Pregnancy May Mask Heart Disease Symptoms

BY SHERRY BOSCHERT San Francisco Bureau

SAN FRANCISCO — Maternal peripartum cardiomyopathy, seen in 1 in 3,000 live births, generally carries a good prognosis, Dr. Michael Crawford said at a meeting sponsored by the California chapter of the American College of Cardiology.

Diagnosis of peripartum cardiomyopathy-or of other heart diseases during pregnancy-often is delayed because the

symptoms of pregnancy can mimic the heart disease symptoms, said Dr. Crawford, professor of medicine at the University of California, San Francisco,

A majority of women with peripartum cardiomyopathy recover after delivery, but 10%-20% require heart transplantation and 1%-2% die, data suggest. The patient's ejection fraction 2 months after diagnosis appears to be the best prognostic factor, he said at the meeting, also sponsored by the university.

(see CLINICAL PHARMACOLOGY, Clinical Studies). The results from observational studies are generally consistent with those of the WHI clinical frial and report no significant variation in the risk of breast cancer among different estrogens or progestins, doess, or routes of administration. The CEMPA some and follow-up of 6 syears. Observational studies are also reported an increased risk for estrogen progestin combination therapy, and a smaller increased risk for estrogen alone therapy, after several years of use. In the WHI trial and from observational studies, the excess risk for estrogen progestin combination therapy, and a smaller increased risk for estrogen alone therapy, after several years of use. In the WHI trial and from observational studies, the sexess risk increased with fuention of use. From observational studies, the risk of breast cancer was gradier and became papernet earlier, with estrogen/progestin combination therapy. The apparent tearlier, with estrogen/progestin combination herapy as compared to estrogen alone therapy. In the CEMPA substudy, 20% of the women reported prior use of estrogen alone and/or estrogen/progestin combination hormone therapy. After a mean follow-up of 5.6 years. Duservational studies was 44.9 w. 25 cases per 10.000 women-years, for CEMPA compared with plaebo. Among women who reported prior use of hormone therapy, the relative risk of invasive breast cancer was 1.4 (26% confidence interval 1.01-1.54), and the overall absolute risk was 41 w. 33 cases per 10.000 women-years, for CEMPA compared with plaebo. Among women whore ported for use of hormone therapy, the relative risk of invasive breast per 10.000 women-years, for CEMPA compared with plaebo. Among women whore ported for use of hormone therapy. The relative risk of invasive breast cancer was 1.96, and the absolute risk was 40.9.8 cases per 10.000 women-years, for CEMPA compared with plaebo. The women-years for CEMPA compared with plaebo. The women-yeary for CEMPA compared with plaebo. The women reported to resul

and prior mammogram results. 3. Dementia In the estrogen alone Women's Health Initiative Memory Study (WHIMS), a sub-study of WHI, 2,947 hysterectomized women aged 65 to 79 years were randomized to CE or placebo. In the estrogen plus progestin WHIMS substudy, 4,532 postmenopausal women aged 65 to 79 years were randomized to CE/MPA or placebo.

oo tu / 9 years were randomized to CE/MPA or placebó. In the estrogen alone substudy, after an average follow-up of 5.2 years, 28 women in the estrogen alone group were diagnosed with probable dementia. The relative risk of probable dementia for estrogen alone versus placebo was 1.49 (95% CI 0.83-266). The absolute risk of probable dementia for estrogen alone versus placebo was 149 (95% CI 0.83-266). The absolute risk of probable dementia for estrogen alone versus placebo was 1.49 (95% CI 0.83-266). The absolute risk of probable dementia for estrogen alone versus placebo was 1.49 (95% CI 0.83-266). The absolute risk of probable dementia for estrogen alone versus placebo was 1.49 (95% CI 0.83-266). The absolute risk of probable dementia for estrogen alone versus placebo was 1.49 (95% CI 0.83-266). The absolute risk of probable dementia for estrogen alone versus placebo was 1.49 (95% CI 0.83-266). The absolute risk of probable dementia for estrogen alone versus placebo was 1.49 (95% CI 0.83-266). The absolute risk of probable dementia for estrogen alone versus placebo was 1.49 (95% CI 0.83-266). The absolute risk of probable dementia for estrogen alone versus placebo was 1.49 (95% CI 0.83-266). The absolute risk of probable dementia for estrogen alone versus placebo was 37 versus 25 cases per 10.000 women-years. It is unknown whether these findings apply to youngen postmenopausal women (See CLINICAL PHARMACOLOGY, Clinical Studies and PRECAUTIONS, Berlatric Use.)

