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Ultrasound Triage of Postmenopausal Bleeding

James M. Shwayder, MD, JD

Rethinking hormones in menopause
Two expert opinions

LEGALLY SPEAKING
Fibroid—or sarcoma?

GME at a crossroads

SEPTEMBER 2014 | VOLUME 59, NUMBER 9
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Graduate medical education at the crossroads

If we want to ensure that future generations of medical students have access to first-rate ob/gyn training, we need to join the growing debate over graduate medical education (GME) funding. If you are like me, you had no idea who provided the money to pay your salary as a resident. I just assumed it was my hospital. But the federal government spends more than $15 billion per year on residency and fellowship training, and many are asking why physicians deserve this special largesse denied other professionals.

A recent Institute of Medicine (IOM) report called for a complete restructuring of federal GME payments to achieve greater transparency and accountability in meeting the nation’s physician workforce needs. Critics contend that adopting the IOM recommendations would lead to major cuts in GME funding, threatening the world’s best training programs and jeopardizing patient care.

What are the issues behind this debate—and should we be concerned about the viability of future ob/gyn training?

Federal support for GME

Hospitals with accredited GME programs receive $6.8 billion in indirect medical education (IME) and $2.8 billion in direct graduate medical education (DGME) funding from Medicare. The former is doled out to hospitals as part of their Medicare prospective payment system remuneration using a complex formula derived from outdated 1980s cost data and designed to cover debatable “indirect” expenses accruing from resident training.

We should be concerned about the viability of future ob/gyn training.

In contrast, DGME funds are used to directly support the salaries and benefits of residents, program directors, and select faculty. Both IME and DGME payments are dependent on a hospital’s volume of Medicare inpatients, disadvantaging programs with large pediatric, obstetric, and non-elderly adult populations.

Most states also provide Medicaid GME, matched by the federal government, totaling about $4 billion. The Veterans Health Administration (VA) and the Health Resources and Services Administration (HRSA) supply an additional $1.44 billion and $464 million, respectively, in GME funds. The VA keeps its IME payments and provides DGME funds to affiliated academic GME sponsors, while HRSA funds are used to support children’s hospital residency programs, primary care loan repayment programs, and, more recently, community-based family medicine training programs.

However, both VA and HRSA funds depend on politically unreliable Congressional discretionary appropriations, rather than Medicare’s mandatory appropriations. The Department of Defense sponsors 200 GME programs with 3200 trainees, but the exact costs of these programs are not available.

In addition, an unknown level of support is provided by hospitals, physician groups, philanthropy, and even industry, but the preponderance of financial support for GME comes from the federal government.

Federal GME funding under scrutiny

Federal funding of GME has been under intense scrutiny for more than
The controversial IOM recommendations

The IOM Committee on Governance and Financing of GME was formed at the behest of stakeholders including 11 US senators. The Committee assessed workforce assumptions, funding sources, and the quality of current GME training. They concluded that the current GME system is neither transparent nor accountable, has too many specialists and too few PCPs, and is not producing physicians willing to work in rural and underserved areas.

They argued that GME programs are too focused on inpatient rather than community and ambulatory care and that they lack proper emphasis on coordination and cost of care, health information technologies, and cultural competency.

The IOM recommended that there be no further increases in Medicare GME funding and that IME and DGME funding streams be merged and used to directly fund all residents and fellows at a geographic- and inflation-adjusted national per resident amount. The IOM also recommended dividing this funding into operational and transformational components. The former would cover current training programs and the latter would be used to experiment with new GME models.

Operational funds would be progressively reduced by up to 30% to fund transformational projects. The IOM also called for creating a new bureaucracy to oversee GME payments and policies, collect data, and issue reports.

They also opined that GME funds should no longer be distributed to hospitals based on Medicare inpatient volume but to the actual sponsors (eg, medical schools, federally qualified health centers, and academic medical centers) responsible for maintaining accreditation, thus addressing the disconnect between those receiving Medicare funds and those responsible for the academic integrity of GME programs.

After a 10-year transition all Medicare GME payments would reward performance and reflect national, regional, and local workforce needs.

The stakes could not be higher

In response to an impending shortage of an estimated 130,000 physicians by 2025, the number of US medical students has risen 28% over the past decade from 80,180 to 104,498. During that time there has been a 12.8% increase in the number of new US allopathic medical schools, from 125 to 141, and a 17.5% increase in the number of allopathic medical students. The number of new osteopathic schools has increased 70% from 20 to 34, with a 90.2% increase in the number of osteopathic medical students. And even more new medical schools are planned.

Over the same interval, despite the Medicare cap, the number of Accreditation Council for Graduate Medical Education (ACGME)-approved GME slots has increased 17.5%, from 100,176 to 117,717, though the number of new first-year positions has increased only 13.6%. There are another 7498 trainees in osteopathic residencies. Thus, the concern is that at some point in the not-too-distant future the rising number of US medical students will exceed the number of available US hospitals.

2 decades. The primary question is why Medicare serves as the chief underwriter of resident and fellowship training when Medicare patients account for a minority of most physicians' practices. And, why does the bulk of such funding go toward specialist and subspecialist training, when there is a clear national shortage of primary care providers (PCPs)? Why do hospitals receive virtually all Medicare funding when future physicians will predominantly work in ambulatory settings?

It is also legitimate to wonder why most funding goes to urban hospitals, given the surplus of physicians in affluent urban areas and their death in rural locales.

Partly in response to these concerns, but mostly to save money, the federal government “capped” residency slots as part of the 1997 Balanced Budget Act, paying hospitals for the number of residents and fellows they had on December 31, 1996. This “cap” has had the perverse effect of perpetuating geographical and specialty imbalances, though so-called virgin institutions may request new Medicare GME funding with these slots capped after 5 years.

Also in response to critics’ complaints that IME formulas overestimated trainee-related hospital costs, the government has reduced IME funding several times during the past 30 years. More recently, both the White House and House Republicans proposed substantial reductions in GME funding, which were blocked only after a massive lobbying effort led by the Association of American Medical Colleges (AAMC) and other professional societies and hospital trade groups.
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Moreover, many experts worry that implementation of the IOM recommendations could exacerbate the problem by reducing the number of GME slots just as this wave of needed new physicians is graduating.2

For their part, the IOM Committee disputes claims of an impending physician shortage, arguing that they do not take into account likely future improvements in productivity from increased use of physician assistants and advanced practice nurses as well as improved efficiencies resulting from new health information technologies and telemedicine. They argue that these productivity improvements—coupled with reduced physician demand resulting from new medical payment systems such as capitation and patient-centered medical homes—will mitigate future shortages.

The Committee also notes that hospitals increased GME slots, as noted above, despite the Medicare cap.

The essential problem with the IOM position is that if their estimates of increased productivity and decreased physician demand are wrong, and/or if hospitals can’t continue to increase self-funded GME slots in the face of anticipated historic revenue shortfalls, there will be not only many disappointed US medical student graduates unable to find residency slots, but also many patients with reduced or no access to physicians.

On the other hand, if the IOM Committee’s critics are wrong, and GME slots are needlessly increased, there will be a surplus of physicians, reducing market demand and potentially reducing costs.

Which bet would you make?

**Take-home message**

The IOM report makes many compelling arguments and has stimulated a much-needed debate. The IOM Committee makes some excellent suggestions including eliminating distinct IME and DGME payment streams in favor of a simple, transparent per-resident amount. It also favors funding GME sponsors responsible for maintaining accreditation rather than hospitals that directly benefit from trainee work and receive hard-to-justify IME payments.

But at the heart of the debate is the question of how we reconcile national workforce needs with the freedom of students to choose their own career paths.

The IOM argues that Medicare should continue to fund GME because we should not squander this “leverage” for GME reform. I find that argument unconvincing. Indeed, economists contend that there is no economic rationale for taxpayer support of GME because it fails to meet the definition of a public good.3 This argument rings hollow as well since access to effective health care is an obvious public good. Moreover, since all patients and payers ultimately benefit from having a well-trained, competent, and diverse physician workforce, all payers should cover GME costs.

Thus, whether the GME program is based in a rural community health center or quaternary care urban teaching hospital, all payments received from all insurers (private and public) for all patient services rendered at these sites should include a specified component to cover GME costs.

These funds should then go to the academic GME sponsor who pays the trainees’ salaries and covers legitimate administrative and teaching costs.

As to the number of GME slots available and their allocation by specialty, these decisions should be left to the free market—rather than some government agency’s central planning efforts—as far as is practicable. As we move to consumer-directed healthcare plans, traditional labor market supply-and-demand forces will do a far better job of meeting future physician workforce needs.

And where the free market falters, the government can provide incentives through loan forgiveness programs, scholarships, and generous bonuses to encourage graduating medical students to enter primary care fields and serve in rural and under-resourced urban settings.

As for ob/gyns, for many reasons there will be high and sustained market demand for resident graduates for years to come and as long as the government doesn’t interfere, the market will ensure an adequate number of training programs and graduating residents.

**References**

‘GOHO’ course teams residents with ultrasound leaders

The GOHO course returned to the Icahn School of Medicine at Mount Sinai in New York City for its second year last month, bringing learning from ultrasound's leaders to enthusiastic ob/gyn residents. It’s the second year for the free program, hosted by The Gottesfeld-Hohler (GOHO) Memorial Foundation, a nonprofit organization dedicated to improving education and research in ultrasound for ob/gyns.

Speakers at the program, which attracted 63 second-year residents, included Contemporary OB/GYN Editorial Board member Joshua A. Copel, MD, John Hobbins, MD, Larry Platt, MD, Lynn Simpson, MD, Joanne Stone, MD, Ilan Timor, MD, and Mark Sauer, MD. Spanning a full weekend, the 2-day course afforded the students the opportunity for 3 hours of hands-on scanning per day—twice the amount as last year. Attendees rotated through six rooms equipped with ultrasound machines on which they performed biometric scans on live models and two with simulators on which to practice transvaginal ultrasound and view cases involving gynecologic pathology.

The GOHO program was supported by the American College of Obstetricians and Gynecologists (ACOG) Council on Resident Education in Obstetrics and Gynecology (CREOG), and utilized educational materials developed along with the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG), and the American Institute of Ultrasound in Medicine (AIUM).

“I am thrilled that Mount Sinai was selected to host the GOHO resident ultrasound course for the second year in a row,” said Dr. Stone, who is Director of Maternal-Fetal Medicine at Mount Sinai Hospital. “The turnout was incredible. The residents really seemed to learn so much from both the hands-on sessions and the ultrasound lectures. Every
Women's Health Update

Most women who undergo mastectomy following breast cancer do not then undergo breast reconstruction. In light of this, a team of researchers recently conducted a survey to determine if women are satisfied with their choices concerning reconstruction. Specifically, they set out to “examine correlates of breast reconstruction after mastectomy and to determine if a significant unmet need for reconstruction exists.”

The research team included specialists in radiation oncology, plastic surgery, breast surgery, public health, preventative medicine, and general medicine.

The team sent a survey to a sample of 3252 women aged 20 to 79 years diagnosed as having ductal carcinoma in situ or stages I to III invasive breast cancer. Black and Latina women were oversampled to ensure adequate representation of minorities. Of the women who received the initial survey a median of 9 months after diagnosis, 2290 completed it. Those who remained disease-free were surveyed 4 years later; 1536 completed the follow-up survey. Four hundred and eighty-five women who remained disease free at follow-up underwent analysis.

