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Sex and the 50-something woman
Restoring satisfaction
John E. Buster, MD

CLINICIAN TO CLINICIAN
Hysteroscopic myomectomy
Pearls and pitfalls
Morris Wortman, MD

SMFM CONSULT
Screening for thyroid disease in pregnancy

Balancing risks and benefits
Donna Shoupe, MD

ACA IMPACT
Editor-in-Chief’s analysis
Don’t let moderate to severe hot flashes and VVA, as well as bone loss, gang up on your menopausal patients.\(^1\)^\(^3\)

To learn about the WHI estrogen alone substudy and why PREMARIN may be right for the appropriate, postmenopausal, hysterectomized woman in her 50s, visit www.PremarinHCP.com/age

**INDICATION:** PREMARIN® (conjugated estrogens tablets, USP) is indicated in the treatment of moderate to severe vasomotor symptoms due to menopause, treatment of moderate to severe symptoms of vulvar and vaginal atrophy due to menopause, and the prevention of postmenopausal osteoporosis.

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

The Women’s Health Initiative (WHI) estrogen alone substudy reported increased risks of stroke and deep vein thrombosis in postmenopausal women (50 to 79 years of age) during 7.1 years of treatment with daily oral conjugated estrogens (CE) (0.625 mg) alone, relative to placebo. The WHI estrogen plus progestin substudy reported increased risks of DVT, pulmonary embolism, stroke, and myocardial infarction in postmenopausal women (50 to 79 years of age) during 5.6 years of treatment with daily oral CE (0.625 mg) combined with medroxyprogesterone acetate (MPA) (2.5 mg), relative to placebo. In the absence of comparable data, these risks should be assumed to be similar for other doses of CE with or without MPA, and other combinations and dosage forms of estrogens with or without progestins.

The WHI Memory Study (WHIMS) estrogen alone study reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 5.3 years of treatment with daily CE (0.625 mg) alone, relative to placebo. The WHIMS estrogen plus progestin study reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with daily CE (0.625 mg) combined with MPA (2.5 mg), relative to placebo. It is unknown whether these findings apply to younger postmenopausal women.

The WHI estrogen plus progestin substudy demonstrated an increased risk of invasive breast cancer. Estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman. Estrogens with or without progestins should not be used for the prevention of cardiovascular disease or dementia.

PREMARIN® (conjugated estrogens tablets, USP) should not be used in women with any of the following conditions: undiagnosed abnormal genital bleeding; known, suspected, or a history of breast cancer; known or suspected estrogen-dependent neoplasia; active deep vein thrombosis, pulmonary embolism, or a history of these conditions; active arterial thromboembolic disease (for example, stroke and myocardial infarction), or a history of these conditions; known anaphylactic reactions or angioedema; known liver dysfunction or disease; known or suspected pregnancy.

When prescribing solely for the symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered. When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and for whom non-estrogen medications are not considered appropriate.

Please see Brief Summary of Full Prescribing Information, including boxed warning, on the following pages.


PREMARIN® [conjugated estrogens tablets, USP]

**SUMMARY:** This is a brief summary of prescribing information. For current full prescribing information, please visit www.PremarinHCP.com.

**INDICATIONS AND USAGE**

**PREMARIN therapy is indicated for:**

- Treatment of moderate-to-severe symptoms of vulvar and vaginal atrophy due to menopause.
- Treatment of breast cancer (for palliation only) in appropriately selected women and men with metastatic disease.
- Treatment of moderate to severe symptoms of vulvar and vaginal atrophy due to menopause. When prescribing PREMARIN for this indication, please visit www.PremarinHCP.com.
- Treatment of breast cancer (for palliation only) in appropriately selected women and men with metastatic disease.
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5. Hypocalcemia

Estrogen administration may lead to severe hypocalcemia in patients with breast cancer and bone metastases. If hypocalcemia occurs, use of the drug should be stopped and appropriate measures taken to reduce the serum calcium level.

6. Visual Abnormalities

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

7. Anaphylactic Reaction and Angioedema

Cases of anaphylaxis, which developed within 24 hours after the start of taking PREMARIN and require emergency medical intervention, have been reported in postmenopausal women. Sequela include: skin rashes, pruritis, swelling lips, tongue, face, and other respiratory tract (respiratory compromise) or gastrointestinal tract (abdominal pain, vomiting) involvement. In some instances, death has occurred.

Angioedema involving the tongue, larynx, face, hands, and feet requiring medical intervention has occurred in postmenopausal women taking PREMARIN. If angioedema involves the tongue, glottis, or larynx, airway obstruction may occur. Patients who develop an anaphylactic reaction with or without angioedema after treatment with PREMARIN should not receive PREMARIN again.

8. Hereditary Angiodystrophy

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

PRECAUTIONS

1. Administration of a progestogen when a woman has had a hysterectomy

Studies of the addition of a progestogen to 10 or more days of a cycle of estrogen administration, or daily with estrogen in a continuous regimen, have reported a lowered incidence of endometrial hyperplasia and carcinoma. These studies reported no increased risk of breast cancer.

2. Elevated blood pressure

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

3. Hypertension

Women with existing hypertensive disorder, estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis. Consider discontinuation of treatment if pancreatitis occurs.

4. Hepatic impairment and past history of cholestatic jaundice

Estrogen may be metabolized in patients with impaired liver function. For women with a history of cholestatic jaundice associated with past estrogen use or pregnancy, caution should be exercised, and in the case of new use, discontinuation should be considered.

5. Hygrothrombosis

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

6. Fluid retention

Estrogens may cause some degree of fluid retention. Women with conditions that might be influenced by the body, such as cardiac or renal dysfunction, warrant careful observation when estrogens are prescribed.

7. Hypocalcemia

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

8. Exacerbation of endometrial hyperplasia

A few cases of malignant transformation of residual endometrial implants have been reported in women treated post-hysterectomy with estrogen-alone therapy for women known to have residual endometrial rest post hysterectomy, the addition of progestin should be considered.

9. Exacerbation of other conditions

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

10. Laboratory Tests

Pharmacists are advised to discuss the contents of the PREMARIN PATIENT INFORMATION leaflet with patients for whom they prescribe PREMARIN. Laboratory tests are not indicated or necessary and may be employed in evaluating the patient response to therapy. Laboratory studies of estrogen administration should be used to indicate appropriate adjustments of concomitant medications or to monitor unusual circumstances or suspected adverse reactions. Serum levels (by column or by radioimmunoassay) of total and free hormone

11. Drug-Laboratory Test Interactions

1. Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity.

2. Increased thyroid-binding globulin (TBG) levels leading to increased circulating total thyroid hormone levels as measured by protein-bound iodine (PBI), T3, (by column or by radioimmunoassay) or T4, levels by radiometric method. T, T3, and T4, are increased, reflecting the elevated TBG. T3, T3, and T4, concentrations are unaffected. Women on thyroid replacement therapy may require higher doses of their thyroid replacement therapy. These women should have their thyroid function monitored in order to maintain their free thyroid hormone levels in an acceptable range.

3. Fluid retention

Estrogens may cause some degree of fluid retention. Women with conditions that might be influenced by the body, such as cardiac or renal dysfunction, warrant careful observation when estrogens are prescribed.

4. Increased plasma levels of cholesterol (LDL), cholesterol, total cholesterol, triglycerides, and low-density lipoprotein (LDL).

5. Impaired glucose tolerance

6. Carcinogenesis, Mutagenesis, Impairment of Fertility (See BOXED WARNINGS, WARNINGS, and PRECAUTIONS)

Long-term administration of natural and synthetic estrogens in certain animal species increases the frequency of vaginal adenocarcinoma in rats, while no increase of endometrial hyperplasia or carcinoma was observed in rats, mice, and dogs at dose levels considered to be low.

7. Pregnancy

PREMARIN should not be used during pregnancy. (See CONTRAINDICATIONS.) There appears to be little or no increased risk of birth defects in children born to women who have used estrogens and progestins as an oral contraceptive inadvertently during early pregnancy.

8. Nursing Mothers

PREMARIN should not be used during lactation. Estrogen administration to nursing women has been shown to decrease the quantity and quality of the breast milk. Detectable amounts of estrogens have been identified in the breast milk of women receiving estrogens. Caution should be exercised when PREMARIN is administered to a nursing woman.

9. Effects on Laboratory Tests

a. General

b. B. Laboratory Tests

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For nearly a half century, busy practitioners have trusted Contemporary OB/GYN to translate the latest research into outstanding patient care. We are dedicated to providing them with evidence-based information on scientific advances in a clinically useful format.
Individualizing hormone therapy: Weighing risks and benefits

DONNA SHOUPE, MD

A hormone therapy plan based on careful patient selection and other factors can help women achieve improved quality of life after menopause.

Screening for thyroid disease during pregnancy

PUBLICATIONS COMMITTEE, SOCIETY FOR MATERNAL-FETAL MEDICINE, WITH THE ASSISTANCE OF CYNTHIA GYAMFI-BANNERMAN, MD

Should thyroid function screening be done routinely in gestation?

Hysteroscopic myomectomy: Pearls and pitfalls from 24 years of practice

MORRIS WORTMAN, MD, FACOG

The author discusses his practices and preferences for performing hysteroscopic myomectomy.

Sex and the 50-something woman: Strategies for restoring satisfaction

JOHN E. BUSTER, MD

Sexual dysfunction after menopause can significantly impact women’s lives. Learn about available treatments and interventions to discuss with these patients.
You demand accuracy. That’s why Hologic offers a complete portfolio of cervical cancer screening products that are accurate by design. Including the ThinPrep® Pap Test, the ThinPrep Imaging System, the Cervista® HPV High Risk Test and the Cervista HPV 16/18 Genotyping Test. Communicate results that you and your patients can be confident in.

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1 See the ThinPrep, ThinPrep Imaging System, Cervista HPV HR and Cervista HPV 16/18 package inserts for additional information.

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**WHAT’S TRENDING**

1. **Subclinical PID may be linked to lower fertility rates**
   Undiagnosed pelvic inflammatory disease (PID) may be associated with lower fertility rates in women.
   [contemporaryobgyn.net/inflammatory](http://contemporaryobgyn.net/inflammatory)

2. **Stirrups during childbirth don’t cause more tears**
   Women who have their feet in stirrups during childbirth are no more likely to experience a tissue tear during the delivery than women whose feet are on the bed, according to a new study.
   [contemporaryobgyn.net/stirrups](http://contemporaryobgyn.net/stirrups)

3. **Melinda Gates pledges millions for contraception**
   Melinda Gates has pledged $560 million to expand access to contraception for women in poor countries around the world.
   [contemporaryobgyn.net/Gates](http://contemporaryobgyn.net/Gates)

4. **Law denying birth control coverage vetoed**
   Missouri’s Governor vetoed a bill denying insurance coverage for contraception.
   [contemporaryobgyn.net/Missouri](http://contemporaryobgyn.net/Missouri)

5. **Roche’s Avastin rejected for breast cancer**
   Avastin was rejected by UK’s healthcare cost agency as a first-line treatment for advanced breast cancer.
   [contemporaryobgyn.net/Avastin](http://contemporaryobgyn.net/Avastin)

6. **Trial halted for odanacatib**
   The trial of the osteoporosis drug odanacatib has shown that it reduces fracture risk, prompting the study to end early so all trial patients could be offered the treatment.
   [contemporaryobgyn.net/odanacatib](http://contemporaryobgyn.net/odanacatib)

7. **Toxoplasma gondii tied to self-harm, suicide attempts**
   Women with toxoplasmosis may be more likely to hurt themselves or attempt suicide, a new study of over 45,000 new mothers in Denmark suggests.
   [contemporaryobgyn.net/toxoplasmosis](http://contemporaryobgyn.net/toxoplasmosis)

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It’s time to turn OAB on its head.

OAB remains a problem for many patients

As the number of patients diagnosed with overactive bladder (OAB) continues to grow, so does the need for improved prevention, diagnosis, and management.¹ For many Americans now living with OAB, the disease can have a significant negative impact on their quality of life.²,³ Current OAB treatments may work well for some, but they are not for everyone.⁴

Why are many patients suffering despite current therapeutic options?

One potential reason is lack of persistence with OAB therapy.⁵ While discontinuation of therapy is a significant issue among patients with chronic conditions, OAB therapy has demonstrated a higher rate of discontinuation compared with other drug classes.⁵ In a 2008 study investigating discontinuation rates of OAB therapy in the UK,* the median time to discontinuation was 4.76 months, with 77% of patients discontinuing their OAB treatment by 1 year.⁶

References:

* A national health record database of women under the care of general practitioners in the UK (National Health Service).
By upholding the Affordable Care Act (ACA), otherwise known as Obamacare, the US Supreme Court defied conventional wisdom and most experts’ opinions. Far from resolving the issues about healthcare reform, the historic decision raised more eyebrows—and questions—than it resolves for the US healthcare system and our specialty.

Among the surprises was that Chief Justice John G. Roberts Jr, a strict constitutionalist, joined the court’s 4 liberal justices to form a 5-to-4 majority upholding most of the major provisions of the ACA. Justice Roberts and his colleagues argued that the Act’s most controversial provision—the individual mandate requiring most adults obtain insurance or pay a penalty when they file their tax returns—was constitutional. Interestingly, he ruled it constitutional based not upon Congress’s right to regulate interstate commerce (as proponents had argued) but on its power to levy taxes.

The second surprise was the concurrence by 7 of the justices that Congress had no constitutional authority to coerce individual states into participating in the Act’s second most controversial provision. That is, the requirement to expand Medicaid coverage to families whose household income falls below 133% of the federal poverty line (about $31,000 for a family of four). Rules and requirements for qualifying for adult Medicaid coverage currently vary from state to state.

