

May Aid Surgical Planning

Endometriosis from page 1

When laparoscopy was used as the preferred procedure, TVS had a sensitivity of 57% and a specificity of 95% for diagnosing the absence or presence of endometriosis, reported lead author Dr. Tom Holland of the early pregnancy and gynecology assessment unit, University College London Hospitals.

The sensitivity and specificity for diagnosing absent to mild versus moderate to severe disease were 89% and 97%, and

for absent to moderate versus severe endometriosis, 85% and 98%.

The positive and negative likelihood ratios for severe disease were 43.5 and 0.15.

"TVS performed by experienced operators has a high sensitivity and specificity at detecting severe pelvic endometriosis," Dr Holland said.

"TVS is a good method for triaging women with pelvic endometriosis for

optimal surgical care," he added.

In a separate retrospective, observational study of 72 women (mean age 31 years) who had a bowel resection for presumed deep infiltrating endometriosis, preoperative TVS could detect deep infiltrating endometriosis of the rectosigmoid colon in 79% of cases, Dr. Dominique Van Schoubroeck reported during the same session at the meeting. Deep endometriosis nodes were recorded by ultrasound as "yes" in 51 women, "possible" in 6, and "no" in 15 cases, with definite and possible cases considered abnormal. Histology

reported deep nodes as present in 88% and absent in 12% of cases, said Dr. Van Schoubroeck of the obstetrics and gynecology unit, University Hospitals, Catholic University Leuven (Belgium).

She noted that accurate prediction of the extent of distal bowel involvement in cases of deep endometriosis could help in surgical planning.

Conventional laparoscopy will suffice if the endometriotic lesion only superficially involves the bowel wall, whereas deep infiltrating endometriosis into the muscularis necessitates bowel resection.

"It's important for all to get familiar with these images," she said.

The 79% sensitivity in the current study compares favorably with prior studies using TVS to identify rectosigmoid endometriosis, with sensitivities ranging from a low of 67% (Hum. Reprod. 2008;23:2452-7) to a high of 98% using 3-D TVS (Hum. Reprod. 2007;22:3092-7).

Dr. Holland and Dr. Van Schoubroeck disclosed no conflicts of interest. ■

OC/Metformin Combo Beters Lipids in PCOS

WASHINGTON — A combination of metformin and the oral contraceptive Ortho Tri-Cyclen improves lipid profiles more than does an oral contraceptive alone in patients with polycystic ovary syndrome, according to preliminary data from a small pilot study presented at the annual meeting of the Androgen Excess and PCOS Society.

In this randomized, double-blind, placebo-controlled study, Dr. Pauline Essah of Virginia Commonwealth University, Richmond, and colleagues assigned 17 women with PCOS to an OC plus 500 mg of metformin three times daily or an OC plus a placebo three times daily.

After 3 months, there was no difference between the two groups in weight, BMI, fasting insulin, or fasting glucose measurements. However, the OC-metformin group experienced a trend toward higher HDL cholesterol (55.6 vs. 47.6 mg/dL) and lower triglyceride levels (86.8 vs. 152.7 mg/dL) compared with the group that took OCs alone. The combination group also demonstrated a significant increase in acute insulin response to glucose.

Also, patients in the OC-metformin group "went from 4.7% to 9.4% in flow-mediated dilatation," a significant improvement, while patients in the OC-alone group did not experience a significant change, Dr. Essah said. "The combination seems to be more beneficial than OC monotherapy because it enhances beta-cell function and endothelial function, and improvements in these factors may attenuate the cardiovascular risks from OCs." The study was funded by the National Institutes of Health. Dr. Essah said she had no financial conflicts of interest to report.