Of the 485 patients who reported on the initial survey that they had undergone mastectomy and remained disease free, 24.8% underwent immediate reconstruction and 16.8% underwent delayed reconstruction, for a total of 41.6%. Factors significantly associated with not undergoing reconstruction were black race, lower educational level, increased age, major comorbidity, and having undergone chemotherapy. Only 13.3% of women were dissatisfied with the reconstruction decision-making process, but this dissatisfaction was higher among nonwhite patients (adjusted odds ratio, 2.87 [95% CI, 1.27-6.51]; P = .03).

The most common reasons for not having breast reconstruction that women reported were the desire to avoid additional surgery (48.5%), fear of implants (33.8%), and the belief that reconstruction was not important (36.3%). Reasons for avoiding reconstruction varied by race, and reported barriers to reconstruction were more common among nonwhite respondents. Residual demand for reconstruction at 4 years was low, with only 30 of 263 patients who did not undergo reconstruction still considering the procedure.

The researchers concluded that reconstruction rates largely reflect patient demand and that most patients are satisfied with the decision-making process about reconstruction. They recommended developing specific approaches to address lingering patient-level and system factors with a negative effect on reconstruction among minority women.

The study was published online by JAMA Surgery on August 20.
ICD-10 TRAINING

Complications of pregnancy

As physicians and coders transition to the International Classification of Diseases—10th Revision—Clinical Management (ICD-10-CM), several coding and documentation issues related to complications of pregnancy need to be addressed.

Codes for reporting complications of pregnancy, childbirth, and the puerperium are in chapter 15 of ICD-10-CM and begin with the letter O. Including the trimester in which the condition occurs, and seventh digits to identify the fetus affected (when necessary) are the main structural changes. The episode-of-care designations used in ICD-9-CM are no longer an axis of classification in ICD-10-CM.

For complications of pregnancy, the trimester during which the complication occurs is part of the code selection in ICD-10-CM. The number of weeks of gestation determines the code selection. ICD-10-CM has no fifth-digit classification for episode of care. The trimester is included as part of the complete code description.

Chapter-level instructions note that an additional code from category Z3A, "Weeks of gestation," should be assigned to identify the specific week of the pregnancy, and is used only on the maternal record.

For some complication of pregnancy codes, seventh character extensions are required to complete a valid, reportable code. These seventh character extensions identify the fetus affected.

The seventh character ‘0’ is for single gestations and multiple gestations in which the fetus affected is unspecified. The seventh characters 1 to 9 are for cases of multiple gestations to identify the fetus to which the code applies. Further coding instructions may also require that a code from category O30, “Multiple gestation,” be assigned when reporting a code with a seventh character.

The 2 classification systems for reporting diabetes mellitus (DM) in pregnancy have been greatly expanded in ICD-10-CM.

For complications of pregnancy, the trimester during which the complication occurs is part of the code selection in ICD-10-CM.

In ICD-9-CM DM complicating pregnancy, childbirth, or the puerperium is reported with 648.0x, and gestational diabetes is reported with 648.8x, “Abnormal glucose tolerance.” Each requires a fifth digit of 0-4 for the episode of care. ‘DM in pregnancy, childbirth, and the puerperium,’ category O24, has 6 subcategories, each with further subclassified codes for valid reporting. The subcategories are “Pre-existing DM, type 1;” “Pre-existing DM, type 2;” “Unspecified pre-existing DM;” “Gestational DM;” “Other pre-existing DM;” and “Unspecified DM.”

Each subcategories provides codes specifying the trimester of pregnancy, in childbirth, and in the puerperium. Both systems require the use of additional codes to further specify the manifestations.

“Unspecified pre-existing DM” (O24.3-) is reported when the patient had diabetes before pregnancy. However, the type is not specified. Any additional diabetes codes reported from the endocrine chapter used to further identify the particular manifestations must be selected from category E11 for type 2 as the default. “Unspecified DM” (O24.9-) is reported when it is not known whether the diabetes arose during pregnancy or before.

“Other pre-existing DM” (O24.8-) is used when the patient had DM due to another underlying condition, such as Cushing’s syndrome; drug- or chemical-induced DM; DM due to genetic disorders/defects; or other secondary (post-procedural) DM prior to pregnancy.

Additional codes reported with O24.8- for the particular diabetic manifestations must be selected from the category in the endocrine chapter that reflects the appropriate type of other (pre-existing) diabetes. These will be from category E08, E09 or E13. In both classification systems, a code for long-term (current) use of insulin is also provided.

Gestational diabetes codes in ICD-10-CM have a slightly different structure than that of the pre-existing or unspecified DM in pregnancy codes. Gestational diabetes is subdivided into codes that specify whether it is diet-controlled, insulin-controlled, or unspecified control in pregnancy.
A NOVEL TREATMENT WITH AN ALTERNATIVE TO A PROGESTIN
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Help her put moderate to severe hot flashes as well as bone loss in their place

The first and only treatment of its kind
DUAVEE combines conjugated estrogens (CEs) with the SERM* bazedoxifene (BZA):
• CEs provide significant relief of moderate to severe hot flashes due to menopause and prevent postmenopausal osteoporosis
• BZA helps protect the uterine lining from endometrial hyperplasia associated with estrogen-alone treatment

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

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

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

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

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

Estrogen agonists/antagonists, including bazedoxifene, and estrogens individually are known to increase the risk of venous thromboembolism (VTE).
DUAVEE is indicated in women with a uterus for the treatment of moderate to severe vasomotor symptoms associated with menopause and the prevention of postmenopausal osteoporosis.

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

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

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

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

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

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

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

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

Clinical surveillance of all women taking DUAVEE is important. Adequate diagnostic measures, including endometrial sampling, should be performed to detect this condition, which should also be treated. The American College ofObstetricians and Gynecologists recommends annual endometrial sampling in postmenopausal women with unexplained postmenopausal bleeding.

Breast Cancer

DUAVEE is contraindicated in women with a history of breast cancer. Women with newly diagnosed or undiagnosed suspicious breast masses should have a breast biopsy before starting DUAVEE. It is unknown whether the use of DUAVEE in women with breast cancer is safe. Therefore, DUAVEE should be discontinued in women who develop breast masses during DUAVEE therapy.

DUAVEE is a pregnancy Category X drug; therefore, women of childbearing potential should be apprised of the potential hazard to a fetus.

On average, women with hepatic impairment treated with bazedoxifene alone showed a 4.3-fold increase in overall exposures compared with controls [see Use in Specific Populations]. Hence, DUAVEE should be used with caution in patients with hepatic impairment, and only if the benefit exceeds the risk.

Hypocalcemia

Estrogen therapy should be used with caution in women with hypoparathyroidism as estrogens may increase risk of hypocalcemia.

Exacerbation of Other Conditions

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

Prenepausal Women

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

Drug-Laboratory Test Interactions

DUAVEE and its components may affect the results of certain laboratory tests. Women using DUAVEE should be informed of the following interactions:

1. **Drug-Laboratory Test Interactions**
   - **Increased plasma high-density lipoprotein (HDL) and HDL2 cholesterol subfraction concentrations, respectively.**
   - **Free hormone concentrations, such as testosterone and estradiol, may be decreased.**
   - **Other hormone-binding globulin (SHBG), leading to increased total circulating corticosteroids and sex steroids,**
   - **By radioimmunoassay. T3 resin uptake is decreased, reflecting the elevated TBG. Free T4 and free T3 concentrations may be increased.**

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

Increased plasma HDL cholesterol concentrations have been reported in postmenopausal women treated with estrogens. The mechanism of action is not fully understood, but may involve increased hepatic LDL receptor activity. The effect on cardiovascular risk is unknown. Increased plasma HDL cholesterol concentrations have been reported in postmenopausal women treated with estrogens. The mechanism of action is not fully understood, but may involve increased hepatic LDL receptor activity. The effect on cardiovascular risk is unknown.
ADVERSE REACTIONS
The following adverse reactions are discussed in greater detail in other sections of the label:

• Cardiovascular Disorders [see Warnings and Precautions]
• Malignant Neoplasms [see Warnings and Precautions]
• Gastrointestinal Disorders [see Warnings and Precautions]

Mild or moderate GI symptoms are among the most common adverse reactions observed in clinical trials of DUAVEE and are not considered to be related to therapy. The frequency of adverse reactions is based on spontaneous reports provided by patients and investigators during the clinical trials of DUAVEE. The frequency of adverse reactions was summarized by body system and adverse reaction term. Table 1 lists adverse reactions that met predefined criteria for frequency. See Tables 1 and 2 for the list of adverse reactions and frequencies.

DUAVEE is not recommended for use in women greater than 75 years of age. Of the total number of women in phase 3 clinical studies who received DUAVEE, 4.6% (n=224) were 65 years and over. No overall differences in safety or effectiveness were observed between 65-74 years of age and younger women, and other reported clinical experience has not identified differences in responses between the elderly and younger women, but greater sensitivity of some older women cannot be ruled out. An increased risk of probable dementia in women over 65 years of age was reported in the WHIMS ancillary studies of the WHI using daily CE (0.625 mg).

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

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

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

The pharmacokinetics, safety, and efficacy of DUAVEE have not been evaluated in women with hepatic impairment. In a pharmacokinetics study of bazedoxifene 20 mg alone, the Cmax and AUC of bazedoxifene increased 67% and 143%, respectively, in women with mild hepatic impairment (Child Pugh Class A), compared to healthy women. The Cmax and AUC of bazedoxifene increased 32% and 199%, respectively, in women with moderate hepatic impairment (Child Pugh Class B). The Cmax and AUC of bazedoxifene increased 20% and 266%, respectively, in women with severe hepatic impairment (Child Pugh Class C).

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

Use in Women with Body Mass Index (BMI) > 27 kg/m²
A 17% reduction in bazedoxifene exposure was predicted in women with BMI ≥ 27 kg/m² (N=144) compared to those with BMI < 27 kg/m² (N=38) after administration of DUAVEE, based on a population pharmacokinetic model using data from four Phase 1 studies. A reduction in bazedoxifene exposure may be associated with an increased risk of endometrial hyperplasia. Regardless of BMI, adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding.

PATIENT COUNSELING INFORMATION
See FDA-approved patient labeling. (Patient Information).

Venous Thromboembolic Events
Advise patients to immediately report to their physician any signs or symptoms related to venous thromboembolism and thromboembolic events [see Warnings and Precautions].

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

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

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

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

This brief summary is based on the DUAVEE full prescribing information LAB-9582-1.0, October 2013.
EDITORIAL

WHITHER THE BIMANUAL EXAMINATION?

Whither the bimanual examination? The absence of evidence for benefit is not the same as evidence of absence of benefit.

Recently, Qaseem and colleagues published an American College of Physicians (ACP) Clinical Guideline advising against pelvic examinations for the detection of pathological conditions in asymptomatic, nonpregnant, adult women.1

This advisory has generated much commentary in the blogosphere and particularly among ob/gyns. Many women, upon hearing news reports concerning the ACP guidelines, will assume these recommendations are valid and that they no longer need annual pelvic exams. Moreover, some women may assume that since they no longer need such an exam, they also will not need to see their gynecologist annually.

To assess the accuracy, benefits, and harms of screening pelvic examinations, the authors conducted a MEDLINE search of relevant articles addressing these questions published from 1946 to 2014. Based on their conclusions, the study had none of those elements.

First the authors focused only on ovarian cancer and detection of bacterial vaginosis because those were the only conditions about which there were sufficient published data to draw tangential conclusions. (What is the old line about the inebriated fellow looking for his keys under the lamp post because that is where the light is shining?) As such, the authors failed to address the myriad of other reasons ob/gyns carry out bimanual exams, such as for detection of myomas, evidence of pelvic relaxation and stress incontinence, signs of endometriosis, chronic pelvic inflammatory disease, cervical polyps, vaginal cysts, etc.

