, child adoption, and foster care. And more women are choosing child-free living."

The discussion usually entails some education on fertility rates, which according to the current literature, begin to dip near age 32 and significantly drop after age 37. (See the American College of Obstetricians and Gynecologists [ACOG] Committee Opinion No. 413, 2008.) Other relevant discussion points are the increased risks of miscarriage and chromosomal abnormalities in older women.

In simple terms, Dr. McKenzie advises asking patients who are not using contraception, as well as those who are using it, whether they have plans to become pregnant. "You may ask, 'Are you planning to have a family? If so, what path are you planning?' Then you can have the discussion related to age-related fertility," she says.

Data from ACOG show that approximately 20% of women postpone starting their families until after age 35. Dr. McKenzie says it's important to help patients understand that fertility declines with age. "Patients mention celebrities having kids at age 43, for example. How are they doing it? The vast majority of women in that age group are utilizing donor eggs. However, it is also important to realize that there are noninvasive tests that patients can use in their 20s, 30s, and 40s to gauge their own fertility, such as the AMH (Anti-Müllerian Hormone) blood test."

She says AMH normal ranges are usually 2.5 to 4.5. If the value drops below 1, she says, "these women will often have a harder time getting pregnant and often will have higher miscarriage rates."

So at what age is it appropriate to begin talking to patients about fertility, especially because many women want to advance in their careers while also having healthy families?

ACOG guidelines state that clinicians "should encourage women to formulate a reproductive-health plan and should discuss it in a nondirective way at each visit," the *WSJ* article states. ACOG Committee Opinion No. 313 of 2005 addresses discussion points such as a woman's, or a couple's, desire for children; the optimal number, spacing, and timing of

children in the family; and age-related changes in fertility.

"The main point here is having the discussion—bringing it up with patients. They're often erroneously assuming they have a lot of time. Usually there's not as much time as they thought," Dr. McKenzie says.

Different ob/gyns try different tactics, some of which may be more successful than others. For instance, Mark Jostes, MD, in St. Louis, likens initiating the fertility/having-a-baby talk to being a relationship counselor. He told the *WSJ*, "I try to go with general, easy questions to try to feel them out. You can tell if they're willing to talk with a few leading questions."

Another ob/gyn, Victor Klein, MD, with North Shore-LIJ Health System in Great Neck, New York, provides the patient with plenty of facts, according to the *WSJ*. He'll explain that older mothers face greater risks of having a child with Down syndrome, for example.

It may be that practical issues, rather than reluctance, are what prevent ob/gyns from discussing declining fertility with patients. "Often there is so much to cover at the annual well visit—Pap smear guidelines, depression, other female-related issues. As a result, fertility often takes a back seat to other discussions," Dr. McKenzie says. "So often there's a reluctance to bring it up because of time constraints or because physicians feel they are pressuring their patients to get pregnant right away."

Age-related fertility decline. ACOG Committee Opinion No. 413. American College of Obstetricians and Gynecologists. *Obstet Gynecol.* 2008;111:1495–1502.

The importance of preconception care in the continuum of women's health care. ACOG Committee Opinion No. 313. American College of Obstetricians and Gynecologists. *Obstet Gynecol.* 2005;106:665–666.

Reddy S. More doctors broach delicate topic of women's age and fertility rate. June 3, 2013. http://online.wsj.com/article/SB10001424127887324682204578517683273638050.html. Accessed June 10, 2013.

Overweight, obese pregnant women have higher risk of very early delivery

Women who are overweight and/or obese during pregnancy may be at greater risk of preterm—and more notably—extremely preterm delivery, according to results of a new Swedish study published in *JAMA*.

The purpose of the study was to assess early pregnancy body mass index (BMI) and preterm delivery risk by gestational age and by forerunners of preterm delivery.

The population-based retrospective study focused on women with live singleton births in Sweden from 1992 to 2010. Data pertaining to the mothers as well as pregnancy factors were gathered from the Swedish Medical Birth Register. Preterm deliveries were classified as either extremely preterm (22-27 weeks); very preterm (28-31 weeks); or moderately preterm (32-36 weeks). In addition, the results were listed as either spontaneous (preterm contractions or premature rupture of membranes) or medically indicated preterm delivery (cesarean delivery before onset of labor or induced onset of labor).

Risks were adjusted for the mother's age, smoking, level of education, height, country of birth, and year of delivery.

As BMI increased, so did risks of extremely, very, and moderately preterm deliveries

Results showed that for **1,599,551 deliveries** that had data on early pregnancy BMI

- **3082** WERE extremely preterm
- **6893** WERE very preterm
- **67,059** WERE moderately preterm

The results showed that for 1,599,551 deliveries that had data on early pregnancy BMI, 3082 fell into the "extremely preterm" category, 6893 were "very preterm," and 67,059 were "moderately preterm." As BMI increased, so did risks of extremely, very, and moderately preterm deliveries; further, overweight and obesity-specific risks were highest for extremely preterm delivery.

"Considering the high morbidity and mortality among extremely preterm infants, even small absolute differences in risks will have consequences for infant health and survival," the authors said in a statement. "Even though the obesity epidemic in the U.S. appears to have leveled off, there is a sizable group of women entering pregnancy with very high BMI."

For women of normal weight (BMI 18.5 to <25), extremely preterm delivery rate was 0.17%. Compared to women of normal weight, rates (%) of extremely preterm delivery were: BMI 25 to <30 (0.21%), BMI 30 to <35 (0.27%), BMI 35 to <40 (0.35%), and BMI of ≥40 (0.52%). For obese women (BMI ≥30), risk of spontaneous extremely preterm delivery was elevated. Risks of medically indicated preterm deliveries also increased with BMI among overweight and obese women.

FOR MORE INFORMATION on the risks associated with obesity during pregnancy, see this month's cover story on PAGE 26.

Cnattingius S, Villamor E, Johansson S, et al. Maternal obesity and risk of preterm delivery. *JAMA*. 2013;309(22):2362-2370.

Indications and Usage

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

Important Safety Information

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

Estrogen-Alone Therapy

Endometrial Cancer

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

Cardiovascular Disorders and Probable Dementia

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

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

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

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

Estrogen Plus Progestin Therapy

Cardiovascular Disorders and Probable Dementia

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

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

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

Breast Cancer

The WHI estrogen plus progestin substudy also demonstrated an increased risk of invasive breast cancer.

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

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

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

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

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

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

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

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

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

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

WARNING: ENDOMETRIAL CANCER, CARDIOVASCULAR DISORDERS, BREAST CANCER and PROBABLE DEMENTIA: Estrogen-Alone Therapy: Endometrial Cancer: There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding *[see Warnings and Precautions]*. Cardiovascular Disorders and Probable Dementia: Estrogen-alone therapy should not be used for the prevention of cardiovascular disease or dementia *[see Warnings and Precautions]*. The Women's Health Initiative (WHI) estrogen-alone substudy reported increased risks of stroke and deep vein thrombosis (DVT) in postmenopausal women (50 to 79 years of age) during 7.1 years of treatment with daily oral conjugated estrogens (CE) [0.625 mg]-alone, relative to placebo *[see Warnings and Precautions]*. The WHI Memory Study (WHIMS) estrogen-alone ancillary study of WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 5.2 years of treatment with daily CE (0.625 mg)-alone, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women *[see Warnings and Precautions]*. In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and other dosage forms of estrogens. Estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman. Estrogen Plus Progestin Therapy: Cardiovascular Disorders and Probable Dementia: Estrogen plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia *[see Warnings and Precautions]*. The WHI estrogen plus progestin substudy reported increased risks of DVT, pulmonary embolism (PE), stroke and myocardial infarction (MI) in postmenopausal women (50 to 79 years of age) during 5.6 years of treatment with daily oral CE (0.625 mg) combined with medroxyprogesterone acetate (MPA) [2.5 mg], relative to placebo *[see Warnings and Precautions]*. The WHIMS estrogen plus progestin ancillary study of the WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with daily CE (0.625 mg) combined with MPA (2.5 mg), relative to placebo. It is unknown whether this finding applies to younger postmenopausal women *[see Warnings and Precautions]*. Breast Cancer: The WHI estrogen plus progestin substudy also demonstrated an increased risk of invasive breast cancer *[see Warnings and Precautions]*. In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and MPA, and other combinations and dosage forms of estrogens and progestins. Estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

INDICATIONS AND USAGE: Treatment of Atrophic Vaginitis due to Menopause

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

WARNINGS AND PRECAUTIONS: Risks from Systemic Absorption: Vagifem® is intended only for vaginal administration. Systemic absorption occurs with the use of Vagifem®. The warnings, precautions, and adverse reactions associated with the use of systemic estrogen-alone therapy should be taken into account. **Cardiovascular Disorders:** An increased risk of stroke and DVT has been reported with estrogen-alone therapy. An increased risk of PE, DVT, stroke, and MI has been reported with estrogen plus progestin therapy. Should any of these occur or be suspected, estrogen with or without progestin therapy should be discontinued immediately. Risk factors for arterial vascular disease (for example, hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and obesity) and/or venous thromboembolism (VTE) (for example, personal history or family history of VTE, obesity, and systemic lupus erythematosus) should be managed appropriately. *Stroke:* In the WHI estrogen-alone substudy, a statistically significant increased risk of stroke was reported in women 50 to 79 years of age receiving daily CE (0.625 mg)-alone compared to women in the same age group receiving placebo (45 versus 33 per 10,000 women-years). The increase in risk was demonstrated in year 1 and persisted. Should a stroke occur or be suspected, estrogen-alone therapy should be discontinued immediately. Subgroup analyses of women 50 to 59 years of age suggest no increased risk of stroke for those women receiving CE (0.625 mg)-alone versus those receiving placebo (18 versus 21 per 10,000 women-years). In the WHI estrogen plus progestin substudy, a statistically significant increased risk of stroke was reported in women 50 to 79 years of age receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women in the same age group receiving placebo (33 versus 25 per 10,000 women-years). The increase in risk was demonstrated after the first year and persisted. Should a stroke occur or be suspected, estrogen plus progestin therapy should be discontinued immediately. *Coronary Heart Disease:* In the WHI estrogen-alone substudy, no overall effect on coronary heart disease (CHD) events (defined as nonfatal MI, silent MI, or CHD death) was reported in women receiving estrogen-alone compared to placebo. Subgroup analysis of women 50 to 59 years of age suggests a statistically non-significant reduction in CHD events (CE [0.625 mg]-alone compared to placebo) in women with less than 10 years since menopause (8 versus 16 per 10,000 women-years). In the WHI estrogen plus progestin substudy, there was a statistically non-significant increased risk of CHD events reported in women receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women receiving placebo (41 versus 34 per 10,000 women-years). An increase in relative risk was demonstrated in year 1, and a trend toward decreasing relative risk was reported in years 2 through 5. In postmenopausal women with documented heart disease (n=2,763), average 66.7 years of age, in a controlled clinical trial of secondary prevention of cardiovascular disease (Heart and Estrogen/Progestin Replacement Study [HERS]), treatment with daily CE (0.625 mg) plus MPA (2.5 mg) demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with CE plus MPA did not reduce the overall rate of CHD events in postmenopausal women with established coronary heart disease. There were more CHD events in the CE plus MPA-treated group than in the placebo group in year 1, but not during the subsequent years. Two thousand, three hundred and twenty-one (2,321) women from the original HERS trial agreed to participate in an open label extension of the original HERS, HERS II. Average follow-up in HERS II was an additional 2.7 years, for a total of 6.8 years overall. Rates of CHD events were comparable among women in the CE plus MPA group and the placebo group in HERS, HERS II, and overall. *Venous Thromboembolism:* In the WHI estrogen-alone substudy, the risk of VTE (DVT and PE) was increased for women receiving daily CE (0.625 mg)-alone compared to placebo (30 versus 22 per 10,000 women-years), although only the increased risk of DVT reached statistical significance (23 versus 15 per 10,000 women-years). The increase in VTE risk was demonstrated during the first 2 years. Should a VTE occur or be suspected, estrogen-alone therapy should be discontinued immediately. In the WHI estrogen plus progestin substudy, a statistically significant 2-fold greater rate of VTE was reported in women receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women receiving placebo (35 versus 17 per 10,000 women-years). Statistically significant increases in risk for both DVT (26 versus 13 per 10,000 women-years) and PE (18 versus 8 per 10,000 women-years) were also demonstrated. The increase in VTE risk was demonstrated during the first year and persisted. Should a VTE occur or be suspected, estrogen plus progestin therapy should be discontinued immediately. If feasible, estrogens should be discontinued at least 4 to 6 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization. **Malignant Neoplasms:** *Endometrial Cancer:* An increased risk of endometrial cancer has been reported with the use of unopposed estrogen therapy in a woman with a uterus. The reported endometrial cancer risk among unopposed estrogen users is about 2 to 12 times greater than in non-users, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with use of estrogens for less than 1 year. The greatest risk appears associated with prolonged use, with an increased risk of 15- to 24-fold for 5 to 10 years or more and this risk has been shown to persist for at least 8 to 15 years after estrogen therapy is discontinued. Clinical surveillance of all women using estrogen-alone or estrogen plus progestin therapy is important. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding. There is no evidence that the use of natural estrogens results in a different endometrial risk profile than synthetic estrogens of equivalent estrogen dose. Adding a progestin to estrogen therapy in postmenopausal women has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. *Breast Cancer:* The most important randomized clinical trial providing information about breast cancer in estrogen-alone users is the WHI substudy of daily CE (0.625 mg)-alone. In the WHI estrogen-alone substudy, after an average follow-up of 7.1 years, daily CE-alone was not associated with an increased risk of invasive breast cancer *[relative risk (RR) 0.80]*. The most important randomized clinical trial providing information about breast cancer in estrogen plus progestin users is the WHI substudy of daily CE (0.625 mg) plus MPA (2.5 mg). After a mean follow-up of 5.6 years, the estrogen plus progestin substudy reported an increased risk of invasive breast cancer in women who took daily CE plus MPA. In this substudy, prior use of estrogen-alone or estrogen plus progestin therapy was reported by 26 percent of the women. The relative risk of invasive breast cancer was 1.24, and the absolute risk was 41 versus 33 cases per 10,000 women-years, for CE plus MPA compared with placebo. Among women who reported prior use of hormone therapy, the relative risk of invasive breast cancer was 1.86, and the absolute risk was 46 versus 25 cases per 10,000 women-years, for CE plus MPA compared with placebo. Among women who reported no prior use of hormone therapy, the relative risk of invasive breast cancer was 1.09, and the absolute risk was 40 versus 36 cases per 10,000 women-years for CE plus MPA compared with placebo. In the same substudy, invasive breast cancers were larger, were more likely to be node positive, and were diagnosed at a more advanced stage in the CE (0.625 mg) plus MPA (2.5 mg) group compared with the placebo group. Metastatic disease was rare, with no apparent difference between the two groups. Other prognostic factors, such as histologic subtype, grade and hormone receptor status did not differ between the groups. Consistent with the WHI clinical trial, observational studies have also reported an increased risk of breast cancer for estrogen plus progestin therapy, and a smaller increased risk for estrogen-alone therapy, after several years of use. The risk increased with duration of use, and appeared to return to baseline over about 5 years after stopping treatment (only the observational studies have substantial data on risk after stopping). Observational studies also suggest that the risk of breast cancer was greater, and became apparent earlier, with estrogen plus progestin therapy as compared to estrogen-alone therapy. However, these studies have not generally found significant variation in the risk of breast cancer among different estrogen plus progestin combinations, doses, or routes of administration. The use of estrogen-alone and estrogen plus progestin therapy has been reported to result in an increase in abnormal mammograms requiring further evaluation. All women should receive yearly breast examinations by a healthcare provider and perform monthly breast self-examinations. In addition, mammography examinations should be scheduled based on patient age, risk factors, and prior mammogram results. *Ovarian Cancer:* The WHI estrogen plus progestin substudy reported a statistically non-significant increased risk of ovarian cancer. After an average follow-up of 5.6 years, the relative risk for ovarian cancer for

