POLICY & PRACTICE

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College Offers Advertising Advice

It is ethical for physicians to advertise their services, but they must be careful not to mislead the public or imply a lack of competence by their competition, according to an updated policy statement from the American College of Obstetricians and Gynecologists. It advises physicians to use caution when putting together advertisements because the public can easily be mislead. For example, potential patients might assume that any obstetrician advertising under the heading "infertility" has special training or certification in that area. Physicians should also be able to substantiate their claims if they use words like "top" or "pioneer." If a physician is voted a "top doctor" by magazine readers, that fact can be advertised. But if that designation was paid for, that must be disclosed in the ad as well, according to the ACOG policy. Also, doctors should shy away from advertising specific outcomes since treatment success often depends on patient factors. The policy, developed by the ACOG Committee of Ethics, was scheduled to be published in the November issue of Obstetrics and Gynecology.

Public Citizen Attacks Liability Caps

The medical liability reform law enacted in Texas in 2003 has failed to bring down medical costs or attract physicians to the state, according to an analysis by Public Citizen. The consumer-watchdog group said the law, which includes a $250,000 cap on noneconomic damages, benefited malpractice insurance companies and physicians, who saw premiums and payouts decrease, but not the public. The report notes that Medicare spending per beneficiary in Texas has risen 13% faster than the national average and that diagnostic-testing expenses rose 25% more than the national average. Meanwhile, the increase in physicians per capita has slowed to less than half its rate in the years before the law was enacted. But Texas Medical Association President Dr. C. Bruce Malone said in an interview that the state has not boosted its physician population much because it's difficult to attract doctors to a poor state with a large population of uninsured people. Dr. Malone also said that liability reform has improved patients' access to care, especially in obstetrics. There are now many rural areas that have ob.gyns. for the first time, and more obstetricians are willing to take on high-risk pregnancies, he said.

Defending Planned Parenthood

House Democrats are standing up for Planned Parenthood, saying that the organization is being unfairly targeted for political reasons. In September, the Republican-controlled House Energy and Commerce subcommittee on oversight and investigations launched an inquiry into how the Planned Parenthood Federation and its affiliates handle federal funds. In a letter to the subcommittee's chairman, Rep. Cliff Stearns (R.-Fla.), top Democrats on the full committee criticized the investigation as an "unfair and unjustified assault." Rep. Henry Waxman (D.-Calif.) and Rep. Diana DeGette (D.-Colo.) wrote that the investigation was unnecessary because the Health and Human Services Inspector General and state Medicaid programs routinely audit Planned Parenthood and report their findings to the public.

Millions Get Free Mammograms

More than 4 million women have received free mammograms this year as a benefit from the Affordable Care Act. The 2010 health-reform law allows Medicare beneficiaries to receive preventive services, including mammograms and cervical cancer screening, without paying a deductible or other cost. The benefit also includes a free annual wellness visit. The Department of Health

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and Human Services estimated that more than 20 million Medicare beneficiaries have received some type of preventive service this year, from cholesterol screening to bone-mass measurement.

Baby-Friendly Hospitals Sought

Officials at the Centers for Disease Control and Prevention are spending $6 million over 3 years to help hospitals do a better job of supporting breastfeeding by new mothers. The goal is to get more U.S. hospitals to become "baby-friendly" facilities along the lines of a World Health Organization–UNICEF program that recognizes hospitals that follow science-based practices that increase breastfeeding rates. Currently, only about 5% of babies in the United States are born in "baby-friendly" hospitals, according to the CDC. The agency awarded its $6 million to the National Initiative for Children's Healthcare Quality, which will work with hospitals to bring in experts in breastfeeding and quality improvement to develop system-level changes.

Panel: Patients' Needs Overlooked

Even though most doctors realize that improving patient engagement can reduce costs and improve care, physicians still frequently overlook patients' needs and concerns, according to a report from the Institute of Medicine. For example, studies show that quality improves when providers listen carefully to patients and their families, according to the report based on an April workshop. However, other research has shown that physicians typically interrupt within 15 seconds of a patient beginning to raise concerns.

–Mary Ellen Schneider

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 estrogen therapy on blood pressure was not seen.

Hypertriglyceridemia
In patients with pre-existing hypertriglyceridemia, estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis. Consider discontinuation of treatment if pancreatitis occurs.