Thus, this ACP guideline will add yet another barrier to our ability to provide appropriate preventative care to our patients.

LETTERS TO THE EDITOR

THANK YOU, THANK YOU, THANK YOU. At last someone has the courage and the intelligence to speak out against the idea that most of what we ob/gyns have always done for our patients is now irrelevant or even harmful ['Whither the bimanual examination?' August 2014 Contemporary OB/GYN].

You don’t need me to tell you about all the asymptomatic breast masses and pelvic masses I have discovered in 35 years of practice. I thought that it could go no farther, after debasing the value of the annual Pap, but at least that had a bit of validity with HPV co-testing. Hopefully, our patients will raise their voices when we are told not to order annual mammograms or recommend DEXAs or colonoscopies. It had better be the patients who raise those voices, since the majority of my colleagues just go along like sheep in accepting so-called guidelines.

This is also not to mention the lack of support we get from our so-called representative organizations.

Joseph S. Ferroni, MD
Via email

I AGREE WITH YOUR POINTS

and in addition I would like to add the 3 cases of vaginal melanoma that I’ve found over the years on “routine” pelvic exams. I also think that the unique intimate nature of the exam and the trusted doctor-patient relationship that develops because of those yearly visits with “the laying on of hands” leads to discussions that would otherwise go unspoken about all sorts of topics like physical abuse, sexual function and dysfunction, and rectal issues that have translated into appropriate referrals and treatment.

Dr. Dave
Posted on ContemporaryOBGYN.net

DR. LOCKWOOD’S DISCUSSION IS REASONABLE, if not scientifically grounded, based on the current literature until adding “free” ultrasound to the annual visit. One of the foci of the ACP position is the amount of benign “disease” we find that is not clinically relevant to the patient’s long-term well being but elicits worry, increased medical workup, and often unwarranted surgical exploration. The increased risk to the asymptomatic patient cannot be ignored. And the specious argument that this service can/will be provided “free” flies in the face of marketplace realities. In the asymptomatic patient, the greatest benefit we could offer would be early detection of ovarian cancer, one that is clearly not supported in the literature.

And the role of ultrasound in screening for cancer is similarly rejected in current studies. This may be heresy to those of us in clinical practice, but perhaps we are not employing the “Primum non nocere” principle in our current management. Random, evidence-based studies are needed to clarify how we should proceed in the future.

Dr. John P. Gallagher
Posted on ContemporaryOBGYN.net

TOTALLY AGREE WITH ALL YOUR POINTS except that finding certain pathology in asymptomatic patients is unlikely, such as endometriosis. And for internists to not do annual exams may be appropriate since I have yet to meet any who are comfortable or experienced in doing pelvic exams. As to sonography, I use TVS in all symptomatic patients as well as abnormal or questionable findings, especially

Dr. Dr. Dave
Posted on ContemporaryOBGYN.net
in obese patients. I recall a study showing we are at best 50/50 in our bimanual exams, so a large study with “routine” TVS would be quite revealing, although I wonder about the consequences of incidental findings.

Dr. J. E. Mendez
Posted on ContemporaryOBGYN.net

AS DR. MENDEZ SAYS, I, TOO, AGREE with all of your points. Thank you for clarifying an issue that these internists have certainly done a great job of obfuscating. Maybe we should do a MEDLINE analysis to demonstrate that stethoscopes are useless instruments, too!

Did someone actually pay these people to do this “research”? The emperor has no clothes on here.

Dr. Stephen Waszak
Posted on ContemporaryOBGYN.net

THANK YOU, ACP AND ANNALS for doing what others have tried to do for decades or centuries and that is to move back in time. Eliminating the gynecologic examination is a step back into the Victorian age or worse, and picking the failure to find early ovarian carcinoma as a reason to avoid pelvic examinations will clearly lead to loss of function and lives when parallel screening for cervical cancer and STDs is discontinued.

By curtailing female pelvic examinations there will be some short-term financial and time saving for which society will pay dearly when missed diseases bloom and grow.

Should we stop examining the heart and lungs because there are no symptoms? Eliminating the pelvic examination will [lead to] eliminating medical care and physicians, since much of what doctors do is not clearly in response to an identified illness.

Thank you, ACP and Annals, for alerting us to a new direction. What is your next target? Reading and writing? Potable water? Garbage disposal?

Dr. Robert Wallach
Via email

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Do you want more information about the use of medications and vaccines during pregnancy?

MotherToBaby studies conducted by the Organization of Teratology Information Specialists (OTIS) may help provide more answers. The purpose of our research studies is to prospectively evaluate the risks to the fetus from various conditions and the medications used to treat them during pregnancy, including:

- Asthma
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- Vaccines and antiviral medications

For more information about medication and/or vaccine use in pregnancy, or to refer a patient to one of our studies, call toll-free (877) 311-8972 or visit PregnancyStudies.org

MotherToBaby
Medications & More During Pregnancy & Breastfeeding
Ask The Experts
Conducted By The Organization of Teratology Information Specialists (OTIS)
Vaginal itching, discharge, and odor are among the most common complaints in gynecologic and primary care offices. Tailoring treatment to the correct disease process is paramount when managing patients with recurrent vulvovaginal symptoms.

**Recurrent vulvovaginitis**
Tips for treating a common condition
Contemporaryobgyn.net/recurrent-vulvovaginitis

**A few recent tweets and retweets from and about ContempOBGYN**

- CMQCC @cmqcc @ContempOBGYN Infographic: #pregnancy complications increase lifetime risk for #heartdisease #pregnancyheart http://ow.ly/zFFHR
- Doctor Gale @DoctorGale RT @yafshar "Disparities & inequalities in #healthcare a great #infographic @ContempOBGYN pic.twitter.com/US9excAQH*
- Mark Reid, MD @medicalexioms @yafshar @ContempOBGYN Well done! Inspiring is what we do best. :)

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**Center for Fetal Med**
@CfmmFetalMed RT @ContempOBGYN: Fabulous faculty working hard #goaho @MountSinaNYC http://ow.ly/3opQTH.

**Rosemary Theroux, NP**
@rosenp2 Recurrent vulvovaginitis: Tips for treating a common condition http://shar.es/1nsqtb via @ContempOBGYN

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**A conservative oxytocin labor protocol: Is less best?**

In a study performed at Duke University Hospital in Durham, North Carolina, a more conservative oxytocin protocol led to lower oxytocin maximal dosing and lower NICU admission rates...

Now in our August issue, a 60-second synopsis of a new study about labor induction with commentary from Editorial Board member Dr. Haywood Brown.

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

Contemporary OB/GYN August 16 @ContempOBGYN @jacopel starts the 2nd annual GOHO Ultrasound Course for OB/GYN Residents with humor. Like our Facebook page and follow us on Twitter (@contempobgyn) as we provide updates on the class all weekend. (Photo courtesy of Kim Abruz.)

Twitter / KimAbruz: .@ContempOBGYN @jacopel starts ...

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**A conservative oxytocin labor protocol: Is less best?**

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**Recurrent vulvovaginitis**
Tips for treating a common condition
Contemporaryobgyn.net/recurrent-vulvovaginitis

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Koh-Effi cient Helps to Create a “Margin of Safety” by Displacing the Ureters during Colpotomy Incision

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Arnold P. Advincula, MD, FACOG, FACS
Professor & Vice-Chair of Women’s Health
Chief of Gynecology, Sloane Hospital for Women
Columbia University Medical Center
New York-Presbyterian Hospital
Did this ob/gyn fail to timely diagnose uterine sarcoma?

**Facts**

On June 4, 2008, a 40-year-old White Go presented to the defendant ob/gyn with complaints of hair loss, weight gain, and premenstrual dysphoric disorder (PMDD). She reported that her Pap smears were always normal (her most recent one had been in March 2008), but that she had tested positive for human papillomavirus (HPV) in April 2007. More recently, she had amenorrhea for 3 months at the beginning of the year and her follicle stimulating hormone (FSH) levels were consistent with menopause.

During this visit, an ultrasound (U/S) revealed a uterine fibroid measuring 6 x 8 cm, which the ob/gyn felt was possibly related to her Hashimoto’s disease. Because the patient had no symptoms related to the fibroid, the ob/gyn did not initiate estrogen therapy. The patient was directed to return to the office in 6 months. However, she called the office on June 24 and reported that she was having more hair loss and was interested in a hysterectomy and hormone therapy.

The patient called the ob/gyn again on July 2 and reported that her last menstrual period was on May 31. She also reported moodiness and worsening depression. The doctor prescribed estradiol and Prometrium. The patient was seen in the ob/gyn’s office on December 17 and reported that her hair loss was still a problem.

The doctor performed another U/S, which showed that the fibroid was stable and measured 6.2 x 7.6 cm. The patient was next seen by the ob/gyn on March 22, 2010. The doctor documented that she had a long conversation with the patient about feeling unhappy on low-dose estrogen therapy. An U/S performed by the doctor revealed that the fibroid measured 9.0 x 7.0 cm. The patient’s preference for not getting another U/S at an outside facility was also documented. A Pap smear showed no intraepithelial lesion or malignancy. The ob/gyn increased the estrogen dose.

When the patient returned to the doctor on August 16, she reported firmness on her left side and frequent urination. U/S showed the fibroid was “significantly larger,” measuring 10.6 x 9.6 cm. The doctor encouraged her to have a laparoscopically assisted vaginal hysterectomy (LAVH) and removal of the cervix. She also advised her to have a bilateral salpingo-oophorectomy (BSO). The patient was to come back in 3 to 6 weeks to discuss surgical options.

The patient did not return to the doctor’s office until February 9, 2011. An U/S performed at that visit showed fluid in the uterus and that the fibroid was the same size as in August 2010. The doctor ordered another pelvic U/S, which showed a large central myoma of 8.2 x 6.7 x 6.8 cm and a fluid collection of 3.2 x 4.9 x 1.3 cm (~10 mL). The doctor noted that the patient needed to undergo a dilation, endometrial biopsy, and fluid drainage.

The patient was now thinking of undergoing the LAVH and was directed to return to the ob/gyn’s office in ≤ 6 months. But about 3 weeks later, she presented to the hospital emergency department with complaints of right flank pain and lower back pain. A computed tomography (CT) scan of the abdomen and pelvis performed on April 1 showed “few” very large uterine masses, the largest in the left anterior uterine body measuring 15.4 x 9.7 x 10.5 cm. Another mass on the right posterior uterine body was 8.9 x 8.3 x 6.4 cm. The impression was that these masses could represent hyaline degenerating-type fibroids. It was suggested that magnetic resonance imaging (MRI) be obtained. An endovaginal U/S performed the same day showed a large posterior body fibroid of 9.8 x 10.2 x 10.3 cm.

On April 20, the patient underwent an MRI out of state. It was highly...
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References:
2. References available at www.gen-probe.com
3. Aptima® HPV Assay package insert 503789 Rev A 2013, Table 13
4. ADS-00869 ©2013 Hologic, Inc. All rights reserved. Hologic, Aptima, MyoSure, NovaSure, Selenia and ThinPrep and associated logos are trademarks or registered trademarks of Hologic, Inc. and/or its subsidiaries in the United States and/or other countries. For specific information on what products are available for sale in a particular country, please contact your local Hologic representative or email info@hologic.com.
suggestion of malignant degeneration of a fibroid in the right uterine body/lower uterine segment. There was no direct regional invasion of pelvic ascites such as would be expected with a leiomyosarcoma. How-

ever, metastatic lymphadenopathy was visualized in the pelvis, along with cystic/hemorrhagic degeneration of a fundal intramural fibroid and blood products of varying ages in the non-
dilated endometrium with probable internal debris.