Reaction to the Court’s decision was swift and entirely predictable. The right viewed it as a blow to constitutional government and the beginning of European-style socialism with a cradle-to-grave welfare state. The left argued that the decision was proof that the constitution actually works and would ensure access to high-quality care for most Americans. The truth is that we have no idea what this decision really portends.

**What will be the real impact of the individual mandate?**

In essence, the individual mandate requires that most legal residents of the United States obtain a minimal level of health insurance coverage. Those who fail to do so will owe a modest amount of additional income tax. (That is why Justice Roberts was correct in calling the mandate a tax.) However, a bevy of groups are excluded, such as prisoners, Native Americans, Christian Scientists, undocumented aliens, and those with so little income they don’t need to file tax returns. Also excluded are those who are required to contribute more than 8% of their household income for premiums for employer-provided health insurance. To help low-income families, the Medicaid income threshold will be raised to 133% of the federal poverty line and tax credits to purchase insurance in health exchanges will be made available to families with incomes between 133% and 400% of the poverty level.

The problem, however, is that the actual penalty/tax is lower than typical health insurance premiums. For example, the fixed-dollar penalty per individual family member is $95 in 2014, $325 in 2015, $695 in 2016, and indexed to inflation thereafter. Moreover, even that rather modest amount is reduced by 50% for anyone younger than age 18, and the per-family cap is 300% of the individual level. Thus, the ACA is hardly “the largest tax increase” in history, as claimed by...
EDITORIAL

The OTIS Studies 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, including:

- Autoimmune diseases, such as Rheumatoid Arthritis, Psoriasis, Psoriatic Arthritis, Ankylosing Spondylitis, Crohn’s Disease
- Asthma
- Meningitis Vaccine and HPV Vaccine
- H1N1 vaccine, seasonal influenza vaccine, or anti-viral medications

For more information about medication and/or vaccine use in pregnancy, or to enroll in one of our studies, call toll free (877) 311-8972 www.otispregnancy.org

Concerned about the use of medications and vaccines during pregnancy?

The OTIS Studies 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, including:

- Autoimmune diseases, such as Rheumatoid Arthritis, Psoriasis, Psoriatic Arthritis, Ankylosing Spondylitis, Crohn’s Disease
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Will states refuse to expand Medicaid coverage?
The bigger issue is how many states will eschew extending Medicaid coverage, given the Court’s decision to permit that action. At first blush, that would seem to be a non-issue. Why would even the most arch-conservative governor refuse federal dollars when the federal government would pick up the tab for almost all of the attendant increased costs? If the governor of South Carolina, for example, refused federal Medicaid funds, she essentially would be transferring her constituents’ hard-earned federal tax dollars to more liberal-minded states.

But the situation is more complex. Many residents of more conservative states who are currently eligible for Medicaid choose not to enroll because they are healthy, don’t want “charity,” or do not want to be exposed to requisite eligibility scrutiny. Faced with the prospect of a tax penalty for not having health insurance, though, they may want to enroll. Estimates indicate that the cost to the State of Ohio for ACA will rise from $370 million in 2014 to $570 million in 2015 as more Medicaid-eligible residents begin enrolling. Of course, it’s also possible that the state will incur many of these costs even if it does not accept the new federal money.

Moreover, physician and hospital groups will likely put substantial pressure on their state governments to accept federal Medicaid funding because it represents a new revenue source. Hospitals are especially committed to expansion because they will lose their disproportionate share payments in any case. It’s hard to predict exactly how individual states will react when presented with the actual economic impact of expanding coverage and not just the overheated, empty rhetoric of politicians on both sides who want to “demagogue” the issue. My guess is that almost all states will expand coverage—but that is a guess.

Would a Republican Congress and president really dismantle the ACA?
Despite the Republican Party’s current posturing, don’t assume that the ACA will be entirely dismantled if the
November elections result in a Republican landslide. Many of the Act’s provisions are already very popular, according to polling data. Particularly popular components include protection against being denied coverage because of a pre-existing condition, tax credits for small businesses and low-income families to purchase insurance, closure of the Medicare prescription drug coverage “donut hole,” increased access to preventative services, extension of family health insurance coverage to children aged younger than 26 years, and a requirement that insurers spend at least 80% of premium dollars on medical care rather than excess administrative overhead and profits. Those components of the ACA are likely to play an important role in the election debate.

How will the decision affect physicians?
The short answer is not very much. In many ways, the cat is already out of the bag. As has been pointed out repeatedly by myriad experts, the costs of healthcare in this country are simply not sustainable. At the heart of excessive costs is our inefficient, wasteful and occasionally unsafe fee-for-service delivery system. Payment reforms that limit the cost of care—such as bundled physician-hospital payments, accountable care organizations, value-based care, and global payments (a nice way to say capitation)—are now being driven by employers and not just the government. To provide that care, our entire healthcare delivery system needs to be re-engineered with an emphasis on large-scale, high-quality, patient-centered care which is critically dependent on robust information systems. In this new world, the expectation will be better outcomes and more satisfied patients through delivery of fewer interventions and a lower cost—no easy task.

Expense reduction has become the mantra of health system executives. The “word on the street,” according to top health consultants, is that reductions in Medicare and commercial payments could be on the order of 20% to 40% in the next few years. So, expenses need to be reduced by a comparable amount. That helps explain the renewed consolidation and merger frenzy among health systems and the rush to employ physicians and install regional health information exchanges.

Ob/gyns have skin in this game at multiple levels. Fully 40% of deliveries are funded by Medicaid, so we should support extension of coverage for financial as well as humanitarian reasons. Many of our patients are young and have modest incomes, and they may be deferring childbearing because of unstable economic conditions, lack of or inadequate health insurance or uncertainty about continued coverage. Implementation of the ACA’s various provisions could increase obstetrical volume. That, in turn, could increase workforce requirements for obstetricians and midwives.

On the other hand, bundled payments for gynecological surgery will mean lower payments and global fees, and capitation will temper demand for gynecological procedures in favor of medical or interventional radiological interventions. These changes, coupled with progressive alignment of physician groups with health systems and the use of hospitalists, could paradoxically reduce workforce requirements.

Take home message
The recent Supreme Court decision raises as many questions as it answers. But regardless of its impact or that of the impending presidential and Congressional elections, healthcare delivery in the United States is changing rapidly and the focus will be squarely on cost. That will lead to new payment and delivery models, which will impact ob/gyn practices in many ways, some predictable and some not.

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

REFERENCES
Does Endometrial Injury Improve ART Outcomes?

The answer to that question seems to be yes, and the impact may be influenced by the timing of the biopsy or curettage, according to the results of a Cochrane Collaboration review. The researchers analyzed 5 randomized controlled trials (RCT) comparing intentional endometrial injury before embryo transfer in women undergoing assisted reproduction with no intervention or with a simulated procedure that could not cause endometrial injury.

In 4 of the trials, endometrial injury was performed within 1 month before the start of ovulation induction, whereas in the fifth trial, it was performed on the day of oocyte retrieval. Analysis of these 2 subgroups showed a significant increase in odds of live birth and clinical pregnancy for injury in the previous cycle (2 trials, Peto OR 2.45; 95% CI 1.28 to 4.72; I² = 0% and 4 trials, Peto OR 2.51; 95% CI 1.71 to 3.97; I² = 0, respectively). In contrast, injury on the day of oocyte retrieval was associated with a significant reduction in odds of clinical pregnancy (1 trial, Peto OR 0.30; 95% CI 0.14 to 0.63) and of ongoing pregnancy (1 trial, Peto OR 0.28; 95% CI 0.13 to 0.61). No meaningful conclusions could be drawn about odds of miscarriage per clinical pregnancy or multiple pregnancy per clinical pregnancy.

In women undergoing assisted reproduction, the Cochrane researchers concluded, endometrial injury should done before the embryo transfer cycle because it increases clinical pregnancy and live birth rates. Evidence is insufficient, however, to determine the effect of the procedure on rates of multiple pregnancy or miscarriage.


Commentary: This Cochrane review demonstrated a benefit (increased clinical pregnancy and live birth rates) from endometrial injury in women undergoing ART. The timing of this low-grade endometrial injury is important, with a deleterious effect noted if injury is performed within 3 days of the embryo transfer. While these are compelling findings, they must be regarded with caution in light of a conservative number of observed events, as only 50 live births were reported.

-Laurie McKenzie, MD

Jury Still Out on Benefits of Exercise for Prevention of Gestational Diabetes

Data are limited and evidence inconclusive on whether exercise prevents glucose intolerance in pregnant women. So say the results of a Cochrane Collaboration analysis of outcomes from the 5 existing randomized trials in this area, representing experience in more than 1,000 women.

Randomized and cluster-randomized trials assessing the effects of exercise for preventing pregnancy glucose intolerance or gestational diabetes mellitus (GDM) were identified based on a search of the Cochrane Pregnancy and Childbirth Group’s Trials Register, ClinicalTrials.gov, and the WOMBAT Perinatal Trials Registry. Risk of bias was moderate in all 5 trials selected, of which had small sample sizes and 1 of which recruited 855 women and babies.

The analysis found no significant difference in GDM incidence (three trials, 826 women, RR 1.10, 95% CI 0.66 to 1.84), cesarean section (two trials, 934 women, RR 1.33, 95% CI 0.97 to 1.84), or operative vaginal birth (two trials, 934 women, RR 0.83, 95% CI 0.58 to 1.17) between women who received additional exercise interventions and those who received routine antenatal care. No significant differences in insulin sensitivity were found in any of the trials. In the single large trial, no significant difference was seen in incidence of developing pregnancy hyperglycemia not meeting GDM diagnostic criteria, preeclampsia, or admission to the neonatal ward.

Conclusive evidence is not available to guide practice on exercise as an intervention for prevention of GDM, concluded the Cochrane researchers. Larger, well-designed randomized trials with standardized behavioral interventions to assess the effects of exercise on GDM and other adverse pregnancy are needed, they said, noting that seven such studies are in progress and likely to be included in the Cochrane’s next update on the subject.

A Tocolysis Crisis

THE FACTS
The plaintiff was a patient whose 14-week twin gestation was confirmed via ultrasonography (U/S) at codefendant Hospital A on February 23, 2005, where she subsequently received all regular prenatal care. Her previous obstetric history included 4 pregnancies—2 live births and 2 spontaneous abortions.

At approximately 9:55 p.m. on April 28, 2005, at 23 weeks’ gestation, the patient presented to Hospital B’s Emergency Department via ambulance with a complaint of vaginal bleeding. At 10:15 p.m., she was transferred to the Labor and Delivery (L&D) Unit and examined by Dr. B. He recorded the gestational age, ensured that the patient’s vital signs were taken, and ordered laboratory tests, a non-stress test, and 4 doses of dexamethasone (1 dose every 12 hours) to promote lung maturity and decrease risk of intraventricular hemorrhage in the advent of early delivery. Ampicillin was begun for prophylaxis against Group B beta-streptococcus. Dr. B also ordered an immediate intravenous (IV) loading dose of 4 g magnesium sulfate in an attempt to delay preterm delivery and admitted the plaintiff to the L&D Unit. Cervical examination performed between 10:35 p.m. and 10:45 p.m. revealed 2- to 3-cm dilation and the patient was transferred to a birthing room.

Dr. B. next ordered IV administration of 2 g magnesium sulfate per hour as a maintenance dose following the loading dose. Later in the evening, he eventually increased the maintenance dose to 3 g magnesium sulfate per hour. The first dose of dexamethasone was administered at approximately 12 a.m. However, the nurse’s note indicated that administration of the initial 4-g loading dose of magnesium sulfate was delayed. It was not given to the patient until 12:30 a.m. and the increased maintenance dose was administered at 2:25 a.m.

Dr. B saw the patient again at 2 a.m. and 4 a.m. and performed the next cervical examination at 7 a.m., at which time the woman was fully dilated and experiencing irregular contractions. Throughout the course of the evening, she refused to consent to the possibility of cesarean delivery, despite the small size of the fetuses, the breech position of “Twin A,” and the likelihood that the fetuses would not survive a vaginal delivery.

The second dose of dexamethasone was administered at approximately noon on April 29, 2005. Throughout the day and up to the time the patient was taken into the operating room, a fetal heart rate (FHR) monitor indicated no sign of fetal distress. At noon and 3:30 p.m., U/S were taken that showed normal sonographic appearance, concordant growth, and malpresentation of Twin A. At 8:10 p.m., the patient’s magnesium levels were noted to be elevated (7.6) and nonparty Obstetrician C ordered temporary discontinuance of magnesium sulfate.

By 10:05 p.m., the patient had a bloody show, with fetal membranes bulging into her vagina. At that time, the decision was made to deliver the fetuses. The patient’s membranes spontaneously ruptured at 11:21 p.m., and at 11:22 and 11:23 p.m. After speaking with the head of perinatol-
Before you operate, the ovarian mass often whispers helpful advice. We merely turn up the volume.

OVA1 is an FDA-cleared* blood test to help you assess the probability that ovarian masses are malignant or benign prior to a planned surgery. When combined with a physician’s assessment, OVA1 achieved 96% sensitivity and 95% negative predictive value across a broad range of ovarian cancers.\(^1\) Adding OVA1 to your presurgical assessment may help determine whether referral to an oncologist is the best course of action. For more ovarian mass talking points, visit Ova-1.com.

*FDA clearance does not denote official approval.