younger postmenopausal women. (See CLINICAL PHARMACOLOGY, Clinical Sludies and PRECAUTIONS, Gentratic Use.)
 Atter an average follow-up of 4 years, 40 women being treated with CE/MPA (1.8%, n = 2,229) and 21 women in the placebo group (0.9%, n = 2,300) received diagnoses of probable demention. The relative risk for CE/MPA versus placebo was 250 (53%, confidence interval 1.21 – 3.48), and was similar for women with and without histories of menopausal hormone use before WHIMS. The absolute risk of probable demention to CE/MPA versus placebo was 45 versus.
 22 cases per 10,000 women-vears, and the absolute excess risk for CE/MPA was 23 cases per 10,000 women-years. It is unknown whether these findings apply to younger opstmenopausal women. (See CLINICAL PHARMACOLOGY, Clinical Studies and PRECAUTIONS, Geriatric Use.)
 4. Gallibadder disease A 2- to 4-fold increase in the risk of gallibadder disease requiring surgery in postmenopausal women receiving estrogens has been reported.
 5. Hypercaleemia Estrogen administration may lead to severe hypercalemia in patients with breast cancer and bone metastases. If hypercaleemia occurs, use of the drug should be stopped and appropriate measures taken to reduce the serum calcium level.
 6. Usical ahomermalities. Retinal vascular thrombosis has been reported in patients receiving strogen periode.
 7. Wasal ahomermalities. Retinal vascular thrombosis has been reported in patients receiving appropriate measures taken to reduce the serum calcium level.
 7. Wasal ahomermalities. Retinal vascular thrombosis has been reported in galemator remain a patient serving applicatema or reinal vascular lesions, estrogens should be permanently discontinue.

A CENERAL A CENERAL A didition 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 administra-tion or daily with estrogen in a continuous regiment. 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.

TRADE THAT IN USE A precursor to elucified Cancer. The are, however, possible risks that may be associated with the use of progestins with rogens compared to estrogen-alone regimens. These include a possible increased risk reast cancer.

of breast cancer. 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 tria, generalized effect of estrogen therapy on blood pressure was not seen. Blood pressure should be monitored at regular intervals with estrogen use. 3. Hypertriglyceridemia in patients with pre-existing hypertriglyceridemia, estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreati-tis and other complications.

Infrom informer levels in an acceptance range. 6. Fluid referencing Decause estrogen and estrogen/progestin therapy may cause some degree of fluid relention, patients with conditions that might be influenced by this factor, such as a ca-diac or renal dyshunction, warrant carful ubservation when estrogens are prescribed. 7. Hypocalcemia Estrogens should be used with caution in individuals with severe hypocalcemia.

Hyponatremia As an aldosterone antagonist, drospirenone may increase the possi-bility of hyponatremia in high-risk patients.

bility of hyponatremia in high-risk patients. Level to be provided in the used in possibility of hyponatremia in high-risk patients. 9. Ovarian cancer The CE/MPA substudy of WHI reported that estrogen plus progestin increased the risk of ovarian cancer. After an average follow-up of 5.5 gives, the relative risk for ovarian cancer for CE/MPA versus placebo was 1.58 (95% confidence interval 0.77 – 3.24) but was not statistically significant. The absolute risk for CA/MPA versus placebo was 4.2 versus 2.7 cases per 10,000 women-years. In some exploremiologic studies, the use of estrogen alone, in par-ticular for the norme years. The shear associated with an increased risk of ovarian cancer. Other epidemiologic studies have not found these associations. 10. Exacerbation of endometricasis Endometricosis may be exacerbated with adminis-tration of estrogens.

