

Managing Pregnancy in Rheumatic Disease Patients

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CHICAGO — The only “sure thing” about the medical management of pregnant women who have a rheumatic disease is that there are no sure things, advises a rheumatologist with particular expertise in lupus.

“In an ideal world, pregnancy in these women would always be planned; the rheumatic disease would have been in remission for at least 6 months at the time of conception, and there would be a plan for treatment if the disease flares. Unfortunately, clinical medicine isn’t an ideal world,” said Dr. Bonnie L. Bermas, director of the Center for Lupus and Antiphospholipid Antibody at Brigham and Women’s Hospital, Boston.

Exacerbating the challenge is the absence of any one-size-fits-all management formula, Dr. Bermas said, noting that the interplay among the individual patient, disease, and treatment variables—all of which are unpredictable—drives therapeutic decisions.

With rheumatoid arthritis (RA), for example, “the literature supports that about 70%-80% of patients will go into remission during pregnancy, though most will flare post partum,” said Dr. Bermas at a symposium sponsored by the American College of Rheumatology (ACR). Even

though this knowledge provides clinicians with some flexibility with respect to medication during pregnancy, “we really can’t predict who’s going to go into remission, so we can’t say up front, ‘I guarantee you’ll be able to go off treatment once you become pregnant,’” she said.

Systemic lupus erythematosus (SLE), on the other hand, is thought to be associated with a slightly increased risk of flare during pregnancy, said Dr. Bermas. “This means that we will approach a lu-

pus patient differently than a rheumatoid arthritis patient in terms of our management plan, and the answers to the critical questions—‘Will the disease flare? Will the baby be affected by the disease? What medications are safe to take during pregnancy?’—will be different.”

Although the Food and Drug Administration’s use-in-pregnancy ratings for the mainstays of rheumatic disease therapies provide a management framework, there is often a discrepancy between what the

FDA says is allowable during pregnancy and what clinicians feel comfortable prescribing, Dr. Bermas said.

NSAIDs, Cyclooxygenase-2 Inhibitors

Although animal studies have shown an increased risk of congenital anomalies with these agents, “when you get to the human studies, there really is no increased risk of congenital anomalies,” said Dr. Bermas. “There is an increased risk of premature closure of the ductus arteriosus in pa-

Drug Treatment Considerations

The treatment of rheumatic diseases in pregnant women should be based on disease severity and drug safety, according to Dr. Bermas, who suggested the following general guide to treatment options:

Mild Disease

- ▶ For inflammatory arthritis, Dr. Bermas recommends stopping drug therapy before pregnancy or when pregnancy is discovered.
- ▶ For SLE, maintain these patients on hydroxychloroquine.
- ▶ NSAIDs are acceptable up to week 24.

Moderate Disease

- ▶ Steroids should be used at the lowest possible dose.
- ▶ Azathioprine should be used with caution.
- ▶ Cyclosporin A should be used with caution.
- ▶ Sulfasalazine should be used with caution.

Severe Disease

- ▶ High-dose steroids should be used with caution.
- ▶ Azathioprine should be used with caution.
- ▶ Cyclosporin A should be used with caution.
- ▶ Cyclophosphamide should be used only in life-or-death situations.



Evamist™ is indicated for the treatment of moderate-to-severe vasomotor symptoms due to menopause.

WARNING—ENDOMETRIAL CANCER, CARDIOVASCULAR, AND OTHER RISKS

ENDOMETRIAL CANCER 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.

CARDIOVASCULAR AND OTHER RISKS Estrogens with or without progestins should not be used for the prevention of cardiovascular disease or dementia. The Women’s Health Initiative (WHI) estrogen-alone substudy 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 daily oral conjugated estrogens (CE 0.625 mg), relative to placebo.

The estrogen plus progestin WHI substudy reported increased risk of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and DVT in postmenopausal women (50 to 79 years of age) during 5.6 years of treatment with daily oral CE 0.625 mg combined with medroxyprogesterone acetate (MPA 2.5 mg), relative to placebo.

tients exposed to nonsteroidals late in pregnancy, so we counsel patients that they can use nonsteroidals up to 24 weeks' gestation. We could probably protract this out to 30 weeks, but it's easier to say, 'stop the NSAIDs in the third trimester.'"

