CONTEMPORARY OB/GYN MAY 2013, Vol. 58, No. 5

EARLY PREGNANCY FAILURE ■ FETAL PROGRAMMING AND ADULT OBESITY ■ FITNESS APPS AND DEVICES ■ CERVICAL LENGTH SCREENING

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Medical Management of Early Pregnancy Failure

Aileen M. Gariepy, MD, MPH, and Nancy L. Stanwood, MD, MPH

Why a pill may be better for your patients than expectant or surgical management.

Gestational Programming

Is it a factor in adult obesity?

Michael G. Ross, MD, MPH, and Mina Desai, MSc, PhD

TECH TOOLS

Personal health monitors

POINT/COUNTERPOINT

Debating universal cervical length measurement

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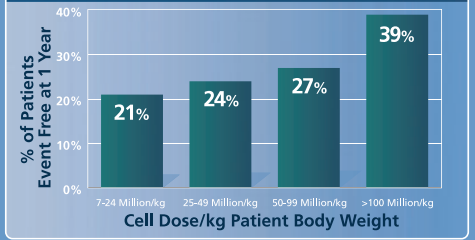

Transplant Success is the % of patients without events defined as death, autologous reconstitution and receipt of a second graft. All such events indicate graft failure.

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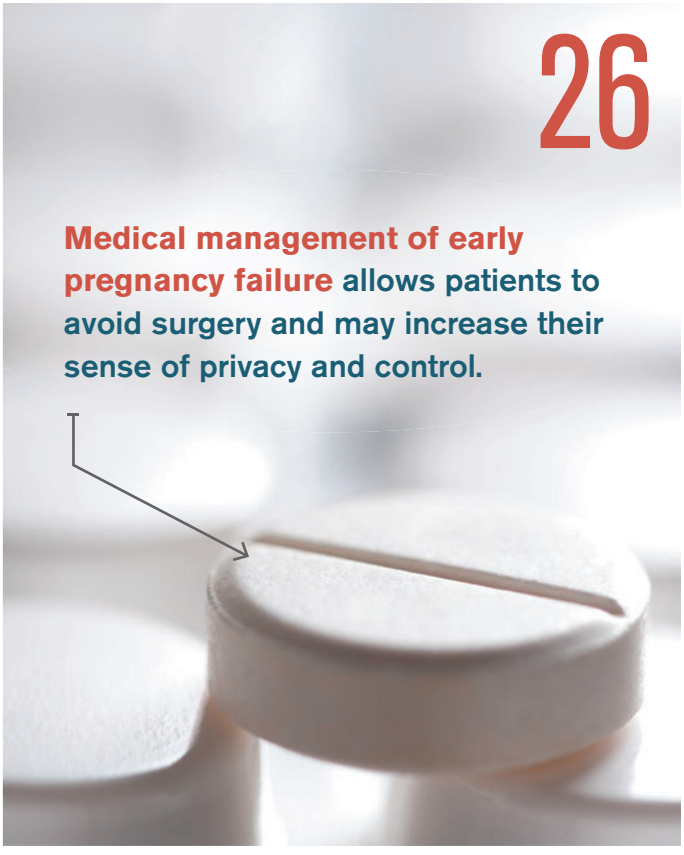

GRAND ROUNDS

TECH TOOLS

POINT/COUNTERPOINT

CLARIFICATION: A Society for Maternal-Fetal Medicine (SMFM) Consult titled "Isolated fetal choroid plexus cysts: Their implications and outcomes," appeared in the April 2013 issue of *Contemporary OB/GYN*. SMFM wishes to clarify the final sentence of the article. It should read: "Therefore, neither serial antenatal ultrasounds nor post-natal evaluation are clinically useful."

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BY **JOSHUA A. COPEL, MD**

Leverage your knowledge and create a legacy

Take the time to mentor students. Our specialty will benefit and thrive.

Ob/gyns work hard. Both academicians and private practitioners take on commitments that inevitably make demands on our time and energy. Some of us make successful clinical careers by being accessible to our patients regardless of time of day or day of the week. Others spend time creating new information and knowledge (that is, researching) and sharing it with colleagues (that is, publishing and speaking).

The critical component to success in medicine—or, for that matter, in business, law, or any career—is the willingness to work harder than the average person, mixed with a little creativity. Often it takes a bit of good fortune as well—meeting the right connection or recognizing a new opportunity before others do.

There is much truth to the saying, "If you want to get something done, ask a busy person." I have been asked why I do all the things I do: the professional association governance work, the committee meetings, the travel. It all takes up time that might be spent with family or pursuing a hobby or other things (for instance, I wrote this at 8 AM on a Sunday). I believe that for many of us, the motive is leveraging ourselves.

"Leverage" is a term with a mixed reputation these days. Excessive leverage, after all, helped burst the housing bubble, and it has brought down banks, hedge funds, and investment houses. But I mean "leverage" as "using given resources to magnify outcome."

Think about it. The average ob/gyn might deliver 10 to 15 babies a month over a 30-year career—let's say 4000 to 5000 in total. Inspire one medical student to enter our field every year by striking up a relationship during his or her clerkship, and you could influence the births of more than 100,000 babies down the road.

One of the things I do to leverage is to socialize with our medical students. Instead of delivering a stuffy lecture in a dark seminar room each rotation, I invite all the students to my house to talk about careers, education, and anything they haven't learned in their clerkship that they think is important. This often includes talking about residency selection, and gives me the opening to talk about the range of practice options available to ob/gyns. On a good night I can almost see light bulbs appearing in cartoon bubbles above the students' heads as they realize, "Maybe I really should do this."

SMFM efforts

Our professional organizations have taken on some of this mentoring as well.

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LETTERS TO THE EDITOR

I read with interest the recent review article in *Contemporary OB/GYN* by Gold and Jamshidi concerning emergency contraception (EC).[1] Left out of this otherwise excellent review is the important report by Glasier et al that looks at the risk factors for failure(s) of EC in the face of unprotected intercourse.

Glasier et al used data from the noninferiority trial of ulipristal acetate (UPA) versus levonorgestrel (LNG) that is mentioned in the above review. In their analysis, the authors state that "the variable with the most highly significant impact on the risk of pregnancy was BMI."[2] This was especially true for LNG users, where the risk of pregnancy rapidly increased with increasing BMI. Indeed, the authors found that at a BMI >26 kg/m^2, the risk of pregnancy was essentially the same as the pregnancy rate in women not using EC at all.

While the intent of the studies in the meta-analysis was not to examine the effects of BMI on the effectiveness of EC, the results are hard to overlook clinically, especially [regarding] obese women presenting for EC.

Gold and Jamshidi rightly point out that there are no contraindications to EC and that administration does not require laboratory tests or physical examination. Calculating a patient's BMI is clearly quite simple and, given the findings noted above regarding BMI and EC effectiveness, there is little if any place for the administration of LNG to women with BMI >25 kg/m^2. Administering LNG to such women borders on the unethical; UPA or copper IUCD insertion is a more appropriate means of EC.

References

1. Gold, AP and Jamshidi, R. Emergency contraception update: Last chance options. *Contemporary OB/GYN*; 2013;58(3):34-39.

2. Glasier, A, Cameron, ST, et al. Can we identify women at risk of pregnancy despite using emergency contraception? Data from randomized trials of ulipristal acetate and levonorgestrel. *Contraception*; 2011;84(4):363-367.

Michael I. Hertz, MD, MPH
Department of Obstetrics and Gynecology, Wayne State University School of Medicine, Detroit, Michigan.
Financial disclosure: trainer for Nexplanon/Merck

THE AUTHORS RESPOND:

We are aware of Dr. Glasier's work looking at the risk factors for EC failure. Given the scope and length requirements of our article, we did not include this data in our review. We appreciate Dr. Hertz's letter, which points out the important finding of the effect of BMI on EC efficacy.

We agree with Dr. Hertz that, for women with BMI >26 kg/m^2, UPA and copper IUD are better options for EC. However, UPA and copper IUD are not as readily available as LNG.

Given that the finding of decreased efficacy of LNG on overweight women was found in this one secondary analysis of data, we would still recommend LNG over nothing at all for women with BMI >26 kg/m^2 who have had unprotected intercourse if UPA and copper IUD are not available.

Alexandra P. Gold, MD, and **Roxanne Jamshidi, MD, MPH**
Department of Obstetrics and Gynecology Johns Hopkins Bayview Medical Center, Baltimore, Maryland.

Editorial

continued **FROM PAGE 8**

In mid-March, the Society for Maternal-Fetal Medicine (SMFM) held its third annual retreat for first-year fellows in MFM. (In the past, these have been held in the fall, but Superstorm Sandy necessitated postponement of last fall's event to the spring.) These events are held at a retreat center outside New York City, a location chosen to allow as many fellows as possible to get there cheaply (that is, by driving).

The retreats are free to all first-year fellows, thanks to support from the SMFM, the Pregnancy Foundation, and the Kenneth Gottesfeld-Charles Hohler Memorial Foundation (in the interest of full disclosure, I am the treasurer of this last group). In addition, this year's retreat received some unrestricted educational grants from corporate sponsors.

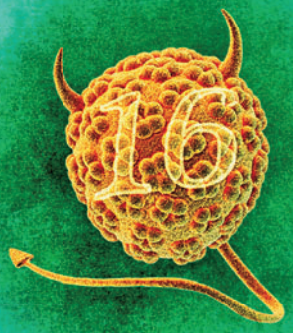
The retreats have 3 major goals. The first is to instill a group identity in the graduating class of fellows. Many of us think of the colleagues we began our careers with—our contemporaries as residents and fellows—as a sort of professional family. No doubt all of us share special bonds with those with whom we worked so intensely and closely in our early professional careers. So, an important goal for the retreats is to leverage that group identity among the community of fellows graduating in the same year, to provide both friendships and opportunities for professional collaboration over a lifetime. We include many team-building activities during the retreats to help the fellows get to know one another.

The second goal is to jumpstart the fellows' knowledge about professional life, especially how to navigate and fully participate in professional societies. The team-building exercises and discussions with the fac-

continued on **PAGE 18**

In cervical cancer screening,

The devil is in the details



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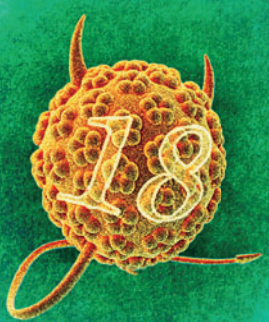

***ATHENA** = **A**ddressing **THE N**eed for **A**dvanced HPV Diagnostics;*
HPV = Human Papillomavirus

1. Wright T, et al. *Am. J Clin. Pathol* 2011; 136: 578–586.
2. American Cancer Society/American Society for Colposcopy and Cervical Pathology/ American Society for Clinical Pathology 3. American Congress of Obstetrics and Gynecologists, 4. Institute of Medicine, 5. National Comprehensive Cancer Network

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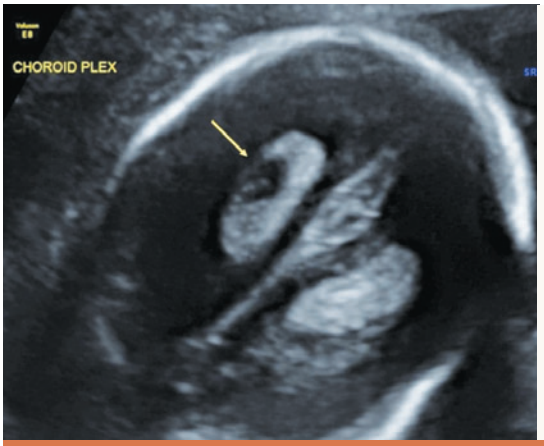

A 33-year-old G1 presents for a fetal anatomic survey at 20 weeks 2 days' gestation. A unilateral choroid plexus cyst is noted; no other sonographic markers of aneuploidy or structural malformations are identified. Read expert answers from the Society for Maternal-Fetal Medicine to key clinical questions about this case in our April issue online.

SMFM consult: Choroid plexus cysts

http://contemporaryobgyn.net/isolated-fetal-choroid-plexus-cysts

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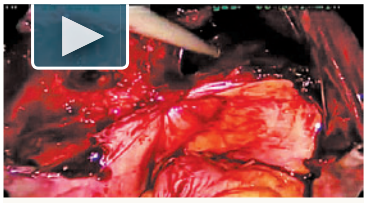
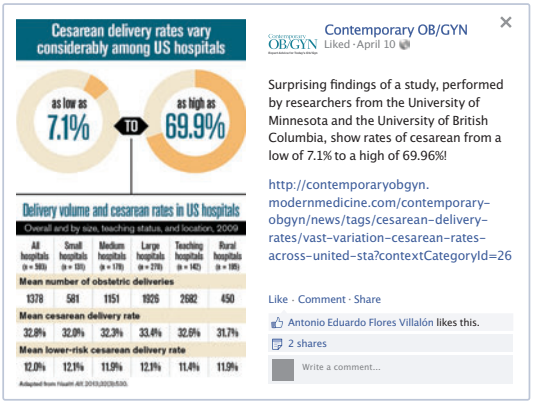


Check out our page for a video of Deputy Editor Jon I. Einarsson, MD, MPH, performing laparoscopic surgery for endometriosis. **Contemporaryobgyn.net/endometriosis-surgery/facebook**



