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OPIATE ABUSE IN PREGNANCY ■ FUNDING FOR ACADEMIC MEDICINE ■ PLACENTAL PATHOLOGY

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OPIATE ABUSE DURING PREGNANCY

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Mona Prasad, DO, MPH

Why send placentas to pathology?

SMFM CONSULT

Risks of CVS and amnio

MEDICAL SCHOOL
Can it be done in 3 years?

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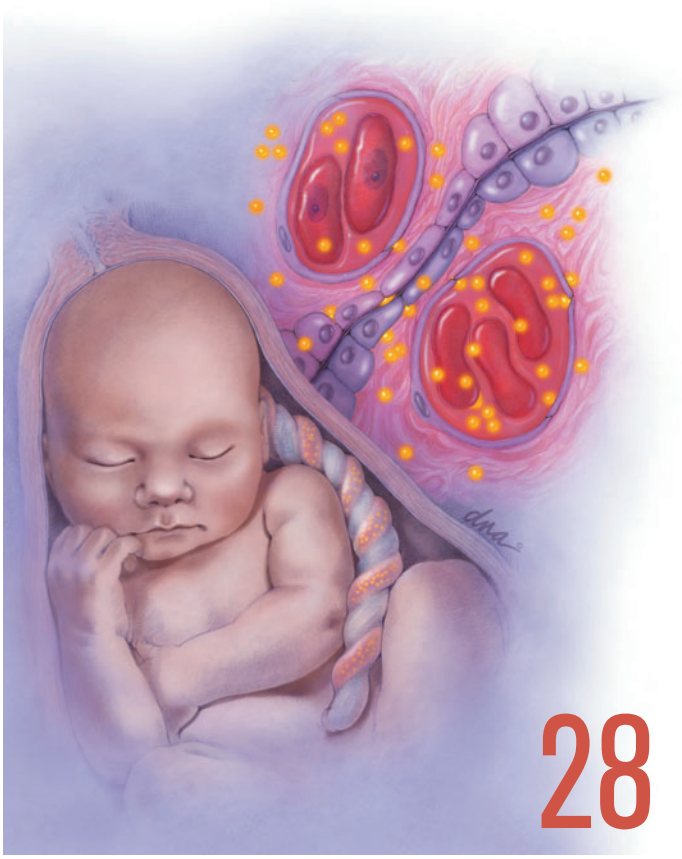

About the cover: A close-up of the placental barrier at the cellular level, showing a fetal capillary with nucleated erythrocytes. The glowing dots represent transfer of opiates from mother to child.

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therapy to pair conjugated estrogens with the estrogen agonist/antagonist bazedoxifene, also known as a selective estrogen receptor modulator (SERM).

- Bazedoxifene is used, instead of progestin, to help protect the uterine lining against hyperplasia that may result from estrogen-alone treatment

DUAVEE™

CONJUGATED ESTROGENS/ BAZEDOXIFENE 0.45 MG/20 MG TABLETS

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

Use DUAVEE for the shortest duration consistent with treatment goals and risks for the individual woman. 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.

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.

To view an educational webcast, visit duaveehcp.com/signup2

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

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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.

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

Academic medicine: A bubble about to burst?

Is funding for medical education, research, and clinical care sustainable?

Remember the dot com frenzy? How about the subprime mortgage crisis? Market bubbles occur when asset prices surge to levels far above their intrinsic value.[1] Bubbles burst when there are too few buyers for such over-valued assets to sustain their prices. The result can be catastrophic for the last group of purchasers and large enough bubbles can damage entire economies.

All 3 missions of US medical schools—education, research, and clinical care—have characteristics of market bubbles about to burst.

The medical education bubble

Asch and associates argue that rising medical school tuition costs have unmistakable "bubble" characteristics.[2] They point out that rising tuition and fees have steadily driven up the debt load of medical school graduates over the past decade. Between 1992 and 2012 medical student debt increased at a compound annual growth rate of 6.3% while the consumer price index, a measure of inflation, rose only 2.5% per year.[3] Thus, by 2012, the median debt of US medical school graduates was $170,000 ($160,000 for public schools and $190,000 for private schools).

How can such escalating debt levels be sustained? Asch and colleagues contend that in the past, prospective medical students were willing to accept ever-higher tuitions because they were convinced that future earnings would more than make up for their "investment." The rapid rise in the ratio of medical student debt to physician annual income between 1996 and 2010, the authors say, indicates that such future earnings expectations may be unrealistic.

The prospect of lower future earnings has already deterred students from entering primary care.[4] Unfortunately, ob/gyn isn't far behind primary care in its rising tuition-debt-to-earnings curve.[3] So how will we know when the bubble has finally burst? Just look at law school applications. Law school students have far higher tuition-debt-to-future-income ratios than medical students and the number of law school applicants is falling steeply.[5] (Please wipe the smiles from your faces!)

Has the academic medicine research bubble already burst?

The Asch et al. article should be sobering to medical school deans, but medical education is only the tip of the iceberg. In 1997 the Senate voted unanimously to double the National Institutes of Health's (NIH) budget between 1998 and 2003.[6] The resultant influx of federal funding fueled dramatic increases in university laboratory construction and hiring of new faculty, technicians, post-docs, and graduate students to scoop up all the new federal dollars.[6]

In the late 1990s, when I worked in New York City, medical schools were racing to construct research facilities in one of the most expensive real estate markets on earth. Well-funded National Academy of Sciences members were the rock stars of academia and academic medicine engaged in its own version of free agency. Predictably there was a massive increase in grant applications to NIH. Then the funding increase stopped.

Since 2004, NIH funding has dropped (corrected for inflation) and grant application success rates have plum-

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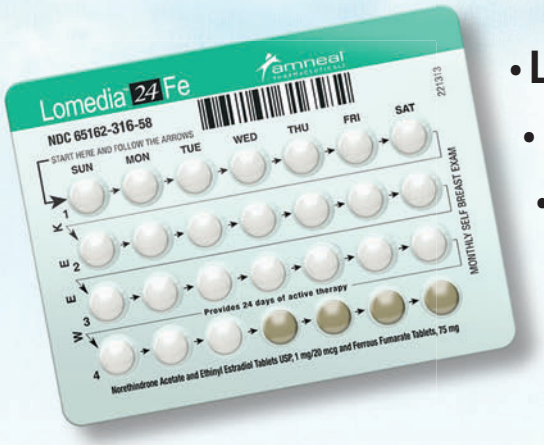

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Brief Summary of Prescribing Information

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with the extent of smoking (in epidemiologic studies, 15 or more cigarettes per day was associated with a significantly increased risk) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.

INDICATIONS AND USAGE

Lomedia™ 24 Fe is indicated for the prevention of pregnancy in women who elect to use oral contraceptives as a method of contraception.

CONTRAINDICATIONS

Oral contraceptives should not be used in women who currently have the following conditions: •thrombophlebitis or thromboembolic disorders, •a past history of deep vein thrombophlebitis or thromboembolic disorders, •cerebrovascular or coronary artery disease (current or history), •valvular heart disease with thrombogenic complications, •severe hypertension, •diabetes with vascular involvement, •headaches with focal neurological symptoms, •major surgery with prolonged immobilization, •known or suspected carcinoma of the breast or personal history of breast cancer, •carcinoma of the endometrium or other known or suspected estrogen-dependent neoplasia, •undiagnosed abnormal genital bleeding, •cholestatic jaundice of pregnancy or jaundice with prior pill use, •hepatic adenomas or carcinomas, or active liver disease, •known or suspected pregnancy, and •hypersensitivity to any component of this product.

WARNINGS

THROMBOEMBOLIC DISORDERS AND OTHER VASCULAR PROBLEMS

Myocardial Infarction

An increased risk of myocardial infarction has been attributed to oral contraceptive use. This risk is primarily in smokers or women with other underlying risk factors for coronary artery disease such as hypertension, hypercholesterolemia, morbid obesity, and diabetes. The relative risk of heart attack for current oral contraceptive users has been estimated to be two to six. The risk is very low under the age of 30.

Thromboembolism

An increased risk of thromboembolic and thrombotic disease associated with the use of oral contraceptives is well established. Case control studies have found the relative risk of users compared to non-users to be 3 for the first episode of superficial venous thrombosis, 4 to 11 for deep vein thrombosis or pulmonary embolism, and 1.5 to 6 for women with predisposing conditions for venous thromboembolic disease.

If feasible, oral contraceptives should be discontinued at least four weeks prior to and for two weeks after elective surgery of a type associated with an increase in risk of thromboembolism and during and following prolonged immobilization. Since the immediate postpartum period is also associated with an increased risk of thromboembolism, oral contraceptives should be started no earlier than four to six weeks after delivery in women who elect not to breastfeed.

Cerebrovascular diseases

Oral contraceptives have been shown to increase both the relative and attributable risk of cerebrovascular events (thrombotic and hemorrhagic strokes) although, in general, the risk is greatest among older (>35 years), hypertensive women who also smoke. Hypertension was found to be a risk factor for both users and nonusers, for both types of strokes, while smoking interacted to increase the risk for hemorrhagic strokes.

Dose-related risk of vascular disease from oral contraceptives

A positive association has been observed between the amount of estrogen and progestogen in oral contraceptives and the risk of vascular disease. The amount of both hormones should be considered in the choice of an oral contraceptive. New acceptors of oral contraceptive agents should be started on preparations containing the lowest estrogen content which is judged appropriate for the individual patient.

Persistence of risk of vascular disease

There are two studies which have shown persistence of risk of vascular disease for ever-users of oral contraceptives. In these studies, the increased risk persisted for up to or more than nine years.

ESTIMATES OF MORTALITY FROM CONTRACEPTIVE USE

One study concluded that with the exception of oral contraceptive users 35 and older who smoke and 40 and older who do not smoke, mortality associated with all methods of birth control is low and below that associated with childbirth. The Fertility and Maternal Health Drugs Advisory Committee recommended that the benefits of oral contraceptive use by healthy nonsmoking women over 40 may outweigh the possible risks.

CARCINOMA OF THE REPRODUCTIVE ORGANS AND BREASTS

Women who currently have or have had breast cancer should not use oral contraceptives because breast cancer is a hormone-sensitive tumor.

Some studies suggest that oral contraceptive use has been associated with an increase in the risk of cervical intraepithelial neoplasia or invasive cervical cancer in some populations of women. However, there continues to be controversy about the extent to which such findings may be due to differences in sexual behavior and other factors.

HEPATIC NEOPLASIA

Benign hepatic adenomas are associated with oral contraceptive use. An estimate of the attributable risk is 3.3 cases/100,000 for users and the risk increases after four or more years of use. Rupture of hepatic adenomas may cause death through intra-abdominal hemorrhage.

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

OCULAR LESIONS

Oral contraceptives should be discontinued if there is unexplained partial or complete loss of vision; onset of proptosis or diplopia; papilledema; or retinal vascular lesions.

ORAL CONTRACEPTIVE USE BEFORE OR DURING EARLY PREGNANCY

Extensive epidemiological studies have revealed no increased risk of birth defects in women who have used oral contraceptives prior to pregnancy. Studies also do not suggest a teratogenic effect, particularly in so far as cardiac anomalies and limb reduction defects are concerned, when taken inadvertently during early pregnancy (see **CONTRAINDICATIONS** section).

The administration of oral contraceptives to induce withdrawal bleeding should not be used as a test for pregnancy.

GALLBLADDER DISEASE

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

CARBOHYDRATE AND LIPID METABOLIC EFFECTS

Oral contraceptives have been shown to cause glucose intolerance in a significant percentage of users. Prediabetic and diabetic women should be carefully observed while taking oral contraceptives.

A small proportion of women will have persistent hypertriglyceridemia while on the pill.

ELEVATED BLOOD PRESSURE

Women with significant hypertension should not be started on hormonal contraceptives. An increase in blood pressure has been reported in women taking oral contraceptives, and this increase is more likely in older oral contraceptive users and with continued use. The incidence of hypertension increases with increasing concentrations of progestogens.

Women with a history of hypertension or hypertension-related diseases, or renal disease should be encouraged to use another method of contraception. If women elect to use oral contraceptives, they should be monitored closely and if significant elevation of blood pressure occurs, oral contraceptives should be discontinued (see **CONTRAINDICATIONS** section).

HEADACHE

The onset or exacerbation of migraine or development of headache with a new pattern which is recurrent, persistent, or severe requires discontinuation of oral contraceptives and evaluation of the cause (see **Thromboembolic Disorders And Other Vascular Problems** in **WARNINGS**).

BLEEDING IRREGULARITIES

Breakthrough bleeding and spotting are sometimes encountered in patients on oral contraceptives, especially during the first three months of use. If bleeding persists or recurs, nonhormonal causes should be considered and adequate diagnostic measures taken to rule out malignancy or pregnancy as in the case of any abnormal vaginal bleeding. If pathology has been excluded, time or a change to another formulation may solve the problem.

Absence of a withdrawal menses may also occur. In the event of amenorrhea for two cycles or more, pregnancy should be ruled out. In the clinical trial with Lomedia™ 24 Fe, 31 to 41% of the women using Lomedia™ 24 Fe did not have a withdrawal menses in at least one of 6 cycles of use.

Some women may experience post-pill amenorrhea or oligomenorrhea (possibly with anovulation), especially when such a condition was preexistent.

PRECAUTIONS

SEXUALLY TRANSMITTED DISEASES

Patients should be counseled that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

PHYSICAL EXAMINATION AND FOLLOW-UP

A periodic personal and family medical history and complete physical examination are appropriate for all women, including women using oral contraceptives. The physical examination should include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology, and relevant laboratory tests. Women with a strong family history of breast cancer or who have breast nodules should be monitored with particular care.

LIPID DISORDERS

Women who are being treated for hyperlipidemias should be followed closely if they elect to use oral contraceptives.

In patients with familial defects of lipoprotein metabolism receiving estrogen-containing preparations, there have been case reports of significant elevations of plasma triglycerides leading to pancreatitis.

LIVER FUNCTION

Discontinue oral contraceptives if jaundice develops. Steroid hormones may be poorly metabolized in patients with impaired liver function.

FLUID RETENTION

Oral contraceptives may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention.

EMOTIONAL DISORDERS

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

CONTACT LENSES

Contact lens wearers who develop visual changes or changes in lens tolerance should be assessed by an ophthalmologist.

DRUG INTERACTIONS

Changes in contraceptive effectiveness associated with co-administration of other products:

Anti-infective agents and anticonvulsants

Contraceptive effectiveness may be reduced when hormonal contraceptives are coadministered with antibiotics, anticonvulsants, and other drugs that increase the metabolism of contraceptive steroids. This could result in unintended pregnancy or breakthrough bleeding. Examples include rifampin, barbiturates, phenylbutazone, phenytoin, carbamazepine, felbamate, oxcarbazepine, topiramate, and griseofulvin.

Anti-HIV protease inhibitors

Several of the anti-HIV protease inhibitors have been studied with co-administration of oral combination hormonal contraceptives; significant changes (increase and decrease) in the plasma levels of the estrogen and progestin have been noted in some cases. The safety and efficacy of combination oral contraceptive products may be affected with coadministration of anti-HIV protease inhibitors.

Herbal products

Herbal products containing St. John's Wort may induce some hepatic enzymes and p-glycoprotein transporter and may reduce the effectiveness of contraceptive steroids, and also may result in breakthrough bleeding.

Increase in plasma levels of estradiol associated *with co-administered drugs*

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

Changes in plasma levels of co-administered drugs

Combination hormonal contraceptives containing some synthetic estrogens (e.g., ethinyl estradiol) may inhibit the metabolism of other compounds. Increased plasma concentrations of cyclosporine, prednisolone, and theophylline have been reported with concomitant administration of combination oral contraceptives. Decreased plasma concentrations of acetaminophen and increased clearance of temazepam, salicylic acid, morphine and clofibric acid, due to induction of conjugation have been noted when these drugs were administered with combination oral contraceptives.

INTERACTIONS WITH LABORATORY TESTS

Oral contraceptives may affect certain endocrine and liver function tests, and blood components, such as (a) increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; and increased norepinephrine induced platelet aggregability; (b) increased thyroid-binding globulin (TBG); (c) other binding proteins may be elevated in serum; (d) sex hormone binding globulins are increased, however, free or biologically active levels remain unchanged; (e) triglycerides may be increased and levels of various other lipids and lipoproteins may be affected; (f) glucose tolerance may be decreased; and (g) serum folate levels may be depressed by oral contraceptive therapy.

PREGNANCY

Pregnancy Category X.