Intended Use: OVA1 is a qualitative serum test that combines the results of 5 immunoassays into a single numerical result. It is indicated for women who meet the following criteria: over age 18, ovarian adnexal mass present for which surgery is planned, and not yet referred to an oncologist. OVA1 is an aid to further assess the likelihood that malignancy is present when the physician’s independent clinical and radiological evaluation does not indicate malignancy.


PRECAUTION: OVA1 should not be used without an independent clinical/radiological evaluation and is not intended to be a screening test or to determine whether a patient should proceed to surgery. Incorrect use of OVA1 carries the risk of unnecessary surgery, and/or delayed diagnosis.
ogy at the hospital between 11:30 p.m. and 12:15 a.m., the patient consented to cesarean section and delivered 2 live twins. Infant A weighed 1 lb, 3 oz; Infant B died hours after his birth of pulmonary hemorrhage.

**ALLEGATIONS**

It was alleged that because defendant B did not timely administer magnesium sulfate to the plaintiff, she delivered Infant A prematurely, which resulted in uncontroverted developmental delays and brain damage. The claim also was made that Hospital B (not our client) improperly cared for Infant A in the neonatal intensive care unit, resulting in ischemia and loss of digits of the right hand.

**TRIAL**

Dr. B testified that he first came in contact with the patient at approximately 10:30 p.m. on April 28 in the hospital’s L&D triage area. He spent about 15 or 20 minutes assessing the patient, including taking a history and performing a speculum vaginal exam, during which he determined that she was already 2- to 3-cm dilated, without contractions. As a consequence, he ordered that the patient be transferred to a L&D room, where an IV was to be started by the nurses for administration of both ampicillin and magnesium sulfate. The magnesium sulfate was to be administered as a “loading dose” of 4 g, followed by maintenance of 2 g per hour. In addition, he ordered that the plaintiff receive dexamethasone injections beginning 12 hours thereafter, until 4 doses had been administered. The doctor testified that at the time he gave this order, he felt there was little likelihood that the pregnancy could be maintained until all 4 doses were administered, but would have been happy if the patient received at least 2 doses of dexamethasone. In the event, only 2 doses of dexamethasone were ultimately administered.

It was the plaintiff’s expert’s opinion that Dr. B delayed in not “promptly” seeing to it that the magnesium sulfate was administered to the patient. It was his opinion that the loading dose was not administered until 12:30 a.m. on April 29, and as a consequence of this “delay” in the drug’s administration, the infant plaintiff suffered from major developmental delays and brain damage.

On cross-examination, we were able to establish that the plaintiff’s expert could not state with any degree of medical certainty as to whether—even if the magnesium sulfate had been administered when he said it should have been administered—the pregnancy could have been delayed “2 minutes, 2 hours, or 2 days.” We then established that he would have been satisfied if the magnesium sulfate was administered within 30 to 40 minutes after the mother had been admitted to Labor Room 3, which did not take place until 11 p.m., based upon the time noted in the nursing L&D flow sheet.

We got the plaintiff’s expert to admit that he would have been satisfied that good and accepted medical practice had been adhered to if, in fact, the magnesium sulfate was administered at some point between 11:20 p.m. and 11:40 p.m. He admitted that his basis for testifying, on direct, that the loading dose of magnesium sulfate had not been administered until 12:30 a.m. was the written testimony of the Nurse and one of the pages of the L&D chart, the single-stat-preop order sheet. The defense maintained that the Nurse wrote this entry at 12:30 a.m. on April 29 and it was not meant to reflect when the loading dose had begun. The plaintiff’s expert was unfamiliar with the specifics of the I&O sheet and the L&D flow sheet and was forced to admit that, assuming the accuracy of these 2 pages of the hospital chart, an argument could be made that the loading dose was, indeed, started at some point between 11:20 p.m. and 11:30 p.m.

The plaintiff’s expert also admitted that the loading dose is always administered before the maintenance dose, that the loading dose takes approximately 30 minutes to administer, and that according to the aforementioned nursing flow sheet, the maintenance dose was certainly running by midnight on April 29. The Nurse testified in support of that position and we produced a pediatric neurologist who opined that the infant suffered from autism. Our obstetric expert supported Dr. B and added that the timing of administration of the magnesium sulfate was irrelevant because it is not particularly effective as a tocolytic.

We were ultimately able to achieve a unanimous defense verdict for Dr. B.

**Editor-In-Chief’s Note** This case is a perfect example of the fundamental flaws in our tort system. First, autism is not caused by preterm delivery, thus, there is no causality and the entire case was unwarranted. Second, although magnesium sulfate should not be used as a tocolytic because it does not work, that was not what was at issue. Rather, when this ineffective agent should have been started is what was in contention.

**MR KAPLAN** is a partner at Aaronson, Rappaport, Feinstein & Deutsch, LLP, specializing in medical malpractice defense and healthcare litigation.
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Individualizing hormone therapy: Weighing risks and benefits

Many women would benefit from hormone therapy during and after menopause. A hormone therapy plan based on careful patient selection, accurate risk-benefit analysis, and risk-minimizing strategies can help them to achieve improved quality of life.

By Donna Shoupe, MD

As women transition into menopause, a gradual, but substantial reduction in ovarian hormone production occurs, precipitating a wide range of symptoms that can affect daily activities and quality of life. Loss of ovarian hormones, progesterone and estrogen, also sets in motion a change in bone metabolism, leading to physiologic losses of bone density and strength. In addition, tissues throughout the body, including those of the urogenital, integumentary, vascular, and central nervous systems, also are negatively affected by a loss of ovarian hormones (Table 1).

Whether hormone therapy (HT) can be safely used to prevent these changes is an important question facing menopausal women and their healthcare providers. However, there is no single correct answer; each woman and her physician must decide whether HT is an appropriate treatment option for her. A large volume of scientific evidence addresses this question; the answer to it depends on performing an accurate risk-benefit analysis. When performing this assessment, it is important to consider 3 factors that profoundly affect the risk-benefit profile for HT: age at initiation, hormone dose, and route of administration.

Age at HT initiation

The beneficial action of estrogen is its ability to prevent changes in healthy tissue. Estrogen deficiency over a period of many years may result in significant, irreversible changes such as bone loss, vaginal and bladder atrophy, and reduced elasticity in the skin. By administering HT to restore the lower levels of premenopausal estrogen, tissue damage can be slowed or halted. The timing of initiation of HT is critical to understanding the therapeutic action of hormones. This timing hypothesis is supported by large numbers of studies that consistently show a therapeutic window for initiation of therapy for several types of tissues, including bone and skin, and the urogenital, cardiovascular, and central nervous systems. Starting HT by age 60 or within 10 years of the onset of menopause maximizes the risk-benefit profile.

HT dosage

A second important influence on the HT risk-benefit profile is the dose of estrogen and progestin. Evidence is substantial that low-dose HT is effective in preventing bone loss and treating menopausal symptoms with less bleeding and other side effects than higher doses. More important, lower doses are also associated with lower risks.

The Nurses’ Health Study (NHS) was a prospective, observational cohort study of 70,533 postmenopausal women that investigated dura-
Illustration for contemporary OB/GYN by Adam Questell, Akyu Design

Route of HT administration
The route of administration of HT is particularly important to potential users who have CVD, multiple cardiovascular risk factors, history of venous thromboembolism (VTE), or known thrombophilic mutations. Women with cardiovascular or thrombotic risk factors or those starting therapy after age 60 or more than 10 years after the onset of menopause may be candidates for low-dose transdermal estrogen because the transdermal route has been shown to have a lower risk of VTE than oral administration. Use of transdermal estrogen also has an additional safety benefit in that it avoids the hepatic "first pass" effect, and thus, associated changes in clotting factors and other hepatic proteins. Studies show no increased risk of blood clots and VTE, even in high-risk postmenopausal women, when transdermal estrogen is used.

Accurate evaluation of HT benefits
If started within the therapeutic window, estrogen therapy has established benefits reported in multiple studies. Among these are relief of menopausal symptoms, protection from bone loss and osteoporotic fracture, and protection from and treatment of urogenital atrophy. In addition, studies have reported that estrogen therapy can prevent CVD; decrease overall mortality; lessen menopause-related fat redistribution; protect against menopause-related collagen loss in skin and subsequent wrinkling; lower rates of arthritis, colon cancer, and tooth loss; decrease rates of Parkinson disease, dementia, and Alzheimer’s disease; and prevent short-term memory loss and improve cognitive thinking.

Estrogen, in a variety of forms, is approved by the US Food and Drug Administration (FDA) for prevention of menopause-related bone loss and osteoporosis. The Women’s Health Initiative (WHI) reported significant reductions in fractures in women treated with estrogen therapy in a general menopausal population (without known osteoporosis). The WHI study noted fewer than 44 to 47 total fractures and fewer than 5 hip fractures per 10,000 women-years in study participants taking combined HT, and fewer than 6 hip fractures and 56 fewer osteoporosis-related fractures overall in the estrogen-alone arm.

Further, in terms of protection against bone loss and fracture, estrogens are not associated with the atypical femoral fractures, mandibular osteodysplasia, and esophageal cancer that have been attributed to use of bisphosphonates for bone protection.

More than 40 years of clinical trials report significant cardiovascular protection from estrogen-only therapy in menopausal women, particularly if the dose is low and therapy is started within the therapeutic window. The ELITE and KEEPS trials are ongoing prospective randomized trials designed to better document and define the cardiovascular benefits of HT.

The WHI reported a non-significant reduction in cardiovascular disease (5 fewer cases/year per 10,000 women/years) in women on estrogen-only therapy compared with placebo during the intervention phase. During the post-intervention phase, the results varied significantly by age, although there continued to be no significant difference in the overall rates of heart disease between the estrogen-only and placebo group. Women in their 50s had a significantly reduced rate of heart attacks, while those in their 70s had an increased risk.

New findings from the WHI coronary artery calcification study recently reported a cardi-protective effect in women initiating therapy between ages 50 and 59. After an average of 8.7 years, those in the estrogen-only cohort had significantly lower coronary...
TABLE 1  Reported adverse effects of short- and long-term ovarian hormone deficiency

<table>
<thead>
<tr>
<th>Vascular</th>
<th>Bladder</th>
<th>Skeletal</th>
<th>Skin/Soft tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hot flushes</td>
<td>Atrophy</td>
<td>Bone loss</td>
<td>Skin atrophy</td>
</tr>
<tr>
<td>Night sweats</td>
<td>Itching</td>
<td>Osteoporosis</td>
<td>Decreased elasticity</td>
</tr>
<tr>
<td>Headaches</td>
<td>Dryness</td>
<td>Hip fracture</td>
<td>Decreased muscle mass</td>
</tr>
<tr>
<td>Rapid heartbeat/Palpitations</td>
<td>Bleeding</td>
<td>Vertebral fracture</td>
<td>Death (Arthritis/Joint pain)</td>
</tr>
<tr>
<td>Fat redistribution</td>
<td>Infection</td>
<td>Back pain</td>
<td>Fat redistribution</td>
</tr>
<tr>
<td>Decreased muscle mass</td>
<td>Discharge</td>
<td>Loss of height</td>
<td>Decreased muscle mass</td>
</tr>
<tr>
<td>Incontinence</td>
<td>Urgency</td>
<td>Immobility</td>
<td>Skin atrophy</td>
</tr>
<tr>
<td>Urinary tract symptoms</td>
<td>Infections</td>
<td>Decreased mobility</td>
<td>Decreased muscle mass</td>
</tr>
</tbody>
</table>

Psychological  Social  Cardiovascular  Central nervous system  Breast

<table>
<thead>
<tr>
<th>Mood changes</th>
<th>Dyspareunia</th>
<th>Accelerated atherosclerosis</th>
<th>Short-term memory loss</th>
<th>Breast pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss of well being</td>
<td>Decreased libido</td>
<td>Cardiovascular disease and death</td>
<td>Dementia</td>
<td>Atrophy</td>
</tr>
<tr>
<td>Fatigue</td>
<td></td>
<td></td>
<td>Alzheimer disease</td>
<td></td>
</tr>
<tr>
<td>Irritability</td>
<td></td>
<td></td>
<td>Macular degeneration</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td></td>
<td></td>
<td>Blindness</td>
<td></td>
</tr>
<tr>
<td>Loss of well being</td>
<td></td>
<td></td>
<td>Insomnia</td>
<td></td>
</tr>
</tbody>
</table>

TABLE 2  Dose-related risk of oral estrogen therapy and CVD

<table>
<thead>
<tr>
<th>Dose</th>
<th>Major CVD RR (95% CI)</th>
<th>Stroke RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Estrogen, 0.625 mg</td>
<td>0.54 (0.44-0.67)</td>
<td>1.35 (1.08-1.68)</td>
</tr>
<tr>
<td>Estrogen, 0.3 mg</td>
<td>0.58 (0.37-0.92)</td>
<td>0.43 (0.22-0.83)</td>
</tr>
<tr>
<td>Estrogen, &gt;1.25 mg</td>
<td>0.62 (0.45-0.84)</td>
<td>1.63 (1.18-2.26)</td>
</tr>
<tr>
<td>Estrogen plus progestin</td>
<td>0.91 (0.75-1.11)</td>
<td>1.45 (1.10-1.92)</td>
</tr>
</tbody>
</table>

Abbreviations: RR, relative risk; CI, confidence interval.
Data from Grodstein et al.21

artery calcium scores than those receiving placebo. The odds ratio for high levels of coronary artery calcium was 30% to 40% lower in intention-to-treat analyses (83.1 vs 123.1; P=0.02). Women who adhered to therapy for at least 5 years had a 64% reduction in coronary artery calcium score (P=0.01). Both arms of the WHI study reported a major reduction in new cases of diabetes during the 7-year trial. This is an important morbidity that was omitted from the arbitrary and invalidated "global index" used by the authors.30,40

Among the 70,533 women followed for 20 years in the NHS, a 0.3-mg dose of conjugated estrogen was associated with an age-adjusted significant reduction in major coronary disease (relative risk [RR], 0.46; 95% confidence interval [CI], 0.29-0.72) and all stroke (RR, 0.43; 95% CI, 0.22-0.83) (see Table 2).15

Further, Hodis, et al reported on a randomized trial of 222 postmenopausal women who were at least 45 years of age and had no preexisting cardiovascular disease and low-density lipoprotein cholesterol levels ≥130 mg/dL. The average rate of progression of subclinical atherosclerosis was significantly lower in those taking estradiol compared with the placebo group (−0.0017 mm/year vs 0.0036 mm/year). Among 77 women not taking lipid-lowering medication, the difference in average rates of progression between the estrogen and placebo groups was +0.0147 mm/y (95% CI, 0.0055 to 0.0240) (P=0.002).21

In a meta-analysis of 23 randomized, controlled trials, women starting HT within 10 years after the start of menopause or younger than age 60 had significantly lower risk of CVD (Table 3). This study included 39,049 participants who were followed for 191,340 patient-years, and concluded that HT reduced the risk of coronary heart disease (CHD) events in younger postmenopausal women (odds ratio [OR], 0.68; 95% CI, 0.48–0.96). In older women, HT increased the risk of CHD events in the first year (OR, 1.47; 95% CI, 1.12–1.92), then reduced events after 2 years (OR, 0.79; 95% CI, 0.67–0.93).

