CONTEMPORARY OB/GYN JANUARY 2014, Vol. 59, No. 1 ACUTE ABNORMAL BLEEDING ■ EHRS AND DOCUMENTATION ■ TECH TOOLS ■ CLINICIAN TO CLINICIAN ■ 40TH ANNIVERSARY EDITORIAL

DR. JOHN QUEENAN ON 40 YEARS OF CONTEMPORARY OB/GYN

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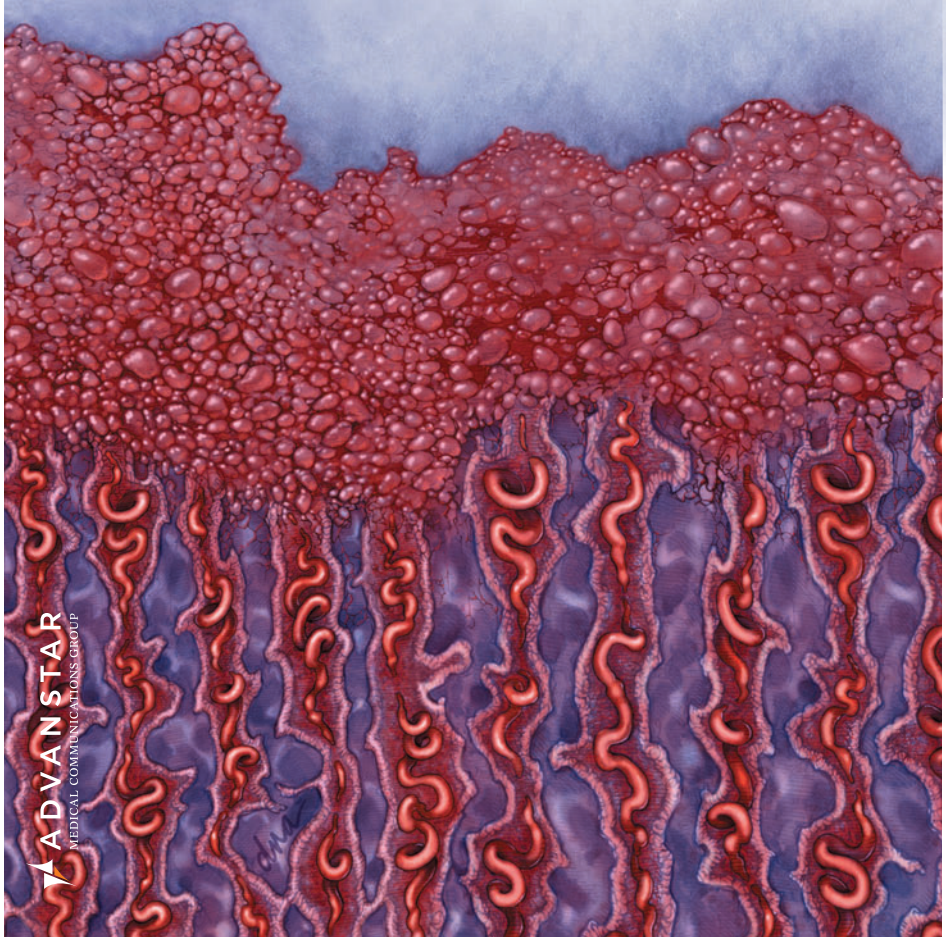
# HEAVY MENSTRUAL BLEEDING
## STAT management strategies

Anita L. Nelson, MD




## The EHR data chasm

## DO WE REALLY NEED THE ROBOT?

TECH TOOLS

## Bioprinting
### Will it be a game-changer?

Hormonal imbalance is a common cause of the friable endometrium that triggers acute, abnormal uterine bleeding in women of reproductive age.

JANUARY 2014 | VOLUME 59, NUMBER 1

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# DUAVEE™

## CONJUGATED ESTROGENS/ BAZEDOXIFENE 0.45 MG/20 MG TABLETS

**THE FIRST AND ONLY** therapy to pair conjugated estrogens with an estrogen agonist/antagonist, also known as a selective estrogen receptor modulator (SERM)[1]

**DUAVEE is indicated in women with a uterus for[1]:**

- Treatment of moderate to severe vasomotor symptoms associated with menopause
- Prevention of postmenopausal osteoporosis

Use DUAVEE for the shortest duration consistent with treatment goals and risks for the individual woman. When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk and non-estrogen therapies should be considered.

**To find out more about DUAVEE and sign up for educational webcasts, visit duaveehcp.com/signup**

### IMPORTANT SAFETY INFORMATION

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

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

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

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

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

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

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

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

Estrogens increase the risk of gallbladder disease. Discontinue estrogen if loss of vision, severe hypertriglyceridemia, or cholestatic jaundice occurs.

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

### INDICATIONS

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

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

**Reference: 1.** DUAVEE [Package Insert]. New York, NY: Pfizer Inc.; 2013.

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

**DUAVEE is expected to be available February 2014!**



October 2013 APC605824-01

Pfizer U.S. Pharmaceuticals

# DUAVEE®

## CONJUGATED ESTROGENS/ BAZEDOXIFENE 0.45 MG/20 MG TABLETS

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

**WARNING: ENDOMETRIAL CANCER, CARDIOVASCULAR DISORDERS, AND PROBABLE DEMENTIA**

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

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

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

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

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

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

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

**INDICATIONS AND USAGE**

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

**Important Limitations of Use**

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

**CONTRAINDICATIONS**

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

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

**WARNINGS AND PRECAUTIONS**

**Drugs Containing Progestins, Estrogens or Estrogen Agonist/Antagonists**

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

**Cardiovascular Disorders**

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

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

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

Stroke

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

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

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

Coronary Heart Disease

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

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

Venous Thromboembolism (VTE)

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

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

**Malignant Neoplasms**

Endometrial Cancer

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

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

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

Breast Cancer

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

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

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

Ovarian Cancer

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

**Probable Dementia**

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

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

**Gallbladder Disease**

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

**Visual Abnormalities**

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

**Elevated Blood Pressure**

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

**Hypertriglyceridemia**

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

**Hepatic Impairment and Past History of Cholestatic Jaundice**

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

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

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

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

**Hypothyroidism**

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

**Fluid Retention**

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

**Hypocalcemia**

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

**Hereditary Angioedema**

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

**Exacerbation of Other Conditions**

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

**Premenopausal Women**

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

**Laboratory Tests**

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

**Drug-Laboratory Test Interactions**

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

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

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

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

Impaired glucose tolerance.

**ADVERSE REACTIONS**

The following adverse reactions are discussed in greater detail in other sections of the label:

- Cardiovascular Disorders *[see Warnings and Precautions]*
- Malignant Neoplasms *[see Warnings and Precautions]*
- Gallbladder Disease *[see Warnings and Precautions]*
- Hypertriglyceridemia *[see Warnings and Precautions]*

**Clinical Trials Experience**

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

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

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

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

| ADVERSE REACTIONS (INCIDENCE ≥ 5%) MORE COMMON IN THE DUAVEE TREATMENT GROUP IN PLACEBO-CONTROLLED TRIALS | | |
|---|---|---|
| | DUAVEE (N=1224) n (%) | Placebo (N=1069) n (%) |
| **Gastrointestinal disorders** | | |
| Nausea | 100 (8) | 58 (5) |
| Diarrhea | 96 (8) | 57 (5) |
| Dyspepsia | 84 (7) | 59 (6) |
| Abdominal pain upper | 81 (7) | 58 (5) |
| **Musculoskeletal and connective tissue disorders** | | |
| Muscle spasms | 110 (9) | 63 (6) |
| Neck pain | 62 (5) | 46 (4) |
| **Nervous system disorders** | | |
| Dizziness | 65 (5) | 37 (3) |
| **Respiratory, thoracic, and mediastinal disorders** | | |
| Oropharyngeal pain | 80 (7) | 61 (6) |

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

**DRUG INTERACTIONS**

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

**Cytochrome P450 (CYP)**

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

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

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

**Uridine Diphosphate Glucuronosyltransferase (UGT)**

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

**Atorvastatin**

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

**USE IN SPECIFIC POPULATIONS**

**Pregnancy** Pregnancy Category X *[see Contraindications]*

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

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

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

**Nursing Mothers**

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

**Pediatric Use**

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

**Geriatric Use**

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

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

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

**Renal Impairment**

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

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

**Hepatic Impairment**

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

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

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

**Use in Women with Body Mass Index (BMI) > 27 kg/m²**

A 17% reduction in bazedoxifene exposure was predicted in women with BMI > 27 kg/m² (N=144) compared to those with BMI ≤ 27 kg/m² (N=93) after administration of DUAVEE, based on a population pharmacokinetic model using data from four Phase 1 studies. A reduction in bazedoxifene exposure may be associated with an increased risk of endometrial hyperplasia. Regardless of BMI, adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding.

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

**Venous Thromboembolic Events**

Advise patients to immediately report to their physician any signs or symptoms related to venous thrombosis and thromboembolic events *[see Warnings and Precautions]*.

**Abnormal Vaginal Bleeding**

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

**Possible Serious Adverse Reactions with Estrogen Therapy**

Inform postmenopausal women of possible serious adverse reactions of estrogen therapy including Cardiovascular Disorders, Malignant Neoplasms, and Probable Dementia *[see Warnings and Precautions]*.

**Possible Less Serious Adverse Reactions with DUAVEE**

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

**Calcium and Vitamin D Intake**

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

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

Contemporary OB/GYN

CONTEMPORARYOBGYN.NET
VOL. 59, NO. 1
JANUARY 2014

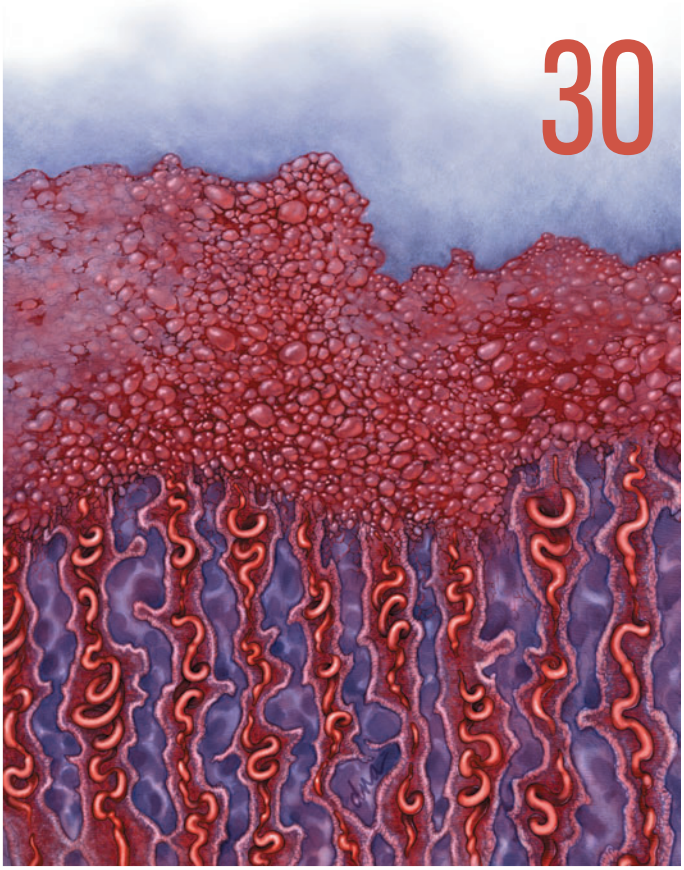




ILLUSTRATION BY ALEX BAKER, DNA ILLUSTRATIONS, INC.

***CONTEMPORARY OB/GYN*** (Print ISSN#0090-3159, DIGITAL ISSN#2150-6264), is published monthly by Advanstar Communications, Inc, 131 West First St, Duluth, MN 55806-2065. One-year subscription rates: $110.00 per year (USA and Possessions); $140.00 per year (elsewhere). Single copies (prepaid only) $12.00 in the USA; $18.00 per copy elsewhere. Include $6.50 per order plus $2.00 for US postage and handling. **Periodicals postage paid** at Duluth, MN 55806 and additional mailing offices. **POSTMASTER:** Please send address changes to *Contemporary OB/GYN*, PO Box 6084, Duluth, MN 55806-6084. Return Undeliverable Canadian Addresses to: IMEX Global Solutions, PO Box 25542, London, ON N6C 6B2, CANADA. Canadian GST number: R-124213133RT001. Publications Mail Agreement Number 40612608. Printed in USA. Subscription inquiries/address changes: toll-free 888-527-7008, or dial direct 218-740-6477.


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BY **JOHN T. QUEENAN, MD**

# Happy 40th birthday to *Contemporary OB/GYN*

As *Contemporary OB/GYN* enters its 41st year of continuous publication, our founding editor looks back at the journal's early years.

Contemporary OB/GYN *begins publication at a time when the specialty faces complex problems, not the least of which involves the very nature of the discipline itself. As we know, there is increasing discussion of the obstetrician-gynecologist's role: Are patients best served by specialists managing every healthy woman from conception through delivery? Or should board-certified obstetrician-gynecologists re-allocate their efforts, directing them largely to the high-risk pregnancy and to the patient with gynecologic dysfunction or disease? In short, how can the discipline best serve its patients?*

Letter from the Editor
*Contemporary OB/GYN*
Volume 1, Number 1
January 1973

When I was 36 years old and a Clinical Associate Professor at The New York Hospital/Cornell Medical Center, Dale Bauer, publisher of *Medical World News* at McGraw-Hill, invited me to start an annual roundup of the key advances in obstetrics and gynecology for *Medical World News*. After that became widely read and successful, Dale asked me to develop a monthly obstetrics and gynecology journal for all practitioners of the specialty called *Contemporary OB/GYN*.

It was 1972 and I had just moved to the University of Louisville, where I was Professor and Chair of Obstetrics and Gynecology while also serving as chair of the Fetal Monitoring Committee for the FDA. Following an FDA meeting in Washington, DC, I went to the airport and was told my flight to Louisville had been cancelled and there would be a 5-hour wait until the next flight. I found a quiet place, took out a yellow legal pad, and started to outline how *Contemporary OB/GYN* would be formatted.

At the time, many medical journals were reporting significant and not-so-significant research. But there was no publication that put scientific knowledge into a format for clinicians. *Contemporary OB/GYN* would steer clear

> We have **added new features and changed formats**, but always with the objective of how the information in the journal would help the practicing physician.

of animal studies and new esoteric reports. Our responsibility would be to look at what was known and proven and translate it into guidance for clinicians. The concept was to publish a journal that was clear, concise, and practical. We would have two targets: clinicians and their charge, the patients.

## Assembling the board

I set out to recruit a working editorial board of outstanding research physicians who also had backgrounds in practice. To my surprise, all but one physician who was invited accepted the challenge to venture into a new world of medical publishing.

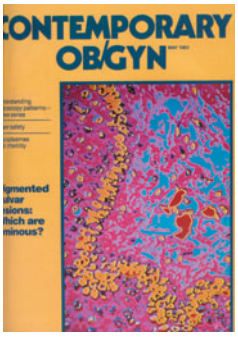
Among the first editorial board members were Drs. Hervy Averette, Ron Chez, Roger Freeman, Paula Hillard, John Lewis, Phil Mead, Jennifer Niebyl, Ralph Richart, Joe Leigh Simpson, Leon Speroff, and Ed Wallach, all leaders in their respective disciplines. (Drs. Hillard and Simpson are still on the board.)

Our efforts were aided by a succession of superb editors over the next 4 decades, including Don Rubin, Evelyn Gross, Jim Swan, Judy Orvos, and Paul Cerrato.

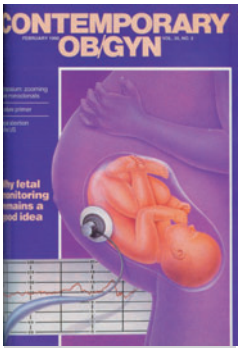
## Expert roundtables

Early on we realized that in some clinical areas—such as ovarian cancer—a large body of evidence–based studies was lacking. Our solution was to assemble a roundtable of four experts who would address key questions and answer them using their best clinical judgment, based on their own research and practice. The roundtables


1973




1983




1990

were valuable opinion pieces with outstanding experts making their best attempt to provide clinical perspective on emerging science. The discussions usually were scheduled at subspecialty meetings with one of the managing editors present.

I remember Jim Swan and subsequently Judy Orvos assembling the group, posing the questions, recording the proceedings, taking photographs of the participants in action, and then editing the transcripts. In an era before meta-analyses, the Agency for Healthcare Research and Quality, and U.S. Public Health Service Task Force reports, these roundtables were very popular.

## A turning point

In 1973, when *Contemporary OB/GYN* made its debut, medical journals were published in a 6 1/2 x 10-inch format. *Contemporary OB/GYN*, in contrast, was 8 x 10 1/2 inches, a format that advertisers, the lifeblood of the publication, preferred. Soon pressure was on the other journals in the market to change their size to match *Contemporary OB/GYN*. Although our editorial board was pleased that the journal had this impact, we still didn't believe we had achieved the gravitas that we had hoped for. Then an event occurred that changed our perception.

Dr. Richard Mattingly, Editor-in-Chief of *Obstetrics & Gynecology,* agreed to chair a roundtable on cancer for *Contemporary OB/GYN* in Key Biscayne, Florida, at the Society of Gynecologic Oncology annual meeting. Just before the roundtable, Dr. Mattingly

emerged from an *Obstetrics & Gynecology* board meeting with a very long face and told me that the board had ruled that he should not participate in a roundtable for a competing publication. Dr. Mattingly was chagrined and I was very disappointed because we had to make a quick substitution. But as the day wore on, I became elated because I recognized the first concrete sign that *Contemporary OB/GYN* had "arrived."

## Keeping up with changes

During the journal's early years, we witnessed many exciting and revolutionary advances that are now taken for granted, including electronic fetal monitoring, sonography, laser surgery, colposcopy, microsurgery, new forms of contraception, hormone replacement therapy, ovulation induction, and in vitro fertilization, to name a just a few. Thus the reporting and debates in the pages of *Contemporary OB/GYN* were interesting and spirited.

Over the years we added new features and changed formats, but always with the objective of how the information in the journal would help the practicing physician. Syndicated industry readership surveys were the best indicator of our effectiveness. *Contemporary OB/GYN* was ranked number one in readership on these studies for 18 years. Based on that success, *Contemporary Pediatrics, Contemporary Urology,* and *Contemporary Oncology* were created.

Twenty-eight years as Editor-in-Chief went by in a flash. Well, not exactly. I did have to write more than 300 editorials, which I loved doing. I occasionally experienced writer's cramp yet was able to come up with an editorial by the deadline.

**An early editorial board meeting**


**In this undated photo, members of the *Contemporary OB/GYN* editorial board, their spouses, and the editor assembled for a group shot.**
***Seated (L to R):*** **Ralph Richart, Hervy Averette, John Lewis, John Queenan.** ***Standing (L to R):*** **Barclay Averette (spouse), Leon Speroff, Sen Speroff (spouse), Ron Chez, Evelyn Gross (editor), Ed Wallach, Joanne Wallach (spouse), Carrie Queenan (spouse).**


1996


2013

## The Lockwood era

One day out of the blue I received a call from Jim Scott asking me to be the Deputy Editor of *Obstetrics & Gynecology*. Although I had recently signed a 5-year contract with *Contemporary OB/GYN,* the publisher agreed to release me. I promptly headed straight to the office of Dr. Charles Lockwood, then at New York University, and asked if he would like to be the Editor-in-Chief of *Contemporary OB/GYN.* Charly agreed and in July 2001, we began a new and exciting era with him in command. He is a superb teacher, researcher and clinician, and so was the perfect person to run *Contemporary OB/GYN.* (He also writes better editorials than I do.)

By continuing its dedication to helping clinicians practice, continually choosing practical subjects, and keeping up its custom of excellent artwork and graphics, Charly has brought the journal through difficult times of low advertising revenue.

As a sign of its success, *Contemporary OB/GYN* is now entering its 41st year in continuous publication and is still the most highly read ob/gyn publication from a number of industry perspectives. Equally important, it is still highly respected.

Bravo, Charly. Bravo to all who have helped along the way. COG

**Dr. Queenan** is Founding Editor of *Contemporary OB/GYN* and Professor and Chair Emeritus in the Department of Obstetrics and Gynecology, Georgetown University School of Medicine, Washington, DC.

# Letter from the editor

CONTEMPORARY OB/GYN begins publication at a time when the specialty faces complex problems, not the least of which involves the very nature of the discipline itself. As we know, there is increasing discussion of the obstetrician-gynecologist's role: Are patients best served by specialists managing every healthy woman from conception through delivery? Or should board-certified obstetrician-gynecologists re-allocate their efforts, directing them largely to the high-risk pregnancy and to the patient with gynecologic dysfunction or disease? In short, how can the discipline best serve its patients?

Keeping up with the immense flow of information and the demands of patients is an increasingly difficult task for the physician. It is estimated, in fact, that those who are now completing their training in obstetrics and gynecology must assimilate twice the amount of information that was available to their counterparts only ten years ago. This magazine's concern is to help all practitioners stay abreast of developments as they occur.

**Editor Queenan is professor and chairman of the department of obstetrics and gynecology, University of Louisville School of Medicine.**

Each month, through signed articles, interviews, symposiums, and news reports, CONTEMPORARY OB/GYN will deliver information on the latest thinking and trends in diagnosis, therapy, and preventive medicine. We will also examine the socioeconomic impact of what we do—or fail to do. Information will be practical, current, and readable, and it will emanate from those specialists who are involved in the subjects under examination.

In the pages that follow, for example, a major article describes the sophisticated high-risk obstetric care being provided at Los Angeles County–USC Medical Center. Future issues will report on this institution's clinical work in reproductive biology and gynecologic oncology.

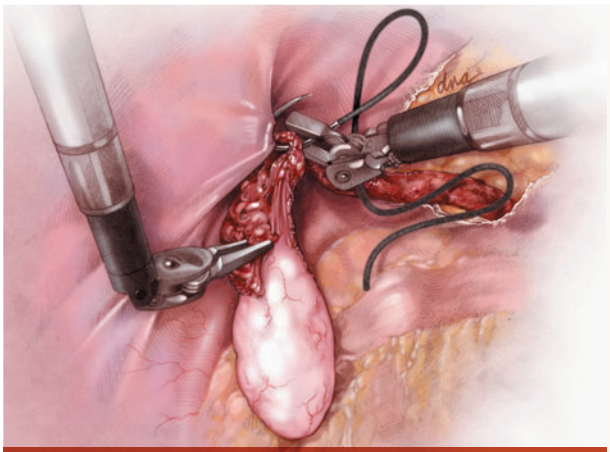
Also in this issue, four laparoscopists hold a symposium on their use of the technique for female sterilization. And we begin a series on high-risk pregnancy with the views of two obstetrician-gynecologists on the medical and obstetric management of the pregnant diabetic. Our first issue also reports on current problems and trends in adoption, a subject on which obstetrician-gynecologists are often consulted.

By reporting what is current and practical, CONTEMPORARY OB/GYN will itself be helping improve the delivery of quality obstetric-gynecologic care.

**John T. Queenan, M.D.**

# TRENDING NOW

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



## Preserving fertility

**in women facing cancer**

**contemporaryobgyn.net/fertility_preservation**

A review of the risks of infertility associated with specific cancer treatments, and fertility preservation strategies for patients who are undergoing them. At left, the left ovary is transposed to the pelvic brim for fertility preservation prior to radiation therapy for pelvic cancer.

## on twitter

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

**CaracasFertility** @FamiliaCFC2013
Consumo de bebidas azucaradas puede aumentar la posibilidad de desarrollar cancer de endometrio http://shar.es/DO1mG vía @ContempOBGYN

**Dr. Arda Lembet** @ArdaLembet
ACOG task force on hypertension in pregnancy--A step forward in management http://shar.es/OuLUT @ContempOBGYN

**Martha Martínez** @martinezcolpos
"@ContempOBGYN: Legal Case: #Preterm labor, SROM result in infant death. http://ow.ly/rIFLR #malpractice"

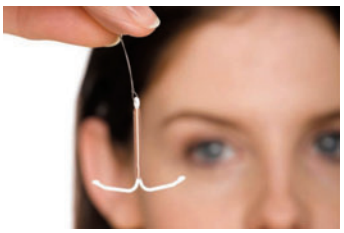
**Her Viewpoint** @HerViewpoint
@drsuzyyhall @DrStrickland @ContempOBGYN loving the attention the IUD is making! pic.twitter.com/q88RkMoxn6

## on facebook

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

**Contemporary OB/GYN**
December 3

Take a look at our resource center containing the latest information on long-acting contraception.
http://contemporaryobgyn.modernmedicine.com/longactingcontraception



**Contemporary OB/GYN**
December 6

Young women with cervical, endometrial, or ovarian cancer who want children face fertility challenges because of their cancer treatment. But today, there are many options for preserving reproductive capacity.