For patients trying to conceive, "we advise that they avoid using COX-2s and NSAIDs during the conception cycle because both can have an impact on implantation," Dr. Bermas noted.

Antimalarials

A single case report of congenital defects in three of four babies born to one mother who took 250 mg of chloroquine two

times a day during each of her four pregnancies earned antimalarials an FDA category C rating, "which is sort of representative of how the literature about medication in pregnancy has been interpreted over the years," said Dr. Bermas. In the meantime, she said, there have been several case series in which no increased risk of congenital anomalies has been seen, and the literature on the use of these drugs as malarial prophylaxis (at higher doses than are used to treat rheumatic disease) has identified no untoward effects in pregnant women.

"For many years, we didn't use any of these drugs during pregnancy, but a recent

ACR survey showed that most rheumatologists today are comfortable leaving patients on antimalarials during pregnancy," said Dr. Berman. "Having said that, if I have an RA patient whose main medication is hydroxychloroquine, that patient probably has fairly mild disease. Considering that most RA patients go into remission during pregnancy, I usually recommend stopping the drug during gestation."

But for a patient with SLE who is well maintained on hydroxychloroquine, "I'd probably keep the medication on board," because additional data show that patients with lupus who remain on therapy have better outcomes.

Steroids

For flares of most rheumatic diseases, steroids are considered "the ace in the hole," said Dr. Bermas.

"During pregnancy, if rheumatoid arthritis, for example, becomes active, most clinicians recommend starting treatment with the lowest dose possible of a glucocorticoid medication, most commonly prednisone." Both prednisone and methylprednisolone cross the placenta, but only at low levels, she said.

The data on steroid safety during pregnancy are mixed. "Originally, there were some case reports of cleft palate formation

Continued on following page

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†At Week 12, mean change of -1.04 from baseline score 2.53 with 1 spray/day vs mean change of -0.26 from baseline score 2.55 with placebo (P<0.0001).

‡Patients should wait at least 2 minutes after applying Evamist before dressing.¹

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(estradiol transdermal spray)

The Women's Health Initiative Memory Study (WHIMS), a substudy of the WHI, reported increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 5.2 years of treatment with daily CE 0.625 mg alone and during 4 years of treatment with daily CE 0.625 mg combined with MPA 2.5 mg, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women.

In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and MPA and other combinations and dosage forms of estrogens and progestins. 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.

Evamist should not be used in women with undiagnosed abnormal genital bleeding; known, suspected, or history of breast cancer; known or suspected estrogen-dependent neoplasia; active deep vein thrombosis, pulmonary embolism, or history of these conditions; active or recent arterial thromboembolic disease; liver dysfunction or disease; or known or suspected pregnancy.

In a clinical trial with Evamist, the most common side effects were headache, breast tenderness, nasopharyngitis, nipple pain, back pain, nausea, and arthralgia.

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Continued from previous page

in offspring, although no increased risk of fetal anomalies was found in a large series of asthma patients treated with steroids throughout pregnancy," said Dr. Bermas. "In a meta-analysis of epidemiological studies, however, there was a 3.4-fold increase in the incidence of cleft palate formation associated with maternal exposure to corticosteroids [Teratology, 2000;62:385-92]," she said. "The key time frame seems to be between weeks 6 and 12, when the palate is forming."

Corticosteroids during pregnancy are also associated with maternal comorbidities,

including gestational diabetes, hypertension, and accelerated osteoporosis. "For this reason, the goal should always be to keep the dose as low as possible," she said.

Azathioprine and 6-Mercaptopurine

The use of azathioprine, a nonbiologic disease-modifying antirheumatic drug, is generally limited to women with severe disease who have not responded to other treatments, Dr. Bermas stated. There are "conflicting data about the safety of this drug during pregnancy. Animal data [suggest that] the drug is teratogenic, and there have been case reports of fetal malformations, but transplant series indicate that the med-

ication doesn't increase the rate of congenital anomalies," she said. Small-for-gestational-age babies and premature rupture of membranes are associated with use of the drug during pregnancy.

As with azathioprine, the nucleoside analog 6-mercaptopurine is teratogenic in animals, and it is plagued by conflicting human data. Some of the human studies suggest that "there is an increased risk of congenital anomalies, but the gastrointestinal literature doesn't support this," Dr. Bermas noted. "From a rheumatology perspective, this medication is rarely used, so I would suggest discontinuing it during pregnancy."