Numerous studies report that estrogen therapy started within the therapeutic window reduces short-term memory loss, improves cognitive thinking, and reduces the long-term risk of dementia and Alzheimer’s disease.16,30 For example, in a prospective study of dementia in 1,357 men and 1,889 women (mean age, 73 years), the incidence of dementia in women increased after age 80 and exceeded incidence in men of similar age. However, women who used HT had an overall 50% reduction in risk of dementia (hazard ratio [HR], 0.59; 95% CI, 0.36–0.96). Although prior hormone use was associated with reduced risk of dementia, current hormone use showed no benefit unless usage exceeded 10 years. At that point, women’s sex-specific increase in risk disappeared entirely. Adjusted hazard ratios in this group were 0.41 (95% CI, 0.17–0.86) for hormone users compared with nonusers 0.77 (95% CI, 0.31–1.67).30

In a population cohort of women aged 65 and older, Carlson et al reported that lifetime hormone exposure was associated with improved global cognition and attenuated the age-related decline in cognition over a 3-year study interval.32

Evidence suggests that when HT is started within the therapeutic window, postmenopausal women have a lower mortality rate. This is largely attributed to estrogen’s cardiovascular protection. For example, 10-year follow-up of 48,470 postmenopausal women from the NHS reported that the age-adjusted relative
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Risk of all-cause mortality in women who used estrogen at any time was 0.81 and cardiovascular mortality was 0.68. After adjusting for other risk factors, the relative risks remained significant. Age-adjusted relative risk of cardiovascular mortality was 0.52 for current estrogen users and 0.77 for former users.

Pooled data from 30 trials with 26,708 participants showed that the odds ratio for total mortality associated with HT was 0.98 (95% CI, 0.87-1.12); however, HT reduced mortality in women younger than age 60 (OR, 0.61; 95% CI, 0.39-0.95) and older (OR, 0.70 for women 50-59 years; 1.05 for women 60-69 years; 1.14 for women 70-79 years; P for trend =.06).

A secondary analysis of the WHI was performed to determine whether the effects of HT on risk of CVD and mortality vary by age or years since menopause. Rossouw et al found a non-significant tendency for the effects of HT on total mortality to favor younger over older women (HR, 0.70 for women 50-59 years; 1.05 for women 60-69 years, and 1.14 for women 70-79 years; P for trend =.06).

In a WHI follow-up study, women starting estrogen between ages 50 to 59 had 12 fewer heart attacks, 13 fewer deaths, and 18 fewer adverse events overall than those taking placebo (expressed as absolute rates per 10,000 women annualized over the 10.7-year follow-up period).

The WHI study reported a significantly reduced risk of colon cancer in women on combination HT (6 less women per 10,000). Other studies have also reported a lower risk of colorectal cancer in women after long-term HT. The estrogen-only arm of the WHI study did not show this benefit.

During the intervention phase of the WHI study, there was a non-significant reduced incidence of breast cancer in women taking estrogen alone, compared with those taking placebo (−7/10,000 women-years). This trend continued throughout the post-intervention phase. At the end of 10.7 years of follow-up, the women who had taken estrogen alone had a significantly reduced risk of breast cancer.

**Risks of HT**

Initiation of HT in women older than age 60 and in those more than 10 years from menopause is associated with less overall benefit and more risks, especially cardiovascular risks. Initial reports from the WHI were not stratified by age of initiation or years since menopause, and reported overall risk for the entire study population. The highest risks reported in the early studies for both the estrogen-plus-progestin and the estrogen-only arms were increased risk of blood clots/VTE events, stroke, and heart disease (Table 5).

Specifically, the WHI reported that in the overall study population, estrogen with and without progesterone increased risk of blood clots (+18 and +7 per 10,000 women-years, respectively) and stroke (+8 and +12 per 10,000 women-years, respectively). Treatment with estrogen plus progesterin also resulted in a higher risk of heart disease (+7 per 10,000 women-years) and breast cancer (+8 per 10,000 women-years). Notably, risk of breast cancer was not increased in the estrogen-only arm.

Although combined HT did not increase endometrial cancer risk, it did increase risk of abnormal vaginal bleeding requiring further testing. In addition, an increased risk of ovarian cancer was not found in either the combined-estrogen-plus-progestin or estrogen-only cohorts.

In an 11-year follow-up study, the death rate in participants who took estrogen plus progesterone for 5 years during the intervention phase was 2.6 per 10,000 women/year compared with 1.3 per 10,000 women-years in the placebo group (HR, 1.96; 95% CI, 1.00-4.04; P=.049). Further, in women who developed breast cancer, 24% of those in the combined HT cohort had tumors that spread to the lymph nodes, compared with 16% of women taking placebo. In a WHI post-hoc analysis, Chlebowski et al reported that in women who had 5 years of combined HT and 3 years of follow-up, the risk of developing lung cancer was not increased, although the risk of dying from lung cancer was increased. Estrogen alone did not increase the risk of lung cancer or of dying of the disease.

In a separate substudy of the WHI, women aged 65 and older (average age, 73 years) who took combined HT had a modestly increased risk of developing dementia, compared with those taking placebo (45 per 10,000 women-years vs 22 per 10,000 women-years).

More recent publications of the WHI have included a number of studies that analyzed the data based on the age at initiation of HT. It is clear from these studies that the risks of treatment, primarily those related to

| TABLE 3 CVD events associated with HT in younger versus older women* |
|-----------------------------|-----------------------------|
| HT vs control               | OR (95% CI)                 |
| All ages                    | 0.99 (0.88-1.11)            |
| >10 years since menopause   | 1.03 (0.91-1.16 in those >60 years old |
| <10 years since menopause   | 0.68 (0.48-0.96) in those <60 years old |
| Younger vs older women      | 0.66 (0.46-0.95)            |

*Meta-analysis of 23 randomized controlled trials (191,340 patient-years). Abbreviations: CVD, cardiovascular disease; HT, hormone therapy; OR, odds ratio; CI, confidence interval. Data from Salpeter et al.
CVD, are profoundly affected by the age at initiation of treatment. The absolute risks of CVD as reported in the estrogen plus progestin, estrogen alone, and combined studies are shown in Table 6.37 There is no increased risk of CVD in women—in fact, often there are reported decreases—if estrogen or estrogen plus progestin is initiated within 10 years of menopause. Table 6 shows the profound effect of age at initiation on differences of CVD, stroke, VTE events, breast cancer, mortality, and global index.

**Individualizing HT options**
A decision about whether to initiate HT should be based on an accurate assessment of the risks and benefits of HT. As previously shown, initiation of HT for treatment of menopausal symptoms in early menopause or perimenopause is associated with low risk and a host of potential beneficial effects. A decision about whether to continue HT for a longer time also should be based on risk-benefit analysis and consideration of low-risk strategies.

Recent consensus statements on HT better reflect balanced re-analyses of all published data from the WHI and other studies on the topic. The North American Menopause Society and the International Menopause Society concur that the risk–benefit ratio is in favor of HT, particularly estrogen therapy, when initiated near the time of menopause.45 In addition, estrogen is FDA-approved for prevention of bone loss and urogenital atrophy and to treat menopausal symptoms.

Multiple studies support the protective effect of estrogen therapy on CVD, dementia and overall mortality if therapy is started within 10 years of menopause or in women younger than age 60. The overall risks associated with low-dose estrogen are low if it is started within 10 years of menopause or in women younger than age 60 year. Women with cardiovascular or thrombotic risk factors, those initiating therapy after age 60 years or more than 10 years since menopause, or those who are morbidly obese can consider low-dose transdermal estrogen after a complete risk-benefit analysis is done.

Finally, women who have undergone oophorectomy or experience premature menopause have increased health risks at an earlier age than those who reach natural menopause near the average age of about 50. These include an increased risk of CHD and conditions related to estrogen and testosterone deficiency (Table 1).

**Available options**
Compounding pharmacies often offer a combination of estradiol, estrone, and estriol with or without progestosterone or testosterone, which can be formulated in transdermal creams or gels or in capsules to be taken orally. Although many women feel more comfortable with these “natural” options, there is no evidence that they are more beneficial than FDA-approved products.

Compounding pharmacies report that they “individualize” the hormones to a particular patient’s needs. The guidelines for this practice are unclear. Monitoring the dose is recommended because the doses can vary among pharmacies.

Women with an intact uterus are generally given estrogen with a progestin for endometrial protection. Continuous combined, intermittent, and cyclic regimens are available as oral or transdermal therapy. Estradiol is available in oral form, patches, creams, gels, mist, and in a vaginal ring. FDA-approved estrogen options include conjugated estrogen, esterified estrogen, and estropipate. Products containing DHEA-S are available without a prescription.

**TABLE 4 Total mortality in HT users**

<table>
<thead>
<tr>
<th>HT use vs nonuse</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All ages</td>
<td>0.98 (0.87-1.18)</td>
</tr>
<tr>
<td>&lt;60 years</td>
<td>0.61 (0.39-0.96)</td>
</tr>
<tr>
<td>&gt;60 years</td>
<td>1.03 (0.90-1.18)</td>
</tr>
</tbody>
</table>

*Meta-analysis of 30 randomized controlled trials (119,118 patient years).

Abbreviations: HT, hormone therapy; OR, odds ratio; CI, confidence interval.

<table>
<thead>
<tr>
<th>Data from Rossouw et al44; Anderson et al.40</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>TABLE 5 Women’s Health Initiative risk in perspective</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Estrogen plus progestin*</th>
<th>Estrogen only*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVD</td>
<td>+7</td>
</tr>
<tr>
<td>Stroke</td>
<td>+8</td>
</tr>
<tr>
<td>VTE</td>
<td>+18</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>+8</td>
</tr>
</tbody>
</table>

*Excess number per 10,000 women compared with women not using hormones.

Abbreviations: CVD, cardiovascular disease; VTE, venous thromboembolism.

Data from Rossouw et al44; Anderson et al.40
INDIVIDUALIZING HORMONE THERAPY

TABLE 6 HT and cardiovascular risk: effect of age at initiation

<table>
<thead>
<tr>
<th>WHI estrogen + progestin</th>
<th>Absolute risk*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Years since menopause</td>
<td></td>
</tr>
<tr>
<td>&lt;10</td>
<td>~4</td>
</tr>
<tr>
<td>10–19</td>
<td>7</td>
</tr>
<tr>
<td>20</td>
<td>30 (P=0.05 for trend)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>WHI estrogen only</th>
<th>Absolute risk*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Years since menopause</td>
<td></td>
</tr>
<tr>
<td>&lt;10</td>
<td>~14</td>
</tr>
<tr>
<td>10–19</td>
<td>~1</td>
</tr>
<tr>
<td>20</td>
<td>7 (P=0.15 for trend)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>WHI combined studies</th>
<th>Absolute risk*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Years since menopause</td>
<td></td>
</tr>
<tr>
<td>&lt;10</td>
<td>~6</td>
</tr>
<tr>
<td>10–19</td>
<td>4</td>
</tr>
<tr>
<td>20</td>
<td>17 (P=0.02 for trend)</td>
</tr>
</tbody>
</table>

*Per 10,000 women-years of HT. Data from Rossouw et al.7

this indication, but multiple trials have confirmed the efficacy of this option.

Although testosterone replacement in aging men has become popular, and several approved transdermal products are available, the only FDA-approved testosterone for women is in a combination of esterified estrogens and methyltestosterone. A testosterone-releasing patch designed to increase sexual desire is currently approved in Europe.

Many pharmacies will compound transdermal creams or gels containing testosterone (usual doses range from 1 to 3 mg/ day). The age-related decline in testosterone in women and men is associated with adverse effects on muscle and bone, skin, mood, energy, sense of well being, cognitive thinking, sexual desire, and libido.

Women who have undergone oophorectomy are at highest risk of hormone deficiency-related conditions, including osteoporosis and urogeital atrophy. Clinicians should consider discussing estrogen and testosterone therapy with these patients.