NURSING MOTHERS

Small amounts of oral contraceptive steroids and/or metabolites have been identified in the milk of nursing mothers and a few adverse effects on the child have been reported, including jaundice and breast enlargement. In addition, combination oral contraceptives given in the postpartum period may interfere with lactation by decreasing the quantity and quality of breast milk. If possible, the nursing mother should be advised not to use combination oral contraceptives but to use other forms of contraception until she has completely weaned her child.

PEDIATRIC USE

Safety and efficacy of Lomedia™ 24 Fe have been established in women of reproductive age. Safety and efficacy are expected to be the same in postpubertal adolescents under the age of 16 years and in users age 16 years and older. Use of this product before menarche is not indicated.

GERIATRIC USE

This product has not been studied in women over 65 years of age and is not indicated in this population.

ADVERSE REACTIONS

The most common adverse events reported by 2 to 6% of the 743 women using Lomedia™ 24 Fe were the following, in order of decreasing incidence: headache, vaginal candidiasis, upper respiratory infection, nausea, menstrual cramps, breast tenderness, sinusitis, vaginitis (bacterial), abnormal cervical smear, acne, urinary tract infection, mood swings, weight gain, vomiting, and metrorrhagia.

Among the 743 women using Lomedia™ 24 Fe, 46 women (6.2%) withdrew because of an adverse event. Adverse events occurring in 3 or more subjects leading to discontinuation of treatment were, in decreasing order: abnormal bleeding (0.9%), nausea (0.8%), menstrual cramps (0.4%), increased blood pressure (0.4%), and irregular bleeding (0.4%).

An increased risk of the following serious adverse reactions has been associated with the use of oral contraceptives (see **WARNINGS** section): •thrombophlebitis, •arterial thromboembolism, •pulmonary embolism, •myocardial infarction, •cerebral hemorrhage, •cerebral thrombosis, •hypertension, •gallbladder disease, and •hepatic adenomas or benign liver tumors.

There is evidence of an association between the following conditions and the use of oral contraceptives: •mesenteric thrombosis and •retinal thrombosis.

The following adverse reactions have been reported in patients receiving oral contraceptives and are believed to be drug related: •nausea, •vomiting, •gastrointestinal symptoms (such as abdominal pain, cramps and bloating), •breakthrough bleeding, •spotting, •change in menstrual flow, •amenorrhea, •temporary infertility after discontinuation of treatment, •edema/fluid retention, •melasma/chloasma which may persist, •breast changes (tenderness, pain, enlargement, and secretion), •change in weight or appetite (increase or decrease), •change in cervical ectropion and secretion, •possible diminution in lactation when given immediately postpartum, •cholestatic jaundice, •migraine headache, •rash (allergic), •mood changes (including depression), •vaginitis (including candidiasis), •change in corneal curvature (steepening), •intolerance to contact lenses, •decrease in serum folate levels, •exacerbation of systemic lupus erythematosus, •exacerbation of porphyria, •exacerbation of chorea, •aggravation of varicose veins, and •anaphylactic/anaphylactoid reactions (including urticaria, angioedema, and severe reactions with respiratory and circulatory symptoms).

The following adverse reactions have been reported in users of oral contraceptives, and a causal association has been neither confirmed nor refuted: •acne, •Budd-Chiari syndrome, •cataracts, •colitis, •changes in libido, •cystitis-like syndrome, •dizziness, •dysmenorrhea, •erythema multiforme, •erythema nodosum, •headache, •hemorrhagic eruption, •hemolytic uremic syndrome, •hirsutism, •impaired renal function, •loss of scalp hair, •nervousness, •optic neuritis (which may lead to partial or complete loss of vision), •pancreatitis, and •premenstrual syndrome.

OVERDOSAGE

Serious ill effects have not been reported following acute ingestion of large doses of oral contraceptives by young children. Overdosage may cause nausea, and withdrawal bleeding may occur in females.

Please see package insert for full prescribing information.

More detailed information is available upon request.

For more information about Lomedia™ 24 Fe contact: Amneal Pharmaceuticals at 1-877-835-5472.

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meted from 31% to 17%, with many institutes now reporting pay lines of 8% for new grant applications.[6] Worse, desperate faculty have increased their grant applications even as the average age of first-time R01 recipients has reached 42 years, and newly minted PhDs increasingly cannot find jobs.[6] Moreover, the true costs of research are virtually never covered by external grant funding. Estimates indicate that 40 cents of university funds are required for each $1 of external grant funding (including direct and indirect costs) received.[7]

Thus, even at the height of NIH funding, before each successful grant's budget was cut by institutes in a vain attempt to maintain success rates, NIH grants never really fully paid for the research they supported. We are truly losing money on every grant and not making it up in volume. The research bubble has already burst.

The academic medicine clinical bubble is the greatest threat to sustainability

In 2012, according to the Association of American Medical Colleges (AAMC), 42.6% of private medical school revenues were derived from faculty practices while 15.2% came from affiliated or owned hospitals.[8] For publically funded medical schools the numbers were 34.4% and 17.9%, respectively. Thus, clinical faculty directly and indirectly (via hospital admissions) cover half the costs of medical schools. This level of cost-subsidization is unsustainable. The accounting firm of PricewaterhouseCoopers (PwC) estimates that 10% of academic medical center revenue will be at risk because of expected reductions in federal indirect medical education funds, disproportionate share hospital payments, and grant revenue, as well as unfavorable changes in payer mix.[9]

> "The advantages of a **3-year medical school** include a 25% reduction in debt."

I believe this PwC number is a significant underestimation of the potential fall in medical school revenues. My argument is based on evolving healthcare payment strategies. We are entering an era in which employers are leaving the healthcare business by converting their workers' health insurance from a defined benefit to a defined contribution. This leaves employees to find high-deductible, high-coinsurance plans on public and private exchanges.

Moreover, poorer workers in small companies may have their commercial insurance replaced by Medicaid as employers drop traditional bare-bones health plans suddenly made more expensive by new federal mandates. Thus, physician fees and hospital margins will come under intense competitive pressures and could drop further as we move to bundled payments and capitation.

Admissions to Chicago-area hospitals have fallen 5% overall and 8% to 9% among patients over 65 years since 2010, mostly through avoidance of unnecessary inpatient care.[10] Interestingly, gynecology led the list of declining admissions at -16%. Because academic medical centers are more expensive than their community hospital competitors, they will be at an increasing competitive disadvantage. Thus, the primary revenue source for medical schools is at significant risk.

How to deflate the bubble before it bursts?

It is time for academic medical centers and their medical schools to end the irrational cross-subsidization of their tripartite mission and ensure that each part is self-sustaining. That calls for bold innovations, among them:

Three-year medical schools

An optional 3-year curriculum should be considered to reduce medical student indebtedness while preserving revenue to pay teachers and provide curricular elements required for LCME accreditation. For example, in-depth exposure to various clinical disciplines could be embedded in a condensed 18-month fundamental science curriculum, followed by 18 months of clerkships and sub-internships that track directly into residency.

Some medical schools are now offering this alternative.[11] Abramson and colleagues from New York University report that the advantages of a 3-year medical school include a 25% reduction in debt coupled with a 1-year gain in earnings, better linkage of undergraduate with graduate medical education, and an increased supply of physicians.

By contrast, Goldfarb and Morrison from the University of Pennsylvania contend that this experiment was tried in the 1970s with combined BA-MD programs, but the rate of students graduating in 6 or 7 years from such programs has been declining.[12] They also argue that the extra year of medical school enhances professional maturity and provides more time for career selection and interviewing for residency programs. They contend that popular 4th-year electives in research, public policy, business, and global health would be lost.[12]

These arguments resonate with me, but some students may not want these options. Students from underprivileged backgrounds may not have the luxury of paying an extra $50,000 to study the macroeconomics of healthcare

policy decisions. When I was a student we were expected to master vast amounts of medical knowledge. Now such knowledge is increasing at a logarithmic rate each decade and up-to-date information is almost instantly accessible online. Thus, I believe that 3-year medical schools should be an option for certain students.

Restructuring the research enterprise

I am passionately committed to research, but in an era of shrinking grant funding, are the increasing time and resources poured into research by faculty and schools really worth the cost? Could such intense focus ironically be impairing our primary mission: to train the next generation of physicians?

Tenure is still preferentially given to NIH-funded researchers over inspiring teachers who enrich their students' lives. Moreover, community-based medical schools with far smaller research operations do an excellent job of training their students. And while the economic benefit of medical research is undeniable (each dollar of NIH funding adds $2.60 to local economies),[13] not all research will improve patient care.

On the other hand, I believe that faculty research creates a culture of inquiry that encourages evidence-based care while research by students better prepares them to critically interpret new discoveries once they are in practice. The challenge, then, is to ensure that medical school research is both effective and financially sustainable. Tough choices will be required about in whom to invest dwindling school resources. Conversely, researchers simply must do a far better job of increasing their salary recovery from direct grant dollars and covering laboratory space costs from indirect grant dollars.

More public-private commercialization should be encouraged through government investment in university biotech parks to speed dissemination of discoveries from bench to bedside and spur local economies. Our obsession with faculty conflicts of interest must be tempered by the need to commercialize discoveries. Finally, philanthropy is needed to generate endowments to support researchers' unfunded salary components rather than depending on cross-subsidizing them with clinicians' income. In short, the whole edifice of academic research needs to be rendered self-sufficient.

Expanding the academic clinical enterprise

Medical schools can no longer depend on clinical enterprises to supply half their revenue. Hospitals will simply not have the margins and faculty will not have the excess clinical income. Obviously waste and inefficiency must be wrung out of the clinical enterprise but no one shrinks to greatness.

In my opinion, the solution, to paraphrase President Reagan, is not to re-slice the pie but to produce a bigger pie.[14] The clinical pie should be expanded by increasing the size of faculty group practices through partnership with community specialty and primary care practices. Academic medical centers can offer support to community practices including facilitated access to electronic health records and subspecialists, telemedicine, leasing their practices, and leveraging size to optimize purchasing and contracting. Partnerships also must be established with low-cost community hospitals.

The ultimate goal is to create an integrated health care delivery system capable of managing an entire population cost-effectively. This will allow acceptance of bundled payments and capitated contracts and, ultimately, the development of a robust set of insurance products. Such consolidation is already occurring throughout the nation.[15] In this way a smaller slice of a larger pie can help sustain the academic mission of medical schools.

Take-home message

American medical schools are the envy of the world. Our curricula are innovative yet, thanks to rigorous accreditation standards, uniformly excellent. So prestigious are our medical schools that other countries now try to "import" them. Our biomedical research enterprise has produced more Nobel prizes and blockbuster medications than the rest of the world combined. And patients travel from around the globe to be treated at our academic medical centers.

However, for the past 2 decades US academic medicine has been sustained by a triad of market bubbles fed by escalating tuitions, an unsustainable period of accelerated NIH funding, and intensifying cost transfers from clinical enterprises whose surplus incomes are sustained by ever-higher prices. We need to take immediate steps to deflate these bubbles before they collapse and we lose one of this nation's most precious assets. COG

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

continued on **PAGE 23**

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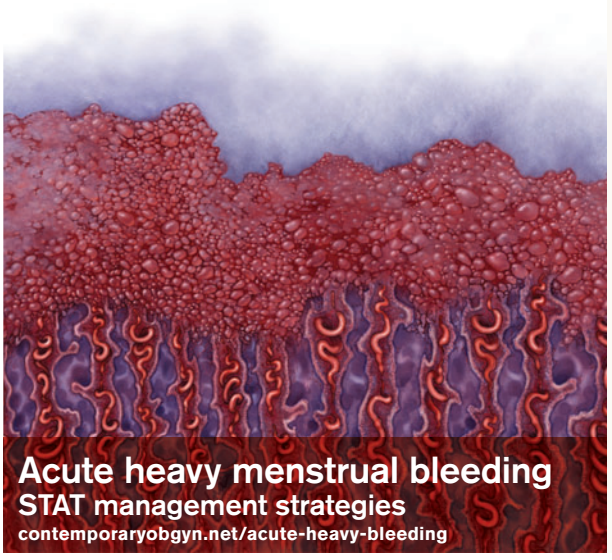

Acute heavy menstrual bleeding
STAT management strategies
contemporaryobgyn.net/acute-heavy-bleeding

A review of hormonal regimens to halt acute abnormal bleeding. Longer treatment therapies should be targeted to treat the underlying etiology of a woman's bleeding, states author Anita L. Nelson, MD.

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January 3

Our Editorial Board members are experts in the specialty and many are known worldwide. In a recent interview with Brazilian publication Tribuna da Bahia Online, Dr. Paula J. Adams Hillard offered information to readers on getting pregnant. http://www.tribunadabahia.com.br/2013/12/28/7-dicas-para-ficar-gravida-rapidamente

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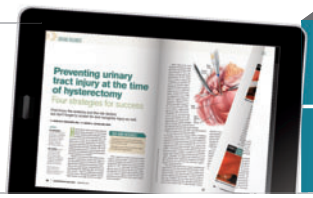

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Surrogacy in India: Boom or bane?

The Kiran Infertility Centre, in Hyderabad, India, recently announced what it called "a new milestone in Indian surrogacy:" the 200th baby born using Indian women as surrogates for American parents. The clinic claims to be "one of the most important clinics in the world [that] has helped thousands of infertile couples from across the world to have their own genetically related child through their IVF and surrogacy program."

In a January press release, the Kiran Infertility Centre reports that the first baby born through surrogacy for Americans there was for a Kentucky couple in 2008. "Since then surrogacy in India for foreign infertile couples has become hugely popular," the press release states. The clinic claims that it has been the birthplace for hundreds of babies through surrogacy and IVF for parents from UK, Brazil, Japan, Australia, Argentina, Uruguay, Singapore, Hong Kong, and Sri Lanka, among others.

The Kiran Infertility Centre is headed by Dr. Kiran D. Sekhar and Dr. Pratima Grover. The January press release quotes Dr. Grover as saying, "the feeling we get upon seeing an intended parent filled with joy after having a baby is unimaginable and invaluable, but this milestone also reminds us of the trust and faith bestowed by our patients on us.

"We are fully conscious of the fact that every milestone comes with an added responsibility, with every new successful birth there are several more hopes associated and we are thriving and working towards making that every dream and hope come true."

The growing trend of overseas surrogacy is being covered by American news outlets and authors as a mostly positive development for infertile couples who may not be able to adopt or to use surrogates within the United States. A November 2013 ABCNews.com article states that Indian surrogacy is now one of the fastest-growing segments of the medical tourism business.[1] The article highlights the experience of one American couple whose three children were born using Indian surrogates. The Indian women who carried the pregnancies each received the equivalent of $6,000 to serve as surrogates.

"The growing trend of overseas surrogacy is being covered by American news outlets and authors as **a mostly positive development** for infertile couples."

Commentary by Laurie J. McKenzie, MD:

Gestational surrogacy in India is booming, driven largely by the decreased costs and the relative ease of finding an available surrogate. But is "reproductive tourism" in the best interests of the child, the intended parent(s), and the surrogate herself?

In 2011, more than 860 IVF cycles in the United States utilized a gestational surrogate (or gestational carrier).[2] Gestational carriers (GCs) can provide a means for an individual or a couple with reproductive challenges to have a child. Common indications for surrogacy include congenital absence of the uterus, hysterectomy, uterine scarring, and medical contraindications to pregnancy.

The use of a GC is regulated by the FDA in accordance with tissue donation, and only after the medical, psychological, and legal prerequisites are completed can treatment proceed. It is a complex road to travel even in the United States. Reproductive statutes vary from state to state, making it imperative to enlist the assistance of an attorney who specializes in reproductive issues and is familiar with the laws in one's specific state. For example, in Texas a couple wishing to use a GC must be married, heterosexual, and have a documented medical need for a GC. In addition, the GC must be of proven fertility. If these specific conditions are not met, the intended parents will not be protected under the current reproductive statutes.

Utilizing a surrogate out of the country may only compound these issues and it raises additional concerns regarding the health screening of the surrogate and her medical care during the fertility treatment and pregnancy. What measures are in place to prevent exploitation of potential GCs? What protections are in place for the intended parents?

I congratulate the Kiran Clinic on their important milestone, and wish them continued success. Their announcement highlights the increasing utilization of gestational carrier arrangements and broaches the question: Is this best accomplished at home or abroad?

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DR. MCKENZIE is Director of Oncofertility, Houston IVF, and Director, Houston Oncofertility Preservation and Education (H.O.P.E.), Texas. She is also a member of the *Contemporary OB/GYN* editorial board.