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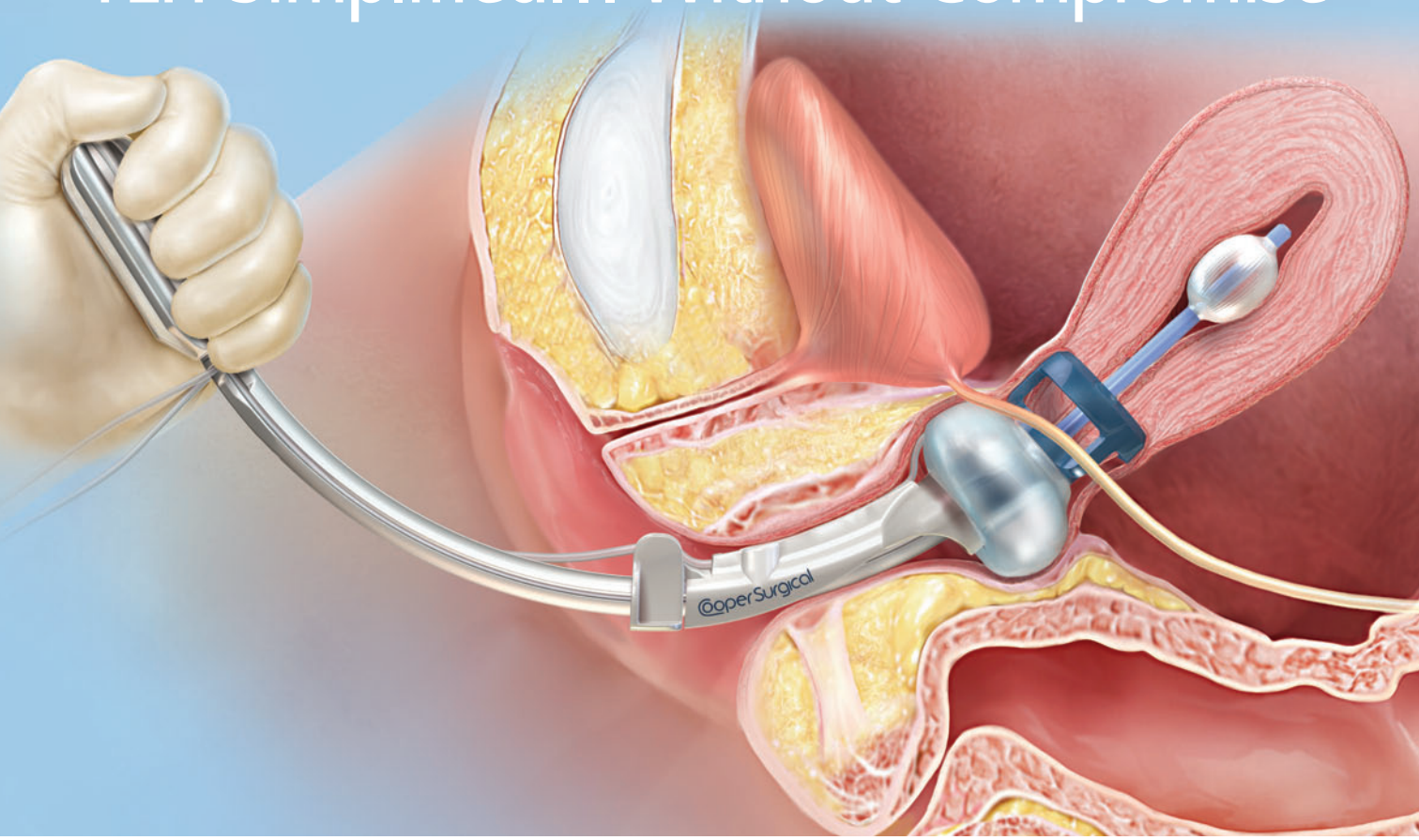

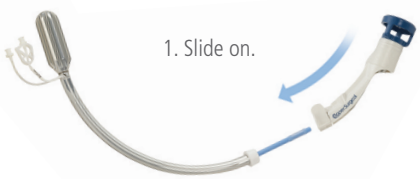

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Age restriction on emergency contraception lifted

On April 5, a US District Court judge ruled that the emergency contraception (EC) pill Plan B One-Step must be made available over the counter to all girls and women, regardless of their age. This ruling by Judge Edward R. Korman was in response to a 2011 move by US Department of Health and Human Services Secretary Kathleen Sebelius.

The US Food and Drug Administration (FDA) recommended in 2011 that the "morning-after pill" be made available to women and girls of all ages without a prescription, but Sebelius overruled this recommendation.

At that time President Obama supported this decision, stating "the reason [Sebelius] made this decision was she could not be confident that a 10-year-old or an 11-year-old go[ing] into a drugstore, should be able—alongside bubble gum or batteries—[. . .] to buy a medication that potentially, if not used properly, could end up having an adverse effect." He also commented, "I think it is important for us to make sure that we apply some common sense to various rules when it comes to over-the-counter medicine."

In his April 5 decision, Korman rebuked Sebelius, writing that her decision was "arbitrary, capricious, and unreasonable," that "the motivation for the Secretary's action was obviously political," and that "the reasons she provided [as to why she overruled the FDA's recommendation] are so unpersuasive as to call into question her good faith."

He further stated, "The obstructions in the path of . . . adolescents in obtaining levonorgestrel-based emergency contraceptives under the current behind-the-counter regime have the practical effect of making the contraceptives unavailable without a doctor's prescription."

The American College of Obstetricians and Gynecologists (ACOG), the American Academy of Pediatrics (AAP), and the Society for Adolescent Health and Medicine (SAHM) all applauded the ruling to lift the age restriction. "The College has long supported making EC available over the counter without an age restriction, so this is welcome news to us and to young women," said James T. Breeden, MD, ACOG president, in a joint press release issued by ACOG, AAP, and SAHM.

"EC is a safe, effective way to help prevent unintended pregnancy after a contraceptive failure, unprotected sex, or sexual assault," he added. "We believe all EC products should be available over-the-counter."

Belluck P. Judge strikes down limits on morning-after pill. *New York Times*. April 5, 2013. http://www.nytimes.com/2013/04/06/health/judge-orders-fda-to-make-morning-after-pill-available-over-the-counter-for-all-ages.html?smid=tw-share&_r=0. Accessed April 9, 2013.

Medical groups praise court ruling lifting age restriction on emergency contraception [news release]. Washington, DC: American College of Obstetricians and Gynecologists; April 5, 2013. http://www.acog.org/~/media/News%20Releases/20130405Release.pdf. Accessed April 9, 2013.

Tummino v Hamburg, 12-CV-763 (ED NY 2013). http://www.washingtonpost.com/blogs/wonkblog/files/2013/04/Tummino-SJ-memo.pdf. Accessed April 9, 2013.

A BRIEF HISTORY OF OTC EC

1999
Plan B becomes the first EC drug approved for prescription-only use in the United States.

2006
The FDA approves nonprescription access to Plan B for women aged 18 years and older, and with a prescription to girls younger than 18.

2009
The FDA is ordered to make Plan B available without a prescription to girls and women aged 17 and older.

2009
Plan B One-Step is approved by the FDA to be made available without a prescription to girls and women aged 17 and older.

2011
The FDA recommends that Plan B One-Step be made available without a prescription and without age restriction. Health and Human Services Secretary Kathleen Sebelius overrules this recommendation.

2013
US District Court Judge Edward R. Korman rules that Plan B One-Step must be accessible OTC to all girls and women, regardless of their age.

Abbreviations: EC, emergency contraception; FDA, Food and Drug Administration; OTC, over the counter.

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FDA approves Diclegis for treatment of morning sickness

The US Food and Drug Administration (FDA) has approved the drug Diclegis (doxylamine succinate 10 mg, pyridoxine hydrochloride 10 mg) for the treatment of nausea and vomiting of pregnancy (NVP) in women who do not respond to conservative management, including dietary and lifestyle modifications. These modifications include eating several small meals instead of 3 large meals, eating bland foods that are low in fat and easy to digest, and avoiding smells that can trigger nausea.

This is the only treatment for NVP, more commonly known as morning sickness, approved by the FDA in more than 30 years. Diclegis, once called Bendectin, was pulled off the market in 1983 after a safety scare prompted by hundreds of lawsuits claiming birth defects. Although the scare proved to be a false alarm, the *Washington Post* reported, the manufacturer withdrew the drug because it could not afford to defend itself in court.

"The approval of . . . Diclegis for morning sickness after the lack of an effective and potentially safe therapeutic option for pregnant women in many years serves as another breakthrough in the availability of drugs to this sensitive population," said Abimbola Farinde, PharmD, MS, clinical staff pharmacist at Clear Lake Regional Medical Center, in Webster, Texas, and an advisor to *Contemporary OB/GYN*'s sister publication *Formulary*.

> "Women taking Diclegis experienced **greater improvement in nausea and vomiting** than did those taking placebo."

"The re-release of the medication . . . which was largely attributed to more scrutiny being placed on the use of the drug during pregnancy, offers hope to pregnant women who may experience more severe morning sickness and require the use of Diclegis after other steps have failed to achieve relief."

The FDA granted Diclegis Pregnancy Category A status, which means that the results of controlled studies have not shown an increased risk to an unborn baby during pregnancy. The 2 active ingredients in Diclegis that reduce nausea and vomiting in pregnancy—doxylamine succinate and pyridoxine hydrochloride, or vitamin B_6—have been recommended as a first-line pharmacotherapy by American College of Obstetricians and Gynecologists guidelines for the past 9 years.

Diclegis was studied in 261 women experiencing NVP. Study participants in the clinical trial were at least 18 years old and had been pregnant for at least 7 weeks and up to 14 weeks. Women were randomly assigned to receive 2 weeks of treatment with Diclegis or a placebo.

The study results showed that women taking Diclegis experienced greater improvement in nausea and vomiting than did those taking placebo. In addition, observational (epidemiological) studies have shown that the combination of active ingredients in Diclegis does not pose an increased risk of harm to the fetus.

Initially, a patient takes 2 Diclegis delayed-release tablets orally at bedtime (day 1). If symptoms persist into the afternoon of day 2, the patient takes the usual dose of 2 tablets at bedtime that night and then adds 1 tablet the following morning on day 3. If symptoms still persist on day 4, the patient takes 1 tablet in the morning, 1 tablet mid-afternoon, and 2 tablets at bedtime. The maximum recommended dose is 4 tablets (1 in the morning, 1 at mid-afternoon, and 2 at bedtime) daily. Diclegis is taken as a daily prescription and not on an as-needed basis to help control symptoms throughout the day.

Drowsiness and sleepiness, which can be severe, are the most common adverse effects reported by women taking Diclegis. Women should avoid using Diclegis when engaging in activities requiring mental alertness, such as driving or operating heavy machinery, until cleared to do so by their physicians.

FDA approves return of treatment for morning sickness, decades after false alarm over safety. *Washington Post.* April 9, 2013. http://www.washingtonpost.com/national/health-science/fda-approves-return-of-treatment-for-morning-sickness-decades-after-false-alarm-over-safety/2013/04/09/31d8b816-a11f-11e2-bd52-614156372695_story.html. Accessed April 9, 2013.

American Urogynecologic Society voices opposition to restrictions on transvaginal mesh

In a new development in the ongoing controversy regarding the use of transvaginal mesh, the American Urogynecologic Society (AUGS) has released a position statement against bans of surgical options such as mesh.

"The American Urogynecologic Society strongly opposes any restrictions by state or local medical organizations,

healthcare systems, or insurance companies which ban currently available surgical options performed by qualified and credentialed surgeons on appropriately informed patients with pelvic floor disorders," the statement reads.

In a letter to AUGS members regarding the position statement, AUGS President Anthony G. Visco, MD, explained that in recent months a state medical organization, a healthcare system, and a malpractice insurance company have considered restricting or have banned the use of transvaginal mesh for prolapse.

"A ban on mesh would have a chilling effect on research in this area and would severely limit the advancement of science and future innovations that could significantly help women," Visco said in the letter. "We recommend preserving all surgical options, including transvaginal mesh for pelvic organ prolapse, adopting recently published credentialing guidelines, standardizing the informed consent process, and establishing a robust mechanism to track both surgeons and products being implanted to fully assess safety and efficacy."

AUGS provided several justifications for the position statement, including:

- A complete restriction on the use of surgical mesh was not the stated intent of the July 2011 US Food and Drug Administration (FDA) safety communication regarding mesh.
- The decision on surgical alternatives should be made by the patient and her surgeon.
- A ban on surgical mesh would prohibit the surgical studies mandated by the FDA and recommended by the National Institutes of Health, the American College of Obstetricians and Gynecologists, and AUGS.
- In some circumstances, transvaginal mesh for pelvic organ prolapse may be the most appropriate surgical option.
- Any restriction of mesh slings for the treatment of stress urinary incontinence is clearly not supported by any professional organization or the FDA.
- Any restriction of mesh placed abdominally for the treatment of prolapse is clearly not supported by any professional organization or the FDA.
- Instead of a ban on mesh, AUGS recommends the implementation of credentialing guidelines so that mesh procedures are performed by qualified surgeons.

"It is imperative that local hospitals and health systems establish and strictly enforce robust processes to both credential and audit surgeons with specific expertise, experience, training, and skill to perform these procedures," AUGS said in the position statement.

Visco AG. AUGS position statement on the restriction of surgical options for pelvic floor disorders. http://www.augs.org/p/bl/et/blogid=6&blogaid=160. Published March 26, 2013. Accessed April 9, 2013.

Guidelines blur treatment decisions for PID

Many physicians who treat adolescent girls with pelvic inflammatory disease (PID) are uncertain about choosing hospitalization or outpatient care for their patients by using current guidelines, a new study has found.

Centers for Disease Control and Prevention (CDC) guidelines recommend outpatient rather than in-hospital treatment for PID, but leave physicians room for interpretation about treatment choice and outcome from patient to patient. However, data show that adolescent girls with PID often do not follow outpatient treatment regimens and miss follow-up appointments.

> "Data show that **adolescent girls with PID often do not follow outpatient treatment regimens** and miss follow-up appointments."

Researchers from Johns Hopkins Children's Center who conducted the study say the flexibility that the guidelines allow create confusion. They presented 102 clinicians with 17 scenarios for which they had to make decisions about inpatient or outpatient treatment for a fictional 15-year-old patient with PID. The clinicians had to consider factors such as the patient's age, severity of illness, whether the patient was pregnant or had had any recent surgical procedure, if the patient was willing to share the diagnosis with a sexual partner, and whether the patient was able and willing to follow an outpatient treatment regimen.

Findings showed that ambivalence was common when the clinicians were uncertain about patients' ability to care for themselves, their willingness to take medications, or their willingness to share diagnoses with partners. Male clinicians and those who were not parents themselves were more likely to hospitalize patients than were female clinicians and clinicians with their own children. Many clinicians were uncomfortable with sending a patient home with a complicated treatment regimen, then asking her to return for follow-up, even though the guidelines state that this should be done.

The investigators point out that clinical guidelines should offer clear decision-making algorithms while giving physicians autonomy and flexibility. Lack of clear guidance forces clinicians to make decisions based upon personal bias rather than upon evidence from best practices, they say.

MORE THAN 750,000 girls and women in the United States are diagnosed with PID each year

The CDC reports that more than 750,000 girls and women in the United States are diagnosed with PID each year. Ten percent of them develop infertility as a result. COG

Trent M, Lehmann H, Butz A, et al. Clinician perspectives on management of adolescents with pelvic inflammatory disease using standardized patient scenarios. *Sex Transm Dis*. 2013. Epub ahead of print.

