

Antiangiogenic State May Be Key in Preeclampsia

BY SHARON WORCESTER
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MIAMI BEACH — Serum levels of soluble endoglin and soluble fms-like tyrosine kinase 1 are increased months before onset of clinical disease in patients with preeclampsia, Dr. Richard Levine said at the annual meeting of the Society for Maternal-Fetal Medicine.

The findings suggest that a circulating antiangiogenic state is important in the

pathogenesis of this maternal syndrome, said Dr. Levine of the National Institute of Child Health and Human Development, Bethesda, Md.

“We believe that soluble endoglin [a cell surface receptor for the proangiogenic protein transforming growth factor- β] and soluble fms-like tyrosine kinase 1 [an antiangiogenic factor that binds placental growth factor and vascular endothelial growth factor] act in concert to produce the maternal syndrome of preeclampsia,” he said.

A nested case-control study of the Calcium for Preeclampsia Prevention (CPEP) trial cohort of healthy nulliparas showed that compared with serum samples from gestational age-matched controls, the levels of these factors were significantly higher beginning 9-11 weeks before preterm preeclampsia. After preeclampsia onset, soluble endoglin (sEng) levels were almost fivefold higher (46 vs. 10 ng/mL) and soluble fms-like tyrosine kinase 1 (sFlt1) levels were nearly threefold higher (6,356 vs.

2,316 pg/mL). Placental growth factor (PlGF) levels were approximately fourfold lower (144 vs. 546 pg/mL), Dr. Levine said.

The findings were based on an analysis of 867 serum samples obtained from 120 controls; 120 patients with term preeclampsia; 72 patients with preterm preeclampsia; 9 patients with hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome; and 8 patients with eclampsia. In patients with term preeclampsia, sEng was increased beginning at 12-14 weeks, free PlGF decreased beginning at 9-11 weeks, and sFlt1 increased less than 5 weeks before preeclampsia onset. Alterations in angiogenic factors were more pronounced in early preeclampsia patients and in patients with preeclampsia plus a small-for-gestational age fetus, HELLP syndrome, or eclampsia, he noted.

Laboratory studies have suggested independent roles for both sEng and sFlt1 in the development of preeclampsia. The present study was designed to test the hypothesis that in preeclampsia, excess soluble endoglin is released from the placenta into the circulation and that it may then synergize with sFlt1, which binds PlGF and vascular endothelial growth factor to cause endothelial dysfunction, he explained. Women in this analysis with high levels of either sEng or sFlt1—but not both—had small elevations in preeclampsia risk. ■

Late Progesterone Also Cuts Repeat Preterm Births

MIAMI BEACH — Progesterone prevents recurrent preterm delivery to the same degree whether it is initiated earlier or later in the second trimester, according to a poster presentation at the annual meeting of the Society for Maternal-Fetal Medicine.

“We were thinking that those who started earlier would have some benefit. But essentially it doesn't matter if you start progesterone at 16-18 weeks or between 19 and 21 weeks,” said Dr. Gretchen Koontz of the ob.gyn. department at Wake Forest University in Winston-Salem, N.C.

In a 2003 study, researchers randomized women with a history of previous spontaneous preterm birth (before 37 weeks) to weekly injections of either 17 α -hydroxyprogesterone caproate (17P) or placebo (N. Engl. J. Med. 2003;348:2379-85). Of the 306 women who received 17P between 16 and 21 weeks' gestation, 36% delivered before 37 weeks, compared with 55% of the 153 women in the placebo group, a statistically significant difference.

As a secondary analysis of the original study data, Dr. Koontz compared 227 women who began weekly injections of 17P between 16 and 18 weeks, with 272 others who began 17P between weeks 19 and 21. Results showed that 36.5% of participants in the 16- to 18-week group delivered preterm, compared with 36.1% of those in the 19- to 21-week group.

—Damian McNamara

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BRIEF SUMMARY

ESTROGENS INCREASE THE RISK OF ENDOMETRIAL CANCER

Close clinical surveillance of all women taking estrogen 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 at equivalent estrogenic doses. (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 Women's Health Initiative (WHI) study 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 5 years of treatment with oral conjugated estrogens (CE 0.625 mg) combined with medroxyprogesterone acetate (MPA 2.5 mg) relative to placebo (See **CLINICAL PHARMACOLOGY, Clinical Studies, WARNINGS, 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 dementia in postmenopausal women 65 years of age or older during 4 years of treatment with oral conjugated estrogens plus medroxyprogesterone acetate relative to placebo. It is unknown whether this finding applies to younger postmenopausal women. (See **CLINICAL PHARMACOLOGY, Clinical Studies, WARNINGS, Dementia and PRECAUTIONS, Geriatric Use.**)

Other doses of conjugated estrogens with medroxyprogesterone acetate, and other combinations of estrogens and progestins were not studied in the WHI 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.