Pregnant women and the law

Alicia Beltran is famous for her recent Kafka-esque pregnancy experience. She had stopped using painkillers and weaned herself off the antiaddiction medication. She provided full information to her health care provider. But instead of receiving prenatal care, she was ordered by the state to resume using antiaddiction medication. When she declined, she was arrested and, although she screened negative for all evidence of drug dependence or abuse, was committed to a facility for months before finally being released after a federal complaint was filed on her behalf.[1]

In a Perspective piece in the January 16 edition of *The New England Journal of Medicine*, R. Alta Charo, JD, discusses the Beltran case and others involving women who have been punished for actions during their pregnancies that were thought to have the potential to harm their unborn children. "It is the latest example of a disturbing pattern of legislative and judicial misrepresentation and misuse of medical information in the pursuit of partisan aims focused on women and pregnancy," Charo writes. (Charo is a professor of law and bioethics at the University of Wisconsin at Madison. She served on President Obama's transition team in 2008.)

She claims that "legislatures have been encroaching on the realm of medicine" for 2 decades, in part in attempts to limit the availability and frequency of abortion. Although lawmakers act "under the guise of protecting women," she writes, laws are being passed that penalize them for their legally protected choices.

> "Should the State be able to force us as physicians to do things that are **medically unindicated,** unnecessary, and possibly frankly harmful?"

Commentary by Joshua A. Copel, MD:

It seems surreal: A woman who has a past history of drug abuse but is now totally clean, proven by negative toxicology tests, is actually sent to prison for refusing to take completely unnecessary anti-addiction medication. Left unclear in the commentary in *The New England Journal of Medicine*: Where were this patient's doctors? Should the State be able to force us as physicians to do things that are medically unindicated, unnecessary, and possibly frankly harmful? After all, most of us counsel our pregnant patients to take only necessary medications and avoid anything unnecessary.

Sadly, many state legislatures are passing paternalistic laws that predominantly affect women and children. Mandatory ultrasounds before abortions, fetal pain laws unsupported by any facts, incarceration of pregnant women to coerce use of medications—all are documented in Attorney Charo's far-reaching editorial. One need only look at recent news for further signs of inappropriate intervention in medical care by lawmakers. The case of a "brain-dead" woman in Texas being kept on life support against her family's wishes because she was pregnant at the time of her death has sparked debate and outrage across the nation.[2]

It may seem ironic that I, a liberal who is predisposed to favor government intervention, am horrified by these laws, but it is not inconsistent. The actions documented in this Perspective piece are all jarringly at odds with good medical practice (ie, evidence-based, relying on scientifically valid data).

Would we tolerate a law saying that all men with chest pain must have a cardiac drug-eluting stent placed? I thought not.

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

Indication

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

Important Safety Information

WARNING: Endometrial Cancer and Cardiovascular Disorders

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

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

*Improved certain physical changes, which were superficial cells and parabasal cells and pH of the vagina.
†Most bothersome symptom was defined as the most bothersome moderate to severe symptom at baseline.

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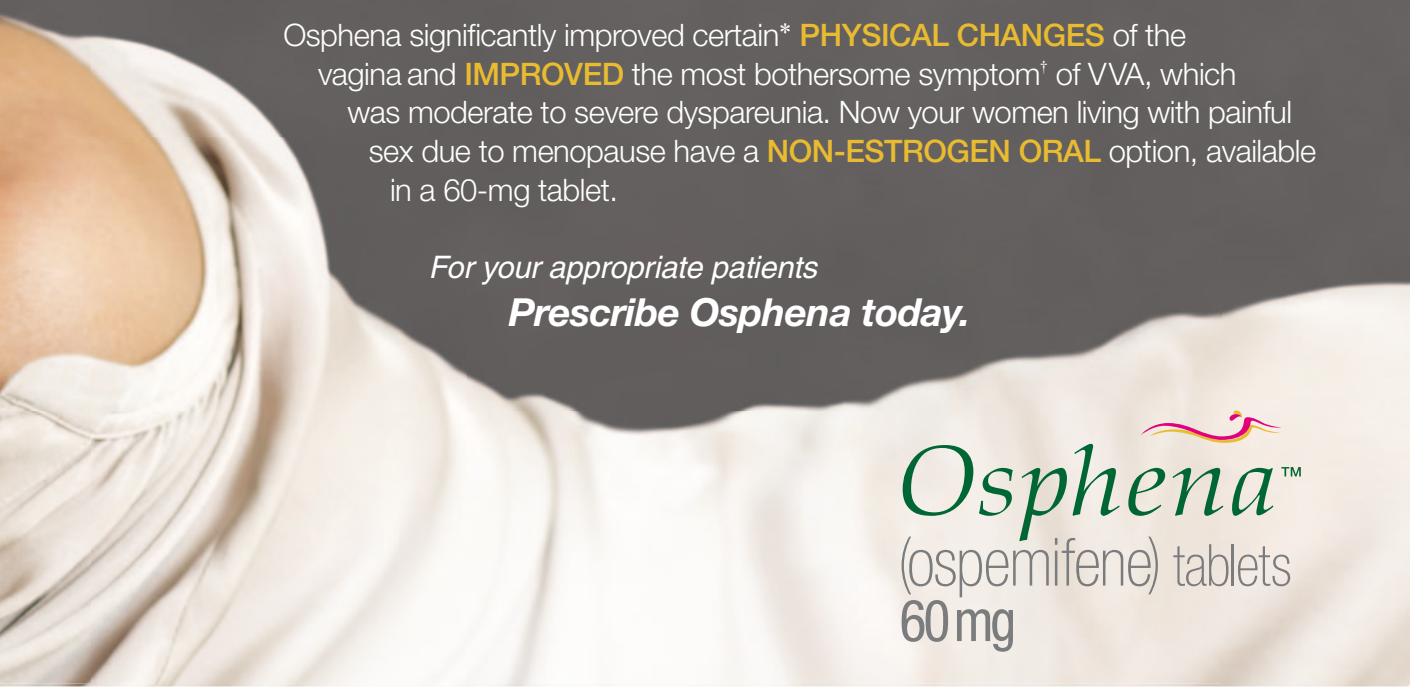

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Prescribe Osphena today.

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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.

Regarding 'The transcervical Foley balloon': A connection to cord prolapse?

TO THE EDITOR:

I read with interest the article titled "The transcervical Foley balloon" in the November 2013 issue of *Contemporary OB/GYN* and wanted to share my personal experience with this method of induction.

I first learnt of this method of induction about 2 years ago from the residents at my hospital, and I started using it on almost all the patients I admitted for induction from then on. I used a 30 ml Foley balloon and inflated it to 60–80 ml and attached it to the patient's leg with traction with excellent results.

In July of this year, however, a patient of mine, whom I was inducing using this method, developed cord prolapse. And the same thing happened again with another patient in October of 2013. Two cord prolapses in a span of 3 months, compared with one in a span of 13 years previously, made me rethink the safety of this method of induction.

David Khodadadian, MD
New York, New York

IN REPLY:

We appreciate Dr. Khodadadian sharing his experience with the Foley balloon for cervical ripening. Though there is a theoretical risk for cord prolapse, and no doubt some cases have occurred, the data on this sequela are limited. Existing data do not show a significant increased risk of cord prolapse with the usual inflation volume with the Foley balloon cervical ripening.

In a study by Yamada et al inflation of the balloon with a large amount of fluid (70–250 ml) was associated with a higher rate of cord prolapse when compared to 70–150 ml. However, the rate of cord prolapse with the lower inflation volume (70–150 ml) was only 0.15%, and even that inflation volume is higher than what is typically used for cervical ripening (30–60 ml). Although the 2 cases of cord prolapse that Dr. Khodadadian reports are interesting, such a high rate of cord prolapse is not supported by the literature.

Tania F. Esakoff, MD
Sarah J. Kilpatrick, MD, PhD

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Risks of chorionic villus sampling and amniocentesis

A 31-year-old underwent first-trimester screening with nuchal translucency and maternal serum PAPP-A and beta-hCG. Her risk for Down syndrome is increased at 1 in 80. She received genetic counseling, opted to undergo diagnostic testing, and is deciding between chorionic villus sampling (CVS) and amniocentesis.

Q. What is the risk of fetal loss associated with CVS or amniocentesis in a singleton pregnancy?

A.

Fetal loss after CVS

CVS is a procedure in which a small sample of placental tissue (chorionic villi) is obtained either transcervically (TC) or transabdominally (TA) under ultrasound guidance. It is performed at 10 to 13 weeks' gestation. Advances in first-trimester aneuploidy screening have increased the need for early prenatal diagnosis, and CVS is the only diagnostic test currently available in the first trimester.[1,2]

One study suggested that, of women who would consider pregnancy termination, 50% would only undergo termination in the first trimester.[3] The maternal death rate is 1/100,000 following first-trimester termination, compared with 7/100,000 to 10/100,000 in mid-pregnancy.[4] While there are clear advantages to earlier diagnosis, CVS is not widely utilized, partly because of its limited availability, and partly because of the perception that CVS confers increased risks compared with amniocentesis.[5]

In order to make an informed decision about invasive testing, patients need accurate information on risks of fetal loss. The total pregnancy loss after an invasive procedure consists of a procedure-related loss plus the background loss rate. Unfortunately, spontaneous fetal loss rates are difficult to estimate, as large populations have not been followed from early pregnancy.[6] Attempts to estimate background loss rates are biased by different definitions of fetal loss, variability in length of follow-up and different intervals between ultrasound assessment of viability and fetal demise.[6,7]

The majority of data about fetal loss after CVS come from studies comparing loss rates in patients undergoing CVS with those undergoing amniocentesis (Table 1).[8-11] Rather than evaluating *procedure-related losses*, these studies looked at *total pregnancy losses*, which include losses related to the procedure plus background losses. In some studies, termination for aneuploidy was also included in the definition of a pregnancy loss.[8,10]

The total pregnancy loss rate is necessarily higher following CVS than following amniocentesis, because CVS is performed at an earlier gestational age (GA), when the risk of spontaneous pregnancy loss is higher. However, procedure-related losses following CVS, particularly transabdominal CVS, are not generally considered to be greater than procedure-related losses following amniocentesis.

Large series have varied in reporting no significant differences, small differences, or moderate differences in pregnancy loss following CVS and amniocentesis (Table 1).[8-11] One study demonstrated a substantially higher loss rate in women undergoing CVS compared to amniocentesis.[10] Several factors may help to explain this finding. First, recruitment was across 31 centers, with some centers having a

TABLE 1 Summary of controlled studies on fetal loss rates in patients undergoing CVS vs amniocentesis

Ref, year	Study design	Primary indication for procedure	Definition of loss	CVS (% loss)	AC (% loss)	Difference in loss rate (%)	*P* value
8, 1989	Multicenter randomized trial TC CVS vs. AC	AMA	Total loss <28 week (includes spontaneous losses, terminations and stillbirths)	7.6	7.0	0.6 (1/166)	ns
9, 1989	Non-randomized prospective trial TC CVS vs. AC	AMA	Total loss delivery Total loss <28 weeks	7.2 1.2	5.7 1.0	0.8 (1/125)	ns
10, 1991	Multicenter randomized trial TC (72%) and TA (28%) CVS and AC	AMA	Non-survival at birth (includes spontaneous losses, terminations, stillbirths and neonatal deaths) Loss <28 weeks	14	9	4.6 (1/21) 2.9 more in CVS (1/34)	*P* < 0.01
11, 2009	Retrospective cohort study TA CVS and AC	AMA, prior pregnancy with abnormality or risk for hereditary disease	Loss < 24 weeks	1.9	1.4		
Total for studies above			total loss up to delivery or loss <28 weeks	2.9 (1067/36,413)	2.0 (724/36,286)	0.9	

Abbreviations: AC, amniocentesis; AMA, advanced maternal age; CVS, chorionic villus sampling; TA, transabdominal; TC, transcervical

disparately small number of subjects. In addition, 17% of CVS procedures were described as difficult vs. 5% of amniocenteses, and 31% of CVS procedures involved more than one insertion, compared with only 6% of amniocenteses.[10]

Considering that the criteria for performing CVS were limited to only 30 cases, these findings together suggest that there may have been less operator experience with CVS than with amniocentesis.

A large national registry-based cohort study in singletons who had an amniocentesis (n=32,852) or CVS (n=31,355) in Denmark between 1996 and 2000 also demonstrated a higher loss rate with CVS compared to amniocentesis. A significant difference in loss rates between CVS and amniocentesis was identified (1.9% vs. 1.4%), but it was attributed to the difference in GA at the time of procedures, with the earlier GA of CVS allowing for a greater time for loss to occur.

A Cochrane review of amniocentesis and CVS found that the total pregnancy loss rate following TA CVS was equivalent to that of second-trimester amniocentesis, whereas TC CVS was associated with a slightly higher risk of miscarriage.[12] The most recent systematic review of complications after prenatal diagnostic procedures included 29 observational studies of amniocentesis and 16 studies of CVS, all published after 1995.[13] Pregnancy loss rates for CVS vs. amniocentesis were 0.7% vs. 0.6% within 2 weeks post-procedure, 1.3% vs. 0.9% up to 24 weeks, and 2.0% vs. 1.9% for the entire pregnancy, suggesting similar risks.

Series have compared patients undergoing CVS with a control group of women who did not undergo any invasive procedure (Table 2). After adjusting for potential confounding variables, and when data were limited to pregnancies since 1998, the loss rate following CVS was not significantly increased above the background pregnancy loss rate.[14,15]

Notably, these series were conducted by centers with expertise in CVS, which has a learning curve for safety (loss rates) and efficiency

TABLE 2 Summary of controlled studies on fetal loss rates in patients undergoing CVS vs. no procedure

Ref, year	Study design	Primary indication for procedure	Definition of loss	CVS (% loss)	No procedure (%)	Difference in loss rate (%)	*P* value
14, 2006	Retrospective cohort study TA and TC CVS vs. no procedure over time (1990-2006)	Elevated MSAFP, AMA	All losses <28 weeks (adjusted) used to calculate total below	2.4	0.50	1.9 (1/53)	*P* <0.001
			Recent losses 1998–2003 <28 weeks (adjusted)	1.2	0.3	0.9 (1/111)	ns
15, 2008	Retrospective cohort study TA and TC CVS vs. no procedure over time (1990-2006)	AMA abnormal screen	Fetal loss <24 weeks	2.7	3.3	After controlling for potential confounders, CVS group trended toward lower losses OR 0.82, 95% CI 0.6-1.0	ns
Total			total losses <24 or <28 weeks	2.9 (446/15,034)	2.2 (179/8233)	0.7 (1/143)	

Abbreviations: AMA, advanced maternal age; CVS, chorionic villus sampling; MSAFP, maternal alpha-fetoprotein; TA, transabdominal; TC, transcervical

(number of passes and adequacy of sample).[16]

Fetal loss after amniocentesis

Amniocentesis is usually performed between 15 and 18 weeks for diagnosis of aneuploidy, although it can be performed at any GA at or beyond 15 weeks. The procedure-related fetal loss rate following amniocentesis has ranged from 1/100 to 1/1,600 in randomized and nonrandomized trials, a difference which failed to reach statistical significance in the majority of series (Table 3).[17-24]

An exact number is difficult to provide due to the paucity of prospective trials. The only prospective randomized study, which was performed in the 1980s, identified a 1% increase risk of fetal loss.[17] In contrast, 3 recent retrospective series comparing losses in women undergoing amniocentesis with those not undergoing any procedure did not detect any difference in loss rates between groups.[21,23,24]

Eddleman et al compared pregnancy losses between 31,907 women in the FASTER trial who did not undergo amniocentesis with 3096 who did, and found that the difference between the 2 groups was 0.06% or 1/1600.[21]

Odibo et al compared outcomes in 11,746 women undergoing amniocentesis with 39,811 controls not having amniocentesis.[23] The fetal loss rate prior to 24 weeks was not significantly different between the 2 groups (0.97% in the amniocentesis group and 0.84% among controls), and the loss rate attributable to amniocentesis was 0.13% or 1/769.[23]

Finally, Towner et al found no difference in loss rates <24 weeks in women with abnormal serum screening who underwent amniocentesis (69/15,005 or 0.46%) compared with controls not undergoing a procedure (90/17,045 or 0.53%).[24]

Compared to amniocentesis, CVS may be associated with a higher pregnancy loss rate (defined either as total losses or losses up to 28 weeks) of 0.9% (Table 1). These data seem to be driven by a slightly higher rate of loss associated with TC compared to TA CVS. In fact, fetal loss rates following amniocentesis and transabdominal CVS appear to be similar, and they are probably lower than the often-quoted rate of 1/200.