Strategies to minimize risks

Many women desire the benefits associated with HT, including protection from CVD, osteoporosis, bone fractures, urogeital atrophy, skin atrophy, dementia, and mortality. All women should consider a risk-benefit analysis before initiating or continuing HT.

When selecting a hormone option for a patient, the following issues should be considered to maximize the benefits and minimize the risks:

Timing is important. Starting hormone therapy in healthy women younger than age 60 years or within 10 years of menopause is not associated with an increased risk of heart disease. Many studies report that estrogen therapy actually protects the coronary vessels and reduces the risk of cardiovascular events.20,21,23,24,26–29,37,38

Continuing low-dose therapy through age 60 and beyond appears to continue this protection.20,21,23,26,27,28,38

Minimize the dose. Selecting the lowest effective dose for menopausal symptoms lowers the risk of side effects and bleeding problems. Low-dose therapy is associated with beneficial effects on bone metabolism and vaginal tissue.44 As women age, their metabolic rate declines and gradual dose reduction should be considered.

Delivery method is important for certain users. Use of non-oral estrogen delivery systems—such as patches, gel, mist, vaginal creams, vaginal suppositories, or vaginal rings—minimizes the effect of estrogen on hepatic proteins. Non-oral delivery methods are recommended for women with CVD, clotting abnormalities, thromboembolic history, pronounced obesity, or prolonged hypertension, diabetes, or immobilization.

Consider adding a progestin. Adding a progestin to estrogen therapy is recommended to protect the endometrium from overstimulation. An advantage of using low-dose estrogen is that it allows the clinician to minimize the dose of progestin. Currently available combination products are designed with balanced levels of estrogen and progestin and generally minimize uterine bleeding and side-effects. A variety of progestins and estrogens can be used. Differences in the progestins may offer clinical advantages. Generally, these differences are minimized when low-dose progestins are used.

Consider contraindications. Women with a personal history of breast cancer, active liver disease, active thromboembolic disease, or undiagnosed vaginal bleeding are generally advised to avoid or defer HT. Those with CVD or serious illnesses are generally at higher risk of complications from HT.23,29

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Submucous leiomyomas measuring less than 4 cm, which are generally small enough to permit hysteroscopic removal, often announce themselves by producing menorrhagia, infertility, and pregnancy wastage. Although the basic technique of hysteroscopic myomectomy, introduced by Neuwirth in 1976, has remained largely unchanged, the integration of ultrasound (U/S) guidance, strict fluid monitoring, careful cervical preparation, and mechanical grasping devices can enhance safety and efficacy while reducing the need for subsequent surgery. This article reviews both “pearls” and “pitfalls” garnered during my 24 years of experience performing more than 600 hysteroscopic myomectomies.

PEARLS
Perform diagnostic hysteroscopy in combination with U/S guidance
There is still controversy regarding the best screening tool for menstrual disorders, infertility, and pregnancy wastage. Some physicians advocate sonohysterography, whereas others favor diagnostic hysteroscopy. Both tests have limitations, but together they can provide abundant information.

Hysteroscopy is not only an important diagnostic tool, but it also provides information about the cervix, such as the presence of stenosis or its failure to descend well into the vagina. These are vital preoperative considerations in assessing a patient’s candidacy for hysteroscopic myomectomy. However, hysteroscopy provides limited information regarding myoma size, degree of myometrial penetration, or the location and breadth of its attachment point. A simultaneous abdominal U/S examination allows both a panoramic view of the uterine cavity and a sonohysterogram; the latter provides precise information regarding the size, grade, and location of the myoma and the nature of its attachment point (Figure 1).

Technically, this combined examination is achieved by first obtaining a clear hysteroscopic view of the cavity while holding the distal lens at the internal os. As an assistant holds the tenaculum, the surgeon places the abdominal transducer in both the sagittal and transverse planes, as necessary, to obtain critical U/S measurements. The assistant’s other hand allows her to freeze, measure, and store the images while the surgeon positions the hysteroscope and U/S probe for optimum views.

This combined procedure not only simulates what the surgeon may encounter during a subsequent operation, but also enhances the preoperative assessment. The physician can thereby provide realistic expectations for the patient and plan carefully for instrumentation (Table) and the use of adjuvants, including gonadotropin-releasing hormone (GnRH) analogues and laminaria.

Use U/S guidance for hysteroscopic surgery
U/S-guided hysteroscopic surgery was reported independently by Shalev and Zuckerman and Lin et al.
As a noninvasive adjuvant to resectoscopic surgery, U/S provides the operator a 3-dimensional understanding of the intrauterine pathology, taking advantage of the different echogenic characteristics of the distended bladder, myometrium, leiomyomas, and intrauterine distention fluid.

U/S guidance allows for the safe removal of most grade 2 leiomyomas measuring less than 4 cm; it also allows for the resection of cavity-filling myomas by the myoma "coring" technique (Figure 2), and the safe use of mechanical forceps to enhance myoma extraction, a technique first described by Goldrath. Goldrath’s method can be used to supplement the standard resectoscopic technique, expediting removal of large quantities of tissue without exposing the patient to the risks of fluid intravasation.

Mastering U/S-guided hysteroscopic surgery is facilitated by working with the same sonographer over time, beginning with simple cases involving grade 0 submucous myomas and progressing to more complex cases.

Establish the MAFA_{limit} limit
Hysteroscopic myomectomy has often been associated with excess fluid absorption, the results of which can be tragic. The American Association of Gynecologic Laparoscopists (AAGL) has established fluid monitoring guidelines that should be followed carefully. I favor a more stringent protocol that accounts for the patient’s body mass using the formula: MAFA_{limit} = 17.6 mL/kg. Both sets of guidelines establish an absolute limit of 1500 mL of low-viscosity anionic distention fluid (LVADF).

Provide adequate pressure through the fluid management system
Adequate visualization allows one to obtain a panoramic perspective of the uterus while avoiding disorientation, inadvertent uterine perforation, and incomplete removal of intrauterine pathology. These goals are dependent on both adequate intrauterine pressure and sufficient flow. Inexperienced surgeons tend to set fluid pump pressures too low, a problem that is fostered by the AAGL fluid monitoring guidelines, which state that “adequate visualization can generally be obtained with a maximum delivery pressure of 75 to 100 mm Hg.” This setting is not based on randomized controlled trials and, in my opinion, it is often far below what is required for adequate visualization during hysteroscopic myomectomy. The practice of setting the pump pressure below the mean arterial pressure, first suggested by Garry et al, makes little practical sense. As Loffler pointed out, the fluid deficit is the factor “that should guide the conduct of any case.”

I prefer to begin a case with the pump pressure at 140 to 180 mm Hg and to decrease it until the infusion pressure is at the minimum level necessary for adequate visualization. One should remember that the actual intrauterine pressure varies depending on the adjustment
of the outflow port of the resectoscope. High pump pressures translate into high intrauterine pressures only when the outflow valve is shut, which is an uncommon situation during resectoscopic surgery.

**Understand the critical importance of cervical dilation**

Hysteroscopic myomectomy requires a well-dilated cervix to allow the easy introduction, removal, and reintroduction of a resectoscope, an important and oft-repeated sequence in hysteroscopic myomectomy. In fact, cervical stenosis may be a relative contraindication to the removal of all but the smallest myomas.

Inadequate cervical preparation may result in forceful dilation and excessive traction on the cervical tenaculum. The former increases the risk of uterine perforation and endocervical lacerations, and the latter increases the risk of ectocervical lacerations. Cervical dilation can be enhanced with the use of intravaginally administered misoprostol or the placement of a 3- to 4-mm laminaria japonica the afternoon before surgery. In most instances, these adjuvants permit the easy introduction of a 9-mm resectoscope the following day with minimal dilatory effort. Dilatory forces can be further reduced by intracervical injection of vasopressin. My practice is to inject vasopressin, 2.5 units diluted in 20 mL of saline, to a depth of 2 to 4 cm into the cervical stroma at the 3- or 9-o’clock positions.

In other instances, the cervix may be patulous and overdilated. This results in unwanted egress of distention fluid, resulting in poor uterine distention, inadequate visualization, and disorientation; these conditions in turn increase the risk of accidental perforation and incomplete myoma removal. This condition is easily managed by sequential placement of tenacula at the 3 and 9-o’clock positions until an adequate seal develops between the resectoscope and the cervical os.

**Use appropriate instrumentation**

The Table summarizes my preferred instruments and their indications. Operative hysteroscopes for myomectomy include both electrosurgical resectoscopes and the newly available mechanical hysteroscopic morcellators. The latter are not well studied and I have little experience with them. Although a 9-mm unipolar resectoscope will suffice for most hysteroscopic myomectomies, cervical stenosis may require the use of a smaller 7-mm resectoscope or a small-diameter hysteroscopic morcellator. Other instruments, such as the hysteroscopic injection needle, mechanical forceps, cervical dilators, and multiple tenacula, are useful to manage an array of clinical scenarios.

Electrosurgical resectoscopes are available as both unipolar and bipolar models. The former are generally offered in a 9- and a 7-mm version. Unipolar systems
provide excellent cutting and coagulation with a sturdy electrode that does not easily deform or fracture; however, these require an LVADF and a MAFA that are more restrictive compared with normal saline. Significant cervical stenosis often requires the use of a 7-mm resectoscope, which results in longer operative times because the smaller 19F electrocautery loop removes less tissue.

Bipolar resectoscopes are helpful in patients with a low body mass, requiring one to carefully limit the use of LVADF, or with large or multiple myomas, for which long resection times are anticipated. The use of normal saline for distention with bipolar instruments allows greater net fluid absorption; this reaches 2,500 mL in most cases. One shortcoming of bipolar systems is that they provide relatively poor tissue coagulation compared with unipolar systems. In a unipolar system, the coagulation current travels through the tissue to a ground plate. That same current also travels through the area of least impedance, along blood vessels that run perpendicular to the surface of the uterus or myoma. In a bipolar system, the current returns to a negative electrode about 1 cm away (located on the resectoscope). In vivo models have demonstrated that the temperatures reached in unipolar systems and the resulting tissue penetration is greater than what can be achieved with bipolar systems. For this reason, I prefer to use a 9-mm unipolar resectoscope for the vast majority of cases.

You may begin a case with unipolar electrosurgery and transition to a bipolar system, provided that you adhere to the fluid management guidelines of both systems. This practice often allows completion of a procedure once the MAFA of LVADF has been reached.

When the pedicle can be clearly visualized, direct injection of vasopressin helps reduce bleeding during the hysteroscopic myomectomy. The same dilution of vasopressin used for intracervical injection is employed. The total amount of vasopressin should not exceed 5 units in 40 minutes. I prefer to use a 40 cm x 21-gauge G injection needle (Vita Needle Company, Needham, MA), which is passed down the operative port of a standard 26-F resectoscope.

In 1990, Goldrath described the technique of “vaginal” myomectomy, which involved the insertion of laminaria tents to accomplish cervical dilation and the blind removal of leiomyomas using various forceps. In his series of 151 patients, the hysterectomy avoidance rate was 92% and there were 2 uterine perforations (1.3%). With the use of US guidance, this technique need no longer be performed blind. Provided the cervix is well dilated, there are 3 clear advantages to this technique. First, it obviates the need for any distention media and thereby precludes the issues associated with excess fluid absorption. Second, the procedure is extremely efficient; well-selected leiomyomas can be removed quickly provided that they are pedunculated grade 0 leiomyomas that have been reduced to less than 3 cm. Third, the procedure eliminates the need for relatively expensive uterine morcellators.

The major risks of this procedure are 2-fold. First, uterine perforation is still possible in inexperienced hands. Second, in some circumstances the combination of the myoma and grasping forceps cannot be delivered through the endocervical canal, precluding removal of the instrument or the fibroid. To prevent this occurrence, one should be able to disarticulate all grasping forceps used for this purpose at their fulcrum. Surprisingly large fibroids can be removed in this fashion (Figure 3).

Small flexible dilators such as Cooper Surgical os finders are often helpful in managing marked or moderate cervical stenosis. Their flexible tip helps avoid inadvertent perforation. Routine dilation to 9 mm is best performed with Hegar dilators, which have a short dilating surface that also helps avoid uterine perforation, a concern with a short, very anteflexed, or retroflexed uterus. When greater dilation is necessary, for example with the use of mechanical forceps, large-diameter Hegar dilators (up to 16 mm) or Denniston dilators (up to 14 mm) should be inserted under sonographic guidance.

As already noted, I often use multiple tenacula to limit unwanted fluid egress between the resectoscope and the cervix. The placement of tenacula is similarly useful after mechanical forceps are used to extract a submucous leiomyoma.

Consider administration of GnRH analogues
Selective use of a GnRH analogue may enhance the feasibility and safety of hysteroscopic myomectomy, particularly for myomas larger than 4 cm. Crosignani et al reported that use of a GnRH analogue before surgery for uterine leiomyomas produced a temporary 40% to 50% reduction in mean uterine volume. Perino et al observed a 35.1% reduction in operative time along with a marked improvement in procedure completion rates with the use of leuprolide acetate depot. I have observed similar advantages using leuprolide depot 3.75 mg (Lupron Depot; Abbott Laboratories, Abbott Park, Illinois) for 2 months before surgery.
Use appropriate electrosurgical generator settings

Myomas vary considerably in density; therefore, there is no single correct power setting for all myomectomies. If a loop electrode begins to deform because of mechanical drag, increase the current density until true electrosurgical cutting is achieved. Settings between 140 and 240 W work well and should be selected based on their bioeffects.