CONTRAINDICATIONS

Estrasorb 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 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. Liver dysfunction or disease.
7. Estrasorb should not be used in patients with known hypersensitivity to its ingredients.
8. Known or suspected pregnancy. There is no indication for Estrasorb in pregnancy. There appears to be little or no increased risk of birth defects in women who have used estrogens and progestins from oral contraceptives inadvertently during early pregnancy. (See **PRECAUTIONS.**)

WARNINGS

See **BOXED WARNINGS.**

1. Cardiovascular disorders

Estrogen and estrogen/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. Coronary heart disease and stroke

In the Women's Health Initiative (WHI) study, an increase in the number of myocardial infarctions and strokes has been observed in women receiving CE compared to placebo. In the CE/MPA substudy of WHI an increased risk of coronary heart disease (CHD) events (defined as non-fatal myocardial infarction and CHD death) was observed in women receiving CE/MPA compared to women receiving placebo (37 vs 30 per 10,000 person-years). The increase in risk was observed after the first year and persisted. (See **CLINICAL PHARMACOLOGY, Clinical Studies.**)

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. (See **CLINICAL PHARMACOLOGY, Clinical Studies.**)

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/2.5 mg per day) 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 1, but not during the subsequent years. Two thousand three hundred and twenty 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 HERS, 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 risks of nonfatal myocardial infarction, pulmonary embolism, and thrombophlebitis.

b. Venous thromboembolism (VTE)

In the Women's Health Initiative (WHI) study, an increase in VTE has been observed in women receiving CE compared to placebo.

In the CE/MPA substudy of WHI, a 2-fold greater rate of VTE, including deep venous thrombosis and pulmonary embolism, was observed in women receiving CE/MPA compared to women receiving placebo. The rate of VTE was 34 per 10,000 person-years in the CE/MPA group compared to 16 per 10,000 person-years in the placebo group. The increase in VTE risk was observed during the first year and persisted. (See **CLINICAL PHARMACOLOGY, Clinical Studies.**)

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 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 the use of estrogens for less than 1 year. The greatest risk appears associated with prolonged use, with increased risks of 15- to 24-fold for use over 5 to 10 years or more, and this risk has been shown to persist at least 8 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 estrogen dose. Adding a progestin 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 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) substudy of CE/MPA (See **CLINICAL PHARMACOLOGY, Clinical Studies.**) The results from observational studies are generally consistent with those of the WHI clinical trial and report no significant variation in the risk of breast cancer among different estrogens or progestins, doses or routes of administration.

The CE/MPA substudy of (WHI) reported an increased risk of breast cancer in women who took CE/MPA for a mean follow-up of 5.6 years. Observational studies have 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 increased with duration of use. From observational studies the risk appeared to return to baseline in about five years after stopping treatment. In addition, observational studies suggest that the risk of breast cancer was greater, and became apparent earlier, with estrogen/progestin combination therapy as compared to estrogen alone therapy.

In the CE/MPA substudy, 26% 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 during the clinical trial, the overall relative risk of invasive breast cancer was 1.24 (95% confidence interval 1.01-1.54), and the overall absolute risk was 41 vs 33 cases per 10,000 women-years for CE/MPA compared with placebo. Among women who reported prior use of hormone therapy, the relative risk of invasive breast cancer was 1.86 and the absolute risk was 46 vs 25 cases per 10,000 women-years, for CE/MPA compared with placebo. Among women who reported no prior use of hormone therapy, the relative risk of invasive breast cancer was 1.09, and the absolute risk was 40 vs 36 cases per 10,000 women-years for CE/MPA compared with placebo. In the same substudy, invasive breast cancers were larger and diagnosed at a more advanced stage in the CE/MPA 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 health care 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 Women's Health Initiative Memory Study (WHIMS), 4,532 generally healthy postmenopausal women 65 years of age and older were studied, of whom 35% were 70 to 74 years of age and 18% were 75 or older. After 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=2,303) received diagnoses of probable dementia. The relative risk for CE/MPA versus placebo was 2.05 (95% 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 dementia for CE/MPA versus placebo was 45 versus 22 cases per 10,000 women-years, 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 postmenopausal women. (See **CLINICAL PHARMACOLOGY, Clinical Studies 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 sudden onset of proptosis, diplopia, or migraine. If examination reveals papilledema 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 lower 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 treatment. These include a possible increased risk 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 trial, a generalized effect of estrogens 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 pancreatitis and other complications.

4. Impaired liver function and past history of cholestatic jaundice

Although topically administered estrogen therapy avoids first-pass hepatic metabolism, estrogens may be poorly metabolized in patients with impaired liver function. For patient 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 T₄ and T₃ 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 CE/MPA substudy of WHI reported that estrogen plus progestin increased the risk of ovarian cancer. After an average follow-up of 5.6 years, 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 CE/MPA versus placebo was 4.2 versus 2.7 cases per 10,000 women-years. In some epidemiologic studies, the use of estrogen alone, in particular for ten 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. A few cases of malignant transformation of residual endometrial implants have been reported in women treated post-hysterectomy with estrogen only therapy. For patients known to have residual 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 patients with these conditions.

