

# Rising GD Incidence Calls for Aggressive Screening

BY BETSY BATES  
Los Angeles Bureau

SAN FRANCISCO — The “fast and furious” increase in obesity in the United States and a correlative rise in the incidence of gestational diabetes justify aggressive screening of pregnant women for the disorder, Dr. E. Albert Reece said at Perspectives in Women’s Health sponsored by OB.GYN. NEWS.

“The numbers are quite staggering,”

said Dr. Reece, dean of the school of medicine and vice president of medical affairs at the University of Maryland, Baltimore.

Fifteen years ago, the incidence of gestational diabetes was 1%-3%. Today, it’s 4%-8%, he said.

Screening is aimed at reducing the risk of perinatal loss, but it also confers what Dr. Reece termed “fringe benefits,” namely, reducing the risk of fetal macrosomia, operative delivery, birth trauma, and

metabolic derangements in the neonate.

Screening raises awareness of the long-term possibility of type II diabetes arising in the mother and, years later, the offspring.

“Diabetes begets diabetes,” said Dr. Reece, who advocates screening every pregnant woman for gestational diabetes at least once during pregnancy.

The tradition of screening at 24-28 weeks’ gestation is “entirely arbitrary”—chosen by convention to pick up 85% of

cases while there is still time in the pregnancy to intervene.

However, clinicians should be aware that 15% of cases will be missed by screening at that time point.

“If you are very suspicious, due to habitus or history, repeat it at 33-34 weeks,” he advised.

Choosing which test to use can be important, according to Dr. Reece.

Intravenous glucose tolerance testing is nonphysiologic, failing to simulate the

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### ESTROGENS INCREASE THE RISK OF ENDOMETRIAL CANCER

Close clinical surveillance of all women taking estrogens is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal 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. (See **WARNINGS, Malignant neoplasms, Endometrial cancer**.)

### CARDIOVASCULAR AND OTHER RISKS

Estrogens with or without progestins should not be used for the prevention of cardiovascular disease or dementia. (See **WARNINGS, Cardiovascular disorders and Dementia**.)

The estrogen-alone substudy of the Women’s Health Initiative (WHI) reported increased risks of stroke and deep vein thrombosis (DVT) in postmenopausal women (50 to 79 years of age) during 6.8 years of treatment with oral conjugated estrogens (CE 0.625 mg) per day relative to placebo. (See **CLINICAL STUDIES** in full Prescribing Information and **WARNINGS, Cardiovascular disorders**.)

The estrogen-plus-progestin substudy of the WHI reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis in postmenopausal women (50 to 79 years of age) during five years of treatment with oral conjugated estrogens (CE 0.625 mg) combined with medroxyprogesterone acetate (MPA 2.5 mg) per day relative to placebo. (See **CLINICAL STUDIES** in full Prescribing Information and **WARNINGS, Cardiovascular disorders and Malignant neoplasms, Breast cancer**.)

The Women’s Health Initiative Memory Study (WHIMS), a substudy 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 CE 0.625 mg alone and during four years of treatment with CE 0.625 mg combined with MPA 2.5 mg, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women. (See **CLINICAL STUDIES** in full Prescribing Information and **WARNINGS, Dementia and PRECAUTIONS, Geriatric Use**.)

Other doses of conjugated estrogens and medroxyprogesterone acetate, and other combinations and dosage forms of estrogens and progestins, were not studied in the WHI clinical trials, and in the absence of comparable data, these risks should be assumed to be similar. Because of these risks, 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

Premarin therapy is indicated in the:

- Treatment of moderate to severe vasomotor symptoms associated with the menopause.
  - Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered.
  - Treatment of hypoestrogenism due to hypogonadism, castration or primary ovarian failure.
  - Treatment of breast cancer (for palliation only) in appropriately selected women and men with metastatic disease.
  - Treatment of advanced androgen-dependent carcinoma of the prostate (for palliation only).
  - 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 for whom non-estrogen medications are not considered to be appropriate. (See **CLINICAL STUDIES** in full Prescribing Information.)
- The mainstays for decreasing the risk of postmenopausal osteoporosis are weight-bearing exercise, adequate calcium and vitamin D intake, and when indicated, pharmacologic therapy. Postmenopausal women require an average of 1500 mg/day of elemental calcium. Therefore, when not contraindicated, calcium supplementation may be helpful for women with suboptimal dietary intake. Vitamin D supplementation of 400-800 IU/day may also be required to ensure adequate daily intake in postmenopausal women.