Terminate the procedure if necessary

It is not always possible to complete a hysteroscopic myomectomy in a single procedure. Foreseeable factors that increase the likelihood of a 2-stage procedure include a low body mass, which results in a lower MAFAlimit; and large, complex, or numerous leiomyomas. An unforeseeable risk factor for a 2-stage procedure is the “hyper-absorber,” or the occasional woman who absorbs a great deal of distention fluid despite low pump pressures. The reason some women absorb large quantities of distention fluid is neither predictable nor well understood.

As surgeons, we tend to be goal oriented and to forget that unlike many operative procedures, hysteroscopic myomectomy does not need to be completed. Cases should be discontinued in the presence of excessive bleeding, disorientation, or uterine perforation, or if the patient’s MAFAlimit has been reached. Occasionally it is necessary to have your patient return in 8 to 12 weeks for a second procedure, depending on her clinical response. Postoperative bleeding can be managed by inserting a Foley catheter with a 30-mL balloon and removing it after 2 hours. Prospective surgical candidates must understand the occasional requirement for a 2-stage procedure to avoid the serious consequences associated with excess fluid absorption.

Select patients carefully

Patient selection depends on a variety of factors, including the size, number, grade, and location of myomas. Both Wamsteker et al and Lasmar et al have published classification systems for leiomyomas in an attempt to aid the surgeon in predicting outcomes. Wamsteker et al distinguished various degrees of penetration into the myometrium, whereas Lasmar et al considered parameters such as the distance from the base of the myoma to the serosa, the size of the nodule, and the topography of the uterine cavity. However, other patient-selection factors are omitted if one relies solely on these classification systems.

Because the MAFAlimit varies with the patient’s weight, women who weigh less than 50 kg and have a single large myoma (3-4 cm) or numerous smaller myomas should be warned of the possible requirement for a 2-stage procedure. Another important factor is the quality of the images obtained during a combined hysteroscopy and sonohysterogram because a poor ultrasound image may limit the surgeon’s ability to safely excise some leiomyomas. Other factors that may represent intraoperative challenges include cervical stenosis and excessive cervical length (>4 cm) or uterine length (>10 cm).

Finally, the patient should have a realistic understanding of the possible short- and long-term complications. Short-term complications may include uterine perforation, excessive fluid absorption, and the need to discontinue a case before its completion; long-term sequelae include the effect of myomectomy on a subsequent pregnancy or the possible need for future surgery.

PITFALLS

Surgeons may encounter several possible pitfalls while planning and performing hysteroscopic myomectomy. Many of these are discussed above, including excessive fluid absorption or bleeding, poor visualization of the uterine cavity and myoma(s), risk of inadvertent uterine perforation, risk of incomplete removal of intrauterine pathology, inadequate cervical dilation with possible laceration, leakage of distention fluid, large or multiple myomas, and unfavorable patient characteristics such as low body mass and cervical stenosis. Both short-term and long-term complications can occur after the procedure.
Solutions to these issues are also discussed above. Calculation of the MAFA_{crit} is critical to help avoid excess fluid absorption. Other strategies include the implementation of U/S guidance; use of adequate intrauterine pressure and flow; selection of an appropriate electrosurgical generator setting; cervical preparation with misoprostol, laminaria, vasopressin, and cervical dilators; proper use of instruments; and consideration of GnRH analogues. When necessary, a procedure should be discontinued and a second procedure scheduled later. Surgeons can also avoid pitfalls through careful patient selection based on myoma characteristics, body weight, quality of U/S images, and other factors such as cervical stenosis, cervical length, and uterine length.

**SUMMARY**

Hysteroscopic myomectomy requires an array of instrumentation to accommodate a variety of intraoperative scenarios. Physicians should avoid scheduling a case unless the required equipment is available, and every operating room should have redundant equipment because instrument failures do occur. Evaluation of each patient must include an assessment of whether the cervix is amenable to hysteroscopic surgery. Surgeons should avoid performing hysteroscopic myomectomy on patients who have unrealistic expectations or taking on surgical challenges that are beyond their current abilities. Likewise, ob/gyns should not be pressured into performing a procedure if they do not believe it can be done safely and should not complete a procedure complicated by poor visualization and excessive fluid absorption; doing so invites both frustration and danger. Because patients do not present themselves in order of increasing complexity, it is best to begin with simple cases so that the surgeon and team can develop skills and confidence.

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Sex and the 50-something woman: Strategies for restoring satisfaction

Many women experience sexual dysfunction after menopause, and it can have a significant impact on their lives. But the conditions it encompasses are treatable and ob/gyns need to be aware of available interventions and willing to engage in dialogue with patients about this sensitive subject.

By John E. Buster, MD

For many women, the 50s are a milestone decade. Typically marked by onset of menopause, these can be years for celebrating fulfillment of life’s goals and expressing sexuality free from the need for contraception. For some women, however, the menopausal transition brings with it female sexual dysfunction (FSD), a continuum of psychosexual disorders centered on loss of sexual desire with interrelated problems of arousal, orgasm, and sexual pain. FSD impact is subtle but insidious. It can be minor and short term or of long duration and debilitating, leading to emotional disturbances that affect quality of life in both family relationships and the workplace.

Despite the consequences of FSD, however, physicians rarely ask women older than age 50 if they are having issues with their sexuality, because if the answer is yes, many clinicians are uncomfortable with the dialogue that is sure to follow. This article reviews criteria for recognized categories of FSD and hallmarks for diagnosis and provides an overview of pharmacologic and nonpharmacologic treatments that help restore a patient’s sexual satisfaction.

Sex after 50 matters

Sexual health matters to patients, and statistics indicate that FSD impacts many women age 50 and beyond. A sexual problem (desire, arousal, or orgasm, specifically) was reported by nearly 44% of the 31,581 US women aged 18 to 65+ in the recent PRESIDE survey, and the unadjusted prevalence of hypoactive sexual desire was 38.7%. Hypoactive sexual desire associated with distress is classified as Hypoactive Sexual Desire Disorder (HSDD). The prevalence of that diagnosis is reportedly 8.9% in 18- to 44-year-olds, 12.3% in 45- to 64-year-olds, and 7.4% in women aged 65 and older.

FSD has a reputation for being intractable and difficult to treat, but informed physicians know otherwise and no longer ignore these conditions just because women do not ask about them. As shown in Table 1, several legitimate ICD-9 diagnostic codes exist for FSD.

Endocrinology of sexual aging

Aging has an adverse impact on endocrinology in women aged 50 and beyond, which in turn can undermine sexual desire, alter its clinical expression, and impact diagnosis and treatment of FSD.

Estrogen and androgen production, which both are involved with initiation and maintenance of female sexual response, decline with age.

Estradiol secretion, chaotic during perimenopausal years, declines to very low levels...
after menopause. Estrogen withdrawal increases tissue fragility, vaginal and urinary infections, irritation, dryness, urogenital pain, and susceptibility to vaginal tissue trauma. Declining estrogen impairs sexual desire indirectly, in that it induces vulvovaginal atrophy, leading to sexual pain and trauma during intercourse. Finally, neuroendocrine estrogen depletion adversely impacts sexual response, as expressed in mood swings, hot flushes, irritability, memory lapses, and insomnia.

Androgens produced in vivo are secreted into the circulation from the ovary or converted from adrenal dehydroepiandrosterone sulfate (DHEA-S) within target tissues. Production from both sources declines with age. Androgens produced in vivo are secreted into the circulation from the ovary or converted from adrenal dehydroepiandrosterone sulfate (DHEA-S) within target tissues. Production from both sources declines with age.3-5 Testosterone secretion in both pre- and postmenopausal women derives principally from the ovaries.6-8 During the reproductive years, a mid-cycle rise in testosterone occurs in conjunction with the luteinizing hormone (LH) surge; this is directly linked to increased mid-cycle sexual desire in reproductive-aged women.6,9 In postmenopausal women, ovarian testosterone is secreted tonically in association with chronically elevated LH, but the midcycle surge is lost.

With age, levels of dehydroepiandrosterone sulfate (DHEA-S), a pro-hormone secreted by the androgen adrenal cortex, relentlessly decline.3,4 DHEA-S originates almost exclusively from the zona reticularis, or innermost zone, of the adrenal cortex.4 The zona reticularis undergoes genetically determined atrophy (apoptosis) with age, leading to age-related decline in DHEA-S production.3,5 As a pro-hormone, DHEA-S must be converted into testosterone and dihydrotestosterone (DHT) in target tissues.3

Causes and diagnosis of FSD

FSD is diagnosed when a woman’s symptoms are causing her personal distress.2 The American Psychiatric Association’s Diagnostic and Statistical Manual of Mental Disorders, or DSM-IV-TR, lists 4 interrelated clinical categories of FSD that have been accepted in evolving iteration.2 The DSM-IV-TR describes FSD as any sexual complaint or problem resulting from disorders of desire, arousal, orgasm, or sexual pain (Figure 1).2

The 4 FSDs flow outward from HSDD and into each other as circular continuums. HSDD is depicted at the center of Figure 1 because sexual desire is a driving force at the heart of all FSDs. Nothing happens without sexual desire. Successful resolution of HSDD frequently resolves or significantly augments resolution of the other disorders.

The DSM-IV-TR defines HSDD as persistent or recurrent deficient or absent sexual fantasies/thoughts and/or desire for or receptivity to sexual activity. The diagnosis is made when loss of sexual desire causes distress or interpersonal difficulty.2

Unhappy life events, psychosocial dysfunction, depression, drugs, medical and gynecological disorders, and natural or iatrogenic disruptions in androgen production—alone or in combination—can precipitate HSDD.10,11 Healthy female sexual desire requires a safe environment, self-esteem, and an attractive and available partner. HSDD is common in conjunction with a broken relationship or the death of a partner. Table 1 lists drugs associated with HSDD.10,11 Antidepressants, particularly selective serotonin reuptake inhibitors (SSRIs), are associated with HSDD and also probably inhibit orgasm.10,11 SSRIs often are given to depressed patients who complain of HSDD but these drugs only make the condition worse.

Advancing age and declining endocrinology significantly amplify all causes of HSDD. Decreased sexual desire can result from inadequate treatment of chronic diseases such as diabetes, hypertension, obesity, hypopituitarism, or breast cancer. Atrophic vaginitis leads to dyspareunia, sexual aversion, and lost sexual desire. Oral estrogens commonly used for hormonal therapy...
increase sex hormone-binding globulin (SHBG), bind circulating testosterone, and impair testosterone effect. Transdermal estrogens do not affect SHBG. Glucocorticoids suppress adrenal androgen production, and therefore, may be associated with HSDD. In some circumstances, age-associated androgen depletion may be accelerated. For example, bilateral oophorectomy, which is associated with a 40% to 50% drop in serum testosterone, often precipitates HSDD, whereas hysterectomy without oophorectomy usually has no effect on sexual desire.

Premature ovarian failure results in loss of the midcycle testosterone surge and the increase in sexual desire that occurs in association with ovulation in reproductive-aged women. Women with panhypopituitarism and adrenal insufficiency often suffer from HSDD. Pelvic radiation may induce premature ovarian failure. Exposure to chemotherapy for breast cancer, tamoxifen, and aromatase inhibitors, may trigger HSDD. The condition can be further aggravated by a distorted self-image after disfiguring breast surgery.

Treating HSDD

HSDD treatment centers on managing causes. Situational HSDD from adverse life events, particularly in younger women, can be managed with reassurance or with marital counseling. Sometimes a new and attractive partner is all that is needed. Use of antidepressants such as SSRIs is commonly associated with HSDD in women and the problem can be addressed by lowering drug dosage, and it may even be eliminated as the depression lifts and a patient’s circumstances change or she responds to cognitive therapy. For women with milder depression linked to HSDD, antidepressants can be tapered (and in some cases, eliminated) as the therapy begins to resolve symptoms. Many drugs used to treat medical disorders are less obvious culprits in FSD but they need to be identified and a patient’s therapy changed (Table 1). Successful treatment of chronic diseases, such as hypertension, diabetes, hypopituitarism or breast cancer, also helps to restore sexual desire. Treatment of atrophic vaginitis with systemic or topical estrogens or DHEA, combined with mechanical dilatations, is highly effective.

For women whose androgen production is depleted, testosterone is a rational therapy for HSDD. Table 2 lists transdermal testosterone preparations under investigation for use in women or approved for use in men and used off-label in women. An abundance of high-quality evidence documents transdermal

<table>
<thead>
<tr>
<th>Medication</th>
<th>Desire disorder</th>
<th>Arousal disorders</th>
<th>Orgasm disorders</th>
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<td>Narcotics</td>
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Abbreviations: GnRh, gonadotropin-releasing hormone; MAO inhibitors, monoamine oxidase inhibitors; SSRIs, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants. Adapted from: Kennedy SH, et al10; Zemishlany Z, et al11; Association of Reproductive Health Professionals12; Drugs that cause sexual dysfunction: an update.13
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ATHTENA = Addressing THE Need for Advanced HPV Diagnostics;
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testosterone’s effectiveness in restoring sexual desire (Table 3).\textsuperscript{15-22} Many well-powered, well-designed clinical trials performed over the past decade have provided Level I evidence that transdermal testosterone, in physiologic to slightly super-physiological doses, is effective for treatment of HSDD.\textsuperscript{15-22}

The most extensively investigated formulation, transdermal testosterone delivered by matrix patch (Intrinsa®, Procter and Gamble) (Table 3), has been tested in 8 randomized, blind clinical trials involving 3,200 postmenopausal women with HSDD.\textsuperscript{15-22} All of the trials have demonstrated dose-related significant increases in sexual desire with testosterone patches versus placebo when doses are maintained at 300 mg per day or higher (Table 3).