11. Application of sunscreen

Estrasorb should not be used in close proximity to sunscreen application because estradiol absorption may be increased. (See **CLINICAL PHARMACOLOGY, Pharmacokinetics, Absorption.**)

B. PATIENT INFORMATION

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

C. LABORATORY TESTS

Estrogen administration should be initiated at the lowest dose approved for the indication and then guided by clinical 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 antigen, VIII coagulant activity, IX, X, XII, VII-X complex, II-VII-X complex, and beta-thromboglobulin; decreased levels of antithrombin 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, 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, and sex hormone binding globulin), leading to increased circulating corticosteroids and sex steroids, respectively. Free or biologically active hormone concentrations are unchanged. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).

4. Increased plasma HDL and HDL₂-cholesterol subfraction concentrations, reduced LDL cholesterol concentration, and increased triglyceride levels.

5. Impaired glucose tolerance.

6. Reduced response to meprobamate test.

E. CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Long-term continuous administration of estrogen, with and without progestin, in women with and 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

Estrasorb 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 Estrasorb is administered to a nursing woman.

H. Pediatric Use

Estrasorb is not indicated in children.

I. Geriatric Use

There have not been sufficient numbers of geriatric patients involved in studies utilizing Estrasorb to determine whether those over 65 years of age differ from younger subjects in their response to Estrasorb.

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 18% (n=803) were 75 and over. Most women (80%) had no prior hormone therapy use. Women treated with conjugated estrogens plus medroxyprogesterone acetate were reported to have a two-fold increase in the risk of developing probable dementia. Alzheimer's disease was the most common classification of probable dementia in both the conjugated estrogens plus medroxyprogesterone acetate group and the placebo group. Ninety percent of the cases of probable dementia occurred in the 54% of women that were older than 70. (See **WARNINGS, Dementia.**)

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 effects that appear to be related to drug use and for approximating rates.

Table 4 summarizes the treatment-emergent adverse events with Estrasorb therapy.

Table 4. Number (%) of Patients Reporting \geq 5% Treatment-Emergent Adverse Events

Body system/ Preferred term	Statistic	Treatment group	
		Placebo (n = 134)	Estrasorb 3.45 grams (n = 139)
Number of subjects with \geq 1 TEAE	n (%)	82 (61)	95 (68)
Body as a whole	n (%)	40 (30)	49 (35)
Headache	n (%)	17 (13)	12 (9)
Infection	n (%)	10 (7)	16 (12)
Respiratory	n (%)	15 (11)	19 (14)
Sinusitis	n (%)	6 (4)	9 (6)
Skin and appendages	n (%)	7 (5)	15 (11)
Pruritus	n (%)	0	5 (4)
Urogenital	n (%)	20 (15)	44 (32)
Breast pain	n (%)	4 (3)	14 (10)
Endometrial disorder	n (%)	11 (8)	21 (15)
TEAE = Treatment-emergent adverse event.			

The following additional adverse reactions have been reported with estrogen and/or progestin therapy:

1. Genitourinary system

Changes in vaginal bleeding pattern and abnormal withdrawal bleeding or flow; breakthrough bleeding, spotting; dysmenorrhea; increase in size of uterine leiomyomas; vaginitis including vaginal candidiasis; change in amount of cervical secretion; changes in cervical ectropion; ovarian cancer, endometrial hyperplasia; endometrial cancer.

2. Breasts

Tenderness, enlargement, pain, nipple discharge, galactorrhea; fibrocystic breast changes; breast cancer.

3. Cardiovascular

Deep and superficial venous thrombosis; pulmonary embolism; thrombophlebitis; myocardial infarction; stroke; increase in blood pressure.

4. Gastrointestinal

Nausea, vomiting; abdominal cramps, bloating; cholestatic jaundice; increased incidence of gall bladder disease; pancreatitis, enlargement of hepatic hemangiomas.

5. Skin

Chloasma or melasma that may persist when drug is discontinued; erythema multiforme; erythema nodosum; hemorrhagic eruption; loss of scalp hair; hirsutism; pruritus, rash.

6. Eyes

Retinal vascular thrombosis, intolerance to contact lenses.

7. Central Nervous System

Headache, migraine, dizziness; mental depression; chorea; nervousness; mood disturbance; irritability; exacerbation of epilepsy, dementia.

8. Miscellaneous

Increase or decrease in weight; reduced carbohydrate tolerance; aggravation of porphyria; edema; arthralgia; leg cramps; changes in libido; urticaria; angioedema, anaphylactoid/anaphylactic reactions; hypocalcemia; exacerbation of asthma; increased triglycerides.

OVERDOSAGE

Serious ill effects have not been reported following acute ingestion of large doses of estrogen-containing products by young children. Overdose of estrogen may cause nausea and vomiting, and withdrawal bleeding may occur in women.

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