Editorial

continued **FROM PAGE 10**

ulty also help them understand how to build their professional identities within their institutions.

Finally, by bringing in a large group of prominent faculty members and creating multiple opportunities for informal interaction, we give the fellows "face time" with leaders in the field and (we hope) inspire them to follow similar career paths.

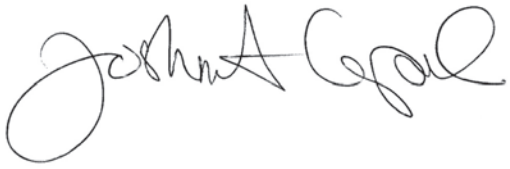
These are ambitious goals, and all of us who attend believe it is well worth a couple of days away from home to leverage ourselves and help these young colleagues.

Another great example of creating opportunities for the next generation also comes from the SMFM, as an outgrowth of the creative thinking of several members and its affiliated Pregnancy Foundation, chaired by Thomas Garite, MD. Through the efforts of *Contemporary OB/GYN* Founding Editor John T. Queenan, MD, and Larry Platt, MD, we held a fundraiser at the last SMFM meeting to support a new program to be called Quilligan Scholars, named after Ted Quilligan, MD, who is known as a mentor's mentor. The plan is to create opportunities for promising residents in ob/gyn who have the potential to be leaders in MFM, and provide them with early exposure to the best we have to offer in meetings and education. Again, this will help to leverage our specialty for the next generation.

But this isn't something just for national organizations or ivory-tower academics to take on. Grassroots, everyday interactions are critically important in getting the most talented students into our field in the first place. There is nothing more disheartening to medical students considering our field than to hear us grouse endlessly in the locker room and physicians' lounge about our miseries. Yes, we face challenges, but we have to show students what a great specialty ob/gyn really is.

The private physicians here at Yale spend a couple of afternoons each year teaching preclinical medical students how to tie knots. Clinicians in private practice may need to make more of an effort to connect with medical students, but it can be done. Try letting an undergraduate student from your alma mater shadow you for a couple of days to see what life is like in the real world, and why he or she should go into ob/gyn. Talk to students about their lives, and yours, so they can see what life is like beyond school and residency.

Find a way to leverage yourself and create your own legacy.



DR. COPEL is Professor, Obstetrics, Gynecology, & Reproductive Sciences, and Pediatrics, Yale University School of Medicine, New Haven, Connecticut. He is also a member of the *Contemporary OB/GYN* editorial advisory board.

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

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*In women who experienced withdrawal bleeding, the mean median intensity of withdrawal bleeding decreased from Cycle 2 (1.83/3.0) to Cycle 13 (1.64/3.0).

†Please see adjacent page for details.

IMPORTANT SAFETY CONSIDERATIONS

Women who are over 35 years old and smoke should not use Generess® Fe. Cigarette smoking increases the risk of serious cardiovascular events from combination oral contraceptive use.

Please see Important Safety Information and brief summary of full Prescribing Information on adjacent pages.

Watson

Model is for illustrative purposes only.

†**Savings will apply after your patient pays up to the first $25. Maximum savings card benefit is $50 per 30-day prescription.** So, if your patient's copay is $75 or more, Watson will contribute $50 via the savings card, but the patient is responsible for the remaining amount. See complete details at iamgeneress.com.

References: 1. Data on file, Watson Laboratories, Inc. **2.** Generess® Fe full Prescribing Information, Watson Pharma, Inc. March 2012.

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

IMPORTANT SAFETY INFORMATION

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

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

Brief Summary

For full prescribing information, see package insert. Rx only

WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS

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

1 INDICATIONS AND USAGE

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

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

4 CONTRAINDICATIONS

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

- A high risk of arterial or venous thrombotic diseases. Examples include women who are known to:
  - Smoke, if over age 35 *[see Boxed Warning,* and *Warnings and Precautions (5.1)]*
  - Have deep vein thrombosis or pulmonary embolism, now or in the past *[see Warnings and Precautions (5.1)]*
  - Have cerebrovascular disease *[see Warnings and Precautions (5.1)]*
  - Have coronary artery disease *[see Warnings and Precautions (5.1)]*
  - Have thrombogenic valvular or thrombogenic rhythm diseases of the heart (for example, subacute bacterial endocarditis with valvular disease, or atrial fibrillation) *[see Warnings and Precautions (5.1)]*
  - Have inherited or acquired hypercoagulopathies *[see Warnings and Precautions (5.1)]*
  - Have uncontrolled hypertension *[see Warnings and Precautions (5.4)]*
  - Have diabetes with vascular disease *[see Warnings and Precautions (5.6)]*
  - Have headaches with focal neurological symptoms or have migraine headaches with or without aura if over age 35 *[see Warnings and Precautions (5.7)]*
- Breast cancer or other estrogen- or progestin-sensitive cancer, now or in the past *[see Warnings and Precautions (5.2)]*
- Liver tumors, benign or malignant, or liver disease *[see Warnings and Precautions (5.3), Use in Specific Populations (8.7),* and *Clinical Pharmacology (12.3)]*
- Undiagnosed abnormal uterine bleeding *[see Warnings and Precautions (5.8)]*
- Pregnancy, because there is no reason to use COCs during pregnancy *[see Warnings and Precautions (5.9)* and *Use in Specific Populations (8.1)]*

5 WARNINGS AND PRECAUTIONS

5.1 Thrombotic and Other Vascular Events

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

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

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

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

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

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

5.2 Carcinoma of the Breasts and Reproductive Organs

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

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

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

5.3 Liver Disease

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

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

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

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

5.4 High Blood Pressure

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

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

5.5 Gallbladder Disease

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

5.6 Carbohydrate and Lipid Metabolic Effects

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

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

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

5.7 Headache

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

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

5.8 Bleeding Irregularities

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

Patient diaries from the clinical trial of GENERESS Fe showed that on the first cycle of use, 37% of subjects taking GENERESS Fe had unscheduled

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

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

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

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

5.9 COC Use Before or During Early Pregnancy

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

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

5.10 Depression

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

5.11 Interference with Laboratory Tests

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

5.12 Monitoring

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

5.13 Other Conditions

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

6 ADVERSE REACTIONS

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

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

Adverse reactions commonly reported by COC users are:

- Irregular uterine bleeding
- Nausea
- Breast tenderness
- Headache

6.1 Clinical Trial Experience

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

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

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

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

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

7 DRUG INTERACTIONS

No drug-drug interaction studies were conducted with GENERESS Fe.

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

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

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

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

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

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

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

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

7.3 Changes in Plasma Levels of Co-Administered Drugs

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

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

Women who do not breastfeed may start COCs no earlier than four weeks postpartum.

8.3 Nursing Mothers

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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

8.6 Renal Impairment

The pharmacokinetics of GENERESS Fe have not been studied in subjects with renal impairment.

8.7 Hepatic Impairment

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

8.8 Body Mass Index

The safety and efficacy of GENERESS Fe in women with a BMI > 35 kg/m^2 have not been evaluated.

10 OVERDOSAGE

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

For all medical inquiries contact:
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Medical Communications Parsippany, NJ 07054 USA
800-272-5525

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Watson Pharma, Inc. Parsippany, NJ 07054 USA

Manufactured By:
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Revised: March 2012

BY ANDREW I KAPLAN, ESQ

Was this patient's death preventable?

This difficult defense—a young woman dying shortly after a routine tubal ligation—was further complicated by conflicting reports about who said what to whom and when.

Facts

A 41-year-old G3P1 signed consent for a tubal ligation on February 17, 2010. She was diabetic and obese (5 ft, 1 in and 188 lb). Preoperative testing, which consisted of a chest x-ray, EKG, and blood workup, was performed at the defendant hospital on February 26, 2010.

On March 5, 2010, the patient presented for the tubal ligation. A consent was signed authorizing resident Dr. A to perform a bilateral tubal ligation. The risks of the procedure were bleeding, blood transfusion, infection, injury to the surrounding viscera, conversion to laparotomy, failure of procedure, and ectopic pregnancy.

According to the operative note dictated and signed by Dr. A, Dr. A and Dr. B performed the procedure. A 10-mm incision was made in the infraumbilical fold and was then carried down using blunt dissection with Kelly clamps. The surgeons encountered difficulty in reaching the fascial layer "due to a very thick subcutaneous fat layer."

> "Conversations with Dr. D and Dr. A present a **conflict in the events that transpired.**"

Attending Dr. C was called for an intraoperative consult, and introduced a Veress needle into the peritoneal cavity, confirmed placement, and then placed a trocar and sleeve. The placement was confirmed by laparoscope. The placement of a second trocar was done under direct visualization. The fallopian tubes were then fulgurated, closing them off, the instruments were removed, and the field was inspected by laparoscope. The inspection was negative and the patient was closed.

The patient was transferred to the recovery room in stable condition, accompanied by Dr. A and Dr. B. While in the recovery room, the patient received Toradol at 10:55 AM for complaints of pain of 10 on a scale of 1 to 10. Morphine was given at 11:45 AM, which reduced her pain level to 5/10. At 1:28 PM, a nurse wrote a discharge note that documented an elevated pulse of 84 (the patient's pulse was 60 on admission). She was discharged at 1:52 PM.

The patient re-presented to the defendant hospital's emergency department (ED) at 8:54 PM with tachycardia (110) and complaints of "constant aching." Her respiratory rate was normal. Her blood glucose was elevated at 261. Her hemoglobin and hematocrit were essentially the same as they had been on admission earlier that day. However, her white blood cell count was elevated at 12.1 (it had been 6.4 preoperatively) with a left shift.

A morphine IV push (10 mg) was given at 9:35 PM, on order by defendant Dr. D. By midnight, the patient was feeling better. A nurse noted that Dr. A saw the patient

and recommended to see the patient in the clinic. (There is no note by Dr. A.)

There is a gap in the records until Dr. D wrote a note at approximately 4:14 AM on March 6, 2010. The patient may have left at midnight, according to a nurse's note, which indicates the patient had a "steady gait." The discharge sheet with the instructions given to the patient is not contained within the medical records.

Conversations with Dr. D and Dr. A present a conflict in the events that transpired. Dr. D states he handed the chart to Dr. A for a consult even though a formal consultation request is not documented. Dr. A states she spoke to the patient, but was not asked to do a consult and did not perform one. Neither Dr. D nor Dr. A ever notified co-defendant attending Dr. C that the patient was in the ED postoperatively.

> "The patient was discharged with . . . drugs . . . but the **etiology of the pain was never determined.**"

The patient returned to the hospital via ambulance on March 6 at 5:19 PM with complaints of abdominal pain. Her blood pressure was 108/70, and she was tachycardic with a pulse of 141. The triage nurse noted that the patient was unable to provide a reliable history regarding her underlying clinical condition. A family member reported that the pain worsened after the patient was discharged and that she had increased abdominal girth, weakness, lethargy, shortness of breath, and chest pain. The history was documented at 7:20 PM (although she initially presented about 2 hours earlier). Her blood glucose was 327.

An immediate bedside U/S was performed by Dr. E. The study showed free fluid throughout the lower abdomen. Dr. E called in a stat gynecological consult and requested the chief and attending to prepare the OR. Nonparty attending gynecologist Dr. F noted at 7:20 PM that the patient's abdomen was distended with positive rebound. Her blood pressure was 85/67, heart rate 120, and respiratory rate 40. Dr. F's impression was hemorrhagic shock.

Dr. F took the patient to the OR for an exploratory laparotomy. Upon entry into the peritoneal cavity, approximately 600 cc of copious fecal material and pus were elicited. The anesthesiologist was aware of the suspected diagnosis of septic shock secondary to fecal peritonitis. At the beginning of the ligament of Treitz, the bowel was run, revealing a small through-and-through puncture site in the small bowel exuding fecal matter.

Dr. F called in an emergency surgical intraoperative consultant who performed a small bowel resection and end-to-end anastomosis. The perforation sites in the middle part of the small intestine were identified as 2 small perforations about 4 mm each in diameter and 1 cm apart from each other. There was a small through-and-through perforation of adjacent mesentery without mesenteric hematoma or bleeding noted. A segment about 5 cm long was resected from the small intestine.

During the resection procedure, the patient developed desaturation and diminished breath sounds of the left chest, followed by cardiac arrest. The patient coded at 8:52 PM. Cardiopulmonary resuscitation was started. A pneumothorax was suspected because of diminished breath sounds on the left side, and left chest tube thoracotomy drainage was performed.

Codes were again called at 9:20 PM, 9:37 PM, and 9:49 PM. The patient did not respond to continued cardiopulmonary resuscitation. She expired at 9:59 PM. According to the autopsy, the primary cause of death was peritonitis secondary to small bowel perforations.

Allegations

The plaintiffs claimed that the defendants negligently performed the tubal ligation by only utilizing a 10-mm incision for trocar placement, causing a bowel perforation that they failed to recognize and repair in a timely manner. They further contended that the patient was not adequately evaluated on either the March 5 or March 6 return to the hospital ED, and that the failure to notify the attending ob/gyn of the patient's return resulted in improper and premature discharge without an accurate diagnosis of perforation and sepsis. They asserted that, as a result, the patient went into septic shock and ultimately expired.

Discovery

The ED expert was unable to defend the care given in the first ED visit and found departures on the part of Dr. D and Dr. A in that a gynecological consult must be obtained on a postoperative patient 7½ hours after discharge from surgery when she presents to the ED with abdominal pain. Our expert felt this was very likely a preventable death. While an ED attending would not be expected to perform an U/S under these circumstances,

> **Rather than risk a verdict at trial . . .** our team decided to resolve the case before engaging in more meaningful, and potentially harmful, discovery.

a gynecologist most likely would have performed an U/S had a proper consult been obtained.

Further, the complaint of abdominal pain was not appropriately assessed. This patient had complaints of pain 10/10 with the pain medication Toradol already on board. A maximum amount of morphine permitted in one dose (10 mg) was given in an IV push, which our expert felt masked the pain. The patient was discharged with these 2 drugs on board, but the etiology of the pain was never determined.

Additionally, while Dr. D reviewed the CBC and differential with respect to the Hgb and Hct, he missed the signs of sepsis already beginning with the left shift in the differential. Had the patient been admitted and administered antibiotics, our expert felt, she likely could have survived.