CE plus MPA versus placebo was 1.58 (95 percent CI, 0.77-3.24). The absolute risk for CE plus MPA versus placebo was 4 versus 3 cases per 10,000 women-years. In some epidemiologic studies, the use of estrogen plus progestin and estrogen-only products, in particular for 5 or more years, has been associated with an increased risk of ovarian cancer. However, the duration of exposure associated with increased risk is not consistent across all epidemiologic studies, and some report no association. **Probable Dementia:** In the WHIMS estrogen-alone ancillary study of WHI, a population of 2,947 hysterectomized women 65 to 79 years of age was randomized to daily CE (0.625 mg)-alone or placebo. After an average follow-up of 5.2 years, 28 women in the estrogen-alone group and 19 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE-alone versus placebo was 1.49 (95 percent CI, 0.83-2.66). The absolute risk of probable dementia for CE-alone versus placebo was 37 versus 25 cases per 10,000 women-years. In the WHIMS estrogen plus progestin ancillary study of WHI, a population of 4,532 postmenopausal women 65 to 79 years of age was randomized to daily CE (0.625 mg) plus MPA (2.5 mg) or placebo. After an average follow-up of 4 years, 40 women in the CE plus MPA group and 21 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE plus MPA versus placebo was 2.05 (95 percent CI, 1.21-3.48). The absolute risk of probable dementia for CE plus MPA versus placebo was 45 versus 22 cases per 10,000 women-years. When data from the two populations in the WHIMS estrogen-alone and estrogen plus progestin ancillary studies were pooled as planned in the WHIMS protocol, the reported overall relative risk for probable dementia was 1.76 (95 percent CI, 1.19-2.60). Since both ancillary studies were conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women. **Gallbladder Disease:** A 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in postmenopausal women receiving estrogens has been reported. **Hypercalcemia:** Estrogen administration may lead to severe hypercalcemia in women with breast cancer and bone metastases. If hypercalcemia occurs, use of the drug should be stopped and appropriate measures taken to reduce the serum calcium level. **Visual Abnormalities:** Retinal vascular thrombosis has been reported in women receiving estrogens. Discontinue medication pending examination if there is a sudden partial or complete loss of vision, or a sudden onset of proptosis, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, estrogens should be permanently discontinued. **Addition of a Progestin When a Woman Has Not Had a Hysterectomy:** Studies of the addition of a progestin for 10 or more days of a cycle of estrogen administration, or daily with estrogen in a continuous regimen, have reported a lowered incidence of endometrial hyperplasia than would be induced by estrogen treatment alone. Endometrial hyperplasia may be a precursor to endometrial cancer. There are, however, possible risks that may be associated with the use of progestins with estrogens compared to estrogen-alone regimens. These include an increased risk of breast cancer. **Elevated Blood Pressure:** In a small number of case reports, substantial increases in blood pressure have been attributed to idiosyncratic reactions to estrogens. In a large, randomized, placebo-controlled clinical trial, a generalized effect of estrogens on blood pressure was not seen. **Hypertriglyceridemia:** In women with pre-existing hypertriglyceridemia, estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis. Consider discontinuation of treatment if pancreatitis occurs. **Hepatic Impairment and/or Past History of Cholestatic Jaundice:** Estrogens may be poorly metabolized in women with impaired liver function. For women with a history of cholestatic jaundice associated with past estrogen use or with pregnancy, caution should be exercised, and in the case of recurrence, medication should be discontinued. **Hypothyroidism:** Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Women with normal thyroid function can compensate for the increased TBG by making more thyroid hormone, thus maintaining free T_4 and T_3 serum concentrations in the normal range. Women dependent on thyroid hormone replacement therapy who are also receiving estrogens may require increased doses of their thyroid replacement therapy. These women should have their thyroid function monitored in order to maintain their free thyroid hormone levels in an acceptable range. **Fluid Retention:** Estrogens may cause some degree of fluid retention. Women with conditions that might be influenced by this factor, such as a cardiac or renal dysfunction, warrant careful observation when estrogen-alone is prescribed. **Hypocalcemia:** Estrogen therapy should be used with caution in women with hypoparathyroidism as estrogen-induced hypocalcemia may occur. **Exacerbation of Endometriosis:** A few cases of malignant transformation of residual endometrial implants have been reported in women treated post-hysterectomy with estrogen-alone therapy. For women known to have residual endometriosis post-hysterectomy, the addition of progestin should be considered. **Hereditary Angioedema:** Exogenous estrogens may exacerbate symptoms of angioedema in women with hereditary angioedema. **Exacerbation of Other Conditions:** Estrogen therapy may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraine, porphyria, systemic lupus erythematosus, and hepatic hemangiomas and should be used with caution in women with these conditions. **Local Abrasion:** A few cases of local abrasion induced by the Vagifem® applicator have been reported, especially in women with severely atrophic vaginal mucosa. **Laboratory Tests:** Serum follicle stimulating hormone (FSH) and estradiol levels have not been shown to be useful in the management of moderate to severe symptoms of vulvar and vaginal atrophy. **Drug-Laboratory Test Interactions:** Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, II-VII-X complex, and beta-thromboglobulin; decreased levels of antifactor Xa and antithrombin III, decreased antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity. Increased thyroid-binding globulin (TBG) levels leading to increased circulating total thyroid hormone as measured by protein-bound iodine (PBI), T_4 levels (by column or by radioimmunoassay) or T_3 levels by radioimmunoassay. T_3 resin uptake is decreased, reflecting the elevated TBG. Free T_4 and free T_3 concentrations are unaltered. Women on thyroid replacement therapy may require higher doses of thyroid hormone. Other binding proteins may be elevated in serum, for example, corticosteroid binding globulin (CBG), sex hormone-binding globulin (SHBG), leading to increased total circulating corticosteroids and sex steroids, respectively. Free hormone concentrations, such as testosterone and estradiol, may be decreased. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin). Increased plasma high-density lipoprotein (HDL) and HDL_2 cholesterol subfraction concentrations, reduced low-density lipoprotein (LDL) cholesterol concentrations, increased triglyceride levels. Impaired glucose tolerance.

ADVERSE REACTIONS: The following serious adverse reactions are discussed elsewhere in the labeling: Cardiovascular Disorders *[see Boxed Warning, Warnings and Precautions]*; Malignant Neoplasms *[see Boxed Warning, Warnings and Precautions]*. **Clinical Trials Experience:** Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. In a 12-month randomized, double-blind, parallel group, placebo-controlled study, a total of 309 postmenopausal women were randomized to receive either placebo or Vagifem® 10 mcg tablets. Adverse reactions with an incidence of ≥ 5 percent in the Vagifem® 10 mcg group and greater than those reported in the placebo group are listed in Table 1.

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

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

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

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

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

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

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

Postmarketing Experience: The following adverse reactions have been identified during post-approval use of Vagifem® 25 mcg. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. *Genitourinary System:* Endometrial cancer, endometrial hyperplasia, vaginal irritation, vaginal pain, vaginismus, vaginal ulceration. *Breast:* Breast cancer. *Cardiovascular:* Deep vein thrombosis. *Gastrointestinal:* Diarrhea. *Skin:* Urticaria, erythematous or pruritic rash, genital pruritus. *Central Nervous System:* Aggravated migraine, depression, insomnia. *Miscellaneous:* Fluid retention, weight increase, drug ineffectiveness, hypersensitivity, blood estrogen increase. Additional postmarketing adverse reactions have been reported in patients receiving other forms of hormone therapy.

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

More detailed information is available upon request.

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VAGIFEM®
estradiol vaginal tablets

BY ANDREW I KAPLAN, ESQ

Ob/gyn's neglect of records leads to claim of HSV exposure

Facts

On October 7, 2008, a woman began prenatal treatment at the defendant clinic. Her expected date of delivery was calculated to be April 26, 2009. Her medical history was significant for having suffered from seizures (which were treated with medication) during adolescence. She had routine visits and normal ultrasounds through March 2009. On March 4, she reported having some slight light-brown vaginal discharge on 2 occasions. She was instructed that if she had bright red bleeding or black secretions to go directly to the labor and delivery department.

On March 17, the patient was at 34.2 weeks and reported having had an episode of dysuria. The fetus was noted to have positive movement and there was no evidence of any loss of fluid or vaginal bleeding. The fetal heart rate (FHR) was 140. The patient was to undergo weekly visits and to have a group B *Streptococcus* (GBS) test at 36 weeks.

At this point, the record indicates that the patient's care was transferred to the defendant ob/gyn's private clinic, where she presented for the first time on March 23. At that time, the patient was complaining of a sore near her anus. The patient underwent an endocervical culture. This study was negative for chlamydia and gonorrhea. At the same visit, she also underwent a vaginal/rectal swab to rule out herpes simplex virus (HSV). The patient was to return in 1 week and to follow up on the HSV culture.

On March 25, ultrasound (U/S) revealed normal amniotic fluid volume with the placenta anterior in implantation, grade II in appearance and no placenta previa. The fetal growth appeared normal and the anatomy details were normal. The infant had a regular fetal heart rate of 155. The gestational age was 34 weeks, 4 days.

The report of the HSV and GBS cultures indicated that the specimen taken on March 23 was "negative to date" and that the status was "preliminary." According to the defendant ob/gyn, both these forms were printed from the hospital computer, to which she had access in her office. The vaginal/rectal swab culture was reported as positive for "herpes simplex virus, Type II, isolated" on April 1.