**TABLE 1 Fertility preservation strategies for reproductive aged women with cancer**

| | |
|---|---|
| GYNECOLOGIC SURGERY | • Early-stage cervical cancer: radical trachelectomy<br>• Early-stage endometrial cancer: progestin therapy<br>• Early-stage ovarian cancer: conservative surgery |
| RADIATION THERAPY | • Pelvic shielding<br>• Ovarian transposition<br>• Embryo cryopreservation<br>• Oocyte cryopreservation |
| CHEMOTHERAPY | • Embryo cryopreservation<br>• Oocyte cryopreservation |

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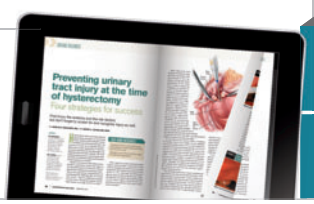

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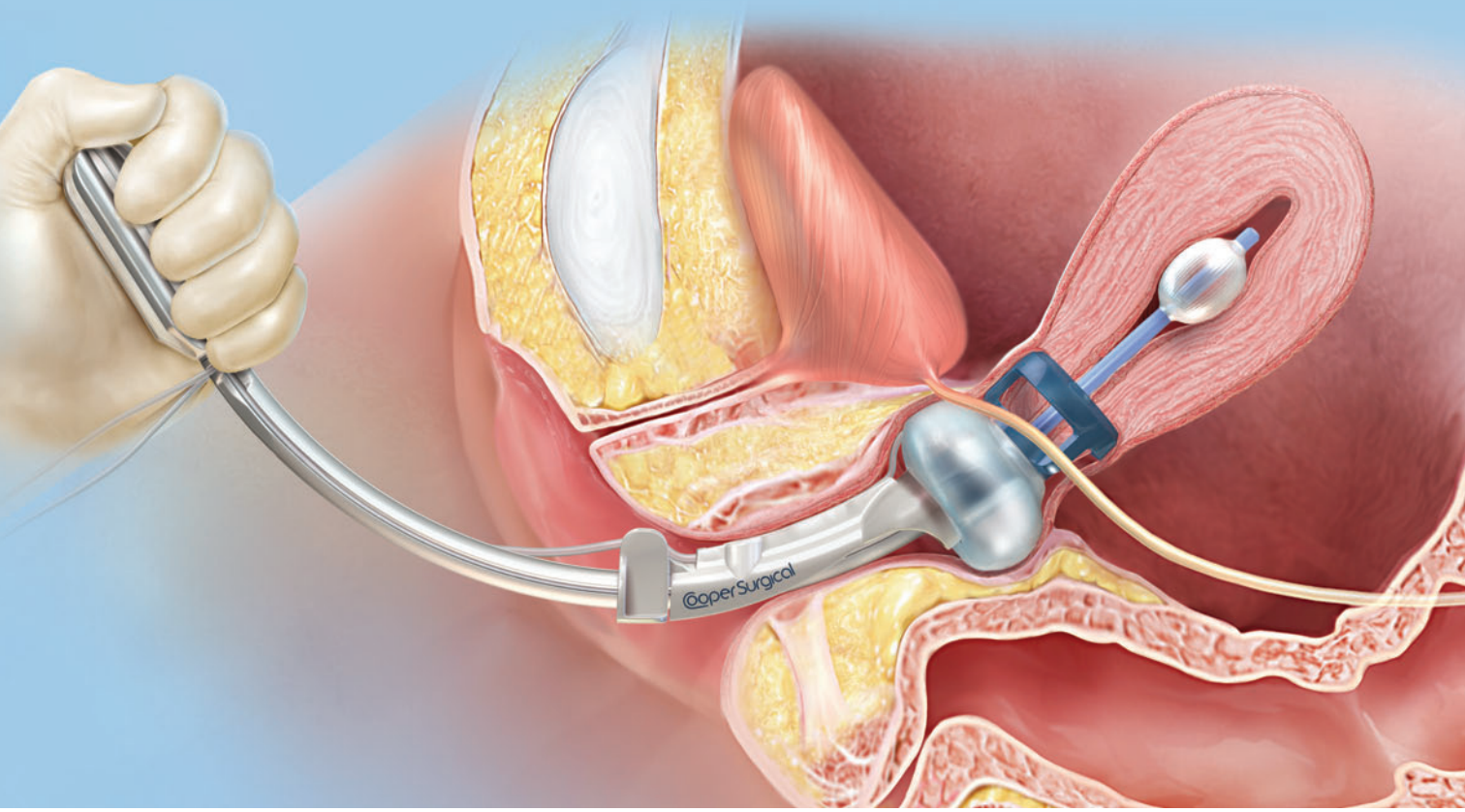
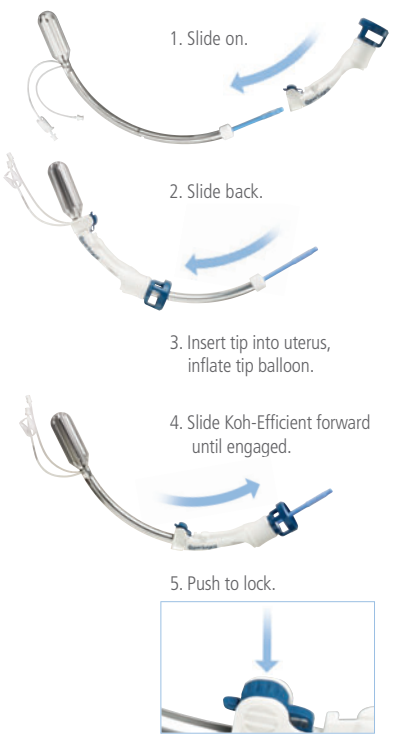
ILLUSTRATION BY ALEX BAKER, DNA ILLUSTRATION, INC.

# TLH Simplified… Without Compromise

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# The Advincula Arch™

"The Advincula Arch is an innovative uterine manipulator. When combined with the Arch Koh-Efficient™ it provides ease of use and functionality during all the critical stages of a TLH"

- Arnold Advincula, MD FACOG, FACS

## Designed for Ease of Use and Functionality

### Simple

- Faster setup – Integrated Koh Cup™ and pre-attached occluder balloon facilitates assembly
- Simple, lightweight design
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### Uncompromised Functionality

- Durability – Provides unprecedented simplicity in a reusable design compared to disposable manipulators that "buckle under pressure"
- Superior visualization and control – the right colpotomy cup for every TLH
- Outstanding anteversion and retroversion in a durable configuration

During TLH procedures, the Koh-Efficient creates a 'margin of safety' by providing a visual landmark and backstop for full circumferential colpotomy, as well as distancing the ureters during the incision. Vaginal length is maximized and pneumoperitoneum is maintained.

To schedule a demonstration or trial, call 800.243.2974 or 203.601.5200. To learn more visit coopersurgical.com or see us at youtube.com/coopersurgical

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## Supreme Court prepares to hear arguments over contraception mandate

The Supreme Court's decision in late November to hear arguments in 2 cases challenging the federal government's contraceptive mandate should provide clarity as health insurers work to comply with the Affordable Care Act (ACA), according to a lawyer who advises managed care organizations.

George B. Breen, a partner in the Washington, DC, law firm of Epstein Becker Green and chairman of its healthcare and life sciences practice, says conflicting decisions in more than 80 pending lawsuits challenging the mandate's constitutionality have rendered a Supreme Court decision imperative. ACA rules require health plans to offer members FDA-approved contraceptives with no cost sharing, based on national recommendations from a preventive-service task force.

While religious organizations are exempt and religiously affiliated organizations have a workaround, private, for-profit employers do not. The center of the issue calls into question whether a corporation—perhaps one that is family-owned, such as retailer Hobby Lobby—has the protection of religious freedom and can object to providing employees free contraceptives based on religious objections.

A high-court decision either for or against the ACA mandate will impact claims adjudication, financial management, customer service, medical policy, and more, Breen says.

"There are just a number of potential repercussions that come into play in the event there is a decision made that it's unconstitutional or whether there's provision that there are certain types of contraceptive services somehow permitted to not be subject to the requirement. It creates further confusion in the industry at a number of levels," he says.

With regard to pricing, for example, plans are left to wonder how services will be provided and who will pay for them.

"The law, as it stands now, says this is an essential health benefit that cannot have any cost-sharing on the part of the member," Breen says. "How do costs get accounted for if you now have a change in the law?"

It's a continuation of the confusion that insurers have faced. Breen says it leaves a sense of uncertainty as to how the contraceptive coverage rules will ultimately play out.

**In both cases, the companies argue that they are protected by the Religious Freedom Restoration Act (RFRA) signed into law in 1993 by President Bill Clinton.**

The court is expected to hear arguments this spring regarding 2 cases, *Kathleen Sebelius v. Hobby Lobby* and *Conestoga Wood Specialties v. Sebelius*, in which for-profit corporations claim that the federal mandate that businesses provide certain contraceptive drugs and devices for their employees violates their companies' religious freedom. Both companies take exception with 4 drugs the FDA classifies as contraception that prevent implantation of a fertilized egg, which those who believe life begins at conception say is tantamount to abortion.

In both cases, the companies argue that they are protected by the Religious Freedom Restoration Act (RFRA) signed into law in 1993 by President Bill Clinton. RFRA protects "a person's exercise of religion," and, according to Congress's Dictionary Act, a corporation is a person under the law.

At issue, then, is whether a for-profit corporation can be protected by RFRA, and whether it is a violation of the RFRA to require a business to provide insurance for contraceptives when that coverage violates the owners' personal religious beliefs, according to a women's health policy brief prepared by the Kaiser Family Foundation (KFF).

continued on **PAGE 23**

Published as an educational, promotional supplement to Contemporary OB/GYN®
January 2014

# APTIMA® HPV ASSAY PERFORMANCE: Correlation Between Detection of Human Papillomavirus E6/E7 mRNA and Clinically Relevant Cervical Disease Detection

*By Mark H. Einstein, MD, MS*

*Professor and Vice Chair for Research,*

*Department of Obstetrics & Gynecology and Women's Health*

*Albert Einstein College of Medicine and Albert Einstein Cancer Center*

*Montefiore Medical Center*

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# APTIMA® HPV ASSAY PERFORMANCE:
## Correlation Between Detection of Human Papillomavirus E6/E7 mRNA and Clinically Relevant Cervical Disease Detection

*By Mark H. Einstein, MD, MS*
*Professor and Vice Chair for Research,*
*Department of Obstetrics & Gynecology and Women's Health*
*Albert Einstein College of Medicine and Albert Einstein Cancer Center*
*Montefiore Medical Center*

## *RELATIONSHIP BETWEEN HPV INFECTION AND CERVICAL CANCER*

The discovery of the role of human papillomavirus (HPV) as a necessary etiologic agent in the development of cervical cancer 35 years ago marks a key discovery in our understanding of cervical cancer, and the eventual development of screening and prevention strategies to target HPV. In particular, it has resulted in important leaps in the development of a new primary prevention strategy of HPV vaccination and utilizing molecular methods to assist providers in screening and management of precancerous lesions. Although there are more than 100 types of HPV, 14 types (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68) have oncogenic potential and are considered "high-risk" HPV types (HR-HPV); of these HR-HPV types, HPV 16 and 18 are the types responsible for 70% of cervical cancers worldwide.[1]

**About 80% of sexually active women are estimated to become infected with one or more HPV types in their lifetime.[2]**

HPV is the most common sexually transmitted infection, and about 80% of sexually active women are estimated to become infected with one or more HPV types in their lifetime.[2] Young women are more likely to be infected with HPV, but when compared to older women, are also more likely to have regression of clinically detectable infection.[3,4]

## *MOLECULAR BIOLOGY OF HPV INFECTION*

HPV infection of the cervix most often originates from skin to skin contact, typically from exposure through sexual activity. Once in the female reproductive tract, the virus infects cervical squamous


Funding and content provided by Hologic, Inc.

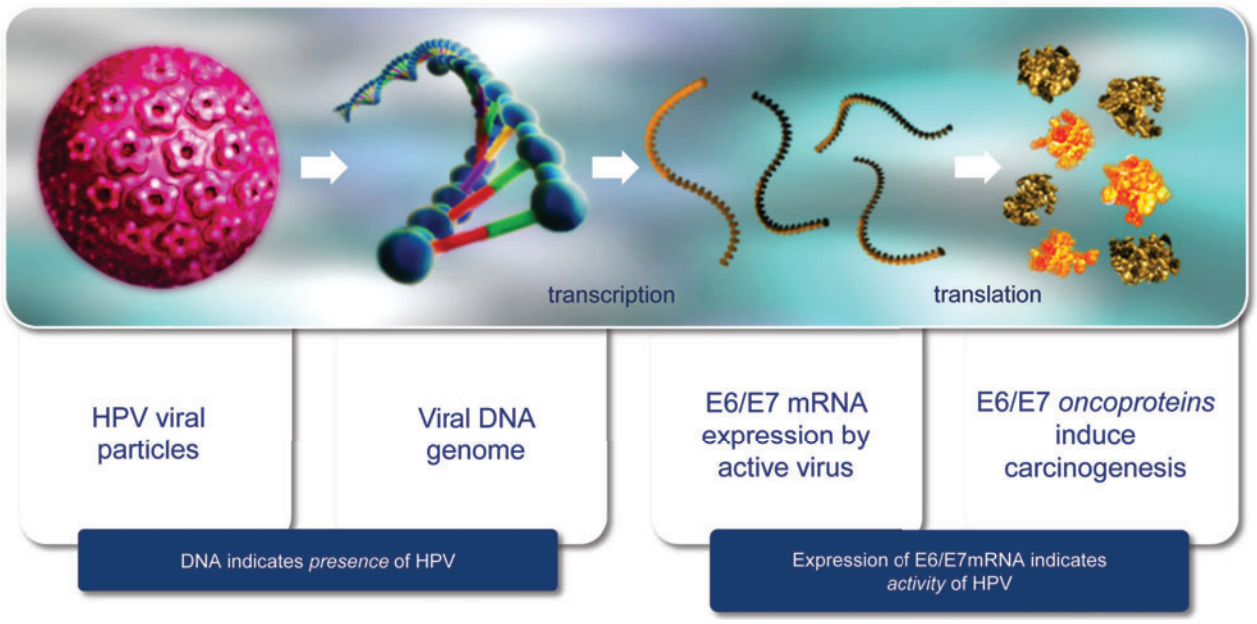


**Figure 1. Molecular biology of HPV infection.** HPV viral particles enter cervical epithelial cells. In active infections, the viral genome integrates into the host cell genome. This leads to the expression of HPV E6 and E7 mRNA and oncoproteins, which induces carcinogenesis.

epithelial cells. In infected cells, HPV DNA (~8 kb) can remain either in episomal form (free) or integrate into the cell genome.[5,6] Integration often induces the expression of HPV E6 and E7 mRNA and proteins (Fig. 1). These oncoproteins interact with various proteins of the host cell (which they can inhibit or degrade), leading to the inability of the cell to inhibit apoptosis and allow for DNA repair.[7] For instance, E6 protein causes degradation of the tumor suppressor protein p53, increasing the rate of random mutations that can lead to transformation.[8] E7 inhibits the function of the Rb protein which regulates the cell cycle,[9] which, when inhibited, can also drive the cell into a path of neoplastic transformation (Fig. 1).

**The presence of E6/E7 mRNA indicates that the infection has become more biologically and likely clinically "active," i.e., potentially oncogenic.**

Thus, while the presence of HPV DNA indicates the existence of an infection, the presence of E6/E7 mRNA indicates that the infection has become more biologically and likely clinically "active," i.e., potentially oncogenic. The key involvement of E6 and E7 in oncogenesis is supported by the fact that E6 and E7 mRNAs are expressed in cervical cancer cells[10] and the expression of E6 and E7 mRNAs increases with increasing severity of cervical disease.[11] Moreover, many studies have shown the association between E6/E7 expression and cell transformation and the maintenance of a transformed phenotype.[7] Altogether, these findings suggest that E6/E7 mRNAs are excellent markers

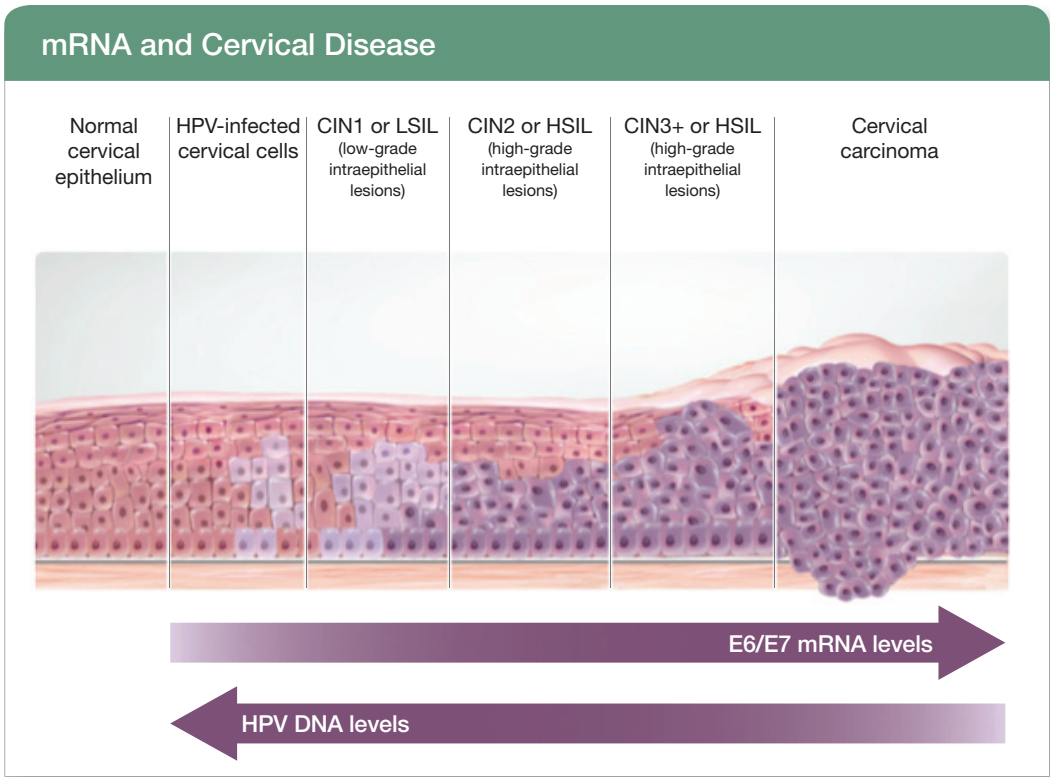


**Figure 2.** Progression from initial HPV infection to cervical disease.

for the detection of underlying and developing cervical disease.

## *DISEASE PROGRESSION*

The development of cervical cancer from the initial HPV infection is illustrated in Figure 2. Initial HPV infections can often manifest themselves as an abnormal cervical cytology, such as atypical squamous cells of undetermined significance (ASC-US) or low-grade squamous intraepithelial lesion (LSIL) cytology, shortly after infection of cervical epithelial cells. In most cases, these low-grade lesions are merely cytomorphological manifestations of a transient HPV infection, and most often regress. Rarely, often over many years, do they progress to a high-grade cervical intraepithelial neoplasia (CIN). Progression from a high-grade lesion to cervical cancer takes over a decade. It appears to take longer for a CIN3 lesion to evolve into cervical cancer than for an initial infection to evolve into a high-grade lesion.[1]

Persistence of HPV infection is mandatory for the transformation of low-grade lesions into high-grade lesions. As most (70%) HPV infections regress within 1 year after detection of the virus,[12-14] so do most equivocal CIN lesions: of the CIN2 lesions, 40% are likely to regress within 2 years.[15] Once CIN3 (or worse) lesions have developed, regression is unlikely and this needs to be treated.[16]

## *APTIMA HPV ASSAY*

The Aptima HPV assay (Hologic, Inc.) was developed to qualitatively detect E6/E7 mRNA from 14 HR-HPV types (HPV


Funding and content provided by Hologic, Inc.

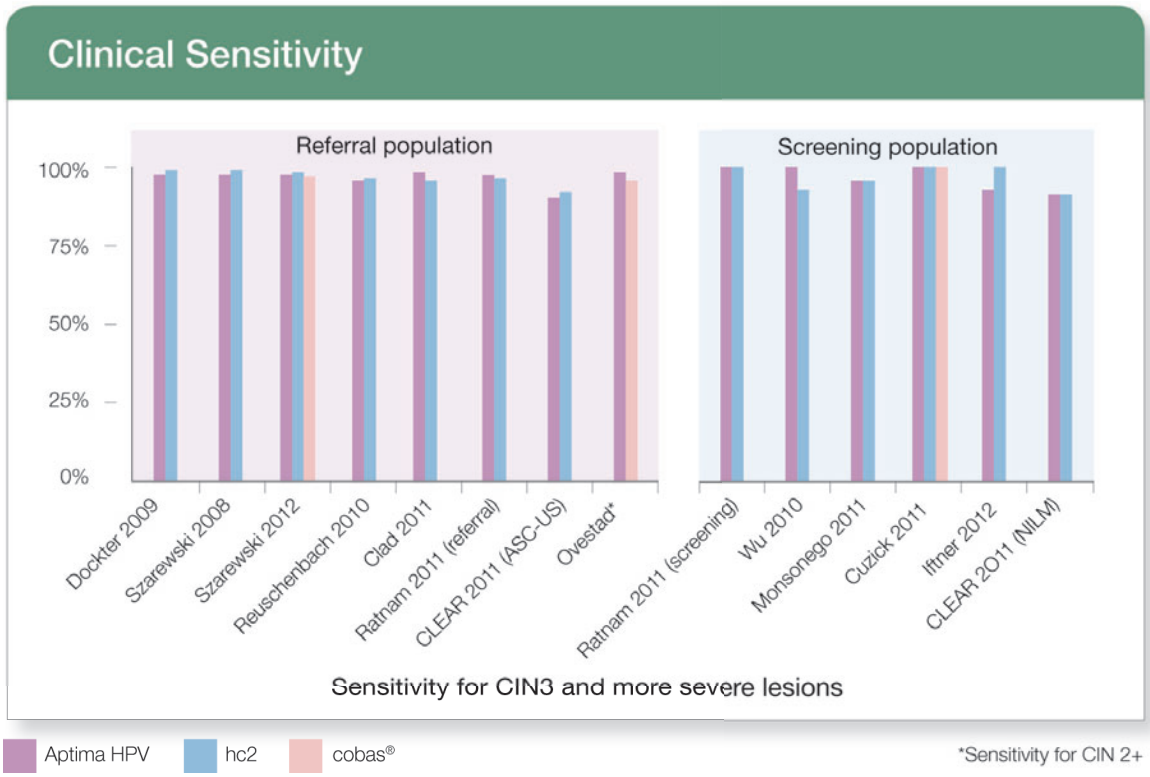


Figure 3. Sensitivity of Aptima HPV versus DNA-based HPV tests – Data from the literature. HC2 = Digene® Hybrid Capture® 2 HPV DNA Test®; Cobas = Roche Cobas® AMPLICOR® HPV Test.[17, 20-30]

16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) based on the fact that the presence of HPV E6/E7 mRNAs is an excellent indicator of cervical disease. This clinically validated mRNA assay uses a different technology as compared to other clinically validated HPV DNA tests. The assay involves three main steps, which take place in a single tube at one temperature: (i) target capture of the target mRNA using capture oligomers and magnetic microparticles; (ii) target mRNA amplification using Transcription-Mediated Amplification; and (iii) detection of the amplification products (amplicons) using the Hybridization Protection Assay.[17]

**This clinically validated mRNA assay uses a different technology as compared to other clinically validated HPV DNA tests.**

*Sensitivity*

The sensitivity of the Aptima HPV assay for the detection of CIN3 or worse lesions has been reported to be higher than 90%, and statistically equivalent to that of DNA-based tests in comparative studies performed in referral and screening populations (Fig. 3). A meta-analysis showed that the sensitivity of the Aptima HPV test is equivalent to that of Hybrid Capture 2, the reference HPV test, when the two assays were compared side-by-side for the detection of CIN2+ or CIN3+ lesions in women with ASC-US or LSIL cytology (Table 1).[18]

**Table 1.** Pooled relative sensitivity and specificity of Aptima HPV vs. HC2

| Triage group | Outcome | Parameter | Ratio (APTIMA/HC2) |
|---|---|---|---|
| ASC-US | CIN2+ | Sensitivity | 1.01 (0.97-1.06) |
| | | Specificity | 1.19 (1.08-1.31) |
| | CIN3+ | Sensitivity | 1.01 (0.96-1.06) |
| | | Specificity | 1.18 (1.08-1.29) |
| LSIL | CIN2+ | Sensitivity | 0.96 (0.92-1.03) |
| | | Specificity | 1.37 (1.22-1.54) |
| | CIN3+ | Sensitivity[1] | 0.98 (0.91-1.06) |
| | | Specificity[1] | 1.35 (1.11-1.66) |

*Reproduced (without modification) from Arbyn 2013 article (reference 18) with the authors' permission. Specificity data are pooled data from references 17, 20, 23-25, 27, 28, 31.*

As shown in multiple prospective cohorts, HPV testing is typically more sensitive than cytology in a screening population. A study of compiled data from European and North American studies comparing cytology and HPV testing showed that cytology alone has a much lower sensitivity than screening strategies that include both cytology and HPV testing.[19]

*Specificity*

The Aptima HPV assay has shown an excellent, if not greater specificity, than other HPV DNA-based tests. This suggests that Aptima HPV might yield fewer false positive results than HC2 in a screening population. In a pooled analysis of eight studies, the Aptima HPV assay had a significantly higher specificity than the HC2 reference test for the detection of CIN2+ in women with ASC-US (Table 1).[18] Even in an LSIL population, it appears that in older women, HPV testing might offer improved triage risk stratification. Because of its improved specificity, the Aptima HPV test might also offer such risk stratification. This higher specificity of the Aptima HPV test has the potential to help reduce the number of unnecessary colposcopies, which are a recognized harm to patients in the most recent treatment guidelines.[16]

**It appears that in older women, HPV testing might offer improved triage risk stratification.**

## *APTIMA HPV ASSAY IS IN COMPLIANCE WITH GUIDELINES*

The Aptima HPV assay has been approved by the U.S. Food and Drug Administration (FDA) for the detection of HPV in clinical samples (ThinPrep® Liquid Cytology Specimens). For the assay to be used internationally, it is required to meet international guidelines mandating that the assay meets the criterion of non-inferiority in comparison to a reference assay as well as intra- and inter-laboratory reproducibility criteria.[32] A recently published study showed that the Aptima HPV assay had a clinical sensitivity and specificity similar to that of a GP5+/6+-PCR-based assay ($P = 0.039$ and $P = 0.00016$, respectively), an intra-laboratory reproducibility over time of 96.0% (kappa 0.89) and an inter-laboratory agreement of 96.7% (kappa 0.91).[33] Thus, the Aptima HPV assay meets the cross-sectional clinical and reproducibility criteria of the international guidelines for HPV test requirements for cervical screening.



