

Mood in Pregnancy May Impact Fetal Development

BY PATRICE WENDLING
Chicago Bureau

PITTSBURGH — Pregnant women with anxiety or depression have higher levels of α -amylase, a measure of adrenergic system activity, and lower morning cortisol levels, preliminary results from a longitudinal study demonstrated.

The findings suggest that the sympathetic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis may be

affected in opposite directions by stress during pregnancy, Alison Shea, Ph.D. candidate, and her associates reported in a poster at the International Congress of Neuroendocrinology.

The analysis included 60 women who were among the first of 250 pregnant women to be recruited as part of the multicenter Maternal Adversity, Vulnerability, and Neurodevelopment (MAVAN) study led by Dr. Meir Steiner, of McMaster University, Hamilton, Ont.

The women were divided into three groups: those presenting with symptoms of depression or anxiety who chose psychotherapy only, those with symptoms who chose antidepressants, and a control group with no current or past psychiatric illness.

A battery of psychological tests was performed at baseline (gestational age 14-24 weeks), and morning salivary samples were collected daily to measure stress indicators such as cortisol, dehydroepi-

androsterone (DHEA), and α -amylase. A follow-up assessment was performed at 24-30 weeks and included psychological testing, salivary samples, and a 24-hour Holter ECG.

Infants are being followed during the postpartum period until 3 years of age.

The results indicate that depression and anxiety scores during pregnancy are positively correlated with α -amylase levels and negatively correlated with morning cortisol levels.

Both associations were statistically significant, reported Ms. Shea, of the Women's Health Concerns Clinic, St. Joseph's Healthcare, Hamilton.

Compared with controls, both the cortisol response to awakening and the 24-hour heart rate variability were lower for mothers with anxiety and depression, particularly among those not taking antidepressants.

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Reduced heart rate variability indicates the body's inability to respond to stress in a changing environment, and is thought to improve with the use of antidepressants, Ms. Shea said in an interview. Interestingly, the study found that the greater the gravida's heart rate variability, the longer the gestation. "It makes sense, but it's never been looked at in pregnant women," she said.

Head circumference at birth was strongly correlated with maternal 24-hour mean heart rate during pregnancy, even after controlling for birth weight and gestational age.

Among women with depression and anxiety, the higher the heart rate during pregnancy, the smaller the head circumference. Head circumference is purported to be a measure of brain volume and has been found to be smaller among babies born to women with posttraumatic stress disorder, she said.

Birth length was significantly smaller for babies born to women with anxiety or depression (49.64 cm), compared with those born to women treated with antidepressants (50.91 cm) and controls (53.01 cm).

Ponderal index, which is an indicator of infant body mass index, also was significantly higher among babies of women suffering from anxiety and depression (2.65 g/cm³), compared with those of women treated with antidepressants (2.55 g/cm³) and of controls (2.3 g/cm³). The lower the maternal cortisol levels during pregnancy, the higher the ponderal index, which suggests some type of modulation of the HPA axis that would impact birth outcomes and growth, Ms. Shea said.

The data provide some insights into the mechanisms by which stress, depression, and anxiety impact fetal development. But Ms. Shea cautioned that the data remain preliminary and the number of patients is small.



Only (For full Prescribing Information and Patient Information, visit www.PremarinVaginalCream.com)

ESTROGENS INCREASE THE RISK OF ENDOMETRIAL CANCER

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 Women's Health Initiative (WHI) study reported increased risks of stroke and deep vein thrombosis in postmenopausal women (50 to 79 years of age) during 6.8 years of treatment with conjugated estrogens (0.625 mg) relative to placebo. (See **CLINICAL PHARMACOLOGY, Clinical Studies** in full Prescribing Information and **WARNINGS, Cardiovascular disorders.**)

The 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 (0.625 mg) combined with medroxyprogesterone acetate (2.5 mg) relative to placebo. (See **CLINICAL PHARMACOLOGY, 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 increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 5.2 years of treatment with oral conjugated estrogens alone and during 4 years of treatment with conjugated estrogens combined with medroxyprogesterone acetate, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women. (See **CLINICAL PHARMACOLOGY, Clinical Studies** in full Prescribing Information, **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 considered 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 (conjugated estrogens) Vaginal Cream is indicated in the treatment of atrophic vaginitis and kraurosis vulvae.