Additional contributors to the slightly higher loss rate may be operator experience and earlier GA at time of CVS, allowing for more time for a loss to occur. Compared to no procedure, CVS is associated with a difference in loss rate (defined as loss <24 or <28 weeks) of 0.7% (Table 2).

Compared to no procedure, amniocentesis is associated with a difference in loss rate (mostly defined as loss <24 weeks) of 0.1% (Table 3). Several nonrandomized observational studies suggest that loss rates from either TA CVS or amniocentesis are somewhat similar to those in women

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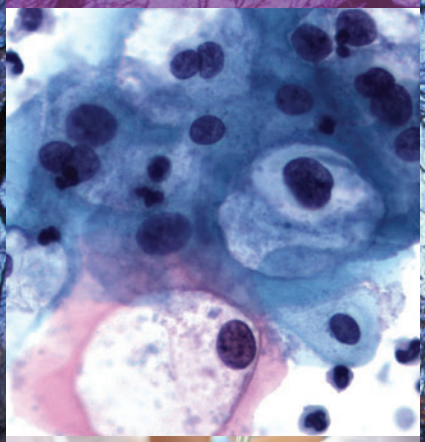

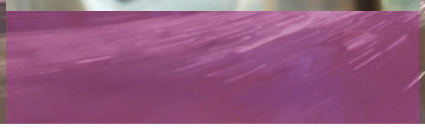

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When opiate abuse complicates pregnancy

Drug abuse during pregnancy has become more common in recent years. Here's how to intervene in a way that will most benefit both mother and baby.

BY **MONA PRASAD, DO, MPH**

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When women learn that they are pregnant, they tend to stop drinking caffeine and alcohol, stop smoking, and even stop coloring their hair. Why, then, would any pregnant woman choose to continue to expose her unborn child to drugs?

Drug use rarely starts during pregnancy. More often, women enter pregnancy already abusing or dependent on drugs. The risks of such exposures to the fetus are well known. Incidence of neonatal abstinence syndrome (NAS), which is opiate withdrawal, rose 300% between 2000 and 2009.[1] Risks of prenatal opiate exposure are not limited to the fetus. The Centers for Disease Control and Prevention recently reported that deaths from opiate overdose among women have increased 400% since 1999 (compared to 265% among men).

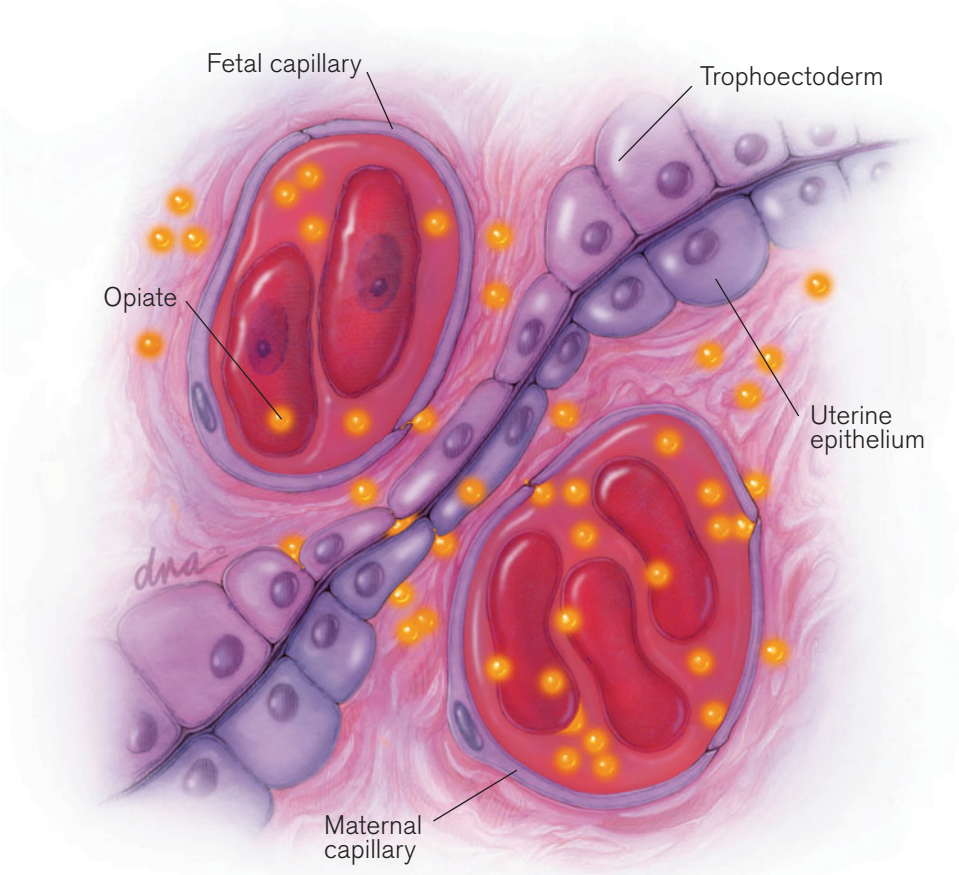
This translates to about 18 women dying per day, and for every woman who dies, 30 are treated in emergency departments for painkiller misuse or abuse.[2] The stigma associated with drug abuse and limited resources available to physicians make tackling this problem difficult. Pregnancy, however, may be the point of entry to the healthcare system that allows us to initiate the process.

Screening for opiate abuse

Ob/gyns are well positioned to screen patients for substance abuse and dependence and offer intervention because of the impact that the problem has on women. Substance-abusing patients come from all socioeconomic strata, racial and ethnic groupings, and ages; therefore, screening methods targeted toward "high-risk" patients will invariably fail to identify all women in need of services.[3,4]

Despite the adverse outcomes associated with exposure to tobacco, alcohol, and illicit drugs, only approximately 20% of ob/gyns effectively screen patients for illicit drug use.[5] Barriers to screening include physician embarrassment with posing appropriate questions, fear that patients will change practitioners if they are offended by the questions, and uncertainty about where to turn when a woman screens positive.

Many general instruments exist for screening pregnant women for substance abuse. The 4Ps Plus, for example, is a 5-question screening instrument that has been validated for use in identifying substance abuse in pregnancy with a sensitivity of 87% and specificity of 76%.[6] Questions include:



• Did your parents have trouble with drugs?

• Does your partner have a problem with drugs or alcohol?

• Have you ever drunk beer, wine, or liquor in the month before you knew you were pregnant? How many cigarettes did you smoke?

• In the month before you knew you were pregnant how much beer/wine/liquor did you drink?[6]

Another such instrument is the CAGE-AID screening questionnaire (Table).[7] A single "yes" response renders 79% sensitivity and 77% specificity for identifying drug abuse.[7] Again, the detection of drug abuse is considered to be clinically important. Although single-item screening has not been validated specifically in pregnancy, physicians may consider simply asking, "How many times in the past year have you used an illegal drug or used a prescription medication for nonmedical reasons?" In the primary-care setting a positive response to this single question is 100% sensitive and 74% specific for a drug use disorder.[8]

Biochemical screening can be used as an adjunct to such self-report screening tools. Samples that can be tested include urine, blood, hair, saliva, and sweat. Urine is the most accessible and simple, but assessment of substance abuse by biochemical screening alone is not without limitations. Negative tests do not rule out substance abuse and positive tests do not identify how much drug is used. The American College of Obstetricians and Gynecologists (ACOG) does not endorse biochemical screening as a sole method of detecting substance abuse during pregnancy.[9] If performed, full consent should first be obtained.

The neonate can be screened for in utero drug exposure by testing meconium and urine. Universal meconium screening (reflective of drug exposure in the weeks prior to delivery) is a strategy sometimes applied in locations where opiate abuse is highly prevalent. As with maternal screening, ethical issues surrounding the population that is tested (eg, universal or targeted) and disclosure of results must be carefully evaluated.[9]

The most effective approach to screening for substance abuse during pregnancy may be through a series of nonjudgmental questions. ACOG recommends that all pregnant women be questioned thoroughly regarding substance abuse. Universal, structured self-reported screening for substance abuse will make ob/gyns more comfortable with this discussion, reduce interviewer bias, and reduce the stigma associated with substance use and abuse.

In addition, it allows for brief intervention, which may have an important effect on pregnancies ex-

TABLE **CAGE-AID questions**

- Have you ever felt you needed to cut down on your drinking or drug use?
- Have people annoyed you by criticizing your drinking or drug use?
- Have you ever felt bad or guilty about your drinking or drug use?
- Have you ever had a drink or used drugs first thing in the morning to steady your nerves or get rid of a hangover?

Source: Brown RL, Rounds LA.[7]

continued from **PAGE 29**

posed to substance abuse.[9]

Brief intervention

Evidence for the effectiveness of brief interventions such as SBIRT (Screening, Brief Intervention, and Referral to Treatment) in reducing risky drug use is not as robust as has been demonstrated in reducing risky alcohol consumption, but it is accumulating and promising.[10] The point of brief intervention is to seize the moment when substance abuse is identified, and in a time-limited, structured, goal-directed way, reduce the risk of harm from continued use of substances. Examples of brief interventions include asking clients to try nonuse to see if they can stop on their own, encouraging interventions directed toward attending a self-help group such as Alcoholics Anonymous or Narcotics Anonymous, and engaging in efforts to help pregnant patients stop using.[11]

The 6 elements critical for effective brief interventions can be recalled by the acronym **FRAMES**:

Feedback about personal risk or impairment;

Responsibility for change placed on the participant;

Advice given by the provider;

Menus of alternative or self-help treatment options offered to the participant;

Empathetic counseling style; and

Self-efficacy or optimistic empowerment.[11]

The goal of intervention for pregnant women found to be substance dependent is to recommend the optimal behavior change and level of care. In the setting of opiate abuse, opiate maintenance along with counseling and self-help are appropriate.

Opioid abuse and its effects

A wide variety of opiates are abused including heroin, methadone, and oxycodone. Abuse of any of these agents carries risks of adverse pregnancy outcomes. Opiates can be inhaled, injected, snorted, ingested, or used subcutaneously ("skin popping"). The term "speed-balling" refers to combined use of opiates and cocaine. Oxycodone derivatives intended for sustained release contain 20 times the normal amount of active ingredient. When crushed, the slow-release polymer is destroyed and the product can then be swallowed, snorted, or injected, with results similar to the heroin high.[12] Urine toxicology will identify opiate metabolites (morphine, codeine, methadone) for 1 to 3 days after use, but screening should occur with maternal consent and education.[13]

heroin.[14] Pregnant women are uniquely vulnerable to the impact of opiate abuse: opiates are exceedingly addictive, trading sex for drugs is common, heroin use is strongly associated with the behaviors of a male partner, women tend to initiate use earlier in life than men, and their transition from use to abuse is more rapid.[14]

Opiates exert their effect by binding to the mu-opioid and kappa-opioid receptors found in the limbic and limbic-related areas of the brain. Like most drugs of abuse, the addictive response is mediated by dopamine. After binding to opiate receptors a signal is sent to dopamine terminals to release dopamine. Dopamine then binds dopamine receptors, stimulates the postsynaptic cell, and results in a positive emotional response.

Opiate pathways play a role in reward and reinforcement, modulation of response to pain and stress, and homeostatic regulation. While mu-opioid receptors produce analgesia, euphoria, and miosis, and reinforce the reward behavior, kappa-opioid receptors produce the subjective sensation of dysphoria, spinal analgesia, sedation, and miosis.[12] Opiates are highly addictive, and once used, the likelihood of transition to abuse is significant. Recovery success rates are not encouraging: 71% of users relapse within 6 weeks of nonmedication rehabilitation efforts.[15]

Opioid maintenance with methadone

In an ideal world abstinence from drugs and medications would be a goal. At present, however, opioid detoxification's role in pregnancy is minimal. Detoxification via opiate taper in pregnancy does not appear to have obvious adverse effects, but miscarriage, preterm birth, meconium passage, stillbirth, and elevated epinephrine and norepinephrine levels are found in case reports.[16-18] The major reason not to attempt detoxification is that it is generally unsuccessful, with relapse rates of 50% or more.[19] If attempted, it is best to wait until the end of the first trimester because limited data suggest that miscarriage rates may be higher in the first trimester.[19]

If attempting detoxification late in the third trimester, antenatal surveillance should be undertaken. Only a single study has compared various detoxification regimens in pregnancy to a methadone maintenance (MM) comparison group.[20] The 5 participant groups in that study were those receiving 3-day methadone-assisted withdrawal (MAW) alone (n=67), 3-day MAW followed by MM (n=8), 7-day MAW alone (n=28), 7-day MAW followed by MM (n=20), and a continuous MM sample (n=52). On average, patients in the 3 MM groups remained in treatment longer, attended more obstetric visits, and delivered at the program hospital more often than the patients in the 2 MAW-alone groups. The researchers concluded that MM should be considered as primary treatment for opioid-dependent pregnant women.[20]

Fortunately, treatment is available for opiate maintenance, both to decrease the impact of high-risk activities and to improve neonatal outcomes. The classic opiate maintenance drug is methadone, a full mu-opioid agonist and weak N-methyl-D-aspartate (NMDA) receptor antagonist, metabolized by the cytochrome P 450 system. It has many favorable qualities: high bioavailability, long half-life, low cost, convenient (daily) dosing, and slow onset to withdrawal syndrome. It has been used for more than 40 years to treat opiate addiction and has demonstrated benefits in deterring high-risk behaviors, incarceration, and spread of infectious disease.[21]

Methadone maintenance therapy for addiction occurs in US federally funded opiate maintenance programs. In this setting, patients are dosed daily and participate in counseling and drug screening per the regulations of the facility. Such MM programs are not widely available, and transportation issues and need for daily compliance may be barriers to participation.

In spite of potential challenges, the benefits of MM have been demonstrated in the pregnant population. Methadone maintenance has been associated with earlier and more-compliant prenatal care, improved nutrition and weight gain, fewer children in the foster system, and improved enrollment in substance abuse treatment and recovery programs. Pregnant women remain opiate dependent, but generally become more functional.[22] The goal of treatment is to provide sufficient dosing to prevent drug cravings, eliminate illicit use, and keep additional opiates from creating euphoria.

The model of use of opiate maintenance in pregnancy is that of harm reduction, rather than elimination through abstinence. There is no ceiling of benefit to dosing methadone. Because it is a full mu-opioid agonist, increasing doses offer increasing benefit. The average MM dose needed to achieve clinical stability is between 80 and 120 mg daily.[23] A dose lower than 60 mg is believed to be insufficient to prevent drug-seeking behavior. Due to the physiology of pregnancy, split dosing is sometimes recommended.

Opioid maintenance with buprenorphine

In addition to methadone, buprenorphine has been gaining recognition as a treatment for opioid addiction during pregnancy. Buprenorphine is a synthetic opioid and partial mu-opioid agonist with a very high affinity for the mu-opioid receptor. It can therefore displace circulating opiates. It disassociates slowly from the receptor and is unlikely to be displaced by other competing opiates. A ceiling effect of buprenorphine benefit is believed to exist; dosing beyond 24 to 32 mg daily may not have any additional benefits. The autonomic withdrawal associated with buprenorphine is said to be less significant than with other opiates. Buprenorphine demonstrates favorable qualities similar to methadone, such as decreasing drug cravings with daily dosing, with the additional benefit of being prescribed by specifically certified physicians as opposed to federally funded clinics. This benefits patient autonomy and opiate maintenance.

In pregnancy, buprenorphine alone is favored over buprenorphine/naloxone because of lack of data regarding the combination product, and concerns that naloxone may produce maternal and subsequently fetal hormonal changes.[24,25] The naloxone component was added to limit the abuse potential of buprenorphine, because when the combination is taken sublingually naloxone is not bioavailable and does not accumulate to clinically significant concentrations. If buprenorphine/naloxone is injected or snorted, however, it will precipitate withdrawal in opioid-dependent individuals. We routinely use the combination in our clinics, and data are forthcoming regarding the relative safety of its use. Nevertheless, until more research is available use of buprenorphine alone remains standard for pregnant patients despite its high abuse potential.

Numerous comparisons of methadone and buprenorphine have been performed to assess their efficacy in the treatment of opioid dependence in pregnancy.[26] Because withdrawal symptoms associated with buprenorphine are purportedly less intense than with methadone, researchers sought to determine the impact of methadone versus buprenorphine on NAS.[27] The 2010 MOTHER (Maternal Opioid Treatment: Human Experimental Research) study found that buprenorphine was associated with significantly lower doses of morphine for treatment of NAS, shorter duration of treatment, and shorter hospital stay than methadone.[27] This report has had a significant impact on the treatment of opiate dependence in pregnancy, and use of buprenorphine for the treatment of opiate maintenance in pregnancy is increasing.