On the morning of April 2, the patient presented to the "triage room" and stated that she had fallen in the subway (although she had not fallen on her abdomen). At that visit, the patient reported a surgical history of polypectomy cone biopsy but indicated that her Pap smears had been normal since then. She was found to be 3- to 4-cm dilated and was given intravenous (IV) hydration, reevaluated, and discharged home with labor precautions and instructions to follow up with the defendant ob/gyn "on Monday." There is no reference in the record to the positive culture results.

> **There is no reference in the record** to the positive culture results.

On the following day, the patient came to the triage area with complaints of a small amount of spotting. She also complained of the fetus having "jerky movement."

A vaginal examination was performed by the defendant ob/gyn and the patient was noted to be 4-cm dilated and 90% effaced. Furthermore, the FHR was normal at 150, with positive accelerations, no decelerations, and runs of marked variability. The patient was noted to have irregular contractions, and an U/S indicated the amniotic fluid index to be normal at 10 and the fetus

in vertex position with an anterior placenta. The fetus was cephalic. After being monitored, the patient was sent home with instructions. Again, there is no mention of the positive HSV culture results in these records.

The defendant ob/gyn saw the patient on April 6 and April 13. Her records contained the final report regarding the HSV culture, but she did not convey the results of the final culture to the patient, nor did she start her on any prophylactic treatment for herpes on either of those visits.

At around 2 AM on April 23, the patient presented to the triage area in active labor. She denied any history of sexually transmitted infection (STI). A vaginal examination revealed that the patient was fully dilated with bulging membranes and that the fetus was at +1 station. The patient was immediately transferred to a labor room, accompanied by a resident and an attending physician. The patient's membranes ruptured at or around the time of transfer and the fluid was noted to be clear. At 2:27 AM, the infant was delivered with Apgar scores of 9 and 9. Following the delivery the attending physician wrote the following note:

> "The nasal culture was positive for **HSV Type II**, isolated."

HSV positive—pt. did not know the results of this test—she stated during our rapid history in triage before delivery that she had no STD. After delivery, I was reviewing her labs and she was HSV 2 positive. She states she was told by Defendant OB she was HSV 2 negative. She states she may have had a lesion around her anus. I informed the patient of the risk of pediatric herpes, meningitis/encephalitis with an active lesion. If we had known that she had an active lesion, she would have been advised for cesarean section, but, now the baby was possibly exposed to the virus. Pediatrics was informed.

According to the neonatal attending physician's admission note, the infant was transferred to the neonatal intensive care unit (NICU) because the mother possibly had an active herpes lesion at the time of delivery. He further indicated that "on 03/23, there was a lesion noted near her anus, which grew out HSV Type II. She had no knowledge of having had a herpes infection."

After delivery, the infant was noted to be vigorous and without any lesions. When admitted to the NICU, the infant was active and pink and in no acute distress. The infant was started on acyclovir and cultures were ordered on April 23. He had an active sepsis workup and a lumbar puncture. The infant's neurological exam was appropriate for his gestational age. The records indicate that the rectum, nose, and umbilicus cultures were negative for HSV. In addition, on April 25, blood, urine, and cerebrospinal fluid (CSF) cultures were also reported to be normal. As of April 27, the infant was noted to be asymptomatic and was pink and well saturated on room air. The infant had no episodes of apnea or bradycardia. He was feeding well. The plan was to discharge the infant home with close follow-up by his pediatrician, who was to perform weekly HSV surface cultures (conjunctival, anal, and nasal) until the infant was 1 month old. The infant was discharged on April 28.

On May 5, all of the infant's cultures were again negative. On May 15, the cultures were repeated and both the conjunctival and rectal swabs were reported to be negative. However, the nasal culture was positive for "herpes simplex virus, Type II, isolated."

As a result, the pediatrician referred the infant to an emergency room on May 15. Following an evaluation that indicated the infant was having no problems, he was admitted to the hospital for IV acyclovir. He remained in the hospital until May 31. During that stay, a sepsis work-up was performed and all cultures, including CSF, were normal. At the time of discharge, the family was instructed to return if the infant's fever rose above 100.4°F or if he had a rash, vomiting, diarrhea, decreased oral intake, decreased urine output, or any other problems.

On June 2, the infant was treated in the pediatric clinic and was found to be "clinically well, with no skin lesions, no fevers, eating very well." The infant's head circumference was 15.05 in. He was described as very alert, active, and vigorous. His extraocular muscle was intact bilaterally and he was normal cephalically. The mother said that he cried just before feeding. At the next visit on July 7, the parents "denied problems." At this point, the infant was 2 months old and physical examination demonstrated a "well baby," with no evidence of any skin lesions, fevers, rashes, or vesicles.

Injuries

The plaintiff alleged that as a result of the defendant's negligence, the infant-plaintiff suffered from HSV Type II; underwent multiple lumbar procedures; received IV fluids and IV antiviral regime; and experienced (or would experience) excruciating pain, swelling, inflammation, marked tenderness, fatigue, blanching, discoloration, blisters, redness, severe disfigurement, a chronic and per-

> **The physician's oversight was obvious**, and while it may have been innocent, it was indefensible.

manent disease that will require administration of medication for the duration of his life, unsightly appearance, discomfort, interference of future sexual encounters and relations, wound injections, scarring, severe and permanent disability, post-traumatic depression, embarrassment, self-consciousness, inferiority complex, mental distress, anxiety, anger, irritability, tension, and loss of self-esteem.

Discovery

We retained an expert in pediatric infectious diseases, who expressed the opinion that the failure to read the final culture report diagnosing the mother with Type II HSV was a departure by the defendant ob/gyn. It was also a departure not to advise the mother that she had Type II HSV and to prescribe treatment. It is not uncommon for the preliminary results of the culture to be negative and the final results to be positive, since the culture can take up to 8 days.

The defendant should have scheduled a cesarean delivery in order to prevent the HSV from being spread to the infant. While ob/gyns are taught to prescribe Valtrex to the mother during pregnancy to prevent outbreaks, this is not proven to prevent transmission of HSV to the infant. The only true "prevention" is cesarean delivery.

While the child was HSV-positive, it does not necessarily mean that he suffered from herpes. Four scenarios could occur: First, the child could never develop HSV; second, the child could have a skin, eye, and/or mouth (SEM) occurrence; third, the child could develop encephalitis; and fourth, the child could develop disseminated disease.

Because this child was not symptomatic in the first few days of life, he will not have genital herpes or central nervous system or disseminated herpes as an adult. The expert felt, given the results of testing, that at most the child might suffer from SEM occurrences in the future.

The defendant ob/gyn said that she never saw the word "preliminary" on the report and as a result did not look for any other report in her file. The facility's policy was that the lab would fax "final" results to the ob/gyn's office. It was the responsibility of her medical assistant to log in the results and then place them in the patient's record.

Resolution

The plaintiff's initial demand was $1.75 million. At a later settlement conference, that demand was lowered to $950,000. Although the defendants were interested in early resolution in lieu of depositions given the fairly clear liability in the case, we were not interested in negotiating at those numbers because there was little likelihood the infant would suffer from much more than fever blisters in the future. After settlement conferences and continued negotiations between the parties, with the assistance of the Court, the case ultimately settled for $200,000.

Analysis

I frequently stress the importance of documentation to the defense of malpractice litigation. In this case, documentation played a crucial role in 2 distinct ways: the defendant physician's failure to be aware of test results that her office had received and the hospital staff's decision to document that failure in the patient's chart. These incidents rendered this case untenable to defend through trial. The physician's oversight was obvious, and while it may have been innocent, it was indefensible.

Any time a physician orders testing it is his or her responsibility to follow up on it, no matter the "office protocol." The attending physician had every right to protect herself by documenting the manner in which she discovered the mother was HSV-positive, but she could have noted the series of events without throwing the defendant ob/gyn under the proverbial bus. That note eliminated any other less damning explanation. Fortunately for the defendants and the infant, the oversight did not have severe (if any) consequences, so the opposing parties were able to resolve the case quickly and reasonably. COG

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

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Obesity and weight gain in pregnancy

The fact is that pregnancy is an ideal time for obese patients to make lifestyle changes

BY **AMY FLICK, MD,** AND **RAUL ARTAL, MD**

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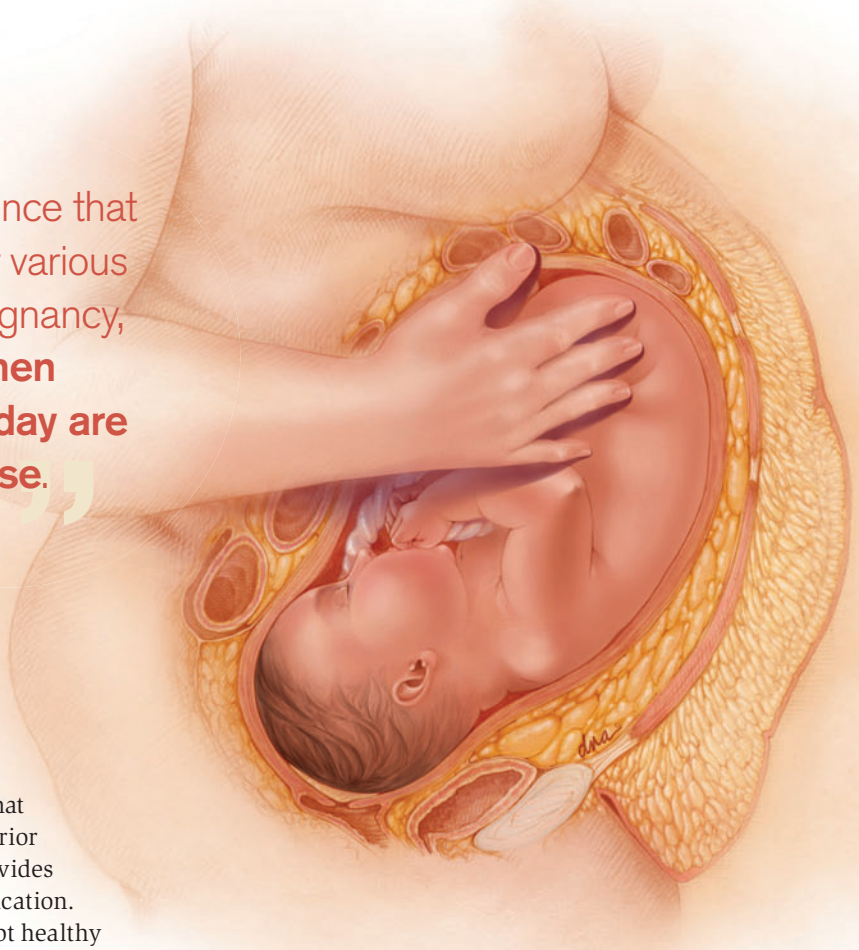
Q A 33-year-old G3P2002 presents at 16 weeks' gestation with a history significant for morbid obesity (body mass index [BMI], 42), gestational diabetes with her most recent pregnancy, and chronic hypertension. What are the main risk factors for her during this pregnancy and how should she be counseled?

A Over the last few decades, the prevalence of overweight (BMI, 25.0–29.9) and obesity (BMI >30) in women has more than doubled.[1] This unabated epidemic has led to more than two-thirds of women being classified as overweight and obese. Approximately 8% of women are now considered to have extreme obesity, defined as a BMI of 40 or greater.[2]

TAKE-HOME MESSAGES

- Physicians have an obligation to dispel the myth that pregnancy is not a time for lifestyle modifications in obese patients.
- It is safe for obese pregnant women to be physically active, maintain their weight, and even lose weight.

Pregnancy is associated with permanent weight increases in every BMI category and is a major contributor to the obesity epidemic.[3] Obesity itself is associated with an increased risk of hypertension, type 2 diabetes mellitus, obstructive sleep apnea, and hypercholesterolemia. These risks increase as BMI increases. Obesity in pregnancy is associated



> In spite of mounting evidence that obesity is a risk factor for various adverse outcomes in pregnancy, **almost half of women becoming pregnant today are overweight or obese.**

with risks to both the mother and the fetus. It also contributes significantly to escalating healthcare costs.

Q What are the risks to the patient?

A It cannot be emphasized enough that the ideal time for counseling is prior to conception. Pregnancy, however, provides a unique opportunity for lifestyle modification. Pregnant women are more prone to adopt healthy lifestyles, have better and more frequent access to medical care, and are under close medical supervision.

Nevertheless, overweight and obese women have higher rates of menstrual irregularities and infertility. This means that they are more likely to delay prenatal care because they may not realize they are pregnant. Thus early ultrasounds should be performed to verify dating, to exclude multiple gestations, and for early diagnosis of congenital anomalies, such as anencephaly, via transvaginal ultrasound.