Sulfasalazine

"Case reports of fetal malformations linked to sulfasalazine from the inflammatory bowel disease literature didn't pan out in larger studies," said Dr. Bermas. "This drug can be used in pregnancy. It does cause azoospermia in men, however, so if you have a male patient who is interested in trying to get his partner pregnant, advise him to stop taking sulfasalazine for 3 months before conception for spermatogenesis."

Penicillamine

Occasionally used in the treatment of progressive systemic sclerosis, penicillamine

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BRIEF SUMMARY

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WARNING—ENDOMETRIAL CANCER, CARDIOVASCULAR AND OTHER RISKS

ENDOMETRIAL CANCER

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 [see Warnings and Precautions].

CARDIOVASCULAR AND OTHER RISKS

Estrogens with or without progestins should not be used for the prevention of cardiovascular disease or dementia [see Warnings and Precautions and Clinical Studies].

The Women's Health Initiative (WHI) estrogen-alone substudy 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 daily oral conjugated estrogens (CE 0.625 mg), relative to placebo [see Warnings and Precautions and Clinical Studies].

The estrogen plus progestin WHI substudy reported increased risk of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and DVT in postmenopausal women (50 to 79 years of age) during 5.6 years of treatment with daily oral CE 0.625 mg combined with medroxyprogesterone acetate (MPA 2.5 mg), relative to placebo [see Warnings and Precautions and Clinical Studies].

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In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and MPA and other combinations and dosage forms of estrogens and progestins. 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

Evamist™ (estradiol transdermal spray) is an estrogen indicated for the treatment of moderate to severe vasomotor symptoms due to menopause.

DOSAGE AND ADMINISTRATION

General Dosing Information

When estrogen is prescribed for a postmenopausal woman with a uterus, generally, a progestin should also be initiated to reduce the risk of endometrial cancer. A woman without a uterus does not need progestin.

Use of estrogen, alone or in combination with a progestin, should be with the lowest effective dose and for the shortest duration consistent with treatment goals and risks for the individual woman. Patients should be re-evaluated periodically as clinically appropriate (for example at 3-month to 6-month intervals) to determine if treatment is still necessary.

Treatment of Moderate to Severe Vasomotor Symptoms

Evamist™ therapy should be initiated with one spray per day. Dosage adjustment should be guided by the clinical response.

Before applying the first dose from a new applicator, the pump should be primed by spraying 3 sprays with the cover on. The container should be held upright and vertical for spraying.

One, two or three sprays are applied each morning to adjacent, non-overlapping areas on the inner surface of the forearm, starting near the elbow. Sprays should be allowed to dry for approximately 2 minutes and the site should not be washed for 30 minutes. Application of Evamist to other skin surfaces has not been adequately studied. Evamist should not be applied to skin surfaces other than the forearm.

CONTRAINDICATIONS

Evamist should not be used in women with any of the following conditions:

- Undiagnosed abnormal genital bleeding
- Known, suspected, or history of cancer of the breast
- Known or suspected estrogen-dependent neoplasia
- Active deep vein thrombosis, pulmonary embolism, or history of these conditions
- Active or recent (within the past year) arterial thromboembolic disease (for example, stroke and myocardial infarction)
- Known liver dysfunction or disease
- Known or suspected pregnancy

WARNINGS AND PRECAUTIONS

Cardiovascular Disorders

An increased risk of stroke and deep vein thrombosis (DVT) has been reported with estrogen-alone therapy. An increased risk of stroke, DVT, pulmonary embolism, and myocardial infarction has been reported with estrogen plus progestin therapy. Should any of these occur or be suspected, estrogens with or without progestins should be discontinued immediately.

Risk factors for arterial vascular disease (for example, hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and obesity) and/or venous thromboembolism (for example, personal history or family history of venous thromboembolism [VTE], obesity, and systemic lupus erythematosus) should be managed appropriately.

Stroke

In the Women's Health Initiative (WHI) estrogen-alone substudy, a statistically significant increased risk of stroke was reported in women receiving daily conjugated estrogens (CE 0.625 mg) compared to placebo (45 versus 33 per 10,000 women-years). The increase in risk was demonstrated in year 1 and persisted [see Clinical Studies].