Hepatic Impairment and/or Past History of Cholestatic Jaundice
Estrogens may be poorly metabolized in women with impaired liver function. For women with a history of cholestatic jaundice associated with past estrogen use or with pregnancy, caution should be exercised, and in the case of recurrence, medication should be discontinued.

Hypothyroidism
Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Women with normal thyroid function can compensate for the increased TBG by making more thyroid hormone, thus maintaining free T_4 and T_3 serum concentrations in the normal range. Women dependent on thyroid hormone replacement therapy who are also receiving estrogens may require increased doses of their thyroid replacement therapy. These women should have their thyroid function monitored in order to maintain their free thyroid hormone levels in an acceptable range.

Fluid Retention
Estrogens may cause some degree of fluid retention. Patients with conditions that might be influenced by this factor, such as cardiac or renal dysfunction, warrant careful observation when estrogens are prescribed.

Hypocalcemia
Estrogens should be used with caution in individuals 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.

Angioedema
Exogenous estrogens may induce or exacerbate symptoms of angioedema, particularly 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.

Effects on Barrier Contraception
PREMARIN Vaginal Cream exposure has been reported to weaken latex condoms. The potential for PREMARIN Vaginal Cream to weaken and contribute to the failure of condoms, diaphragms, or cervical caps made of latex or rubber should be considered.

Laboratory Tests
Serum follicle stimulating hormone and estradiol levels have not been shown to be useful in the management of moderate to severe symptoms of vulvar and vaginal atrophy.

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

Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T_4 levels (by column or by radioimmunoassay) or T_3 levels by radioimmunoassay. T_3 resin uptake is decreased, reflecting the elevated TBG. Free T_4 and free T_3 concentrations are unaltered. Women on thyroid replacement therapy may require higher doses of thyroid hormone.

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

Increased plasma HDL and HDL_2 cholesterol subfraction concentrations, reduced LDL cholesterol concentrations, increased triglyceride levels.

Impaired glucose tolerance.

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

- Cardiovascular Disorders *[see Boxed Warning, Warnings and Precautions (5.2)]*
- Endometrial Cancer *[see Boxed Warning, Warnings and Precautions (5.3)]*

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

In a 12-week, randomized, double-blind, placebo-controlled trial of PREMARIN Vaginal Cream (PVC), a total of 423 postmenopausal women received at least 1 dose of study medication and were included in all safety analyses: 143 women in the PVC-21/7 treatment group (0.5 g PVC daily for 21 days, then 7 days off), 72 women in the matching placebo treatment group; 140 women in the PVC-2x/wk treatment group (0.5 g PVC twice weekly), 68 women in the matching placebo treatment group. A 40-week, open-label extension followed, in which a total of 394 women received treatment with PVC, including those subjects randomized at baseline to placebo. In this study, the most common adverse reactions ≥ 5 percent are shown below (Table 1) *[see Clinical Studies (14.1)* ***in full prescribing information****]*.

Table 1: Number (%) of Patients Reporting Treatment Emergent Adverse Events ≥ 5 Percent Only

	Treatment			
Body System[a] Adverse Event	PVC 21/7 (n=143)	Placebo 21/7 (n=72)	PVC 2x/wk (n=140)	Placebo 2x/wk (n=68)
	Number (%) of Patients with Adverse Event			
Any Adverse Event	95 (66.4)	45 (62.5)	97 (69.3)	46 (67.6)
Body As A Whole				
Abdominal Pain	11 (7.7)	2 (2.8)	9 (6.4)	6 (8.8)
Accidental Injury	4 (2.8)	5 (6.9)	9 (6.4)	3 (4.4)
Asthenia	8 (5.6)	0	2 (1.4)	1 (1.5)
Back Pain	7 (4.9)	3 (4.2)	13 (9.3)	5 (7.4)
Headache	16 (11.2)	9 (12.5)	25 (17.9)	12 (17.6)
Infection	7 (4.9)	5 (6.9)	16 (11.4)	5 (7.4)
Pain	10 (7.0)	3 (4.2)	4 (2.9)	4 (5.9)
Cardiovascular System				
Vasodilatation	5 (3.5)	4 (5.6)	7 (5.0)	1 (1.5)
Digestive System				
Diarrhea	4 (2.8)	2 (2.8)	10 (7.1)	1 (1.5)
Nausea	5 (3.5)	4 (5.6)	3 (2.1)	3 (4.4)
Musculoskeletal System				
Arthralgia	5 (3.5)	5 (6.9)	6 (4.3)	4 (5.9)
Nervous System				
Insomnia	6 (4.2)	3 (4.2)	4 (2.9)	4 (5.9)
Respiratory System				
Cough Increased	0	1 (1.4)	7 (5.0)	3 (4.4)
Pharyngitis	3 (2.1)	2 (2.8)	7 (5.0)	3 (4.4)
Sinusitis	1 (0.7)	3 (4.2)	2 (1.4)	4 (5.9)
Skin And Appendages	12 (8.4)	7 (9.7)	16 (11.4)	3 (4.4)
Urogenital System				
Breast Pain	8 (5.6)	1 (1.4)	4 (2.9)	0
Leukorrhea	3 (2.1)	2 (2.8)	4 (2.9)	6 (8.8)
Vaginitis	8 (5.6)	3 (4.2)	7 (5.0)	3 (4.4)