Funding and content provided by Hologic, Inc.

Recent guidelines for the prevention and detection of cervical cancer by the American Cancer Society, the American Society for Colposcopy and Cervical Pathology, and the American Society for Clinical Pathology in consensus with a number of other scientific and patient stakeholders[34] as well as the abnormal screening test management guidelines[16] recommend a preferred strategy of using HPV testing in conjunction with cytology (a strategy termed 'co-testing') for primary screening in women 30 to 65 years. Incorporating HPV testing in primary screening strategies is based on the higher sensitivity and negative predictive value of HPV testing when compared to cytology. The benefit of incorporating HPV testing into primary screening would be to increase disease detection while reducing the number of unnecessary colposcopies, which is a recognized harm to patients. The criteria set forth in the guidelines for HPV testing are that (i) the HPV test must detect HR (oncogenic) HPV types, mainly HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59; (ii) the HPV test must have been analytically and clinically validated with proven acceptable reproducibility, clinical sensitivity, specificity, and positive and negative predictive values for CIN2+, as documented by U.S. FDA licensing and approval or publication in peer-reviewed scientific literature;[16] (iii) sensitivity of HPV testing for CIN3+ and CIN2+ should be greater than or equal to 90%, and (iv) the percentage of women in the general population who test (screen) positive, as a measure of false positive results, should be less than or equal to established thresholds from well-validated HPV DNA tests.[34] The Aptima HPV assay meets all of these criteria and is suitable for use in screening and co-testing strategies for the detection of cervical cancer, according to the most recent U.S. guidelines. When used as per guidelines, screening strategies utilizing Aptima HPV and other highly sensitive molecular HPV tests ultimately improve the identification of clinically worrisome cervical disease and help risk-stratify those women who might need shorter interval follow-up. This helps focus on those few women at significant risk of cervical cancer, while safely informing providers of the many who can be managed conservatively, which ultimately minimizes patient harm.

**The benefit of incorporating HPV testing into primary screening (co-testing) would be to increase disease detection while reducing the number of unnecessary colposcopies…**

**The Aptima HPV assay is suitable for use in screening and co-testing strategies for the detection of cervical cancer, according to the most recent U.S. guidelines.**

## ACKNOWLEDGEMENTS

The author would like to acknowledge Florence Paillard for her editorial assistance.

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Funding and content provided by Hologic, Inc.

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continued from **PAGE 16**

The court also must decide whether the contraceptive coverage requirement violates the First Amendment's protection for free exercise of religion and if the owners' rights are violated by the mandate, the brief explains.

The decision, which is expected by summer, impacts most health plans, since only private plans that excluded contraception before the ACA's passage are grandfathered.

"Any new, private plan that's been changed since March 23, 2010, is not grandfathered and must provide coverage for all prescribed, FDA-approved methods of contraception," says Laurie Sobel, senior health policy analyst with KFF's women's health policy team.

Sobel, who co-authored the policy brief, sees broad ramifications ranging from additional health procedures such as blood transfusions and vaccinations to civil rights and fair housing protections, if an exception to the mandate is granted to corporations. Breen said such ramifications were unlikely.

## No significant link between SSRIs, autism

According to a new Danish study, use of serotonin reuptake inhibitors (SSRIs) during pregnancy showed no significant association with autism spectrum disorder (ASD). The study is the largest to date on the potential connection.

**When compared with no SSRI use, either before or during pregnancy, SSRI use during pregnancy was not significantly associated with ASD**

Researchers from Statens Serum Institute in Copenhagen studied every singleton live birth in Denmark from 1996 to 2008: 626,875, with follow-up through 2009. Danish population registries were used to identify maternal use of SSRIs before and during pregnancy, ASD diagnosed in the child, and potential confounders.

After 5,057,282 person-years of follow-up, the investigators found 3892 cases of ASD (incidence rate, 77.0 per 100,000 person-years). Fifty-two cases during 42,400 person-years of follow-up involved children of women who had SSRI exposure during pregnancy (incidence rate, 122.6 per 100,000 person-years). When compared with no SSRI use, either before or during pregnancy, SSRI use during pregnancy was not significantly associated with ASD (fully adjusted rate ratio, 1.20, 95% confidence interval [CI], 0.90 to 1.61). The fully adjusted rate ratio was 1.46 (95% CI, 1.17 to 1.81) among women who had SSRI exposure before pregnancy, but no exposure during their pregnancy.

The study authors concluded that there was no significant association between SSRIs and ASD. Because of the confidence interval, however, they indicated that they could not rule out a relative risk up to 1.61 and felt that the association required even further study.

Hviid A, Melbye M, Pasternak B. Use of selective serotonin reuptake inhibitors during pregnancy and risk of autism. *N Engl J Med.* 2013;369(25):2406–2415.

## Out-of-pocket infertility costs vary widely

Out-of-pocket costs for couples being treated for infertility range from a low of $912 for medication only to $19,234 for in vitro fertilization (IVF), according to researchers who say their data will help couples plan for the expenses they may incur. The current study is published online in the *Journal of Urology* ahead of the February 2014 print issue.

Many couples who seek infertility care have only partial or no insurance coverage, and the costs may be too burdensome for them, according to lead author James F. Smith, MD, MS, of the University of California, San Francisco. Even for couples who are receiving fertility care, socioeconomic status may influence the success of fertility treatment. These problems are compounded by the lack of comprehensive infertility insurance coverage in the United States.

In the study, couples were recruited from 8 reproductive endocrinology clinics. They were followed for 18 months from the start of treatment and were asked to maintain

continued on **PAGE 44**

# Defending an obstetric case the second time around

A child's disabilities are found to be unrelated to problems at her birth.

**THE PRIMARY FOCUS** of most malpractice cases—particularly concerning deliveries—is whether the practitioners departed from good practice in their care of mother and infant. Equally important and compelling, however, is whether the infant's medical issues have anything to do with the practitioners' actions.

## Facts

An $8 million verdict for the plaintiffs was rendered in a case in which negligence was alleged during a labor and delivery on January 5, 2001. On appeal, the court ruled that errors during that trial warranted retrial, and the case was transferred to our office. The plaintiff alleged that her infant sustained, among other things, brain damage (specifically, hypoxic ischemic encephalopathy [HIE]), cerebral palsy (CP), and a fractured humerus as a result of failure to perform a timely cesarean delivery.

The plaintiff also had a 9-year-old, a 6-year-old, and an 18-year-old from a previous marriage. Significantly, the eldest had suffered a fractured clavicle during delivery. This obstetrical history was not disclosed by the plaintiff during her prenatal care at the defendant hospital or at the time of the 2001 delivery.

The plaintiff learned that she was approximately 2 weeks pregnant following a vomiting episode in 2000. She visited a clinic where she was given prenatal vitamins and told that her due date was January 9, 2001.

On June 5, 2000, the plaintiff presented to the defendant hospital with complaints of bleeding for 45 minutes following sexual intercourse. She denied abdominal pain. The differential diagnosis included possible miscarriage. Her medical history indicated that she was 9 weeks pregnant but did not include the clavicle fracture sustained by her oldest daughter. The plaintiff was examined, stabilized, and discharged with instructions to follow up with her ob/gyn.

On November 29, the woman presented to the defendant hospital with complaints of shortness of breath and decreased fetal movement. She denied any medical history. She was examined, the fetal heart rate (FHR) was checked, both were deemed fine, and she was discharged home with labor instructions.

On December 24, she presented to the clinic with complaints of contractions, was examined, and was advised that she had not dilated. She testified during her deposition that following an ultrasound (U/S) she was told that she was carrying a "big baby." She was discharged and instructed to return to the hospital if her complaints continued. On December 31 she returned to the clinic, again with complaints of contractions. It was determined that she was approximately 1 cm dilated. The woman was advised that the baby was doing well and she was discharged. Her EDD was January 1, 2001.

On January 4, 2001, the plaintiff presented to the hospital emergency department (ED) with contractions. She was connected to an external fetal monitor and advised that the FHR and her contractions were fine. She testified that after an U/S she was told that her baby would be 9 or 10 lb. Her contractions were 8 minutes apart. She was told that she was "not fully dilated," and was discharged with instructions to drink fluids, walk, and return to the ED when she was in "active labor."

On January 5, the plaintiff awoke during the night and realized that her water had broken, revealing clear fluid. She testified that she arrived at the defendant hospital at approximately 4:15 AM and remained in the L & D unit

until about 5 PM. The record indicates that she was admitted to the hospital at 4:20 AM. The ED notes, authored by a certified nurse-midwife (CNM), indicate that on arrival the plaintiff stated "my baby is coming out." The CNM's notes reference the patient's first delivery of a baby weighing 8 lb, 13 oz. Her contractions were 2–5 minutes apart, lasting 55 seconds. She was 1 cm dilated and 50% effaced, with the baby at -3 station.

On January 5 at 6:55 AM, ob attending Dr. A noted that the patient's prenatal care was provided at a clinic and that she had previously delivered an 8 lb, 12 oz baby. The ob also noted that the baby seemed larger than 9 lb. She indicated that she would "observe labor" and proceed to cesarean delivery if no progress.

At 9 AM, the patient received an epidural, which remained in place until 2:05 PM. At 9:30 AM, ob attending Dr. B examined the patient and noted that the FHR was in the 140s, positive for accelerations and negative for decelerations. An exam revealed that she was 4 cm dilated and 100% effaced, with the baby at -3 station. The estimated fetal weight was greater than 9 lbs. Dr. B's plan included placement of an internal fetal monitor and close monitoring of labor. An hour later, Dr. B noted that the patient's temperature was 101.1°F and she remained 4 cm dilated. The FHR remained in the 140s, positive for accelerations and negative for decelerations. Dr. B's plan included considering antibiotics for the patient's elevated temperature.

A 10:43 AM nursing note states "fetal decels in the 110's." The patient was turned and given oxygen by mask. It was noted that Dr. B was made aware of the FHR. At 11:30 AM, Dr. B noted that the patient's temperature was 100.6°F. She also noted that the FHR remained in the 140s, positive for accelerations and negative for decelerations. Her plan included administering ampicillin and gentamycin by IV, Pitocin augmentation, and normal spontaneous vaginal delivery. Ten minutes later, Dr. B noted that the patient was 6 cm dilated and 100% effaced, with the baby in -2 station. There is also a note that the patient had an adequate pelvis.

A nursing note at 11:45 AM stated that there were mild variable decelerations and that the patient was given oxygen by mask. The epidural continued to drip and the patient was complaining of discomfort. She was having mild to moderate contractions and fetal tachycardia continued (FHR in the 170s). At 12:30 PM Dr. B was made of aware of these events and a nursing note indicated that FHR tracings were nonreassuring (in the 180s).

At 1 PM the patient's temperature was 101.0°F and FHR was in the 160s, positive for accelerations and negative for decelerations with good "beat to beat variability." Contractions were 4–5 minutes apart. Dr. B's impression included chorioamnionitis.

At 2 PM, the patient's temperature had risen to 101.6°F. At 2:30 PM, FHRs (170-180s) were nonreassuring and the patient was leaking clear fluid and blood-stained amniotic fluid. At 4 PM, fetal tachycardia persisted. The patient was "crying for pain relief." She testified that the epidural "wore off at some point."

At 4:35 PM, Dr. B noted that the patient's temperature was 101.0°F. The FHR was in the 160s, positive for accelerations and negative for decelerations with good "beat to beat variability." The patient was 8 cm dilated and 100% effaced, with the baby at -1 station. Contractions were 3 minutes apart. She remained on IV ampicillin and gentamycin. Dr. B noted "consider Caesarean section if patient does not progress." The doctor discussed with the patient the need for a cesarean delivery. A 4:50 PM progress note by Dr. B said that the patient was 8 cm dilated and 100% effaced, with the vertex presenting at 0 station. Dr. B's impression included chorioamnionitis and "failure to dilate," likely secondary to fetal macrosomia.

At 5 PM, Dr. B noted "need to perform STAT [Caesarean] section on another patient. Will continue to monitor [the] patient with close surveillance. To have available MD informed for Caesarean section."

At 5:30 PM, Dr. C, the ob attending, wrote a lengthy "OB on-call delivery note," stating that on arrival at 5 PM, she reviewed the patient's chart and was advised by the nursing staff that the patient was "fully dilated, +2 station" and was being transferred to the OR secondary to a large infant.

Significantly, Dr. C noted that the patient had a medical history of a first delivery involving shoulder dystocia necessitating a broken clavicle for normal spontaneous delivery. She was apparently advised that this occurred approximately 12 years before. This information was conveyed only after the infant was delivered.

Dr. C noted that the baby's head was delivered easily with a large amount of molding over a median episiotomy. She placed the patient in the McRoberts position and applied suprapubic pressure with the staff holding the mother's legs. A corkscrew maneuver was attempted but Dr. C was not able to fully rotate the shoulders and noted that the posterior shoulder would not deliver, with the anterior shoulder remaining wedged behind the pubic bone. The posterior arm was in full extension and an attempt to flex the arm at the elbow was unsuccessful. Dr. C broke the humerus and the baby was delivered at approximately 5:25 PM.

The infant's Apgars were 7/8/9. She weighed 9 lb, 13.8 oz, and was noted as being limp and floppy. She responded well to suction and intubation, becoming pink

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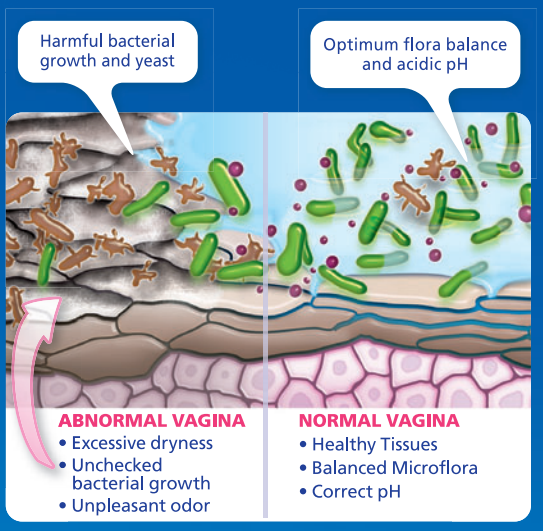


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and spontaneously moving her extremities, except for the left arm. The placenta was delivered intact and spontaneously and the episiotomy was repaired. The plaintiff's temperature was 101.4°F. The infant was treated in the neonatal intensive care unit (NICU) for exposure to the mother's elevated temperature. The plaintiff's physical condition following delivery was normal and the records note that she visited the infant in the NICU.

Dr. C's notes indicate that cord blood and gases were obtained at delivery. The pH was 7.266 and $PCO_2$ 54.3. A second set of values (venous cord blood) showed a pH of 7.215 and a $PCO_2$ of 62.7.

An x-ray showed the left humerus was completely fractured and displaced. The arm was pink and warm with no spontaneous movement. No intervention was performed other than immobilization of the arm. The mother was discharged on January 7. The infant's discharge was delayed until January 9 so that she could undergo antibiotic prophylaxis because of her mother's fever during labor.

On January 22, as instructed, the infant was brought to an orthopedic clinic, where an x-ray revealed that the fracture was healing. On February 26, it was noted that the fracture had healed.

Records describe an infant with delays in her cognitive, fine motor, expressive, and receptive language skills. Psycho-educational testing placed her at a high probability of autism. An individualized education program report prepared in May 2005 states that the child presented as echolalic (showing repetitive speech patterns) with frequent fleeting eye contact, poor attention span, and difficulty in fine motor, visual motor, and behavioral skills. (Echolalia is known to present with autism.)

In August 2006, the child, then 5 years old, was classified as autistic. She continued to receive speech and occupational therapy. Significantly, the child was never classified as having CP, nor is there any suggestion that she had gross motor deficits or disabilities. Furthermore, she never received physical therapy.

## Trial

After a 5-week trial, 3 primary allegations—or departure from good practice questions—went to the jury.

The first "departure" question was whether the CNM made appropriate inquiries of the plaintiff to determine her obstetric history on presentation on January 5, 2001. The plaintiff's liability expert claimed that sufficient questions were not asked and, for that reason, none of the health care professionals who attended the plaintiff up to delivery were made aware of the fact that the plaintiff's first child had shoulder dystocia and had her clavicle fractured.

The second question was why the healthcare professionals did not perform fetal scalp stimulation to assess the fetus's well-being. The plaintiff's expert claimed that in light of the lengthy and continuous tachycardia, it should have been done to determine if the fetus was suffering hypoxia, which went on to cause HIE. Our expert testified that there was no reason to perform fetal scalp stimulation because the FHR strips gave no indication of hypoxia. On my cross-examination the plaintiff's ob expert agreed that although fetal scalp stimulation is a simple test, it is not a routine one, and need be done only if there is evidence of a problem.

The third question was whether a cesarean delivery should have been performed before 4:45 PM. We argued that there was no reason to perform a cesarean delivery because there was never any evidence of a problem, notwithstanding the more than 7 hours of continuous tachycardia.

The bulk of our defense addressed the issue of "proximate cause." We emphasized that this child did not sustain any injury and, in fact, suffers from autism. Even if the jury found against the defendants with respect to departures, the undeniable fact, based upon the cross-examination of both the plaintiff's ob expert and pediatric neurology expert, was that the child showed no evidence of hypoxia and is autistic.

## Outcome

After 2 days of deliberations, the jury returned a verdict in favor of the defendants.

## Analysis

Retrial of a case that was previously lost is always difficult because one is bound by the testimony elicited during the first trial. The witnesses' testimony may be used against them if their answers change. In this case, however, we were able to successfully bolster prior testimony with expert support for the proposition that the CNM took an appropriate history from the plaintiff, who failed to advise of the difficulties attendant to her first delivery.

More importantly, expert testimony supported that cesarean delivery was never indicated. Expert testimony also confirmed the absence of evidence of CP or HIE, enabling us to successfully contend that acts or omissions alleged by the plaintiff did not substantially contribute to the outcome. COG

**MR. KAPLAN** is a partner at Aaronson, Rappaport, Feinstein & Deutsch, LLP, specializing in medical malpractice defense and healthcare litigation. He welcomes feedback on this column via email to aikaplan@arfdlaw.com. This case was tried successfully by his partner, Mark Aaronson.

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**1.** Savino F et al. *Pediatrics*. 2010;126:e526-e533.
**2.** Savino F et al. *Pediatrics*. 2007;119:e124-e130.
**3.** Szajewska H et al. *J Pediatr*. 2013;162:257-262.


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# Managing acute heavy menstrual bleeding

Patients with excessive bleeding need treatment *now*. First-line options include progestin-only therapies, the Munro regimen, and DMPA and short-course oral MPA.

BY **ANITA L. NELSON, MD**

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She reports receiving salary/honoraria from Actavis, Bayer, Merck, Pfizer, and Teva; consulting fees from Agile, Bayer, Merck, Pfizer, and Teva; and grants from Bayer, Merck, Pfizer, and Teva.

*A 32-year-old G4P2022 with a body mass index (BMI) of 32 kg/m$^2$ presents with a history of heavy and prolonged bleeding for 10 days. She is slightly fatigued but denies any dizziness or shortness of breath. She reports that she has soaked 12 thick sanitary napkins in the last 24 hours. Normally her menses occur every 28 to 32 days and last for 4 days with moderate flow (3–4 pads per day). She relies on her husband's vasectomy for birth control. She is slightly tachycardic, but has no orthostatic changes in her vital signs. Her hemoglobin is 9.1. Pelvic exam reveals moderate blood flow from her cervical os. She has a slightly enlarged uterus with no signs of infection. Her urine pregnancy test is negative.*

## TAKE-HOME MESSAGES

- Recommended hormonal regimens are inconsistent, and there is very little or no scientific evidence of efficacy for any of them in acute abnormal uterine bleeding.
- Once acute bleeding has been stopped, it is important to prevent its recurrence.

Acute abnormal uterine bleeding is not an uncommon challenge facing practitioners who care for women. The new International Federation of Gynecology and Obstetrics (FIGO) classification system defines it as an episode of heavy bleeding that, in the opinion of the clinician, is of sufficient quantity to require immediate intervention to prevent future blood

loss.[1] The evaluation that a woman with acute abnormal uterine bleeding needs has been outlined in 2 recent American College of Obstetricians and Gynecologists (ACOG) bulletins and one ACOG Committee Opinion.[2-4] Those guidelines emphasize that the workup for acute excessive uterine bleeding depends upon a woman's age, her medical and menstrual history, her risk factors for endometrial pathology, and her prior laboratory results.

This patient is hemodynamically stable and does not need transfusion or hospitalization. It will not be possible to determine her formal diagnosis until the results of her tests are available.[1-4] However, the challenge facing the clinician is that the patient needs treatment *now* to stop her excessive bleeding.

Hormonal management is first-line medical therapy for patients with acute abnormal uterine bleeding.[4,5] However, there is no consistency among the hormonal regimens recommended and very little or no scientific evidence of efficacy for any of them. For example, medroxyprogesterone acetate (MPA) 10 mg a day for 10 days is often prescribed in emergency departments. Obstetrician-gynecologists themselves have developed different so-called oral contraceptive (OC) tapers with 4-3-2-1 OC tablets prescribed for consecutive days or 3-3-2-2-1 birth control pills to be taken on specified days.

A recent European Consensus group offered 4 oral options for hormonal treatment of acute bleeding in women without underlying bleeding disorders: birth control pills with either 30 mcg or 50 mcg of ethinyl estradiol (EE) in combination with any progestin to be taken every 6 hours until bleeding stops (with a re-evaluation at 48 hours); norethindrone acetate 5 mg–10 mg every 4 hours; or MPA 10 mg every 4 hours (up to 80 mg per day). Each regimen had an accompanying taper protocol.[5] Interestingly, the source for these options was an adolescent health protocol; no clinical studies were cited.

## Historical perspective

Given the current state of practice, it would be helpful to briefly trace the history of medical management of acute excessive bleeding to appreciate how very weak the evidence is for most of the therapies that are currently recommended, but also to recognize where important evidence is available.[4]

The earliest reports of medical management of acute bleeding were usually retrospective and involved the use of very high doses of estrogens. For example, for hospitalized adolescents with hemoglobin levels less than 10 g/100 mL, Claessens et al reported using conjugated equine estrogen (CEE) 40 mg intravenously every 4 hours (for up to 12 doses) coupled with 5 mg norethindrone acetate taken orally 4 times a day, to which could be added a combined oral contraceptive (COC) pill containing 5 mg of progestin and 100 to 150 mcg of mestranol given as 2 tablets initially followed by 1 tablet every 6 hours. Antiemetic agents were given if nausea developed. The birth control pill doses were to be gradually tapered over the following month.[6]

By contrast, the 25-mg doses of CEE given initially, at 3 hours, and at 5 hours by DeVore et al appear modest.[7] This is the most frequently cited study on the subject, even though it reported the experiences of only 17 women given estrogen and 17 women given placebo. The mean baseline hemoglo-

**Hormonal imbalance is a common cause of the friable endometrium that triggers acute, abnormal uterine bleeding in women of reproductive age.**

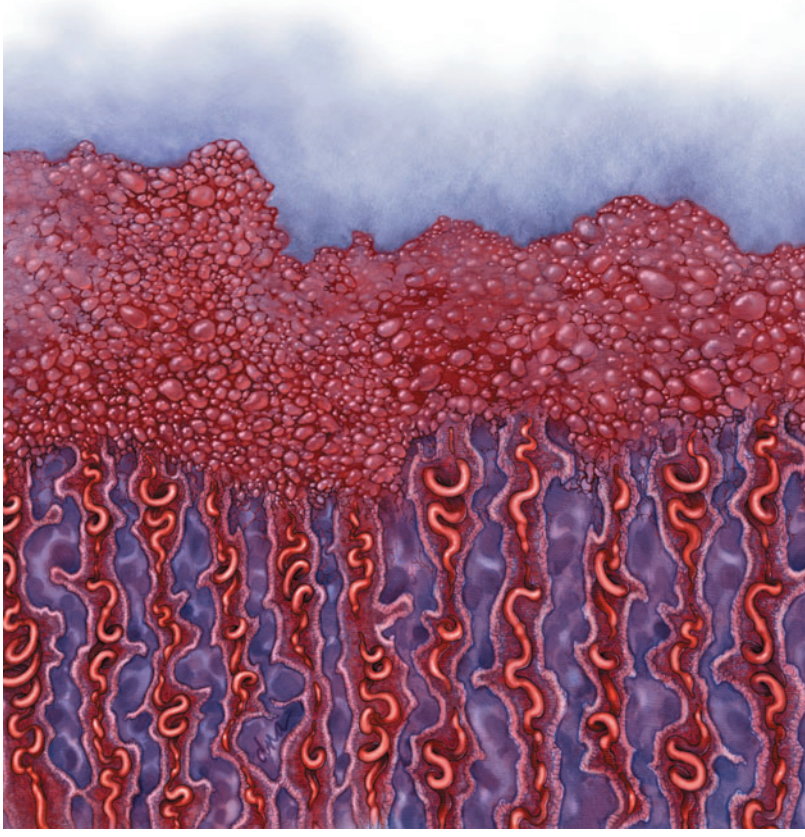

ILLUSTRATION BY ALEX BAKER, DNA ILLUSTRATIONS, INC.