### CONTRAINDICATIONS

Estrogens should not be used in individuals with any of the following conditions:

- Undiagnosed abnormal genital bleeding.
- Known, suspected, or history of cancer of the breast except in appropriately selected patients being treated for metastatic disease.
- Known or suspected estrogen-dependent neoplasia.
- Active deep vein thrombosis, pulmonary embolism or a history of these conditions.
- Active or recent (e.g., within past year) arterial thromboembolic disease (e.g., stroke, myocardial infarction).
- Liver dysfunction or disease.
- Premarin tablets should not be used in patients with known hypersensitivity to their ingredients.
- Known or suspected pregnancy. There is no indication for Premarin in pregnancy. There appears to be little or no increased risk of birth defects in children born to women who have used estrogen and progestins from oral contraceptives inadvertently during pregnancy. (See **PRECAUTIONS**.)

### WARNINGS

#### See **BOXED WARNINGS**.

#### 1. Cardiovascular disorders

Estrogen and estrogen-plus-progestin therapy have been associated with an increased risk of cardiovascular events such as myocardial infarction and stroke, as well as venous thrombosis and pulmonary embolism (venous thromboembolism or VTE). Should any of these occur or be suspected, estrogens should be discontinued immediately. Risk factors for arterial vascular disease (e.g., hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and obesity) and/or venous thromboembolism (e.g., personal history or family history of VTE, obesity, and systemic lupus erythematosus) should be managed appropriately.

#### a. Stroke and coronary heart disease

In the estrogen-alone substudy of the Women’s Health Initiative (WHI) study, a statistically significant increased risk of stroke was reported in women receiving CE 0.625 mg daily compared to women receiving placebo (44 vs. 32 per 10,000 women-years). The increase in risk was demonstrated in year one and persisted. (See **CLINICAL STUDIES** in full Prescribing Information.)

Also, in the estrogen-alone substudy of WHI, no overall effect on coronary heart disease (CHD) events (defined as non-fatal MI, silent MI, or death, due to CHD) was reported in women receiving estrogen alone compared to placebo. (See **CLINICAL STUDIES** in full Prescribing Information.)

In the estrogen-plus-progestin substudy of WHI, a statistically significant increased risk of stroke was reported in women receiving CE/MPA 0.625 mg/2.5 mg daily compared to women receiving placebo (31 vs. 24 per 10,000 women-years). The increase in risk was demonstrated after the first year and persisted.

Also, in the estrogen-plus-progestin substudy of WHI, no statistically significant increase of CHD events was reported in women receiving CE/MPA compared to women receiving placebo (39 v. 33 per 10,000 women-years). An increase in relative risk was demonstrated in year one, and a trend toward decreasing relative risk was reported in year 2 through 5. In postmenopausal women with documented heart disease (n=2,763, average age 66.7 years) a controlled clinical trial of secondary prevention of cardiovascular disease (Heart and Estrogen/progestin Replacement Study; HERS) treatment with CE/MPA 0.625 mg conjugated estrogens/2.5 mg medroxyprogesterone acetate daily demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with CE/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/MPA-treated group than in the placebo group in year one, but not during the subsequent years. Two thousand three hundred and twenty-one 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/MPA group and the placebo group in the HERS, the HERS II, and overall. Large doses of estrogen (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast, have been shown in a large prospective clinical trial in men to increase the risk of nonfatal myocardial infarction, pulmonary embolism, and thrombophlebitis.

#### b. Venous thromboembolism (VTE)

In the estrogen-alone substudy of WHI, the risk of VTE (DVT and pulmonary embolism [PE]) was reported to be increased for women taking conjugated estrogens (28 vs. 21 per 10,000 women-years), although only the increased risk of DVT reached statistical significance (21 vs. 15 per 10,000 women-years). The increase in VTE risk was demonstrated during the first year. (See **CLINICAL STUDIES** in full Prescribing Information.)