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

Coronary heart disease

In the estrogen alone substudy of WHI, no overall effect on coronary heart disease (CHD) events (defined as non-fatal myocardial infarction [MI], silent MI, or CHD death) was reported in women receiving estrogen alone compared to placebo [see Clinical Studies].

In the estrogen plus progestin substudy of WHI, no statistically significant increase of CHD events was reported in women receiving CE/MPA compared to women receiving placebo (39 versus 33 per 10,000 women-years). An increase in relative risk was demonstrated in year 1, and a trend toward decreasing relative risk was reported in years 2 through 5 [see 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 daily CE 0.625 mg/MPA 2.5 mg 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-one (2,321) 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.

Venous Thromboembolism (VTE)

In the estrogen-alone substudy of WHI, the risk of VTE (DVT and pulmonary embolism [PE]) was reported to be increased for women receiving daily CE compared to placebo (30 versus 22 per 10,000 women-years), although only the increased risk of DVT reached statistical significance (23 versus 15 per 10,000 women-years). The increase in VTE risk was demonstrated during the first two years [see Clinical Studies].

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

Malignant Neoplasms

Endometrial Cancer

An increased risk of endometrial cancer has been reported with the use of unopposed estrogen therapy in women with a uterus. The reported endometrial cancer risk among unopposed estrogen users is about 2 to 12 times 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 1 year. The greatest risk appears associated with prolonged use, with an increased risk of 15- to 24-fold for 5 to 10 years or more. This risk has been shown to persist for at least 8 to 15 years after estrogen therapy is discontinued.

Clinical surveillance of all women using estrogen plus progestin therapy 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.

Breast Cancer

The use of estrogens and progestins by postmenopausal women has been reported to increase the risk of breast cancer in some studies. Observational studies have also reported an increased risk of breast cancer for estrogen plus progestin therapy, and a smaller increased risk for estrogen-alone therapy, after several years of use. The risk increased with duration of use, and appeared to return to baseline over about 5 years after stopping treatment (only the observational studies have substantial data on risks after stopping). Observational studies also suggest that the risk of breast cancer was greater, and became apparent earlier, with estrogen plus progestin therapy, as compared to estrogen-alone therapy. However, these studies have not found significant variation in the risk of breast cancer among

different estrogen plus progestin combinations, doses, or routes of administration.

The most important randomized clinical trial providing information about this issue is the Women's Health Initiative (WHI) substudy of daily conjugated estrogens (CE 0.625 mg) plus medroxyprogesterone acetate (MPA 2.5 mg) [see Clinical Studies]. In the estrogen alone substudy of WHI, after an average of 7.1 years of follow-up, daily CE 0.625 mg was not associated with an increased risk of invasive breast cancer (relative risk [RR] 0.80, 95 percent nominal confidence interval [nCI] 0.62-1.04).

In the estrogen plus progestin substudy, after a mean follow-up of 5.6 years, the WHI substudy reported an increased risk of breast cancer in women who took daily CE/MPA. In this substudy, prior use of estrogen alone or estrogen plus progestin therapy was reported by 26 percent of the women. The relative risk of invasive breast cancer was 1.24 (95 percent nCI, 1.01-1.54), and the absolute risk was 41 versus 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 versus 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 versus 36 cases per 10,000 women-years for estrogen plus progestin 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 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 and perform monthly breast self-examinations. In addition, mammography examinations should be scheduled based on patient age, risk factors, and prior mammogram results.

Ovarian Cancer

The estrogen plus progestin substudy of WHI reported that daily CE/MPA 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 percent nominal confidence interval [nCI], 0.77-3.24) but was not statistically significant. The absolute risk for CE/MPA 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 10 or more years, has been associated with an increased risk of ovarian cancer. Other epidemiologic studies have not found these associations.

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 daily conjugated estrogens (CE 0.625 mg) or placebo. In the estrogen plus progestin WHIMS substudy, a population of 4,532 postmenopausal women 65 to 79 years was randomized to daily CE 0.625 mg plus medroxyprogesterone acetate (MPA 2.5 mg) or placebo.