Neonatal aspects

A recent literature review of comparisons of methadone and buprenorphine supports 3 conclusions. First, buprenorphine produces a less-severe NAS than does methadone. Second, buprenorphine's efficacy in the treatment of opioid dependence during pregnancy does not negate methadone's utility in this regard, because no single treatment will likely be maximally effective for all patients. Finally, more research on the long-term effects of buprenorphine and methadone is needed.

No obvious embryopathy has been attributed to opiate exposure, but NAS is a risk for all opiate-exposed babies. Seen in 40% to 90% of methadone-exposed babies and characterized by central nervous system irritability, respiratory distress, gastrointestinal dysfunction, and autonomic instability, NAS is treated most commonly with opiates (morphine/methadone), but phenobarbital can also be used.[28] The decision to treat an infant is standardized by adherence to measurement instruments such as the Finnegan NAS measure.[29] The usual onset of NAS is in days 2 to 3 of life. Duration of therapy depends on neonatal response and ranges from days to weeks. depending upon response to treatment.

Debate is ongoing on the role that methadone dose plays in the development of NAS. Several authors have reported that higher doses of methadone have no impact on the severity of NAS.[30-33] Conversely, others have published that dose does matter.[34-36] The most comprehensive literature review, using 29 reports, concluded that "Severity of the neonatal abstinence syndrome does not appear to differ according to whether mothers are on high- or low-dose methadone maintenance therapy."[37] Thus, providers should be focused on treating the pregnant patient with a methadone dose that is most effective in preventing her use of other opioids. "Effective" implies that the mother is free of illicit drugs, so elimination of drug cravings is a key component of therapy. The difficulty of dosing methadone during pregnancy is that pregnancy-associated somatic complaints (musculoskeletal pains, nausea, sleep-

lessness, anxiety, irritability) can mimic suboptimal dosing. In addition, the physiology of pregnancy, with associated decreased absorption, rapid elimination, and higher clearance of drug, may mandate higher doses at the end.

Breastfeeding

Advice regarding breastfeeding and opioid intake needs to take into consideration whether the mother is abusing an opioid and is not otherwise receiving opioid-agonist pharmacotherapy treatment or is in opioid-agonist treatment with methadone or buprenorphine. Women who abuse heroin or prescription opioids and nurse run the risk of exposing their infants to levels of opioids high enough to cause tremors, restlessness, vomiting, poor feeding, and even addiction. The general advice in that case should be to avoid breastfeeding. In contrast, women who are in opioid-agonist treatment with methadone or buprenorphine should be encouraged to breastfeed because research has clearly demonstrated that methadone and buprenorphine concentrations in breast milk are low. For doses of methadone 50 to 105 mg daily, the neonatal dose is less than 0.2 mg per day, unlikely to have any clinical effect.[38] Therefore, breastfeeding should be recommended for agonist-maintained women unless contraindicated by existing medical conditions (eg, HIV). Cessation of breastfeeding is not likely to precipitate withdrawal because mothers do not generally abruptly stop nursing their infants.

Summary

Opiate abuse in pregnancy is highly prevalent, and if we pursue appropriate screening, cases will be identified that require brief intervention and referral to treatment. Leveraging community resources will empower us to more aggressively treat the problem.

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Divigel® is indicated for the treatment of moderate to severe vasomotor symptoms due to menopause.

What a sigh of relief feels like

- Divigel® 1 mg/day eliminated nearly 9 out of 10 daily hot flashes at week 12[1]
- Reductions in median daily frequency of moderate to severe vasomotor symptoms, which include night sweats, by dose at week 12: 87% (1 mg/day), 79% (0.5 mg/day), 71% (0.25 mg/day), and 48% (placebo)[1,2]*

*In a study of 488 postmenopausal women (34-89 years of age) who received 1 mg (n=124), 0.5 mg (n=119), or 0.25 mg (n=121) of Divigel®, or placebo gel (n=124) daily.

References: 1. Divigel® [package insert]. Minneapolis, MN: Upsher-Smith Laboratories, Inc; 2012. **2.** Data on file. Upsher-Smith Laboratories, Inc.

Divigel® (estradiol gel) 0.1%
0.25 mg 0.5 mg 1 mg
www.divigel.com

Important Safety Information for Healthcare Providers

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

See Full Prescribing Information for complete Boxed Warning

Estrogen-Alone Therapy
- There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens
- Estrogen-alone therapy should not be used for the prevention of cardiovascular disease or dementia
- The Women's Health Initiative (WHI) estrogen-alone substudy reported increased risks of stroke and deep vein thrombosis (DVT)
- The WHI Memory Study (WHIMS) estrogen-alone ancillary study of the WHI reported an increased risk of probable dementia in postmenopausal women 65 years of age or older

Estrogen Plus Progestin Therapy
- Estrogen plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia
- The WHI estrogen plus progestin substudy reported increased risks of stroke, DVT, pulmonary embolism (PE), and myocardial infarction (MI)
- The WHI estrogen plus progestin study reported increased risks of invasive breast cancer
- The WHIMS estrogen plus progestin ancillary study of WHI reported an increased risk of probable dementia in postmenopausal women 65 years of age and older

Divigel® should not be used in women with undiagnosed abnormal genital bleeding; known, suspected, or history of breast cancer; known or suspected estrogen-dependent neoplasia; active DVT, PE, or history of these conditions; active arterial thromboembolic disease or a history of these conditions; known anaphylactic reaction or angioedema to Divigel®; known liver impairment or disease; known protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders; or known or suspected pregnancy.

Estrogens increase the risk of gallbladder disease.

Discontinue estrogen if severe hypercalcemia, loss of vision, severe hypertriglyceridemia or cholestatic jaundice occurs.

Monitor thyroid function in women on thyroid replacement therapy.

The most common adverse reactions (incidence ≥ 5 percent) are breast tenderness, metrorrhagia, vaginal mycosis, nasopharyngitis, and upper respiratory tract infection.

Patients should be started with the lowest effective dose and the dose should be evaluated periodically.

Alcohol-based gels are flammable. Patients should avoid fire, flame or smoking until the gel has dried.

Please see Full Prescribing Information, including Boxed Warning and Patient Counseling Information. For more information, call 1-888-650-3789 or visit www.divigel.com.

You are encouraged to report negative side effects to Upsher-Smith Laboratories, Inc. at 1-855-899-9180 or to the FDA by visiting www.fda.gov/medwatch or calling 1-800-FDA-1088.

Please see accompanying Brief Summary on adjacent page.

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Divigel® (estradiol gel) 0.1%

Brief Summary of Prescribing Information

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

Estrogen-Alone Therapy

Endometrial Cancer

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

Cardiovascular Disorders and Probable Dementia

Estrogen-alone therapy should not be used for the prevention of cardiovascular disease or dementia. The Women's Health Initiative (WHI) estrogen-alone substudy reported increased risks of stroke and deep vein thrombosis (DVT) in postmenopausal women (50 to 79 years of age) during 7.1 years of treatment with daily oral conjugated estrogens (CE) [0.625 mg]-alone, relative to placebo.

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

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

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

Estrogen Plus Progestin Therapy

Cardiovascular Disorders and Probable Dementia

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

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

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

Breast Cancer

The WHI estrogen plus progestin substudy also demonstrated an increased risk of invasive breast cancer. In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and MPA, and other combinations and dosage forms of estrogens and progestins.

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

INDICATIONS AND USAGE

Divigel is an estrogen indicated for the treatment of moderate to severe vasomotor symptoms due to menopause.

CONTRAINDICATIONS

Divigel® should not be used in women with any of the following conditions:

- Undiagnosed abnormal genital bleeding
- Known, suspected, or history of breast cancer
- Known or suspected estrogen-dependent neoplasia
- Active DVT, PE, or history of these conditions
- Active arterial thromboembolic disease (for example, stroke and MI), or a history of these conditions
- Known anaphylactic reaction or angioedema to Divigel
- Known liver impairment or disease
- Known protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders
- Known or suspected pregnancy

WARNING AND PRECAUTIONS

Cardiovascular Disorders- An increased risk of stroke and DVT has been reported with estrogen-alone therapy. An increased risk of PE, DVT, stroke and MI has been reported with estrogen plus progestin therapy. Should any of these occur or be suspected, estrogen with or without progestin therapy should be discontinued immediately. Risk factors for arterial vascular disease (for example, hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and obesity) and/or venous thromboembolism (VTE) (for example, personal history or family history of VTE, obesity, and systemic lupus erythematosus) should be managed appropriately. *Stroke* - In the WHI estrogen-alone substudy, a statistically significant increased risk of stroke was reported in women 50 to 79 years of age receiving daily CE (0.625 mg)-alone compared to women in the same age group receiving placebo (45 versus 33 per 10,000 women-years). The increase in risk was demonstrated in year 1 and persisted. Should a stroke occur or be suspected, estrogen-alone therapy should be discontinued immediately. Subgroup analyses of women 50 to 59 years of age suggest no increased risk of stroke for those women receiving CE (0.625 mg)-alone versus those receiving placebo (18 versus 21 per 10,000 women-years). In the WHI estrogen plus progestin substudy, a statistically significant increased risk of stroke was reported in women 50 to 79 years of age receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women in the same age group receiving placebo (33 versus 25 per 10,000 women-years) .The increase in risk was demonstrated after the first year and persisted. Should a stroke occur or be suspected, estrogen plus progestin therapy should be discontinued immediately. *Coronary Heart Disease*- In the WHI estrogen-alone substudy, no overall effect on coronary heart disease (CHD) events (defined as nonfatal MI, silent MI, or CHD death) was reported in women receiving estrogen-alone compared to placebo[2]. 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)[1]. In the WHI estrogen plus progestin substudy, there was a statistically non-significant increased risk of CHD events reported in women receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women receiving placebo (41 versus 34 per 10,000 women-years)[1]. An increase in relative risk was demonstrated in year 1, and a trend toward decreasing relative risk was reported in years 2 through 5. In postmenopausal women with documented heart disease (n=2,763, average 66.7 years of age), in a controlled clinical trial of secondary prevention of cardiovascular disease (Heart and Estrogen/Progestin Replacement Study [HERS]), treatment with daily CE (0.625 mg) plus MPA (2.5 mg) demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with CE plus MPA did not reduce the overall rate of CHD events in postmenopausal women with established coronary heart disease. There were more CHD events in the CE plus MPA-treated group than in the placebo group in year 1, but not during the subsequent years. Two thousand, three hundred and twenty-one (2,321) women from the original HERS trial agreed to participate in an open label extension of HERS, HERS II. Average follow-up in HERS II was an additional 2.7 years, for a total of 6.8 years overall. Rates of CHD events were comparable among women in the CE plus MPA group and the placebo group in HERS, HERS II, and overall. *Venous Thromboembolism*- In the WHI estrogen-alone substudy, the risk of VTE (DVT and PE) was increased for women receiving daily CE (0.625 mg)-alone compared to placebo (30 versus 22 per 10,000 women-years), although only the increased risk of DVT reached statistical significance (23 versus 15 per 10,000 women-years). The increase in VTE risk was demonstrated during the first 2 years[3]. Should a VTE occur or be suspected, estrogen-alone therapy should be discontinued immediately. In the WHI estrogen plus progestin substudy, a statistically significant 2-fold greater rate of VTE was reported in women receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women receiving placebo (35 versus 17 per 10,000 women-years). Statistically significant increases in risk for both DVT (26 versus 13 per 10,000 women-years) and PE (18 versus 8 per 10,000 women-years) were also demonstrated. The increase in VTE risk was demonstrated during the first year and persisted[4]. Should a VTE occur or be suspected, estrogen plus progestin therapy should be discontinued immediately. If feasible, estrogens should be discontinued at least 4 to 6 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization. **Malignant Neoplasms**- *Endometrial Cancer*- An increased risk of endometrial cancer has been reported with the use of unopposed estrogen therapy in a woman with a uterus. The reported endometrial cancer risk among unopposed estrogen users is about 2 to 12 times greater than in non-users, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with use of estrogens for less than 1 year. The greatest risk appears associated with prolonged use, with increased risk of 15- to 24-fold for 5 to 10 years or more and this risk has been shown to persist for at least 8 to 15 years after estrogen therapy is discontinued. Clinical surveillance of all women using estrogen-alone or estrogen plus progestin therapy is important. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding. There is no evidence that the use of natural estrogens results in a different endometrial risk profile than synthetic estrogens of equivalent estrogen dose. Adding a progestin to postmenopausal estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. *Breast Cancer*- The most important randomized clinical trial providing information about breast cancer in estrogen-alone users is the WHI substudy of daily CE (0.625 mg)-alone. In the WHI estrogen-alone substudy, after an average follow-up of 7.1 years, daily CE-alone was not associated with an increased risk of invasive breast cancer *[relative risk (RR) 0.80]*[2]. The most important randomized clinical trial providing information about breast cancer in estrogen plus progestin users is the WHI substudy of daily CE (0.625 mg) plus MPA (2.5 mg). After a mean follow-up of 5.6 years, the estrogen plus progestin substudy reported an increased risk of invasive breast cancer in women who took daily CE plus MPA. In this substudy, prior use of estrogen-alone or estrogen plus progestin therapy was reported by 26 percent of the women. The relative risk of invasive breast cancer was 1.24, and the absolute risk was 41 versus 33 cases per 10,000 women-years, for CE plus MPA compared with placebo. Among women who reported prior use of hormone therapy, the relative risk of invasive breast cancer was 1.86, and the absolute risk was 46 versus 25 cases per 10,000 women-years, for CE plus MPA compared with placebo. Among women who reported no prior use of hormone therapy, the relative risk of invasive breast cancer was 1.09, and the absolute risk was 40 versus 36 cases per 10,000 women-years for CE plus MPA compared with placebo. In the same substudy, invasive breast cancers were larger, were more likely to be node positive, and were diagnosed at a more advanced stage in the CE (0.625 mg) plus MPA (2.5 mg) group compared with the placebo group. Metastatic disease was rare, with no apparent difference between the two groups. Other prognostic factors such as histologic subtype, grade and hormone receptor status did not differ between the groups[6]. Consistent with the WHI clinical trial, observational studies have also reported an increased risk of breast cancer for estrogen plus progestin therapy, and a smaller increased risk for estrogen-alone therapy, after several years of use. The risk increased with duration of use, and appeared to return to baseline over about 5 years after stopping treatment (only the observational studies have substantial date on risk after stopping). Observational studies also suggest that the risk of breast cancer was greater, and became apparent earlier, with estrogen plus progestin therapy as compared to estrogen-alone therapy. However, these studies have not generally found significant variation in the risk of breast cancer among different estrogen plus progestin combinations, doses, or routes of administration. The use of estrogen-alone and estrogen plus progestin has been reported to result in an increase in abnormal mammograms requiring further evaluation. All women should receive yearly breast examinations by a healthcare provider and perform monthly breast self-examinations. In addition, mammography examinations should be scheduled based on patient age, risk factors, and prior mammogram results. *Ovarian Cancer* - The WHI estrogen plus progestin substudy reported a statistically non-significant increased risk of ovarian cancer. After an average follow-up of 5.6 years, the relative risk for ovarian cancer for CE plus MPA versus placebo was 1.58 [95 percent CI, 0.77-3.24]. The absolute risk for CE plus MPA versus placebo was 4 versus 3 cases per 10,000 women-years.[7] In some epidemiologic studies, the use of estrogen plus progestin and estrogen-only products, in particular for 5 or more years, has been associated with an increased risk of ovarian cancer. However, the duration of exposure associated with increased risk is not consistent across all epidemiologic studies, and some report no association. **Probable Dementia-** In the WHIMS estrogen-alone ancillary study of WHI, a population of 2,947 hysterectomized women 65 to 79 years of age was randomized to daily CE (0.625 mg)-alone or placebo. After an average follow-up of 5.2 years, 28 women in the estrogen-alone group and 19 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE-alone versus placebo was 1.49 (95 percent CI, 0.83-2.66). The absolute risk of probable dementia for CE-alone versus placebo was 37 versus 25 cases per 10,000 women-years[8]. In the WHIMS estrogen plus progestin ancillary study, a population of 4,532 postmenopausal women 65 to 79 years of age was randomized to daily CE (0.625 mg) plus MPA (2.5 mg) or placebo. After an average follow-up of 4 years, 40 women in the CE plus MPA group and 21 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE plus MPA versus placebo was 2.05 (95 percent CI, 1.21-3.48). The absolute risk of probable dementia for CE plus MPA versus placebo was 45 versus 22 cases per 10,000 womenyears[8]. When data from the two populations in the WHIMS estrogen-alone and estrogen plus progestin ancillary studies were pooled as planned in the WHIMS protocol, the reported overall relative risk for probable dementia was 1.76 (95 percent CI, 1.19-2.60). Since both ancillary studies were conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women[8]. **Gallbladder Disease-** A 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in postmenopausal women receiving estrogens has been reported. **Hypercalcemia -**Estrogen administration may lead to severe hypercalcemia in women with breast cancer and bone metastases. If hypercalcemia occurs, use of the drug should be stopped and appropriate measures taken to reduce the serum calcium level. **Visual Abnormalities-** Retinal vascular thrombosis has been reported in 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, estrogens should be permanently discontinued. **Addition of a Progestin When a Woman Has Not Had a Hysterectomy-** Studies of the addition of a progestin for 10 or more days of a cycle of estrogen administration, or daily with estrogen in a continuous regimen, have reported a lowered incidence of endometrial hyperplasia than would be induced by estrogen treatment alone. Endometrial hyperplasia may be a precursor to endometrial cancer. There are, however, possible risks that may be associated with the use of progestins with estrogens compared to estrogen-alone regimens. These include an increased risk of breast cancer. **Elevated Blood Pressure-** In a small number of case reports, substantial increases in blood pressure have been attributed to idiosyncratic reactions to estrogens. In a large, randomized, placebo-controlled clinical trial, a generalized effect of estrogens on blood pressure was not seen. **Hypertriglyceridemia-** In women with pre-existing hypertriglyceridemia, estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis. Consider discontinuation of treatment if pancreatitis occurs. **Hepatic Impairment and/or Past History of Cholestatic Jaundice-** Estrogens may be poorly metabolized in patients with impaired liver function. For women with a history of cholestatic jaundice associated with past estrogen use or with pregnancy, caution should be exercised, and in the case of recurrence, medication should be discontinued. **Hypothyroidism-** Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Women with normal thyroid function can compensate for the increased TBG by making more thyroid hormone, thus maintaining free 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 to maintain their free thyroid hormone levels in an acceptable range. **Fluid Retention-** Estrogens may cause some degree of fluid retention. Women with conditions that might be influenced by this factor, such as a cardiac or renal impairment, warrant careful observation when estrogen-alone is prescribed. **Hypocalcemia-** Estrogen therapy should be used with caution in women with hypoparathyroidism as estrogen-induced hypocalcemia may occur. **Exacerbation of Endometriosis-** A few cases of malignant transformation of residual endometrial implants have been reported in women treated post hysterectomy with estrogen-alone therapy. For women known to have residual endometriosis post-hysterectomy, the addition of progestin should be considered. **Hereditary Angioedema** Exogenous estrogens may exacerbate symptoms of angioedema in women with hereditary angioedema. **Exacerbation of Other Conditions** Estrogen therapy may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraine, porphyria, systemic lupus erythematosus, and hepatic hemangiomas and should be used with caution in women with these conditions. **Photosensitivity/Photoallergy** The effects of direct sun exposure to Divigel application sites have not been evaluated in clinical trials. **Application of Sunscreen and Topical Solutions** Studies conducted using other approved topical estrogen gel products have shown that sunscreens have the potential for changing the systemic exposure of topically applied estrogen gels. The effect of sunscreens and other topical lotions on the systemic exposure of Divigel has not been evaluated in clinical trials. **Flammability of Alcohol-Based Gels - Alcohol based gels are flammable.** Avoid fire, flame, or smoking until the gel has dried. Occlusion of the area where the topical drug product is applied with clothing or other barriers is not recommended until the gel is completely dried. **Potential for Estradiol Transfer and Effects of Washing** There is a potential for drug transfer from one individual to the other following physical contact of Divigel application sites. In a study to evaluate transferability to males from their female contacts, there was some elevation of estradiol levels over baseline in the male subjects; however, the degree of transferability in this study was inconclusive. Patients are advised to avoid skin contact with other subjects until the gel is completely dried. The site of application should be covered (clothed) after drying. Washing the application site with soap and water 1 hour after application resulted in a 30 to 38 percent decrease in the mean total 24-hour exposure to estradiol. Therefore, patients should refrain from washing the application site for at least one hour after application. **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 increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity. Increased thyroid binding globulin (TBG) levels leading to increased circulating total thyroid hormone levels, 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-l-antitrypsin, ceruloplasmin). Increased plasma high-density lipoprotein (HDL) and HDL2 cholesterol subfraction concentrations, reduced low-density lipoprotein (LDL) cholesterol concentration, increased triglyceride levels. Impaired glucose tolerance.