In the estrogen-plus-progestin substudy of WHI, a statistically significant 2-fold greater rate of VTE was reported in women receiving CE/MPA compared to women receiving placebo (35 vs. 17 per 10,000 women-years). Statistically significant increases in risk for both DVT (26 vs. 13 per 10,000 women-years) and PE (18 vs. 8 per 10,000 women-years) were also demonstrated. The increase in VTE risk was demonstrated during the first year and persisted. 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.

#### 2. Malignant neoplasms

##### a. Endometrial cancer

The use of unopposed estrogens in women with intact uterus has been associated with an increased risk of endometrial cancer. The reported endometrial cancer risk among unopposed estrogen users with an intact uterus is about 2- to 12-fold 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 one year. The greatest risk appears associated with prolonged use, with increased risks of 15- to 24-fold for five to ten 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 taking estrogen-plus-progestin combinations is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal 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.

##### b. Breast cancer

In some studies, the use of estrogens and progestins by postmenopausal women has been reported to increase the risk of breast cancer. The most important randomized clinical trial providing information about this issue is the Women’s Health Initiative (WHI). (See **CLINICAL STUDIES** in full Prescribing Information.) The results from observational studies are generally consistent with those of the WHI clinical trial.

Observational studies have also reported an increased risk of breast cancer for estrogen-plus-progestin combination therapy, and a smaller increased risk for estrogen-alone therapy, after several years of use. For both findings, the excess risk increased with duration of use, and appeared to return to baseline over about five years after stopping treatment (only the observational studies have substantial data on risk after stopping). In these studies, the risk of breast cancer was greater, and became apparent earlier, with estrogen-plus-progestin combination therapy as compared to estrogen-alone therapy. However, these studies have not found significant variation in the risk of breast cancer among different estrogens or among different estrogen-plus-progestin combinations, doses, or routes of administration.

In the estrogen-alone substudy of WHI, after an average of 6.8 years of follow-up, CE (0.625 mg daily) was not associated with an increased risk of invasive breast cancer (RR 0.77, 95% nCI 0.59-1.01).

In the estrogen-plus-progestin substudy, after a mean follow-up of 5.6 years, the WHI substudy reported an increased risk of breast cancer. Prior use of estrogen alone or estrogen-plus-progestin combination hormone therapy was reported by 26% of the women. The relative risk of invasive breast cancer was 1.24 (95% nCI 1.01-1.54), and the absolute risk was 41 vs. 33 cases per 10,000 women-years, for estrogen-plus-progestin compared with placebo, respectively. 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 vs. 25 cases per 10,000 women-years, for estrogen-plus-progestin 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 vs. 36 cases per 10,000 women-years for estrogen plus progestin compared with placebo. In the WHI trial, invasive breast cancers were larger and diagnosed at a more advanced stage in the estrogen-plus-progestin 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. The use of 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.

#### 3. Dementia

In the estrogen-alone Women’s Health Initiative Memory Study (WHIMS), a substudy of WHI, a population of 2,947 hysterectomized women aged 65 to 79 years was randomized to CE (0.625 mg daily) or placebo. In the estrogen-plus-progestin WHIMS substudy, a population of 4,532 postmenopausal women aged 65 to 79 years was randomized to CE/MPA (0.625 mg/2.5 mg daily) or placebo.

In the estrogen-alone substudy, 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 was 1.49 (95% nCI 0.83-2.66). The absolute risk of probable dementia for CE alone was 37 vs. 25 cases per 10,000 women-years.

In the estrogen-plus-progestin substudy, after an average follow-up of four years, 40 women in the estrogen-plus-progestin group and 21 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for estrogen plus progestin vs. placebo was 2.05 (95% nCI 1.21-3.48). The absolute risk of probable dementia for CE/MPA vs. placebo was 45 vs. 22 cases per 10,000 women-years.

When data from the two populations were pooled as planned in the WHIMS protocol, the reported overall relative risk for probable dementia was 1.76 (95% nCI 1.19-2.60). Since both substudies were conducted in women aged 65 to 79 years, it is unknown whether these findings apply to younger postmenopausal women. (See **BOXED WARNINGS and PRECAUTIONS, Geriatric Use**.)