In spite of mounting evidence that obesity is a risk factor for various adverse outcomes in pregnancy, almost half of women becoming pregnant today are overweight or obese.[4]

Once pregnant, obese women are at increased risk of gestational diabetes mellitus (GDM) (odds ratio [OR], 2.6; 95% confidence interval [CI], 2.1–3.4), gestational hypertension (OR, 2.5; 95% CI, 2.1–3.0), preeclampsia (OR, 1.6; 95% CI, 1.1–2.25), and cesarean delivery (33.8% risk increase).[5]

Obese pregnant patients are also at significant risk of subsequent type 2 diabetes, multiple gestations, and chronic hypertension. These risks increase by obesity class.[6] Studies have shown that early screening for GDM or type 2 diabetes and hypertension are beneficial, as these patients often do not realize they have any underlying medical conditions.[7]

Obese patients should undergo an early 50-g, 1-hour oral glucose challenge test. Studies are currently evaluating the screening/diagnostic values for hemoglobin A1c to diagnose GDM or pre-existing type 2 diabetes as early as possible in addition to routine follow-up testing. Previous studies have demonstrated that hemoglobin A1c correlates well with glucose tolerance test, however, the high incidence of false negative and

TABLE 1 Screening questions for obstructive sleep apnea

- ☐ Do you snore?
- ☐ Do you wake up tired after a full night of sleep?
- ☐ Do you fall asleep during the day?
- ☐ Have you been told you stop breathing at night while you are sleeping?
- ☐ Do you have a history of hypertension?

Note: If yes to 2 or more questions, consider referral to a sleep specialist

ILLUSTRATION BY ALEX BAKER, DNA ILLUSTRATIONS, INC.

positive for hemoglobin A1c as a screening test GDM requires further studying which is being done now.[8]

All obese patients should also be assessed for obstructive sleep apnea, because its prevalence correlates with weight (Table 1).

Q How should we be counseling our obese patients about weight gain?

A Physicians have an obligation to dispel the myth that has dominated for generations that pregnancy is not a time for lifestyle modifications in obese patients. Among the myths that may make physicians reluctant to recommend judicious weight management and physical activity in pregnancy, the most common are:

MYTH: We need additional studies to demonstrate benefits and no adverse consequences of weight loss to the mother and/or fetus.

FACT: Studies are already available showing that additional weight gain is detrimental.[3,9]

MYTH: "Obligatory physiological changes" during pregnancy should result in a "net maternal gain" to reflect the products of conception and increases in the breasts, uterus, etc.

FACT: Overweight and obese women are able to generate the additional calories needed to sustain these changes from their own reserves.[10]

MYTH: Ketonuria/ketonemia as a result of dieting causes delayed neurodevelopment.

FACT: No credible data supports this myth.[11,12] The studies published were conducted in pregnant diabetics who had inadequate glycemic control and other comorbidities. In one study the maternal IQ was not recorded or evaluated.[11] Maternal IQ is known to play a crucial role in child development.

MYTH: Weight loss will result in small-for-gestational-age (SGA) newborns.

FACT: In 2013 we have better tools for early diagnosis of SGA than in the past, and we intervene as indicated.[13] Current gestational weight gain guidelines do "not make a distinction among infants who are constitutionally or hereditarily small, growth-restricted and small, and not small but growth-restricted relative to their potential."[14]

Excessive or any weight gain in overweight and obese patients is detrimental to pregnancy outcome.

TABLE 2 Gestational weight gain and pregnancy outcome in class I–III obese women

	Weight Gain in Pregnancy (lb)		
	Gain <11 (n=30)	Gain 11–20 (n=25)	Gain >20 (n=37)
Variable	n (%)	n (%)	n (%)
Preeclampsia	0 (0.0)	3 (12.0)	10 (27.0)
LGA	3 (10.0)	3 (12.0)	10 (27.0)
SGA	3 (10.0)	1 (4.0)	4 (10.8)

Abbreviations: LGA, large for gestational age; SGA, small for gestational age

From: Artal R. 2013 Ongoing Study (data not previously published)

The 2009 Institute of Medicine (IOM) guidelines modified the recommended weight gain in pregnant women with BMI of 30 and greater to between 11 and 20 lb.[15] Research prior to these recommendations and since has shown that no weight gain, and in fact weight loss, is associated with decreased rates of preeclampsia, cesarean deliveries, large for gestational age (LGA), operative vaginal deliveries, low Apgar scores, and admissions to a neonatal intensive care unit (Table 2).[16,17] Because of this, many authorities have advocated for lesser weight gain and even weight loss for patients in the upper tiers of obesity.[18]

In recognizing that modest weight gain and even weight loss in the presence of an adequately growing fetus is beneficial in obese patients, a recent committee opinion from the American College of Obstetricians and Gynecologists states: "For an obese pregnant woman who is gaining less weight than recommended but has an appropriately growing fetus, no evidence exists that encouraging increased weight gain to conform with the updated IOM guidelines will improve maternal or fetal outcomes."[13]

Physical activity, weight maintenance, and even weight reduction have not proven harmful in obese pregnant patients according to studies in the recent literature.

Q What are the risks to the fetus and neonate of maternal obesity?

A Not only is obesity problematic for the pregnant mother, but it has also been associated with an increased risk of adverse fetal, neonatal outcomes and altered fetal programming, which impacts subsequent generations. Obese women have a higher

Indication

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

Select Important Safety Information

Boxed WARNING: Endometrial Cancer and Cardiovascular Disorders

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

The Women's Health Initiative (WHI) estrogen-alone substudy reported an increased risk of stroke and deep vein thrombosis (DVT) in postmenopausal women (50 to 79 years of age) during 7.1 years of treatment with daily oral conjugated estrogens (CE) [0.625 mg], relative to placebo. Osphena 60 mg had thromboembolic and hemorrhagic stroke incidence rates of 0.72 and 1.45 per thousand women vs. 1.04 and 0 per thousand women for placebo and a DVT incidence rate of 1.45 vs. 1.04 per thousand women for placebo. Osphena should be prescribed for the shortest duration consistent with treatment goals and risks for the individual woman.

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

Select Important Safety Information

Contraindications

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

Warnings and Precautions

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

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

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

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

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

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

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

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

New Osphena™
(ospemifene) tablets
60 mg

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

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

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OSPHENA™ (ospemifene) 60 mg tablets

BRIEF SUMMARY – See Package Insert for Complete Prescribing Information.

WARNING: ENDOMETRIAL CANCER AND CARDIOVASCULAR DISORDERS

Endometrial Cancer

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

Cardiovascular Disorders

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

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

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

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

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

WARNINGS AND PRECAUTIONS

Cardiovascular Disorders

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

Stroke

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

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

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

Coronary Heart Disease

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

Venous Thromboembolism

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

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

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

Malignant Neoplasms

Endometrial Cancer

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

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

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

Breast Cancer

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

Severe Hepatic Impairment

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

ADVERSE REACTIONS

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

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

Clinical Trial Experience

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

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

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

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

DRUG INTERACTIONS

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

Estrogens and estrogen agonist/antagonist

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

Fluconazole

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

Rifampin

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

Ketoconazole

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

Warfarin

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

Highly Protein-Bound Drugs

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

Multiple Enzyme Inhibition

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

USE IN SPECIFIC POPULATIONS

Pregnancy

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

Nursing Mothers

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

Pediatric Use

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

Geriatric Use

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

Renal Impairment

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

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

Hepatic Impairment

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

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

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

OVERDOSAGE

There is no specific antidote for OSPHENA.

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

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rate of iatrogenic prematurity due to maternal conditions such as preeclampsia. It has been known for several years that the risk for neural tube defects in fetuses of obese women is roughly twice that of those with normal weights prior to pregnancy.[19] Obese, and especially morbidly obese, pregnant women have a higher likelihood of having a fetus with congenital anomalies (Table 3).[20]

Studies have also shown a correlation with increasing BMI and increased risks of late stillbirths (OR, 2.2; 95% CI, 1.2–4.1 for women of normal weight and OR, 4.3; 95% CI, 2.0–9.3 for obese women).[21] The diagnosis of these disorders or fetal weight is often difficult due the poor ultrasound resolution obtained in obese and morbidly obese pregnant patients. A complete ultrasound malformation screen may not be possible.

The risk for macrosomic fetuses is significant and so is the risk for dystocias, birth injuries, and cesarean deliveries. These neonates go on to have higher rates of childhood obesity and complications, such as diabetes, associated with obesity.[22]

There is also an increased risk in the morbidly obese pregnant population for fetal growth restriction (8.1% vs 0.9%, $P=0.03$) due to underlying medical conditions such as chronic hypertension seen in the obese pregnant patient.[23]

Fetal heart rate testing can be difficult to perform given the patient's adiposity. Often ultrasounds for biophysical profiles are the only option.

Q What should the physician expect during labor?

A Labor and delivery in obese women requires not only a labor floor equipped to handle obese patients but also proactive care and team management. Most obese patients have poor Mallampati scores (used to predict the ease of intubation).[24] Epidural anesthesia is not only desirable but also highly indicated in these patients, because it decreases oxygen consumption in labor and increases cardiac output. Spinal anesthesia may be difficult to place because of difficulty in locating landmarks. Thus consultation with anesthesia staff is best done antepartum, or at least early intrapartum, for best care of the patient.[25]

Although there is a risk of indicated premature delivery, most obese and morbidly obese women have an increased need for induction of labor due to postdates (OR, 0.57; 95% CI, 0.54–0.60, and OR, 0.43; 95% CI, 0.40–0.47, respectively) in comparison to women with a normal BMI at the start of pregnancy (OR, 1.21; 95% CI, 1.15–1.27).[26] These women, however, often fail labor induction. Those who start labor spontaneously are more likely to have a slower rate of cervical dilation and a more protracted labor course than those with a normal BMI.[27] Monitoring maternal contractions and fetal heart rate becomes more difficult as maternal BMI increases. This can make augmenting labor tedious.

For those who do deliver vaginally it is best to have adequate nursing and physician staff present, including staff from neonatology and anesthesia, given that obese patients have a greater risk of requiring an operative vaginal delivery.[5] The risk for shoulder dystocia, and thus birth trauma, is increased primarily because of fetal macrosomia.[28]

The physician should assess whether or not to have blood products available because both LGA/macrosomic infants and prolonged labor are risks for postpartum hemorrhage. Finding the fundus for fundal massage is often difficult in morbidly obese patients.

Obese pregnant patients have an increased risk for both emergent and elective cesarean deliveries.[9] Emergent cesarean deliveries are difficult due to:

TABLE 3 Congenital anomalies with increased prevalence in obese patients

Neural tube defects	Anal atresia
Cardiac defects	Cystic kidney
Orofacial clefts	Diaphragmatic hernia
Hydrocephaly	Omphalocele
Hypospadias	

Adapted from: Blomberg MI, Källén B.[19]

FACEBOOK POLL HOW DO YOU DEAL WITH OBESITY AND WEIGHT GAIN IN PREGNANCY IN YOUR PRACTICE? LET US KNOW AT FACEBOOK.COM/CONTEMPOBGYN

What course of action do you recommend to your obese pregnant patients?

- Weight maintenance
- Weight loss
- Weight gain

WEBSITES FOR PHYSICIANS AND PATIENTS

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

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

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

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

challenges if an epidural is not already placed or is not functioning well; presence of the pannus; adiposity that must be gone through even with elevation of the pannus; and difficulty of locating the fundus for assistance of fetal delivery. Personal and other experience has shown that for morbidly obese women with a large pannus, the easiest and most recommended incision is high transverse.[29]

Cesarean deliveries in obese pregnant women result in higher estimated blood losses, longer operative times, increased rates of wound infections, and increased rates of wound breakdowns.[30] A higher dose of antibiotics is needed to reach adequate levels. Rho(D) immune globulin should be administered intravenously to prevent failures.[31] Studies have shown that closure of the subcutaneous layer is beneficial in decreasing wound breakdown.[32]

It should also be ensured that the operating room table can handle the patient's weight and that there is enough operative staff to assist with the delivery. Failure rates for those women who required a cesarean delivery with a previous pregnancy and want to attempt a trial of labor after cesarean have been documented to be as high as 39%.[33]

Q What are the concerns about postpartum care?

A One of the biggest concerns postpartum is the risk of venous thromboembolism after surgery. There is insufficient evidence to support the use of low-molecular-weight heparin or unfractionated heparin to prevent venous thromboembolism rather than pneumatic compression devices and early ambulation.[34] In our opinion and experience, however, obese patients who are unable to ambulate should receive prophylactic anticoagulants.

Other concerns include higher rates of endometritis, decreased breastfeeding initiation and increased early discontinuation of breastfeeding, retained pregnancy weight, and postpartum depression.