—Joyce Frieden

ACTIVELLA® (estradiol/norethindrone acetate) tablets

1.0 mg/0.5 mg

0.5 mg/0.1 mg

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CARDIOVASCULAR AND OTHER RISKS

Estrogens with or without progestins should not be used for the prevention of cardiovascular disease or dementia. (See **CLINICAL STUDIES** in prescribing information and **WARNINGS, Cardiovascular disorders and Dementia**.) The estrogen plus progestin subcategory of the Women's Health Initiative (WHI) reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary embolism, and deep vein thrombosis in postmenopausal women (50 to 79 years of age) during 5.6 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 prescribing information and **WARNINGS, Cardiovascular disorders and Malignant neoplasms, Breast cancer**.) The estrogen-alone subcategory of the WHI reported increased risks of stroke and deep vein thrombosis (DVT) in postmenopausal women (50 to 79 years of age) during 6.8 years and 7.1 years, respectively, of treatment with oral conjugated estrogens (CE 0.625 mg) per day, relative to placebo. (See **CLINICAL STUDIES** in prescribing information and **WARNINGS, Cardiovascular disorders**.) The Women's Health Initiative Memory Study (WHIMS), a substudy of the WHI study, reported increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with CE 0.625 mg combined with MPA 2.5 mg and during 5.2 years of treatment with CE 0.625 mg alone, relative to placebo. It is unknown whether the finding applies to younger postmenopausal women. (See **CLINICAL STUDIES** in prescribing information, **WARNINGS, Dementia and PRECAUTIONS, Geriatric Use**.) Other doses of oral conjugated estrogens with 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 trials, 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 Activella 1.0 mg/0.5 mg and 0.5 mg/0.1 mg are indicated in women who have a uterus for the:

1. Treatment of moderate to severe vasomotor symptoms associated with menopause.
2. Prevention of postmenopausal osteoporosis. When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should be reserved for women at significant risk of osteoporosis and non-estrogen medications should be carefully considered. The mainstay 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.

Activella 1.0 mg/0.5 mg is also indicated in women who have a uterus for the:

3. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with menopause. When used solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered.
- CONTRAINDICATIONS** Activella should not be used in women with any of the following conditions:
 1. Undiagnosed abnormal genital bleeding.
 2. Known, suspected, or history of cancer of the breast.
 3. Known or suspected hormone-dependent malignancy.
 4. Active deep vein thrombosis, pulmonary embolism, or history of these conditions.
 5. Active or recent (e.g., within the past year) arterial thromboembolic disease (e.g., stroke, myocardial infarction).
 6. Liver dysfunction or disease.

7. Known hypersensitivity to the ingredients of Activella 1.0 mg/0.5 mg or Activella 0.5 mg/0.1 mg.
8. Known or suspected pregnancy. There is no indication for Activella in pregnancy. There appears to be little or no increased risk of congenital anomalies with the use of progestin alone, estrogens and progestins from oral contraceptives inadvertently during early pregnancy. (See **PRECAUTIONS**.)

WARNINGS

See **BOXED WARNINGS**.

- 1. Cardiovascular disorders** Estrogen-plus-progestin therapy has been associated with an increased risk of myocardial infarction as well as stroke, venous thrombosis and pulmonary embolism. Estrogen-alone therapy has been associated with an increased risk of stroke and deep vein thrombosis (DVT). Should any of these events 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.
- 2. Stroke** In the estrogen plus progestin subcategory of the Women's Health Initiative (WHI), a statistically significant increased risk of stroke was reported in women receiving CE/MPA 0.625mg/2.5mg 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. (See **CLINICAL STUDIES** in prescribing information.) In the estrogen-alone subcategory of the WHI, 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.
- 3. Coronary heart disease** In the estrogen-plus-progestin sub-study of WHI, no statistically significant increase in CHD events (defined as non-fatal, MI, silent MI, or death due to CHD) was reported in women receiving CE/MPA compared to women receiving placebo (39 vs. 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 years 2 through 5. (See **CLINICAL STUDIES** in prescribing information.) In the estrogen-alone subcategory of WHI, no overall effect on coronary disease (CHD) events was reported in women receiving estrogen alone compared to placebo. (See **CLINICAL STUDIES** in prescribing information.)