#### 4. Gallbladder Disease

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

#### 5. Hypercalcemia

Estrogen administration may lead to severe hypercalcemia in patients 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.

#### 6. Visual abnormalities

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

### PRECAUTIONS

#### A. General

##### 1. 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: a possible increased risk

of breast cancer; adverse effects on lipoprotein metabolism (e.g., lowering HDL, raising LDL) and impairment of glucose tolerance.

#### 2. Elevated blood pressure

In a small number of case reports, substantial increases in blood pressure have been attributed to idiosyncratic reactions to estrogens. In a large, randomized, placebo-controlled clinical trial, a generalized effect of estrogen therapy on blood pressure was not seen. Blood pressure should be monitored at regular intervals during estrogen use.

#### 3. Hypertriglyceridemia

In patients with pre-existing hypertriglyceridemia, estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis and other complications. In the HERS study, the mean percent increase from baseline in serum triglycerides after one year of treatment with Premarin 0.625 mg, 0.45 mg, and 0.3 mg compared with placebo were 34.3, 30.2, 25.1, and 10.7, respectively. After two years of treatment, the mean percent changes were 47.6, 32.5, 19.0, and 5.5, respectively.

#### 4. Impaired liver function and past history of cholestatic jaundice

Estrogens may be poorly metabolized in patients with impaired liver function. For patients 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.

#### 5. Hypothyroidism

Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Patients 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. Patients dependent on thyroid hormone replacement therapy who are also receiving estrogens may require increased doses of their thyroid replacement therapy. These patients should have their thyroid function monitored in order to maintain their free thyroid hormone levels in an acceptable range.

#### 6. Fluid retention

Because 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.

#### 7. Hypocalcemia

Estrogens should be used with caution in individuals with severe hypocalcemia.

#### 8. Ovarian cancer

The estrogen-plus-progestin substudy of WHI reported that after an average follow-up of 5.6 years, the relative risk for ovarian cancer for estrogen plus progestin vs. placebo was 1.58 (95% nCI 0.77 - 3.24), but was not statistically significant. The absolute risk for estrogen plus progestin vs. placebo was 4.2 vs. 2.7 cases per 10,000 women-years. In some epidemiologic studies, the use of estrogen-only products, in particular for 10 or more years, has been associated with an increased risk of ovarian cancer. Other epidemiologic studies have not found these associations.

#### 9. Exacerbation of endometriosis

Endometriosis may be exacerbated with administration of estrogen therapy. Malignant transformation of residual endometrial implants have been reported in women treated post-hysterectomy with estrogen-alone therapy. For patients known to have residual endometriosis post-hysterectomy, the addition of progestin should be considered.

#### 10. 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 patients with these conditions.

#### B. Patient Information

Physicians are advised to discuss the contents of the **PATIENT INFORMATION** leaflet with patients for whom they prescribe Premarin.

#### C. Laboratory Tests

Estrogen administration should be initiated at the lowest dose for the treatment of postmenopausal moderate-to-severe vasomotor symptoms and moderate-to-severe symptoms of postmenopausal vulvar and vaginal atrophy and then guided by clinical response rather than by serum hormone levels (e.g., estradiol, FSH). Laboratory parameters may be useful in guiding dosage for the treatment of hypoestrogenism due to hypogonadism, castration and primary ovarian failure.

#### D. 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 anti-factor 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) levels leading to increased circulating total thyroid hormone levels 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. Patients on thyroid replacement therapy may require higher doses of thyroid hormone.
- Other binding proteins may be elevated in serum, i.e., corticosteroid binding globulin (CBG), sex hormone binding globulin (SHBG), leading to increased total circulating corticosteroids and sex steroids, respectively. Free hormone concentrations may be decreased. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1 antitrypsin, ceruloplasmin).
- Increased plasma HDL and HDL<sub>2</sub> cholesterol subfraction concentrations, reduced LDL cholesterol concentrations, increased triglyceride levels.
- Impaired glucose tolerance.
- Reduced response to metyrapone test.

#### E. Carcinogenesis, Mutagenesis, Impairment of Fertility

(See **BOXED WARNINGS, WARNINGS, and PRECAUTIONS**.) Long-term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testis, and liver.