Tration of estrogens. 11. Exacerbation of other conditions Estrogens may cause an exacerbation of asthma, dia-betes mellitus, epilepsy, migraine, porphyria, systemic lupus erythematosus, and hepatic hemangiornas, and should be used with caution in women with these conditions. B. YATIENT INFORMATION Physicians are advised to discuss the PATIENT INFORMATION leaflet with patients for whom they prescribe ANGELIO. CLADED TEACH TEACH CONTRACT AND AND ADDITION TO A CONTRACT AND A C

Leafer with patients for whom they prescribe ANGELIO. C. LABORATORY TESTS: Estrogen administration should be initiated at the lowest dose for the approved indication and then guided by clinical response, rather than by serum

D. URUG/LABORATORY TEST INTERACTIONS 1. Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII antigen, VIII coagulant activi-ty, IX, XII, VII-X complex, II-VII-X complex, and beta-thromboglobulin; decreased levels of anti-factor X and antithrombin III, decreased antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity. 2. Increased throich-binding globulin (TBG) levels leading to increased circulating total thry-rold hormone, as measured by protein-bound iodine (PBI). T4 levels (by column or by radioimmunoassay. T3 resin uptake is decreased, reflect-ing the elevated TBG. Free T4 and free T3 concentrations are unaltered. Patients on thyroid replacement therapy may require higher doces of thyroid hormone.

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PRECAUTIONS

There are, how

Treatment for cardiomyopathy differs for pregnant women compared with nonpregnant patients because some drugs shouldn't be used until after delivery.

ACE inhibitors and warfarin are teratogenic, and β -blockers can lead to fetal bradycardia.

"You get by with diuretics, digoxin, and hydralazine during pregnancy" for peripartum cardiomyopathy, Dr. Crawford said.

In a recent study at a large medical center, ejection fractions improved at least

3. Other binding proteins may be elevated in serum (i.e., corticosteroid binding globulin (CBG), sex hormone-binding globulin (CBG) (Bading to increased circulating corticosteroids and sex storids, respectively. Free hormone concentrations may be decreased. Other plasma proteins may be increased (angiotensinogen/reini substrate, alpha-1-antitrypsin, ceruloplasmin). 4. Increased plasma HDL and HDL-2 subfraction concentrations, reduced LDL cholesterol concentration, increased triglyceride levels. Impaired glucose tolerance.

Reduced response to metyrapone test. . CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term continuous administration of estrogen, with and without progestin, in womer with and without a uterus, has shown an increased risk of endometrial cancer, breas cancer, and ovarian cancer. (See **BOXED WARNINGS**, **WARNINGS** and **PRECAUTIONS**.

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, iterus, cerviv, vagina, testis, and liver. (See BOXED WARNINGS, CONTRAINDICATIONS, and WARNINGS sections.) In a 24 month oral carcinogenicity study in mice doesd with 10 mg/kg/day drospirenone alone or 1 + 0.01, 3 + 0.03 and 10 + 0.1 mg/kg/day drospirenone adhetiny (estraidio, 0.24 to 10.3 times the exposure (AUC of drospirenone) of women taking a 1 mg does, there was an increase in car-cinomas of the harderian giand in the group that received the high does of drospirenone alone. In a similar study in rats given 10 mg/kg/day drospirenone alone or 0.3 + 0.003, 3 + 0.03 and 10 + 0.1 mg/kg/day drospirenone and ethinyl estraidio, 2.3 to 5.1 times the exposure of women taking a 1 mg does, there was an increased incidence of being and total (being) and malignami). Drospirenone was not mutagenic in a number of *in witro* (Ames, Chinese Hamster Lung gene mutation and chronosomal damage in human lymphocytes) and *in wivo* (mouse micronucleus) genotoxicity tests. Drospirenone increased unscheduled DNA synthesis in rat hegatocytes and formet adducts with rodent liver DNA but not with human liver DNA. (See WARNINGS section.) **F. PEEGNAUCY ANGELIQ** should not be used during repranor, **Cee CONTRAIND(SECTIONS.)**.