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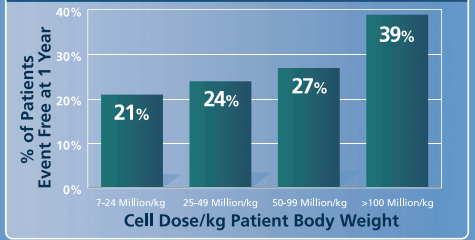

Transplant Success is the % of patients without events defined as death, autologous reconstitution and receipt of a second graft. All such events indicate graft failure.

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Q When is counseling best performed?

A Preconception counseling is important for encouraging weight loss and to assist in decreasing the risks not only to the mother but also to the fetus. Weight loss has also been associated with improved fertility rates and decreased adverse maternal outcomes without having a detrimental effect on fetal outcome.[35] COG

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GBS screening
An update on guidelines and methods

Great advances have been made in preventing neonatal GBS sepsis of both early and late onset. Despite recommendations, however, screening is not universal or uniform.

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Maternal screening and antibiotic prophylaxis guidelines for group B *Streptococcus* (GBS) have significantly evolved over the past 2 decades. Gaps in current maternal screening and treatment remain, however, impacting efforts to prevent infection in the potentially at-risk neonate.

This review article provides an overview of screening and addresses rapid screening and augmented screening techniques that impact sensitivity. It also outlines other potential opportunities for appropriate antibiotic prophylaxis against neonatal infection.

TAKE-HOME MESSAGES

- Antenatal screening and maternal antibiotic treatment during labor have reduced the burden of disease.
- There is a need to further define those at risk of early-onset infection and standardize screening methods.

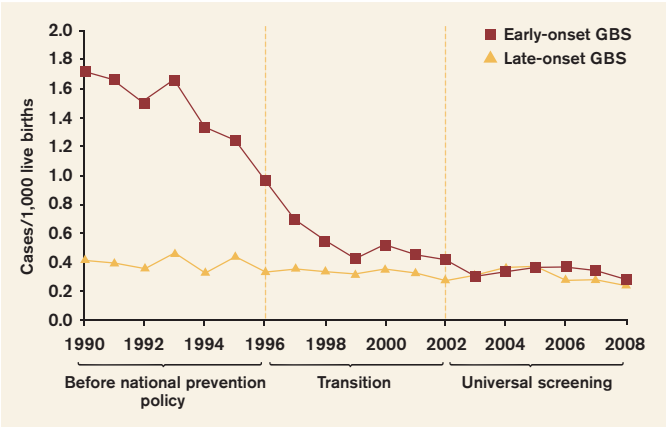
Neonatal GBS disease epidemiology

GBS screening in pregnancy is focused on prevention of neonatal disease via transmission during vaginal delivery. GBS was first studied in the peripartum period in the 1930s in an attempt

to explain frequent cases of maternal sepsis.[1,2] It took another 30 years for studies to associate GBS infection in mothers with transmission to the neonate.[3] Neonatal GBS sepsis is classified as early or late onset, with the former type occurring within the first week of life.

Disease incidence for early-onset GBS neonatal sepsis in the United States was as high as 2 per 1000 live births in the 1970s.[4] In 2008, the Centers for Disease Control and Prevention (CDC) reported that the figure had fallen to approximately 0.3 per 1000 live births, which translates to an estimated 1200 cases per year (Figure 1). Antenatal screening and maternal antibiotic treatment during labor have primarily reduced the burden of disease. Advances in pediatric medicine also have significantly reduced the case fatality rate from an estimated 50% in the 1970s to 4% to 6% in recent years. Because intrapartum treatment does not impact late-onset GBS, the epidemiology has not changed.

FIGURE 1 Trend of early and late-onset GBS



Incidence of early-and late-onset GBS disease in the Active Bacterial Core (ABC) surveillance areas from 1989 to 2008. The yellow line represents late-onset disease; the red line represents early-onset disease.
Source: www.cdc.gov/groupbstrep/downloads/Clinical_slideset.ppt

Screening guidelines: history and revisions

The first formal screening guidelines for GBS in pregnancy were released in 1992, based on the joint efforts of The American College of Obstetricians and Gynecologists (ACOG) and the American Academy of Pediatrics (AAP) (Figure 2).[5] These guidelines supported GBS screening and treatment aimed at reducing early-onset GBS neonatal disease.

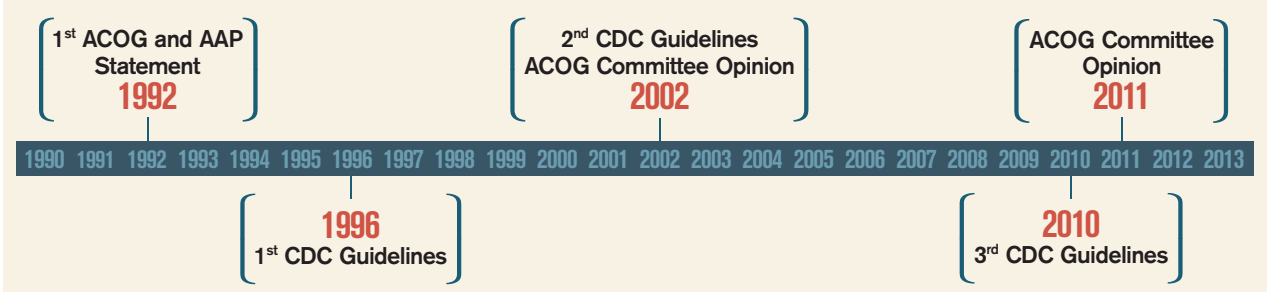
In 1994, Rouse et al evaluated 19 different protocols for screening/treatment and the 2 most effective ones were endorsed in the CDC's 1996 guidelines.[6] Those guidelines included a screening-based approach of providing intrapartum antibiotic prophylaxis based on positive antepartum screening *or* risk-based treatment (that is, <37 weeks' gestation, duration of membrane rupture >18 hours, or temperature >100.4° F), defined the appropriate methods of collection from the lower vagina and rectum, and specified the time point for screening as 35 to 37 weeks' gestation.[7] This time point was based on the premise that standard culture had a negative predictive value of 95% to 98%, which dramatically fell to 80% after 5 weeks.[8]

In its 2002 revised guidelines, the CDC recommended *universal* antepartum screening between 35 and 37 weeks' gestation.[9] Evidence for that recommendation was based on a population study of more than 600,000 women that showed that the screening strategy prevented 54% more cases of early-onset GBS neonatal disease than the risk-based approach.[10] In 2010, the CDC updated the 2002 guidelines and included additional information about preterm labor and preterm premature rupture of membranes (PPROM), elimination of erythromycin use, and optimal administration of intrapartum antibiotic prophylaxis for 4 hours prior to delivery, and provided an algorithm for the penicillin-allergic patient.[11]

The gaps

Despite the positive impact of universal screening, GBS neonatal infections still occur, which suggests opportunities to further define those at risk of early-onset infection. A recent prospective cohort analysis of almost 400,000 infants from 2006 to 2009 showed that in 160 neonates diagnosed with early-onset GBS sepsis, only 63% of the term mothers and 44% of the preterm mothers were screened, clearly reinforcing the need for education regarding screening among patients and providers.[12] Furthermore, in neonates with early-onset GBS disease, approximately 81% of the term mothers who were screened had a GBS-negative result, suggesting either suboptimal collection techniques or a true change in maternal colonization status.[12]

FIGURE 2 Timeline of formal GBS screening guidelines and recommendations



Collection recommendations and actual practices: discordance

The most recent ACOG Committee Opinion on prevention of early-onset GBS in newborns, dated April 2011, outlines methods for specimen collection and handling:

Swab the lower vagina (vaginal introitus), followed by the rectum (i.e. insert swab through the anal sphincter) using the same swab or two different swabs. Cultures should be collected by the health care provider or, with appropriate instruction, the patient herself. Cervical, perianal, perirectal, or perineal specimens are not acceptable, and a speculum should not be used for culture collection.[13]

Cervical samples yield 40% fewer positive cultures than do single vaginal swabs.[14] Studies have shown that sampling the vaginal and rectal regions in combination yields a significantly higher percentage of GBS colonization.[15,16] Perianal swabs may be equivalent to rectal swabs.[17,18] However, perianal collection may be suboptimal and therefore is not formally endorsed.[13] Updates of CDC and ACOG bulletins have attempted to clarify the sampling methods in order to standardize provider practices and to minimize the likelihood of suboptimal collection and false-negative results.

Self-collection of GBS cultures, with appropriate instruction, is considered an acceptable alternative. A randomized crossover study of 330 women in Canada showed that the sensitivity for the self collection—87.5% (95% CI, 77.0–93.8)—was fairly high when compared with clinician-obtained sensitivity of 96.9% (95% CI, 88.7–99.8).[19] A study involving 251 pregnant women found 98.4% sensitivity among those who self-collected GBS swabs.[20]

Disease incidence for early-onset GBS neonatal sepsis in the United States **was as high as 2 per 1000 live births in the 1970s**. In 2008, the Centers for Disease Control and Prevention (CDC) reported that the **figure had fallen to approximately 0.3 per 1000 live births**.

Lab testing: culture media to rapid testing

Laboratory testing with culture media, which typically requires 36 to 72 hours of incubation time, remains the gold standard. The most recent CDC guidelines recommend rapid testing, which takes < 30 minutes for results and has > 90% accuracy.[11]

The technical limitation with the original blood agar plates was overgrowth of other bacteria, which would limit the detection of GBS.[21] Modifications to this technique included addition of agents to suppress other bacteria and an enrichment broth to promote GBS growth.[22] The current gold standard after inoculation is to use selective enrichment broth (that is, Lim Broth, TransVag Broth, or Carrot Broth) and incubate for 18 to 24 hours. That is followed by a subculture using selective media for another 18 to 24 hours. If colonies are present, they undergo ex-

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TABLE 1 PCR or nucleic acid amplification test (NAAT) validation for GBS screening†

PCR Studies	n, sample size	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Time to run test (mins)	Test – Site
Bergeron et al 2000[27]	112	97.0 (82.5-99.8)	100 (86.9-100)	30-100	Conventional PCR vs. new fluorogenic PCR – Single center
Davies et al* 2004[28]	803	94.0 (90.1-97.8)	95.9 (94.3-97.4)	40	IDI Strep – Multicenter
Gavino et al* 2007[29]	55	95.8 (76.9-99.8)	64.5 (45.4-80.2)	<75	Xpert GBS Assay – Single center
Edwards et al 2008[30]	784	91.1 (86.1-94.7) 79.3 (72.8-84.8)	96.0 (94.0-97.4) 95.4 (93.4-96.9)	75	Xpert GBS Assay vs. IDI Strep – Multicenter
Money et al* 2008[31]	190	90.7 (79.7-96.9)	97.6 (93.1-99.5)	99	IDI Strep – Canadian single center
El Helali et al 2009[32]	968	98.5 (94.8-99.6)	99.6 (98.8-99.9)	<75	Xpert GBS Assay – French single center
Young et al* 2011[33]	559	90.8 (84.6-95.2)	97.6 (95.6-98.8)	41	Xpert GBS Assay – Single center

† Vaginal/rectal samples and intrapartum standard culture as gold standard.
*These studies also had comparisons with antepartum culture results.

traction to determine if Group A or B streptococcus is present and, if necessary, susceptibility testing for antibiotics (another 12 to 24 hours).

The need for prolonged incubation does not allow for point-of-care testing in labor. Therefore, many forms of rapid testing have been tried during the past 30 years. Rapid testing was first examined, using latex agglutination methods, in the 1980s, but it had poor sensitivity in those lightly colonized.[23] Optical immunoassay, enzyme immunoassay, and DNA hybridization all involved binding of GBS-unique antigens or RNA segments. Despite the dramatic reduction in processing time, these methods are suboptimal because of the wide range of sensitivity and specificity values.[24]

In the past 15 years, the use of polymerase chain reaction (PCR) or nucleic acid amplification tests (NAAT) has been intensely studied to improve speed and accuracy of GBS antepartum and intrapartum testing.[25,26] The two main tests—Xpert GBS Assay and IDI-Strep—utilize primers targeting specific DNA regions unique to GBS and do not require incubation with broth media. The most recent versions of the tests consistently have sensitivities of greater than 90% (Table 1).[27-33]

PCR tests have not been universally implemented in hospitals and outpatient laboratories, primarily due to cost and inability to run susceptibility testing if a culture tests positive. However, as technology advances and costs are driven down by increased utilization, the high sensitivity values make PCR-based tests more attractive options for intrapartum and possibly even antepartum cultures. Cost/benefit analysis models have shown a potential $6 benefit per birth if intrapartum PCR testing were used, compared with standard culture at 35 to 37 weeks' gestation.[34]

Rapid intrapartum GBS screening is ideal for women who have scant or no prenatal care, or those who present with preterm labor or PPROM. Utilizing PCR tests that give results in 1 to 2 hours for certain high-risk patients is more optimal than treatment according to risk factors. If a delay in receiving antibiotics is a concern, these patients may empirically receive 1 dose after the intrapartum screening. Then once the results are back, their care can be modified

The most recent CDC guidelines recommend **rapid testing**, which takes **<30 minutes for results** and has **>90% accuracy.**

A recent prospective cohort analysis of almost 400,000 infants from 2006 to 2009 showed that **in 160 neonates diagnosed with early-onset GBS sepsis, only 63% of the term mothers and 44% of the preterm mothers were screened.**

based on the results, thereby minimizing unnecessary exposure of the neonate to empiric antibiotic treatment.