#### F. Pregnancy

Premarin should not be used during pregnancy. (See **CONTRAINDICATIONS**.)

#### G. Nursing Mothers

Estrogen administration to nursing mothers has been shown to decrease the quantity and quality of the milk. Detectable amounts of estrogens have been identified in the milk of mothers receiving this drug. Caution should be exercised when Premarin is administered to a nursing woman.

#### H. Pediatric Use

Estrogen therapy has been used for the induction of puberty in adolescents with some forms of pubertal delay. Safety and effectiveness in pediatric patients have not otherwise been established.

Large and repeated doses of estrogen over an extended time period have been shown to accelerate epiphyseal closure, which could result in short stature if treatment is initiated before the completion of physiologic puberty in normally developing children. If estrogen is administered to patients whose bone growth is not complete, periodic monitoring of bone maturation and effects on epiphyseal centers is recommended during estrogen administration.

Estrogen treatment of prepubertal girls also induces premature breast development and vaginal cornification, and may induce vaginal bleeding. In boys, estrogen treatment may modify the normal pubertal process and induce gynecomastia. (See **INDICATIONS AND USAGE AND DOSAGE AND ADMINISTRATION**.)

#### I. Geriatric Use

Of the total number of subjects in the estrogen-alone substudy of the Women’s Health Initiative (WHI) study, 46% (n=4,943) were 65 years and over, while 7.1% (n=767) were 75 years and over. There was a higher relative risk (CE vs. placebo) of stroke in women less than 75 years of age compared to women 75 years and over.

In the estrogen-alone Women’s Health Initiative Memory Study (WHIMS), a substudy of WHI, a population of 2,947 hysterectomized women, aged 65 to 79 years, was randomized to CE (0.625 mg daily) or placebo. After an average follow-up of 5.2 years, the relative risk (CE vs. placebo) of probable dementia was 1.49 (95% nCI 0.83-2.66). The absolute risk of developing probable dementia with estrogen alone was 37 vs. 25 cases per 10,000 women-years with placebo.

Of the total number of subjects in the estrogen-plus-progestin substudy of the Women’s Health Initiative study, 44% (n=7,320) were 65-74 years of age, while 6.6% (n=1,095) were 75 years and over. There was a higher relative risk (CE/MPA vs. placebo) of non-fatal stroke and invasive breast cancer in women 75 and over compared to women less than

75 years of age. In women greater than 75, the increased risk of non-fatal stroke and invasive breast cancer observed in the estrogen-plus-progestin combination group compared to the placebo group was 75 vs. 24 per 10,000 women-years and 52 vs. 12 per 10,000 women-years, respectively.

In the estrogen-plus-progestin WHIMS substudy, a population of 4,532 postmenopausal women, aged 65 to 79 years, was randomized to CE/MPA (0.625 mg/2.5 mg daily) or placebo. In the estrogen-plus-progestin group, after an average follow-up of four years, the relative risk (CE/MPA vs. placebo) of probable dementia was 2.05 (95% nCI 1.21-3.48). The absolute risk of developing probable dementia with CE/MPA was 45 vs. 22 cases per 10,000 women-years with placebo.

Seventy-nine percent of the cases of probable dementia occurred in women that were older than 70 for the CE group, and 82 percent of the cases of probable dementia occurred in women who were older than 70 in the CE/MPA group. The most common classification of probable dementia in both the treatment groups was Alzheimer’s disease.

When data from the two populations were pooled as planned in the WHIMS protocol, the reported overall relative risk for probable dementia was 1.76 (95% nCI 1.19-2.60). Since both substudies were conducted in women aged 65 to 79 years, it is unknown whether these findings apply to younger postmenopausal women. (See **BOXED WARNINGS and WARNINGS, Dementia**.) With respect to efficacy in the approved indications, there have not been sufficient numbers of geriatric patients involved in studies utilizing Premarin to determine whether those over 65 years of age differ from younger subjects in their response to Premarin.

### ADVERSE REACTIONS

#### See **BOXED WARNINGS, WARNINGS, and PRECAUTIONS**.

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 adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

During the first year of a 2-year clinical trial with 2,333 postmenopausal women between 40 and 65 years of age (88% Caucasian), 1,012 women were treated with conjugated estrogens and 332 were treated with placebo. Table 6 summarizes adverse events that occurred at a rate of  $\geq 5\%$ .