PREGNANCY ANGELIQ 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 ANGELIQ is administered to a nursing woman.

Identified in the milk of mothers receiving this drug. Caution should be exercised when ANGELU is administered to a nursing vorman. After administration of an oral contraceptive containing drospirenone about 0.02% of the drospirenone does was exercented into the breast milk of postpartum women within 24 hours. This results in a maximal daily does of about 3 mog drospirenone in an infant. H. PEDIATRIC USE ANGELU is not indicated in children. I. GENATRIC USE There have not been sufficient numbers of geratric patients involved in clinical studies utilizing ANGELU to determine whether those over 65 years of age dif-fer from younger subjects in their response to ANGELU. In the Women's Health Initiative Memory Study, including 4,532 women 65 years of age and older, followed for an average of 4 years, 82% (n = 3,729) were 65 to 74 while 13% (n = 030) were 75 and over. Most vomen (80%) had no prior hormone therapy use. Women treated with conju-gated estrogens plus methoryprogresterone acatate were reported to have a two-foll increase in the risk of developing protable dementia. Abreimer's disease was the most common classifica-tion of probable dementia in toot the conjugated estrogens plus medroxyprogesterone acatate group and the placebo group. Ninety percent of the cases of probable dementia occurred in the 54% of women who were older than 70. (See WARNINGS, Dementia.) ADVERSE FEACTIONS

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 identi-fying the adverse events that appear to be related to drug use and for approximating rates. The following are adverse events reported with ANGELIO occurring in >5% of subjects

Table 4. Adverse Events Regardless of Drug Relationship Reported at a Frequency of >5% in a 1-year Double-blind Clinical Trial

ADVERSE EVENT	E2 1 MG (N=226) n (%)	ANGELIQ (N=227) n (%)
BODY AS A WHOLE		
Abdominal pain	29 (12.8)	25 (11)
Pain in extremity	15 (6.6)	19 (8.4)
Back pain	11 (4.9)	16 (7)
Flu syndrome	15 (6.6)	16 (7)
Accidental injury	15 (6.6)	13 (5.7)
Abdomen enlarged	17 (7.5)	16 (7)
Surgery	6 (2.7)	12 (5.3)
METABOLIC & NUTRITIONAL DISORDERS		
Peripheral edema	12 (5.3)	4 (1.8)
NERVOUS SYSTEM		
Headache	26 (11.5)	22 (9.7)
RESPIRATORY SYSTEM		
Upper respiratory infection	40 (17.7)	43 (18.9)
Sinusitis	8 (3.5)	12 (5.3)
SKIN AND APPENDAGES		
Breast pain	34 (15.0)	43 (18.9)
UROGENITAL		
Vaginal hemorrhage	43 (19.0)	21 (9.3)
Endometrial disorder	22 (9.7)	4 (1.8)
Leukorrhea	14 (6.2)	3 (1.3)
ne following additional adverse reactions have been reported with estrogen and o		

Centiourinary system Changes in vaginal bleeding pattern and abnormal withdrawa eleeding or flow; breakthrough bleeding, spotting, dysmenorthea, increase in size of uterina isomyomata, vaginitis, including vaginal candidiass, change in amount of cervical secretion hanges in cervical ectropion, ovarian cancer, endometrial hyperplasia, endometrial cancer.