**TABLE 1 High-dose COCs versus MPA for treatment of acute abnormal uterine bleeding**

| | |
|---|---|
| **Regimen 1:** | 35 mcg EE/1.0 mg norethindrone acetate, 1 tablet by mouth 3 times a day for 7 days, then, "COC": 20 mcg EE/1 mg norethindrone, 1 tablet by mouth once a day for an additional 21 days |
| **Regimen 2:** | 10 mg medroxyprogesterone acetate, 2 tablets by mouth 3 times a day for 7 days, then, "MPA": 10 mg medroxyprogesterone acetate, 2 tablets by mouth once a day for an additional 21 days |

Source: Lysteda [package insert].[21]
Abbreviations: COCs, combined oral contraceptives; EE, ethinyl estradiol; MPA, medroxyprogesterone acetate.

bin of these subjects was 12. The outcomes which the authors chose to use for their conclusions were bleeding cessation rates at 5 hours—the time when the double-blinded portion of the study was concluded. At that 5-hour mark, 72% of hormone-treated women had stopped bleeding compared with 38% of those who received normal saline. Of note, at 3 hours, the placebo was more effective (22% CEE vs 36% placebo of women had stopped bleeding). The researchers noted that women with endometritis did not respond to the estrogen therapy.

High-dose COCs became the standard for outpatient treatment of acute excessive bleeding, although there were only 2 prospective studies published in the literature and even though each of those studies reported the experiences of only 9 patients.[8,9] These regimens initially called for 50 mcg EE-containing pills to be given 3 to 4 times a day for several days to stop bleeding, and then slowly tapered over a month. Virtually all other reports on this topic were retrospective analyses, review articles, or textbook recommendations.[10-14] Over the years, the recommended hormone dose has dramatically diminished. The most recent edition of a highly respected textbook in reproductive endocrinology recommends that any 35 mcg EE-containing birth control pill can be given 2 tablets the first day followed by 1 tablet a day for the remainder of the pill pack.[15]

> "Over the years, the recommended hormone dose **has dramatically diminished.**"

## Progestin-only therapies

Progestin-only therapies were first used to treat adolescent women. Aksu et al reported that all the teen women hospitalized for acute uterine bleeding stopped bleeding within 4 days when given 60 mg to 120 mg MPA on day 1, followed by 20 mg MPA daily for an additional 9 days.[16] Bleeding in this patient population is generally due to anovulatory cycling or to bleeding disorders and could, therefore, reasonably have been expected to respond well to such progestin-only therapy.

Munro et al demonstrated that progestin-only therapies could also be successfully used in an outpatient setting to treat adult women with acute excessive uterine bleeding. In the largest prospective, randomized, comparative study of hormonal options, high-dose COCs (n=20) were compared to high-dose MPA (n=20) (Table 1).[17]

The median age of these women was greater than 40 years and the mean BMIs were 29.0 and 30.3 kg/m$^2$, respectively. Contrary to conventional wisdom, women in the MPA arm responded at least as well as women in the COC arm. All women in the MPA group avoided surgery. In the COC group, 5% (1 woman) needed an emergency surgical procedure.

The percentage of women who stopped bleeding was the same in the MPA and COC groups (75% vs 88%, RR 0.87 [95% CI, 0.56–1.31]). Median time

# DID YOU KNOW?

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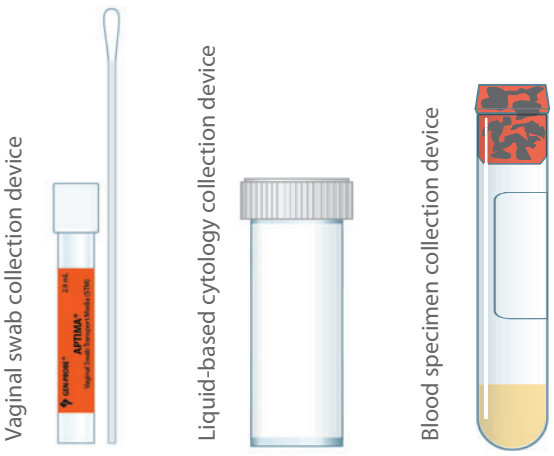


### Acceptable specimens for other women's health-related tests

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- ***Treponema pallidum*/syphilis:** Blood
- **Group B strep:** Vaginal/rectal specimen collected with a bacterial transport swab (screening according to CDC guidelines[1])
- **Bacterial vaginosis**—Requires a vaginal sample. Endocervical specimens from a Pap vial are not acceptable specimens or collection devices.

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1. Centers for Disease Control and Prevention. Prevention of perinatal Group B Streptococcal disease. *MMWR.* 2010 Nov 19;(59)RR-10:1-33.

**TABLE 2 High-dose oral MPA and intramuscular DMPA**

❯ **10 mg MPA, 2 tablets by mouth 3 times a day for 3 days, *plus* 150 mg intramuscular DMPA**

Source: Ammerman SR, Nelson AL.[18]
Abbreviations: DMPA, depot medroxyprogesterone acetate; MPA, medroxyprogesterone acetate.

to bleeding cessation was 3 days in both groups. Where the groups did differ, however, was in patient satisfaction; 81% of the MPA patients said they would use the medication again, while only 69% of the COC users said they would do so (RR 1.18 [95% CI, 0.73–0.98]).

Another progestin-only option (3 days of high-dose oral MPA with intramuscular depot medroxyprogesterone acetate [DMPA], Table 2) has been shown to be very effective in rapidly stopping acute abnormal bleeding in a wide range of women judged to be candidates for outpatient therapy. In their single-arm pilot trial, Ammerman et al treated 48 women aged 19–53 years with mean BMI of 34.9 kg/m$^2$ (range 21.5–51.2 kg/m$^2$).[18] The mean duration of the presenting episode of bleeding was 30.6 days. The baseline hemoglobin of the subjects was 10.9 g/100 mL. The women reported having used an average of 8.5 sanitary protection pads in the 24 hours prior to presentation.

Women were followed until all bleeding stopped by 5 days. One-quarter of women stopped bleeding in the first 24 hours, and the women who were still bleeding at that time reported far less blood loss; they used only 2 pads in that 24-hour interval. In this study, virtually every woman (44 of the 48) had an endometrial biopsy performed prior to initiation of treatment, following local protocols designed for women who have only episodic access to health care. This liberal use of biopsies provided histology that represented almost the full spectrum of benign lesions seen in practice (Table 3), but all women responded to the same high-dose progestin therapy, including those with endometritis and secretory endometrial tissue. Patient satisfaction was also very high; all the women in this study reported that they would recommend this treatment to a friend. The researchers did not formally follow the subjects beyond the 5-day study period, but they noted that of the few women who did return within 90 days with bleeding complaints, all responded to additional medical therapy.

## Decisions for practitioners

Practitioners may prefer to offer the short-term (1 month) oral high-dose progestin-only treatment with MPA recommended in the Munro study. That 1-month time frame is usually sufficient to obtain test results and to have the patient consider her longer-term treatment options. For women (or medical systems) with less timely access to follow-up care, the potential of the intermediate-term approach offered in the Ammerman regimen may be more appropriate.

Of course, any bleeding that persists despite one of these therapies warrants further evaluation, often hysteroscopically directed biopsies. It should be noted that no other progestin formulations have been tested for efficacy for this clinical application even though the European Consensus Group has recommended

**TABLE 3 Histology in women with acute abnormal uterine bleeding treated in the Ammerman trial***

| | |
|---|---|
| Proliferative endometrium | 21 |
| Secretory endometrium | 7 |
| Sloughing endometrium | 7 |
| Chronic endometritis | 3 |
| Fragments | 2 |
| Simple hyperplasia without atypia | 2 |
| Complex hyperplasia without atypia | 1 |
| Polyp | 3** |

*All women successfully treated with high-dose oral MPA and intramuscular DMPA.
**2 women with proliferative endometrium also had polyps.
Source: Ammerman SR, Nelson AL.[18]

> "Longer treatment therapies should be targeted to treat the **underlying etiology** of a woman's bleeding."

both MPA and norethindrone acetate.

One practical issue that clinicians need to consider is that while ob/gyns may be familiar with these high-dose progestin-only therapies, many pharmacists may not be. Pharmacists are much more accustomed to filling prescriptions for MPA 10 mg and have been known to decline to fill prescriptions for higher doses, assuming they were in error. To help those colleagues recognize that this is not a dosing error, I write "yes, I mean 20 mg" on the prescription itself. Since I have started using this extra notation, no patient has had any problems filling her prescription. When I fail to make this notation, patients have been told that this is a dangerous dose and are not given the medication.

Nonhormonal therapies can also be used in the setting of acute bleeding, but usually as adjuncts to hormonal therapies. Higher-dose nonsteroidal anti-inflammatory agents (NSAIDS) (Table 4) have been shown to reduce blood loss in women with chronic heavy menstrual bleeding by 20%–30% when started at the beginning of menses.[19] It is not clear how much NSAIDs contribute to halting acute bleeding when started later, but they may also help control cramping pain. Women with gastritis, bleeding disorders, or platelet function abnormalities should not use NSAIDs.[20]

The ACOG Committee Opinion also suggests the use of tranexamic acid 1.3 mg by mouth 3 times a day for 5 days, based on a consensus from the previously mentioned international expert panel, although this therapy has not been tested in any clinical trials involving acute bleeding.[4,5] The FDA recommends against use of tranexamic acid in women using estrogen-containing pills or in women with a history of venous thromboembolism.[21]

Once acute bleeding has been stopped, it is important to prevent its recurrence. Longer treatment therapies should be targeted to treat the underlying etiology of a woman's bleeding and should consider her risk factors for developing future pathology in the context of her near-time fertility desires. Often hormonal therapies are also first-line treatment options for managing chronic heavy or prolonged menses.[3,22]

**TABLE 4** NSAIDs used to reduce chronic heavy menstrual bleeding

| |
|---|
| **Mefenamic acid** |
| › 500 mg TID first 4–5 days of menses |
| › 500 mg TID from 4–5 days prior to menses to cessation |
| › 500 mg initially; 200 mg QID for 3–5 days |
| **Naproxen** |
| › 500 mg at onset and 3–5 hours later; 500 mg BID for 5 days |
| › 500 mg in am and 250 in PM for 2 days; 250 mg BID for 7 days |
| › 500 mg; 250 mg QID for 4 days |
| › 550 mg; 275 mg QID for 5 days |
| **Ibuprofen** |
| › 800 mg TID for 5 days |

Source: Munro MG, Mainor N, Basu R, Brisinger M, Barreda L.[17]

## Summary

For outpatient management of acute abnormal uterine bleeding, hormonal therapies are first-line choices.

> "Nonhormonal therapies can also be used in the setting of acute bleeding, but usually as **adjuncts to hormonal therapies**."

Progestin-only methods are at least as effective as estrogen-progestin therapies. The Munro regimen with high-dose oral progestin provides a higher level of patient satisfaction than high-dose COCs and can be used safely by greater numbers of women. The DMPA and short-course oral MPA option may be more appropriate for women with challenges accessing medical services. COG


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# What's missing from the electronic health record?

Don't let important patient information fall into the documentation chasm.

BY **HEATHER STRAUB, MD,** AND **RICHARD K. SILVER, MD**

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Neither author has a conflict of interest to disclose with respect to the content of this article. This work was funded through intramural support by the Department of Obstetrics and Gynecology at NorthShore University HealthSystem. The funding source had no role in the preparation, review, or approval of the manuscript, or the decision to submit the manuscript for publication.

*A 37-year-old woman without a primary care provider comes to the emergency department (ED) for a recurrent severe yeast infection. An obstetrician-gynecologist is consulted and recommends screening for diabetes. The patient's serum glucose is found to be 230 mg/dL, prompting a hemoglobin A1C to be sent, which returns as 8.1% after the patient is discharged. The emergency physician calls her home and leaves a message explaining the need for follow-up. However, the telephone encounter is not documented in the electronic health record (EHR) and an appropriate diagnosis ("Rule out diabetes") is not added to the problem list.*

*The patient does not follow up as suggested but is seen for 2 subsequent medical visits in the same year; first for an atypical migraine that is treated by a neurologist and second, at an ED after a car accident for which she is discharged without any specific therapy. Both visits are documented using the same EHR.*

## TAKE-HOME MESSAGES

- Incomplete documentation effectively thwarts one of the putative "virtues" of this technology and can lead to adverse outcomes.
- EHRs must be carefully created and maintained so that they are more than just expensive versions of their paper ancestors.

*Two years later at age 39, the patient presents to the ED with vaginal bleeding. She is found to be unexpectedly pregnant. An ultrasound reveals fetal malformations consistent with caudal regression, likely related to her untreated diabetes of at least 2 years' duration. Her spot glucose is 332 mg/dL and her hemoglobin A1C is 9.6%. She receives counseling regarding the ultrasound findings, aggressive diabetes management as well as outpatient endocrine and obstetrical referrals.*

> Data not entered in the electronic chart or **hidden from view** are equivalent to a paper record locked in a medical office filing cabinet or a hospital's health records department.

## Patient adherence and the EHR

This clinical vignette reflects the reality that only one-quarter to one-third of patients follow up as directed after ED visits.[1] Thus, dependence on patient adherence to care recommendations will continue to result in missed opportunities for both health maintenance and disease prevention. The EHR, which might have provided a safety net in this instance, failed to do so because an otherwise conscientious physician did not document a suspected diagnosis. In this case, the EHR's utility was significantly limited by incomplete data entry.

How might the EHR have altered the course of events that led to the adverse reproductive outcome in this patient? Had the suspected diagnosis of diabetes been recorded, subsequent caregivers would have had the opportunity to see it in the problem list and to have acted upon it. Incomplete ED documentation effectively thwarted one of the putative "virtues" of this technology, namely, linkage of health information directly to the patient rather than to the provider of care.

Data not entered in the electronic chart or hidden from view are equivalent to a paper record locked in a medical office filing cabinet or a hospital's health records department. In either circumstance, important patient information is unavailable precisely because it is sequestered by the care provider.

## Disease prevention and the EHR

In response to anecdotal evidence as well as evidence supporting the effectiveness of prenatal health promotion,[2,3] we evaluated our own EHR for its potential to help our patients avoid adverse outcomes.

Recognizing the frequency of unplanned pregnancy and the fact that 30% of women who conceive have modifiable risk factors that could be treated to improve pregnancy outcome,[3] we created a case-finding algorithm to screen all outpatient encounters from our health system's unified EHR (EPIC, Verona, WI).

Patient data are routinely transferred each evening into an enterprise-wide data warehouse (EPIC Clarity with Oracle and IBM COGNOS) allowing for subsequent data mining for quality improvement, care innovation and research.

We sought to identify reproductive-age women of child-bearing potential and use their data entries to identify risk factors for adverse maternal or fetal outcome. Child-bearing potential was defined as women of reproductive age lacking a history of either sterilization or hysterectomy, and without documented contraceptive use, while the preconception risk factors chosen included morbid obesity, hypertension, poorly controlled diabetes, anemia, renal insufficiency, teratogen exposure, and alcohol, tobacco and illicit drug use.

The algorithm was designed to mitigate incomplete charting by cross-referencing multiple electronic data fields (problem lists, medical and surgical histories, clinical diagnoses, laboratory results, medication orders, and ICD-9 codes), so that multiple dimensions of the record for each risk factor were queried.[4]

## Where the EHR falls short

Although our case-finding strategy showed promise, accurate identification of women of child-bearing potential was problematic because up to 25% of patients were incorrectly classified due to incomplete electronic records.[4] Poor data quality has been noted by others to confound the EHR[5,6] and administrative

CONTINUED ON **PAGE 43**

# Making the EHR your partner in patient care

By Andrea Downing Peck

For many doctors, leveraging the EHR to enhance patient-doctor engagement during an office visit is an elusive goal.

Most physicians receive no instruction on best practices for using the EHR in an exam room. Instead, EHR training typically focuses on data entry tasks and a system's features. Yet there are ways physicians can help ensure that their EHR enhances the doctor-patient relationship rather than creating a barrier to patient communication.

Jason Mitchell, MD, director of the Center for Health Information Technology at the American Academy of Family Physicians (AAFP), says the first step is recognizing the computer is "a third party in the room."

"Acknowledging that the computer can be a significant distraction from interaction with the patient is absolutely essential," Mitchell says. "You have to find ways to mitigate that and draw the patient into the interaction you are having with the computer."

"As you gain comfort using any kind of system, whether it is a piece of paper and pen or a computer keyboard, it becomes more of a tool and less of a concern," says Jennifer Brull, MD, of Plainville, Kansas. Brull now considers her EHR an invaluable partner in patient care, but she admits she did not initially view it that way.

"The discussion around the EHR and computers is because so many physicians of my generation and older generations felt uncomfortable using the computer," Brull says. "We wound up directing so much attention to the computer that it took attention away from the patient."

## Let patients see what you're doing on the EHR

In the exam room, Brull allows patients to view the computer screen at all times to see charts and graphs as well as double-check that Brull's note-taking accurately reflects the patient's words. "I love the tools our EHR gives us," she says. "I can talk to a patient about weight gain but when I show them a graph of their weight over several years, they can see it. A picture does mean a thousand words."

William Ventres, MD, a family physician who in 2006 coauthored one of the first tip sheets on doctor-patient communication using EHRs, is not convinced much progress has been made in overcoming the barriers to patient engagement posed by computers.

"The good news, apparently, is that my coauthors and I got to look at these issues early on after EHRs were first introduced," Ventres says. "The bad news is that it is still common for healthcare systems to plop down computers in front of their clinicians without any training or instruction about how to use them to enhance, and not detract from, the therapeutic relationships between doctors and patients."

Ventres' original advice to physicians on how to use an EHR to enhance in-office communication still holds true. Those recommendations range from the obvious (learn how to type and master basic computer skills) to overlooked details such as:

- listening to a patient's concerns before opening the computer screen;
- telling patients what you are doing at the computer when entering information;
- pointing to the computer screen when sharing data or results with patients;
- understanding when it is important to push the computer screen away; and
- encouraging patient participation in building charts.

## Filling the knowledge void

Though physicians continue to receive little formal instruction on using EHRs in the presence of their patients, there are signs that the knowledge void may be starting to fill. At its 2013 annual meeting, the American Medical Association (AMA) approved a policy pledging to develop resources for members on effectively using computers

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and EHRs in patient-physician interactions and to encourage physicians to incorporate questions regarding use of computers and EHRs in patient-satisfaction surveys.

The AMA Board of Trustees' report calling for the policy change outlined recommendations from Ventres' 2006 Family Practice Management article and Kaiser Permanente's tips to its clinicians. Kaiser Permanente uses the acronym LEVEL to foster integration of computers into patient-doctor encounters:

- **L**et the patient look on: Move the computer screen so the patient can see it, invite the patient to view information, ask the patient to verify information as entered.
- make **E**ye contact: Greet the patient, maintain eye contact.
- **V**alue the computer as a tool: Acknowledge the computer; let the patient know how it improves care.
- **E**xplain what you are doing: Inform the patient about actions and decisions, tell the patient what you are doing, such as ordering labs.
- **L**og off and say that you are doing so: Tell the patient you are logging off to safeguard his or her information.

Medical schools also are recognizing the need to teach physicians how to maximize the EHR in patient interactions. At the University of Arizona (UA) College of Medicine-Phoenix, first-semester students are receiving a 20-minute training session on how to use the EHR in a "relationship enhancing way."

Howard Silverman, MD, associate dean for information resources and educational technology at the UA College of Medicine-Phoenix, says the college's observational studies showed today's computer-savvy students make the same missteps as older generations when using an EHR in an exam room, such as turning their backs to patients while using the computer, and apologizing for having to use the computer.

"There's an assumption the new generation of medical students are computer literate so they will [engage patients] naturally," Silverman says. "We have very good data [showing that] that is not the case."

## Students need training too

Accordingly, the school developed a training intervention that teaches students to begin an office visit by explaining to patients why the computer is important to the visit, has them reassure patients about confidentiality, and directs them to position the computer screen so that the patient can see the screen to review information such as medication lists, laboratory values, and X-rays.

Students are also told to recognize cues to close their laptops and focus solely on the patient, such as when the patient starts discussing sensitive information or before beginning a physical exam. Another tip involves alerting patients that the doctor's attention temporarily will be focused on the computer screen before beginning computer-intensive tasks such as recording a patient's medical history.

"When you shift into that mode, say 'I am going to ask you some rapid-fire questions. I want to record your answers in the computer because I want to make sure I get this down accurately so I can give you the best possible care,'" Silverman explains.

"Now the clickety-clack has been reframed as a positive thing as opposed to 'I am playing video poker and you don't know what I'm doing.'"

Silverman is confident that practicing physicians would benefit from EHR training similar to that developed for UA College of Medicine-Phoenix students, which aims to elevate the doctor-patient relationship.

"The issue with EHR ergonomics is not to make the EHR tolerable," he says. "It is to make the encounter better than it would have been without the EHR.

"Everybody's assumption is that the interaction degrades because the computer is there. It could be the same or it could be better. We prefer the better alternative."

CONTINUED FROM **PAGE 39**

databases from insurance claims and birth certificates are also notorious for missing information.[7]

In the domain of funded clinical research, a standard for precise data entry has existed for decades. Agencies including the National Institutes of Health place great emphasis on complete data capture and auditing, often insisting on robust data monitoring committees for just this purpose.

One needs only to reflect on the new norm of electronic banking to realize how important data precision is to our wealth, but, apparently, not yet to our health.

We believe it is time to insist that electronic medical records are assiduously created and carefully maintained so that they are more than just expensive versions of their paper ancestors. We suggest that caregivers need to conceptualize data entered on behalf of patients as of the highest value to their current and future health status, making accurate completion of the EHR an act of professionalism.

> **"Caregivers need to conceptualize data** entered on behalf of patients as of the highest value to their current and future health status."

It is not a coincidence that Stage I meaningful use criteria include proper utilization of the problem list as an essential element in electronic recordkeeping.[8] Accurate and comprehensive charting is no different than other measures designed to improve patient health and safety. While the activity may not feel particularly important on its face, our clinical vignette should leave no doubt as to the potential consequences of getting this wrong.

## Bridging the EHR documentation chasm

The good news is that we do not have to be alone in this process. We can enlist the help of those office- and hospital-based health professionals who already participate directly in patient care (nurses, physician assistants, and others), asking them to be particularly attentive to complete and accurate EHR documentation as part of their workflow.

We can also leverage our patients' desires to engage in their own health care management by encouraging them to augment and audit their own records at regular intervals (through secure, Web-based patient portals), as well as when they receive episodic care, similar to our current process for medication reconciliation.

We contend that the possibilities for both disease prevention and health maintenance in the context of an accurate EHR are real, but such potential will be governed by the processes surrounding our information capture. We should all strive to close this documentation chasm promptly so that opportunities to innovate using the EHR and improve our patients' health can be fully realized. COG

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continued from **PAGE 23**

monthly cost diaries of out-of-pocket expenses, including clinic visits, medication, and miscellaneous expenses such as travel, parking, and food. A total of 332 couples completed cost diaries and had data available on treatment and outcomes.

More than half of the couples (55%), many of whom had incomes of more than $100,000, underwent IVF. Of the remaining couples, 19% received non-cycle-based therapy, 4% used medication to induce ovulation only, and 22% underwent intrauterine insemination.

**Couples using medication only had the lowest out-of-pocket expense at about $912, while those who underwent IVF had the highest at $19,234.**

The overall out-of-pocket expense was about $5,338. Couples using medication only had the lowest out-of-pocket expense at about $912, while those who underwent IVF had the highest at $19,234. Couples spent about $6,955 for each additional IVF cycle.

Couples with male-factor fertility paid around $9,404 more than those with female-factor infertility only. Couples with insurance coverage for fertility care spent $2,152 less than couples without insurance. The out-of-pocket expense was not significantly associated with successful pregnancy.

"These data provide real-world estimates of out-of-pocket costs, which can be used to help couples plan for expenses that they may incur with treatment," said Dr. Smith. "Communicating these costs clearly with patients at the onset of fertility care can help them prepare for treatment and make informed decisions about their options."

In related news, the American Society for Reproductive Medicine (ASRM) has partnered with the Choosing Wisely campaign to provide recommendations on common tests for the evaluation of infertility that should be questioned by physicians before being ordered. The recommendations include:

- Don't perform advanced sperm function testing, such as sperm penetration or hemizona assays, in the initial evaluation of the infertile couple. Studies document that extreme variability exists among these tests, with very little correlation between results and outcomes, according to ASRM. They have also been shown not to be cost-effective and often lead to more expensive treatments.

- Don't perform immunologic testing as part of the routine infertility evaluation. Diagnostic testing of infertility requires evaluation of factors involving ovulation, fallopian tube patency, and spermatogenesis based on clinical history. Although immunologic factors may influence early embryo implantation, ASRM says routine immunologic testing of couples with infertility is expensive and does not predict pregnancy outcome.

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## Longer maternity leave reduces depression risk

Women who take maternity leave for 6 or more months had a lower risk of developing postpartum depressive symptoms than their counterparts who return to work more quickly, according to a study published in the *Journal of Health Politics, Policy, and Law*.