The patient was referred to a gyn-
ecologic oncologist to discuss surgical options. The last note in the ob/ gyn's office chart is a summary of a phone conversation with the patient. The doctor documented that the patient was seen out of state and that an MRI showed a second fibroid that was suspicious for sarcoma. The plan was for the patient to see an oncologist and possibly undergo a total ab-
dominal hysterectomy (TAH).

On May 2, the patient underwent an exploratory laparotomy, TAH with BSO and right pelvic node dissection, and right peri-aortic lymph node dis-
section at an outside hospital. The pathology report noted: “High-grade sarcoma; tumor measur-
ing 15.5 x 9.2 x 7.8 cm with marked lymphovascular space invasion and lymph node metastasis.

The patient underwent a positron emission tomography scan on May 11, which revealed expected postop-
erative physiologic changes and no additional disease. She began chem-
otherapy and underwent radiation therapy until September 19. Chemo-
therapy was restarted on November 3 and ended December 20, 2011.

Allegations

The plaintiff alleged that the ob/gyn negligently interpreted the various U/S that were performed while the patient was under her care and failed to advise the plaintiff of surgical options.

The alleged injuries were: Stage III C2 uterine sarcoma; tumor measur-
ing 15.5 x 9.2 x 7.8 cm with marked lymphovascular space invasion and tumor necrosis; positive lymph nodes; lobectomy revealing metastatic high-

grade sarcoma with necrosis and lymphovascular invasion in the right lung; TAH; BSO; peri-aortic and retroperi-
toneal lymph node dissection; che-
motherapy; radiation; alopecia; anxi-
ety; headaches; weakness; dizziness;
weight loss; fatigue; bloating; nausea/
vomiting; pelvic discomfort; loss of enjoyment of life; and lost earnings.

Trial

At trial, the defendant ob/gyn testified that she had never considered that the plaintiff had a uterine sarcoma at any time that she was treating her up to and including the office visit of August 16, 2010. She confirmed that she never visualized (on U/S) 2 masses in the plaintiff’s uterus or suspected she had 2 masses in the uterus during that period.

The plaintiff’s counsel established that the fibroid size was stable when the plaintiff began hormone therapy. He then established that the fibroid was noted to grow significantly from March 2010 to August 2010, although the patient had been on a relatively lower dose of hormone therapy. (His strat-

egy was to establish that the growth of the fibroid could not be attributed to the hormone therapy and therefore should have been suspicious.) He also argued that the growth was “significant” enough to warrant fur-
ther testing, including CT or MRI.

The ob/gyn testified that the plain-
tiff was perimenopausal, so she was still making estrogen. Therefore, the fibroid growth was not suspicious. She testified that the plaintiff’s clinical picture was consistent with a growing fibroid and not suspicious for cancer.

The plaintiff’s obstetrical expert testified that the fibroid growth was significant. He testified to a “rule” that when a mass such as this grows by 1 cm in any one direction, or more than .4 cm in 2 directions, the growth should be considered suspicious and testing is warranted. He testified that the growth was significant here in light of the fact that the patient was postmenopausal and not making any estrogen. In his opinion, the hormone
The patient testified that when she saw the defendant on March 22, 2010, she complained that her abdomen was swollen. The plaintiff’s experts relied upon this testimony in an attempt to document that the patient’s clinical picture was consistent with a fibroid from a uterine sarcoma. He testified it was not incumbent upon the ob/gyn to investigate the fibroid growth in March and August 2010, as it was not unusual or suspicious for cancer.

Our final witness, a gynecologic oncology expert, also refuted the “4-mm rule” and said that there was nothing suspicious about the fibroid growth as documented in March and August 2010. He testified that the patient’s clinical picture fit perfectly with a growing fibroid and was not suspicious for cancer.

He also testified that because the patient was perimenopausal and on hormone replacement therapy, it was reasonable to conclude that the fibroid growth was related to the hormone therapy.

The “doubling time” theory, he said, was flawed and not based upon accepted science. He pointed out that the plaintiff’s statistics concerning survival rate for Stage I uterine sarcoma patients were incorrect because they included patients with low-grade sarcomas, which have a much higher cure rate than high-grade sarcomas.

The verdict
The verdict sheet asked whether it was a departure for the ob/gyn not to have suspected cancer and/or order further testing on March 22 and August 16, 2010. The jury unanimously answered “no.” A verdict was rendered in favor of the defendant.

ANDREW I. KAPLAN, ESQ, is a partner at Aaronson, Rappaport, Feinstein & Deutsch, LLP in New York City. This case was successfully tried to verdict by his partner, Neil F. Brenes, Esq.
Ultrasound triage of postmenopausal bleeding

BY JAMES M. SHWAYDER, MD, JD

Endometrial cancer is the most common gynecologic cancer in the United States. In 2014, an estimated 52,630 new cases will be diagnosed, with 8590 women dying from cancer of the uterine body, with uterine sarcomas comprising approximately 2% of uterine cancers. Approximately 3 out of 4 cases are diagnosed in women aged 55 years and older. Ninety percent of postmenopausal patients with endometrial cancer present with vaginal bleeding. Conversely, up to 14% of patients who present with postmenopausal bleeding (PMB)—defined as an episode of bleeding 12 months after the last menstrual period—will have endometrial cancer. These patients require timely and efficient evaluation.

Endometrial evaluation

Historically, the routine evaluation of PMB was by dilatation and curettage (D&C) performed in an operating environment. Evaluation then progressed to the office, first with the Vabra aspirator (1970s), then the Novak curette (1980s), and ultimately (in the 1990s) the suction-piston biopsy instrument, commonly known as a Pipelle endometrial suction curette. The Pipelle reportedly detected almost 98% of endometrial cancers. However, subsequent studies have found that the sensitivity of detecting endometrial cancer with Pipelle endometrial sampling ranges from 83% to 98%. Two studies highlight the limitations of a blind Pipelle endometrial sample. Rodriguez et al. compared the surface area sampled by a Vabra aspirator and a Pipelle endometrial sampler in 25 patients scheduled for hysterectomy. The Vabra aspirator sampled 41.6% of the endometrium, while the Pipelle device sampled only 4.2%. Guido et al. performed Pipelle endometrial sampling prior to hysterectomy in 65 patients with known endometrial cancer. Pipelle sampling missed the cancer in 11 of 65, or 17% of patients. The cancer involved less than 50% of the cavity surface in all patients with a missed diagnosis. In 4 patients, less than 25% of the surface area was involved, while less than 5% was involved in 3 patients. Pipelle sampling missed 5 cancers confined to polyps. Since endometrial cancer can be a focal rather than global disease, blind sampling is prone to error. In addition, sampling failure, defined as an inadequate sample or inability to perform a biopsy, can be as high as 54%. In patients with tissue insufficient for diagnosis (TIFD) the incidence of significant endometrial disease was 20%, with endometrial cancer found in 3% of patients.
TVS and endometrial thickness

Transvaginal sonography (TVS) gained popularity for evaluating PMB in the early 1990s due to its ready office availability and its value in ruling out significant endometrial disease. Initial studies indicated that an endometrial thickness >5 mm would identify 96% of endometrial cancers. Conversely, an endometrial thickness ≤5 mm was associated with a 4% chance of endometrial cancer. The negative predictive value of a thin endometrium was quite good. Initial recommendations required no additional evaluation if the endometrium was ≤5 mm in double-layer thickness.

Subsequent studies evaluated the merit of even thinner thresholds for further evaluation. Gupta et al. determined that the probability of endometrial cancer was reduced the thinner the endometrium on initial evaluation: 5 mm = 2.3%; 4 mm = 1.2%; and 3 mm = 0.4%. Timmermans et al. also found that decreasing the threshold endometrial thickness improved cancer detection, with sensitivities of 90% at 5 mm, 95% at 4 mm, and 98% at 3 mm. They recommended decreasing the cutoff for excluding endometrial cancer to 3 mm. Clearly, decreasing the thickness that prompts further endometrial evaluation increases the sensitivity but decreases the specificity of TVS. Most studies recognize that a threshold endometrial thickness >4 mm adequately screens for >98% of endometrial cancers.

ACOG recommendation

In August 2009, American College of Obstetricians and Gynecologists (ACOG) Committee Opinion Number 440 elucidated the role of ultrasound (U/S) in evaluating postmenopausal bleeding. This opinion recommends either vaginal U/S or an endometrial biopsy in the initial evaluation of patients with PMB. The presence of a thin, distinct endometrial echo ≤4 mm is associated with a risk of malignancy of 1 in 917. Thus, further endometrial evaluation is not required. An endometrial biopsy is technically possible in 82% of patients with endometrial thickness <5 mm, but a sample adequate for diagnosis is obtained in only 27%. U/S is a screening tool used to identify those patients with a low risk of cancer who do not require further evaluation at the initial assessment.

If an endometrial biopsy is performed initially and reveals TIFD, it cannot be relied upon to eliminate significant endometrial disease (Figure 1). Patients with TIFD require further evaluation, which can be done with TVS. If TVS demonstrates the endometrium is <4 mm, the initial evaluation is complete. If the endometrium is >4 mm, further endometrial evaluation is recommended with saline infusion sonohysterography (SIS) or hysteroscopy.

Recurrent bleeding after initial evaluation

Some clinicians are reluctant to rely on U/S without having a tissue diagnosis. A 2003 report by Gull et al. offers guidance. This study evaluated 339 patients with TVS and endometrial sampling 10 years after an initial benign evaluation with TVS and D&C for PMB. None of the patients without bleeding during the 10-year period was found to have endometrial cancer. In contrast, 11.5% of patients with recurrent bleeding were found to have cancer. Thus, cancer is highly unlikely if the endometrial thickness on the initial U/S is <4 mm and the patient has no recurrent bleeding. However, recurrent bleeding requires further evaluation with endometrial sampling, at a minimum, preferably in combination with SIS or hysteroscopy.

continued on PAGE 31
**Lo Loestrin® Fe**

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*FDA draft guidance on labeling states that women taking combined oral contraceptives should take those with the least amount of estrogen and progestin to remain effective and fit the medical needs of the patient.*³

---

**INDICATION AND USAGE for Lo Loestrin® Fe**

Lo Loestrin Fe is an estrogen/progestin combination oral contraceptive (COC) indicated for use by women to prevent pregnancy. The efficacy of Lo Loestrin Fe in women with a body mass index (BMI) of >35 kg/m² has not been evaluated.

**SELECTED SAFETY INFORMATION about Lo Loestrin Fe, including Boxed Warning**

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

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

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

Lo Loestrin Fe should not be prescribed for women with uncontrolled hypertension or hypertension with vascular disease. Women who are pre-diabetic or diabetic, should be monitored while using Lo Loestrin Fe.
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In the clinical trial for Lo Loestrin Fe, serious adverse reactions included deep vein thrombosis, ovarian vein thrombosis, and cholecystitis. The most common adverse reactions (incidence ≥2%) were nausea/vomiting, headache, bleeding irregularities, dysmenorrhea, weight fluctuation, breast tenderness, acne, abdominal pain, anxiety, and depression.

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Please see Brief Summary of Full Prescribing Information for Lo Loestrin Fe, including Boxed Warning, on adjacent pages.

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

**BRIEF SUMMARY:** Consult the Package Insert for Complete Prescribing Information

**WARNINGS:** CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS

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

**1 INDICATIONS AND USAGE**

Lo Loestrin® Fe is indicated for use by women to prevent pregnancy. The efficacy of Lo Loestrin Fe in women with a body mass index (BMI) of > 35 kg/m² has not been evaluated.