Our expert ob/gyn could not defend the care given by Dr. D or Dr. A. He found no departures in the standard of care by co-defendant attending Dr. C, although he felt that Dr. C and Dr. A exercised poor judgment in making only a 10-mm incision on this obese patient without documentation of attempting to enlarge it once problems were encountered. A closed laparotomy was then undertaken, which was when the perforation likely occurred.

With respect to the ED care, our expert found it inexplicable that defendant Dr. A participated in the surgery earlier in the day, dictated the OR note at 6 PM, and saw the patient later that evening in the ED, yet claimed she was not asked to do a consult on the patient and therefore did not examine the patient, write a note, or notify the ob/gyn attending.

He also felt that Dr. D did not do anything to evaluate the cause of the abdominal pain and should have done "something," such as abdominal x-ray, U/S, or CT-scan. Instead, he medicated her with morphine and discharged her without determining the etiology of her pain.

Outcome

The case settled prior to engaging in pretrial depositions of the parties for $1,000,000 as to the hospital, ob/gyn resident Dr. A, and ED attending Dr. D; with attending Dr. C contributing another $250,000 for her release.

Analysis

This difficult defense—a young woman dying shortly after a routine tubal ligation—was further complicated by conflicting reports about who said what to whom and when. There was disagreement between Dr. D (the ED attending), who believed he had asked ob/gyn resident Dr. A (who had assisted in the tubal ligation) to consult on and evaluate the patient, and Dr. A, who denied this and claimed to have "just said hello" in passing. In the absence of having a consult documented within the chart, Dr. D's discharge of the patient was premature, and the failure to evaluate the patient, who had just been operated on and was now back in the hospital complaining of pain, was a departure on the part of Dr. A.

Furthermore, notification of attending Dr. C, who had operated on the patient, was warranted because a more experienced pair of eyes, ears, and hands may have recognized the signs and symptoms of post-tubal ligation bowel perforation. Rather than risk a verdict at trial, or having Dr. D and Dr. A further complicate the defense by testifying in a conflicting manner at deposition, our team decided to resolve the case before engaging in more meaningful, and potentially harmful, discovery.

Often an unwanted result balances the tightrope between known complication and departure from good practice. When the entire constellation of events, taken as a whole, however, reveals a series of missteps and mishaps surrounding that sentinel event, it becomes increasingly difficult to defend that initial complication and its aftermath as something that can occur in the absence of negligence. COG

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Medical management of early pregnancy failure

Patient preference should guide a clinician's management of first-trimester pregnancy failure because safety and efficacy are similar for all currently available treatment options.

BY **AILEEN M. GARIEPY, MD, MPH,** AND **NANCY L. STANWOOD, MD, MPH**

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Early pregnancy failure (EPF; that is, pregnancy failure in the first trimester) can be devastating for women and their partners. The diagnosis may be preceded by days or weeks of cramping, bleeding, and hoping. Once the diagnosis is made, women are most satisfied when they are given management options and can choose the one that best fits their needs (Table 1).[1] Medical management of EPF is a safe and desirable option for some women.

Epidemiology of EPF

EPF is an inclusive term that comprises incomplete, complete, or inevitable spontaneous abortion; anembryonic gestation (blighted ovum); and embryonic demise (missed abortion) at less than 14 weeks.[2]

TAKE-HOME MESSAGES

- Optimal dose and route of administration for misoprostol have not been determined by randomized trials.
- Bleeding with medical management is heavier and longer in duration than with surgical management, but rarely requires intervention.

Approximately 15% to 20% of clinically recognized pregnancies end in EPF.[2,3] Many EPFs occur before pregnancies have been clinically recognized (that is, women mistake them for "late cycles"). It is estimated that up to 60% of all conceptions end in early losses.[4] Chromo-

somal abnormalities, most commonly translocations and aneuploidy, are responsible for more than half of all spontaneous EPFs.[5] Other genetic defects that are currently impossible to discern by simple karyotype may be the cause of many spontaneous losses.

Diagnosis of EPF

The diagnosis of EPF may be suspected on signs and symptoms (vaginal bleeding, lower abdominal cramping, dilation of cervix) but is usually made by transvaginal ultrasound (U/S) and/or symptoms and serial beta human chorionic gonadotropin (BhCG) levels. Women with EPF may also be asymptomatic.

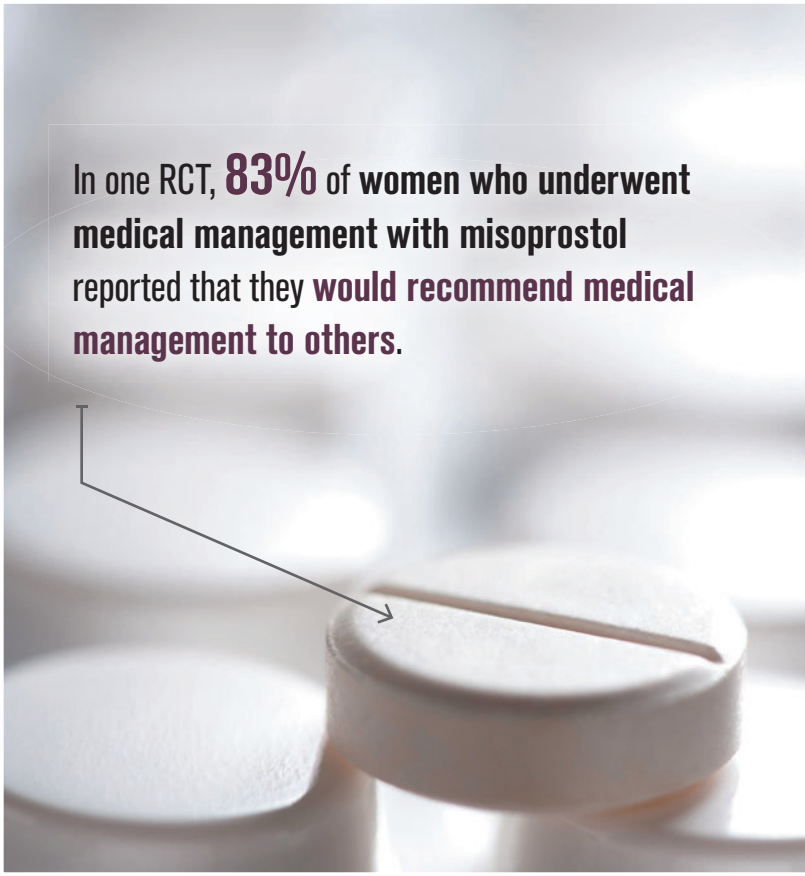
The term "spontaneous abortion" includes complete abortion, incomplete abortion, inevitable abortion, anembryonic pregnancy, and embryonic or fetal demise. In the case of a complete abortion, the patient has had a positive pregnancy test, has experienced vaginal bleeding with passage of tissue, and has a closed cervical os.[6] In the case of incomplete abortion, the patient has had a positive pregnancy test, vaginal bleeding, and may have a closed or open cervical os. An endometrial thickness measurement distinguishing incomplete from complete abortion has not been established.[2,6,7]

An EPF that is characterized by a history of a positive pregnancy test, vaginal bleeding without passage of tissue, and an open cervical os is termed an inevitable abortion.[8] Anembryonic pregnancy, which was previously termed "blighted ovum,"[6] describes the absence of a visible yolk sac with a mean sac diameter (MSD) of 13 mm, the absence of an embryonic pole with MSD of 20 mm, or the presence of an empty amnion. Embryonic or fetal demise, previously termed "missed abortion," describes the failure of a previously identified embryo to grow or show cardiac activity, or the absence of cardiac motion in embryos ≥5 mm.[6,9]

Management options for EPF

In general, there are 3 options for management of EPF: expectant, medical, and surgical management (Table 1).[1] Expectant management consists of no intervention and awaiting natural passage of tissue. Medical management uses medication to expel uterine tissue. Surgical management is defined by mechanical removal of tissue from the uterus.

Successful management of EPF entails complete evacuation of the uterus. The success of each of these approaches depends on several factors including the type of loss (eg, with or without symptoms such as bleeding and cramping) and the gestational age.



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Medical management of EPF

Medical management is a safe and effective alternative to expectant management or surgical management of EPF.[1] Medical management allows patients to avoid surgery and anesthesia. Patients may also feel that medical management is more "natural," private, and under their control. Several medications have been studied for medical management.

Mifepristone is an antiprogestin that causes weakening of the uterine attachment of a pregnancy, resulting in capillary breakdown and synthesis of prostaglandins. Trials of mifepristone added to misoprostol have had conflicting results.[10,11]

Misoprostol, a prostaglandin E1 analogue, is a uterotonic that results in cervical softening and contractions that expel the products of conception. It may be administered vaginally, orally, buccally, or sublingually. Adverse effects vary based on route of administration.[9,12]

Misoprostol: route, dose, and safety

There is published literature on a wide range of thera-

TABLE 1 Management of spontaneous abortion/early pregnancy failure at ≤14 weeks

	Advantages	Disadvantages	Success	Contraindications	Follow-up/Other
Expectant management No intervention. Awaiting natural passage of tissue.	Possible avoidance of: -Surgery, anesthesia, medicine. Perception of more: -Natural, privacy, control. Safe option for most.	Time until resolution is unpredictable, which may cause anxiety. No tissue for karyotyping. Highest chance of: -Unscheduled surgery. -More bleeding. POCs may be recognizable if >10 weeks.	Depends on type of abortion (ie, incomplete vs anembryonic) and length of follow-up. By day 7: 25-50% success By day 14: 50-80% success	Hemodynamically or medically unstable patients. Pelvic infection or sepsis. Pregnancy of unknown location, ectopic, or molar pregnancy. Caution if Hb ≤9.5 g/dL. History of coagulopathy or current anticoagulants.	Transvaginal ultrasound in 1 week. Look for expulsion of gestational sac (GS). Endometrial thickness is not predictive of success or need for surgery. BhCG follow-up **not** needed if GS expulsed.
Medical management Use of medications to expel uterine tissue. *Misoprostol 800 mcg vaginally, with repeat dose on day 3 if needed, is the most well-studied regimen.*	Possible avoidance of: -Surgery, anesthesia. Perception of more: -Natural, privacy, control. Safe option for most.	Increased rates of: -Nausea, vomiting, diarrhea, cramping (compared with surgical). No tissue for karyotyping. POCs may be recognizable if >10 weeks.	Highest for women with symptoms (cramping and bleeding). Differs by type: Incomplete/ inevitable: 93% Embryonic/fetal demise: 88% Anembryonic gestation: 81%	Same as above, plus: Allergy or contraindication to prostaglandins.	Same as above. Counseling: average of 12 days bleeding after misoprostal.
Surgical management Mechanical removal of tissue from uterus.	Predictable start and finish. Anesthesia available. Standard of care for septic abortion, hemorrhage, molar pregnancy.	Patient may have delay until surgery can occur. Risk of anesthesia. Surgical risk.	>97% Does not vary by gestational age.	None. May be challenging in patients with morbid obesity or uterine anomalies.	If chorionic villi or gestational sac obtained, BhCG follow-up **not** needed. Can be performed in office or OR.

No difference in complications after medical versus surgical management for:

-Hemorrhage requiring hospitalization with or without blood transfusion (1%)
-Hospitalization for endometritis (<1%)
-Fever (3–4%)
-ED visit to hospital within 24 hr of treatment (2–3%)
-Unscheduled hospital visits (17–23%)
-Decrease in hemoglobin ≥2 g/dL (4–9%)
-Decrease in hemoglobin ≥3 g/dL (1–5%)

All options are medically safe, so patient preference should be guiding force deciding EPF management.
All patients need blood type documented and Rh Ig if Rh negative.
Abbreviations: BhCG, beta human chorionic gonadotropin; ED, emergency department; EPF, early pregnancy failure; GS, gestational sac; Hb, hemoglobin; Ig, immunoglobulin; OR, operating room; POC, products of conception.
Adapted from Gariepy A, et al.[1]

peutic misoprostol regimens.[2,13,14] Optimal dose and route of administration of misoprostol have not been determined by randomized trials. Overall, misoprostol is safe and well tolerated.[9]

Route: Patients receiving misoprostol vaginally rather than orally have decreased adverse gastrointestinal effects and prolonged duration of action.[9] Oral misoprostol is less effective than vaginal misoprostol in emptying the uterus. Sublingual misoprostol is equivalent to vaginal misoprostol in inducing complete uterine emptying but is associated with more frequent diarrhea. There

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> The World Health Organization recommends a **single oral dose of 600 mcg misoprostol** for medical management of **incomplete abortion** and a **single vaginal dose of 800 mcg misoprostol** for medical management of **anembryonic pregnancy and embryonic/fetal demise**.

is no advantage to "wet" preparation (moistened with water) versus "dry" preparation of vaginal misoprostol.

Dosage: When compared with lower dosages, a dose of 800 mcg vaginal misoprostol is more effective at completing uterine emptying, although it results in a similar incidence of nausea.[9] Based on international trials in settings with limited resources, the World Health Organization recommends a single oral dose of 600 mcg misoprostol for medical management of incomplete abortion and a single vaginal dose of 800 mcg misoprostol for medical management of anembryonic pregnancy and embryonic/fetal demise.[15,16]

A single dose of misoprosotol 600 mcg administered sublingually is an alternative regimen.[16] However, it is well proven that the success of medical management of EPF increases with multiple-dose regimens.[17] Misoprostol 800 mcg administered vaginally is the most studied regimen for medical management of EPF.

Success of medical management for EPF

Success of medical management should be determined by expulsion of the gestational sac, rather than by endometrial thickness on transvaginal U/S. Studies that use an endometrial thickness of >15 mm to define failure of medical management may underestimate success rates of expectant and medical management.[2]

Patients with symptoms such as cramping and bleeding, which are indicative of a clinical diagnosis of an incomplete or inevitable spontaneous abortion, experience greater success with medical management.[17,18] Success of medical management increases with multiple dose regimens.[17] The most studied multiple-dose regimen of misoprostol is 800 mcg vaginal misoprostol, repeated on day 3 if there is incomplete expulsion, as diagnosed by a persistent gestational sac on transvaginal U/S.[17,19]

Medical versus surgical management

In a Cochrane review (9 randomized, controlled trials [RCTs]; n=1766) with incomplete abortion before 13 weeks, where misoprostol was used orally or vaginally, there was no significant difference in success defined by complete miscarriage.[18] Not surprisingly, women using misoprostol have fewer surgical procedures and a higher risk of unplanned procedures.