**7% of the studied women had returned to work by 6 weeks**

**46% returned by 12 weeks**

**87% had returned by 6 months**

Researchers from the University of Maryland School of Public Health and the University of Minnesota School of Public Health looked at data collected from more than 800 women aged 18 years or older, who delivered children in 3 Minnesota hospitals. The women were interviewed in person during their initial hospital stay and were subsequently interviewed via telephone at

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**The United States is currently 1 of only 3 countries that do not provide paid maternity leave; Papua New Guinea and Swaziland are the other 2.**

6 weeks (n = 716), 12 weeks (n = 661), 6 months (n = 625), and 12 months (n = 575). Depressive symptoms, measured by the Edinburgh Postnatal Depression Scale; mental and physical health, measured by the SF-12 Health survey; and maternal childbirth-related symptoms were measured at each time interval.

Using a 2-stage least squares analysis, the investigators found that the relationship between leave duration and postpartum depressive symptoms formed a U shape, with increased leave being associated with a lower rate of depressive symptoms until 6 months postpartum.

The authors concluded that the leave duration—12 weeks unpaid—provided by the Family and Medical Leave Act may not be enough for women at risk of postpartum depression. Indeed, 7% of the studied women had returned to work by 6 weeks; 46% returned by 12 weeks; and 87% had returned by 6 months. The United States is currently 1 of only 3 countries that do not provide paid maternity leave; Papua New Guinea and Swaziland are the other 2 countries.

Dagher RK, Mcgovern PM, Dowd BE. Maternity leave duration and postpartum mental and physical health: Implications for leave policies. *J Health Polit Policy Law.* 2013; ePub ahead of print.

## Teenaged birth rate at historic low

The birth rate for teenagers in the United States continued to fall in 2012, reaching 29.4 births per 1,000 girls aged 15 to 19 years, which represents a 6% decrease from 2011 and a historic low for the nation, according to the National Center for Health Statistics at the Centers for Disease Control and Prevention (CDC).

The report, "Births: Preliminary Data for 2012," documents that since 2007, the birth rate among teenaged girls has dropped about 30% (from 41.5 births per 1000) and is now about half the 1991 rate of 61.8 births per 1,000.

The birth rate for the youngest teenagers, those aged 10 to 14 years, remained stable at 0.4 births per 1,000 in 2012. However, because the number of girls in this age group declined slightly, the number of births to these girls declined as well to 3,674, which is the fewest births to girls aged younger than 15 years since 1945.

From 2011 to 2012, birth rates fell by 8% for 15- to 17-year-olds and by 5% for 18- to 19-year-olds, making the total drops since 1991 63% and 45%, respectively.

Looking at racial and ethnic differences, declines from 2011 to 2012 for 15- to 19-year-olds ranged from 3% for American Indian/Alaska Native teens to 5% to 7% for non-Hispanic white, non-Hispanic black, Asian and Pacific Islander, and Hispanic teens. The largest decline since 2007 occurred among Hispanic girls, down 39% to 46.3 per 1,000 in 2012.

**In 2012**
**29.4 births per 1,000 girls aged 15 to 19 years**
**VS.**
**61.8 births per 1,000 girls in 1991**

The effects of teenaged pregnancy are far-reaching. According to the CDC, in 2008, teenaged pregnancy and childbirth cost US taxpayers about $11 billion per year. Only about half of all teenaged moms receive high school diplomas by age 22 years. The children of teenaged mothers are more likely to have lower school achievement, drop out of high school, have more health problems, be incarcerated during adolescence, give birth as teenagers, and face unemployment as adults. COG

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

# Bioprinting

## Creative disruptive technology

3-D printing has applications across the field of medicine and will drastically change training, treatment, and even transplantation.

In the early 2000s, bioengineer Dr. Thomas Boland, one of the forefathers of bioprinting, retrofitted a standard inkjet printer so that it would use cells as ink. By 2003 he had started to develop "organ printers" with the concept that a desktop printer could print gels, single cells, and aggregates of cells in a sequential layer-by-layer manner so that organs could be printed and assembled *de novo*.[1]

In a thought-provoking paper, Boland and collaborators state that the "combination of an engineering approach with the developmental biology concept of embryonic tissue fluidity enables the creation of a new rapid prototyping 3-D organ printing technology, which will dramatically accelerate and optimize tissue and organ assembly."

### Disruption materializing

More than 10 years later, 3-dimensional (3-D) printing and bioprinting are a reality and will be commonplace in the very near future. In a report released by Goldman Sachs last summer titled "The Search for Creative Destruction," 3-D printing was among 8 industries highlighted for their disruptive capabilities.[2] The report states that the 3-D printing industry is already a $2.2 billion market; analysts estimate that the industry will grow to more than $10 billion by 2021. Although it makes up less than 20% of the current market, the 3-D printing industry has the potential to revolutionize many aspects of health care.

It is important to recognize that 3-D printing and bioprinting are 2 different yet interrelated concepts. 3-D printing, a technology that has been around for more than 20 years, takes computer-based digital information and creates a 3-D solid object by adding layers of a material in structured sequence. The printing typically requires architectural design or computer-aided design (CAD) software, but once the 3-D blueprint has been assembled, all you have to do is push the print button! At Yale University's Center for Engineering Innovation and Design (CEID), more than 500 students and faculty have been trained in the use of 3-D printers. According to Dr. Joseph Zinter, the assistant director of CEID, "In the past year, we have 3-D-printed everything from scientific research tools to key chains, ancient Egyptian artifacts to trombone mouthpieces,

**Dr. Thomas Boland**

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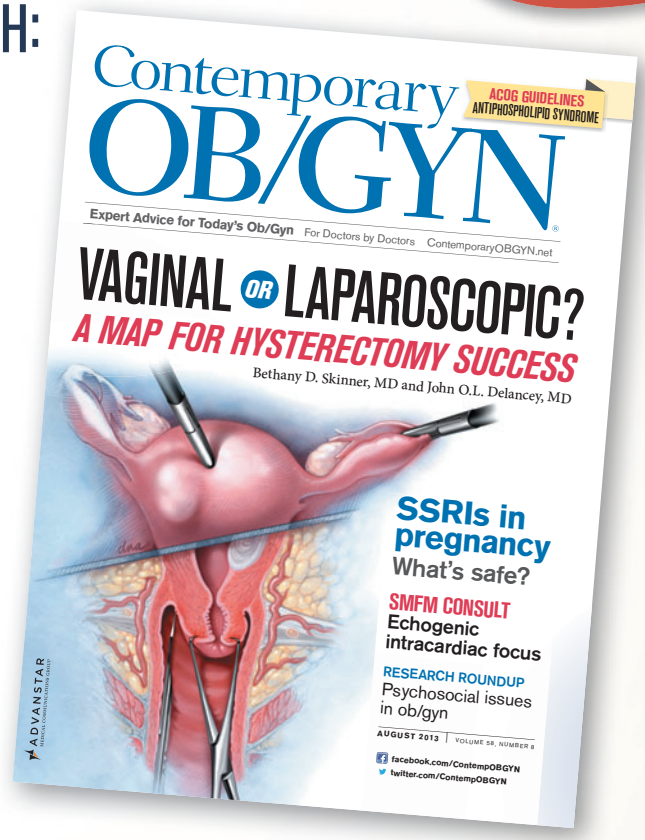


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## Prosthetics and organs

Part of the excitement about the biomedical applications of 3-D printing is generated by the ability to recreate objects that have precise sizes, contours, and measurements. For example, radiographic data can be used to create segments of missing bone for trauma patients, teeth can be perfectly printed for those who need dental implants, and prosthetic eyes can be printed in a matter of minutes, as opposed to the hours or days required for handmade/hand-painted prosthetic eyes.[4]

Bioprinting builds upon the technology used in the printing of sequential layers. In this setting, cells are laid upon the scaffold and become self-supporting, with the potential for continued cellular growth. The backbone of the structure can be either a living scaffold composed of cells or a dissolvable scaffold, allowing the structure to become self-supporting with continued cellular growth.

In 2011, Dr. Anthony Atala, speaking at a TED (technology, entertainment, design) conference, reported that soon it may be possible to "print" a functional kidney.[5] (To see Dr. Atala's talk, visit www.ted.com/talks/anthony_atala_printing_a_human_kidney.html.) With more than 120,000 US patients now waiting for organ donations, the possibility of printing a perfectly matched kidney is a goal of many bioprinting engineers. Although it is conceptually plausible, the printing of a functional organ requires not only producing the required size and shape, but also laying down the microscopic architecture and function of the organ (ie, tubules, blood vessels, etc.).

Because of the commercial potential of such technologies, many companies have entered this new space, and representatives from companies such as Organovo have openly said that they are focused on "building human tissues for surgical therapy and transplantation."[6] Other companies are working on developing biologically active skin grafts, vessel grafts, replacement valves, and almost every other structure that can be replaced in the body.

## Research and training

Beyond solid organ transplantation, bioprinting functional liver samples may allow researchers to perform research and development at levels of scrutiny that were previously attainable only through patient-derived studies. This could not only accelerate the pace and economics of pharmaceutical development, but also potentially protect many patients from the risks of toxicity in early drug studies.

> "Printing a perfectly matched, **functional kidney** is a goal of many bioprinting engineers."

In the training and evaluation of surgeons,[7] bioprinters can be used to print 3-D replicas of tumors on which residents can outline surgical approaches and even practice resections. By combining printing media, it is possible to create 3-D structures that have multiple textures and tissue types, which could adequately and reproducibly simulate a surgery. Therefore, 3-D printers may improve the ability to simulate many of the surgical skills that need to be mastered before completing training.

## Bioprinting and ob/gyn

Within our field, the potential applications of 3-D printing and bioprinting are boundless. In fact, we would argue that ob/gyns have the most to gain from this technology.

It is easy to imagine the use of such technology in training future ob/gyns, creating size-appropriate prostheses and/or organs or tissues for fetuses with anomalies (ie, defective heart valves, cleft lips, etc.), mapping out gynecological oncologic surgeries, creating urogynecologic surgical adjuvants, and creating perfectly contoured embryo catheters. The future is ours to print (in 3-D)! COG


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LAURIE J. MCKENZIE, MD
SECTION EDITOR

# Do we really need the robot?

Four physicians debate whether the robot is the future of gynecologic surgery.

## PRO

### Robotic surgery's time has come

**Amy K. Schutt, MD, and Ertug Kovanci, MD**

Hysterectomy is the second-most-common surgical procedure in the United States and estimates indicate that 1 in 9 women will undergo it in their lifetime. Before the robotic platform was approved by the US Food and Drug Administration for gynecologic surgery, rates of laparoscopic hysterectomy in the United States remained underwhelmingly stagnant.

Although the first laparoscopic hysterectomy was performed in this country more than 20 years ago, in 1990 and 2003 only 0.3% and 11.8% of hysterectomies, respectively, were performed laparoscopically.[1]

Conversely, the rate of robot-assisted hysterectomies increased rapidly from 0.5% in 2007 to 9.5% of all hysterectomies in 2010, a span of just 3 years. In hospitals with a robot, the rate of robotic hysterectomy increased to 22.4% of all hysterectomies in the 3 years after the first robotic procedure was performed.[2] These statistics illustrate that, despite multiple documented benefits of minimally invasive surgery (decreased hospital stay, decreased pain, faster recovery times, and fewer infections), laparoscopic hysterectomies remained underutilized for years until the advent of the robot.

In 2005, 64% of hysterectomies in the United States were performed abdominally, a number that remained unchanged for decades. From 2007 to 2010, as robotic hysterectomies increased, abdominal hysterectomies decreased overall from 53.6% to 40.1%.[3] In essence, gynecologic surgeons viewed the robot as a catalyst to overcome the barriers associated with adopting laparoscopic hysterectomy techniques.

For many surgeons, a lack of previous training combined with the

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

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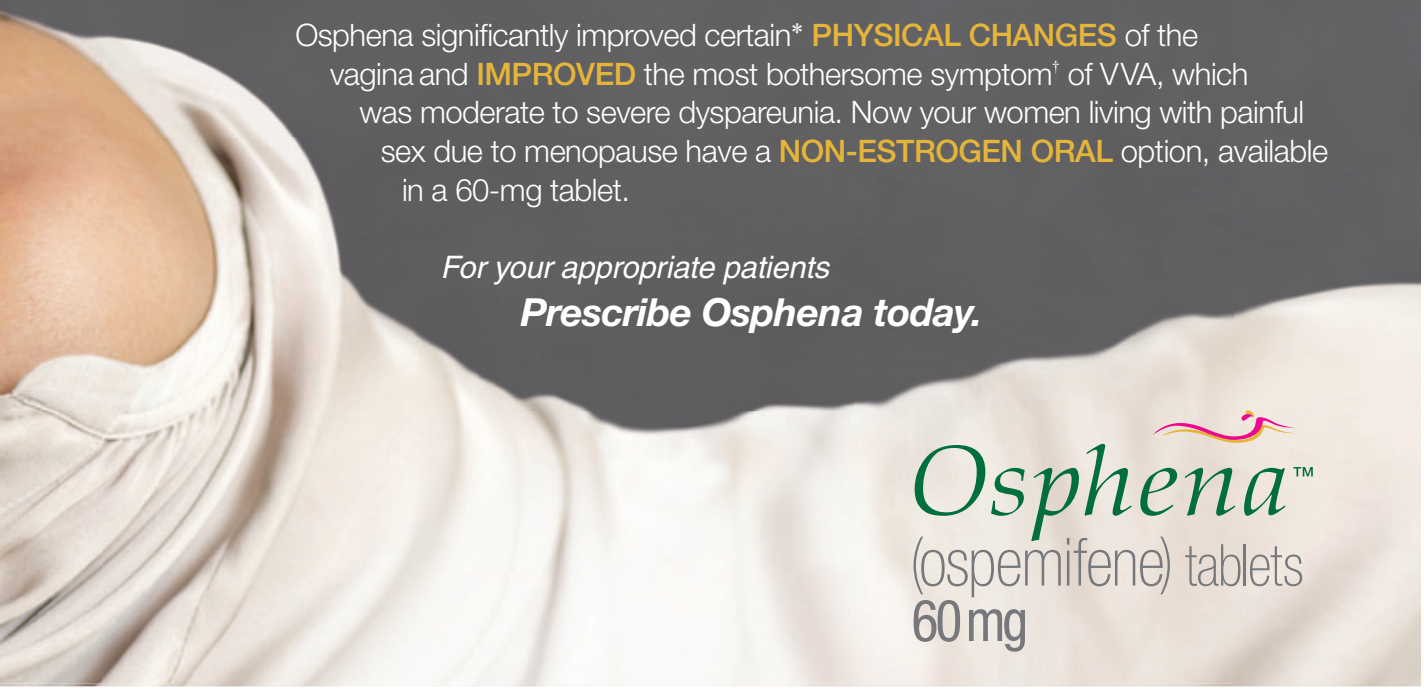

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60 mg

## Important Safety Information

### Contraindications

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

### Warnings and Precautions

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

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

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

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

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

osphena.com

**OSPHENA™ (ospemifene) 60 mg tablets**

**BRIEF SUMMARY – See Package Insert for Complete Prescribing Information.**

**WARNING: ENDOMETRIAL CANCER AND CARDIOVASCULAR DISORDERS**

**Endometrial Cancer**

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

**Cardiovascular Disorders**

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

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

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

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

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

**WARNINGS AND PRECAUTIONS**

**Cardiovascular Disorders**

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

*Stroke*

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

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

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

*Coronary Heart Disease*

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

*Venous Thromboembolism*

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

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

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

**Malignant Neoplasms**

*Endometrial Cancer*

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

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

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

*Breast Cancer*

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

**Severe Hepatic Impairment**

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

**ADVERSE REACTIONS**

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

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

**Clinical Trial Experience**

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

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

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

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

**DRUG INTERACTIONS**

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

**Estrogens and estrogen agonist/antagonist**

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

**Fluconazole**

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

**Rifampin**

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

**Ketoconazole**

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

**Warfarin**

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

**Highly Protein-Bound Drugs**

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

**Multiple Enzyme Inhibition**

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

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

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

**Nursing Mothers**

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

**Pediatric Use**

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

**Geriatric Use**

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

**Renal Impairment**

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

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

**Hepatic Impairment**

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

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

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

**OVERDOSAGE**

There is no specific antidote for OSPHENA.

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

**SHIONOGI INC.**

## PRO CONTINUED

promise of longer operative times, painful ergonomics, and a steep learning curve were powerful deterrents preventing the switch in surgical approach. Most gynecologic surgeons understand that laparoscopic hysterectomies are associated with better profiles for recovery and postoperative complication than abdominal hysterectomies, but the approach was not feasible until the robotic surgical platform became commercially available.

The vaginal approach remains the gold standard for minimally invasive hysterectomy, but complex pathology such as pelvic adhesive disease from endometriosis, chronic pelvic inflammatory disease, and uterine fibroids presents significant challenges for the gynecologic surgeon. In these cases, opting for a robotic hysterectomy may prevent an abdominal hysterectomy. The robot serves as a powerful mechanism for gynecologic surgeons to dramatically (and more comfortably) shorten the learning curve for laparoscopic hysterectomy.

The robotic surgical platform should be embraced as a tool that allows the average gynecologic surgeon to excel in laparoscopic surgery—performing fewer abdominal hysterectomies while offering more patients the benefits of minimally-invasive surgery when a vaginal approach is deemed inappropriate. In hospitals with a robot, the platform has resulted in a reduction in the rate of abdominal hysterectomies by more than 20% in just 3 years, a figure previously unchanged for decades. The robot has existed in gynecologic surgery for only 8 years and it has already radically altered the future of minimally invasive surgery. When compared to traditional laparoscopy, the trajectory for the adoption of the robotic surgical platform in gynecology aims higher: to help patients achieve better outcomes with fewer complications and to help surgeons perform hysterectomies efficiently, skillfully, and safely.

> "The robot serves as a powerful mechanism for gynecologic surgeons to **dramatically (and more comfortably)** shorten the learning curve for laparoscopic hysterectomy."

When Dr. Kurt Semm, the founder of laparoscopic surgery, submitted a manuscript documenting a laparoscopic appendectomy to the *American Journal of Obstetrics and Gynecology*, it was declared unfit for publication due to "unethical" surgical technique. Critics in the 1960s mockingly suggested that Dr. Semm undergo a brain scan as "only a person with brain damage would perform laparoscopic surgery."[4] Now Dr. Semm's laparoscopic techniques are used by gynecologic surgeons around the world.

Ever since the world accepted Dr. Semm's endorsement of laparoscopic surgery in the 1990s, gynecologic surgeons have been at the forefront of technological innovations. Resistance to the most advanced tool we have today is a reminder of the resistance to video laparoscopy that occurred earlier; critics decried the increased expense, longer operating times, and necessity of the new technology, arguing instead for mini-laparotomy and vaginal surgery.[5] We find it hard to believe that we will be performing surgery with "straight sticks" in 20 years. The next generation of laparoscopy is here and the time has come to embrace this change. COG


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

# CON

## Conventional surgery is more cost-effective and patient-centered

**Linda Shiber, MD, and Resad Pasic, MD, PhD**

Minimally invasive approaches to benign gynecologic surgery have been shown to result in superior clinical outcomes. In recent years, robotic systems have been adopted in benign gynecology, at great cost to the healthcare system and with no validated clinical benefits.

There is no clear indication for preferential use of robot-assisted laparoscopy over conventional laparoscopy in benign gynecology.[1,2] Some may argue that the robotic approach is helpful in surgeries requiring extensive dissection and/or suturing, such as myomectomy or sacrocolpopexy. Existing evidence has shown no significant difference in complication rates or surgical outcomes; to the contrary, evidence has indicated robot-assisted procedures are longer and far more costly.[3-5] Arguments regarding benefits of robotic surgery in obese gynecologic patients lack the insight that obese patients benefit from *any* minimally invasive approach. And it remains unclear whether robotics provides any technical advantages over laparoscopy in these patients.

We do acknowledge the fact that adoption of robot-assisted laparoscopic hysterectomy may decrease rates of abdominal hysterectomy among surgeons not skilled in conventional laparoscopy. However, we argue it is paramount to be skilled in the basics prior to adopting a new technology. If a robotic procedure cannot be completed as such, the default should be conventional laparoscopy, not laparotomy, necessitating a solid laparoscopic skill set before attempting robotics. Once a surgeon acquires this skill set, the "need" for robotic assistance is obviated.

The significant cost of robotic technology cannot be ignored in today's medico-economic environment. It is estimated that for hysterectomy alone, robotic procedures cost, on average, $2,600 more per surgery than laparoscopic procedures.[4] This number does not include the net cost of each robot system, which is approximately $1 million to $2.5 million (excluding maintenance costs, single-use appliances, etc.).[5,6] The American Association of Gynecologic Laparoscopists (AAGL) estimates that if all hysterectomies in the United States were performed robotically, an additional $960 million to $1.9 billion would be added to healthcare system costs.[2] It is exceedingly difficult to justify this astronomical and additive cost for a surgical approach that has not been shown to be clearly indicated or to afford short/long term clinical benefits in benign gynecologic surgery.

Furthermore, as our national healthcare environment evolves and Accountable Care Organizations continue to audit cost-effectiveness and quality of healthcare, we feel that the growing use of robotic technology in benign gynecology will not be sustainable.

In conclusion, we echo the recent AAGL position statement, as well as the findings of the 2012 Cochrane Review, when we state that robot- assisted laparoscopic surgery should *not* be the preferred approach for patients with benign gynecologic disease. With evidence indicating no surgical or clinical advantage to robotic surgery and cost analyses consistently showing the incredible burden of robotics on healthcare spending, clinicians should critically and thoroughly evaluate the clinical necessity of choosing a robotic approach over vaginal or conventional laparoscopy for patients with benign gynecologic conditions. Focusing on improving laparoscopic training for practicing gynecologists, as well as ob/gyn residents, would be a far more cost-effective and patient-centered way of allocating healthcare dollars. COG


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# The Roadmap to Clinical Utility

## Cord Tissue Mesenchymal Cells

Since umbilical cord blood stem cell banking was established over 20 years ago, the stem cells of more than one million newborns have been stored in private family cord blood banks. Now, emerging research is underway regarding the preservation of stem cells from the umbilical cord tissue—newborn cells with regenerative, transplantation and treatment application potential.

This special supplement to the October 2013 issue of ***Contemporary OB/Gyn***, "The Roadmap to Clinical Utility: Cord Tissue Mesenchymal Cells," examines the emerging utility of this unique source of cells as therapeutics in a variety of important clinical indications such as type 1 diabetes, rheumatoid arthritis, and Parkinson's disease.

Learn the key advantages to be gained from storing stem cells for future use, as well as data on the co-administration of cord blood stem cells and cord tissue mesenchymal stem cells. This information may be beneficial in discussions with parents considering cord blood banking to better understand why the arrival of their newborn may represent the best opportunity to preserve access to a potentially powerful biology.

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Banking cord blood does not guarantee that treatment will work and only a doctor can determine when it can be used. Cord tissue stem cells are not approved for use in treatment, but research is ongoing.

BY **NICOLA PERONE, MD, FACOG, FACS**

# Bringing operative vaginal delivery into the 21st century

The use of forceps and the vacuum extractor shouldn't be allowed to become a lost art.

Operative vaginal delivery (OVD) still plays a valuable role in obstetrics, despite its continuing decline. Many factors account for such a decline, including, in particular, doctors' fear of litigation and reduced competency. Modern technology may preserve the use of forceps and vacuum extractor before it becomes a lost art.

The rate of OVDs has been declining in most countries since the mid-1970s. In the United States, it has gone from 28% in 1970 to 9.01% in 1990, with a further drop to 3.5% in 2011.[1] The rate of forceps use has dropped from almost 30% in the late 1960s to less than 1% in 2005, where it has remained. Vacuum extraction (VE) was seldom used in the United States until the early 1980s, but subsequently became the most common method of OVD after a marked increase from 3.5% in 1989 to 6.2% in 1997. Since then the rate of VE has steadily declined to a low of 2.85% in 2011.[2]

## Reasons behind OVD loss of favor

A number of factors account for the decline in the rate of OVD, however medico-legal concerns may play a major role. In the 2012 ACOG professional liability survey, 77.3% of respondents said that they had been sued at least once, with an average of 2.64 claims per ob/gyn.[3] Plaintiff attorneys frequently blame forceps and VE for bad obstetrical outcomes, although it is widely believed that the indication for their use is probably a more important causative factor than the delivery itself.[4] This is particularly so in the case of neonatal neurologic damage, similar to what has been observed in case of cesarean delivery,[5] which, despite its increasing rate, has not caused a reduction in cerebral palsy. In fact, a recent systematic literature review and meta-analysis has shown an increased risk of this neurologic condition in association with emergency cesarean delivery, confirming the important causative role of antepartum risk factors.[6]

The reduced use of OVD and increased use of cesarean delivery at many teaching institutions has reduced resident competency in OVD. This may set in motion a vicious cycle, wherein lack of expertise causes errors when using forceps or VE, leading to more lawsuits, which in

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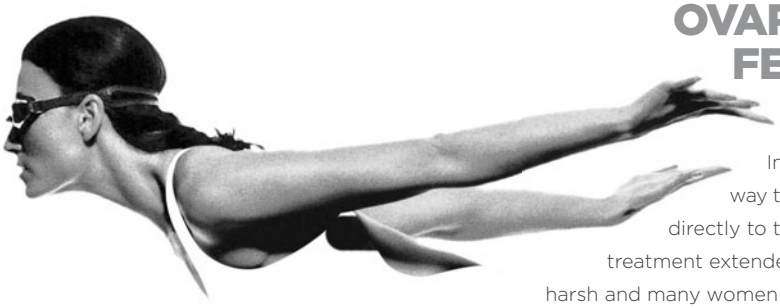
# WE'RE CHANGING THE WAY

## OVARIAN CANCER PATIENTS FEEL ABOUT THE FUTURE



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

Magee-Womens Hospital of UPMC

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

> Since their introduction in **the 17th century,** forceps have undergone only few changes.

turn further discourages OVD. The important questions facing our specialty today are whether we want to passively witness OVD become "a lost art"[7] while the cesarean delivery rate continues to climb, or whether we should actively attempt to reverse the current trend and, if so, how.