ADVERSE REACTIONS

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

- Cardiovascular Disorders *[see Boxed Warning]*.
- Malignant Neoplasms *[see Boxed Warning]*.

DRUG INTERACTIONS

No drug-drug interaction studies have been conducted for Divigel. **Metabolic Interactions -** *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 plasma concentrations of estrogens and result in side effects.

USE IN SPECIFIC POPULATIONS

Pregnancy Divigel should not be used during pregnancy *[see Contraindications (4)]*. There appears to be little or no increased risk of birth defects in children born to women who have used estrogens and progestins as an oral contraceptive inadvertently during early pregnancy. **Nursing Mothers-** Divigel should not be used during lactation. Estrogen administration to nursing women has been shown to decrease the quantity and quality of the breast milk. Detectable amounts of estrogens have been identified in the breast milk of women receiving estrogen therapy. Caution should be exercised when Divigel is administered to a nursing woman. **Pediatric Use-** Divigel is not indicated in children. Clinical studies have not been conducted in the pediatric population. **Geriatric Use-** There have not been sufficient numbers of geriatric women involved in studies utilizing Divigel to determine whether those over 65 years of age differ from younger subjects in their response to Divigel. *The Women's Health Initiative Studies* In the WHI estrogen-alone substudy (daily CE [0.625 mg]-alone versus placebo), there was a higher relative risk of stroke in women greater than 65 years of age. In the WHI estrogen plus progestin substudy (daily CE [0.625 mg] plus MPA [2.5 mg] versus placebo), there was a higher relative risk of nonfatal stroke and invasive breast cancer in women greater than 65 years of age.

The Women's Health Initiative Memory Study In the WHIMS ancillary studies of postmenopausal women 65 to 79 years of age, there was an increased risk of developing probable dementia in women receiving estrogen-alone or estrogen plus progestin when compared to placebo. Since both ancillary studies were conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women[8]. **Renal Impairment-** The effect of renal impairment on the pharmacokinetics of Divigel has not been studied. **Hepatic Impairment-** The effect of hepatic impairment on the pharmacokinetics of Divigel has not been studied.

OVERDOSAGE

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

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Placental pathology: Is it time to get serious?

Opinions differ on the value of sending placentas for pathology examinations. The author calls for standardizing when, why, and how this occurs.

BY **RAYMOND W. REDLINE, MD**

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

Thousands of placentas are submitted to pathology departments across the United States each year at considerable expense to patients and the healthcare system. The benefits derived largely depend on the interest, knowledge, and experience of clinicians and pathologists. Attitudes toward placental pathology vary among clinicians. Some feel it is of no value whatsoever. At the other extreme are those who feel that the placenta is the key to everything if only we understood it.

Attitudes among pathologists range from the opinion "of no interest, simply verify tissue identity" to a belief that all placentas should be examined because their pathology answers every clinical question.

The truth lies between the extremes. We already know a great deal about which patterns of placental injury are clinically important. In specific situations, these data can enhance patient care. Unfortunately, the potential utility of placental pathology is under-realized. On the clinical side, there is lack of clarity regarding which placentas to submit and what placental diagnoses mean. In some pathology departments, there is an appalling lack of diagnostic accuracy and clinical

TAKE-HOME MESSAGES

- The potential utility of placental pathology is under-realized.
- The importance of providing the pathologist with appropriate clinical history cannot be overemphasized.
- Pathology practice will not improve without compelling clinical demand.

TABLE 1 Indications for submitting a placenta to pathology

Maternal
Delivery at <37 wks or more than 42 wks (alternative: <34 wks only)
Unexplained or recurrent pregnancy complications
Systemic disorders, gestational or underlying, including malignancy with concern for mother or infant
Peripartum fever or infection
Excessive third-trimester bleeding
Thick or prolonged meconium
Severe oligohydramnios/polyhydramnios
Fetal/neonatal
Stillbirth or neonatal death
NICU admission
SGA/LGA (birthweight <10th or >90th percentile for gestational age)
Birth depression/pH <7.0 / 5-minute Apgar <7/ assisted ventilation >10 min
Neonatal hematocrit <35
Neonatal seizures
Suspected infection or sepsis
Hydrops fetalis of unknown etiology
Multiple pregnancy (alternative: fused placentas, same-sex twins, and/or twins with discordant fetal growth)
Placental
Structural abnormalities or masses involving the placental disc, umbilical cord, or membranes
Abnormal size for gestational age
Fragmented, possibly incomplete placenta

Source: College of American Pathologists Practice Guideline, 1997

responsiveness that would not be tolerated in any other subspecialty.[1]

This article discusses the logistics of getting the right placentas to the right pathologists and briefly reviews the most important patterns of placental pathology. The focus here is on 6 common categories of placental injury, 2 rare lesions of extreme severity and high recurrence risk, and 2 placental findings that reflect underlying fetal processes and how they each relate to different adverse pregnancy outcomes. Specialized topics such as multiple gestation, congenital infections, and hydrops fetalis are beyond the scope of this review. Detailed consideration of these and other topics can be found in standard textbooks.[2,3] The article concludes with some perspective on how to improve the wide variation in current pathology practice relating to placental diagnosis.

Why send placentas to pathology?

Four categories of placental pathology have clinical utility: (1) findings relevant to the immediate care of the mother or baby; (2) findings predictive of possible recurrence that could guide care in subsequent pregnancies; (3) diagnoses that help explain adverse pregnancy outcomes; and (4) findings that may be important in medicolegal investigation of perinatal mortality and long-term morbidity.

An example of a pathologic finding relevant to immediate care would be a peripheral abscesses on the surface of the umbilical cord in a premature placenta. That is diagnostic for *Candida* infection, information that should be immediately communicated to the neonatal intensive care unit (NICU) so that antifungal therapy can be initiated. A finding in the second category would be a placenta from a stillborn fetus showing "maternal floor infarction." Such a lesion is associated with extremely high rates of recurrence and perinatal mortality, risks that can be ameliorated with early surveillance and indicated preterm delivery in subsequent pregnancies. Pertinent to the last 2 categories of placental pathology is neonatal encephalopathy leading to cerebral palsy (CP), which is among the most devastating pregnancy outcomes. Fetal thrombotic vasculopathy indicates antenatal as opposed to intrapartum causation, which can help explain a confusing clinical picture and be informative for both parents and physicians.

What placentas should be sent and what should be expected from the pathologist?

The goal is to ensure that the right placentas get to the right pathologist in a timely manner. Guidelines for placental submission were published in 1997 by a task force of pathologists and obstetricians sponsored by the College of American Pathologists (Table 1).[4] These are suggestions based on the probability of finding significant patterns of injury, but need to be tempered by the specifics of each pregnancy. Not every placenta from each category needs to be submitted and some placentas that fall outside the guidelines will reveal important findings.

Because some babies present with problems in

TABLE 2 Associations between pathological processes and adverse clinical outcomes

	Recurrent pregnancy loss	Preterm labor or PROM	Preterm FGR or IUFD	Term FGR	Term IUFD	CNS injury
Histologic chorioamnionitis	0	+++	0	0	0	+
Maternal arterial malperfusion	+	+	+++	++	0	+
Marginal abruption	0	++	+	0	0	0
Maternal floor infarction/ histiocytic intervillositis	+++	++	++	+	+	+
Villitis of unknown etiology	++	0	0	++	++	++
Fetal vascular obstruction/ thrombotic vasculopathy	0	0	+	+	++	+++
Distal villous maldevelopment	0	0	+	+	++	+
Elevated circulating NRBC	0	0	+	+	++	++
Prolonged meconium exposure	0	0	0	0	+	++

Abbreviations: CNS, central nervous system; FGR, fetal growth restriction; IUFD, intrauterine fetal demise; NRCB, nucleated red blood cells; PROM, premature rupture of membranes
0, rare; +, uncommon; ++, common; +++, very common

the days following apparently normal deliveries, it is prudent to develop a system for short-term retention of all placentas on the labor and delivery floor. Placentas can be stored unfixed in a refrigerator for up to 7 days without compromising placental pathology. The importance of providing the pathologist with appropriate clinical history cannot be overemphasized. At a minimum, gestational age, gravidity, parity, birth weight, Apgar scores, and relevant clinical conditions should always be included.

Timely reporting is critical for patient care. If the pathology department receives a placenta by noon, it is not unreasonable to expect a final diagnosis by the end of the next business day. If there are concerns about the accuracy or relevance of the initial placental diagnoses, it may be necessary to discuss the findings with the pathologist and solicit an expert review. Looking down the road, slide scanning technologies that allow for online consultation may facilitate development of regional centers with specific expertise in placental diagnosis.

Common patterns of placental pathology, what causes them, and how they relate to clinical practice

Described below are the constellation of histopathologic findings that either directly affect placental function or serve as biomarkers for processes occurring in the mother or fetus. Figure 1 illustrates their site of action and Table 2 summarizes their correlation with selected important adverse pregnancy outcomes. The relative importance of particular lesions varies in reports by different authors because of varying clinical material, definitions used, and statistical approaches.[5-7]

Maternal arterial malperfusion develops as a consequence of deficient trophoblastic invasion and remodeling of the spiral arterioles in early pregnancy.[8] It is the major cause of early-onset fetal growth restriction (FGR), particularly associated with preeclampsia, indicated early delivery, and stillbirth in preterm pregnancies. It is less common with FGR at term. In some studies, it is a risk factor for CP. Complications include development of maternal preeclampsia due to release of antiangiogenic mediators by ischemic villous trophoblast and abruptio placentae secondary to rupture of inadequately remodeled spiral arterioles.