The largest multicenter RCT (n=652) compared women with EPF (94% anembryonic gestation or embryonic/fetal demise, 6% incomplete/inevitable abortion) treated with 800 mcg vaginal misoprostol (n=491) or surgical management (n=161).[19] In the misoprostol arm, women received 800 mcg vaginal misoprostol, repeated on day 3 if expulsion was incomplete (diagnosed by persistence of gestational sac). Surgical aspiration was performed on day 8 if expulsion was incomplete.

With 1 dose of misoprostol, there was 71% successful evacuation. Success increased with a second 800-mcg dose of vaginal misoprostol if the gestational sac was still present on U/S on day 3. The overall success was 84% with misoprostol and 97% with surgical management. Success of medical management did not vary by gestational age, but did differ by type of EPF: 93% for incomplete/inevitable abortion, 88% for embryonic/fetal demise, 81% for anembryonic pregnancy. There was no difference in hemorrhage or endometritis between the groups (<1%).

Since medical management with misoprostol is an acceptable alternative to surgical evacuation, patient preference should guide decision making.[18,19]

Medical versus expectant management

In 24 RCTs (n=1888) comparing medical to expectant management for embryonic/fetal demise or anembryonic pregnancy, medical management was shown to be significantly more effective than ex-

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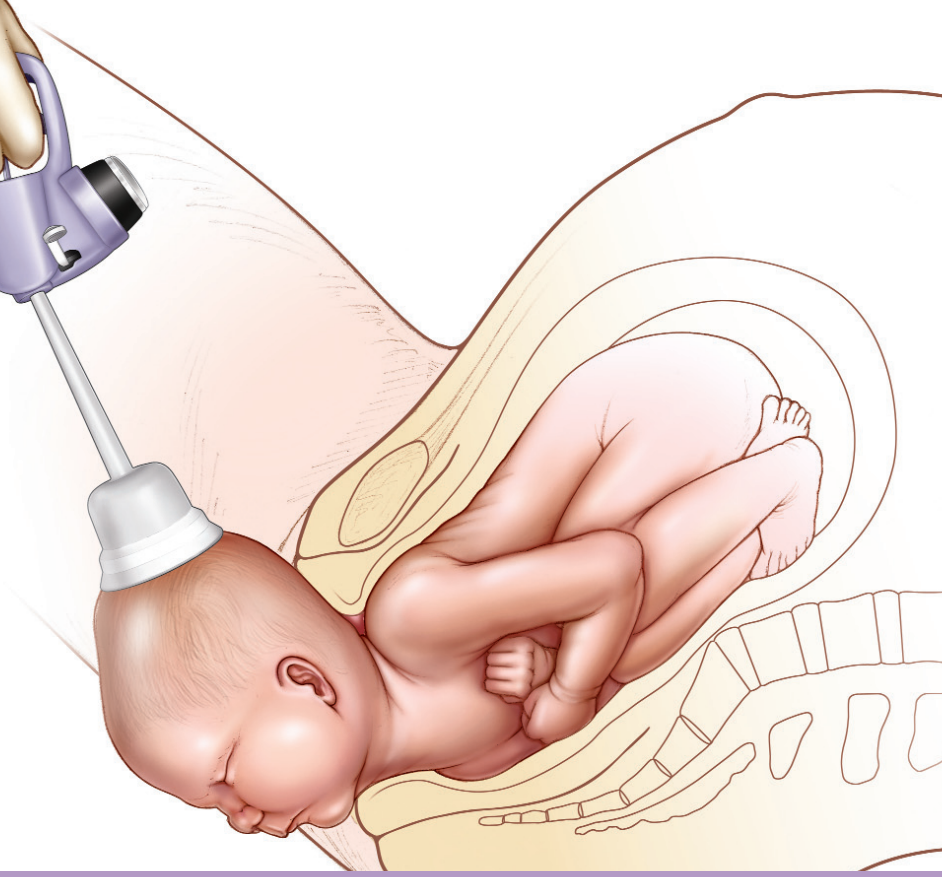

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TABLE 2 Contraindications to medical management

Hemodynamically or medically unstable patients
Signs of pelvic infection and/or sepsis
Suspected molar or ectopic pregnancy
Caution should be used in women with hemoglobin ≤9.5 g/dL
History of coagulopathy or current use of anticoagulants
Allergy to prostaglandins

Adapted from: Royal College of Obstetricians and Gynaecologists[13]; Blum J, et al[15]; Zhang J, et al.[19]

pectant management.[9,18] Most studies investigated vaginal misoprostol.[9]

Compared with expectant management, vaginal misoprostol shortens the time to achieve complete uterine evacuation at less than 24 hours after treatment and at less than 48 hours after treatment.

Patient counseling

Patients choosing medical management of EPF should have appropriate counseling regarding expected symptoms. Bleeding with medical management is heavier and longer in duration than with surgical management, but rarely requires intervention.[20] Women report approximately 12 days of bleeding after medical management. Bleeding will most likely be heavy for about 3 to 4 days, followed by light bleeding or spotting for several weeks.[15]

Patients should be counseled to contact their physicians if they experience heavy vaginal bleeding (soaking through more than 2 extra-large sanitary pads per hour for 2 consecutive hours) or signs of infection.[15]

Some women experience fever and/or chills during the first 24 hours after misoprostol use.[15] Patients should call their doctors and be evaluated for infection if fever and/or chills persist beyond 24 hours. Nausea and vomiting may occur and will usually resolve 2 to 6 hours after taking misoprostol.

Contraindications and complications

Table 2 presents a list of contraindications to medical management.[13,15,19]

Complications after medical management of EPF are rare. The incidence of gynecologic infection after surgical, expectant, or medical management of EPF is low (2%-3%). There is no evidence to show a differential risk of infection by management choice.[21]

In the largest RCT (n=652) comparing medical with surgical management, there were no differences in the following complications: hemorrhage requiring hospitalization with or without blood transfusion (1%); hospitalization for endometritis (<1%); fever (3%-4%); emergency visit to hospital within 24 hours of treatment (2%-3%); unscheduled hospital visits (17%-23%); decrease in hemoglobin ≥2 g/dL (4%-9%); and decrease in hemoglobin ≥3 g/dL (1%-5%).[19]

Failure of medical management

Failure of expectant or medical management results in the need for surgical evacuation.

Follow-up

No RCTs have assessed optimal follow-up after EPF. We recommend a follow-up visit that includes a clinical history and bimanual exam 7 to 14 days after medication use.[15] In general, BhCG levels do not need to be followed after either expectant or medical management.

Transvaginal U/S after medical management of EPF can be used to confirm successful expulsion of the gestational sac.[15] Endometrial thickness after medical management should not be measured as it is not predictive of success.[7] Endometrial thickness does not predict retained products of conception or need for surgical evacuation.

Future fertility

A long-term study of women who had had expectant, medical, or surgical management of EPF found that the method of management for EPF does not affect future fertility. In this RCT, there was no significant difference in the live birth rate 5 years after miscarriage: 79% among women who had expectant management; 79% among women who had medical management; and 82% among women who had surgical management.[22]

Cost-effectiveness

When accounting for multiple cost-associated variables, surgical management with office manual vacuum aspiration is generally more cost-effective than medical management. However, medical management is more cost-effective than surgical management in an operating room. For incomplete or inevitable abortion, medical management is the most cost-effective treatment method.[23]

Patient acceptability

In a large RCT comparing medical and surgical management of EPF, women who had undergone medical management reported more symptoms such as cramping and bleeding. However they reported similar quality-of-life and acceptability measurements as women who had surgical management.[24] In another large RCT comparing medical and surgical management, 83% of women who underwent medical management with misoprostol reported that they would recommend medical management to others. Seventy-eight percent reported that they would "probably" or "absolutely" use medical management again.[19]

Patient preference

Preferences regarding management of EPF are diverse.[25] Women's preferences may depend upon their desire for privacy, their reluctance to undergo surgery, and their expectations concerning EPF management options.

Since all currently available options for treatment of EPF are similar in safety and efficacy, patient preference should guide physicians. COG

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Fetal programming and adult obesity

Studies show that in utero conditions that lead to low birth weight contribute to increased risks of adult obesity. Thus, helping patients avoid extremes of nutrition in pregnancy can help optimize long-term health for their offspring.

BY **MICHAEL G. ROSS, MD, MPH,** AND **MINA DESAI, MSC, PHD**

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She has no conflict of interest to disclose with respect to the content of this article.

Mary Jane is a 28-year-old G2P1 whom you are seeing for prenatal care at 8 weeks' gestation. She is 5 ft 6 in tall and weighs 105 lb. She works in a highly visible technology position and strongly desires to maintain her body image during pregnancy. In her first pregnancy, she gained only 10 lb and delivered a healthy infant at 39 weeks weighing 4.85 lb. How should you counsel the patient regarding nutrition and weight gain in this pregnancy?

Prenatal care

Formalized prenatal care in the United States originated in the early 1900s with a program of just 3 pregnancy visits. Maternal mortality rates at the beginning of the 20th century approached 1% of pregnancies, with the principle etiologies being that of preeclampsia, infection, and hemorrhage. Accordingly, prenatal care focused on 3 complications: Patients' blood pressure and urine protein were measured at each visit for the diagnosis of preeclampsia, urinalysis was performed for urinary tract infection, and hematocrit was determined to prevent anemia and consequences of

TAKE-HOME MESSAGES

- Low birth weight is associated with a significant increase in adult heart disease, impaired glucose tolerance, and diabetes.
- Human studies indicate that exposure to maternal obesity leads to an increased risk of childhood and adult obesity.
- The relation of fetal growth to offspring obesity is a continuum and there may be an optimal newborn weight at which programming of obesity potential is minimized.

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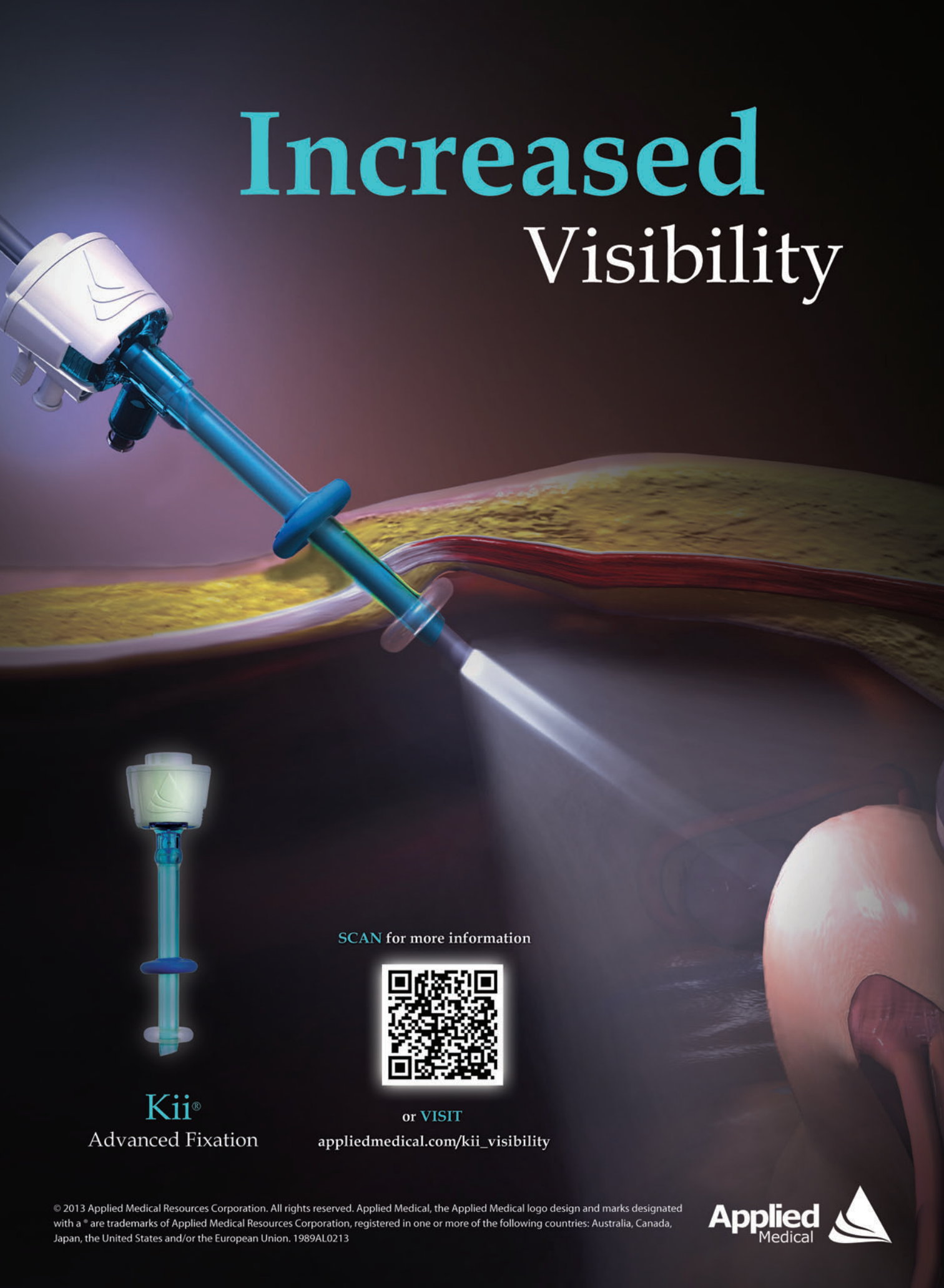

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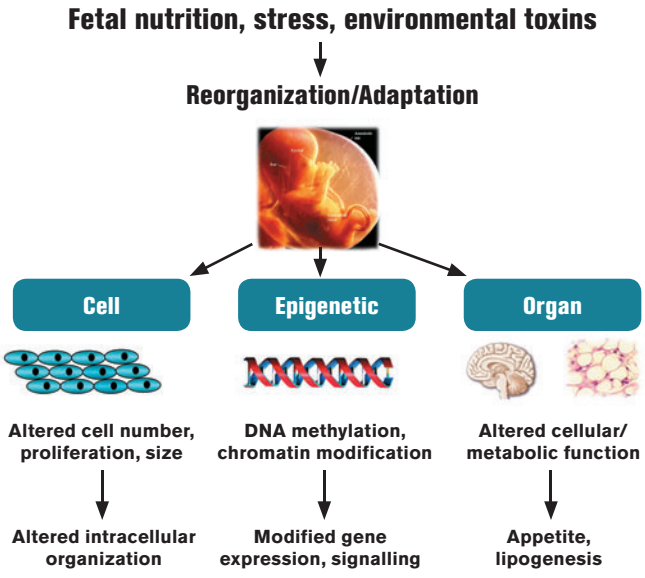
FIGURE 1 Mechanism of developmental programming



The fetal in utero environment is affected by maternal environmental conditions such as maternal nutrition, stress, and endocrine disruptors. This can result in fetal growth restriction and adaptation for survival, which, in turn, cause: (1) alteration of cellular composition through altered proliferation/differentiation; (2) modification of the epigenome through DNA methylation, histone methylation/acetylation, and RNA interference; and (3) changes in cellular/organ metabolic function such as appetite and fat storage.

hemorrhage. These interventions, as well as other healthcare improvements (blood banking, attention to asepsis, antibiotics), resulted in a dramatic reduction in maternal mortality, to rates now approaching 1 per 10,000 pregnancies in the United States. With this dramatic reduction in maternal mortality, the goals of prenatal care shifted to the reduction of fetal and neonatal morbidity and mortality, prematurity,[1] and, more recently, to the diagnosis (diagnostic ultrasound, biomarkers, amniocentesis), prevention (folate supplementation), and treatment (in utero and neonatal surgery) of congenital anomalies.