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 (0.625mg/2.5mg per day) demonstrated no cardiovascular benefit. There was 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 1, but not during the subsequent years. Participation in an open-label extension of the original HERS trial (HERS II) was agreed to by 2,321 women. 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 HERS, HERS II, and overall. Large doses of estrogen (5 mg) conjugated estrogens per day, comparable to those used in the HERS and HERS II studies, have been shown in a large prospective clinical trial in men to increase the risk of nonfatal myocardial infarction, pulmonary embolism, and thrombophlebitis.

c. Venous thromboembolism In the estrogen-plus-progestin subcategory of the Women's Health Initiative (WHI), a statistically significant 2-fold greater rate of VTE (DVT and pulmonary embolism [PE]), 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. 3 per 10,000 women-years) were also demonstrated. The increase in VTE risk was demonstrated during the first year and persisted. (See **CLINICAL STUDIES** in prescribing information.) In the estrogen-alone subcategory of WHI, the risk of VTE was reported to be increased for women taking conjugated estrogens (30 vs. 22 per 10,000 women-years), although only the increased risk of DVT reached statistical significance (23 vs. 15 per 10,000 women-years). The increase in VTE risk was demonstrated during the first two years, 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. 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 CE/MPA subcategory of the WHI study (See **CLINICAL STUDIES** in 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. In a cohort study of women followed up to 5.6 years, the WHI subcategory reported an increased risk of breast cancer. In this subcategory, 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% CI 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 of

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.

In the estrogen-alone subcategory of WHI, after an average of 7.1 years of follow-up, CE (0.625 mg daily) was not associated with an increased risk of invasive breast cancer (RR 0.80, 95% CI 0.62-1.04). In a one-year follow-up study, among women who received either estrogen alone or a combination of 1 mg estradiol plus one of three different doses of NETA (0.1, 0.25, and 0.5 mg), seven new cases of breast cancer were diagnosed, two of which occurred among the group of 295 women treated with Activella 1.0 mg/0.5 mg and two of which occurred among the group of 294 women treated with 1 mg estradiol/0.1 mg NETA.

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 health care provider. Breast self-examination should be encouraged. In addition, mammography examinations should be scheduled based on patient age, risk factors, and prior mammogram results.

b. Endometrial cancer The use of unopposed estrogens in women with intact uteri has been associated with an increased risk of endometrial cancer. The reported endometrial cancer risk among unopposed estrogen users is about 2 to 12 fold greater than in nonusers, 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 one year. The greatest risk appears associated with prolonged use, with an increased risk of 15- to 24-fold for five to ten years or more. This risk has been shown to persist for at least 10 to 15 years after estrogen therapy is discontinued.

Clinical surveillance of all women taking estrogen/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 potency. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which appears to be a precursor to endometrial cancer. Endometrial hyperplasia (a possible precursor of endometrial cancer) has been reported to occur in approximately 1% or less with Activella in one large clinical trial.

3. Dementia In the estrogen-plus-progestin Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, 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 WHIMS subcategory, 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 subcategory, a population of 1,585 hysterectomized women, aged 65 to 79 years, was randomized to estrogen-plus-progestin group and 1,011 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for estrogen plus progestin was placebo was 2.05 (95% CI 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.

In the estrogen-alone subcategory, after an average follow-up of 5.2 years, 28 women in the estrogen-alone group and 18 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE alone vs. placebo was 1.49 (95% CI 0.82-2.66). The absolute risk of probable dementia for CE alone vs. placebo was 37 vs. 25 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 of probable dementia was 1.76 (95% CI 1.19-2.60). Since both substudies were conducted in women aged 65 to 79, it is unknown whether these findings apply to younger postmenopausal women. (See **BOXED WARNINGS and PRECAUTIONS, Geriatric Use**.)

4. Gallbladder disease A two- to four-fold increase in the risk of gallbladder disease requiring surgery in women receiving estrogen therapy has been reported. The absolute risk of gallbladder disease requiring surgery in women receiving estrogen therapy was 4.9 (95% CI 0.82-2.66). The absolute risk of probable dementia for CE alone vs. placebo was 37 vs. 25 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 of probable dementia was 1.76 (95% CI 1.19-2.60). Since both substudies were conducted in women aged 65 to 79, it is unknown whether these findings apply to younger postmenopausal women. (See **BOXED WARNINGS and PRECAUTIONS, Geriatric Use**.)