TABLE 6. NUMBER (%) OF PATIENTS REPORTING  $\geq 5\%$  TREATMENT EMERGENT ADVERSE EVENTS

Body System	— Conjugated Estrogens Treatment Group —			
	0.625 mg (n=348)	0.45 mg (n=338)	0.3mg (n=326)	Placebo (n=332)
Any adverse event	323 (93%)	305 (90%)	292 (90%)	281 (85%)
Body as a Whole				
Abdominal pain	56 (16%)	50 (15%)	54 (17%)	37 (11%)
Accidental injury	21 (6%)	41 (12%)	20 (6%)	29 (9%)
Asthenia	25 (7%)	23 (7%)	25 (8%)	16 (5%)
Back pain	49 (14%)	43 (13%)	43 (13%)	39 (12%)
Flu syndrome	37 (11%)	38 (11%)	33 (10%)	35 (11%)
Headache	90 (26%)	109 (32%)	96 (29%)	93 (28%)
Infection	61 (18%)	75 (2		

normal process of glucose disposal, and therefore useless, he said.

Random blood glucose value testing isn't much better, since it is an insensitive test. "It should be used only when nothing else is available," he said. "It is better than nothing at all."

Capillary whole blood glucose testing uses a pinprick to obtain blood that is analyzed by a portable meter. It is convenient and cost-effective, but the meter should be calibrated regularly with results obtained in a hospital laboratory to ensure its accuracy.

Most common, of course, are fasting oral glucose tolerance tests.

These tests are most accurate when the pancreas is adequately primed prior to a 3-hour glucose tolerance test. This cannot always be ensured when people skip meals or follow unusual diets, said Dr. Reece.

That's why he advises patients to eat two to three slices of bread with each meal for 3 days before the test, which involves drinking a glucose solution and having blood drawn 1 hour later.

Nicotine, caffeine, many drugs, bed rest,

## Mild GD Raises Infants' Risk of Cryptorchidism

Mild gestational diabetes significantly raises the risk of cryptorchidism in male offspring, reported Dr. Helena E. Virtanen of the University of Turku, Finland, and her associates.

Even mothers who had an abnormal result on a single oral glucose tolerance test (OGTT) but no diabetes diagnosis were at increased risk of delivering a boy with cryptorchidism, the researchers reported (*J. Clin. Endocrin. Metab.* 2006 Oct. 10 [Epub doi:10.1210/jc.2006-1420]).

They reviewed the pregnancy records of 1,288 singleton boys born at one hospital who had participated in previous research. The 125 boys with congenital cryptorchidism served as cases in this study, and the 1,163 boys who had normal testicular descent at birth served as controls.

Among the cases, 13 mothers (10%) had diet-treated gestational diabetes, and an additional 7 (6%) had at least one abnormal result on OGTT but no diabetes diagnosis, for an overall 16%. In contrast, among the controls, only 47 mothers (4%) had a diabetes diagnosis and an additional 54 (5%) had an abnormal OGTT result, for an overall 9%.

The significantly elevated risk for cryptorchidism remained constant after the data were adjusted for known confounders such as advanced maternal age and maternal smoking, as well as for proposed risk factors that might confound the association, such as prematurity and low birth weight.

Maternal diabetes status had no apparent effect on the rate of spontaneous testicular descent by the age of 3 months or on the rate of bilateral vs. unilateral cryptorchidism. "Considering our results, the increasing prevalence of gestational diabetes may have considerable effect on [future] male reproductive health," Dr. Virtanen and her associates noted.

—Mary Ann Moon

and exertion may also interfere with test results.

If a patient vomits Glucola, the standard glucose solution used in fasting oral glucose tolerance testing, a culinary glucose polymer, Polydose, can be used instead, said Dr. Reece.

Even more palatable for some women is the jelly bean test, standardized by Boyd and associates and found to be "incredibly consistent" with Glucola in terms of sensitivity and specificity, and positive predictive value.