Developmental programming

Prenatal care is just now beginning to focus on the longer-term consequences of optimizing fetal health so as to prevent childhood and adult disease. Developmental programming may be defined as the permanent alteration in tissue structure or function as a result of the in utero environment. The concept of fetal programming has gained increased credence supported by strong findings from human epidemiologic studies and animal models.[2,3] Specifically, in utero exposures to altered maternal nutrition (excess and deficient), stress (eg, glucocorticoids), or environmental toxins, among others, may alter organ structure or function. As approximately 50% of all cell divisions for growth occur from conception to birth, it is not surprising that environmental stresses may impact cell number. Although the genotype of programmed offspring does not change, modified gene expression may be a consequence of exposure-mediated epigenetic changes, thus altering the expression of regulatory peptides and organ function (Figure 1).

In fact, 2 common historical obstetrical "teratogens" act via epigenetic programming. Thalidomide, which was prescribed in the 1950s as a sedative and morning sickness prescription, and included in more than 50 over-the-counter products, acts to truncate limb development by an epigenetic process that inhibits angiogenesis.[4] Of equal concern, diethylstilbestrol (DES) was used off label in women with a history of miscarriage prior to US Food and Drug Administration (FDA) approval in 1947. Only in 1971 did the FDA respond to evidence that DES-programmed female offspring have an increased risk of vaginal clear cell carcinoma, a response that occurs via an epigenetic process of gene hypermethylation in utero.[5]

Low birth weight

Obstetricians are well aware that genetic mutations, which occur typically over long epochs, are beneficial for species survival, and are generally irreversible. In contrast, developmental programming may have evolutionarily developed to permit an individual fetus to prepare for a postnatal environment, particularly an environment of drought and famine. Under conditions of famine, maternal nutrient reduction results in low-birth-weight (LBW) infants who, historically, would experience a continued environment of limited food access throughout their lives. Notably, LBW infants often exhibit a "thrifty phenotype," marked by increased appetite and food intake, efficient metabolism, and reduced energy expenditure—a programmed "couch potato" (Figure 2).[6] Thus, Hales and Barker have postulated that LBW thrifty phenotype infants would have a survival advantage in an environment of reduced nutrient availability.

However, pregnancies in the United States result in a phenomenon of "inadvertent thrifty phenotype" newborns. Women with significant med-

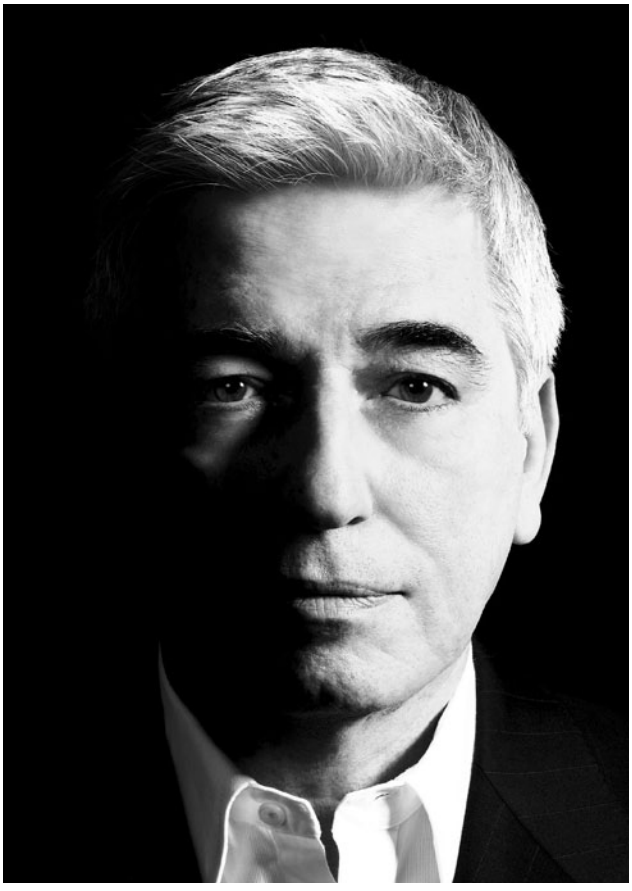


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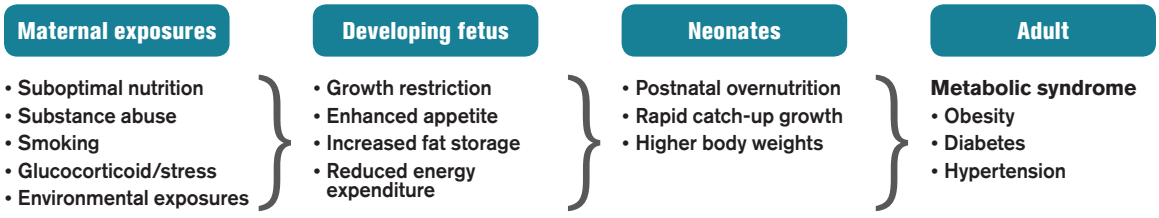
FIGURE 2 Developmental programming of obesity



Decreased maternal nutrition, substance abuse, and altered hormonal/metabolite milieu result in fetal growth restriction and low-birth-weight newborns who develop a "thrifty phenotype." Specifically, they exhibit enhanced appetite, reduced satiety, increased fat cell proliferation, and increased propensity for fat storage. Overnutrition (eg, formula feeding, high-fat diets) during the postnatal period causes rapid catch-up growth, resulting in childhood and adult obesity. From Hales CN, et al.[6]

ical illnesses often deliver LBW infants, whereas less than a century ago these women would often not live to the age of conceiving or childbearing. A plethora of abused substances (eg, cocaine, methamphetamine, tobacco) contribute importantly to growth restriction, while in vitro fertilization has resulted in an explosion of LBW offspring from multiple gestations. Whereas in the past many, if not most, extremely LBW infants would not survive, the tremendous improvement in neonatal care has enhanced survival such that infant viability is now commonly defined at .97 lb. These surviving LBW infants, programmed as thrifty phenotype, are then exposed to the high-fat/high-calorie diet with the low energy-requiring environment of modern Western society.

Programmed obesity

In part a consequence of perinatal programming, obesity is a preeminent public health problem, with more than 66% of US adults overweight, and 36% of US adults obese.[7] Race/ethnicity is independently related to childhood and adolescent obesity with higher prevalence occurring among African Americans, Mexican Americans, and Native Americans as compared with other ethnic groups.[8,9] Epidemiologic studies confirm the effects of maternal undernutrition on the programming of metabolic syndrome. Barker and colleagues demonstrated a marked increase in the rates of metabolic syndrome with decreasing birth weight.[2] As an index of the contribution to morbidity, LBW is associated with a significant increase in adult heart disease, impaired glucose tolerance, and diabetes. Notably, the prevalence of LBW infants is highest among black women (11.8%) as compared with white (7.1%), Hispanic (5.3%), and Asian/Pacific Islander (8.4%) women.[10]

As discussed above, the thrifty phenotype fetus has been "prepared" for an extrauterine environment of low nutrition. Gluckman and Hanson elaborated a "match-mismatch" thesis whereby programmed obesity becomes evident when the thrifty phenotype fetus is exposed to an abundance or excess of nutrients postnatally followed by a Western high-fat diet.[11] Indeed, rapid "catch-up" growth of LBW newborns may be a predictor of childhood and adult obesity (Figure 2).[6]

Mechanisms of programmed obesity

Laboratory animal studies have revealed several potential mechanisms of metabolic programming by nutrient and hormonal signals and epigenetic pathways.[12-14] Hormones may respond to intrauterine conditions to maximize the survival in utero and after birth, while predisposing the adult to altered physiological functions and, ultimately, disease. Numerous studies have demonstrated that dietary deficiencies or supplementation can dramatically alter a heritable phenotype in mice via epigenetic processes that change DNA methylation and/or chromatin packaging (eg, histone acetylation, methylation). Critical growth and development genes that may be epigenetically regulated include the glucocorticoid receptor, appetite/satiety regulatory peptides, leptin, and glucose transporters.

Studies by our laboratory and others have confirmed that LBW offspring eat more, as a result of increased appetite and reduced satiety responses. Brain appetite centers (ie, arcuate nucleus) demonstrate impaired satiety signaling to leptin and re-

duced neuronal populations of satiety neurons. Compounding the effects of increased food intake, LBW adipose tissue is programmed for enhanced fat proliferation and lipid storage.[15] Additional organ systems including the kidney (impaired nephrogenesis), lung (reduced alveolar development), placenta (increased apoptosis) and vascular bed (reduced vasculogenesis) likely contribute to the phenotype of adult metabolic syndrome.

Studies throughout the world are exploring the mechanistic pathways, biomarkers of programmed obesity, and novel preventive and therapeutic approaches. Obesity is not simply a lack of self-control; rather individuals are clearly programmed to have enhanced appetite and fat storage.

Maternal obesity

In addition to the effects of LBW, human studies indicate that exposure to maternal obesity leads to an increased risk for childhood and adult obesity.[16] The 25% to 36% increase in maternal BMI over the last decade has translated to an approximately 25% increase in the incidence of high-birth-weight babies, who show increased adipose tissue mass and an increased risk of adult obesity and diabetes in later life. Importantly, as the prevalence of obesity among pregnant women continues to rise, increasing numbers of children are exposed to an "obese intrauterine environment" during development. This portends a self-perpetuating cycle of increasing obesity rates. Animal studies confirm the developmental programming effects of in utero overnutrition.

Thus, epidemiologic studies confirm that the relationship between human birth weight and adult obesity, hypertension, and/or insulin resistance is a U-shaped curve. Perhaps most importantly, the relation of fetal growth to offspring obesity and metabolic syndrome is a continuum rather than a threshold response. There may well be an optimal newborn weight (potentially specific to an individual mother) at which the programming of obesity potential is minimized.

The sequela of gestational programming was originally focused on metabolic syndrome. It is now recognized that a myriad of childhood and adult medical disorders may be influenced by the in utero environment, including psychological/behavioral disturbances, autism, cognitive limitations, Alzheimer disease, childhood asthma, autoimmune disorders, and osteoporosis, among others. In particular, the substantial increase in prevalence of autism[17] has been associated with potential perinatal risk factors, including LBW.[18] Furthermore, children with autism are at risk for overweight and obesity.[19] Epigenetic dysregulation of DNA methylation and histone modifications could play a prominent role in the pathophysiology of autism.[20-22]

Environmental endocrine disruptors

Recent studies indicate that environmental pollutants and environmental agents that act as endocrine disruptors may have similar adverse effects on offspring programming.[23] In July 2012, the FDA issued an announcement that infant baby bottles and drinking cups can no longer contain bisphenol A (BPA), a common plastic agent that is known to have potent estrogenic and potential programming effects. Of note, BPA is found in hundreds of plastic items, from water bottles to CDs.

Although exposure to BPA may have potential adverse effects on babies and young children, exposure during pregnancy may have silent effects on fetal development that are only exhibited in the adult offspring. Animal studies have shown that in utero or neonatal exposure to BPA is associated with higher body weight, increased breast and prostate cancer, and altered reproductive function.[24-26] The proadipogenic effects of BPA are well acknowledged with specific effects on adipocyte proliferation, differentiation, and lipogenic function.[23]

In addition to adipogenic effects, maternal BPA exposure has been shown to accelerate neurogenesis and neuronal migration in mice, and result in aberrant neuronal network formation.[27,28] There is compelling evidence of BPA-mediated epigenetic effects that have potential for transgenerational effects. BPA causes hypomethylation of DNA in mice and maternal dietary supplementation (methyl donors such as folic acid or the phytoestrogen genistein) negates the DNA hypomethylating effect of BPA.[24]

Clinical implications, therapies, and conclusions

We are at the precipice of a transition in prenatal care to incorporate a goal of optimizing fetal and neonatal health so as to prevent or reduce adult-onset diseases. Yet, simple decisions remain a dilemma: What is the optimal nutrition and weight gain for underweight or overweight gravidas? Is it of benefit to deliver small-for-gestational-age fetuses pre-

continued on **PAGE 44**

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.

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®
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RACIAL HEALTH DISPARITIES AND FETAL PROGRAMMING

In the United States, the rate of maternal and infant mortality and adverse perinatal outcomes for African Americans is 2 to 4 times greater than for whites. The disparity in African-American maternal mortality has been linked to comorbidities that include hypertension and obesity.[1] In fact, hypertension and heart disease are major contributors to overall maternal mortality. Furthermore, pregnancy complications such as prematurity and preeclampsia significantly affect risk for early-onset cardiovascular events such as stroke and myocardial infarction. Racial and ethnic health disparities in perinatal outcomes and adult diseases, such as obesity, hypertension, and diabetes, are not just a matter of quality of care and socioeconomic status.

Hypertension, diabetes, and obesity are generational, but not necessarily "genetic," in African Americans. Studies dating back several decades indicate higher rates of low-birth-weight and preterm infants born to African-American women. Is the racial disparity seen in hypertension and obesity in adulthood and thereby in pregnancy a matter of inheritance, or is it a matter of generational fetal programming that cannot be overcome without achieving ideal birth weights?