CONTRAINDICATIONS

Premarin Vaginal Cream 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 a history of these conditions.
5. Active or recent (e.g., within past year) arterial thromboembolic disease (e.g., stroke, myocardial infarction).
6. Liver dysfunction or disease.
7. Premarin Vaginal Cream should not be used in patients with known hypersensitivity to its ingredients.
8. Known or suspected pregnancy. There is no indication for Premarin Vaginal Cream 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.

Systemic absorption may occur with the use of Premarin Vaginal Cream. The warnings, precautions, and adverse reactions associated with oral Premarin treatment should be taken into account.

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 estrogen alone substudy of the Women's Health Initiative (WHI) study, an increased risk of stroke was observed in women receiving Premarin compared to women receiving placebo (44 vs 32 per 10,000 women-years). The increase in risk was observed in year one and persisted. (See **CLINICAL PHARMACOLOGY, Clinical Studies** in full Prescribing Information.)

In the estrogen plus progestin substudy of WHI, an increased risk of coronary heart disease (CHD) events (defined as nonfatal myocardial infarction and CHD death) was observed in women receiving PREMPRO (0.625 mg conjugated estrogens plus 2.5 mg medroxyprogesterone acetate) per day compared to women receiving placebo (37 vs 30 per 10,000 women-years). The increase in risk was observed in year one and persisted.

In the same estrogen plus progestin substudy of the WHI, an increased risk of stroke was observed in women receiving PREMPRO compared to women receiving placebo (29 vs 21 per 10,000 women-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 clinical trial of secondary prevention of cardiovascular disease (Heart and Estrogen/progestin Replacement Study; HERS) treatment with PREMPRO (0.625 mg conjugated estrogen plus 2.5 mg medroxyprogesterone acetate per day) demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with PREMPRO did not reduce the overall rate of CHD events in postmenopausal women with established coronary heart disease. There were more CHD events in the PREMPRO-treated group than 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 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 PREMPRO group and the placebo group in HERS, HERS I, 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 estrogen alone substudy of the Women's Health Initiative (WHI) study, an increased risk of deep vein thrombosis was observed in women receiving Premarin compared to placebo (21 vs 15 per 10,000 women-years). The increase in VTE risk was observed during the first year. (See **CLINICAL PHARMACOLOGY, Clinical Studies** in full Prescribing Information.)

In the estrogen plus progestin substudy of WHI, a 2-fold greater rate of VTE, including deep venous thrombosis and pulmonary embolism, was observed in women receiving PREMPRO compared to women receiving placebo. The rate of VTE was 34 per 10,000 women-years in the Prempro group compared to 16 per 10,000 women-years in the placebo group. The increase in VTE risk was observed 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 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 increased 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 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 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) trial of estrogen plus progestin (see **CLINICAL PHARMACOLOGY, Clinical Studies** in full Prescribing Information.) The results from observational studies are generally consistent with those of the WHI clinical trial. After a mean follow-up of 5.5 years, the WHI trial reported an increased risk of breast cancer in women who took estrogen plus progestin. 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. 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/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/progestin combinations, doses, or routes of administration.

In the WHI trial of estrogen plus progestin, 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 estrogen plus progestin 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 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 41 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 observational Million Women Study in Europe reported an increased risk of mortality due to breast cancer among current users of estrogens alone or estrogens plus progestins compared to never users, while the estrogen plus progestin sub-study of WHI showed no effect on breast cancer mortality with a mean follow-up of 5.6 years. 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 Premarin (0.625 mg) or placebo. In the estrogen plus progestin WHIMS substudy, a population of 4,532 postmenopausal women aged 65 to 79 years was randomized to PREMPRO (0.625 mg/2.5 mg) 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 Premarin alone versus placebo was 1.49 (95% CI 0.83-2.66). The absolute risk of probable dementia for Premarin alone versus placebo was 37 versus 25 cases per 10,000 women-years.

In the estrogen plus progestin substudy, after an average follow-up of 4 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 versus placebo was 2.06 (95% CI 1.21-3.48). The absolute risk of probable dementia for PREMPRO versus placebo was 45 versus 22 cases per 10,000 women-years.

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 postmenopausal 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 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.** 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 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. **Hypercalcemia.** Estrogens should be used with caution in individuals with severe hypercalcemia.