However, that accuracy is ensured only if one uses the exact protocol described by Boyd or one later tested by Lamar and

colleagues: 18 or 26 Brach's jelly beans, with blood drawn 1, 2, and 3 hours later (*Am. J. Obstet. Gynecol.* 1995;173:1889-92 and *Am. J. Obstet. Gynecol.* 1999;181[5 pt. 1]:1154-7).

Two relatively new methods—glycohemoglobin A<sub>1</sub> and a fructosamine-based test—are too insensitive to be used in screening for gestational diabetes, Dr. Reece said.

A breakfast tolerance test involving a specific 600-kcal meal before the blood draw achieves a sensitivity of 75% and specificity of 95% if a 120-mg/dL value is used, and a sensitivity of 96% and specificity of 74% if a threshold is set at 100

mg/dL. It's acceptable, but "cumbersome" to adjust the thresholds, he said.

"I've never used it."

A diagnosis of gestational diabetes is generally reserved for patients who have at least two abnormal oral glucose tolerance tests. Research suggests, however, that potential adverse pregnancy outcomes can occur with just one abnormal result, reflecting impaired glucose metabolism.

Dr. Reece believes one abnormal test warrants at least dietary therapy and retesting, while two abnormal tests during pregnancy may require more aggressive interventions, including oral glucose therapy and possibly insulin. ■

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It's simple  
It's convenient  
It's effective<sup>1</sup>  
It's well tolerated<sup>2</sup>

It's easy to see why women stay with VAGIFEM.

**FREE VAGIFEM SAMPLES! WHAT'S NOT TO LOVE?**

To order VAGIFEM samples, visit [www.novomedlink.com](http://www.novomedlink.com) or call 1-888-VAGIFEM.



Please see adjacent page for brief summary of prescribing information including boxed warning.

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OTHER THERAPY SHE CAN STAY WITH

**VAGIFEM<sup>®</sup>** 25µg  
estradiol vaginal tablets

### IMPORTANT SAFETY INFORMATION

#### ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA.

Three independent, case-controlled studies have reported an increased risk of endometrial cancer in postmenopausal women exposed to exogenous estrogens for more than one year. This risk was independent of the other known risk factors for endometrial cancer. These studies are further supported by the finding that incident rates of endometrial cancer have increased sharply since 1969 in eight different areas of the United States with population-based cancer-reporting systems, an increase which may be related to the rapidly expanding use of estrogens during the last decade.

The three case-controlled studies reported that the risk of endometrial cancer in estrogen users was about 4.5 to 13.9 times greater than in nonusers. The risk appears to depend on both duration of treatment and on estrogen dose. In view of these findings, when estrogens are used for the treatment of menopausal symptoms, the lowest dose that will control symptoms should be utilized and medication should be discontinued as soon as possible. When prolonged treatment is medically indicated, the patient should be reassessed, on at least a semiannual basis, to determine the need for continued therapy.

Close clinical surveillance of all women taking estrogens is important. In all cases of undiagnosed persistent or reoccurring abnormal vaginal bleeding, adequate diagnostic measures should be undertaken to rule out malignancy. There is no evidence at present that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equi-estrogenic doses.

Other warnings include: induction of malignant neoplasms, gallbladder disease, effects similar to those caused by estrogen-progestogen oral contraceptives (such as thromboembolic disease, hepatic adenoma, elevated blood pressure, worsening of glucose tolerance), hypercalcemia, and rarely, trauma induced by the Vagifem<sup>®</sup> applicator.

In a placebo-controlled clinical trial, the most commonly reported adverse events included: headache (9%), abdominal pain (7%), upper respiratory tract infection (5%), genital moniliasis (5%), and back pain (7%).

The use of Vagifem<sup>®</sup> is contraindicated in women who exhibit one or more of the following: known or suspected breast carcinoma, known or suspected estrogen-dependent neoplasia, e.g., endometrial carcinoma, abnormal genital bleeding of unknown etiology, known or suspected pregnancy, porphyria, hypersensitivity to any Vagifem<sup>®</sup> constituents, active thrombophlebitis or thromboembolic disorders, or a past history of thrombophlebitis, thrombosis, or thromboembolic disorders associated with previous estrogen use (except when used in treatment of breast malignancy).