**4 CONTRAINDICATIONS**

Do not prescribe Lo Loestrin Fe to women who are known to have the following conditions:
- A high risk of arterial or venous thrombotic diseases. Examples include women who are known to:
  - Smoke, if over age 35 [see Boxed Warning and Warnings and Precautions (5.1)]
  - Have deep vein thrombosis or pulmonary embolism, now or in the past [see Warnings and Precautions (5.1)]
  - Have cerebrovascular disease [see Warnings and Precautions (5.1)]
  - Have coronary artery disease [see Warnings and Precautions (5.1)]
  - Have thrombogenic valvar or thrombogenic rhythm diseases of the heart (for example, subacute bacterial endocarditis with valvular disease, or atrial fibrillation) [see Warnings and Precautions (5.1)]
  - Have inherited or acquired hypercoagulopathies [see Warnings and Precautions (5.1)]
  - Have uncontrolled hypertension [see Warnings and Precautions (5.4)]
  - Have diabetes mellitus with vascular disease [see Warnings and Precautions (5.6)]
  - Have headaches with focal neurological symptoms or have migraine headaches with or without aura if over age 35 [see Warnings and Precautions (5.7)]
  - Breast cancer or other estrogen- or progesterin-sensitive cancer, now or in the past [see Warnings and Precautions (5.2)]
  - Liver tumors, benign or malignant, or liver disease [see Warnings and Precautions (5.3)]
  - Undiagnosed abnormal uterine bleeding [see Warnings and Precautions (5.8)]
  - Pregnancy, because there is no reason to use COCs during pregnancy [see Warnings and Precautions (5.9) and Use in Specific Populations (8.1)]

**5 WARNINGS AND PRECAUTIONS**

**5.1 Thrombotic and Other Vascular Events**

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

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

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

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

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

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

**5.2 Carcinoma of the Breast and Cervix**

Women who currently have or have had breast cancer should not use Lo Loestrin Fe because breast cancer is a hormonally-sensitive tumor. There is substantial evidence that COCs do not increase the incidence of breast cancer. Although some past studies have suggested that COCs might increase the incidence of breast cancer, more recent studies have not confirmed such findings.

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

**5.3 Liver Disease**

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

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

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

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

**5.4 High Blood Pressure**

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

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

**5.5 Gallbladder Disease**

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

**5.6 Carbohydrate and Lipid Metabolic Effects**

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

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

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

**5.7 Headache**

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

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

**5.8 Bleeding Irregularities and Amenorrhea**

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

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

A total of 1,257 women (85.9 percent) experienced unscheduled bleeding and/or spotting at some time during Cycles 2 to 13 of this study. The incidence of unscheduled bleeding and/or spotting was highest during Cycle 2 (53 percent) and lowest at Cycle 13 (36 percent). Among these women, the mean number of days of unscheduled bleeding and/or spotting during a 28-day cycle ranged from 1.8 to 3.2 days.
Scheduled (withdrawal) bleeding and/or spotting remained fairly constant over the one year study, with an average of less than 2 days per cycle. Women who are not pregnant and use Lo Loestrin Fe may experience amenorrhea (absence of scheduled and unscheduled bleeding/spotting). In the clinical trial with Lo Loestrin Fe, the incidence of amenorrhea increased from 32 percent in Cycle 1 to 49 percent by Cycle 13. If scheduled (withdrawal) bleeding does not occur, consider the possibility of pregnancy. If the patient has not adhered to the prescribed dosing schedule (missed one or more active tablets or started taking them on a day later than she should have), consider the possibility of pregnancy at the time of the first missed period and take appropriate diagnostic measures. If the patient has adhered to the prescribed regimen and misses two consecutive periods, rule out pregnancy.

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

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

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

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

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

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

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

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

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

Adverse reactions commonly reported by COC users are:

• Irregular uterine bleeding
• Nausea
• Breast tenderness
• Headache

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

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

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

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

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

• barbiturates
• bosentan
• carbamazepine
• felbamate
• griseofulvin
• oxicarbazepine
• 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 progesterin have been noted in some cases of co-administration of HIV protease inhibitors or of non-nucleoside reverse transcriptase inhibitors.

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

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

7.2 Increase in Plasma Levels of Ethinyl Estradiol Associated with Co-Administered Drugs
Co-administration of atorvastatin and certain COCs containing ethinyl estradiol increase AUC values for ethinyl estradiol by approximately 20 percent. Ascorbic acid and acetaminophen may increase plasma ethinyl estradiol levels, possibly by inhibition of conjugation. CYP3A4 inhibitors such as itraconazole or ketoconazole may increase plasma hormone levels.

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

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

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

Women who do not breastfeed should not start COCs earlier than 4 weeks postpartum.
8.3 Nursing Mothers
When possible, advise the nursing mother to use other forms of contraception until she has weaned her child. Estrogen-containing OCs can reduce milk production in breastfeeding mothers. This is less likely to occur once breastfeeding is well-established; however, it can occur at any time in some women. Small amounts of oral contraceptive steroids and/or metabolites are present in breast milk.

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

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

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

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

8.8 Body Mass Index
The safety and efficacy of Lo Loestrin Fe in women with a body mass index (BMI) > 35 kg/m² has not been evaluated.

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

17 PATIENT COUNSELING INFORMATION
See FDA-approved patient labeling.
Technical aspects of measuring the endometrial echo

U/S can be performed at any time in postmenopausal patients who are on no hormone therapy or on continuous combined therapy. Patients on cyclical hormonal therapy should have the U/S performed shortly after their bleeding episode. The endometrial thickness, also called the endometrial echo complex (EEC), should be measured only in the sagittal or longitudinal midplane view. To be reliable, the EEC should be visualized from the endocervical canal to the fundus (Figure 2). Many clinicians feel compelled to measure any white, linear area and deem it the endometrial echo. This leads to unreliable results. If the endometrium cannot be seen in its entirety, which occurs in more than 10% of cases, the clinician should state that the endometrium is “not well visualized” or “indistinct” and recommend further evaluation, such as SIS or hysteroscopy. When the EEC is adequately visualized, both layers of the endometrium should be measured together to arrive at the endometrial thickness. When identifying fluid within the endometrial cavity, each layer of endometrium should be measured separately and added together for the total endometrial thickness (Figure 3). Early reports about fluid within the endometrial cavity raised concerns for cancer of the ovary, fallopian tube, cervix, or endometrium. More recent reports indicate that most patients (84%) have atrophic endometrium, with the fluid collection likely due to some degree of cervical stenosis.

Doppler at the time of TVS

Color flow and power Doppler imaging enhances the ability to diagnose endometrial polyps. The presence of a central vessel in the EEC is highly predictive of an endometrial polyp (Figure 4). Amit et al. studied 60 women with PMB and found that power Doppler had a sensitivity of 86% and a specificity of 89% in detecting endometrial polyps. SIS can confirm this finding and help plan for surgical removal.

Advantages of U/S-based triage

Cost

Two studies, one in the Netherlands and one in the United States, determined that U/S-based evaluation was less costly than initial evaluation with an endometrial biopsy. Dijkhuizen et al. concluded that a strategy starting with endometrial biopsy was most cost-effective when the prevalence of endometrial cancer was >15.3%. Dijkhuizen et al. concluded that a strategy starting with endometrial biopsy was most cost-effective when the prevalence of endometrial cancer was >15.3%. TVS combined with biopsy was the most cost-effective strategy in cases in which the endometrial thickness was >9 mm. Weber et al. also concluded that vaginal U/S was more cost-effective than endometrial biopsy as the initial diagnostic test. This was based on a $72 cost for TVS and a cost for endometrial biopsy, including processing and interpretation, of $200. Using TVS resulted in a cost savings of $14 to $20 per patient. This analysis was based...
on cost, not charges. Charges could well affect this analysis and change the authors’ overall conclusion.

Adnexal evaluation

Vaginal U/S has the added advantage over hysteroscopy of allowing evaluation of adjacent organs including the ovaries and bladder. Gupta et al. compared Pipelle and TVS performed prior to hysteroscopy and curettage in evaluating 76 patients with PMB.25 They found that TVS was more sensitive and specific than Pipelle sampling in diagnosing endometrial abnormalities (83% and 77% vs 70% and 70%, respectively). In addition, 5 ovarian masses were detected on TVS: 3 that were missed on pelvic exam and 2 that were malignant. Thus, 2.6% (2 of 76) of patients presenting with PMB were found to have ovarian cancer. These cases illustrate the additional advantages of TVS over hysteroscopy and endometrial biopsy. The ability to assess adjacent organs separates TVS from the other technologies.

Type I versus II endometrial cancer

Conventional understanding holds that a thin EEC does not exclude type II endometrial cancers.26 Type II cancers include endometrioid adenocarcinomas, serous adenocarcinomas, clear cell adenocarcinomas, and mixed adenocarcinomas, which all have a poor prognosis.27 A report by Hosoi et al. found that the endometrium was >4 mm in 89% of type I endometrial cancers and 93% of type II cancers, a difference that was not statistically significant.27 This report concluded that the “4-mm (5-mm) rule” was applicable even with type II cancers.

Bladder evaluation

TVS also allows evaluation of the bladder. A representative case is that of a 70-year-old presenting with PMB. This patient was referred for a SIS. Her initial TVS revealed a 2.0-mm endometrial thickness, which was confirmed on SIS with a 1.9-mm bi-layer thickness (Figure 6). Her endometrial biopsy revealed atrophic findings. However, a cystic mass was found in the base of the bladder with adjacent wall thickening (Figure 6), which proved to be a ureteral cyst with transitional cell carcinoma of the bladder.

These cases illustrate the additional advantages of TVS over hysteroscopy and endometrial biopsy. The ability to assess adjacent organs separates TVS from the other technologies.

Sonohysterography

Sonohysterography offers an excellent alternative to hysteroscopy in diagnosing endometrial abnormalities. It is indicated when patients are found to have an indistinct or thickened endometrium (Figure 7).

Epstein et al. evaluated 105 women with PMB with TVS, SIS, and hysteroscopy.28 They found 96% agreement between SIS and hysteroscopy in identifying endometrial polyps and submucous myomas, both with 80% sensitivity.28 Of interest, they also found a 7-fold greater risk of malignancy (odds ratio 7.3) in patients whose cavities were difficult to distend at SIS. Ultimately, two-thirds of women with a poorly distensible cavity were di-
agnosed with endometrial cancer.28

**Technique**

A complete TVS exam should be performed prior to SIS. This allows assessment of the uterine orientation and evaluation of the adnexa and bladder. SIS is indicated in patients with an indistinct or thickened endometrium, or in those with suspected focal lesions on TVS. The cervix is visualized and prepped with a suitable antiseptic solution, e.g., povidone-iodine or chlorhexidine gluconate solution, prior to insertion of the catheter.

Many suitable catheters are available. If there is a small cervical opening, a Shepherd insemination catheter is helpful because it has a 5.4 F diameter with a small hollow stylet within the catheter. The stylet is rigid and allows molding of the catheter to the curve of the uterine cavity. A balloon catheter is helpful in the presence of a patulous cervix or large fibroids. The catheter enhances distension and improves SIS image quality in most cases. Finally, if an endometrial biopsy is anticipated, specifically designed catheters such as a Goldstein SonoBiopsy catheter or a Bernard catheter can be used for both saline infusion and subsequent biopsy, facilitating one-step in-office evaluation.