Caranges in conversion conversion and conversion thrombophlebitis, myocardial infarction, stroke, increase in blood pressure. 4. Gastrointestinal Nausea, vormiting, abdomian carmps, bloading, cholestatic jauncice, increased incidence of gal bladder disease, pancreatitis, enlargement of hepatic hermangiomas. 5. Skin Chloasma or melasma, which may persist when drug is discontinued, erythema mul-tiforme, erythema nodosum, heromortagie eruption, loss of scalp hair, linsuism, pruritus, rash. 6. Eyes Retinal vascular thrombosis, intolerance to contact lenses. 7. Central nervous system Haadche, migraine, dizziness, mental depression, chorea, nervousness, mood disturbances, irribability, exacerbation of epilepsy, dementia.

Intervoisness, modu discurances, minimum, exacer datario in epineps, deminima.
8. Miscellaneous Increase or decrease in weight, reduced carbolydrate tolerance, aggravation of porphyria, edema, arthralgias, leg cramps, changes in libido, anaphylac-toid/anaphylactic reactions including untitaria and angioedema, hypocalcemia, exacerbation of asthma, increased triglycerides. OVERDOSAGE

OVERDOSAGE In cases of ANGELIQ overdose, monitor serum concentrations of potassium and sodium since drospirenone has antimimeralocorticoid properties. Serious III effects have not been reported following acute ingestion of large doses of progestin/setrogen-containing oral contraceptives by young children. Overdosage may cause nause and withdrawal bleeding may occur in temales. Manufactured for: Berlex, Montville, NJ 07045

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15% in 62% of women with peripartum cardiomyopathy, remained unchanged in 25%, and declined in 13% (Am. Heart J. 2006;152:509-13).

Ejection fractions returned to normal in 45%. Ten percent of patients required transplantation. No patients died during an average 43-month follow-up. "That's encouraging," he noted.

The initial echocardiogram, obtained between 1 month prepartum and 5 months post partum, did not predict which patients required transplantation, nor which had final ejection fractions below or above 50%. "Don't get discouraged with the first echo," Dr. Crawford said. Echocardiograms 2 months later predicted outcomes in that study.

Patients with ejection fractions below 20% probably are headed for transplant. Those with ejection fractions between 20%

	and 50% should
ECGs in normal	see some im-
pregnancies often	provement but are unlikely to
detect sinus	return to nor-
tachycardia, and	mal. If the 2- month ejection
may show	fraction is above
nonspecific ST-T	40%, the patient is likely to re-
changes. As the	cover fully (de-
pregnancy	fined as an ejec-
advances, the	tion fraction greater than
heart's axis shifts.	50%), he said.
	Shortness of

fraction than he said. Shortness of breath and decreased exercise capacity, which are symptoms of cardiomyopathy, also are symptoms of a normal pregnancy. Fatigue, orthopnea, and dizziness or syncope, which might be symptoms of

toms of pregnancy. Electrocardiograms in normal pregnancies often detect sinus tachycardia, and may show nonspecific ST-T changes. As the pregnancy advances, the heart's axis shifts more to the left.

other heart disease, also are normal symp-

Physical findings in normal pregnancies may include jugular venous distension, an enlarged left ventricle apex, right ventricle heave, a palpable pulmonary artery pulse, third heart sounds, systolic ejection murmurs, venous hums, or a mammary souffle noise if you listen over the breast.

"It can be confusing," Dr. Crawford said.

The most common peripartum cardiovascular problem is venous thromboembolism, which is the leading cause of death in pregnancy, he added.

Consider prophylactic medication in women with risk factors (thrombophilia, history of thrombosis, antiphospholipid syndrome, lupus erythematosus, sickle cell anemia, or any kind of heart disease that would lead to thrombus formation).

Coronary artery disease during pregnancy is more common than one might think, perhaps because more women are having children later in life, he added.

Maternal MI occurs in 6 out of 100.000 deliveries, three to four times more common than is expected in age-matched nonpregnant women.