The 2011 ACOG Committee Opinion provides an algorithm for women with unknown culture results and those with preterm labor or PPROM. While the Opinion does not suggest the use of rapid screening in these situations, it seems a logical alternative to empiric antibiotic prophylaxis or prolonged treatment in the neonatal period. Furthermore, a negative rapid test result has specific implications in a penicillin-allergic patient for whom clindamycin or vancomycin is the alternative antibiotic, in that such a drug would not be necessary under a negative-rapid-test scenario.

More recent work has been published using 35- to 37-weeks' gestation antepartum cultures and correlating those results with intrapartum cultures. In contrast to the 87% sensitivity reported by Yancey et al,[8] sensitivity values have been as low as 54.3% to 69.2% (Table 2).

As mentioned previously, interval conversion of maternal colonization also may contribute to the lower sensitivity values for standard antepartum cultures. However, suboptimal collection methods and lower levels of colonization also may be contributors to false-negative results. More sensitive DNA amplification assays may be beneficial in confirming a true positive in women with lower levels of colonization.

TABLE 2 Sensitivity of antepartum standard culture vs intrapartum NAAT*

Study	Antepartum standard culture sensitivity	Intrapartum NAAT sensitivity
Davies et al 2004[28]	54.3%	94.0%
Gavino et al 2007[29]	83.3%	95.8%
Money et al 2008[31]	84.3%	90.7%
Young et al 2011[33]	69.2%	90.8%

*Intrapartum standard culture as gold standard

Improved sensitivity for GBS detection potentially can be achieved with available modified testing techniques. These GBS tests first utilize a broth enrichment step, and then incubation for 18 to 24 hours, followed by PCR amplification of a GBS-specific primer to *Streptococcus agalactiae*, which takes approximately 1 hour. Illumigene, an example of such a modified test, targets the highly conserved 213 base-pair sequence of the *S agalactiae* genome found in all 8 GBS strains. The combination of steps yields a sensitivity of 98.6% (95% CI, 96.5–99.5) and specificity of 93.2% (95% CI, 91.6–94.5). This test was designed to improve accuracy of *antepartum* GBS screening and is not intended for intrapartum use.

Data demonstrating greater sensitivity than standard culture are based on the fact that 64 culture-negative specimens were positive by both illumigene GBS and an independent molecular method. BD GeneOhm is another combination PCR test that has a somewhat wider range of sensitivity, depending on the culture media used for enrichment (92.5%–100%).[26] Further studies will verify the potential benefits of these methods in confirming higher sensitivity in detecting antepartum GBS colonization.

Additional studies are needed to re-evaluate the optimal time for screening, because testing closer to the time of delivery may identify more women who are false-negative. Efforts at minimizing false-negatives are central to identifying women who should receive intrapartum antibiotic prophylaxis to prevent neonatal GBS disease. COG

WHAT YOU NEED TO KNOW

- Early-onset GBS neonatal sepsis has significantly declined with widespread screening and treatment in labor over the past 20 years.
- ACOG defines proper sample collection to include a swab of the lower vagina (vaginal introitus) and the rectum (inside the anal sphincter).
- Rapid testing by PCR amplification will be increasingly useful in patients who are late entries to prenatal care or have preterm labor or PPROM and can potentially avoid overuse of neonatal antibiotics and prolonged neonatal hospital stay.
- Wider use of DNA amplification assays may provide a benefit of higher sensitivity and minimize false negatives.
- Further investigation is needed to reevaluate the timing for antepartum screening.

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Editorial continued from **PAGE 10**

Many possible RPL genes may be found to code for proteins crucial to early embryonic and fetal development as well as those, as reported above, associated with lethal arrhythmias. Epigenetic and even microRNA abnormalities may also be involved.[12]

Eventually, relatively inexpensive multi-gene panels and other high throughput screens may be used to screen for genetic causes of isolated and recurrent pregnancy loss providing closure to patients as to the cause of heartbreaking losses and eliminating often irrational impulses of guilt and anger that can have professional liability consequences. It will also dissuade physicians from employing aggressive, expensive and/or unproven treatments in an effort help desperate patents.

In the interim, additional studies should be initiated to determine the prevalence of arrhythmogenic mutations as a cause of otherwise unexplained fetal losses. This approach has the added advantage of identifying affected parents who can then be offered life-saving interventions. COG

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Managing heavy menstrual bleeding in adolescents

Diagnosis and treatment involve ruling out bleeding disorders and determining the appropriate management modalities.

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Heavy menstrual bleeding (HMB) is one of the most common adolescent gynecologic complaints, with prevalence rates ranging widely from 12.1% to 37%.[1,2] The differential diagnosis is broad: anovulatory bleeding is common, and hypothyroidism should be considered. Bleeding disorders may be the underlying cause in approximately 20% of cases.[3–5] The importance of early recognition of HMB and its underlying cause is underscored by the negative impact on quality of life, which may include missed school days, lifestyle disruption, development of iron deficiency, and fatigue.[6,7] HMB is objectively defined as prolonged (>7 days) or excess blood loss of over 80 mL per menstrual cycle.[8]

Estimating menstrual blood loss is difficult: a pictorial bleeding assessment calendar (PBAC) score has been developed and validated in adult women, with more than 80% sensitivity and specificity for scores higher than 100 being associated with blood loss of more than 80 mL.[9] The PBAC experience in an adolescent population is limited,[10] leading some clinicians to question its use and interpretation in the clinical setting. Clinical characteristics that predict HMB include clots larger than 1 inch, low serum ferritin, the need to change a pad or tampon because it is saturated more than hourly, or flooding.[8]

Differential diagnosis

HMB in adolescents is often related to an immature hypothalamic-pituitary-ovarian (HPO) axis, resulting in anovulatory cycles. Up to 85% of cycles are anovulatory in the first year after menarche and up to 44% of cycles at 4 years after menarche.[11] However, when a patient presents with significant bleeding, an astute clinician will still entertain a bleeding diathesis superimposed on the HPO immaturity/anovulation mechanism. Polycystic ovary syndrome occurs in 5% to 10% of adolescents[12] and may result in HMB episodes due to prolonged periods between menses and over-thickening of the endometrial lining. Other endocrinopathies, such as hyper/hypothyroidism and Cushing syndrome, can

TABLE 1 Clinical manifestations of bleeding disorders

Symptom	PFD/ VWD	Clotting Factor Deficiencies
Location of bleeding symptoms	Mucocutaneous: epistaxis, oral cavity, GI, GU	Deep-tissue: joints and muscles
Heavy menstrual bleeding	Common (up to 60%)[23]	Common (up to 50%)[24]
Ecchymoses	Common, superficial, may be associated with small subcutaneous hematomas	Large subcutaneous and soft-tissue hematomas
Petechiae	Common	Uncommon
Bleeding after minor cuts	Common	Uncommon
Deep tissue bleeding (joint and muscle bleeds)	Uncommon	Common and spontaneous in severe factor deficiencies. Provoked by injury in mild-to-moderate deficiencies.
Bleeding with invasive procedures	Immediate	Delayed
Manifestations other than bleeding	Generally none Rare subtypes of PFD can be associated with hearing loss, mental retardation, albinism.	Generally none Dysfibrinogenemia has an increased risk of thrombosis. FXIII deficiency is marked by poor wound healing. Both are associated with recurrent miscarriages.

Abbreviations: FXIII, factor XIII; GI, gastrointestinal; GU, genitourinary; PFD, platelet function disorder; VWD, von Willebrand disease.

also result in HMB. Because up to 62.3% of teens are sexually active by grade 12,[4] pregnancy-related complications need to be considered and ruled out. Anatomic abnormalities, such a duplication of the Müllerian system and double vagina, may present with the perception of tampon overflow. Polyps and fibroids are rare causes of bleeding in this age group.

The differential diagnosis should guide the features of the physical examination and the investigations chosen. These *may* include: a speculum examination, a pregnancy test, cervical swabs for *Trichomonas*, *Neisseria gonorrhoeae* and *Chlamydia trachomatis*, and an ultrasound of the pelvis. A speculum examination is not always indicated, especially when the teen is precoital and the bleeding is unlikely to be from the lower genital tract. If a more complete examination is indicated in a young teenager or "tween," vaginoscopy is a valuable tool and less traumatic than a speculum exam.

A complete blood count and platelet count are important to rule out anemia or thrombocytopenia. Serum ferritin is useful to rule out iron deficiency. Thyroid-stimulating hormone screening should be performed in all patients because hypothyroidism can result in HMB. It is important to note that a normal blood count, platelet count, or coagulation studies (prothrombin time/interational normalized ratio and partial thromboplastin time do not exclude most bleeding disorders.

Menorrhagia and bleeding disorders

A congenital bleeding disorder is suspected when there is a personal or family history of bleeding. An acquired bleeding problem may be suspected with anticoagulant therapy, medications that inhibit platelet function, or when there are comorbidities such as renal disease, liver disease, and hypothyroidism. No single bleeding symptom is pathognomonic of a specific bleeding disorder, and significant overlap exists among the clinical manifestations of all the bleeding disorders (Table 1). Among patients with bleeding disorders, HMB is very common and may be the only bleeding symptom in 20% of adolescents.[6]

Philipp et al developed a screening tool with sensitivity of 82% for women with HMB to try to better identify an underlying bleeding disorder. The screen is positive if the patient reports (1) duration of menses ≥ 7 days, "flooding," or impairment of daily activities with menses; (2) a history of treatment for anemia; (3) a family history of a diagnosed bleeding disorder; or (4) a history of excessive bleeding with tooth extraction, tonsillectomy, adenoidectomy, delivery, or miscarriage, or bleeding complications from surgery.[13] Combining this screen with a positive PBAC increases sensitivity to 95%. In addition, women who meet the criteria summarized in Table 2 should be evaluated for a bleeding disorder.[14] Because an adolescent will not have been exposed to many hemostatic challenges such as delivery or surgery, a history of significant bleeding in the patient's mother may indicate an unrecognized bleeding disorder and should prompt investigations. Frequently diagnosed bleeding disorders in women with HMB include von Willebrand disease (VWD), mild platelet function disorders (PFD), and mild factor deficiencies (eg, Factor XI).

The approach to investigation is outlined in Table 3. Intra-patient variation in coagulation studies,

particularly von Willebrand factor (VWF), is influenced by physiologic stressors and hormones. Testing should be avoided in stressed, ill, or pregnant patients, including in the context of acute severe hemorrhage. Serial testing (on ≥ 2 different occasions) for VWD is often required to make the diagnosis. Platelet function testing is poorly standardized and most abnormalities are mild and difficult to interpret. Thus, bleeding disorder investigations should be ordered and interpreted in collaboration with a hematologist.

HMB may also be multifactorial. Therefore, a gynecologic etiology does not rule out an underlying bleeding disorder. In fact, women with bleeding disorders and HMB may experience other gynecologic conditions at an increased frequency. In a case-control study, Kirtava et al found that 30% of women with VWD reported a history of endometriosis and 52% reported a history of ovarian cysts, as compared to 13% and 22% of controls.[15] On the other hand, a retrospective review of adult women with bleeding disorders failed to demonstrate the same degree of gynecologic burden.[16] Regardless, a low index of suspicion is required in the approach to investigation of HMB.

Treatment

In all patients with HMB, iron deficiency should be assessed and treated. No one iron preparation is more effective than another, so a patient should be encouraged to try different preparations if adverse effects are limiting. The target dose is in the range of 150 mg/day to 200 mg/day of *elemental iron* in 1 to 3 divided doses/day. To aid in absorption, iron supplements should be taken on an empty stomach with a glass of orange juice. The duration of replacement should extend at least 3 months beyond normalization of hemoglobin to allow for replenishment of iron stores.

Treatment of HMB will be determined by the underlying etiology, the patient's need for contraception, her adherence or compliance capabilities, and the acceptability of adverse effects, costs, and interventions. There is a significant overlap in the management of patients with and without bleeding disorders.[4,14,17] Combined hormonal contraception such as oral contraceptive pills, the transdermal patch, and the vaginal ring are effective in the treatment of HMB. Eighty-six percent of adolescents with VWD will have a significant decrease in their PBAC scores using combined hormonal contraception.[18]

Both cyclic and continuous use of combined hormonal contraception are efficacious, with adolescents often preferring an extended cycle.[19] Oral progestin therapy can be effective but is often poorly tolerated and therefore rarely used.[4,19] After an informed discussion about impact on bone density, potential for nuisance irregular bleeding or amenorrhea, and possible weight gain, long-acting injectable or subcutaneous progestins can be considered.