Placentas affected by maternal arterial malperfusion may be small, both in absolute weight and relative to fetal weight. Histologically, it is characterized by increased syncytial knotting, intervillous fibrin deposition, and villous agglutination. When

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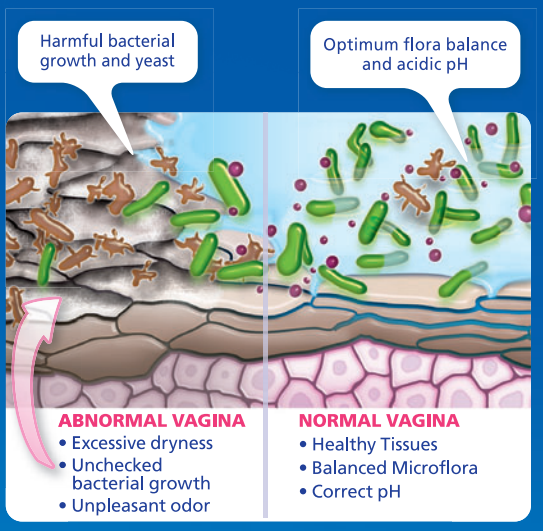

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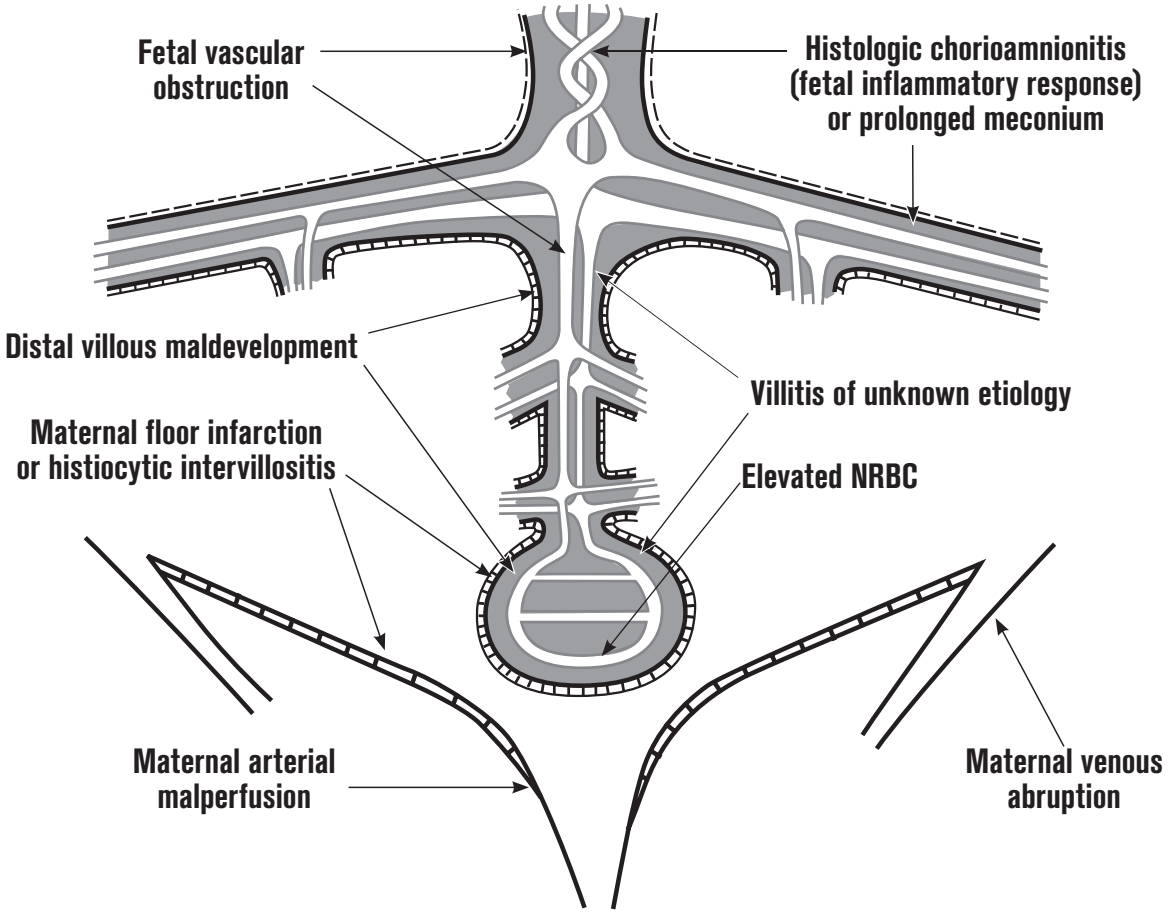
FIGURE 1 Schematic placental diagram with sites of action for major patterns of injury



severe, it is also often accompanied by patchy hypoplasia of the distal villous tree and 1 or more villous infarcts. Features of increased extravillous trophoblasts and multinucleated trophoblasts at the maternal floor also may be evident.[5] Recurrence risk is moderate, particularly when associated with early-onset preeclampsia, and affected women should be entered into high-risk screening programs for their next pregnancies.

Abruptio placenta is characterized by large central retroplacental hematomas, often with overlying intravillous hemorrhage or recent villous infarction).[5,9] Underlying risks include chronic hypertension and preeclampsia. Marginal abruptions are common causes of spontaneous preterm birth, particularly in the context of ascending infection, and when chronic can be associated with FGR. Chronic abruption is associated with organizing marginal or subchorionic hematomas, circumvallate membrane insertion, and deposition of hemoglobin pigments (usually hemosiderin) in the placental membranes.[10]

Chronic fetal vascular obstruction, as reflected by the pathologic finding of significant numbers of avascular villi (AV), is a clinically silent process strongly associated with adverse clinical outcome.[11] Numerous small foci of AV reflect the effects of globally decreased villous perfusion on the most distal terminal villi and are often seen with other indicators of chronic intermittent umbilical cord obstruction. Larger foci of AV indicate thrombosis of major

chorionic or stem villous vessels (fetal thrombotic vasculopathy).

Although maternal diabetes and inherited fetal thrombophilias can be associated with fetal thrombotic vasculopathy, the major risk factor is stasis, again related to compromised umbilical blood flow. Significant numbers of AV are a major risk factor for central nervous system (CNS) injury at term. The frequent finding of large areas of contiguous AV with degenerative changes antedating the estimated time of fetal demise suggests that chronic fetal vascular obstruction is also a major cause of stillbirth at term.[7] Significant numbers of AV are a robust indicator of a serious underlying process and can be very helpful in both clinicopathologic correlation and medicolegal contexts.[12]

Histologic chorioamnionitis is the gold standard for defining the maternal and fetal inflammatory responses to microbial organisms in the amniotic fluid.[13] Early inflammation is extremely sensitive and may occur before organisms are detectable in tissue. Clinical symptoms such as fever and leukocytosis are notoriously unreliable in this context. Chorioamnionitis is the major cause of spontaneous preterm birth and other neonatal complications. Assessing the stage and grade of inflammation may help to distinguish between chorioamnionitis as the cause of spontaneous preterm birth and a secondary response following preterm labor and/or rupture of membranes.

Recognizing specific patterns of inflammation can suggest specific organisms, such as *Candida* or *Listeria*, that require special attention. Risk of recurrence is low for chorioamnionitis that develops outside of the context of cervical insufficiency. Most cases of chorioamnionitis develop due to ascending infection by cervicovaginal flora, but some may represent hematogenous seeding by oral flora.[14] Appropriate periodontal care can potentially decrease recurrence of the latter in subsequent pregnancies.

Villitis of unknown etiology (VUE) is widely believed to be a host-versus-graft response by the mother directed at fetal antigens in the villous stroma.[15] This break in fetomaternal tolerance depends on maternal-fetal traffic through defects in the trophoblastic barrier and is promoted by previous fetal antigen exposure (multiparity), degree of antigenic disparity (increased VUE in ovum donation pregnancies), and less specific conditions such as diabetes and obesity. It is largely restricted to the third trimester. A related lesion, chronic chorioamnionitis, recently has been associated with spontaneous preterm birth.[16] High-grade VUE (>10 contiguous villi) is associated with term and near-term FGR and, when complicated by inflammatory fetal vascular changes (obliterative fetal vasculopathy), is a major risk factor for CNS injury and stillbirth. VUE has a significant recurrence risk of 20% to 30%.

Distal villous maldevelopment is a more heterogeneous and less well understood category of placental pathology. Distinct patterns include diffuse distal villous hypoplasia, distal villous immaturity (decreased vasculosyncytial membranes), villous capillary proliferative lesions (chorangiosis/ chorangiomatosis), and dysmorphic villi (proximal-distal villous disproportion and abnormal villous contour).[17-20] Distal villous hypoplasia is characteristically associated with abnormal uterine artery Dopplers secondary to poor perfusion in villous vessels. The latter 3 processes can all occur independently, but in severe cases often overlap. They represent aberrant morphogenesis of the villous tree in response to environmental factors such as maternal glucose intolerance, smoking, anemia, pregnancy at high altitudes, and air pollution, or genetic/epigenetic abnormalities such as confined placental mosaicism, aneuploidy, or Beckwith-Wiedemann syndrome.

Maternal floor infarction (massive perivillous fibrinoid deposition) and ***chronic histiocytic intervillositis*** (massive chronic intervillositis) are extremely rare and poorly understood placental lesions that share 2 characteristics.[21-22] They are risk factors for virtually all adverse outcomes ranging from miscarriage to CNS injury, and they have recurrence risks approaching 50% to 75%, meaning that many affected women will never achieve a successful pregnancy. Immunologic, developmental, and genetic etiologies are under investigation with no clear conclusions at this time. Many therapeutic strategies have been proposed, including corticosteroids, aspirin, heparin, other immunosuppressive agents, intravenous immunoglobulin, and paternal leukocyte immunization. There are no controlled studies, but anecdotal evidence supports use of the first 3 agents.

Prolonged meconium exposure and ***increased circulating nucleated red blood cells (NRBCs)*** are not true placental lesions but a fetal response to placental hypoxia, independent of its cause. Meconium is released in up to 50% of term and post-term deliveries and does not require placental pathology for diagnosis. However, prolonged meconium exposure, as indicated by a large number of meconium-laden

macrophages in the chorionic plate and especially by meconium-associated medial necrosis of chorionic or umbilical vessels, is a recognized risk factor for CNS injury.[12,23] Increased NRBCs are detectable within fetal capillaries and can serve as a biomarker for significant fetal hypoxia of at least 6 to 12 hours.[24] A placental NRBC count >10 NRBC/10 high-power fields in a term placenta has been shown to correlate with a circulating NRBC count of >2500/mm^3 in the infant.

How can we improve the system?

Examination of all placentas by an expert placental pathologist would be ideal, but in this cost-conscious era, submission of placentas could be drastically curtailed if we fail to address current limitations. Progress is required on 2 fronts: Improving the body of evidence about placental pathology and addressing the lack of rigor in placental diagnosis and clinical interpretation while also avoiding oversimplification.

A general framework exists that relates placental lesions to pathophysiology and clinical outcomes, but continuing studies correlating placental phenotypes to specific clinical biomarkers and the underlying placental genome, epigenome, proteome, and interactome are essential. To increase rigor in diagnosis and interpretation, in my view, requires explicit recognition of the value of placental pathology by major professional organizations in obstetrics and gynecology.

Pathology practice will not improve without compelling clinical demand. Assuming that demand can be mustered, the most urgent priorities are establishment of: (1) a uniform system of nomenclature and criteria for the diagnosis and scaling of placental lesions; (2) practice guidelines for the structure of the clinical report; (3) benchmarks for turnaround time; and (4) continuing medical education, evaluation of competency, and appropriate referrals to ensure that placental pathology is diagnosed and interpreted by appropriately trained professionals. COG

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BY DAWN COLLINS, JD

Transfer of patient in active labor leads to death

Ignoring the Federal Emergency Treatment and Active Labor Act (EMTALA), an ED staff transfers a woman with preeclampsia who is in active labor.

Facts

A PREGNANT MICHIGAN WOMAN went to a hospital emergency department (ED) with signs and symptoms of severe preeclampsia, but was mistakenly diagnosed with pneumonia. No treatments for hypertension or seizure prevention were administered. The emergency physician contacted the woman's attending obstetrician, who was 45 miles away and refused to come to the hospital. The obstetrician wanted her admitted to the internal medicine service but the Internal Medicine service refused because it was determined that obstetric care was needed.

Unknown to the ED physician, the obstetrician then tried to transfer the woman to a maternal-fetal medicine (MFM) specialist at a tertiary care center. Transfer was refused because the patient was deemed too unstable and a cesarean delivery was recommended.

The ED physician could not get the obstetrician to come in or to arrange for another obstetrician to see the patient, so he decided to transfer the patient to another hospital roughly 50 miles away even though she was now in active labor. A different MFM specialist accepted transfer, and after 5 hours in the ED the patient was taken by ambulance to the other hospital.

During transport the patient suffered a placental abruption and hemorrhage and by the time she arrived at the receiving hospital, she was in critical condition. A cesarean delivery was immediately performed, but the woman died. The infant was born severely brain damaged and later died.

In the lawsuit that was filed on their behalf claiming negligence in the patient's treatment, it was alleged that both the mother and the baby would have survived with proper treatment.

The verdict

A $900,000 settlement was reached.

Analysis

The care of this patient in the ED in this case would be subject to the Federal Emergency Treatment and Active Labor Act (EMTALA), 42 US Code 1395dd. This statute should be well known to most EDs, physicians, and obstetricians and requires that any patient presenting to an ED with a request for examination or treatment for a medical condition must be provided an appropriate medical screening examination, including any ancillary services routinely available, to determine the presence of an emergency medical condition or active labor, regardless of the patient's ability to pay.

The statute is very specific in its definitions of medical screening and requirements for appropriate transfer.

In this case, the care at the original hospital is problematic for the defense for many reasons. The lawsuit claimed that the ED physician not only withheld critical

information from the transferring physician—including the patient's severe hypertension, proteinurea, and edema—but he also did not conduct an evaluation of the woman before departure and certified the transfer even though she was highly unstable and in active labor.

It is unlikely the care would meet the standard for the EMTALA statute, and therefore the hospital would be subject to fines as well as the malpractice case settlement.

Delay in diagnosis of ruptured uterus after prior cesarean

Facts

A 34-YEAR-OLD VIRGINIA WOMAN was scheduled for a repeat cesarean delivery, but went into labor 9 days early in 2010. Labor progressed quickly and she delivered vaginally with no complications. After the delivery the patient complained of sharp abdominal pain, which was rated as 10/10 and unrelieved by morphine. Moderate bleeding was noted. The obstetrician decided to perform a manual exploration and dilation and curettage procedure.

After the procedure, uterine scar rupture was ruled out and the patient was treated for uterine atony. No blood products were ordered and for 1.5 hours the woman was consistently hypotensive and tachycardic; the nurses noted moderate bleeding.

The obstetrician was kept informed of the patient's condition, including hemoglobin and hematocrit levels, which were lower than prior to delivery.

When the obstetrician came to the woman's bedside, the patient was becoming restless and short of breath. Within minutes of the physician's arrival she coded; she was resuscitated and blood transfusions were started.

A second obstetrician took over the woman's care and for the next 4 to 5 hours, she was monitored closely, receiving 7 units of packed red blood cells (RBCs) and 7 units of fresh frozen plasma. Her blood results revealed low hemoglobin and hematocrit values and her bleeding was noted as being "off and on."

The patient was ultimately taken to an operating room for a hysterectomy. She coded again and required resuscitation. By the time the operation was complete she had received a total of 14 units of packed RBCs and 14 units of fresh frozen plasma, along with other blood products. Her bleeding stopped after the hysterectomy, but she remained on a ventilator for 9 days, suffered renal failure and adrenal insufficiency, and her condition necessitated calling 2 additional codes while she was hospitalized.

The patient suffered brain damage and did not remember giving birth or the events thereafter. Her injuries required transfer to a rehabilitation facility to re-learn how to walk, talk, climb stairs, and write, and to regain her strength. She also suffered permanent kidney damage and underwent a kidney transplant from a cadaver donor approximately 1 year after the delivery.

She is expected to require at least 2 more kidney transplants in her life and will require care and medication to monitor her kidney function and possible rejection.

> "The defense argued . . . that the **conservative measures** were proper."

The woman sued those involved with the delivery and postpartum management, alleging that she had suffered a uterine scar rupture and the obstetrician was negligent in not diagnosing and treating it with a hysterectomy earlier.

The hysterectomy operative report noted a uterine scar "defect" from the prior cesarean section, and the patient argued that the medical records referred to a uterine scar "rupture" or "dehiscence" interchangeably as the source of the bleeding and hemorrhagic shock.

The defense argued that this injury was a prior uterine scar "dehiscence," not a complete rupture, and that the conservative measures were proper.

The verdict

A $4 million verdict was returned, which was reduced to $2 million under the state cap. COG

MS. COLLINS is an attorney specializing in medical malpractice in Long Beach, California. She welcomes feedback on this column via email to dawncfree@gmail.com.

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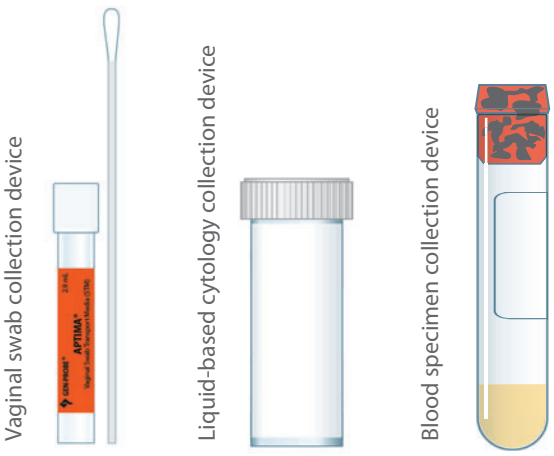

Acceptable specimens for other women's health-related tests

- **Cystic fibrosis carrier screening genetic test:** Blood or buccal swab
- ***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.

Note: A single collection device is not appropriate for processing a combination of tests that fall into multiple categories, such as genetic, bacterial, and molecular infectious disease.