ANGELIQ[®] TABLETS Co.5mg/1mg BRIEF SUMMARY OF PRESCRIBING INFORMATION (for full prescribing information and patient information, please visit our website at www.angelie_us.com)

Rx only

WARNING

WARNING Estrogens with or without progestins should not be used for the prevention of cardiovascu-lar disease or dementa. (See WARNINGS, Cardiovascular disorders and Dementia.) The Women's Health Initiative (WHI) study reported increased risks of myocardial infarc-tion, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis in post-menopausal women (50 to 79 years of age) during 5 years of treatment with oral conjugated equine estrogens (CE D 625mg) combined with medroxyprogesterone acatate (MPA 2.5mg) relative to placebo (see CLINICAL PHARMACOLOGY, Clinical Studies and WANNINGS, Cardiovascular disorders and Malignant neoplasms, Breast cancer.) The Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, reported increased risk of developing probable demention in postmeropasal women 65 years of age or older dur-ing 62 years of treatment with conjugated estrogens alone and during 4 years of treatment with oral conjugated strogens plus metroxyprogestores acatate, relative to placebo. It is unknown whether this finding applies to younger postmeropausal women (See CLINICAL PHARMAwhether this finding applies to younger postmenopausal women. (See CLINICAL PHA COLOGY, Clinical Studies, WARNINGS, Dementia and PRECAUTIONS, Geriatric Use: Other deservations of the second studies of the second studies

CULUSY, Clinical Studies, WARNINGS, Dementia and PHEADUINS, Genaric Use.) Other doese of oral conjugate storgens with medroxyprogetemone 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 consis-tent with retarment goals and risks for the individual woman.

INDICATIONS AND USAGE

INDICATIONS AND USAGE AMGEUIs inductatin women who have a uterus for the: 1. Treatment of moderate to severe vaso motor symptoms associated with the menopause. 2. Treatment of moderate to severe symptome of whar and vaginal atrophy associated with the menopause. When presenting solely for the treat ment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered

ment of symptoms of vulvár and vaginal atrophy, topical vaginal products snouio be considered. CONTRAINDICATIONS Progestogenskerstorgens should not be used in individuals with any of the following condi-tions: 1. Undiagnosed abnormal gential bleeding. 2. Known, suspected, or history of cancer of the breast. 3. Known or suspected estrogen-dependent neoplasia. 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. Renal insufficienzy. 7. Liver dystunction or disease. 8. Adrenal insufficienzy. 9. AMGELU subjected prepanary. There is no indication for AMGELU in prepanary. There against to be little or no increased risk of birth defects in children born to women who have used estrogens and progestins from cal contraceptives inadvertently during early pregnancy. (See PRECAUTIONS). WARNINGS

WARININGS MARELIC conclains 0.5 mg of the progestin drospirenone that has antialdosterone activi-ty, including the potential for hyperkalemia in high-risk patients. ANGELIO should not be used in patients with conditions that predispose to hyperkalemia (i.e. ernal insufficiency, hepatic dystunction, and adrenal insufficiency).

r.e. retai insuitivency, negatic systunction, and adrenal insufficiency). Use caution when prescribing ANGELID to women who regularly take other medications that can increase potassium, such as NSAIDs, potassium-sparing diuretics, potassium supple-ments, ACE inhibitors, angiotensin-II receptor antagonists, and heparin. Consider checking serum potassium levels during the first treatment cycle in high-risk patients. See BOXED WARNINGS.

Cardiovascular disorders. Estrogen and estrogen/progestin therapy has been associa ed with an increased risk of cardiovascular events such as myocardial infarction and strok

ed with an increased risk of cardiovašcular events šuch as myocardial infarction and stroke, as well as venous thrombosis and pulmonary embolism (venous thromboembolism of VTE). Should any of these occur or be suspected, estrogens should be discontinued immediately. Risk factors for cardiovascular disease (e.g., hypertension, diabetes mellitus, tobacco use, hyper-cholesterolemia, and obesity) and/or venous thromboembolism (e.g., personal history or family history of VTE, obesity, and systemic lupus enthmentaxies) should be discontinued immediately. **a.** Coronary heart disease and stroke in the Women's Health Initiative study (WHI), an increase in the number of myocardial infractions and strokes has been observed in women receiving oral CE compared to placebo. (See CLINICAL PHARMACOLOGY, Clinical Studies sections.)