TABLE 2 Criteria that prompt evaluation for bleeding disorders

Gynecological or obstetrical bleeding symptoms
• Heavy menstrual bleeding since menarche • Hemorrhage from a corpus luteum • Postpartum hemorrhage
Family history
• Family history of a bleeding disorder • Family history of significant bleeding complications that has not yet been investigated
Personal history of ≥1 of the following symptoms:
• Epistaxis (>10 min, or requiring medical attention), spontaneous bruising (>2 cm), or minor wound bleeding (>5 min) • Bleeding from oral cavity or GI tract without an obvious anatomic lesion • Prolonged or excessive bleeding after dental extraction or surgery • Hemorrhage that required blood transfusion

Adapted from James AH, Kouides PA, Abdul-Kadir R, et al.[14]
Abbreviation: GI, gastrointestinal.

Finally, the levonorgestrel-releasing intrauterine system has been demonstrated to be effective in reducing menstrual blood loss. Despite initial concerns regarding safety and acceptability in adolescents, it appears to be safe and well-tolerated in properly selected teens.[4,14,19]

In patients who do not tolerate hormonal therapies or wish to be fertile, antifibrinolytic inhibitors, such astranexamic acid, 1-1.5 g 3 to 4 times per day, have been shown to be useful for treatment of HMB in a wide range of clinical situations, including VWD and PFD and in those with no bleeding disorder. Desmopressin acetate (DDAVP) induces secretion of VWF from endothelial cells and results in an increase in VWF and FVIII. The best defined indications for DDAVP are VWD[20] and Hemophilia A,[21] where in mild-to-moderate disease, DDAVP raises factor levels 3- to 10-fold.

DDAVP is also clinically useful in PFDs.[22] DDAVP use is associated with response rates of 77% in HMB[18] but is limited by tachyphylaxis and issues surrounding fluid retention and hyponatremia.

TABLE 3 Suggested approach to investigation of bleeding disorders

First Line	• CBC, PBS, APTT, PT, TT, fibrinogen • Ferritin, renal and liver function tests, TSH • VWF:Ag, VWF:RCo, FVIII
Second Line*	• Repeated VWF:Ag, VWF:RCo, FVIII • Platelet function testing
Third Line*	• Factor assays (eg, II, V, VII, XI, XIII) • Further subspecialized testing should be directed by clinical picture

* Testing should be done in consultation with a hematologist.
Abbreviations: APTT, activated partial thromboplastin time; F, factor; PBS, peripheral blood smear; PT, prothrombin time; TSH, thyroid-stimulating hormone; TT, thrombin time; VWF:Ag, von Willebrand factor antigen; VWF:RCo, von Willebrand factor ristocetin cofactor activity.

Use of multiple modalities (such as combination hormonal contraception and tranexamic acid or DDAVP), or replacement of the missing coagulation factors to gain adequate control of menstruation (such as with VWF concentrate in severe VWD) may be necessary in women with severe or refractory cases.

A multidisciplinary approach, with involvement of a hematologist, is recommended. Surgical intervention, including dilation and curettage and Foley balloon tamponade, is rarely necessary and should be reserved for refractory or life-threatening HMB that is unresponsive to medical and less-invasive therapies.

Summary

HMB is a common complaint in adolescence. The differential diagnosis is broad and requires a low threshold for investigation, particularly for bleeding disorders. A multidisciplinary approach with involvement by both gynecologists and hematologists can be beneficial in making the diagnosis of a bleeding disorder and is invaluable in the management of these patients. COG

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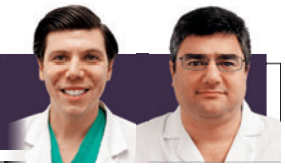


An EHR primer

Part 1: Current laws and incentives

Electronic health records (EHRs) or electronic medical records (EMRs) have become not only commonplace, but a virtual federal mandate. Doctors no longer write, but instead must point, click, and type, and do it quickly. In this 2-part series we will introduce you to current regulations and federal subsidies, discuss software solutions to help improve your daily workflow, review the current technology, and educate you about the jargon-filled email that you receive daily.

For simplicity, we will use the acronym EHR to broadly discuss electronic health records. How to distinguish between an EHR and an EMR? In the purest sense, an EMR contains only the information that your patient generates in your practice, and an EHR is the patient's *complete* health records from all providers who have communicated with your health record system.

The promise of the EHR

In an ideal world, the EHR provides a longitudinal electronic record of a patient's complete medical history. It is populated with the patient's demographics and a complete and detailed outline of the patient's medical history, surgical history, previously taken medications, current medications, allergies, and active medical problems. It includes a comprehensive record of all patient encounters and efficiently links all associated laboratory tests/results, procedures, and interventions. Ultimately, the EHR is designed to streamline the workflow of all who interact with it (eg, physicians, physician assistants, nurses, technicians).

> An EHR should **streamline the workflow** of all who interact with it.

It is important to recognize that first-tier improvements in healthcare outcomes can be achieved by reducing medical errors. Notes can be streamlined for easy understanding. Specific data fields can be linked to laboratory testing and medical orders to help facilitate care. Automated alerts for abnormal laboratory testing and drug interactions can help decrease the risk of complications.

Globally, a properly implemented EHR can track the individual healthcare outcomes of specific patients, groups of patients, or even whole populations. These data can give local health, state, and national agencies the information to make evidence-based healthcare policy decisions. Office practices can become more efficient using an EHR to manage both the patient encounter and ancillary office processes. Chart rooms are downsizing, along with the associated staff needed to process charts and copy records.[1] E-prescribing allows for prescriptions to be directly transmitted to the pharmacy, reducing the potential for error as medication orders move from physicians to nurses to pharmacy assistants and, finally, to pharmacists. Additionally, e-prescribing allows for automated drug interactions and formulary checking, further increasing efficiency. Similarly, ordering laboratory and diagnostic testing electronically reduces another paper-driven and labor-intensive task. Using secure electronic communication further streamlines office practices.

The reality of the EHR

Unfortunately, there is no single manufacturer that has the "ideal" EHR because, quite simply, we do not have a unified healthcare system. Instead, those physicians who are in private practice have the freedom to choose their own EHRs, those associated with hospital-based practices typically have to use a system that communicates

with the hospital's system, and those who practice in government-based systems (ie, the Veterans Health Administration) must use the government-issued EHR. While it can be profitable to be an EHR manufacturer, it can be a bit overwhelming to be an EHR consumer, due to the sheer breadth and depth of the available electronic health solutions.

In an attempt to level the playing field by defraying the mind-boggling costs of implementing an EHR and help bring all providers from paper to computers, President Obama signed the American Recovery and Reinvestment Act (ARRA) in 2009. Within this bill was a section called the Health Information Technology for Economic and Clinical Health Act (also known as the HITECH Act). Under this stimulus package, the federal government laid out a plan to incentivize EHR adoption for Medicare and Medicaid providers. In essence, the government offered subsidies for those Medicaid/Medicare providers who adopted EHRs, but the providers had to demonstrate that the EHR was going to be used in a meaningful way. Providers who were not hospital-based and who participated in Medicare or derived 30% or more of their revenue from Medicaid were eligible to receive subsidies. Although providers could apply for either of these programs, they could not receive subsidies from both.[2,3]

According to the Centers for Medicare & Medicaid Services (CMS), "The Medicare and Medicaid EHR Incentive Programs are staged in 3 steps with increasing requirements for participation. All providers begin participating by meeting the Stage 1 requirements for a 90-day period in their first year of meaningful use and a full year in their second year of meaningful use. After meeting the Stage 1 requirements, providers will then have to meet Stage 2 requirements for 2 full years. Eligible professionals participate in the program on the calendar years, while eligible hospitals participate according to the federal fiscal year." For individual practitioners, CMS outlines a total of 24 "meaningful use objectives;" a provider can apply for a subsidy only after 19 of the 24 objectives are met.[4]

Those Medicare providers who applied in 2011 or 2012 were eligible to receive $18,000 in reimbursements that year, followed by annual payments of $12,000, $8,000, $4,000, and $2,000. Those who apply in 2013 can receive $15,000 in the initial year, followed by 3 years of diminishing payments. Providers who apply in 2014 will receive a first-year subsidy of $12,000 with lower incentives the following 2 years; those who apply after 2014 will receive no subsidies. There are also no payments after 2016.

Thus, a Medicare-eligible professional qualified in 2011 or 2012 would receive a total payment of $44,000. For those qualified in 2013 the total payment would be $39,000, and those who qualified in 2014 would receive a total payment of $24,000. Medicare-eligible professionals who predominantly deliver services in areas designated as Health Professional Shortage Areas (HPSAs) can receive a 10% increase in their annual EHR incentive payments.[5]

TABLE Medicare and Medicaid EMR incentive comparison

Medicaid maximum incentives for EMR users (85% of the cost of purchasing and implementing EMR)						
	Adopt in 2011	Adopt in 2012	Adopt in 2013	Adopt in 2014	Adopt in 2015	Adopt in 2016
2011	$21,250					
2012	$8,500	$21,250				
2013	$8,500	$8,500	$21,250			
2014	$8,500	$8,500	$8,500	$21,250		
2015	$8,500	$8,500	$8,500	$8,500	$21,250	
2016	$8,500	$8,500	$8,500	$8,500	$8,500	$21,250
2017		$8,500	$8,500	$8,500	$8,500	$8,500
2018			$8,500	$8,500	$8,500	$8,500
2019				$8,500	$8,500	$8,500
2020					$8,500	$8,500
2021						$8,500
TOTAL	**$63,750**	**$63,750**	**$63,750**	**$63,750**	**$63,750**	**$63,750**

Medicare maximum incentives for meaningful EMR users						
	Adopt in 2011	Adopt in 2012	Adopt in 2013	Adopt in 2014	Adopt in 2015	Adopt in 2016
2011	$18,000					
2012	$12,000	$18,000				
2013	$8,000	$12,000	$15,000			
2014	$4,000	$8,000	$12,000	$15,000		
2015	$2,000	$4,000	$8,000	$12,000		
2016		$2,000	$4,000	$8,000		
TOTAL	**$44,000**	**$44,000**	**$39,000**	**$35,000**	**$0**	**$0**

Source: Texas Medical Association. http://www.texmed.org/template.aspx?id=18197

The Medicaid system also has a yearly subsidy but the total payment is the same regardless of the year of enrollment (as of June 2013); it is $63,750 over 6 years. The additional 10% HPSA incentive is not available for eligible professionals who participate in the Medicaid EHR Incentive Program (Table).

There are also penalties for not playing well in the proverbial sandbox. Medicare providers who do not adopt EHRs by 2015 will receive diminishing Medicare reimbursements: by 1% in 2015, by 2% in 2016, and by 3% in 2017. Cuts may continue to 5% by 2019. Penalties can also be applied if 75% of office-based physicians in a practice have not achieved meaningful use. As of June 2013, there are no scheduled Medicaid penalties. It is possible to switch between Medicare and Medicaid incentive programs one time but the last payment year during which a switch can occur is 2014.[6]

Even if you are not a Medicare/Medicaid provider, be aware that health insurance companies typically take their cost-saving cues from the federal government. The only twist is that a health insurance company will likely not incentivize the adoption of an EHR.

Making the transition

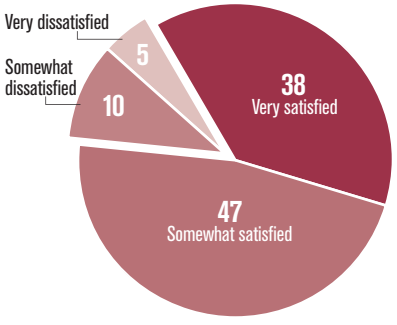
Obviously, transitioning to an EHR is costly. In fact, when evaluating EHR adoption, it is important to factor in 3 specific costs: 1) The cost of purchasing the EHR and the requisite computers/hardware, 2) The time spent in not only learning how to use the EHR, but also uploading patients' charts and altering workflow efficiency, and 3) The cost of continued maintenance, upgrades, and backups. In short, it is hard to make money without spending money.