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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 3 Summary of controlled studies on fetal loss rates in patients undergoing amniocentesis vs. no procedure

Ref, year	Study design	Primary indication for procedure	Definition of loss	AC (% loss)	No procedure (%)	Difference in loss rate (%)	Loss attributed to procedure (%)	*P* value
17, 1986	Randomized trial AC to no procedure	Low-risk women	Fetal loss >16 weeks	1.7	0.7	1.0 (1/100)	1.0 (1/100)	*P* <0.01
18, 1989	Non-randomized AC to no procedure	Unknowns	Not defined	2.2	0.8	1.4 (1/71)		*P* =0.14
19, 1998	Non-randomized AC to matched controls having no procedure	AMA	Fetal loss <28 weeks	1.8	1.4	0.4 (1/250)		ns
20, 2000	Retrospective study AC vs. no procedure	Low-risk women	Fetal loss <24 weeks	2.1	1.5	0.6 (1/167)	If no risk factors for loss, 0.03 (1/3333)	*P* <0.05 ns
21, 2006	Retrospective study of AC vs. no procedure	Abnormal screen	Fetal loss <24 weeks	1.0	0.9	0.1 (1/1,000)	0.06 (1/1667)	ns
23, 2008	Retrospective study AC vs. no procedure over time (1990-2006)	Unknown but AC group older	Fetal loss <24 weeks	0.97	0.84	0.13 (1/769)	0.13 (1/769)	*P* =0.18
24, 2007	Retrospective study AC vs. no procedure	Abnormal screen	Fetal loss <24 weeks	0.46	0.53	-0.7 (-1/142)		*P* =0.38
Total			**majority total losses <24 weeks**	**1.0 (394/39,065)**	**0.9 (852/98,439)**	**0.1 (1/1000)**		

Abbreviations: AC, amniocentesis; AMA, advanced maternal age

continued from **PAGE 26**

not undergoing invasive procedures.

While precise estimates are difficult, based on the more recent, albeit imperfect literature, the procedure-related loss rate following mid-trimester amniocentesis appears to be no higher than about 1/300-500 or even 1/1000 and may be even lower in experienced centers (Table 1).[25]

Q Besides fetal loss, what other complications and management concerns can occur after CVS?

A *Limb-reduction defects:* Historically, CVS was associated with an increased risk of limb-reduction defects, but this complication was limited to procedures performed before 10 weeks GA.[26-28] A World Health Organization review of more than 200,000 CVS procedures did not identify an increase in limb reduction defects following CVS.[29]

Current evidence suggests that performing CVS between 10 and 13 weeks does not increase the risk of limb reduction defects.[30]

Bleeding: Vaginal spotting may occur in up to one-third of women undergoing CVS. However, frank bleeding has been reported in less than 6%, and is more common after TC CVS than TA CVS.[10,12,31] A subchorionic hematoma may be seen on ultrasound exam following as many as 4% of TC

CVS procedures.[32]

Fetomaternal hemorrhage: Placental disruption from the CVS procedure may result in fetomaternal hemorrhage. The actual amount of bleeding is usually small relative to the total fetoplacental blood volume.[30] However, red blood cell and platelet alloimmunization may develop in susceptible pregnancies, and unsensitized Rh-negative women should receive anti-D immunoglobulin following CVS.[33-36] Amniocentesis is considered a better alternative for prenatal diagnosis in pregnancies at risk of alloimmunization because of the increased risk of inciting or worsening alloimmunization with CVS.[36]

Confined placental mosaicism (CPM): CPM is a condition in which more than one cell line is present in the placenta but not in the fetus. It is not a complication of CVS. CPM is reported to occur in 1% to 2% of CVS samples.[37] It is associated with increased risk of fetal growth restriction, and, depending on the chromosome involved, may confer increased risk of fetal abnormalities due to uniparental disomy.[37] If mosaicism is identified, amniocentesis is suggested to determine whether it is indeed confined to the placenta or culture results indicate an abnormal fetal karyotype.

Q Besides fetal loss, what other complications and management concerns can occur after amniocentesis?

Leakage of amniotic fluid: In 1.7% of pregnancies after amniocentesis compared with 0.4% of controls, leakage of amniotic fluid has been reported, although many practitioners would quote a lower figure.[17,39]

The leakage usually stops within 1 week, with normalization of amniotic fluid volume within 3 weeks.[40,41] Perinatal survival is reported in more than 90% of cases.[41]

Fetal injury and neonatal complications: Direct injury to the fetus is extremely rare. When amniocentesis was performed between 11 and 13 weeks in the Canadian Early and Mid-Trimester Amniocentesis Trial (CEMAT), higher rates of talipes equinovarus, amniotic-fluid leakage, and fetal loss were observed, compared with mid-trimester amniocentesis.[42]

Based on these risks, early amniocentesis–prior to 15 weeks—is neither recommended nor indicated.[25]

Q What are the risks of transmission of hepatitis and HIV following CVS or amniocentesis?

Limited information is available regarding the risk of transmission of HIV, hepatitis B (HBV), and hepatitis C (HCV) with invasive procedures, with only observational data available for amniocentesis.[43] Among 4 series that included 125 HBV-infected pregnancies, there were 6 cases of HBV transmission (4%).[44,47]

Ko et al found that transmission was non-significantly increased in women who were HBeAg-positive (30% vs. 14%).[44]

The risk of transmission of HCV is similarly unknown.[45] In one series of 10 pregnancies with infant follow-up, there were no cases of HCV transmission after mid-trimester amniocentesis.[48]

Somewhat more information is available about HIV transmission rates. The rate of vertical HIV transmission following amniocentesis appears to be lowest in those receiving highly active antiretroviral therapy (HAART).

Of 166 pregnancies followed through the French Perinatal Cohort, there were no cases of mother-to-child transmission in 81 women receiving HAART at time of amniocentesis.[49] However, vertical transmission tended to be higher in the amniocentesis group among women not receiving antiretroviral therapy (25% vs. 16%), as well as in women receiving zidovudine monotherapy or a double-nucleoside reverse transcriptase inhibitor combination (6.1% vs. 3.3%).

No cases of mother-to-child transmission following amniocentesis were reported in women receiving HAART in other recent series that included 78 women.[50-53]

Counseling for pregnant women with HIV who are considering amniocentesis should include the potential for a small increased risk of transmission, as this cannot be excluded.[53] If an amniocentesis is anticipated, it is best to first try to achieve viral suppression with HAART. An amniocentesis procedure performed in an HIV-infected pregnancy should be done only if the patient is on HAART, and preferably when the viral load is undetectable.[54,55]

Data are not available for transmission risk associated with CVS procedures, but amniocentesis is preferred because of the lower theoretical risk of all viral transmission. COG

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This opinion was developed by the Publications Committee of the Society for Maternal-Fetal Medicine with the assistance of Joanne Stone, MD, and was approved by the Executive Committee of the Society. Neither Dr. Stone nor any member of the Publications Committee (see the list of 2014 members at www.smfm.org) has a conflict of interest to disclose with regard to the content of this article.

To view the references for this article, visit contemporaryobgyn.net/February2014SMFM.

Committee on Practice Bulletins—Gynecology
ACOG Practice Bulletin Number 135: *Second-Trimester Abortion,* June 2013. *Obstet Gynecol.* 2013;121:1394-1406. Full text of ACOG Practice Bulletin is available to ACOG members at http://www.acog.org/Resources_And_Publications/Practice_Bulletins/Committee_on Practice_Bulletins_--_Gynecology/Second-Trimester_Abortion.

Second-Trimester Abortion

In the United States, more than one half of pregnancies are unintended, with 3 in 10 women having an abortion by age 45 years (1). In 2008, 1.2 million abortions occurred in the United States, of which 6.2% took place between 13 weeks of gestation and 15 weeks of gestation, and 4.0% took place at 16 weeks of gestation or later (2,3). Only 1.3% of abortions are performed at 21 weeks of gestation or later (4). The proportion of abortions performed in the second trimester, usually defined as between 13 weeks of gestation and 26 weeks of gestation (as calculated from the last menstrual period), has remained stable during the past two decades (4). The purpose of this document is to provide evidence-based guidelines for the medical and surgical methods of second-trimester termination as well as for the management of associated complications.

COMMENTARY

Considering the Options for Second-Trimester Termination

By **Sharon T. Phelan, MD**
Dr. Phelan is Professor, Department of Obstetrics and Gynecology, University of New Mexico, Albuquerque, and a member of the *Contemporary OB/GYN* Editorial Board.

The American College of Obstetricians and Gynecologists (ACOG) recently published a Practice Bulletin regarding second-trimester abortions.[1] In 2010, 765,651 legal induced abortions were reported to the CDC from 49 reporting areas. That is an abortion ratio of 228 abortions to 1,000 live births.[2] Since the 1980s, the number of abortions has steadily decreased.[3] Of them, only about 10% occur after 12 weeks' gestation, with fewer than 4% at 16 weeks or greater.[2]

With the advent of increasing antenatal diagnosis using ultrasound and maternal serum rather than amniocentesis, the number of women/couples confronted with unanticipated problems in the second trimester is likely to increase. Because it is standard practice to offer prenatal diagnosis to all patients, obstetricians need to ensure that all management options for pregnancy are available, including continuation of the gestation and termination. Some new developments in testing allow identification of selected genetic issues in the late first trimester but many are still dependent on confirmatory testing at 15 to 20 weeks.

Of course, there are other scenarios in which the decision to terminate a pregnancy is delayed, such as in the case of a teen who hides her pregnancy, a woman who is the victim of intimate partner violence, or a woman with a serious medical condition that worsens with pregnancy. Economic barriers and logistical problems such as difficulty locating a nearby provider may also delay pregnancy termination.[4] Even obesity can contribute to delayed pregnancy awareness because it is associated with irregular menses and other comorbidities.

Ob/gyns, therefore, should be knowledgeable about options for second-trimester termination and if not skilled in the techniques, have identified a provider in the community who is skilled and can provide the service to patients. In the latter case, a timely referral is important to minimize complications. The current ACOG bulletin provides information for patient counseling regarding the techniques as well as evidence-based considerations for physicians.

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> **Ob/gyns need to be careful** that their counseling . . . is balanced and non-directive.

In the past, pregnancy terminations after 16 to 18 weeks were typically medical and the patients were "induced." That necessitated subjecting a woman to labor, but if she desired allowed her to hold her fetus, have "memory" items made, and have a more detailed evaluation of anomalies done in anticipation of future pregnancies. Currently the more common termination option is a dilation and evacuation (D&E), which appears safer than induction in skilled hands. It is more frequently chosen by women when given the choice. It also often may not allow for the mother to hold the fetus or for an autopsy/anatomic evaluation if one is desired or indicated.

Patients need to be aware of both medical and surgical approaches once they make the difficult choice to terminate in the second trimester. Ob/gyns need to be careful that their counseling about the technique is balanced and non-directive.

Determining a woman's needs and desires also is important. If an autopsy or holding the baby is important to a patient, then a medical abortion may be more appropriate. If the woman has medical issues (eg, pulmonary hypertension) or marked anxiety or prefers a procedure to induction, a surgical procedure may be best. If the procedure is to be done in a hospital setting, a discussion of any facility-required policies may be important in the decision-making.

Once a patient understands each procedure and the pros and cons, she needs to decide on the approach that is best for her.

Despite the fact that, overall, a second-trimester termination is safer for a woman than continuing a pregnancy to term, there are greater risks with second-trimester than with first-trimester terminations. That is due, in part, to the indication for the termination (eg, significant maternal disease).

As with any delivery, complications also are possible, such as retained products of conception, uterine rupture/perforation, hemorrhage, infection, and even the rare amniotic fluid emboli. Ob/gyns need to be aware of these possibilities and prepare to treat them if they do occur.

One aspect of second-trimester termination that is not covered in the PB is grief counseling. As previously mentioned, many couples or women seeking such procedures are confronted by unanticipated complications in an otherwise desired pregnancy. The decision to terminate is often a very difficult one.

Regardless of the indications for termination, patients may grieve after it just as do individuals or couples faced with a stillbirth or miscarriage. The ob/gyn needs to acknowledge the termination as a choice between difficult options that could include fetal or neonatal demise, maternal death or morbidity, or a potentially short life for a newborn filled with painful treatments and procedures. Thus, these patients, just like any obstetric patients, should be offered post-termination counseling and followed closely for postpartum depression.

In short, this ACOG bulletin has the information that providers need to counsel more effectively about second-trimester abortion and to understand the procedures and options more clearly. It also outlines the risks and management of complications of these procedures. COG

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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

24-26: North American Society for Pediatric and Adolescent Gynecology Annual Clinical and Research Meeting
Philadelphia, Pennsylvania
http://naspag.org/index.php/pagecourses

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
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WOMEN'S HEALTH AND THE ACA

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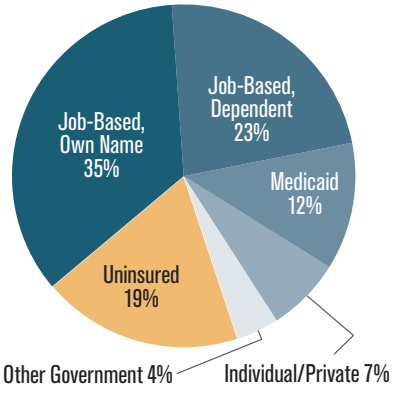
Women's Health Insurance Coverage, 2012



Total = 98.4 Million Women Ages 18 to 64

The Kaiser Family Foundation Women's Health Insurance Coverage. Nov 06, 2013. Data Source: Kaiser Family Foundation and Urban Institute analysis of March 2013 Current Population Survey, U.S. Bureau of the Census. http://kff.org/womens-health-policy/fact-sheet/womens-health-insurance-coverage-fact-sheet/

1.1 million

women between ages **19 and 25** who would have been uninsured have coverage under their parents' employer-sponsored or individually purchased health insurance plan.

24.7 million

women enrolled in **Medicare** received preventive services without cost-sharing in 2011, including an annual wellness visit, a personalized prevention plan, mammograms, and bone mass measurement for women at risk of osteoporosis.

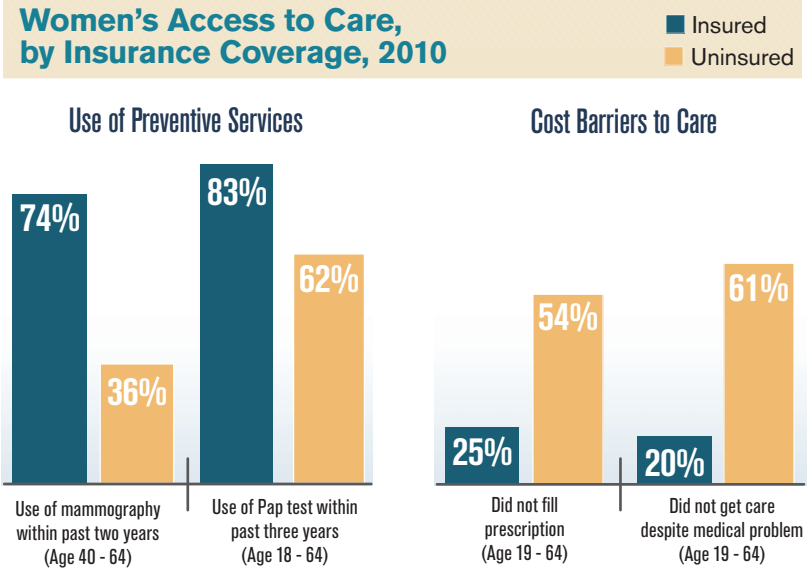
26.9 million

women with **private health insurance** gained expanded preventive services with no cost-sharing in 2011 and 2012, including mammograms, cervical cancer screenings, prenatal care, flu and pneumonia shots, and regular well-baby and well-child visits.

18.6 million

uninsured women will have opportunities for coverage through the Health Insurance Marketplace.

Women's Access to Care, by Insurance Coverage, 2010



The Kaiser Family Foundation Women's Health Insurance Coverage. Nov 06, 2013. Data Source: Kaiser National Center for Health Statistics, National Health Interview Survey in Health, United States 2012. The Commonwealth Fund Biennial Health Insurance Survey, 2010. http://kff.org/womens-health-policy/fact-sheet/womens-health-insurance-coverage-fact-sheet/

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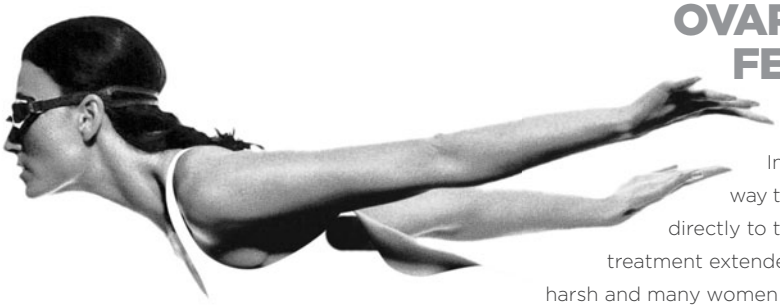

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