## Why proficiency in OVD should be maintained

OVD should not be allowed to become extinct. Proficiency in the use of forceps and VE should be maintained for the following reasons:

- Cesarean delivery is not a panacea for all obstetrical emergencies. In fact, OVD can save the day whenever a cesarean delivery is either relatively contraindicated by maternal conditions or, as it happens more often, preparation for it cannot be made in a timely fashion (only 65% of emergency primary cesarean deliveries are done within 30 minutes of the decision to operate).[8]
- Given current patient safety and health care cost concerns, the potential moderating impact of OVD is widely acknowledged.[9-11] In my opinion, it is no accident that, while OVD rates have gradually decreased, the rate of cesarean delivery has increased by more than 50% since 1996, going from 21% to 32.8 % in 2011. And this upward trajectory appears likely to continue, with estimates of an overall cesarean rate of 56.2% by 2020, if the primary and secondary cesarean rates continue at the same pace as in recent years.[12,13] Of course, it is difficult, if not impossible, to quantitate precisely the effect that more frequent use of OVD would have on these rates. But it is clear that even a small reduction in cesarean deliveries could have considerable economic benefits. In fact, for every 5% increase in the US cesarean delivery rate one can expect $750 million to $1.7 billion in additional healthcare costs.[14]

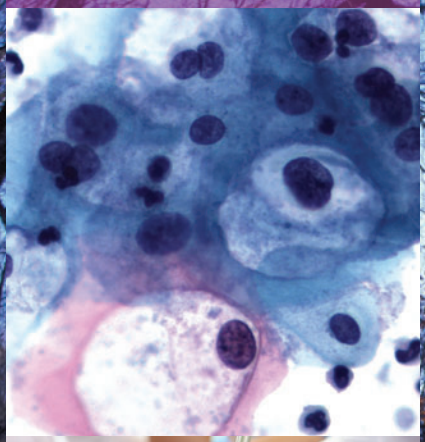
## Preserving the use of forceps and VE with modern technology

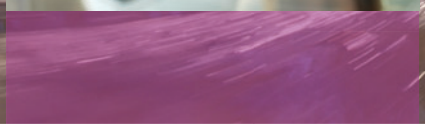
It is my belief that OVD could be revived with the help of modern technology. Since their introduction in the 17th century, forceps have undergone only few changes. Fifty years ago A.R. Fleming lamented that they remained "little more than a shoehorn," an obvious paradox in our era of cutting-edge technology.[15]

Updated technology that made OVD simpler and safer would make obstetricians less reluctant to use this modality. As for the doctors' legal vulnerability, the considerable advances in electronic engineering would reduce it in 2 ways: by improving the instruments' safety and by making it easier for obstetricians to defend themselves in cases of bad outcome associated with, but not caused by, OVD.

With regard to the safety of the instruments, a known limitation of the traditional instruments is that traction is measurable only by subjective feel. Consequently, there is always the possibility of fetal injury secondary to inadvertent use of excessive traction. In fact, this is a likely occurrence, particularly when employed by inexperienced practitioners in the presence of unrecognized cephalopelvic disproportion which can be difficult to predict prospectively. Enhanced technology would help solve the problem of the inadvertent application of excessive traction by making the instruments capable of measuring the pull applied and by alerting the obstetrician when traction exceeds preset safety limits.

Currently, avoidance of excessive traction and, more importantly, when to abandon an OVD attempt and promptly resort to a cesarean delivery is left to the obstetrician's judgment, acquired after years of experience. Yet, we know from clinical and experimental data that, in the case of forceps, a traction force of 50 lb (22.8 kg) should be considered the upper limit of pull with regard to fetal safety[16,17] and in the case of VE, that the traction should be limited to the negative pressure under the cup (generally recommended not to exceed 550–600 mmHg), otherwise detachments are inevitable and with them the possibility of fetal injury. The occurrence of serious fetal scalp lacerations and life-threatening hemorrhagic complications associated mainly with vacuum cup "pop-offs" prompted a 1998 FDA Public Health Advisory.[18]





CERVICAL CANCER SCREENING

# Change the conversation

## The Aptima® HPV test makes it easier.

Detecting HPV DNA identifies the presence of a high-risk HPV infection. HPV is a common transient infection and very few infections will lead to cervical cancer. Looking for the presence of high-risk HPV DNA can lead to unnecessary difficult patient conversations.

The Aptima HPV test targets high-risk HPV mRNA. Studies have shown HPV mRNA identifies the presence and activity of a high-risk HPV infection.[1]

**The Aptima HPV test has shown:**

- **Excellent sensitivity** — demonstrating **equivalent sensitivity** to DNA-based HPV tests in multiple clinical studies involving over 50,000 women worldwide[2]
- **Improved specificity** to DNA-based HPV tests — **reducing false-positives by 24%** in the clinical trial[3]

The combination of excellent sensitivity and improved specificity with the Aptima HPV test may help change patient conversations and may minimize the potential for over-treatment.

**Interested in learning more about mRNA and the Aptima HPV test difference? Contact us.**

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

**Aptima® HPV Test | ThinPrep® Pap Test | NovaSure® Endometrial Ablation System**
**MyoSure® Tissue Removal System | Selenia® Dimensions® 3D Mammography**

**References: 1.** Liverani CA, et al. Am J Transl Res 2012; 4(4): 452-457 **2.** References available at www.gen-probe.com **3.** Aptima® HPV Assay package insert #503789 Rev A 2013,Table 13



HOLOGIC®
Specializing in extraordinary

By giving forceps and VE the capability of measuring the pull applied and of alerting the doctor when "gentle" traction becomes undue traction, we could bring "a modicum of scientific objectivity into a sphere replete with subjectivity," to borrow from JV Kelly.[19] This, in turn, would make the correct use of these instruments less experience-dependent and thus reduce the risk of fetal injury, even in the hands of a novice. In fact, if the pull reaches the upper limit of safety and there is no evidence of progress, the need to desist from further extractive efforts and to abandon the vaginal route in favor of the abdominal one would be obvious.

The availability of unassailable documentation would make it easier to counter the medico-legal allegations of undue force in cases associated with adverse obstetrical outcomes. In fact, in the absence of objective data, as is the case with the instruments currently used, the doctor's recollection of the traction applied is invariably, and often successfully, challenged.

Technology would remedy loss of competency by helping remove barriers that often impede effective teaching of OVD techniques. The answer here lies in the greater use of simulators, ideally of the high-fidelity kind with haptic feedback capability, which require fewer instructors and less time. Simulators not only teach OVD, but also help doctors to maintain and sharpen their skills. In fact, periodic simulator-based training could be made mandatory in order to maintain OVD privileges. The use of simulators, coupled with the designation of a full-time experienced and proactive faculty member to this task, has led to a reported 59% increase in forceps use,[20] which is particularly significant when taking into account that this instrument is technically more demanding than VE.

## Engineering feasibility

Some may consider the improvements suggested to modernize forceps and VE too challenging to become a reality. However, their feasibility has already been demonstrated.[21] In fact, thanks to miniaturized electronics, these instruments can be used without learning new skills and unencumbered by dials, scales, and cables. COG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**DR. PERONE** is a clinical professor in the Department of Obstetrics, Gynecology & Reproductive Sciences at the University of Texas Medical School at Houston. He reports holding a patent for an electronically controlled axis-traction handle and 2 related patents.

# CALENDAR

## FEBRUARY

**3-8: Society for Maternal-Fetal Medicine 34th Annual Meeting**
New Orleans, Louisiana
*https://www.smfm.org/Annual%20Meeting%20Page.cfm*

## MARCH

**22-25: Society of Gynecologic Oncology 45th Annual Meeting of Women's Cancer**
Tampa, Florida
*www.sgo.org/education/annual-meeting-on-womens-cancer/*

**23-26: Society of Gynecologic Surgeons 40th Annual Scientific Meeting**
Phoenix, Arizona
*http://www.sgsonline.org/meetings*

**26-29: Society for Gynecologic Investigation 61st Annual Scientific Meeting**
Florence, Italy
*sfgi.memberclicks.net/2014-sgi-annual-meeting-florence-italy*

## APRIL

**6-9: The North American Society of Psychosocial Obstetrics and Gynecology Annual Meeting**
Columbus, Ohio
*www.naspog.org/index.php/2014-annual-meeting*

**23-26: National Osteoporosis Foundation Interdisciplinary Symposium on Osteoporosis**
New Orleans, Louisiana
*www.nof-iso.org*

**26-30: The American College of Obstetricians and Gynecologists Annual Clinical Meeting**
Chicago, Illinois
*http://www.acog.org/About_ACOG/ACOG_Departments/Annual_Clinical_Meeting*

## JULY

**7-11: American Medical Assocation Annual Meeting**
Chicago, Illinois
*http://www.ama-assn.org/ama/pub/about-ama/our-people/house-delegates/meeting-dates.page*

**21-26: American Urogynecologic Society and International Urogynecological Association Scientific Meeting**
Washington, DC
*http://augs-iuga2014.org/*

## SEPTEMBER

**10-13: Society of Laparoendoscopic Surgeons Minimally Invasive Surgery Week/Annual Meeting and Endo Expo**
Las Vegas, Nevada
*http://www.sls.org/i4a/pages/index.cfm?pageid=1*

**11-13: American Gynecological and Obstetrical Society Annual Meeting**
Chicago, Illinois
*http://agosonline.org/meetings.html*

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Please type "Event" in the subject line.

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# MARKETPLACE



## CONTINUING MEDICAL EDUCATION



## SEMINARS



## MEDICAL EQUIPMENT & SUPPLIES

## SEMINARS





# RECRUITMENT

## ARKANSAS

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**Hospital employed GYN only position joining one obgyn who does obstetrics only and 6 FP/OB physicians in beautiful Ozark Mountains and Forest 90 minutes to Fayetteville/Little Rock and 45 minutes to Branson associated with modern and financially stable 175 bed regional hospital doing 800 annual deliveries. Excellent salary, bonus and benefits. OBGYN Search, 800-831-5475, obgynsrch@aol.com, www.obgynpractices.com**

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## NEW JERSEY

### CENTRAL NEW JERSEY

**Join well established 6 physician obgyn private practice doing 30% obstetrics and 70% Gyn/Surgery in desirable family oriented community with close proximity to Philadelphia-NYC and the shore associated with a modern and financially stable 178 bed Level II NICU hospital with modern L/D. 1-7 call. Excellent salary, production bonus, benefits and future partnership with Occurrence malpractice carrier. OBGYN Search, 800-831-5475, obgynsrch@aol.com, www.obgynpractices.com**

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## NEW YORK

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**✻ F/T or P/T GYN and Family Practice ✻**

☆ Flexible office schedule
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(English and Chinese speaking)

Please email CV to **nycpola@yahoo.com**

## UTAH

**Intermountain is frequently referenced nationally as one of the leaders in delivering high quality/low cost healthcare.** Intermountain Healthcare needs a Urogynecologist to join a group in Provo, Utah. Beautiful university community, with exciting outdoor activities. Contact: Physician Recruiting, 800-888-3134, Physicianrecruit@imail.org, http://physicianjobsutah.org

**Intermountain Healthcare is widely recognized as a leader in transforming healthcare through high quality and sustainable costs.** We are seeking BC/BE OB/GYN physicians to practice with our medical group in Heber, Salt Lake City and Park City, Utah. Contact Intermountain Healthcare, Physician Recruiting, 800-888-3134. Physicianrecruit@imail.org, http://physicianjobsintermountain.org

## VIRGINIA

### VIRGINIA

Independent OB/GYN practice of 6 MD's and 2 WHNP's is seeking an OB/GYN physician to practice in the Tidewater area. 30 minutes from the beach. Call 1/5. Competitive salary and benefits.

**Please email CV to gb@greenbrierob.hrcoxmail.com**



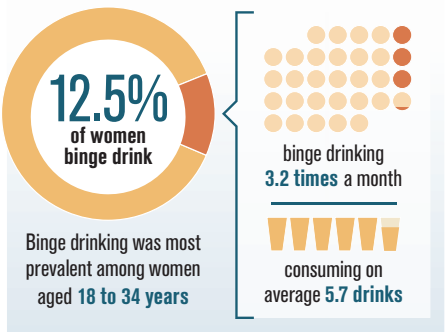


# CONTEMPORARY OB/GYN'S TOP 5 NEWS STORIES OF 2013

Reports making headlines in *Contemporary OB/GYN*'s Newsline coverage in 2013 spanned the gamut of women's health, from contraception to infertility, pregnancy to postmenopause.

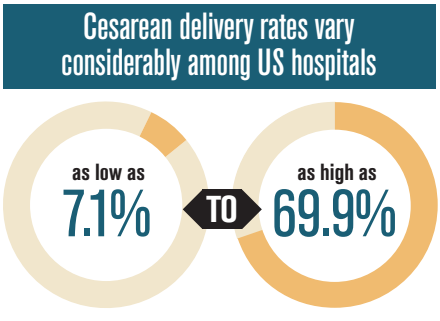
## FEBRUARY 2013
## BINGE DRINKING COMMON AMONG US TEEN GIRLS

In a CDC survey, 54.6% of high-school girls who drank in 2011 reported binge drinking.



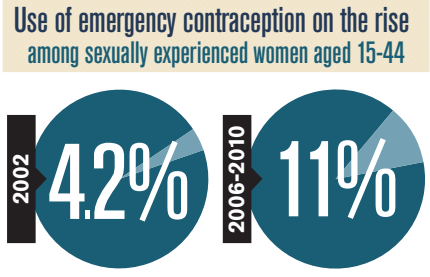

## APRIL 2013
## VAST VARIATION IN CESAREAN RATES ACROSS THE UNITED STATES

A report in *Health Affairs* showed a 10-fold variation in cesarean rates among US hospitals and a 15-fold variation in low-risk pregnancies.



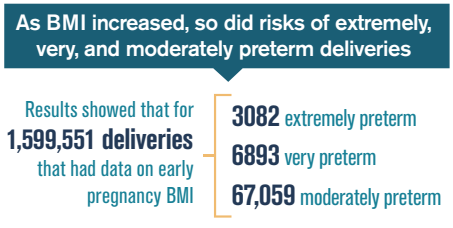

## MARCH 2013
## FEAR OF CONTRACEPTIVE FAILURE DRIVES USE OF EMERGENCY CONTRACEPTION

Nearly half the women in a CDC survey said they turned to EC because of fear of contraceptive failure, not unprotected sex.




## JULY 2013
## HIGHER RISK OF VERY EARLY DELIVERY FOR OVERWEIGHT, OBESE WOMEN

A Swedish study published in *JAMA* found an association between maternal overweight and/or obesity and preterm and extremely preterm delivery.




## MAY 2013
## AGE RESTRICTION ON EMERGENCY CONTRACEPTION LIFTED

In April a US District Court judge ruled that Plan B One-Step must be made available over the counter to all girls and women, regardless of age.

## BRIEF HISTORY OF OTC EC

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

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

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

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

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

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

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

**Rx only**

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

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

## INDICATIONS AND USAGE

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

### Limitations of Use

DICLEGIS has not been studied in women with hyperemesis gravidarum.

## DOSAGE AND ADMINISTRATION

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

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

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

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

## DOSAGE FORMS AND STRENGTHS

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

## CONTRAINDICATIONS

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

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

## WARNINGS AND PRECAUTIONS

### Activities Requiring Mental Alertness

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

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

### Concomitant Medical Conditions

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

### Drug Interactions

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

### Drug-Food Interactions

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

## ADVERSE REACTIONS

The following adverse reactions are discussed elsewhere in labelling:

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

### Clinical Trial Experience

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

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

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

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

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

### Postmarketing Experience

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

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

## USE IN SPECIFIC POPULATIONS

### Pregnancy

### Pregnancy Category A

DICLEGIS is intended for use in pregnant women.

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

### Nursing Mothers

Women should not breastfeed while using DICLEGIS.

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

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

### Pediatric Use

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

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

## OVERDOSAGE

### Signs and Symptoms of Overdose

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

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

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

### Management of Overdose

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

## PATIENT COUNSELING INFORMATION

**See FDA-approved patient labeling (Patient Information)**

### Somnolence and Severe Drowsiness

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

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

### Storage and Handling

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

**Distributed by:**

**Duchesnay USA, Inc.**
**Bryn Mawr, PA, 19010**
**www.diclegis.com**


DUCHESNAY

**2013-0002-01-041213**

# Introducing Diclegis®!

Help control your patient's queasy and woozy feelings of nausea and vomiting of pregnancy (NVP), commonly called morning sickness

**Diclegis is a delayed-release formulation that is a combination of doxylamine succinate (10 mg) and pyridoxine hydrochloride (10 mg).**

- Only Pregnancy Category A prescription treatment for NVP
- Only FDA-approved prescription treatment for NVP
- Only delayed-release formulation to help control NVP symptoms throughout the day when taken as prescribed

**Visit www.Diclegis.com for more information.**

Diclegis®

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

NVP | NAUSEA AND VOMITING OF PREGNANCY

## Indication

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

## Limitations of Use

Diclegis has not been studied in women with hyperemesis gravidarum.

## Important Safety Information

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

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

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

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

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

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

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

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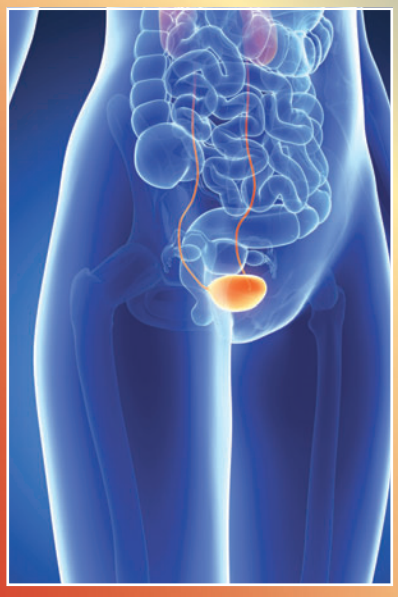
# Overactive Bladder *in Women*

## New Strategies for Simple Diagnosis, Treatment, and Referral



## Proceedings from an Experts Roundtable Discussion


**FACULTY**

**Matt Toren Rosenberg, MD (Co-Chair)**
**Peter Sand, MD (Co-Chair)**
**Mickey Karram, MD**
**Emily Spencer Lukacz, MD**
**David Staskin, MD**



**Release Date:**
January 2014

**Expiration Date:**
January 31, 2015

**Estimated Time to Complete Activity:**
1.5 hours

Jointly sponsored/co-provided by Postgraduate Institute for Medicine and MedEdicus LLC.

This activity is supported by educational grants from Allergan, Inc, and Astellas Pharma US Inc.

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### Target Audience
This activity has been designed to meet the educational needs of physicians and registered nurses involved in the management of patients with overactive bladder (OAB).

### Statement of Need/ Program Overview
Overactive bladder (OAB) is a common condition affecting millions of American women, resulting in a significant effect on numerous quality-of-life measures. This condition is also linked with a tremendous economic burden, with total societal costs approaching $66 billion. The effect on women patients is greater than that on men patients. Findings from multiple studies indicate that OAB is widely underdiagnosed and undertreated, particularly by primary care physicians (PCPs), whose patients are most likely to approach them with concerns about urinary incontinence. There is evidence that education for PCPs on overactive bladder and urinary incontinence improves the recipients' knowledge, confidence, and/or motivation to institute changes in their practice as well as in their delivery of care. Information from various sources highlights a need for increased clinician education on OAB diagnosis and management. A review of recent issues of leading journals for obstetrician/gynecologists and PCPs reveals a paucity of content addressing urinary incontinence/bladder concerns.

### Learning Objectives
After completing this activity, the participant should be better able to:

- Apply appropriate diagnostic strategies to identify new and treatment-refractory OAB in female patients
- Select appropriate management for newly diagnosed or persistent OAB in female patients, including behavioral treatment and pharmacotherapy
- Discuss new treatment options for OAB
- Demonstrate when patient symptoms indicate need for specialist referral
- Incorporate OAB and its treatment into basic patient education
- Provide appropriate care and counsel for patients and their families

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## INTRODUCTION

*Overactive bladder (OAB) syndrome is a common problem associated with significant consequences because of its high economic burden and quality of life (QOL) effect. It is easy to identify and can be managed effectively with available therapies, which include valuable new options for both newly diagnosed and treatment-refractory patients. For a number of reasons, however, OAB is widely underdiagnosed and undertreated.*

*The education of obstetrician/gynecologists (OB/GYNs) and primary care physicians (PCPs) on the importance of eliciting information from patients on bladder voiding issues, approaches for efficient diagnosis and counseling, and current treatment modalities could help to overcome many of the existing barriers to the recognition and care of women with OAB. To that end, a multidisciplinary panel of physicians with expert knowledge of this condition convened to discuss OAB screening, diagnostic evaluation, and clinical management. It is hoped the contents of this program will lead to increased recognition of OAB and help optimize treatment delivery.*

## DEFINITION AND DIAGNOSIS

**Dr Staskin:** Overactive bladder is defined by the International Urogynecological Association/International Continence Society (IUGA/ICS) as the presence of urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence in the absence of urinary tract infection (UTI) or other obvious pathology.[1] However, rather than focusing on the definition, I suggest that a practical approach to OAB diagnosis begins by asking patients a few simple questions that can identify OAB symptoms. Those are: Do you have a problem with bladder control? Do you have a strong urge to go to the bathroom that interrupts your activities? Do you go to the bathroom frequently? Do you lose urine before you can get to the toilet? Do you need to get up at night to go to the bathroom? If the patient answers yes to any of those questions, she deserves further evaluation to establish the diagnosis of OAB by ruling out a few other common conditions that cause similar symptoms.

Some considerations in the differential diagnosis are retention/obstruction, stress urinary incontinence, or cystitis. Further questions that can help to establish or eliminate these other conditions include the following: When you void, do you feel you empty your bladder completely? Do you lose urine with effort—when coughing, sneezing, lifting, or running? Do you have pain with or between voids?

**Dr Rosenberg:** Does the diagnosis of OAB require assessment of fluid intake and output?

**Dr Staskin:** An OAB diagnosis is based on the presence of bothersome symptoms that are affecting QOL and interfering with normal activities. But the physician needs to understand the concept of voided volume because bladder function is related to fluid intake and output.

**Dr Rosenberg:** Dr Lukacz, do you have any additional thoughts about establishing a diagnosis of OAB, particularly in the primary care setting?

**Dr Lukacz:** I think that the IUGA/ICS definition has limitations because not every patient with urgency, frequency, nocturia, and urge incontinence has OAB. I consider OAB a diagnosis of exclusion, but as Dr Staskin noted, there are not a lot of conditions to exclude.

When a patient comes into the office complaining of urgency or frequency, I want to make sure that the symptoms are not related to excessive fluid intake. Having a voiding diary is helpful for that determination, although not absolutely necessary if the patient can give reliable information. I want to rule out UTI, gross or microscopic hematuria, and overt urinary retention, or, at least, risk of urinary retention. In addition, I want to be sure that stress incontinence is not the predominant symptom because I do not want to mistreat stress incontinence with OAB therapies. Measurement of post-void residual urine volume is not necessary unless the patient has a more complicated history, such as with prior surgeries or advanced pelvic organ prolapse.

Overactive bladder is really a fairly simple diagnosis to make in the PCP's or gynecologist's office, although it may take more than a single visit because it may be necessary to exclude other conditions.

**Dr Karram:** It is worthwhile to note that OAB has evolved from being considered a disease to being defined as a symptom complex. According to the IUGA/ICS definition, however, urgency is the hallmark feature: without urgency, the patient does not have OAB.

The important issue providers need to recognize is that OAB affects QOL. If a woman reports she is voiding 7 times a day and

is experiencing a lot of urgency that is bothersome to her, by definition, she has OAB and warrants evaluation and potential therapy. On the other hand, a woman who voids 15 times a day without urgency or bother does not have OAB.

I think clinicians have to take into account the patient's complaints and see how they are corroborated by a voiding diary while ruling out other problems that could explain the presentation. Another point to keep in mind is that OAB is a chronic condition. It would be very rare for a woman to report acute onset of urgency, frequency, and/or incontinence and have OAB.

I also like to consider the subtypes of OAB-wet and OAB-dry when evaluating patients. It is obvious that urgency with incontinence is almost always going to be bothersome. However, when there is urgency without incontinence, I consider whether it is a sensory versus a motor issue. For example, is the woman young with good pelvic floor tone and urinating 15 times a day because she is afraid she might otherwise have an accident? Or, is it someone who has symptoms of irritation that are relieved only by urinating? The former patient would be more of a candidate for traditional OAB therapy whereas the latter woman's complaints of irritation might lead me down a different path for evaluation and management.

**Dr Sand:** I think we have established that OAB is a symptom complex and a QOL issue, and that some significant underlying pathology can cause symptoms that overlap with those of OAB, and hence the importance of ruling out UTI, urolithiasis, or malignancy.

I also agree that concentrating on the semantics of the IUGA/ICS definition can be confusing for clinicians as well as not relevant to patients. The inclusion of nocturia in the ICS definition of OAB can be particularly misleading. Although patients may be getting up to urinate during the night because of involuntary bladder contractions, there are a myriad of other common causes for nocturia.