[a] Body system totals are not necessarily the sum of the individual adverse events, since a patient may report two or more different adverse events in the same body system.

Postmarketing Experience
The following adverse reactions have been reported with PREMARIN Vaginal Cream. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Genitourinary System
Abnormal uterine bleeding/spotting, dysmenorrhea/pelvic pain, increase in size of uterine leiomyomata, vaginitis (including vaginal candidiasis), change in cervical secretion, cystitis-like syndrome, application site reactions of vulvovaginal discomfort, (including burning, irritation, and genital pruritus), endometrial hyperplasia, endometrial cancer, precocious puberty, leukorrhea.

Breasts
Tenderness, enlargement, pain, discharge, fibrocystic breast changes, breast cancer, gynecomastia in males.

Cardiovascular
Deep venous thrombosis, pulmonary embolism, myocardial infarction, stroke, increase in blood pressure.

Gastrointestinal
Nausea, vomiting, abdominal cramps, bloating, increased incidence of gallbladder disease.

Skin
Chloasma that may persist when drug is discontinued, loss of scalp hair, hirsutism, rash.

Eyes
Retinal vascular thrombosis, intolerance to contact lenses.

Central Nervous System
Headache, migraine, dizziness, mental depression, nervousness, mood disturbances, irritability, dementia.

Miscellaneous
Increase or decrease in weight, glucose intolerance, edema, arthralgias, leg cramps, changes in libido, urticaria, anaphylactic reactions, exacerbation of asthma, increased triglycerides, hypersensitivity.

Additional postmarketing adverse reactions have been reported in patients receiving other forms of hormone therapy.

DRUG INTERACTIONS
No formal drug interaction studies have been conducted for PREMARIN Vaginal Cream.

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 may result in side effects.

USE IN SPECIFIC POPULATIONS

Pregnancy
PREMARIN Vaginal Cream 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
PREMARIN Vaginal Cream should not be used during lactation. Estrogen administration to nursing mothers 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 mothers receiving estrogens. Caution should be exercised when PREMARIN Vaginal Cream is administered to a nursing woman.

Pediatric Use
PREMARIN Vaginal Cream 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 clinical studies utilizing PREMARIN Vaginal Cream to determine whether those over 65 years of age differ from younger subjects in their response to PREMARIN Vaginal Cream.

The Women's Health Initiative Study
In the Women's Health Initiative (WHI) estrogen-alone substudy (daily conjugated estrogens 0.625 mg versus placebo), there was a higher relative risk of stroke in women greater than 65 years of age *[see Clinical Studies (14.2)* ***in full prescribing information****]*.

In the WHI estrogen plus progestin substudy, there was a higher relative risk of nonfatal stroke and invasive breast cancer in women greater than 65 years of age *[see Clinical Studies (14.2)* ***in full prescribing information****]*.

The Women's Health Initiative Memory Study
In the Women's Health Initiative Memory Study (WHIMS) 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 *[see Clinical Studies (14.3)* ***in full prescribing information****]*.

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] *[see Clinical Studies (14.3)* ***in full prescribing information****]*.

Renal Impairment
The effect of renal impairment on the pharmacokinetics of PREMARIN Vaginal Cream has not been studied.

Hepatic Impairment
The effect of hepatic impairment on the pharmacokinetics of PREMARIN Vaginal Cream has not been studied.

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

This brief summary is based on PREMARIN Vaginal Cream Prescribing Information W10413C022 ET01, Rev 05/10.

Pfizer