Epidemiologic studies confirm that there is a relationship between low birth weight and adult obesity, hypertension, and/or insulin resistance. The concept of fetal programming and the "thrifty phenotype," with its impact on appetite, food intake, and lifestyle, can now be clearly linked to adolescent and adult medical conditions and pregnancy comorbidities.

The solution to racial perinatal and adult health disparities for coming generations is not simple, especially if they are to overcome intrauterine programming and environmental influences they face through infancy, adolescence, and adulthood.

The health benefits to immediate and long-term breastfeeding for both mother and infant are well established. The duration of breastfeeding is inversely and linearly associated with risk of the infant being overweight. The risk for being overweight or obese decreases by 4% for each month of breastfeeding.[2] Additional long-term adult health benefits for breastfed infants include lower blood pressure and lower risk for cardiovascular disease, metabolic syndrome, and diabetes, which are also inversely related to breastfeeding duration.

In the United States, non-Hispanic black women have lower rates for in-hospital initiation of breastfeeding, breastfeeding at 6 months, and exclusive breastfeeding at 6 months compared with whites, Hispanics, and Asians. Breastfeeding should be considered an infant's first health and life insurance and may cancel out some of the adverse effects of low birth weight from either prematurity or fetal undergrowth. The additional benefits of breastfeeding for the infants of African-American women, particularly low-birth-weight infants, could ultimately impact generational health disparities in both the short and long term.

—Haywood I. Brown, MD

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term, so as to avoid a prolongation of an "adverse" intrauterine environment? Should we avoid plastic cups containing BPA during pregnancy? What is the long-term risk/benefit of maternal glucocorticoids on developmental programming of adult disease? What is the most effective feeding strategy for LBW newborns?

The existing evidence supports that limiting the rapid weight gain in the neonatal period may be beneficial. Similarly, breastfeeding may decrease the incidence of obesity in childhood as well as the weight of the nursing mother.[29,30] Undoubtedly, there is no single mechanism or fixed developmental window that impacts on each organ or system

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development. As a result, the ultimate management of fetuses and newborns is likely to be individualized rather than universal.

Finally, how do we advise our new prenatal patient Mary Jane? Certainly, we should educate our patient that although evidence is limited, extremes of maternal nutrition may have long-term adverse effects on her children. Thus, she should be counseled to achieve normal weight gain and, optimally, deliver a normal-weight infant. Supplementation with folate (which reduces birth defects via epigenetic mechanisms) is advised. Exposures to potential developmental modulators (cigarette smoke, alcohol, pollutants) should be minimized, if possible. Ultimately, prenatal management decisions will await additional studies exploring mechanisms of developmental programming and the consequences or benefits of altered perinatal management. In the interim, we should strive for preconception normalization of maternal weight and balanced maternal nutrition during pregnancy. Pregnancy care providers will increasingly have a role in the optimization of long-term adult health. COG

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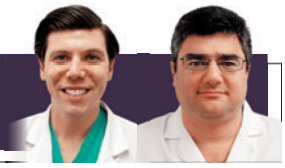

Apps and monitors for patient health

Apps for fitness, diet, and sleep help patients quantify their activity and reach their goals

The 2009 Institute of Medicine recommendations for amount and rate of weight gain during pregnancy indicate that practitioners should discuss "diet and exercise" with their patients.[1] Although most of us have not had formal nutrition training, it is safe to assume that a discussion of a healthy diet (ie, caloric intake, sugars, and saturated fats) is relatively straightforward. In fact, for many of us who follow patients with gestational diabetes, demonstrating the effect of certain foods on blood sugar is a powerful educational tool for helping patients understand the importance of adhering to a diet.

Yet when it comes to discussing exercise, it seems that many of us are at a loss for words. What kind of exercise should we recommend? How much exercise is enough? How much is too much? How do I know that my patient is actually exercising? How do I prescribe exercise?

According to the US Department of Health and Human Services, US adults should engage in moderately intense physical activity for a minimum of 150 minutes each week; this is equivalent to 30 minutes a day, 5 days per week.[2]

While it is relatively easy to keep track of the duration and frequency of exercise, it is much more difficult to quantify the intensity of an activity, let alone ensure that the activity is "moderate" for the entire 30 minutes. In fact, in a 2008 study of women's understanding of "moderate-intensity" physical activity as presented in the popular media, the authors found that it is not enough to simply hear and read a description of physical activity, but that it requires practice.[3]

Using data to measure health and fitness

So, what are we to do? Should we have our patients log their daily activities? Should we have our patients show us sign-in sheets from the local gym? It turns out that the dilemma of how to quantify physical activity has been a hot topic of discussion for more than 50 years. In 1965, a Japanese doctor developed the first pedometer to give people the opportunity to meet measurable goals and thus increase their physical activity. The device was called the Manpo-kei (meaning "10,000-steps meter"). It was based on research by Dr. Yoshiro Hatano that demonstrated that 10,000 steps a day allowed for a proper balance between the traditional Japanese caloric intake and the caloric expenditure of walking approximately 5 miles per day (the average person's stride length is approximately 2.5 ft long, therefore 2000 steps/mile).[4]

The validity of the 10,000-steps model for Americans has been questioned by many researchers, since today's American diet is far more calorie-rich than the 1965 Japanese diet and 5 miles of walking per day may be too much for the average person.

All this leads back to the origi-

HOW MANY STEP/DAY ARE ENOUGH?

A 2004 study that attempted to answer that question and reported:[5]

Walking <5000 steps/day indicates a "sedentary lifestyle"

Walking 5000-7499 steps/day is typical of daily activity excluding sports/exercise and may be considered "low active"

Walking 7500-9999 steps/day likely includes some volitional activities (and/or elevated occupational activity demands) and may be considered "somewhat active"

Walking ≥10,000 steps/day indicates that an individual is "active"

Walking >12,500 steps/day is "highly active"

nal question of how physicians can effectively prescribe exercise to our patients and then assess their compliance. Well, as you can imagine, there are apps for this!

NIKE+

One of the most popular apps, the Nike+ Running App (free, iOS/Android), tracks distance, pace, time, and calories burned using the device's GPS. It also provides users with audio feedback (such as encouragement, statistics, and heart rate) as they run. The app can also be programmed to automatically upload workout information to a website, nikeplus.com, where users can track their running routes, elevations, and progress.

Furthermore, when the app is synced with a Facebook account, users can alert their Facebook friends at the start of their workouts so they can receive real-time "cheers" for each "like" or comment they receive. Although this app is running focused, any walking or running motion is recorded.
http://nikeplus.nike.com/plus/products/gps_app/

RUNKEEPER

Another popular app is RunKeeper (free, iOS/Android). Like the Nike+ app, RunKeeper uses GPS-derived data to track fitness performance. Although the name suggests a running focus, this app can be used to monitor all sorts of physical activity, including running, walking, and cycling. Furthermore, RunKeeper can sync with a number of third-party accessories such as heart-rate monitors and Internet-linked syncing scales to let users collect and analyze their fitness data and monitor their performance.

Other highlights of RunKeeper include the ability to see detailed pace, distance, and time stats; in-ear (headphone) coaching that gives live stats; progress through built-in audio cues; on-demand notification of new personal bests and milestones; and, most importantly, the ability to follow detailed plans to help patients follow specific (personal or prescribed) fitness objectives.
http://runkeeper.com/

FITBIT

Beyond apps that use native smartphone technology, there are also devices that sync to the Internet via smartphone to monitor physical activity. One popular manufacturer, Fitbit, was one of the first companies to allow consumers to measure not only their daily physical activity but also their sleep-related motion, which is associated with sleep efficacy. Their most popular model, the Fitbit One, is $99.99 and works with iOS and Android devices. Its matchbook-sized clip-on monitor has the ability to measure the number of steps walked or run (distance is calculated by a calibrated step), floors climbed, and calories burned, and to track sleep statistics (hours slept, number of times woken, sleep efficiency). The device is designed to be worn 24 hours a day, which is why it is sweat-, rain-, and splash-proof and can be worn in the shower.

Fitbit is also about to release a bracelet-style monitor called the Fitbit Flex that has all the features of the Fitbit One. Fitbit also manufactures a Wi-Fi-enabled scale that tracks body weight, body fat percentage, and body mass index, allowing users to create pictures of their long-term progress. It also wirelessly syncs stats with online graphing and mobile tools to help users integrate their fitness data.
http://www.fitbit.com/

UP

Another popular bracelet-styled device is the UP, made by the famed Bluetooth headset manufacturer Jawbone. The Jawbone UP has many of the features of the Fitbit products and is also designed to work with a smartphone device (iOS or Android).

The strength of the Jawbone app is that UP not only offers users easily understood data on their sleep performance (how long did it take to fall asleep; how long did they have light sleep and deep sleep; how long were they awake during the night; how long were they in bed; did they reach their sleep goal) but it also uses that data to turn a user's phone into a smart alarm that wakes the user at the right

point in the sleep cycle. For example, the power nap monitor wakes the user after 26.5 minutes of sleep, the optimal length of a nap.

Those who may have a propensity to be idle or need a reminder to be active (ie, those who work at a desk for hours on end) can set an alarm as a reminder to take a break and move around. Lastly, the app has a built-in food and drink tracker that allows the user to take a photo of food, scan a barcode, browse the image gallery in UP, or search the ingredient database to record what he or she is eating and drinking. The app will then calculate the daily nutritional intake and display the calories consumed compared to the calories burned. Among devices with custom alerts, UP definitely stands out.
https://jawbone.com/up

PEAR SPORTS

When it comes to smartphone-based training, Pear Sports has created a product unlike any other. Sold at Apple Store locations and online, the $99.99 kit comes with a proprietary Bluetooth wireless heart-rate monitor and secure earphones. After downloading the app and syncing the heart-rate monitor to the device, the user performs a sample workout to calibrate the device.

Once calibrated, the Pear app tells the user when to speed up or slow down, provides useful tips to improve form, explains the purpose and benefits of the workout, and keeps motivating the user through in-ear coaching cues. The app ultimately "learns" the user's fitness level and creates custom heart-rate zones to ensure that each subsequent workout is at the right intensity. Of course, Pear can also display workout-by-workout statistics in graphical and numerical charts to show the user's progress.

Pear has partnered with a number of famous workout coaches to create custom plans that users can purchase in the app to help them achieve certain goals. These include the 30 Minute Functional Strength Circuit Workout for Runners, 30 Minute Fat Burn Run, Zero to Running Plan, 5K Training Plan Level 2, and the Half Marathon Plan.
http://pearsports.com/pear-mobile-gear

We physicians have known for a very long time that diet and exercise are the keys to fitness success. If the sum of the calories burned is greater than the sum of calories consumed, by definition a person should lose weight. However, as discussed above, quantifying the quality and character of caloric output is challenging. This is why it is important to recognize these consumer-level products. In concert with demonstrable app-derived data, it is now feasible not only to recommend a specific exercise program, but also to advise patients about improving their activity.

It is not unreasonable to envision a day when we not only write a prescription for a medication, but also prescribe an application.

"Download two of these and call me in the morning . . . ." COG

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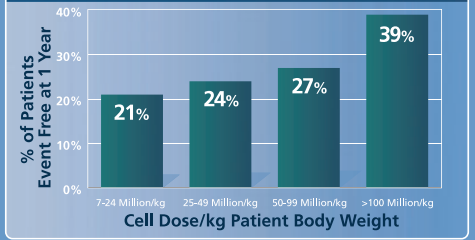

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LAURIE J. MCKENZIE, MD
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Cervical length measurement and preterm birth

Two physicians discuss the pros and cons of universal assessment for ob/gyns and their patients.

PRO

Patients deserve information about cervical length

By Sonia S. Hassan, MD

In 1960, the United States ranked twelfth in the world in infant mortality; this ranking has fallen steadily to forty-third.[1] Preterm birth (PTB)-related deaths are one of the leading causes of this infant mortality rate.[2,3] In 2005, 12.9 million births worldwide were preterm.[4] In 2011, the rate of PTB in the United States was 11.7% (463,361 babies per year).[5,6]

The challenge for providers and researchers has been, first, to predict who will deliver prematurely, and second, to implement an intervention that will prevent PTB. *A sonographic short cervix diagnosed by transvaginal ultrasound (TVUS) is the most powerful predictor of PTB.*

Fifty percent of women with a cervical length <15 mm will deliver <32 weeks.[6,7] TVUS provides the most accurate and reproducible cervical length measurement with no associated risks; it is widely accepted by patients. Yet implementation of a program in which all pregnant women undergo cervical length measurement requires the availability of an intervention that can prevent PTB.

Vaginal progesterone for prevention of PTB and neonatal complications

Two randomized clinical trials have demonstrated that vaginal progesterone reduces the rate of PTB in women with a sonographic short cervix.[8,9]

A randomized clinical trial investigating the use of vaginal progesterone to prevent PTD (<34 weeks) in women with a short cervix (<15 mm) reported a 44% reduction in risk of PTB (19.2% vs 34.4%; relative risk [RR], 0.56; 95% confidence interval [CI], 0.36-0.86).[8] In 2011, a randomized clinical trial[9] demonstrated that administration of vaginal progesterone to women with a short cervix (10 mm-20 mm) was associated with:

--a 45% decrease in the rate of PTB at <33 weeks (primary endpoint), a 38% decrease in the rate of PTB at <35 weeks, and a 50% decrease in the rate of PTB at <28 weeks' gestation;

--a 61% decrease in the rate of respiratory distress syndrome; and

--a decrease in the rate of composite neonatal morbidity.

A meta-analysis of individual patient data from 5 randomized clinical trials revealed that in addition to reducing the rate of PTB and respiratory distress syndrome, administration of vaginal progesterone

to women with a short cervix was associated with a reduction in the rate of mechanical ventilation, admission to neonatal intensive care units (NICUs), and composite neonatal morbidity/mortality.[10]

Impact and implications for the healthcare system

The potential impact of the use of vaginal progesterone in women with a short cervix can be surmised from the estimate that 11 patients need to be treated to prevent 1 PTB <35 weeks, and that 9 patients need to be treated to prevent 1 PTB before 34 weeks' gestation. Furthermore, 15 patients need to be treated to prevent 1 episode of respiratory distress syndrome.[10]

Estimates indicate that 141 pregnant women from the general population need to be screened with TVUS (treating those with a cervical length ≤25 mm with vaginal progesterone) to prevent 1 case of PTB <33 weeks.[9,10]

Cost-effectiveness analysis studies have demonstrated that the preterm prevention strategy of implementing universal cervical length risk assessment with TVUS and using vaginal progesterone is cost-effective.[11-13]

Werner and colleagues[12] have estimated that for every 100,000 women screened, there is a cost savings of more than $19 million annually. In the United States, the total annual cost savings is estimated to be $500 million, based on the 2011 population.