**Dr Lukacz:** I think the vast majority of the adult female population gets up at least once during the night to urinate, and results of a study we conducted evaluating urinary frequency and associated bother among community-dwelling women found women were not really bothered until they needed to get up 2 or more times.[2] In the same study, median daytime urinary frequency was every 3 to 4 hours, and the bother level doubled when the frequency increased from every 3 to 4 hours to every 1 to 2 hours. These data show increasing frequency alone is associated with bother.

## EFFECT OF OVERACTIVE BLADDER

**Dr Rosenberg:** So, we have been talking about "bother" and the importance of diagnosing OAB because its symptoms affect QOL. Dr Sand, what are some of the specific ways that women are affected by OAB?

**Dr Sand:** The effects of OAB manifest through all domains of daily activities and interpersonal relationships. Affected individuals report that incontinence interferes with their social and domestic lives.[3] In addition, depression is a problem among patients with OAB, with some studies reporting a prevalence of approximately 25% to 30%.[4-6] Overactive bladder also affects sexual function and intimacy with partners, which is understandable, considering that 20% to 25% of women who have urgency urinary incontinence with OAB experience incontinence during intercourse.[7] And, OAB has a negative effect on work productivity, whether individuals have urgency alone or with incontinence.[4,8]

**Dr Rosenberg:** I also see OAB as a significant medical problem because urinary urgency that causes someone to rush to get to the bathroom in time puts that individual at risk for a fall. In fact, there are a number of published papers showing a relationship between fracture risk and nocturia events.[9,10] I believe the potential for falls and fractures is why identification of urinary incontinence in women aged 65 years and older is a Physician Quality Reporting System (PQRS) measure, and it has relevance in the primary care setting because it is the PCP who cares for these patients as they go from the hospital to a nursing home setting, where sadly, the morbidity and mortality rates are rather high. The PCP serves as the gatekeeper for identifying urinary issues; therefore, he or she must be educated on the diagnosis of OAB.

**Dr Karram:** I sense that a significant number of women with OAB are socially isolating themselves because of fear of urinary incontinence. When I ask women why they waited so long to speak to a physician, often they tell me that they said something to their doctor years ago, but were told their problems were an expected consequence of aging, or perhaps that they needed to lose weight and then their symptoms would improve. Responses such as those tend to place patients in isolation and illustrate the need for physician education. Regrettably, for a general gynecologist,

### TIPS FOR QUICK OAB DIAGNOSIS

**Be proactive:**

- Make it part of your routine examination to discuss bladder habits with patients, explaining what is normal and mentioning possible problems

**Ask a few simple questions to identify OAB symptoms:**

- Do you have a problem with bladder control?
- Do you have a strong urge to go to the bathroom that interrupts your activities?
- Do you lose urine with a sense of urgency? (Remember OAB can be "wet" or "dry")
- Do you need to get up more than once at night to go to the bathroom?

**If the patient answers "yes", consider the following to rule out common non-OAB causes:**

- Identify if symptom onset was acute
- Ask about fluid intake or consider a voiding diary*
- Review the medication history for drugs causing diuresis or affecting voiding function
- Perform urinalysis to identify signs of UTI, urolithiasis, or malignancy
- Do a limited pelvic examination to identify pelvic masses or organ prolapse
- Ask about loss of urine with effort
- Ask about pain with or between voids

**Rule out urinary retention:**

- Perform bladder palpation to identify overt retention
- Ask about completeness of bladder emptying when voiding

***Link to Printable National Institutes of Health Bladder Diary for Your Patients**

kidney.niddk.nih.gov/kudiseases/pubs/diary/diary_508.pdf

the diagnosis of OAB is not as highly prioritized as other issues that may be presented.

**Dr Rosenberg:** I believe the same holds true for many PCPs.

**Dr Karram:** OB/GYNs and PCPs might ignore patients' expressions of concern or tell them to wait until their symptoms get worse. Alternatively, some physicians might prescribe an antimuscarinic medication without providing any education to the patient or considering a trial of behavioral therapy, or they might refer the patient to a urologist or some other specialist colleague who handles OAB.

The message to PCPs and general gynecologists is that complaints suggestive of OAB should not be ignored. There is a simple approach to its diagnosis and initial management. Physicians who do not themselves offer this care should, at least, refer patients to someone whose practice includes management of OAB.

## STARTING THE CONVERSATION

**Dr Rosenberg:** Let us talk a little about patient care-seeking behavior. A woman whose physician tells her that her bladder problems are a normal consequence of aging that she must learn to live with may be reluctant or embarrassed to talk about the issue with any other physician. Some patients, however, who have significant bother may be motivated to seek specialty care. Dr Lukacz, what have you observed in terms of care-seeking behavior for OAB?

**Dr Lukacz:** Epidemiologic data show that care-seeking among patients with OAB is very low,[11,12] as evidenced by a recent survey focusing on OAB that included a nationally representative sample of more than 1000 American women aged 45 years and older, which revealed that approximately two-thirds of women never discussed bladder health with their doctor.[13] I think the situation has changed recently because of direct-to-consumer pharmaceutical advertising. I have seen many more patients with bladder issues in the last 2 to 3 years who were motivated to seek care because of an advertisement they saw on television. Therefore, I consider this marketing a good thing because it is getting more patients in the door to have the conversation with their physician. Now, with patients becoming more educated about treatments and with care-seeking increasing, it is incumbent on PCPs to become better educated about OAB so that they can respond to this growing demand.

**Dr Rosenberg:** We have said that much of the concern with OAB stems from its effect on QOL. Can busy PCPs devote time to OAB diagnosis and patient care when, in any given day, they are seeing a multitude of patients with life-threatening diseases?

**Dr Staskin:** Physicians need to understand that evaluating a patient for OAB does not, in general, involve complex issues for the differential diagnosis. In most women, urinary frequency is not necessarily indicative of a serious underlying condition, and making the diagnosis of OAB is not complicated because it involves a simple urinalysis, history, and physical examination. In addition, the treatment algorithm for OAB is straightforward. It includes a few initial options, and if those options do not provide benefit, patients should be referred to a specialist who can perform further evaluation if needed, and offer newer, higher-level strategies.

**Physicians need to understand that evaluating a patient for OAB does not, in general, involve complex issues for the differential diagnosis.**

— David Staskin,MD

**Dr Rosenberg:** Speaking from the perspective of the PCPs, physicians may feel that time constraints prevent them from asking patients about bladder issues or from fully evaluating patients with such complaints. How long should it take to evaluate an established patient, for whom the physician already has a complete history, for OAB?

**Dr Sand:** It should take about 10 minutes. The essential evaluation includes establishing the presence of OAB symptoms, which, as Dr Staskin said, involves just a few questions. Then, we want to rule out the presence of microscopic hematuria and pyuria as potential indicators of urolithiasis, neoplasia, or infection. Patients may also have an inflammatory condition within the urethra or bladder that may present with similar symptoms and thus confuse the diagnosis. However, an inflammatory condition may be excluded in the absence of bladder or urethral tenderness. For the vast majority of women, there is no need for further evaluation to rule out urinary retention. Exceptions include presence of a pelvic mass, obvious prolapse causing mechanical obstruction, or history of anti-incontinence surgery or pelvic surgery that could have resulted in retention.

**Dr Rosenberg:** We can break the history down into surgical, medical, medications, and review of systems, which the PCP should have in the chart already. We also want to consider the temporal relationship between onset of the symptoms and other changes in the patient's history, particularly medication use. For example, was the patient recently started on a diuretic and then developed nocturia, or did she begin using a narcotic analgesic after hip surgery that resulted in constipation and consequently urinary frequency and urgency? In addition, physicians should do a brief neurological examination, which could be just a little more than observational.

**Dr Karram:** Because care-seeking for OAB is low in the primary care setting, it is likely that most women might raise concerns about OAB symptoms during a visit that is either for an annual physical examination or regular follow-up for some other chronic condition. I agree that the evaluation for OAB diagnosis takes just a few minutes, and unless the history suggests otherwise, there is no need to check for incomplete bladder emptying. However, if within the context of an appointment made for another purpose, the patient mentions that she is having problems with urgency, frequency, and/or incontinence, would you provide her some written information about OAB and maybe a voiding diary, and recommend she schedule another visit to evaluate the problem further? Or, can the evaluation for OAB be completed at the same visit?

**Dr Rosenberg:** The answer depends on how comfortable the physician is in evaluating the complaint and if this has been brought up with the patient before. Physicians who have not

been paying attention to these urinary problems in their review of systems will probably have to ask the patient to make a separate appointment.

My approach is to routinely ask patients about their bladder function during the review of systems, which fulfills the PQRS measure. Then, I let them know what events are abnormal—having to rush to get to the bathroom, frequently voiding small volumes, leaking urine—and tell them to be sure to let me know if any of those problems occur. I believe the average patient has no idea what constitutes normal and abnormal bladder habits, and so it is up to the physician to initiate the conversation. And, I believe when the physician is proactive about mentioning possible problems, patients are more comfortable coming forth with their concerns. In fact, Dr Lukacz and I were participants in an expert panel on bladder health that was organized in part based on the idea that education on normal bladder structures and functioning can help promote early treatment-seeking for bladder conditions.[14]

I commonly use voiding diaries in the evaluation. When I explain to the patient that I am trying to understand her habits, she generally follows through. Having said that, some patients will make entries in the diary for several days whereas others may do it sporadically. I tell them that any information is helpful.

**I commonly use voiding diaries in the evaluation. . . . some patients will make entries in the diary for several days whereas others may do it sporadically. I tell them that any information is helpful.**

—Matt Rosenberg, MD

Dr Lukacz, what are your thoughts on the role of a pelvic examination as part of the OAB assessment?

**Dr Lukacz:** There is probably not any need to do a pelvic examination when initially evaluating a woman for OAB, unless you are assessing for bulge/prolapse, abnormal bleeding, or pain. Of note, data show that, with few exceptions, prolapse becomes symptomatic only when it is at or beyond the hymen.[15] Therefore, asking patients simply whether they have a bulge or a lump hanging out of the vagina has good sensitivity and specificity for diagnosing advanced prolapse. Beyond that, the initial pelvic evaluation need include only an abdominal examination to check for bladder distension, masses, or pain. In some cases, a more careful, directed physical examination should be performed.

In terms of conversations about urinary problems with a gynecologist, women are already talking about urogenital issues, such as sexual function concerns or menopausal symptoms. Discussing urinary problems is a natural extension of that conversation, and so women may be more comfortable bringing up their OAB situation with their gynecologist.

**Dr Karram:** I think gynecologists have a greater knowledge base than PCPs in terms of evaluating for prolapse and being able to do a quick assessment of pelvic floor muscle tone, which can be potentially helpful when counseling patients on techniques for preventing leakage or identifying women who may need referral to a physical therapist for pelvic floor training.

**Dr Rosenberg:** Dr Lukacz, behavioral therapy is recommended as a first-line approach for managing OAB.[16] Can a physician teach a woman behavioral modification without doing a vaginal examination?

**Dr Lukacz:** Yes, simply telling the patient to contract the same muscles used to interrupt urine flow or prevent passage of gas gives enough information for her to get started. If the patient admits that she is unable to do this, there are various devices online to assist patients with doing Kegel exercises on their own.

**Dr Rosenberg:** Dr Karram, you mentioned asking patients to complete a voiding diary. Do you think it is necessary for diagnosing OAB and determining treatment response?

**Dr Karram:** I think a voiding diary is very useful because it engages patients in their therapy and gives them an understanding of their voiding habits. If you look at the trials for OAB medications that were conducted to gain US Food and Drug Administration (FDA) approval, the data show relatively good improvements in the placebo-treated control groups, and I believe part of the explanation for those responses is that completing a voiding diary itself provides some behavioral therapy.

However, the reality is that many women will not fill out the diary or not do it accurately. Keeping a voiding diary is not mandatory, but I think it is very easy to do and the suggestion to keep one should always be offered.

**Dr Rosenberg:** We might assume that patients seen in a specialist's office have sufficient bother that drives them to self-refer or to request a referral from their PCP. But the diagnosis of OAB may be made in the setting of a primary care office after the physician has initiated the conversation. The goal of the interview is to understand the severity of the symptoms as well as of the bother. The degree of bother generally correlates to the patient's willingness to engage in therapy.

**Dr Staskin:** Bother reflects the effect of OAB on QOL. However, intervention is guided by understanding the reason for the bother. If a woman is complaining about frequency-related bother, is she someone who is voiding 15 or more times a day or someone who is voiding 6 times a day and believes that is excessive? In the case of the former patient, there is a need to determine if there is a behavioral component to the frequency that might be addressed with conservative therapy only vs with medication. The latter patient needs education to understand what is normal, rather than treatment for OAB.

Of course, urinary frequency is not the only cause for bother with OAB; urgency may be the more important symptom for the patient. In addition, some patients may deny bother despite having obvious problems with OAB symptoms—for example, a woman who is voiding 15 times a day or someone who is wearing an adult diaper because she has urgency incontinence.

## INITIATING TREATMENT – BEHAVORIAL THERAPY

**Dr Rosenberg:** Dr Sand, assume a patient comes to see you because she is bothered by urinary frequency with occasional

episodes of leakage. What can we tell such a patient about the efficacy of treatment for OAB?

**Dr Sand:** Based on my experience with treating thousands of women with OAB, I tell patients that more than 90% of women feel much better or completely better with treatment, and sometimes, I quantify the degree of response by telling them that at least 75% of women improve with treatment. The outcome, however, depends on how far an individual is willing to progress along the treatment algorithm *(Figure)*.[16]

I let patients know that there are numerous treatment options for OAB and that there are alternatives to try in order to achieve a satisfactory response if initial interventions fail. I want to give them a blue-sky approach with a bright horizon.

**Dr Rosenberg:** Physicians should inform patients about initiating therapy for OAB, and that if initial therapeutic options are insufficient, opportunities for success with other treatments and specialist care are available.

**Dr Sand:** Yes, patients should know there are multiple options.

Now, let us focus more specifically on choosing initial treatment. According to the most recent American Urological Association (AUA) Diagnosis & Treatment Algorithm, behavioral therapy is first-line treatment for OAB; however, if this is only partially effective, it may be appropriate to add anti-muscarinic pharmacotherapy in the first-line setting.[16] There is good Level 1 evidence that the combination of behavioral therapy and pharmacotherapy is more successful than either therapy used individually. Yet, we always offer behavioral therapy first because unlike with pharmacotherapy, there are no side effects. Keep in mind, though, that behavioral therapy means different things to different people. I think we all would agree that initial behavioral therapy would include patient education about normal lower urinary tract function, discussing bladder diets, offering advice about restricting fluid intake in the evening if nocturia is a problem, and perhaps recommending use of a voiding diary. Behavioral therapy can also include bladder drills with timed voiding or prompted voiding.

**Dr Staskin:** Behavioral therapy, which aims to create changes in behavior, falls within the category of conservative therapy, and is incorrectly referred to as any intervention other than medication

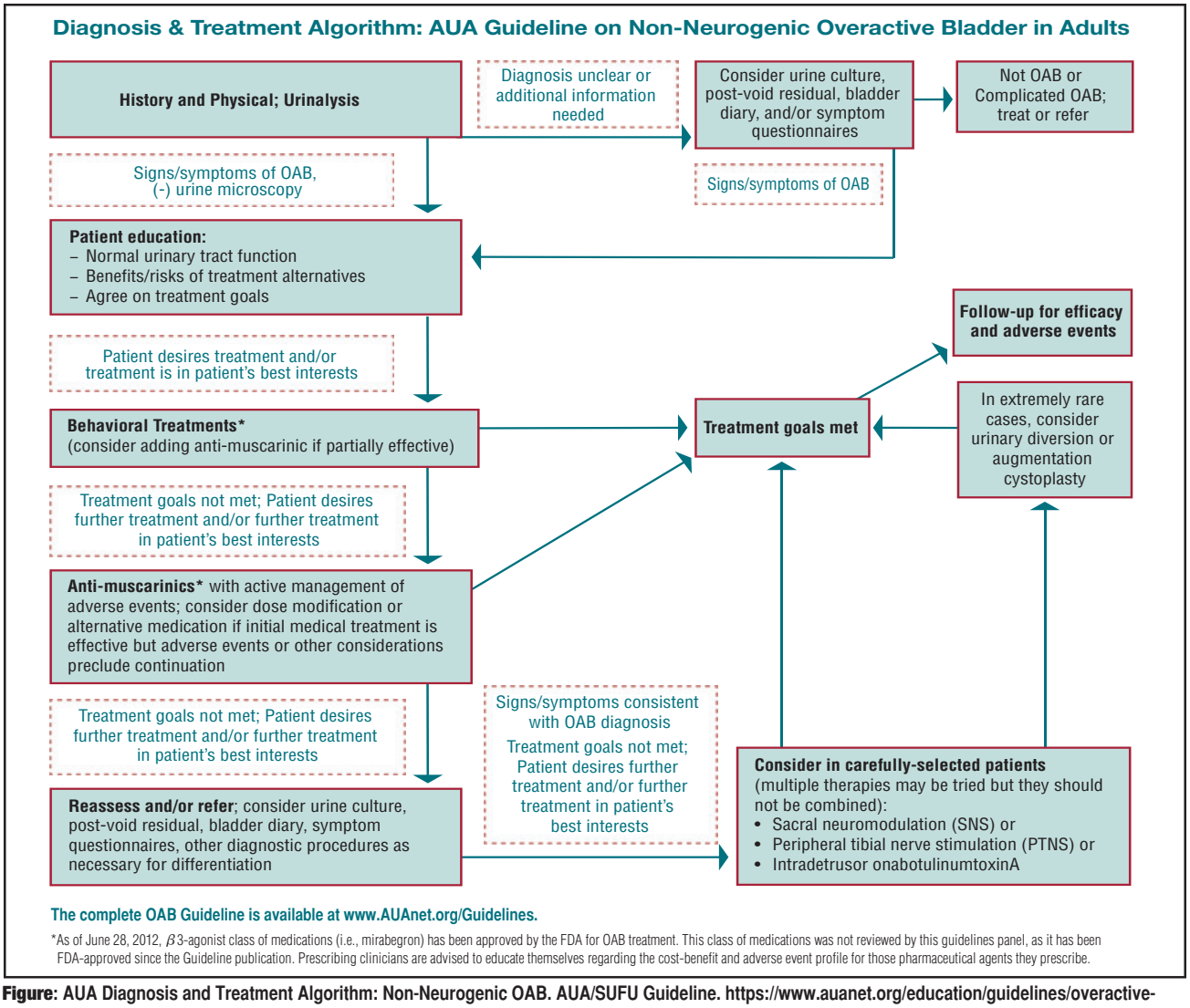


**Figure:** AUA Diagnosis and Treatment Algorithm: Non-Neurogenic OAB. AUA/SUFU Guideline. https://www.auanet.org/education/guidelines/overactive-bladder.cfm. Accessed November 8, 2013. Reprinted with permission from the American Urological Association.

or surgery. Pelvic floor exercises are also a conservative therapy for OAB and should be viewed as a separate intervention.

**Dr Sand:** Dr Lukacz, how often do you use behavioral therapy for initial management of OAB?

**Dr Lukacz:** I explain to patients that there is a pathway for managing OAB that includes many different treatments, but that we like to take a stepwise approach and stop when we are successful, rather than attacking the problem with multiple tools at once and then having to decide later if something can be discontinued.

**I explain to patients that there is a pathway for managing OAB that includes many different treatments, but that we like to take a stepwise approach and stop when we are successful.**

—Emily Spencer Lukacz, MD

I consider behavioral therapy a critical component of successful management of OAB because patients are not going to get better unless they agree to do the work that it takes to get results. Therefore, I try to convince patients to "buy into" the behavioral modification and timed voiding practices. I explain to them that there is evidence from clinical trials showing it will make the medication work better, although it will not necessarily increase the likelihood that they can get off the medication.[17] I also explain that medication alone is rarely going to fix the problem. In terms of an analogy, I remind them that success with losing weight does not come just with careful observance of dietary intake; it also requires that the person participate in an exercise program. I think once patients understand that a whole program is needed, their buy-in is more likely.

That said, decisions on combining behavioral therapy with medications need to be individualized in terms of whether the patient has sufficient bother to be willing to take on the potential side effects of medication, as well as the cost. Behavioral therapy can be a perfectly reasonable first-line approach, and so I give patients the option of using that method alone or with medication.

**Dr Sand:** I would contend that women in research trials represent a motivated population who may be more compliant with behavioral therapy than the general population. In clinical practice, what percentage of patients who start on behavioral therapy for OAB remain compliant after 3 months?

**Dr Lukacz:** I estimate 20% or less in my patient population, which represents women whose bother was so severe that they sought care from a specialist. My guess is that the rate might be higher among women seen in a primary care setting.

**Dr Rosenberg:** Speaking from a primary care perspective and based on the entries in our patients' voiding diaries, I estimate that 50% of women will start behavioral therapy and put effort into it. However, I think adherence with behavioral therapy tapers off a great deal after 3 months, when it may be maintained mostly by patients who have serious bother.

In our practice, behavioral therapy is discussed with every patient who is diagnosed with OAB, regardless of whether she is taking medications or not.

**Dr Karram:** In general, I find the older the patient is, the less likely she is going to be compliant with behavioral therapy. My most motivated patients are those in their third through fifth decades of life. Overall, I would say perhaps 20% to 40% of women are compliant after 3 months.

When educating patients about OAB, I think it is very important they understand that OAB, unlike stress incontinence, does not have a quick fix through surgery. I make it very clear that behavioral therapy can work, but it requires effort.

I think one of the reasons behavioral therapy programs fail is that patients are not properly educated, just as they are not properly educated regarding pelvic floor exercises. When recommending these conservative therapies, PCPs would do their patients a great service by referring them to a setting where there they can receive the detailed counseling and motivation that is necessary for success, such as to a specialist's office or to a physiotherapist.

**I think it is very important they (the patients) understand that OAB, unlike stress incontinence, does not have a quick fix through surgery. I make it very clear that behavioral therapy can work, but it requires effort.**

— Mickey Karram, MD

**Dr Sand:** Are there any factors that predict success or failure with behavioral therapy and that might make you more or less likely to recommend it for a particular patient?

**Dr Karram:** Severity is a consideration because I think behavioral therapy by itself is less apt to be effective in more severe cases of OAB. In addition, a patient who seems to have little warning time and, as a result, has multiple incontinence episodes each day, will not be able to trigger her muscles in time to prevent the leakage and is not going to do well on behavioral therapy by itself.

**Dr Lukacz:** As I mentioned before, the success of behavioral therapy depends on patient commitment and participation. Therefore, I exclude from behavioral therapy cognitively impaired patients or those with limited functional mobility. In my opinion, those individuals require medical therapy outside of self-directed behavioral therapy.

## PHARMACOTHERAPY

### Anti-muscarinic Medications

**Dr Sand:** Now we will discuss pharmacotherapy, which includes anti-muscarinic medications and mirabegron, the new ß-3 adrenergic agonist. In using pharmacotherapy for OAB, are there any considerations you have for individualizing treatment?

**Dr Staskin:** Anti-muscarinic agents are the traditional pharmacologic therapy for OAB. These medications work by blocking the

**Table 1:** Anti-Muscarinic Medication Dosing (Derived From Product Prescribing Information)

| Name | Formulation (available strengths) | Starting Dose (in patients not needing adjustment for comorbidities) | Maximum Dose | Dose Adjustments |
|---|---|---|---|---|
| Darifenacin | ER tablet 7.5, 10 mg | 7.5 mg QD | 15 mg QD | 7.5 mg in moderate hepatic impairment, patients taking potent CYP3A4 inhibitors; not recommended in severe hepatic impairment |
| Fesoterodine | ER tablet 4, 8 mg | 4 mg QD | 8 mg QD | 4 mg maximum if severe renal impairment or concomitant use of a potent CYP3A4 inhibitor; not recommended in severe hepatic impairment |
| Oxybutynin | IR tablet 5 mg | 5 mg BID or TID | 5 mg QID | 2.5 mg BID or TID to start in frail older adults |
| | ER tablet 5, 10, 15 mg | 5-10 mg QD | 30 mg QD | No studies in patients with renal or hepatic impairment |
| | Gel 10% | One sachet QD | No titration | |
| | Gel 3% | Three pumps (84 mg) QD | No titration | |
| | Transdermal patch 3.9 mg/d (Available OTC) | 1 patch twice a week (Q 3-4 days) | 1 patch at a time | |
| Solifenacin | ER tablet 5, 10 mg | 5 mg QD | 10 mg QD | 5 mg maximum in severe renal impairment, moderate hepatic impairment, concomitant use of potent CYP3A4 inhibitors; not recommended in severe hepatic impairment |
| Tolterodine | IR tablet 1 mg | 2 mg BID | 1-2 mg BID | 1 mg BID if significantly reduced hepatic or renal function or taking potent CYP3A4 inhibitors |
| | ER capsule 2, 4 mg | 4 mg QD | 4 mg QD | Reduce by half in mild to moderate hepatic impairment, severe renal impairment, or with concomitant use of potent CYP3A4 inhibitors; not recommended if creatinine clearance <10 mL/min or with severe hepatic impairment |
| Trospium | IR tablet 20 mg | 20 mg QD (on an empty stomach or 1 hour before a meal) | 20 mg BID | Severe renal impairment 20 mg QD; titrate down to 20 mg QD based on tolerability in patients aged 75 years and older |
| | ER tablet 60 mg | 60 mg QD (on an empty stomach or 1 hour before a meal) | 60 mg BID | Not recommended in patients with severe renal impairment |

BID=twice daily; ER=extended release; IR=immediate release; OTC=over-the-counter; QD=once daily; TID=3 times daily.

muscarinic receptors in the bladder, but they can potentially cause bothersome and intolerable side effects by acting on the muscarinic receptors in other tissues. No single anti-muscarinic agent has been established as having superior or inferior efficacy because there have been few head-to-head studies directly comparing different anti-muscarinic agents and no study that compared all of them. There are, however some differences among the available drugs with respect to route of administration, dosing frequency, and their availability as a generic *(Table 1)*, as well as in their side-effect profiles *(Table 2)*.