But EHR transitions are not always negative experiences. In fact, in a recent CDC publication, it was reported that the majority of physicians who adopted an EHR system (85%) were either very satisfied (38%) or somewhat satisfied (47%) with their system (Figure). Only about 15% of providers were either very dissatisfied (5%) or somewhat dissatisfied (10%) with their EHR system. In fact, more than two-thirds of adopters (71%) would purchase their EHR system again. The report goes on to state that the high degree of physician satisfaction was rooted in the ability to access a patient's chart remotely (74%) and to be alerted to critical lab values (52%). A majority of physicians (74%) reported that they felt that their EHR had resulted in better patient care.[7]

And in case you were wondering how many folks have really made the transition, in the same CDC report, it states that as of 2011, 54% of physicians had adopted an EHR, with nearly three-quarters of physicians reporting that their system met federal "meaningful use" criteria. This means that not only are physicians adopting the technology, but also that they are using it and being reimbursed for their actions.[8]

Figure: EHR Satisfaction

Percent distribution of electronic health record satisfaction among office-based physicians: United States, 2011



Notes: Data represent office-based physicians who reported having adopted electronic health record systems (55% of sample). The sample includes nonfederal, office-based physicians and excludes radiologists, anesthesiologists, and pathologists. Missing values are excluded. Source: CDC/NCHS, Physician workflow study, 2011.

Though an EHR's potential is limited only by the creativity of those who design it, it is not a magic remedy for all that ails the healthcare system. Interoperability—the ability to communicate both within a single healthcare system and among different healthcare systems—remains the most significant obstacle to the transition to effective and efficient care.[9] Without seamless communication among the various EHR/EMR products, the goals of improving quality of care, tracking healthcare outcomes, and reducing healthcare costs will remain far short of expectations.

You now have a sense of where EHR technology originated and where it needs to go. In our next installment we will dive into the technical aspects of the "hows," "whats," and "whys" of EHR adoption and implementation. COG

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SECTION EDITOR

Should PGD be used for elective gender selection?

Prebirth sex selection can be seen as a reasonable way to achieve family balance or as the edge of a very slippery slope.

PRO

Benefits for family balance outweigh potential risks

By John A. Robertson, JD

Any talk of sex selection is charged because so many questions are wrapped up in the issue. The methods that may be used—preconception sperm selection, preimplantation embryo screening, and abortion—vary in their efficacy, cost, and moral acceptability. Globally, sex selection is generally used to avoid the birth of females, so the impact on population sex ratios and the role of women in society must be considered. The limits to procreative liberty also have to be discussed. Finally, from the perspective of human dignity, we also should consider whether we should accept yet another technological incursion into how we make families.

For physicians who treat patients using assisted reproductive technology (ART), sex selection poses a special challenge. In vitro fertilization (IVF) is used to treat infertility, and preimplantation genetic diagnosis (PGD) is employed to avoid the birth of children with serious genetic diseases. Sex selection for nonmedical reasons raises questions about why IVF should be used for this purpose. Indeed, the American Society for Reproductive Medicine (ASRM) says that PGD for sex selection should be discouraged. Unless a woman is already undergoing IVF for other reasons, sex selection requires a stimulation cycle solely for this purpose. Also, embryos will be created and destroyed because of their sex alone.

Issues of family balance

I find it useful when unraveling these ethical issues to give strong weight to family balancing (that is, gender variety). Freedom to decide to reproduce or not is important, and should be respected unless there are compelling reasons to limit that freedom. This means that some choice over the genetic characteristics or other characteristics of offspring is included in that liberty, because it is precisely those characteristics—and the expected experience of raising those offspring—that will help couples to decide whether to reproduce.[1]

Once we accept that some degree of prebirth choice over a child's characteristics is acceptable, we must then address the harm that this choice might cause. In the United States, we do not need to fear that PGD for sex selection will upset sex ratios or further entrench patriarchy. Women are treated equally before the law and have ample opportunities for education and employment as well as nearly equal treatment in most relevant respects. Nor is the child likely to be harmed, as long as the technique is medically safe. Even without sex selection parents have expectations

for their children that may vary with their sex. Sex selection alone is not likely to drastically increase those expectations, or do so in a way that is unduly harmful to the chosen child.

Gender bias and gender variety

With controversy still surrounding the issue of sex selection, however, a reasonable way to proceed is to allow parents to select a child that is the opposite sex of one or more of their existing children. The idea here is to introduce gender variety into a family. Rearing boys is a different experience from rearing girls, and I find it reasonable that parents would desire both experiences. Interestingly, it is often the female partner who is motivated to this end, so that she might, for example, have a girl after one or more boys. Justice Ruth Bader Ginsburg, who has strong feminist credentials, wrote in a landmark sex discrimination case that "inherent differences between men and women, we have come to appreciate, remain cause for celebration."[2]

Physicians should not be required to be involved in PGD for gender variety, but I do not find it unethical if one chooses to do so. Selecting the gender of a first child, particularly if the choice is for a male, raises other issues, because of the advantages that some people think accrue to the first-born from greater parental investment in its rearing and well-being. While opting for a first-born female may not pose the same entrenchment-of-patriarchy problems as opting for a first-born male, initially sex selection for gender variety should be limited to second-born and subsequent children. For the time being, using IVF and PGD for the purposes of achieving gender variety poses no risk of serious harm to offspring, society, or women. Use of ART and PGD to choose a child of a different sex than existing children should be acceptable. COG

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CON

Elective sex selection is a slippery slope

By Timothy Hickman, MD

Interest in gender selection has a long history, dating to ancient times. Methods have varied from special modes and timing of coitus to the practice of infanticide. Only recently have medical technologies made it possible to attempt gender selection of children before embryo implantation or even conception. In my opinion, preimplantation genetic diagnosis (PGD) used for gender selection to prevent the transmission of serious genetic disease is ethically acceptable. It is not inherently gender-biased, bears little risk of consequences detrimental to individuals or to society, and is a use of medical resources for reasons of human health.

The question is: Should PGD be used for elective gender selection? Members of the ethics committees of the American Society for Reproductive Medicine (ASRM) and the European Society of Human Reproduction and Embryology (ESHRE) have thought long and hard about this topic, and the latest ASRM Ethics Committee publication on sex selection states, "The initiation of in vitro fertilization (IVF) with PGD solely for sex selection holds even greater risk [than medically indicated PGD] of unwarranted gender bias, social harm, and the diversion of medical resources from genuine medical need. It therefore should be discouraged."[1] The ESHRE Task Force on Ethics and Law states, "the embryo is owed respect as a symbol of future human life."[2]

The 4 areas of concern that I have about non-medically indicated use of PGD for gender selection are: (1) the potential for harm to the embryo in order to obtain the desired information; (2) gender bias; (3) the use of medical resources for reasons other than human health; and (4) the disposition of the normal embryos of the "undesired" gender.

Potential for harm to the embryo

The only reliable technique for determining gender before implantation is embryo biopsy at the cleavage or blastocyst stage. Unfortunately, prefertilization techniques such as sperm centrifugation and flow cytometry are either ineffective (sperm centrifugation) or not available for elective gender selection (flow cytometry, ie, MicroSort). Both embryo biopsy techniques carry intrinsic risk to the future well-being of the embryo being analyzed. It is hard to calculate a precise risk of the procedure but a recent publication by Treff et al[3], in which sibling cleavage-stage embryos or sibling blastocyst-stage embryos were transferred with or without biopsy, suggested that cleavage-stage

embryo biopsy decreases embryo viability by 40%, which in my opinion is far too great a price to pay for the information obtained. The authors calculated that biopsy of blastocyst-stage embryos (also known as trophectoderm biopsy) decreases embryo viability by 4%. Furthermore, reliable DNA sequencing techniques to ascertain accurate results (microarray, real-time PCR, etc.) often take longer than 24 hours; hence, the implantation phase is often missed, and embryos often need to be frozen and subsequently thawed. The freeze/thaw process also undoubtedly has some detrimental effect on embryo viability, since it is illogical that freezing and subsequently thawing an embryo would increase its viability. I am willing to concede this point because I think it is likely that in the near future the science of biopsying, freezing, and thawing of embryos will evolve to the point where little to no risk will exist.

From gender bias to social dysfunction

We need not look any further than the current state of affairs in China to see the result of extreme gender selection. Given the Chinese government's mandate of only 1 child per family and a bias toward male children, approximately 30 million more men than women will reach adulthood by 2020.[4] These men have 2 options: find partners abroad or become "bare branches"—as the Chinese expression goes—unlikely ever to bear fruit. I think that it is extremely unlikely that the use of PGD for gender selection in the United States would lead to anything like China's current situation, but I have a hard time whole-heartedly supporting a policy that could, if taken to extremes, result in such social dysfunction.

Use of medical resources for non-medical reasons

I will leave this argument for the economists and health resource allocation experts. Suffice it to say that the use of IVF in the United States as well as abroad is, at least to some extent, subject to "free market" economics. Until insurers worldwide recognize infertility as a disease state and begin to cover IVF for medical indications, patients have to pay at least some, if not all, of the costs on their own, as is the case with cosmetic plastic surgery and other procedures that are deemed to be elective.

Disposition of normal but 'undesirable' embryos

The disposition issue is the hardest issue to resolve because this technique invariably produces embryos that are ultimately "undesired." If we are to uphold the ethical tenet that "the embryo is owed respect as a symbol of future human life," an adequate answer to the disposition question must be found before the intentional creation of "undesired" euploid embryos. What troubles me most is a scenario in which a couple uses PGD for gender selection and creates embryos that are all of the "undesired" gender, and then discards them. Whether the solution will be attempted use of all euploid embryos by the genetic parents or by nongenetic parents through embryo donation, donation of all undesired embryos to research, or something else, the default destruction of a large percentage of euploid embryos seems to me to be the wrong answer.

Ethics may limit 'reproductive freedom'

Reproductive freedom has never been considered an absolute right, and certainly not if it is extended to include every sort of decision about reproduction or every demand for positive support of a person's reproductive decisions. Still, serious reasons must be provided to justify a limitation on reproductive freedom. Therefore, weighing opposing positions on PGD and gender selection depends on an assessment of the strength of various reasons given for and against it.[1]

Of the 4 concerns about PGD for gender selection I have presented, the issue of disposition of undesired euploid embryos carries with it the most serious ethical questions and reasons for proceeding with caution. The vast majority of medical ethicists, and the general population, agree that the use of PGD to select for traits like eye color, hair color, intelligence, height, athletic ability, musical aptitude, etc. is inappropriate. When we consider ethical concerns surrounding PGD for gender selection and PGD for trait selection they look quite similar.

Moreover, if, as a society, we cannot agree upon an ethical solution on the disposition of normal embryos of "undesired" gender, I see little preventing us from traveling down the slippery slope to a potential reproductive dystopia, where potentially invasive measures are used to obtain information on preimplantation embryos (such as gender and other elective traits) without regard to societal impact. COG

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3. Treff NR. Cleavage stage embryo biopsy significantly impairs embryonic reproductive potential while blastocyst biopsy does not: a novel paired analysis of cotransferred biopsied and non-biopsied sibling embryos. *Fertil Steril*. 2011;96(3):S2.
4. Brooks R. China's biggest problem? Too many men. http://www.cnn.com/2012/11/14/opinion/china-challenges-one-child-brooks. Accessed June 17, 2013.

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AUGUST

28-31: Society of Laparoendoscopic Surgeons Minimally Invasive Surgery Week/Annual Meeting and Endo Expo
Reston, Virginia
FOR MORE INFORMATION: *laparoscopy.blogs.com/ee06*

SEPTEMBER

6-18: 4th Annual Private Practice Physicians of America Multispecialty CME Conference
Celebrity Infinity Cruise Ship leaving Harwich, England
FOR MORE INFORMATION: *rankdad@aol.com*

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

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

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

OCTOBER

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

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

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

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

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

NOVEMBER

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

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

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

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

INDICATIONS AND USAGE

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

Limitations of Use

DICLEGIS has not been studied in women with hyperemesis gravidarum.

DOSAGE AND ADMINISTRATION

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

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

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

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

DOSAGE FORMS AND STRENGTHS

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

CONTRAINDICATIONS

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

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

WARNINGS AND PRECAUTIONS

Activities Requiring Mental Alertness

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

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

Concomitant Medical Conditions

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

Drug Interactions

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

Drug-Food Interactions

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

ADVERSE REACTIONS

The following adverse reactions are discussed elsewhere in labelling:

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

Clinical Trial Experience

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

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

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

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

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

Postmarketing Experience

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

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category A

DICLEGIS is intended for use in pregnant women.

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

Nursing Mothers

Women should not breastfeed while using DICLEGIS.

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

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

Pediatric Use

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

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

OVERDOSAGE

Signs and Symptoms of Overdose

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

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

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

Management of Overdose

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

PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information)

Somnolence and Severe Drowsiness

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

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

Storage and Handling

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

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Indication

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

Limitations of Use

Diclegis has not been studied in women with hyperemesis gravidarum.

Important Safety Information

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

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

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

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

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

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

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

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

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

Please see accompanying Brief Summary of the full Prescribing Information.

Tablet(s) shown are not actual size.

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