Numerous institutions now employ universal TVUS cervical length risk assessment. Delaying implementation at other centers will result in patients missing the opportunity for treatment. This is similar to what happened with antenatal steroids, for which efficacy was demonstrated in 1972.[14] Not until 1994, however, were they widely adopted for use in women at risk of PTB.[15]

Delaying universal sonographic cervical length risk assessment would result in the ethical problem of having an intervention for a diagnosis that we are not seeking in all patients. Vaginal progesterone's efficacy has been demonstrated in women with and without a prior PTB; hence, all patients need to be assessed for cervical length.

As obstetricians, we are becoming obligated to provide pregnant women with the knowledge about the length of their cervices. Therefore, this critical question must be considered: When there is a treatment available to prevent PTB for those with a sonographic short cervix, doesn't every woman have a right to know her cervical length? The answer is yes. COG

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CON

Pragmatic issues argue against screening

By Patrick S. Ramsey, MD, MSPH

Cervical length screening has emerged as an important clinical tool to assess PTB risk. Iams et al demonstrated an inverse relationship between cervical length and PTB risk, creating immense enthusiasm for cervical length screening as a potential screeing tool.[1] However, a *sine qua non* attribute of a screening test is the availability of an effective intervention.

Several recent studies have proposed progesterone for PTB prevention in women with short cervices.[2-4] In a double-blind, placebo-controlled trial of 413 women with cervical length < 15 mm, Fonseca et al demonstrated that micronized progesterone was effective in preventing PTB at < 34 weeks' gestation.[2] Hassan et al, in a double-masked, placebo-controlled trial of 465 women with cervical lengths of 10 mm to 20 mm, noted significant reduction in the PTB rate at < 33 weeks and neonatal morbidity among women treated with progesterone gel.[3]

In contrast, Grobman et al, in a double-masked, placebo-controlled trial of 657 nulliparous women, failed to demonstrate benefit of 17-alpha hydroxyprogesterone caproate to prevent PTB at < 37 weeks in women with cervical lengths < 30 mm.[4] The mixed success of these trials has prompted some to advocate for universal cervical length screening, but significant pragmatic issues strongly argue against it.

First, these trials were executed with uniform recruitment criteria, standardized cervical length screening, compliance assessments, and follow-up visits. While consistent management protocols were used within the trials, their protocols varied.[2-4] Also, the trials differed in gestational age at screening, progesterone intervention employed, and cervical length intervention threshold. Therefore, the basis for universal screening is weak.

A similar historic situation was universal screening and treatment of bacterial vaginosis (BV). Initial trials using variable BV definitions and treatment regimens, largely in high-risk populations, suggested benefit for PTB prevention. Universal screening and treatment of a low-risk population was also prematurely advocated and later abandoned because of lack of efficacy in subsequent large randomized trials.

Another screening test principle is cost-effectiveness. The above trials required screening of massive numbers of women to identify the small proportion of women with short cervices (n = 24,620; 32,091; and 15,435; respectively), raising the issue of cost-effectiveness of universal screening.[2-4]

A 2010 economic analysis concluded that universal sonographic screening for short cervix and vaginal progesterone treatment appeared to be cost-effective and yielded the greatest reduction in PTB at < 34 weeks compared with alternatives.[5] This simplistic analysis did not account for costs and untoward outcomes related to unnecessary interventions such as cerclage, antibiotics, and tocolytics. This is particularly important for 60% of women with short cervices who ultimately do not deliver preterm. Hassan's data suggested that 14 women would require treatment to prevent 1 PTB at < 33 weeks, and 22 women would require treatment to prevent 1 case of respiratory distress syndrome.[3] While these numbers seem favorable, they are a product of the rigorous environment of randomized trials.

Universal cervical length assessment in the general population with ill-defined screening protocols, variable screening techniques, nonstandardized progesterone regimens, and varied alternative interventions in practice will dramatically reduce any benefit and significantly increase costs.

A 2013 Cochrane review concluded, "Currently, there is insufficient evidence to recommend routine screening of asymptomatic or symptomatic pregnant women with transvaginal ultrasound cervical length."[6] Thus, universal cervical length screening should not be supported at this time. COG

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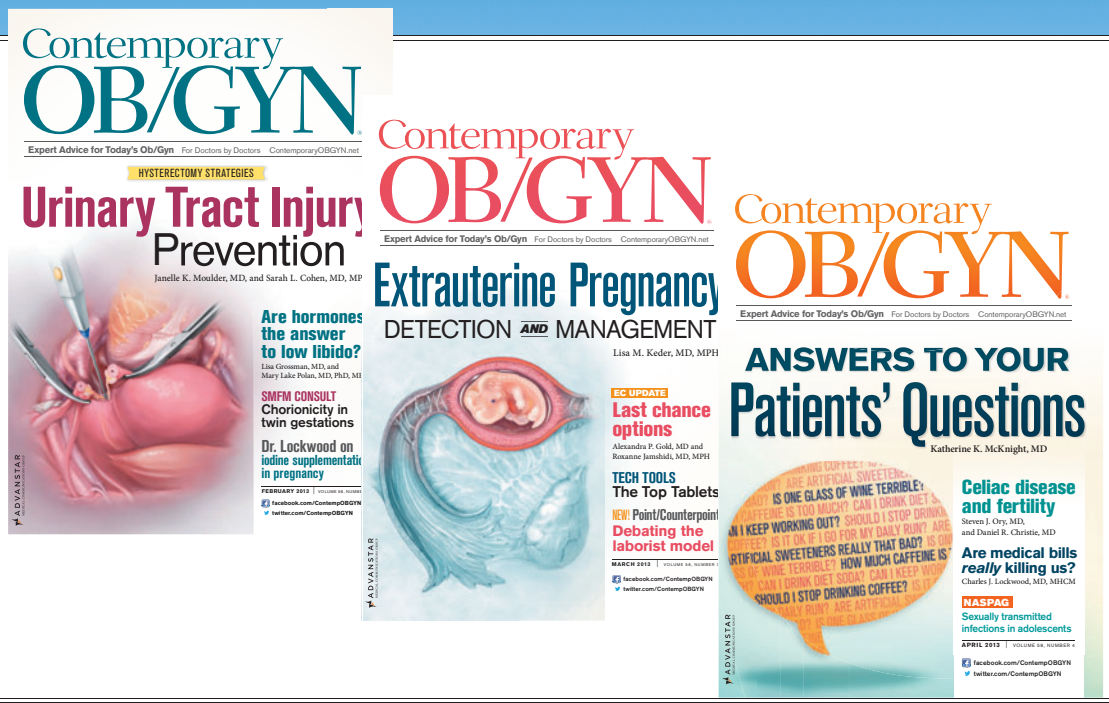

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Jon I Einarsson, MD, MPH

A native of Iceland, Dr. Einarsson joined the faculty at Harvard Medical School as Director and Founder of the Division of Minimally Invasive Gynecologic Surgery (MIGS) at Brigham and Women's Hospital (BWH) in 2006. The MIGS division is a referral practice that accepts challenging cases that are not considered candidates for minimally invasive surgery due to complex pathology or significant medical comorbidities. Dr. Einarsson's personal accomplishments include being the first to use barbed suture in gynecologic laparoscopy, perform laparoscopic uterine artery occlusion for uterine fibroids, perform laparoscopic cerclage for cervical incompetence, and perform laparoscopic hysterectomy for extremely large uteri.

Haywood L Brown, MD

A maternal-fetal medicine specialist, Dr. Brown has been an innovator in developing community programs for outstanding obstetrical care and has cared for women at high-risk for adverse outcomes, particularly women from underserved communities and long been involved in the research of substance abuse and its effects on mothers and children. He was the first African-American President in the history of the Society for Maternal-Fetal Medicine.

Joshua A Copel, MD

Dr. Copel is well known worldwide as an expert in maternal and fetal medicine and in high-risk pregnancy. His passion for working in medical ultrasound derives from his excitement for the possibilities in obstetrics. His time is generously spent on advancing the ultrasound profession, for which he has received numerous awards, ranging from the Nathan Kase Award for Excellence in Clinical Teaching at Yale to the Dru Carlson Memorial Award for Best Research in Ultrasound and Genetics from the Society for Maternal-Fetal Medicine (SMFM).

Robin Farias-Eisner, MD, PhD

Dr. Farias-Eisner and his colleagues have recently demonstrated that serum CA-125 levels, the most commonly utilized biomarker for clinical screening and prognosis in patients with ovarian cancer, do not predict the outcome of cytoreductive surgery in patients with advanced epithelial ovarian cancer. The creation of a panel of biomarker proteins for the early detection and prediction of clinical outcome for any type of cancer is a goal of many researchers and clinicians fighting the war against cancer.

John O DeLancey, MD

Dr. DeLancey is one of the world's foremost surgeon/researchers studying pelvic floor disorders. He and his team have discovered many basic factors involved in pelvic floor structural mechanics related to urinary and fecal incontinence. The team's work has led to insights into the biomechanics of vaginal birth injury that is one of the dominant causes of incontinence and prolapse. He was elected to the IOM in 2012 and recently won the largest-ever grant from NIH for research on birth-related pelvic floor injuries.

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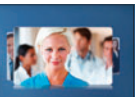

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CALENDAR

MAY/JUNE

MAY 31 - JUNE 4: American Society of Clincal Oncology (ASCO) Annual Meeting
Chicago, Illinois
FOR MORE INFORMATION: *http://chicago2013.asco.org*

JUNE

15-18: ENDO 2013 95th Annual Meeting and Expos of the Endocrine Society
San Francisco, California
FOR MORE INFORMATION: *www.endo-society.org/ENDO-2013-san-francisco.html*

JULY

18-21: 87th Semi-Annual Meeting of the Gynecologic Oncology Group (GOG)
San Antonio, Texas
FOR MORE INFORMATION: *www.gog.org/meetinginformation.html*

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

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*

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 Gyncologic Laparoscopists Global Congress on Minimally Invasive Gynecology
National Harbor, Maryland
FOR MORE INFORMATION: *www.aagl.org/annual-meeting*

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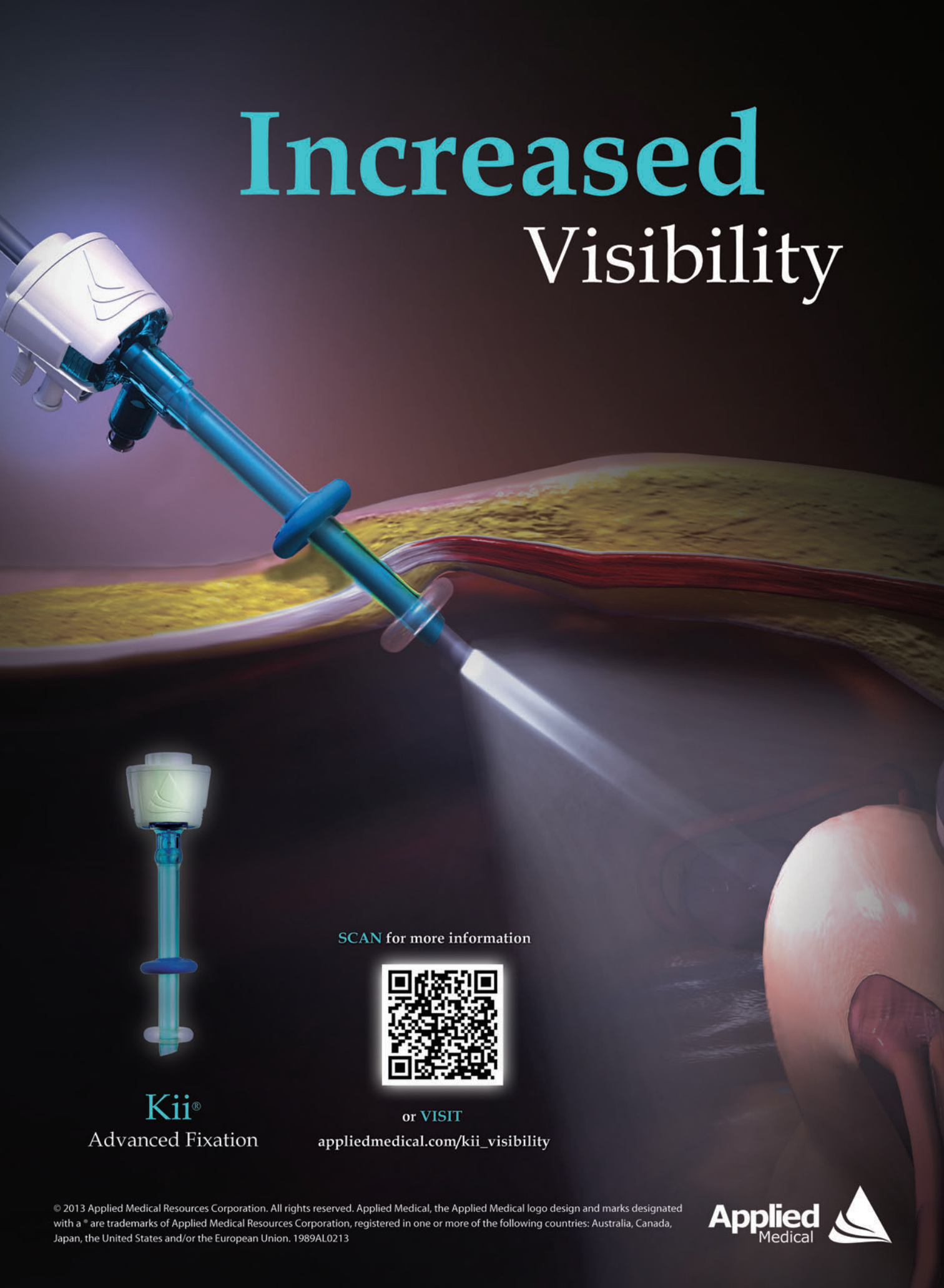

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