Patients using down-dosed (off-label) male products, compounded gels, and creams should be monitored clinically and their testosterone levels documented to ensure that doses delivered are therapeutic and not reaching supraphysiologic levels. Effects from excess dosing can include acne, hirsutism, scalp hair loss, deepening of the voice, and male-like muscle mass. Patients and clinicians should be observant for these problems, which are avoidable.

Consensus reports about testosterone therapy for women from the Endocrine Society, the North American Menopause Society, and the FDA Advisory Committee hearings of 2004 have been cautionary, citing insufficient long-term experience.\textsuperscript{23-25} Subsequent long-term experience with the product, however, has been reassuring.\textsuperscript{26}

### Female arousal disorder

This disorder is defined in the DSM-IV as inability to complete sexual activity with adequate lubrication.\textsuperscript{3} It is diagnosed when compromised sexual arousal causes a patient marked distress or interpersonal difficulty.\textsuperscript{2}

Sexual arousal disorder arises from HSDD or many of the same conditions that cause HSDD. Alone or in combination, unhappy life events, psychosocial dysfunction, depression, exposure to certain drugs, medical and gynecological disorders, and disruption in androgen production can precipitate sexual arousal disorder.\textsuperscript{11} Drugs, particularly antidepressants such as SSRIs, are often associated with sexual arousal disorder (Table 1).\textsuperscript{10-13} Atrophic vaginitis after spontaneous or surgical menopause leads to dyspareunia and difficulties in lubrication sufficient to seriously impair sexual arousal.

Treatment centers on managing causes. HSDD needs to be resolved. Culprit drugs need to be elimi-
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Female orgasmic disorder

This disorder is defined in the DSM-IV as persistent or recurrent delay in, or absence of orgasm, following a normal excitement phase. Primary orgasmic disorder is defined as never having the ability to achieve orgasm. Secondary orgasmic disorder is generally the result of another sexual dysfunction, usually HSDD. Diagnosis of orgasmic disorder is made when failure to achieve orgasm causes a patient marked distress or interpersonal difficulty.

Primary orgasmic disorder is often associated with trauma or abuse, but it may have no explanation. For the latter patients, the problem may be congenital, and some would say, analogous to the origins of conditions such as anosmia and color blindness. Women with primary orgasmic disorder experience every aspect of female sexual response except orgasm. Secondary orgasmic disorder, in contrast, is usually a result of another sexual dysfunction, most often HSDD. Association with pelvic surgery and exposure to drugs such as antidepressants also is common. In some women, secondary orgasmic disorder is linked to chronic gynecological conditions.

Treatment of orgasmic disorder centers on managing inciting factors. For patients with primary orgasmic disorder in whom abuse is a factor, psychotherapy and couples counseling may be helpful. There is no effective therapy for patients with unexplained primary orgasmic disorder who have never had an orgasm and cannot reach orgasm even by masturbating. In secondary orgasmic disorder, however, treatment of the primary dysfunction often results in restoration of a woman’s ability to achieve orgasm.

Sexual pain disorders

Dyspareunia and vaginismus are two subcategories of sexual pain disorder. The DSM-IV defines dyspareunia as recurrent or persistent genital pain associated with sexual intercourse that is not caused exclusively by lack of lubrication or vaginismus. In many women, it is linked to chronic gynecological conditions or drug exposure. In some women, persistent dyspareunia is related to persistent pelvic floor muscle spasm resulting from prior experience and responds to physical therapy. Treatment of dyspareunia centers on managing inciting factors, which are often gynecologic in origin and obvious after a patient is clinically evaluated.

Vaginismus is defined in DSM-IV as recurrent or persistent involuntary spasm of the musculature of the outer third of the vagina that interferes with sexual intercourse. The diagnosis is made when a woman’s symptoms cause her marked distress or interpersonal difficulty. For some women, vaginismus is limited to sexual activity. For others, vaginismus is related only to fear of pelvic instrumentation. Some women enjoy sexual activity and are orgasmic, but still have vaginismus. Only penetration is impossible. Vaginismus is often linked to HSDD and sexual aversion. The most effective treatments are combinations of cognitive and behavioral psychotherapy, typically referred to as systematic desensitization.
should be reduced or the drugs discontinued. Transdermal testosterone should be considered for older women with FSD and androgen depletion.

For some patients, counseling by a psychologist or sex therapist may be required to resolve FSD. Educational resources, such as Internet-based information from the North American Menopause Society (http://www.menopause.org) and Red Hot Mamas (http://redhotmamas.org/online-menopause-resources), also are informative.

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Screening for thyroid disease during pregnancy

Q. A 40-year-old G1 P0 at 8 weeks’ gestation with a singleton pregnancy presents to your practice for her first prenatal visit after successful in vitro fertilization. She is otherwise healthy and has no complaints. She read on the Internet that thyroid function testing is being done by many physicians and wants to know if you recommend it. Should thyroid function screening be done routinely in gestation?

A. Principles of effective screening require that only an asymptomatic population be screened in areas where disease is prevalent, the test be reliable and easily accessible, and a cost-effective established treatment be available. Based on currently available evidence, the American College of Obstetricians and Gynecologists (ACOG) recommends against routine testing in gestation.1

What expert guidance exists on screening for thyroid disease in pregnancy?
In 2005, the American Association of Clinical Endocrinologists, the American Thyroid Association (ATA), and the Endocrine Society published a joint position statement recommending routine TSH evaluation (with fT4 if TSH is abnormal) before conception or as soon as pregnancy is diagnosed. However, ACOG maintains that routine screening of pregnant women for thyroid disease is not recommended, based on currently available data. These conflicting statements have led to confusion about screening pregnant women. Acknowledging that, the ATA convened a group of experts, including obstetrician/gynecologists, and revised their recommendations to state that data are insufficient to recommend for or against universal thyroid screening in pregnancy.2

What are the indications for thyroid function testing in gestation?
Current SMFM recommendations, consistent with ACOG recommendations, include thyroid testing for women “at risk,” such as those with known thyroid disease, symptoms of overt thyroid disease, suspected goiter, and autoimmune medical disorders such as Type 1 diabetes mellitus.3 Signs and symptoms of overt hypothyroidism and hyperthyroidism are listed in Table 1.4,5

What are values for thyroid function in pregnant women?
Table 2 describes changes in thyroid function in pregnant women with thyroid disease.4,5 Overt hypothyroidism is defined as elevated thyroid stimulating hormone (TSH) in conjunction with decreased concentration of free thyroxine (fT4). The normal range for fT4 concentrations during gestation is the same as in non-pregnant women: 0.7-1.8 ng/dL. Gestational age-specific normative ranges for TSH have been described, but in routine practice, most clinicians use laboratory-specific values for nonpregnant adults that most often include an upper range of 2.5 mIU/L to 4.0 mIU/L.2 A threshold of 4.0 mIU/L is the cutoff in an ongoing study of subclinical hypothyroidism in pregnancy sponsored by the National Institute of Child Health and Human Development (NICHD).6 The 3 components of subclinical hypothyroidism are serum TSH 2.5 mIU/L to 10mIU/L, fT4 concentration 0.7 ng/dL to 1.8 ng/dL, and absence of symptoms.2

More on this topic:
Read the Editorial from the June 2012 issue of Contemporary Ob/Gyn at: contemporaryobgyn.net/hypothyroidism.
What are the data on childhood neurodevelopment and hypothyroidism?

Untreated overt hypothyroidism is known to hinder childhood neurodevelopment. The first report of a possible correlation between thyroid disease and mental retardation in offspring came from iodine-deficient areas of Switzerland in 1915. Children of mothers with thyroid dysfunction in the region were more likely to have mental retardation. In the 1960s in a cohort study from New Guinea, researchers described the effect of maternal thyroid concentrations in women with goiter on their newborns. They found neurological manifestations of cretinism, or physical stunting and mental retardation, in women who were not clinically hypothyroid but who had low thyroid hormone concentrations.

The question of an association between maternal hypothyroidism during pregnancy and intellectual development in offspring was reinitiated after several publications in the late 1990s suggested a possible relationship. Pop, et al evaluated a cohort of women and their children from iodine-sufficient areas in the Netherlands in 1999. Using an fT4 below the 10th percentile at 12 weeks’ gestation, they found increased risk of impaired psychomotor development at age 12 months.

Haddow, et al evaluated thyroid levels in an unselected group of 25,216 women with second-trimester prenatal serum screening. The 7- to 9-year-old children of 62 women with thyroid dysfunction (TSH >99.7th percentile) were matched with children of 124 controls. While offspring of women with hypothyroidism were more likely to have an IQ of 85 or lower than children of controls (15% vs 5%, respectively; P=.08), this difference did not reach statistical significance. One of the limitations of this study is that it is unclear from the study design which patients had subclinical disease. Data presented also suggest that hypothyroxinemia, rather than subclinical hypothyroidism, may influence pediatric neurodevelopment.

More recently, Lazarus and colleagues conducted a randomized clinical trial of thyroid screening involving more than 21,000 pregnant women. Women with subclinical hypothyroidism and those with isolated hypothyroxinemia were identified and treated with levothyroxine, starting at median gestational age of 13 weeks. The authors found no differences between treated and nontreated patients in offspring IQ at age 3 years. In an accompanying editorial, Brent noted that the findings “provide support for the position of clinicians who have resisted the call for universal thyroid-function screening in pregnancy.”

Aside from offspring neurodevelopment, the literature is contradictory about whether isolated subclinical hypothyroidism causes other adverse pregnancy outcomes. Negro and colleagues compared a group of antithyroperoxidase-negative women with moderate TSH elevation (2.5 to 5.0 mIU/L, defined in this study as subclinical hypothyroidism) and women with normal TSH. They found a higher rate of pregnancy loss in the former group (6.1% vs 3.6%, respectively). Cleary-Goldman and colleagues evaluated late pregnancy outcomes in women with subclinical hypothyroidism. They found no correlation between subclinical disease and preterm labor, preterm premature rupture of the membranes, or gestational diabetes. However, other authors have found an increased risk of gestational diabetes, placenta abruption, and preterm birth in those with subclinical disease.

Does treatment of subclinical hypothyroidism during pregnancy improve pregnancy outcomes?

Whether treatment of subclinical hypothyroidism, or perhaps more importantly, hypothyroxinemia, would alter pediatric neurodevelopment is unknown. The recent trial by Lazarus, described here, demonstrated neither IQ impairment from subclinical hypothyroidism nor any benefit from its treatment. An ongoing NICHD-Maternal Fetal Medicine Units Network study is also addressing this question. Women with subclinical hypothyroidism or hypothyroxinemia have been randomized to thyroxine treatment or matching placebo during preg-

### Table 2: Relationship between thyroid function tests and various thyroid disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>TSH</th>
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<td>Hypothyroxinemia</td>
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<tr>
<td>Overt hyperthyroidism</td>
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**Abbreviations:** T4, thyroid hormone; TSH, thyroid-stimulating hormone. From Casey, et al; Stagnaro-Green.
nancy. Offspring will be assessed for neurodevelopmental outcomes at age 5 years. This study should address whether screening and treatment of subclinical disease is beneficial. Recruitment for the study ended in 2009; results should be available after 2014. The current evidence supports ACOG’s recommendation against routine screening for thyroid disease in pregnancy and routine treatment of subclinical hypothyroidism in pregnancy.\(^7\)

**What are the indications for treatment of hyperthyroidism during pregnancy?**

The diagnosis of overt hyperthyroidism is made with depressed serum TSH (<0.45 mIU/L) and elevated \(fT_3\) (>1.8 ng/dL) concentration.\(^3\) Overt hyperthyroidism complicating pregnancy is associated with increased risk of spontaneous pregnancy loss, congestive heart failure, thyroid storm, preterm birth, preeclampsia, and fetal growth restriction. The most common cause is Graves' disease.

Women with nausea and vomiting in pregnancy due to hyperemesis gravidarum (HEG) often have high hCG levels and may have transient biochemical hyperthyroidism, that is, suppression of TSH below the normal range, along with elevation of \(fT_3\), but without clinical symptoms of hyperthyroidism.\(^3\) Without treatment, most of these women will have spontaneous resolution in the early second trimester (by 14 to 18 weeks). For this reason, routine measurement of thyroid function is not recommended in women with HEG unless they have other overt signs or symptoms of hyperthyroidism. Subclinical hyperthyroidism (decreased TSH and normal \(fT_3\)) has not been associated with adverse perinatal outcomes and the benefit of treatment during pregnancy remains unclear.\(^4\)

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

**REFERENCES**

SNAPSHOT

Protocol 21 - Autoimmune Disease

AUTHOR: CHARLES J. LOCKWOOD, MD, MHCM, DEAN OF THE COLLEGE OF MEDICINE AND VICE PRESIDENT FOR HEALTH SCIENCES, THE OHIO STATE UNIVERSITY, COLUMBUS, OH

SYNOPSIS: In this protocol, Dr. Lockwood reviews the pathophysiology, diagnosis, and treatment of autoimmune disease in pregnancy. Included are guidelines for management of systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), scleroderma, and rarer autoimmune disorders.

As the author notes, because of their predilection for women and common occurrence in the reproductive age, autoimmune diseases are a relatively common complication of pregnancy. Understanding the effect of pregnancy on the disease and the effect of the disease on pregnancy is a crucial aspect of managing affected pregnant patients.