Attach a 10-mL syringe filled with saline to the catheter and flush prior to insertion to prevent air from entering the cavity and causing image distortion. If the Goldstein SonoBiopsy catheter is being used, the pyramidal “stopper” should be adjusted to approximately .5 cm less than the measured length from the external os to the fundus. This avoids penetrating the fundus with the catheter, while the stopper retards backflow of fluid from the cervix. If using a balloon catheter, fill the balloon with saline to avoid acoustic distortion. Prep the cervix with an appropriate disinfecting solution, locate the catheter within the endometrial cavity, and remove the speculum, being careful to avoid pinching the cervix. The 10-mL syringe allows the catheter and syringe to pass through the opening of a traditional speculum, thus negating the need for an open-sided speculum.

Replace the transducer in the vagina and infuse saline under direct U/S visualization. Take images in the longitudinal and transverse views. If 3D is available, a sweep in the longitudinal plan is often the only image required to reconstruct and measure the endometrium and identify any focal lesions. Retained fluid should be withdrawn by drawing back on the syringe plunger. Advise the patient to anticipate a watery discharge for several days following the procedure. Patients tend to experience mild discomfort during specific maneuvers: traversing the internal cervical os, touching the fundus with the catheter, expanding the balloon (usually 1.5 mL is sufficient), rapidly distending the cavity, and performing a biopsy. Thus, advise the patient accordingly during these times, avoid touching or penetrating the fundus, and expand the balloon slowly.

The discomfort experienced during sonobiopsy (an endometrial biopsy performed with the SIS catheter) is similar to or less than during a suction-piston endometrial biopsy.
New options and additional information add perspective

BY HUGH S. TAYLOR, MD

Judicious use of therapies for treatment of menopausal symptoms has been a topic of debate for more than a decade. Many concerns about hormone therapy (HT) arose from interpretation of results of the Women’s Health Initiative (WHI), a large, prospective, randomized clinical trial (RCT) that evaluated use of menopausal HT and helped to define its risks and benefits. The initial findings from the WHI were concerning, but subsequent detailed analysis and long-term follow-up of women enrolled in these trials have brought perspective. Moreover, new prospective RCTs have shed more light on appropriate use and safety of HT. Finally, several novel FDA-approved therapies for treatment of menopausal symptoms address many concerns. These therapies offer exciting new options for women suffering from menopausal symptoms.

The WHI results astounded the media and the public. Some of the purported benefits of HT were not seen in the population treated, while the risks were initially thought to be similar to or greater than those previously reported. Most prescribers treat women who are newly menopausal and rarely treat women in the seventh and eighth decades of life, as was done in the WHI.

While media reports typically lumped together therapies composed of estrogens or estrogens given concomitantly with progesterins, we have come to learn that the risks and benefits of these therapies are distinct. The combination estrogen and progestin in the WHI studies did not decrease the risk of cardiovascular disease (CVD); in fact, the risk of CVD and stroke was increased in older women using combination HT. Reports on the WHI data eventually clarified that use of estrogen alone was not associated with increased risk in the 50- to 59-year-old age group. In fact, many CVD outcomes were improved in women using conjugated equine estrogens (CEE) alone. Further, coronary calcium, a surrogate marker of atherosclerosis, was significantly reduced in the younger women who used CEE alone. This finding suggests that the development of CVD was indeed reduced in newly menopausal women after hysterectomy who were using unopposed estrogen.

Although the risks for both combination and estrogen-based therapies increased with age, current data from the WHI suggest that...
these therapies can be safely administered without increased risk in women in and around the menopausal transition.\textsuperscript{5} Further, the use of CEE alone in women who have undergone hysterectomy may have some cardiovascular benefits before age 60.\textsuperscript{3,6}

More recent prospective RCTs have confirmed the safety of combination HT in newly menopausal women; the Kronos Early Prevention Study showed no evidence of coronary artery calcium deposition or worsening of progression of coronary artery atherosclerosis when combination HT was used in newly menopausal women for 4 years.\textsuperscript{7,8} Taken together, these studies show that in younger patients typically treated for menopausal symptoms, CVD is not increased by menopausal HT and there may be real cardiovascular benefits with the use of unopposed estrogen.

Other findings from the WHI were not surprising. HT reduced the risk of fracture and HT is known to increase the risk of breast cancer.\textsuperscript{16} Subsequent studies showed that not only was this risk increased, there was also an accompanying increase in breast cancer among women who used CEE. Contrary to popular misconceptions, estrogen and progestins are distinct hormones with different effects on the breast. For a well-informed woman who has had a hysterectomy and is not at risk of venous thromboembolism (VTE), the decision to use HT should be an easy one.

**New HT options**

For women who have not undergone hysterectomy and require a progestin for protection against endometrial cancer, several new alternatives to traditional combination HT are available with greater safety and minimal side effects.

New products include paroxetine, an antidepressant, for reduction in VMS.\textsuperscript{12,13} It does not have the same level of efficacy as traditional menopausal HT, but paroxetine provides relief for women who want a non-hormone-based alternative.

Selective estrogen receptor modulators (SERMs), which have tissue-specific selective targeting through the estrogen receptor (ER), also have potential in treatment of menopausal symptoms. Raloxifene, a SERM approved for prevention and treatment of osteoporosis, effectively targets ERs in bone while not stimulating those in breasts.\textsuperscript{14,15} Like many SERMs, it has an antagonistic hormone effect on breasts, reducing the risk of breast cancer.\textsuperscript{16}

Because raloxifene does not effectively provide an estrogen-like effect in the central nervous system and may increase the incidence and severity of VMS. However, other SERMs that may offer benefits have been introduced. Osapemifene, an oral SERM that targets the vagina, provides relief from vaginal atrophy without stimulating the endometrium.\textsuperscript{17} VVA can be targeted through the oral or vaginal route. This decision includes balancing the risks of systemic therapy (eg, VTE) with the convenience of oral administration.

Perhaps the most innovative and novel therapy to be approved in the United States is the first tissue-selective estrogen complex—a combination of CEE and the SERM bazedoxifene (BZA).\textsuperscript{18,19} BZA’s unique properties allow it to be specifically coupled with estrogens without the need for a progestin. Its tissue-specific selectivity antagonizes estrogen action on the breast and uterus, but does not effectively counteract the benefits of estrogen on the brain or bone.

Replacing a progestin with a SERM is expected to result in a much more favorable risk profile than combination HT.\textsuperscript{20} Clinical trials of CEE/BZA have shown effective relief of VMS and improved bone density.\textsuperscript{21,24} Remarkably, the combination of CEE and BZA produced bleeding rates comparable to placebo, far less than traditionally noted with any estrogen and progestin combination HT.\textsuperscript{25} Further, it does not increase breast tenderness as was seen with estrogen and progestin.

Mammograms obtained in women using CEE/BZA in clinical trials...
showed no increase in mammographic density, which is in contrast to the increase seen with combination HT.\textsuperscript{26}

**Summary**

More than a decade after the first WHI results, detailed follow-up analysis has revealed a clearer picture of the actual benefits and risks of menopausal HT. Many of the risks that led women to reject therapies for VMS have finally been put into perspective. The distinctive risks of CEE alone versus combination therapy are now unambiguous. The important effect of age has also become apparent. Newly menopausal women can feel confident that they have a full and accurate assessment of the risks and benefits of HT. The reduction in breast cancer risks with use of CEE alone is still underappreciated, but important to our patients to relieve their fears and enable them to make more informed decisions.

Finally, several new products have become available, offering more options and potentially greater safety. Nonhormonal and tissue-specific hormonal therapies have been added to our armamentarium. Perhaps the most promising therapy for women with a uterus is CEE/BZA.

A renaissance in treatment of menopausal symptoms has begun. We are better informed than ever about the side effects and risks of HT and armed with new options. It is time to reengage and inform our patients; we can help them to make knowledgeable decisions.

**References**

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*Laparo-Endoscopic Single-Site Surgery
This is an ideal time to review the benefits and risks of hormone therapy (HT) in menopause, in light of the recent publication of the Women’s Health Initiative (WHI) outcomes, ACOG’s Practice Bulletin update on the management of menopausal symptoms, and recent research documenting that ob/gyn residents have inadequate experience and exposure to menopausal medicine. In the last year, the FDA has approved 2 nonhormonal therapies for treatment of menopausal symptoms: an oral therapy (a selective estrogen receptor modulator [SERM] also called an oral estrogen agonist/antagonist with tissue-selective effects) for moderate to severe dyspareunia caused by menopausal vulvovaginal atrophy (VVA) and a low-dose oral selective serotonin reuptake inhibitor (SSRI) for the treatment of moderate to severe vasomotor symptoms (VMS) that comes without the psychiatric labeling of other SSRIs.

Systemic HT—with just estrogen (in women without a uterus) or estrogen plus progestin (in women with a uterus)—remains the most effective therapy for treating menopausal VMS. Clinicians should individualize care and use the lowest effective dose consistent with the indication for therapy, which does not necessarily imply a limit to therapy. The most important data point in the WHI long-term health outcomes is reduced all-cause mortality with both estrogen alone (in women without a uterus) and combination HT (in women with a uterus) compared to placebo in women within 10 years of menopause who used therapy for more than 5 years.

The benefit of estrogen was mathematically and strikingly demonstrated in a recent analysis that suggested up to 90,000 deaths may have occurred due to post-WHI withholding of estrogen therapy. For some time, Dr. Wulf Utian (the founder of both the International Menopause Society and the North American Menopause Society) has called for an independent commission to re-evaluate the WHI investigators’ reports. It is up to all women’s health practitioners and educators to educate our patients and our trainees about menopause and menopausal HT. The Study of Women Across the Nation revealed that the productivity of menopausal women suffers if their symptoms are not treated. Economic stability is an important component of health and wellness.

In my opinion, the long-term outcomes of the WHI as well as the Danish Osteoporosis Prevention Study swing the pendulum back from using menopausal HT as limited treatment in women severely affected by menopausal hormone deficiency only to using it for primary prevention based on mortality reduction, including bone protection and reduction of cardiovascular disease (CVD).

Hodis and Mack compare the risks of HT with other commonly used medicines. They note that data from randomized clinical trials are very reassuring in that risks associated with HT are rare (fewer than 1 event per 1000 women treated) and even rarer in women who initiate HT within 10 years of menopause. Strikingly, HT reduces CVD and total mortality (while aspirin and statins in women treated for primary cardiovascular prevention do not).

The major risk with the use of HT is venous thromboembolism (VTE). Some have postulated that the use of transdermal estr...
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dio and oral micronized progesterone may reduce the risk of VTE and breast cancer, respectively. With respect to breast cancer, oral conjugated equine estrogen (CEE) used for 11 years in the estrogen-only arm of the WHI was not associated with any increase in breast cancer diagnosis, and in adherent women, was associated with a decrease in breast cancer diagnosis.

Because of miscommunication of the results of the WHI, many women turned to unregulated compounded so-called ‘bio-identical hormone therapy’ (BHT). BHT in the compounded form typically is used in transdermal progesterone cream, which does not achieve high-enough serum levels to reliably protect the endometrium.

Assessing for relief of menopausal symptoms, visually inspecting for resolution of VVA, and assessing bone density are indirect tissue-level assays of estrogen adequacy. Women requesting BHT can be prescribed regulated oral progesterone and oral or transdermal vaginal estradiol. These products are FDA-approved, commercially available, and do not have to be compounded for most women. The table on page 42 describes options for delivering HT.

In general, estrogen alone is used in cases of hysterectomy and progestin is used either continuously with the goal of amenorrhea within 6 months or cycled for 12 days each month. Testosterone is not FDA-approved and therefore not standard of care in the United States. However, for women with androgen deficiency, one generic oral esterified estrogen with oral methyltestosterone combination is available. It can also be considered, along with off-label compounded topical testosterone, for women who have undergone hysterectomy with oophorectomy and have persistent VMS on estrogen alone, but that should be done carefully to avoid supra-physiologic levels.