Overall, the once-daily medications, which are the extended-release (ER) formulations, are associated with lower adverse event rates than are the immediate-release (IR) products, based primarily on pharmacokinetic differences in peak serum concentration and fluctuation.[16,18] There also appear to be differences among anti-muscarinic drugs in their association with constipation, because of differences in drug selectivity for various muscarinic receptor subtypes.

Labeling for all the oral anti-muscarinic drugs used to treat OAB includes a warning that patients should be monitored for signs of

**Table 2.** Adverse Event Rates With Anti-Muscarinics (Derived From Product Prescribing Information)

| Medication | Dry Mouth | Constipation | Other (>10%) |
|---|---|---|---|
| Darifenacin ER | 7.5 mg 20.2%<br>15 mg 35.3% | 7.5 mg 14.8%<br>15 mg 21.3% | |
| Fesoterodine ER | 4 mg 19%<br>8 mg 35% | 4 mg 4%<br>8 mg 6% | |
| Oxybutynin IR | 71.4% | 15.1% | Dizziness 16.6%<br>Somnolence 14.0% |
| Oxybutynin ER | 34.9% | 8.7% | Somnolence 12.0% |
| Oxybutynin gel 10% | 7.5% | | |
| Oxybutynin gel 3% | 12.1% | | Application site reactions 14.2% |
| Oxybutynin transdermal patch | 4.1%-9.6% | 3.3% | Application site pruritus 14.0%-16.8% |
| Solifenacin | 5 mg 10.9%<br>10 mg 27.6% | 5 mg 5%<br>10 mg 13.4% | |
| Tolterodine IR | 35% | 7% | |
| Tolterodine ER | 23% | 6% | |
| Trospium IR | 20.1% | 9.6% | |
| Trospium ER | 10.7% | 8.5% | |

anticholinergic central nervous system (CNS) effects. Overall, CNS side effects were not systematically measured in clinical trials of anti-muscarinic treatments for OAB, and these studies also excluded the geriatric patients who may be most at risk for adverse CNS effects.[16,19] There is some evidence of between-drug differences in the likelihood of cognitive impairment and other CNS adverse effects that in theory may be explained by differences in muscarinic receptor subtype selectivity as well as in various factors influencing drug penetration across the blood-brain barrier.[16,20] Limited data from studies evaluating healthy older adults show little to no risk of CNS side effects with the use of darifenacin, trospium, solifenacin, and tolterodine, whereas oxybutynin has been shown to adversely affect cognition.[21] However, individual responses can vary and physicians should be particularly cautious when prescribing anti-muscarinic medications in older patients with preexisting dementia or who are taking other medications with anticholinergic activity.[16,21]

Table 3 summarizes strategies that can help minimize adverse events with the use of anti-muscarinic treatments.[16]

**Table 3. Strategies for Optimizing Tolerability of Anti-muscarinic Medications[16]**

| Dosing |
|---|
| • Initiate with conservative doses in older patients<br>• Choose extended-release or topical products vs immediate-release products<br>• Reduce the dose if bothersome side effects develop<br>• Check medication history to identify concomitant drug therapies with anticholinergic effects |
| **Limiting Constipation** |
| • Counsel patients on adequate dietary fiber and fluid intake<br>• Consider psyllium-based fiber supplements<br>• Encourage regular exercise |
| **Limiting Dry Mouth** |
| • Counsel patients on the possible use of oral lubricants<br>• Advise patients to avoid mouthwashes with alcohol<br>• Consider recommending small sips of water throughout the day, as well as use of sugar-free hard candies and sugar-free gum to limit dry mouth |

**Dr Karram:** Also, I think we all would agree that some sort of dose titration is necessary to achieve the desired response in a significant proportion of patients, and flexible dosing is not a feature of all the anti-muscarinic medications.

**Dr Lukacz:** We probably each have personal preferences for choosing among the available anti-muscarinic medications that are not evidence-based, and as other physicians gain experience with these drugs, they too will develop their own "style" for prescribing them. However, formulary coverage and cost also may be issues in determining initial therapy. In my community, generic oxybutynin and other generic IR anti-muscarinic medications are probably prescribed most often for initial therapy because of insurance constraints, and off-label use of imipramine, a tricyclic antidepressant that has anti-muscarinic activity, may even be considered as initial drug therapy for some women because of cost.

**Dr Rosenberg:** Formularies often drive our prescribing decisions, and most, if not all, formularies will force us to try a generic medication first. After that, there may be more variation among formularies as to what is allowed, but the fact is that while there are a lot of options on the market, physicians are not always free to choose among them. However, regardless of what drug is selected, physicians should understand that titration may be important and that the first dose might not work.

**Dr Sand:** Recently, transdermal oxybutynin became available as the first over-the-counter (OTC) anti-muscarinic medication for OAB. What effect do you think it will have on patient care-seeking behavior? Will cost or some other factor be a barrier to patients trying an OTC medication? Will it lead to more women seeking care from a physician?

**Dr Rosenberg:** I think patients generally believe that OTC medications are not as effective as those available by prescription. In some cases, patients may try the OTC medication first, and then if the medication is not helpful, they may go to the provider for a prescription.

**Dr Lukacz:** I expect the manufacturer's marketing strategy will be important in determining product sales. Patients may be willing to try the OTC medication if they believe it could allow them to avoid a physician visit and, with that, the need for an uncomfortable conversation and a co-pay. Then, if the medication is not helpful, they may consider making an appointment with their doctor.

## Mirabegron

**Dr Sand:** Mirabegron is a first-in-class ß-3 adrenergic agonist for the treatment of OAB. Dr Staskin, please explain its mechanism of action and dosing.

**Dr Staskin:** Mirabegron stimulates ß-3 adrenergic receptors in the detrusor muscle, leading to detrusor relaxation during the storage phase and increased bladder capacity. It is available in 25-mg and 50-mg ER tablets and is recommended to be initiated at a dose of 25 mg once daily. Then, the dose can be increased to 50 mg if the drug is well tolerated and the patient desires greater efficacy.

**Dr Sand:** Dr. Rosenberg, how effective was mirabegron in treating OAB in clinical trials?

**Dr Rosenberg:** End points in the clinical trials looked at incontinence, urinary frequency, and urinary volume per void, and mirabegron was significantly more effective than placebo for improving those measures.[22] However, what physicians probably want to know is how this agent compares with the anti-muscarinic medications. Some interesting data have emerged from recent trials. In the TAURUS study, mirabegron 50 mg and mirabegron 100 mg were compared with tolterodine ER 4 mg.[23] All 3 treatments effectively improved OAB symptoms over the 12 months of follow-up, but this study was not designed to demonstrate a statistically significant difference in efficacy among treatment groups. In the SCORPIO trial, mirabegron 50 mg and 100 mg resulted in a statistically significant decrease in mean number of incontinence episodes and micturition episodes, while tolterodine 4 mg also improved mean number of incontinence and micturition episodes; however, the changes with tolterodine did not reach statistical significance.[24] Recently, the SYMPHONY study also compared the combination of solifenacin and mirabegron against solifenacin monotherapy, and found

that combination therapy was more efficacious with respect to improving micturition frequency and mean volume voided per micturition.[25] However, results pertaining to incontinence were inconclusive.

The main point about mirabegron is that it represents an efficacious medication of a novel class for treating OAB. Results of a study presented at the 2012 ICS meeting showed improvement in OAB symptoms and patient satisfaction with the use of mirabegron as a second-line therapy for those patients who were refractory to or who discontinued anti-muscarinic agents.[26] For whatever reason, some patients do not respond to a certain medication class, and so mirabegron has value for allowing a different pharmacologic approach to treating OAB.

**Dr Sand:** Dr Karram, what are the safety issues associated with mirabegron?

**Dr Karram:** Mirabegron was very well tolerated in clinical trials and had a favorable side-effect profile with similar rates of dry mouth and constipation when compared with placebo, and lower rates than those seen with anti-muscarinics *(Table 4)*.[22]

Hypertension is a potential concern, but in the 3 registration trials that included more than 3000 patients, the rate of drug-related hypertension was the same when comparing placebo with mirabegron.[22] Nevertheless, mirabegron should not be used in patients with uncontrolled hypertension, and it also is not recommended for patients with severe hepatic or renal impairment. Prescribers also should know that mirabegron may cause urinary retention in patients with bladder outlet obstruction or in those who are already taking anti-muscarinic drugs for OAB. In addition, they should consider potential drug interactions because mirabegron inhibits the activity of CYP2D6.

**Dr Sand:** Dr Rosenberg, earlier you made the point that a patient who fails anti-muscarinic therapy might do better with a trial of medication from a different class. Does mirabegron have any role as first-line therapy before trying an anti-muscarinic agent?

**Dr Rosenberg:** As noted in the AUA/SUFU (Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction) guidelines, pharmacotherapy decisions for OAB should be based on understanding of the cost-benefit and adverse-event profile of the agents.[16] In practice, the choice of medication may frequently be formulary-driven. If formularies are not an issue, the data are supportive of using an anti-muscarinic or a β-3 adrenergic agonist as first-line therapy.

**Dr Lukacz:** In terms of switching within the anti-muscarinic class, data indicate that a particular formulation may be more effective than another in certain patients, based on differences in metabolic phenotypes.[27] My practice is to try at least 2 anti-muscarinic medications before switching to mirabegron. In general, I counsel women that they should expect some level of improvement in the first month and encourage them to try at least 3 months of therapy, as data from clinical trials suggest there is a plateau in efficacy at this time point. However, I can justify using mirabegron as my first-line drug if the patient has a contraindication to anti-muscarinic therapy, such as narrow-angle glaucoma. I also would switch to mirabegron immediately if a patient's failure with an initial anti-muscarinic medication was caused by severe constipation or some other intolerable anticholinergic side effect.

**Dr Rosenberg:** Eventually, we will be selecting drug therapies based on genetic testing that can include determination of the activity of metabolizing enzymes. For now, my practical advice to PCPs and gynecologists is that it is probably better to switch to a different medication class if a patient fails treatment with an anti-muscarinic medication, assuming that is not impossible because of formulary restrictions.

## REFRACTORY OVERACTIVE BLADDER

**Dr Sand:** Referral to a specialist is indicated if patients have failed behavioral therapy and are refractory to or intolerant of medical therapy. Proper referral will allow the patient access to alternative therapies that include sacral nerve stimulation (SNS), percutaneous tibial nerve stimulation (PTNS), and onabotulinumtoxinA injections into the bladder.

**Referral to a specialist is indicated if patients have failed behavioral therapy and are refractory to or intolerant of medical therapy.**

—Peter Sand, MD

### Sacral Nerve Stimulation

**Dr Sand:** Dr. Karram, please explain SNS.

**Dr Karram:** Sacral nerve stimulation is approved by the FDA for treatment of frequency urgency syndrome, urge incontinence,

**Table 4.** Rates of Treatment-Emergent Adverse Events (TEAEs) From Pooled Data in 3 Phase 3 Mirabegron Clinical Trials[22]

| TEAE | Overall Rate[a] (drug-related rate[b]) | | | |
|---|---|---|---|---|
| | Placebo (n=1380) | Mirabegron 25 mg (n=432) | Mirabegron 50 mg (n=1375) | Tolterodine ER 4 mg (n=495) |
| Hypertension | 7.6% (4.6%) | 11.3% (6.9%) | 7.5% (4.7%) | 8.1% (6.1%) |
| Urinary Tract Infection | 1.8% | 4.2% | 2.9% | 2.0% |
| Headache | 3.1% (1.3%) | 2.3% (0.9%) | 3.4% (2.0%) | 3.6% (2.2%) |
| Dry Mouth | 2.1% (1.6%) | 1.9% (1.6%) | 1.7% (0.9%) | 10.1% (9.5%) |
| Constipation | 1.4% | 1.6% | 1.6% | 2.0% |

[a]TEAEs reported by ≥3% in total mirabegron group.
[b]Drug-related TEAEs reported by ≥2% in any group (drug-related=possible or probable relationship to drug as assessed by the investigator, or records where relationship was missing).

nonobstructive urinary retention, and fecal incontinence, and it is very effective in treating all those conditions. It involves electrical stimulation of the sacral nerves at the level of the third sacral nerve (S3) using an implantable pulse generator. The exact mechanism of action of SNS in improving OAB is unknown, although the sacral nerves innervate the bladder, urethral sphincter, and pelvic floor muscle.

Patients first undergo a screening test to assess treatment benefit. Historically, that has involved a stage-one implant procedure in the operating room. Patients undergo full implantation of a tined lead into the S3 foramen that is connected to an external pulse generator. If the patient does well over a test period of approximately 2 weeks, the external device is replaced with a permanent, implanted pulse generator.

Over the past few years, percutaneous nerve evaluation has become more popular for the test stimulation. This is an office-based procedure done with or without fluoroscopy guidance in which a very thin electrode is placed in the S3 foramen. If the patient is responding well after a test period of 5 to 7 days, the full implantation is done. Response with either test procedure is determined using voiding diary entries and is considered positive if the patient has a 50% or greater improvement in frequency or incontinence.[28-30]

**Dr Sand:** Approximately how many women will attain that degree of improvement with a percutaneous nerve evaluation?

**Dr Karram:** The data are not entirely clear, but some studies report a 50% improvement in frequency and incontinence in approximately 55% to 66% of women.[30,31]

**Dr Sand:** After a successful test stimulation, what is your expectation for achieving complete resolution of urgency or incontinence episodes once the electrode lead is implanted?

**Dr Karram:** The majority of patients will maintain the degree of improvement that they achieved with the test stimulation.[29,30]

**Dr Sand:** What are the risks and complications associated with SNS?

### CONSIDERATIONS FOR SPECIALIST REFERRAL – AUA GUIDELINES[16]

- Uncertain diagnosis
- Complicating factors such as neurologic diseases, poorly controlled/complicated diabetes, chronic pelvic pain, bowel motility difficulties, general mobility impairment
- History of recurrent UTIs, gross hematuria, prior pelvic surgeries, pelvic cancer, or pelvic radiation
- Female patients with significant pelvic prolapse
- Urgency incontinence (especially in younger patients), or severe symptoms
- Current microscopic or gross hematuria not associated with UTI
- Symptoms refractory to medical therapy/Candidates for third-line therapies
- Suspected malignancy

**Dr Lukacz:** Risks associated with this minimally invasive procedure are common to those of any surgical intervention and include infection, pain, and other adverse events such as bleeding and anesthetic complications. There also are some unique complications associated with the implant *(Table 5)*.[16]

**Table 5.** Sacral Nerve Stimulation Adverse Events[16]

| |
|---|
| Pain at the stimulator site (3.3%–19.8%) |
| Pain at the lead site (4.5%–19.1%) |
| Lead migration (2.2%–8.6%) |
| Infection/Irritation (2.2%–14.3%) |
| Electric shock (5.5%–7.9%) |
| Need for surgical revision (6.25%–39.5%) |

**Dr Sand:** What percentage of patients require surgical revision or explantation of the device?

**Dr Lukacz:** A recent retrospective study publication reported that approximately 38% of patients undergo surgical revision or device explantation long term.[32]

## Percutaneous Tibial Nerve Stimulation

**Dr Sand:** Dr Lukacz, you have been using PTNS. Please explain that option.

**Dr Lukacz:** PTNS involves electrical stimulation of the posterior tibial nerve via a percutaneously placed acupuncture needle inserted posterior to the lateral malleolus of the ankle. Just as with SNS, the mechanism of action of PTNS is not known for sure. The premise is that the posterior tibial nerve lies in the same meridian as S3 and the bladder.

The therapy is delivered in 30-minute sessions once a week for 12 weeks. It is noninvasive, involves no operating room time, and is low risk with relatively few contraindications. Patients who are not candidates for PTNS include those who have a pacemaker, severe peripheral edema, or lower extremity problems that would prevent safe placement of the needle, such as presence of venous stasis disease or open wounds.

PTNS has downsides, however. Cost and convenience issues accompany the need for patients to come into the office for their initial treatments, and PTNS is only a temporary fix. Patients need maintenance therapy that typically requires returning for monthly treatment sessions, although ongoing studies are evaluating the possibility of repeat sessions on an as-needed basis—when symptoms worsen—rather than routinely.

**Dr Sand:** How successful is PTNS?

**Dr Lukacz:** The success rate with PTNS appears to be similar to that attained with SNS, approximately 60% improvement, according to a systematic review of pooled data.[33] There are no head-to-head trials, however, comparing PTNS with SNS.

**Dr Sand:** We conducted a sham-controlled trial showing that PTNS was clearly effective in reducing symptoms, number of voids per day, and urge incontinence episodes.[34] In another trial,

PTNS was as effective as tolterodine ER 2-4 mg daily, although the end points were not as clear as in the sham trial.[35] Those studies measured outcomes after 3 months. Data from longer follow-up to 24 or 36 months show efficacy is sustained.[36,37]

PTNS is well tolerated. Patients may experience bruising and bleeding at the needle site, and tingling and mild pain have been reported, but these events occur at a low rate, approximately 1% to 2%, and are mild and transient.[38] In terms of limitations of PTNS, as Dr Lukacz mentioned, patients have to keep 12 weekly visits, and then return for the stimulation on a regular monthly basis. In addition, onset of benefit takes at least 6 weeks. Are there situations in which there are advantages to PTNS over SNS?

**Dr Lukacz:** PTNS is suited for the patient who is not a surgical candidate because of medical contraindications, or who has a short life expectancy that would not justify an expensive surgical procedure. PTNS is *not* ideal for somebody with a busy, active lifestyle who is working and cannot take the time to come into the office for the treatment. Its use really depends on the individual patient's ability to participate in the treatment regimen.

**Dr Sand:** The implanted SNS device is a contraindication for use of magnetic resonance imaging, and so PTNS allows an opportunity for treating medically refractory patients with OAB using electrical neuromodulation. While not yet commonly done in the United States, I do know from Dutch colleagues that patients using PTNS may purchase a less expensive stimulation device for home use.

## OnabotulinumtoxinA

**Dr Sand:** The use of botulinum toxin is another minimally invasive treatment option that exists for patients with idiopathic OAB. Several forms of botulinum toxin have been studied, with onabotulinumtoxinA being the sole agent in its class to gain FDA approval for the treatment of idiopathic OAB. Dr Staskin, please provide your insights about its use.

**Dr Staskin:** OnabotulinumtoxinA is a new option for treating patients with refractory OAB that acts by inhibiting the release of acetylcholine at the synapse to impair bladder muscle contraction, and it also may interfere with sensory impulses traveling up to the CNS.[39] The recommended dose of onabotulinumtoxinA for treatment of idiopathic (non-neurogenic) OAB is 100 units, and the neurotoxin was shown in the pivotal controlled trials to be more effective than sham injection with saline at reducing incontinence episodes and urinary frequency *(Table 6)*.[40,41]

Treatment with onabotulinumtoxinA requires a cystoscopy procedure that can be done in the office. There is a risk of urinary retention necessitating clean intermittent self-catheterization. In the pooled analysis of 2 pivotal clinical trials using the 100-unit dose, urinary retention occurred at a rate of approximately 6.5% vs 0.4% in the placebo group, and the treatment increased the risk of UTI as well, compared with placebo (25.5% vs 9.6% in a pooled analysis).[42]

**Dr Sand:** Dr. Karram, who is a candidate for onabotulinumtoxinA, in your opinion?

**Table 6.** Pivotal Trial Data for OnabotulinumtoxinA[40,41]

| | Urinary Incontinence Episodes/d[a] | | Micturitions/d[a] | |
|---|---|---|---|---|
| | Onabotulinum-toxinA | Placebo | Onabotulinum-toxinA | Placebo |
| **Study 1[b]** | | | | |
| Baseline | 5.5 | 5.1 | 12.0 | 11.2 |
| Mean change at week 12 (primary end point) | –2.7 | –0.9 | –2.2 | –0.9 |
| **Study 2[c]** | | | | |
| Baseline | 5.5 | 5.7 | 12.0 | 11.8 |
| Mean change at week 12 | –3.0 | –1.0 | –2.6 | –0.8 |

[a]Statistically significant improvement with onabotulinumtoxinA compared with placebo.
[b] OnabotulinumtoxinA N= 280, Placebo N=277.
[c] OnabotulinumtoxinA N=277, Placebo N=271.

**Dr Karram:** Currently, in my practice, we are using either SNS or onabotulinumtoxinA to treat refractory OAB. Because of the possibility of urinary retention, I prefer that patients who will receive onabotulinumtoxinA have the ability and willingness to perform self-catheterization. That is not, however, a mandatory selection criterion because the risk of urinary retention is low. Otherwise, patients who do not have any contraindications to either option are given information on both treatments so they can participate in the decision-making process. We recently looked at uptake of these procedures in our office and it seems patients have been about evenly split between choosing SNS or onabotulinumtoxinA.

**Dr Rosenberg:** In the past, I think PCPs were reluctant to make referrals to specialists for patients with treatment-refractory OAB because irreversible open surgery was all that could be offered. OnabotulinumtoxinA offers another opportunity that, although still surgical, is minimally invasive. With that knowledge, physicians may be more comfortable initiating the diagnostic evaluation for OAB.

**Dr Lukacz:** It is important to be aware that dry rates vary using different treatments. In the ABC (Anticholinergic vs Botox Comparison Study) trial, which compared onabotulinumtoxinA with solifenacin or trospium ER in women with moderate-to-severe urgency urinary incontinence, complete resolution of incontinence was reported by 27% of women treated with onabotulinumtoxinA and by only 13% of women receiving an anti-muscarinic medication.[43]

Data from the ABC trial also showed that after approximately 4.5 months, the cumulative societal costs for onabotulinumtoxinA were lower than those for anticholinergic therapy.[44] Trospium ER and solifenacin were chosen as the comparators to onabotulinumtoxinA in the ABC trial because they were the most widely prescribed anti-muscarinics for OAB. Generic oxybutynin IR is a much less expensive anti-muscarinic medication option, but it requires 3-times-a-day dosing, and in my practice, consistent with published data,[45] it is associated with a high discontinuation rate.

**Dr Staskin:** Watanabe and colleagues conducted a cost analysis of treatments for patients with OAB who were refractory to

anti-muscarinic therapy; they determined the cumulative cost for the first 3 years was $26,269 for SNS and $7651 for onabotulinumtoxinA.[46] When studying relative cost of therapies in preparation for a recently published paper, we found there were no published cost analyses for PTNS.[38] We calculated, however, that the cost of the first year of treatment with PTNS would be approximately $3500, with a lower annual cost expected thereafter.

## TAKE-HOME MESSAGES

**Dr Sand:** Let us conclude with some take-home messages for PCPs and gynecologists regarding the diagnosis and management of women with OAB.

**Dr Rosenberg:** PCPs have a role as gatekeepers. They need to be mindful of the prevalence of the OAB syndrome and familiar with the diagnostic evaluation and treatment options to ensure that patients receive proper care.

**Dr Karram:** I want to stress the importance of recognizing that OAB is a common problem and the need for patients to receive proper education about their condition and its treatment, because we know that, in general, patients derive significant benefit simply from understanding their problem and being active participants in evaluation and therapy.

**Dr Lukacz:** New pharmacotherapy and nonpharmacotherapy options for the management of OAB have become available recently. Physicians today need to know that OAB is not a difficult diagnosis and that its initial therapies are easy to introduce and can be very effective. In addition, they should recognize that if the initial interventions they offer do not work, there are newer alternatives to give the patient hope, alternatives that do not involve major surgery, cause a lot of complications, or demand a huge time commitment from patients.

**Dr Staskin:** Overactive bladder, at present, is underdiagnosed and undertreated, but it need not be because PCPs can easily identify this symptom complex and initiate treatment for it. Furthermore, if the treatments they can offer are not successful, there is now reason to be highly motivated to refer patients for specialty care because of the availability of newer alternatives for treating OAB.

**Dr Sand:** I want to reiterate that PCPs need to care about identifying and treating women with OAB because it is a common condition that affects a woman's QOL and day-to-day activities. Overactive bladder leads to social isolation and can be a cause for early retirement from the workplace; OAB also triples the risk of depression and may destroy interpersonal and sexual relationships.

The good news is that physicians can make a difference in patients' lives in a short period of time with proper treatment, and so they need to "step up" and be involved. ✪

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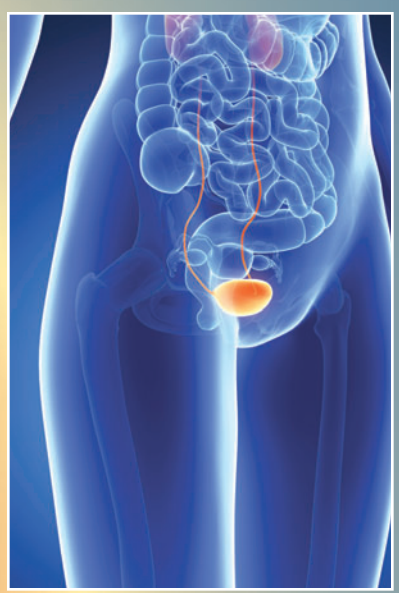

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