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 versus placebo was 1.58 (95% confidence interval 0.77-3.24) but was not statistically significant. The absolute risk for estrogen plus progestin versus placebo was 4.2 versus 2.7 cases per 10,000 women-years. In some epidemiologic studies, the use of estrogen-only products, 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 estrogen therapy. A few cases of 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 women with these conditions.

11. **Barrier contraceptives.** Premarin Vaginal Cream exposure has been reported to weaken latex condoms. The potential for Premarin Vaginal Cream to weaken and contribute to the failure of condoms, diaphragms, or cervical caps made of latex or rubber should be considered.

- B. **Patient Information** Physicians are advised to discuss the contents of the **PATIENT INFORMATION** leaflet with patients for whom they prescribe Premarin Vaginal Cream.

- C. **Laboratory Tests** Estrogen administration should be guided by clinical response at the lowest dose for the treatment of postmenopausal vulvar and vaginal atrophy.

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 antithrombin III and antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity.

2. Increased thyroid-binding globulin (TBG) 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 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), 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).

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

5. Impaired glucose tolerance.

6. Reduced response to methyprylon 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 Vaginal Cream 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 the drug. Caution should be exercised when Premarin Vaginal Cream 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 adult 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; see DOSAGE AND ADMINISTRATION** section in full Prescribing Information.

- 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 (Premarin vs. placebo) of stroke in women less than 75 years of age compared to women 75 years and over.

In the estrogen alone substudy of the 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 Premarin (0.625 mg) or placebo. In the estrogen alone group, after an average follow-up of 5.2 years, the relative risk (Premarin vs. placebo) of probable dementia was 1.49 (95% CI 0.83-2.66).

Of the total number of subjects in the estrogen plus progestin substudy of the Women's Health Initiative study, 44% (n = 3,200) were 65 years and over, while 6.6% (n = 1,093) were 75 years and over. There was a higher relative risk (PREMPRO vs. placebo) of stroke and invasive breast cancer in women 75 and over compared to women less than 75 years of age.

In the estrogen plus progestin substudy of WHIMS, a population of 4,532 postmenopausal women, aged 65 to 79 years, was randomized to PREMPRO (0.625 mg/2.5 mg) or placebo. In the estrogen plus progestin group, after an average follow-up of 4 years, the relative risk (PREMPRO vs. placebo) of probable dementia was 2.06 (95% CI 1.21-3.48).

Pooling the events in women receiving Premarin or PREMPRO in comparison to those in women on placebo, the 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 WARNINGS, Dementia.**)

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

ADVERSE REACTIONS

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

Systemic absorption may occur with the use of Premarin Vaginal Cream. Warnings, precautions, and adverse reactions associated with oral Premarin treatment should be taken into account.

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

1. **Genitourinary system:** Breakthrough bleeding, spotting, changes in vaginal bleeding pattern and abnormal withdrawal bleeding or flow; dysmenorrhea; increase in size of uterine leiomyomas; vaginitis, including vaginal candidiasis; change in cervical erosion and in degree of cervical secretion; cystitis-like syndrome; application site reactions of vulvovaginal discomfort including burning and irritation; genital pruritus; ovarian cancer; endometrial hyperplasia; endometrial cancer; precocious puberty.

2. **Breasts:** Tenderness, pain, enlargement, secretion; breast cancer; fibrocystic breast changes.

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; pancreatitis; increased incidence of gallbladder disease; enlargement of hepatic hemangiomas.

5. **Skin:** Chloasma or melasma which 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, nervousness; mood disturbances; irritability; mental depression; chorea; exacerbation of epilepsy; dementia.

8. **Miscellaneous:** Increase or decrease in weight; reduced carbohydrate tolerance; glucose intolerance; aggravation of porphyria; edema; changes in libido; urticaria, angioedema, anaphylactoid/anaphylactic reactions; hypocalcemia; exacerbation of asthma; increased triglycerides; arthralgias; leg cramps.

OVERDOSAGE

Serious ill effects have not been reported following acute ingestion of large doses of estrogen/progestin containing drug products by young children. Overdosage of estrogens may cause nausea and vomiting, and withdrawal bleeding may occur in females.

This brief summary is based on PREMARIN® (conjugated estrogens) Vaginal Cream Prescribing Information W104130C008 ET01, revised September 12, 2005.

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119451-01