5. Hypocalcemia Estrogen administration may lead to severe hypocalcemia in patients with breast cancer and bone metastases. If hypocalcemia occurs, use of the drug should be stopped and appropriate measures taken to reduce the serum calcium level. **6. Visual abnormalities** Retinal vascular thrombosis has been reported in patients receiving estrogens. Discontinue medication pending examination if there is a sudden partial or complete loss of vision, or a sudden onset of proptosis, diplopia, or migraine. If examination reveals papilloedema or retinal vascular lesions, estrogens should be permanently 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-only therapy. These risks include a possible increase in the risk of endometrial cancer. **2. Elevated blood pressure** In a 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. Blood pressure should be monitored at regular intervals with estrogen use.

3. Hypertiglyceridemia In patients with preexisting hypertriglyceridemia, estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis and other complications.

4. Impaired liver function Estrogen administration should be avoided in women with known or suspected liver disease. Estrogen administration should be avoided in women with known or suspected liver disease. Estrogen administration should be avoided in women with known or suspected liver disease. Estrogen administration should be avoided in women with known or suspected liver disease.

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 T₄ and T₃ serum concentrations in the normal range. Patients dependent on oral thyroid hormone replacement therapy who are also receiving estrogens require increased doses of their thyroid replacement therapy. These patients should have their thyroid function monitored to maintain their free thyroid hormone levels in an acceptable range.

6. 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 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 subcategory 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% CI 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 estrogens. Multinodular transformation of residual endometrial implants has been reported in women treated post-hysterectomy with estrogen-alone therapy. For patients with a history of endometriosis post-hysterectomy, the addition of progestin should be considered.

10. 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.

B. Patient Information Physicians are advised to discuss the contents of the Patient Information leaflet with patients for whom they prescribe Activella 1.0 mg/0.5 mg or Activella 0.5 mg/0.1 mg.

C. Laboratory Tests Estrogen administration should be followed at the low dose approved for the indication and then guided by precise receptor, rather than by serum hormone levels (e.g., estradiol, FSH).

D. Drug/Laboratory Test Interactions

1. Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, and beta-thromboglobulin; decreased levels of anti-fibrinogen Xa and antithrombin III; decreased antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity.
2. Increased thyroid-binding globulin (TBG) levels leading to increased circulating total thyroid hormone levels as measured by protein-bound iodine (PBI), 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. Patients on thyroid replacement therapy may require higher doses of thyroid hormone.
3. Other binding proteins may be elevated in serum (i.e., corticosteroid binding globulin [CBG], 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).
4. Increased plasma HDL and HDL cholesterol subfraction concentration, reduced LDL cholesterol concentration, increased triglyceride levels.
5. Impaired glucose tolerance.
6. Reduced response to methylphenidate.

E. Carcinogenesis, Mutagenesis, Impairment of Fertility Long-term continuous administration of estrogen, with or without progestin, in women with or without a uterus, has shown an increased risk of endometrial cancer, breast cancer, and ovarian cancer. (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 Activella 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 breast milk. Detectable amounts of estrogens have been identified in the milk of mothers receiving this drug. Caution should be exercised when Activella is administered to a nursing mother.

H. Pediatric Use

Activella is not indicated in children.

I. Geriatric Use Clinical studies of Activella did not include sufficient number of subjects aged 65 and over to determine if they responded differently from younger subjects.

J. Pediatric Use Clinical studies of Activella did not include sufficient number of subjects aged 65 and over to determine if they responded differently from younger subjects. Of the total number of subjects in the estrogen-plus-progestin subcategory of the Women's Health Initiative (WHI) study, 4.4% (n=20) were 65-74 years of age, while 8.8% (n=1,058) 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 Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, a population of 4,532 hysterectomized 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% CI 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.

Of the total number of subjects in the estrogen-alone subcategory of WHI, 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 WHIMS subcategory, 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% CI 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. Seventy-nine percent of the cases of probable dementia occurred in women who were older than 70 for the CE-alone group, and 62 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 group and placebo 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% CI 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**.)

ADVERSE REACTIONS

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

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