Wollieri rezeving of al cz compared to placebo. Cele CLINICAL PRAVIMACUCUT, CLINICAL Studies sections.) In the CE/MPA substudy of WHI an increased risk of coronary heart disease (CHD) events (defined as non-ratal myocardial infarction and CHD death) was observed in women receiv-ing CE/MPA compared to women receiving placebo (37 vs 30 per 10.000 person years). The increase in risk was observed in year one and persisted. In the same substudy of WHI, an increased risk of stroke was observed in women receiving CE/MPA compared to women receiving placebo (29 vs 21 per 10.000 person-years). The increase in risk was observed after the first year and persisted. In postmenopausal women with documented heart disease (n = 2,763, average age 66.7 years) a controlled cinical trial of secondary prevention of cardiovacular disease (Heart and Estroger/Progestin Replacement Study, HERS) treatment with CE/MPA-0625mg/2.5mg per day demonstrated no cardiovaccular benefit. During an average follow-yoi 61.1 years, treatment with CE/MPA did not reduce the overall rate of CHD events in the CE/MPA-0625mg/2.5mg per day ished coronary heart disease. There were more CHD events in the CE/MPA-062mg/2 to get parts the acebo years 1, but not during the subsequent years.

therapy may be associated with elevations of plasma triggventies reading to planchartizand the complications.
4. Inpaired liver function and past history of cholestatic jaundice. Estrogens may be poorly metabolized in plantens with inpaired liver function. For plantens 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. The clearance of drospierneen was decreased in plattens with moderate hepatic impairment.
5. Hypothyroidism. Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Patients with normal thyroid function can compensate for the increased TBG was provide thyroid hormone, thus maintaining free 14 and 13 serum concentrations in the normal range. Patients dependent on thyroid hormone replacement therapy. These patients should have their thyroid hormone levels on an acceptable range.
6. Fuild refeating Because Strogen and estrogen/progestin therapy may cause some degree.

In the placebo group in year 1, but not during the subsequent years. Two thousand three hundred and twenty one women from the original HERS trial agreed to par-tiopate in an open label extension of HERS, HERS II. Wareage follow-up in HERS II was an addi-tional 27 years, for a total of 6.8 years overall. Rates of CHD events were comparable among women in the CEVMPA group and the pacebo group in HERS, HERS II. and overall. Large doses of strogen (5 mg conjugated estrogens per day), comparable to thuse used to treat cancer of the prostle and breast, have been shown in a lange prospective clinical trial in men to increase the risks of nonfatal myocardial infarction, pulmonary embolism, and thrombophiebilis. **b. Venous thrombophiebilism (VTE)** In the Women's Health Initiative study (WHI), an increase in VTE has been observed in women receiving CE compared to placebo. (See **CLINICAL PHAR-MACDLOEY** and **Clinical Subties** sections.)

D. ventous information of the provided and the provide

was ouserveu uuring uie mist 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 thromboemboliism, or during periods of pro-longed immobilization

longed immobilization. 2. Malignant neoplasms a. 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 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 one year. The great-est risk appears associated with prolonged use, with increased risks of 15- for 24-fold for the 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.

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 matignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is no evidence that the use of natural estrogen secusit is a different endometrial risk profile than synthetic estrogens of equivalent estrogen does. Adding a pro-gestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. **b.** Breast cancer The use of estrogens and progestins by postmenopausal women has been regorded to increas the risk of breast cancer. Theoris important randomized clinical trial pro-viding information about this issue is the Women's Health Initative (WHI) substudy of CE/MPA

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hormone levels (e.g., estradiol, FSH). D. DRUG/LABORATORY TEST INTERACTIONS