Pellets of estrogen, progesterone, and testosterone are not FDA-approved and are not recommended. Data do not support the use of progestin alone, testosterone alone, compounded BHT, phytoestrogens, herbal supplements, and/or lifestyle modifications to treat menopausal VMS.

Half of all women have vasomotor symptoms, and for some they last for decades.

Benefits of HT include relief of VMS (which can include hot flashes, night sweats, and rarely formication, which is a sense of something crawling on the body) and treatment of VVA. If VVA is the only menopausal symptom, local estrogen or the new non-hormonal ospemifene should be considered. The major risk with this systemic SERM is the risk of VTE.

Local estrogens are available in 2 creams, 1 vaginal ring and 1 vaginal tablet. Some women prefer oral therapy to local vaginal therapy and may be candidates for systemic HT or oral ospemifene alone.

The only nonhormonal agent approved to treat VMS is low-dose paroxetine, which has shown statistical significance at week 4 and week 12 with persistence of benefit of treating VMS at week 24. Coadministration of paroxetine can alter concentrations of other drugs such as tamoxifen. The lower doses of paroxetine do not appear to be associated with weight gain and sexual dysfunction.

Many other SSRI and norepinephrine serotonin reuptake inhibitors (NSRI) have been studied, although only low-dose paroxetine is FDA-approved. Choosing an appropriate therapy requires careful assessment of the risk-benefit as well patient preference and comorbid medical conditions.

Other benefits associated with HT use include reduction in type 2 diabetes, colon cancer, and fracture and improvement in minor mood and neurocognitive symptoms associated with sleep deprivation from VMS. Estrogen also may benefit skin and hair among women who are estrogen-deficient but who have endogenous levels of androgens promoting hair thinning and acne, and in some women, even a deepening of the upper register of the voice. Risks besides VTE and invasive breast cancer (with long-term combination HT) include a higher incidence of all cardiovascular events, gall bladder disease, and probable dementia. Among the nuisance side effects are breast tenderness and uterine bleeding.

Endometrial hyperplasia and endometrial cancer are associated with unopposed estrogen use. Oral estrogen can be associated with increase in blood pressure in some women and elevated triglyceride levels and gallstones. Fluctuating hormone levels can affect migraine headaches. Women with seizure disorders need adequate progestin therapy as estrogen can lower the seizure threshold.

Several societies, including the International Menopause Society and the Endocrine Society, have issued helpful guidelines. The North American Menopause Society’s most recent position admits that the data support the initiation of HT around the time of menopause to treat symptoms and to prevent osteoporosis in women at high risk of fracture. Risks of stroke, dementia, and myocardial infarction are highest in women initiating therapy several decades from menopause.
I’m a gynecologist, not a financial expert.

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Menopause is a potential endocrinopathy. If a patient has premature menopause or early menopause, pressing long-term consequences of hormone deficiency include premature death, CV disease, osteoporosis, sexual dysfunction, and neuropsychiatric problems. Many women produce enough steroid hormones to be free of symptoms or to experience only asymptomatic bone loss and later-onset VVA. Some women will never experience VMS even with castration. However, half of all women have VMS, and for some they last for decades. Half of all women experience an osteoporotic fracture in their lifetime, which is generally related to estrogen deficiency. A vast majority experience VVA, which may not be symptomatic, but if it progresses and/or is not treated, can lead to structural changes in the vagina, vulva, trigone of the bladder, and urethra, and elevation in vaginal pH.

Women who have had menopausal-onset neuropsychiatric problems and/or sleep disorders such as insomnia should continue on long-term HT even after their condition has stabilized. The newest HT approved by the FDA is oral conjugated estrogen plus bazedoxifene (BZA), a SERM. It is approved for treatment of VMS and prevention of osteoporosis. BZA replaces the progestin medroxyprogesterone acetate (MPA) in Prempro. BZA has estrogen antagonistic endometrial effects and independent agonistic effects on bone. Many menopausal women have osteopenia, not osteoporosis, and thus are not candidates for other osteoporosis therapies. Therefore, systemic HT or systemic estrogen plus a SERM like CEE/BVA (or if no VMS and osteopenia or osteoporosis and increased risk of breast cancer then oral daily raloxifene) should be considered.

<table>
<thead>
<tr>
<th>TABLE</th>
<th>Options for postmenopausal hormone therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Estrogen Only</strong></td>
<td><strong>Dosages</strong></td>
</tr>
<tr>
<td><strong>Oral Formulations</strong></td>
<td></td>
</tr>
<tr>
<td>Premarin (conjugated estrogen)</td>
<td>0.3 mg, 0.45 mg, 0.625 mg, 0.9 mg, 1.25 mg, 2.5 mg daily</td>
</tr>
<tr>
<td>Menest (esterified estrogen)</td>
<td>0.3 mg, 0.45 mg, 0.625 mg daily</td>
</tr>
<tr>
<td><strong>Transdermal Formulations</strong></td>
<td></td>
</tr>
<tr>
<td>Divigel (gel)</td>
<td>0.025 mg, 0.05 mg, 0.10 mg daily</td>
</tr>
<tr>
<td>Elestrin (spray)</td>
<td>1 to 2 sprays daily</td>
</tr>
<tr>
<td>Evamist (spray)</td>
<td>1 to 3 sprays daily</td>
</tr>
<tr>
<td>Climara (transdermal patch)</td>
<td>0.025 mg, 0.0375 mg, 0.05 mg, 0.060 mg, 0.075 mg, 0.100 mg weekly</td>
</tr>
<tr>
<td>Vivelle-dot (transdermal patch)</td>
<td>0.025 mg, 0.0375 mg, 0.050 mg, 0.075 mg, 0.010 mg twice weekly</td>
</tr>
<tr>
<td>Minivelle (transdermal patch)</td>
<td>0.0375 mg, 0.050 mg, 0.075 mg, 0.010 mg twice weekly</td>
</tr>
<tr>
<td><strong>Vaginal Ring</strong></td>
<td></td>
</tr>
<tr>
<td>Estring</td>
<td>0.05 mg, 0.10 mg once every 3 months</td>
</tr>
<tr>
<td>Femring</td>
<td></td>
</tr>
<tr>
<td><strong>Estrogen + Progestin</strong></td>
<td><strong>Dosages</strong></td>
</tr>
<tr>
<td><strong>Oral Formulations</strong></td>
<td></td>
</tr>
<tr>
<td>PremPro (estradiol/progesterone)</td>
<td>0.625 mg/2.5 mg, 0.4 mg/1.5 mg, 0.3 mg/1.5 mg daily</td>
</tr>
<tr>
<td>Activella (estradiol/norethindrone acetate)</td>
<td>0.5 mg, 0.1 mg, 1 mg/0.5 mg daily</td>
</tr>
<tr>
<td>FemHRT (estradiol/norethindrone)</td>
<td>5 mcg/1 mg daily</td>
</tr>
<tr>
<td>Angeliq (estradiol/drospirenone)</td>
<td>0.5 mg/0.25 mg, 2.5 mg/0.5 mg daily</td>
</tr>
<tr>
<td><strong>Transdermal Formulations</strong></td>
<td></td>
</tr>
<tr>
<td>Climara-Pro (estradiol/levonorgestrel)</td>
<td>0.045 mg/0.015 mg weekly</td>
</tr>
<tr>
<td>CombiPatch (estradiol/norethindrone acetate)</td>
<td>0.05 mg/0.14 mg, 0.05 mg/0.25 mg twice weekly</td>
</tr>
<tr>
<td><strong>Progestin Only</strong></td>
<td><strong>Dosages</strong></td>
</tr>
<tr>
<td>Oral Formulations*</td>
<td></td>
</tr>
<tr>
<td>Prometrium (micronized progesterone)</td>
<td>100 mg nightly, 200-mg cycled</td>
</tr>
</tbody>
</table>

*Should be taken with food for better absorption and taken at night for its potential sedative hypnotic effect. Prometrum should not be used by women who are allergic to peanuts.
oxifene is FDA-approved to prevent and treat osteoporosis and to reduce risk of diagnosis of estrogen receptor (ER)-positive breast cancer. All systemic estrogens and all SERMs can increase the risk of VTE 2 fold.

**Work-up for menopause**
When evaluating a woman for menopause, first ascertain whether she is menopausal. Not all amenorrhea is menopause and not all midlife symptoms are menopause. Next, does she have a uterus? If she has had a hysterectomy, is she a candidate for estrogen alone? If she has had a provoked VTE in the past, it is best to consider transdermal HT.17 If she has active ER-positive breast cancer, unstable CVD, or uterine cancer, then non-estrogen alternatives should be considered.

Fear of breast cancer is not a reason to avoid oral estrogen. If she has a uterus/endometrium, then the decision to use progestin cyclically or continuously needs to be made. If she decides to use progestin cyclically or progestin is needed for 12 days only once or twice a year in women with a uterus and has been FDA-approved for the last decade.12

**Summary**
When evaluating menopausal women for menopausal HT, it is important to look at the totality of the data, review recent position papers by national societies, and individually evaluate your patients.

The pendulum is swinging back to primary prevention with HT. It is up to you to communicate this to your patients and offer the newer FDA-approved non-hormonal options to those for whom they are appropriate.22

**References**

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**POSTMENOPAUSAL HORMONE THERAPY**
Summary

TVS for initial triage of PMB identifies patients who do not need further endometrial evaluation at the initial visit, i.e., those whose EEC is well-visualized and <4 mm thick. The risk of underlying cancer in these patients is quite low (1/917). TVS offers the additional advantage of evaluating the adnexa and the bladder. If the endometrium is >4 mm thick, proceed to SIS or tissue sampling. SIS allows reliable detection of focal intracavitary lesions, such as endometrial polyps or submucous myomas. Patients with thickened, asymmetric, or irregular EEC should undergo endometrial sampling following SIS.

Patients with focal intracavitary lesions should be triaged to surgical removal. Management of the remaining patients is based on endometrial biopsy results. If endometrial biopsy is not performed initially and a patient has recurrent bleeding, SIS and endometrial biopsy should be performed, with surgical treatment as indicated. TVS, followed by SIS when indicated, allows prompt in-office evaluation of patients with PMB, offering a reliable assessment of endometrial pathology, while minimizing cost and inconvenience to the patient.

REFERENCES

Coming in October

Surgical Technology:
From Promise to Practice

Look for a special section in next month’s edition of Contemporary OB/GYN on gynecologic surgery advances and innovations. Edited by Jon I. Einarsson, MD, PhD, MPH, it features authoritative, peer reviewed information on procedures, techniques, tools, and controversies including:

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- A “how I do it” article from a top expert on identification of the ureter in hysterectomy
- Point/Counterpoint debates on the future of robotics in gynecologic surgery and use of mesh for prolapse

Only Contemporary OB/GYN brings you so much practical advice on gynecologic surgery in a single focus issue.
Noninvasive prenatal testing: A new standard of care

The presence of fetal DNA in maternal plasma and serum was first reported nearly 20 years ago. Fetal DNA is believed to be primarily placenta-derived and comprises 3% to 13% of total cell-free maternal DNA. Studies of women who have conceived by in vitro fertilization have demonstrated that fetal DNA can be detected in maternal serum as early as the seventh week of gestation and there is an increase in cell-free fetal DNA (cfDNA) concentration as pregnancy progresses, although cfDNA is cleared from the maternal blood within hours of childbirth.

Although recent data suggest that invasive tests such as amniocentesis and chorionic villus sampling (CVS) are much safer than initially surmised (with risks of miscarriage 0.11% and 0.22%, respectively), obtaining information about a conceptus at an early stage is still the holy grail of prenatal diagnosis.