KEY MESSAGES:

⦁ SLE is triggered by an abnormal humoral antibody response that causes the production of antibodies that cross-react with a variety of tissues in genetically susceptible individuals. The antibodies form non-specific antibody complexes, which cause inflammation, leading to related conditions such as antiphospholipid antibody syndrome (APAS). One theory about SLE with direct implication in pregnancy outcome is activation of complement by APAS, causing vascular inflammation and changes within the fetus and placenta.

⦁ Lupus flares occur in 50% of pregnant patients and are more common in the first trimester. Half of SLE patients have clinical evidence of glomerulonephritis.

⦁ Twenty-five percent of SLE patients have APAS, which causes second- and third-trimester fetal death, intrauterine growth restriction (IUGR), preeclampsia, and maternal thromboembolic phenomenon. Risk of recurrent pregnancy loss is 70% in patients whose SLE and APAS are untreated. Twenty-five percent of patients with SLE have anti-SSA (Ro) antibodies, which are associated with an HLA-DR3 haplotype and...
linked to congenital heart block in 1% to 2% of cases and neonatal rash in 10% to 20% of infants.

- Congenital SLE is far more common in female neonates (14:1 for cutaneous and systemic involvement and 2:1 for isolated congenital heart block [CHB]). Lesions generally appear within 6 weeks of birth and persist for 1 year.

- SLE diagnosis is established when four or more of the American College of Rheumatology criteria are present: 1) malar rash; 2) discoid rash; 3) photosensitivity; 4) oral ulcers; 5) non-erosive arthritis; 6) pleuritic or pericarditis; 7) renal disease; 8) neurological abnormalities; 9) hematological abnormalities; 10) laboratory findings; 11) positive antinuclear antibody test.

- Patients with SLE should have a complete blood count (CBC), 24-hour urine collection, and other laboratory studies and indices of disease activity performed at the first prenatal visit. First-trimester ultrasonography and aneuploidy screening are recommended. Fetal echocardiography should be performed at 18 weeks and then monthly by an experienced physician in patients with SLE at risk for neonatal lupus or CHB on the basis of anti-SSA antibodies.

- Presence of lupus anticoagulant or moderate- to high-level anticardiolipin antibodies in a pregnant patient with SLE is an indication for treatment with low-dose aspirin and either prophylactic or therapeutic heparin or low-molecular-weight heparin.

- In patients with SLE whose disease is uncomplicated and not worsening, delivery can be delayed until 40 weeks, provided there is no superimposed preeclampsia, fetal growth is normal, and twice-weekly fetal testing initiated at 36 weeks is reassuring. Protocols for delivery in the presence of deteriorating maternal or fetal health vary depending on the fetus's gestational age.

- RA is the most common autoimmune disease in women of childbearing age, with a prevalence of 1 per 2,000 pregnancies. RA is primarily a clinical diagnosis and improves in 70% of pregnant patients, with a 90% postpartum exacerbation rate. RA uncomplicated by APAS or anti-SSA/SSB antibodies does not appear to be associated with an increase of spontaneous abortion, perinatal mortality or IUGR.

- Initial treatment of RA in pregnancy should include local steroid injections into affected joints. If the response to local measures is inadequate, begin prednisone 5 mg every morning and 2.5 mg every evening.

- Scleroderma is a rare autoimmune disease associated with progressive fibrosis and vasculitides. The disease course is unaffected by pregnancy. Scleroderma does not appear to cause a higher incidence of spontaneous abortion, but is associated with a modestly higher risk of stillbirth and preterm delivery linked to the severity of renal disease and hypertension.

- Pregnant patients with scleroderma should be followed for evidence of deteriorating renal function and worsening hypertension. Management in pregnancy includes serial assessment of 24-hour urine collection for creatinine clearance and total protein, serum creatinine in each trimester, and antihypertensive therapy with calcium channel blockers but not ACE inhibitors.
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**BRIEF SUMMARY OF PRESCRIBING INFORMATION**
The following is a brief summary only; see full Prescribing Information for complete product information.

**INDICATIONS AND USAGE**
Toviaz is a muscarinic antagonist indicated for the treatment of overactive bladder with symptoms of urgent urinary incontinence, urgency, and frequency.

**CONTRAINDICATIONS**
Toviaz is contraindicated in patients with urinary retention, gastric retention, or uncorrected narrow-angle glaucoma. Toviaz is also contraindicated in patients with known hypersensitivity to the drug or its ingredients, or to tolterodine tartrate tablets or tolterodine extended-release capsules.

**WARNINGS AND PRECAUTIONS**
Angioedema:
Angioedema symptoms of the face, lips, tongue, and/or larynx have been reported with fesoterodine. In some cases angioedema occurred after the first dose. Angioedema associated with upper airway swelling may be life-threatening. If involvement of the tongue, hypopharynx, or larynx occurs, fesoterodine should be promptly discontinued and appropriate therapy and/or measures to ensure a patent airway should be promptly provided.

Bladder Outlet Obstruction:
Toviaz should be administered with caution to patients with clinically significant bladder outlet obstruction because of the risk of urinary retention.

Decreased Gastrointestinal Motility:
Toviaz, like other antimuscarinic drugs, should be used with caution in patients with decreased gastrointestinal motility, such as those with severe constipation.

Controlled Narrow-Angle Glaucoma:
Toviaz should be used with caution in patients being treated for narrow-angle glaucoma, and only where the potential benefits outweigh the risks.

Hepatic Impairment:
Toviaz has not been studied in patients with severe hepatic impairment and therefore is not recommended for use in this patient population.

Renal Impairment:
Doses of Toviaz greater than 4 mg are not recommended in patients with severe renal impairment.

Concomitant Administration with CYP3A4 Inhibitors:
Doses of Toviaz greater than 4 mg are not recommended in patients taking a CYP3A4 inhibitor (e.g., ketoconazole, clarithromycin, diltiazem). No dosing adjustments are recommended in the presence of moderate CYP3A4 inhibitors (e.g., erythromycin, fluconazole, diltiazem, verapamil and grapefruit juice). While the effect of weak CYP3A4 inhibitors (e.g., clindamycin, nevirapine) was not examined by clinical study, some pharmacokinetic interaction is expected, albeit less than that observed with moderate CYP3A4 inhibitors.

Malignant Grasias:
Toviaz should be used with caution in patients with malignant grasias, a disease characterized by decreased cholinergic activity at the neuromuscular junction.

**ADVERSE REACTIONS**
Clinical Trials Experience:
The safety of Toviaz was evaluated in Phase 2 and 3 controlled trials in a total of 1,065 patients, 458 patients in Phase 2 trials and 607 patients in Phase 3 trials. Of these, 571 received Toviaz 4 mg/day, 575 received Toviaz 8 mg/day in Phase 2 or Phase 3 studies with treatment periods of 8 or 12 weeks. Approximately 80% of these patients had 10 or more patients exposed to Toviaz in these trials. A total of 5164 patients participated in Phase 2 and Phase 3 Phase 3 efficacy and safety studies and subsequent open-label extension studies. In these two studies combined, 554 patients received Toviaz 4 mg/day and 566 patients received Toviaz 8 mg/day. In Phase 2 and 3 placebo-controlled trials conducted, the incidences of serious adverse events in patients receiving placebo, Toviaz 4 mg, and Toviaz 8 mg were 1.8%, 3.9%, and 2.9%, respectively. All serious adverse events were judged to be not related or unlikely to be related to study medication by the investigator; except for four patients receiving Toviaz who reported one serious adverse event each: angina, chest pain, gastritis, and QT prolongation on ECG.

The most commonly reported adverse event in patients treated with Toviaz was dry mouth. The incidence of dry mouth in those taking 8 mg/day was 32% compared to those taking 4 mg/day (19%), as compared to placebo (7%). Dry mouth was not associated with degree of impairment or in 0.4%, and 0.4% of patients receiving placebo, Toviaz 4 mg, and Toviaz 8 mg, respectively. For those patients who reported dry mouth, most had their first occurrence of the event within the first month of treatment.

The second most commonly reported adverse event was constipation. The incidence of constipation was 2% in those taking placebo, 4% in those taking 4 mg/day, and 6% in those taking 8 mg/day.

Table 1 lists adverse events, regardless of causality, that were reported in the combined Phase 3, randomized, placebo-controlled trials of 12 weeks treatment duration in those taking placebo, 4% in those taking 4 mg/day, and 6% in those taking 8 mg/day.

**Race:** Available data indicate that there are no differences in the pharmacokinetics of fesoterodine between Caucasian and Black healthy subjects following administration of Toviaz.

**OVERDOSAGE**
Overdose with Toviaz can result in severe anticholinergic effects. Treatment should be symptomatic and supportive. In the event of overdose, ECG monitoring is recommended.

**DISPONABILITY**
Toviaz is manufactured by:

**REFERENCES**

**USE IN SPECIFIC POPULATIONS**

**Pregnancy:** Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women.

No dose-related teratogenicity was observed in reproduction studies performed in mice and rabbits. In mice, at 6 to 27 times the expected exposure at the maximum recommended human dose (MRHD) of 8 mg based on AUC (75 mg/kg/day, oral), increased resorptions and decreased live fetuses were observed. In rats at 9 to 11 times the MRHD (4.5 mg/kg/day, subcutaneous), maternal toxicity and incompletely ossified sternum were observed in fetuses (an increase in the background histological range). In rats at 3 to 11 times the MRHD (1.25 mg/kg/day, oral), incompletely ossified sternum (formation of bone development) were observed in fetuses. In rabbits at 9 to 11 times the MRHD (4.5 mg/kg/day, subcutaneous), maternal toxicity and incompletely ossified sternum were observed in fetuses (an increase in the background histological range). In rats at 3 times the MRHD (1.25 mg/kg/day, subcutaneous), decreased maternal food consumption in the absence of any fetal effects was observed. Oral administration of 30 mg/kg/day fesoterodine to mice in a pre-and post-natal development study resulted in decreased body weight of the dams and delayed vaginal opening of the pups. No effects were noted on mating and reproduction of the f, dam, or on the f, offspring.

**Toviaz** should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

**Nursing Mothers:** It is unknown whether fesoterodine is excreted in human milk. Toviaz should not be administered during nursing unless the potential benefit outweighs the potential risk to the neonate.

**Pediatric Use:** The pharmacokinetics of fesoterodine have not been evaluated in pediatric patients. The safety and effectiveness of Toviaz in pediatric patients have not been established.

**Geriatric Use:** No dose adjustment is recommended for the elderly. The pharmacokinetics of fesoterodine are not significantly influenced by age.

Of 1567 patients who received Toviaz 4 mg/day or 8 mg/day in the Phase 2 and 3, placebo-controlled, efficacy and safety studies, 515 (33%) were 65 years of age or older, and 140 (9%) were 70 years of age or older. No overall differences in safety or effectiveness were observed between patients younger than 65 years of age and those 65 years of age or older in these studies; however, the incidence of anticholinergic adverse events, including dry mouth, constipation, dyspepsia, increase in residual urine, dizziness (at 8 mg only) and urinary tract infection, was higher in patients 75 years of age and older as compared to younger patients.

**Renal Impairment:** Patients in severe renal impairment (CLr <30 mL/min), Ccr are included (30-80 mL/min), Ccr and AUC of the active metabolite are increased 1.5-1.8 fold, respectively, compared to healthy subjects.

**Hepatic Impairment:** Patients with severe hepatic impairment (Child-Pugh C) have not been studied; therefore Toviaz is not recommended for use in these patients. In patients with moderate (Child-Pugh B) hepatic impairment, Ccr, and AUC of the active metabolite are increased 1.4-2.1 fold, respectively, compared to healthy subjects. No dose adjustment is recommended in patients with mild or moderate hepatic impairment.

**Gender:** No dose adjustment is recommended based on gender. The pharmacokinetics of fesoterodine are not significantly influenced by gender.

**Race:** Available data indicate that there are no differences in the pharmacokinetics of fesoterodine between Caucasian and Black healthy subjects following administration of Toviaz.
TOVIAZ is a muscarinic antagonist indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency.

**Important Safety Information**

TOVIAZ is contraindicated in patients with urinary retention, gastric retention, or uncontrolled narrow-angle glaucoma, and in patients with known hypersensitivity to the drug or its ingredients or to DETROL® (tolterodine tartrate) tablets or DETROL® LA (tolterodine tartrate extended release capsules).

Angioedema of the face, lips, tongue, and/or larynx has been reported with fesoterodine, in some cases after the first dose. Patients should be advised to promptly discontinue fesoterodine therapy and seek immediate medical attention if they experience edema of the tongue, laryngopharynx, or difficult breathing.

TOVIAZ tablets should be used with caution in patients with clinically significant bladder outlet obstruction, decreased gastrointestinal motility, controlled narrow-angle glaucoma, or myasthenia gravis.

The recommended starting dose of TOVIAZ is 4 mg once daily swallowed whole. Based upon individual response and tolerability, the dose may be increased to 8 mg once daily. Doses greater than 4 mg are not recommended in patients with severe renal insufficiency (CLCr <30 mL/min), or in patients taking a potent CYP3A4 inhibitor. TOVIAZ is not recommended for use in patients with severe hepatic impairment (Child-Pugh C).

The most frequently reported adverse events (≥4%) for TOVIAZ were: dry mouth (placebo, 7%; TOVIAZ 4 mg, 19%; TOVIAZ 8 mg, 35%) and constipation (placebo, 2%; TOVIAZ 4 mg, 4%; TOVIAZ 8 mg, 6%).

**References:**


For more information, visit www.ToviazHCP.com.

Please see brief summary of prescribing information on next page.