One of the first reproducible applications of cfDNA analysis was detecting fetal RhD sequences in maternal serum of Rh-negative (sensitized) women. That study helped advance prenatal diagnosis technology by demonstrating that fetal single-gene disorders could be detected prenatally using DNA isolated solely from maternal serum.

Noninvasive prenatal testing has the ability to capitalize on robust tools for genetic evaluation.

Part of the motivation for developing maternal blood-based or noninvasive prenatal testing (NIPT) is rooted in the ability to achieve an early diagnosis; even nuchal translucency and analyte-based aneuploidy testing followed by CVS for positive tests generates significant delay between testing and ultimate diagnosis (anywhere between 12 and 14 weeks). However, because genetic technologies appear to be experiencing the same kind of exponential growth as computing technology, NIPT has the ability to capitalize on robust tools for genetic evaluation, allowing for more accurate early diagnoses beyond aneuploidy and single-gene defects.

Many studies have validated NIPT to accurately detect trisomy 13, trisomy 18, and trisomy 21 using shotgun sequencing and massively parallel genomic sequencing (MPGS) while other researchers have capitalized on the power of other next-generation sequencing (NGS) modalities to detect fetal autosomal trisomies, sex chromosome aneuploidies, and triploidy.

In the first part of this 2-part genetic-technology review, we will discuss the current NIPT landscape and compare/contrast NIPT technologies. Table 1 gives information about cost and turnaround times for the 4 commercially available NIPT technologies.

Option 1 MaterniT21
The first NIPT to come to the commercial market was MaterniT21,
which was developed by Sequenom and designed for trisomy 21 detection. It was released in 2011, followed in 2012 by MaterniT21 PLUS, which has the ability to diagnose not only trisomy 21, but also trisomy 13 and 18. Sequenom is also utilizing MPGS for their test.

In theory, NGS allows for multiple studies of multiple pieces/regions of DNA to be analyzed in parallel (at the same time), which allows for efficient evaluation of the whole genome rather than just specific targets that are representative of a discrete chromosome, as is done with fluorescence in situ hybridization (FISH). In Sequenom’s initial clinical validation studies of nearly 2000 specimens for each trisomy, they were able to achieve almost 100% sensitivity and specificity; trisomy 21: 99.1%/99.9%, trisomy 18: >99.9%/99.6%, trisomy 13: 91.7%/99.7%, Down syndrome and other trisomies: >99.9% detection.9-11

OPTION 2

Verifi

The next test to come to market was Verinata Health’s Verifi, which similarly capitalizes on the power of MPGS but also utilizes a propriety algorithm called SAFeR. According to the Verinata Health website, the SAFeR method calculates a normalized chromosome value (NCV) for each chromosome, thereby reducing data variation. They state that in a large-scale study population (no reference is provided on their website), “approximately 0.2% to 0.6% of results were classified as ‘Aneuploidy Suspected’ for each particular chromosome.” Because both aneuploid and euploid samples can be categorized as “Aneuploidy Suspected,” the chances of a false positive are higher without the SAFeR method.12

Interestingly, screening for fetal aneuploidy in twin gestations is challenging because of the lower levels of DNA available for analysis from each fetus as a result of the smaller uteroplacental junctional areas seen in monozygotic twins.13 By expanding the sensitivity and overall capability to detect aneuploidies, Verinata Health openly states that their test can be used for twins. However, it would not be possible to distinguish which twin has an abnormal result without further invasive testing.

OPTION 3

Harmony Prenatal Test

At approximately the same time that Verifi was released, Ariosa Diagnostics launched the Harmony Prenatal Test. That technique addresses one of the main concerns about MPGS, which is that it requires a large amount of DNA for sequencing because of the requirement to analyze the entire genome.

The Harmony Prenatal Test utilizes a proprietary technology known as digital analysis of selected regions (DANSR), which sequences loci from only the chromosomes under investigation. As such, the assay requires approximately 10 times less DNA sequencing than MPGS approaches. To further enrich their platform, Ariosa Diagnostics also integrated their own statistical algorithm, fetal-fraction optimized risk of trisomy evaluation (FORTE). Essentially, the algorithm integrates age-related risks and the percentage of fetal DNA in the sample to provide an individualized risk score for trisomy.

In what some view as one of the landmark studies demonstrating the utility of NIPT, researchers at the University of London screened subjects who were at risk of aneuploidies and had undergone CVS. The DANSR/
FORTE combined analysis distinguished all cases of trisomy 21 and 98% of trisomy 18 cases from euploid pregnancies.14 In an online commentary about the study, the senior author noted that plasma samples were obtained from high-risk pregnancies with some evidence of impaired placental function. (As previously discussed, cfDNA is believed to originate in the placenta.) “As such, the ability to detect aneuploidy with cfDNA is dependent upon assay precision and fetal DNA percentage in the sample rather than the prevalence of the disease in the study population.”15

That issue was highlighted in a recent report about a study in which aneuploid samples were significantly more likely to not return a result; the number of aneuploidy samples was especially increased among samples with low fetal fraction.16

OPTION 4
Panorama Prenatal Test
In 2012, California-based Natera released the Panorama Prenatal Test, which is the only test to analyze single nucleotide polymorphisms (SNP). The advantage of using a SNP-based technology is that it requires less cfDNA and, unlike other noninvasive methods, can detect genetic abnormalities such as short insertions/deletions/aberrations that cause Mendelian disorders.

Noninvasive prenatal testing is widely available and likely will soon become the standard of care.

At the time of this article, Panorama is able to detect trisomies 21, 18, and 13 as well as 45,X (Turner syndrome). Studies have shown that the test has high sensitivity and specificity in high-risk and low-risk cohorts (≥99% detection rate for trisomies 21, 18, and 13 and a ≥90% detection rate for 45,X).17,18 It is important to note, however, that while SNP-based analyses are powerful tools, they have discrete limitations. Because SNP-based sequencing utilizes a reference sample of the maternal blood to distinguish maternal from fetal DNA, although such cases are rare, Panorama cannot be used for pregnancies conceived with an egg donor or those that used a gestational carrier, and cannot be performed on women who have received a bone marrow transplant.

Summary
Taking all of these advances together, the field of NIPT is incredibly exciting. In less than 2 years, 4 distinct robust technological tools have been added to the obstetrical armamentarium. Each tool has its strength and weakness, and it is important to know which tool to use for which clinical scenario (twins, singleton, donor egg, etc.). We also need to recognize that while NIPT is widely available and likely will soon become the standard of care, as obstetricians and gynecologists, we still have to practice within the guidelines and recommendations of the American College of Obstetricians and Gynecologists. The 2012 ACOG Committee Opinion on Noninvasive Prenatal Testing for Fetal Aneuploidy cautioned that the use of cfDNA testing should be an active, informed choice and not part of routine prenatal laboratory testing (Table 2).

Lastly, we will all have to learn how to best utilize the new information that this testing generates. For many of us, NIPT will forever change how we practice medicine. Many of us have become facile in using technology such as ultrasound to help identify potential pregnancy complications. But in the recently
ACOG cautions that cfDNA testing should be an active, informed choice, not part of routine prenatal laboratory testing.

released International Society of Ultrasound in Obstetrics and Gynecology consensus statement on the impact of NIPT on prenatal ultrasound practice, the authors caution that “so-called ‘genetic sonogram,’” which includes looking for soft markers of trisomy 21, should not be performed in women with a normal NIPT result due to ultrasound’s high false-positive rate and poor positive predictive value.19 Therefore, as uptake of NIPT increases, we will not only have to learn how and when to use NIPT, but we will also have to unlearn to use many older technologies.20

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Neither author has a conflict of interest to report with respect to the content of this article.

REFERENCES


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15–18: North American Menopause Society Annual Meeting
Washington, DC
http://www.menopause.org/annual-meetings/future-meetings

18–22: American Society for Reproductive Medicine Annual Meeting
Honolulu, Hawaii
http://www.asrm.org/ASRM2014/

21–26: Pacific Coast Obstetrical and Gynecological Society
Marana, Arizona
http://www.pcogs.org/meetings.cfm

24–28: Transforming the Future of Women’s Health & Fetal Medicine
Houston, Texas
https://www.smfm.org/events/6-transforming-the-future-of-womens-health-fetal-medicine

26–29: International Society for the Study of Hypertension in Pregnancy
New Orleans, Louisiana
http://isshp2014.com/

NOVEMBER
5–7: Cambridge Health Institute 2nd Annual Meeting, Advances in Prenatal Molecular Diagnostics
Boston, Massachusetts
http://www.healthtech.com/prenatal-diagnostics

7–12: Association of American Medical Colleges Annual Meeting
Chicago, Illinois
https://www.aamc.org/meetings/annual/2014/

17–21: 43rd AAGL Global Congress on Minimally Invasive Gynecology
Vancouver, British Columbia
https://www.aagl.org/globalcongress/

20–22: World Symposium of Perinatal Medicine
San Diego, California
http://www.worldsymposium.net

FEBRUARY 2015
2–7: The Society for Maternal-Fetal Medicine 35th Annual Pregnancy Meeting
San Diego, California

https://www.smfm.org/the-pregnancy-meeting

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

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

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

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

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PERSONAL HEALTH TRACKING

Nearly two-thirds of US adults keep track of at least one personal health indicator, such as weight, diet, exercise, or a symptom, according to a national telephone survey of 3,014 adults by Pew Research Center’s Internet & American Life Project. Most (49%) monitor progress “in their heads” but 34% track health data on paper and 21% use an electronic method. Only about one-third of trackers share their data with anyone and of them, only half do so with a clinician.

**Chronic conditions**

US adults who track

- **62%** track personal weight, diet, or exercise routine
- **40%** track other health indicators (eg, blood pressure, sleep, headaches)
- **19%** track for a loved one

**Sharing of data**

- **34%** of trackers share records or notes with another person or group, online or offline
- **52%** of the 34% share with clinicians

**Informing health decisions**

- **53%** vs **33%** of trackers living with 2+ conditions say tracking has led them to ask a doctor new questions or seek a second opinion

Source: Pew Internet/CHCF Health Survey, August 7–September 6, 2012. N=3014 adults ages 18+. Interviews were conducted in English and Spanish and on landline and cell phones. Margin of error is +/- 2.4 percentage points for results based on all adults.
For your patients with varicose and spider veins...

IF THESE LEGS COULD TALK.

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

Don’t let vein disease stand in her way.
Our phlebologists will treat your patients with the same care and expertise you have provided them to ensure healthy, strong legs after pregnancy. Refer your patients to the largest network of highly trained vein specialists who have been helping patients since 1981.

Our physicians provide free consultations* for your patients.
To speak to a representative, please call (855) 953-VEIN (8346) or visit veinclinics.com/foryourpatients

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

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

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

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

<table>
<thead>
<tr>
<th>Test Type</th>
<th>Details</th>
</tr>
</thead>
<tbody>
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<td>informaSeq</td>
<td>Appropriate for high-risk patients. Provides only risk assessment for the most common autosomal trisomies.</td>
</tr>
<tr>
<td>informaSeq with Y analysis</td>
<td>Appropriate for high-risk patients. Provides risk assessment for the most common autosomal trisomies and fetal gender, but not sex chromosome aneuploidies.</td>
</tr>
<tr>
<td>informaSeq with XY analysis</td>
<td>Appropriate for high-risk patients with singleton pregnancies. Provides risk assessment for the most common autosomal trisomies, sex chromosome aneuploidies, and fetal gender.</td>
</tr>
</tbody>
</table>

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- The largest commercial genetic counseling team with unparalleled services
- Extensive managed care contracts helping patients maximize their benefits
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