In the estrogen alone substudy, after an average follow-up of 5.2 years, 28 women in the CE alone group and 19 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE alone versus placebo was 1.49 (95 percent CI, 0.83-2.66). The absolute risk of probable dementia for CE alone versus placebo was 37 versus 25 cases per 10,000 women-years [see Use in Specific Populations and Clinical Studies].

In the estrogen plus progestin substudy, after an average follow-up of 4 years, 40 women in the CE/MPA group and 21 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE/MPA versus placebo was 2.05 (95 percent CI, 1.21-3.48). The absolute risk of probable dementia for CE/MPA versus placebo was 45 versus 22 cases per 10,000 women-years [see Use in Specific Populations and Clinical Studies].

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 percent CI, 1.19-2.60). Since both substudies were conducted in women 65 to 79 years, it is unknown whether these findings apply to younger postmenopausal women [see Use in Specific Populations and Clinical Studies].

Gallbladder Disease

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

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.

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 permanently discontinued.

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

has been shown to interfere with collagen biosynthesis and to cause malformations in animal studies, according to Dr. Bermas. "In humans, cases of cutis laxa and connective tissue disorders have been reported with exposure to this medication," she said. As such, "this medication should not be used during pregnancy."

Mycophenolate Mofetil

"We had such high hopes for mycophenolate mofetil. We thought this would be one of those medications that could be safely used during pregnancy," said Dr. Bermas. "Unfortunately, there are increased case reports of congenital anomalies,

including one report of the drug being used during pregnancy in a renal transplant patient. The baby was born prematurely and was noted to have hypoplastic nails and short fifth fingers." Although there is not a rich body of literature yet, "this medication should be avoided during pregnancy," she said.

IVIg

Intravenous immunoglobulin is not a common drug for rheumatologic disorders, and the literature on its use in pregnancy is limited. "In one case report of an individual with steroid-resistant idiopathic thrombocytopenic purpura, IVIg was

used with no adverse effects on the offspring," said Dr. Bermas. "The medication has also been used to manage the obstetrical complications of the antiphospholipid antibody syndrome without inducing congenital malformations." Based on the available data, IVIg, when warranted, is acceptable for use in pregnancy, she said.

Cyclosporin A

The large body of data regarding the use of cyclosporin A during pregnancy comes from the transplant literature. "These medications are not teratogenic, although they are associated with small-for-gestational-age infants and hypertension of

pregnancy," said Dr. Bermas. The drug is not widely used, but in individual cases, if the potential benefit outweighs the possible risk, clinicians may choose to continue treatment with it, she noted.

Chlorambucil and Cyclophosphamide

Both of these cytotoxic agents are teratogenic and should be avoided during pregnancy, Dr. Bermas stressed. "In life-or-death situations, cyclophosphamide has been used in the third trimester," she said.

Methotrexate

Because of the high risk of congenital anomalies, methotrexate is an FDA category X drug for use in pregnancy. In addition to being teratogenic, it is also abortifacient, said Dr. Bermas, noting that, in terms of gestation, the use of methotrexate during weeks 6-8 at dosages greater than 10 mg/day substantially increases the risk of fetal harm. "I recommend that patients, both men and women, discontinue methotrexate for at least 3 months prior to conception," she said.

Leflunomide

Another FDA category X drug for use in pregnancy because of its high teratogenicity, leflunomide "has an extremely long half-life, so either you need to wash out with cholestyramine or discontinue for 2 years before conception," said Dr. Bermas. "As a general rule, I avoid using this in women of childbearing potential."

Anti-TNF- α Agents

Limited data exist regarding the safety of the tumor necrosis factor- α inhibitors during pregnancy, "although case reports of two infants exposed to these drugs in utero being born with anomalies potentially consistent with VACTERL [vertebral, anal, cardiac, tracheal, esophageal, renal, and limb] syndrome give clinicians pause," said Dr. Bermas. On the other hand, animal studies reported no teratogenic or fetotoxic effects, and some reports on human pregnancy in patients taking these drugs did not show an increase in birth defects or adverse pregnancy outcomes, she said. In one large study comprising 131 patients with inflammatory chronic diseases—including 8 patients with RA—who were directly exposed to infliximab, drug exposure during pregnancy resulted in outcomes similar to those seen in the general population of pregnant women (Am. J. Gastroenterol, 2004;99:2385-92).

Rituximab

More commonly used for the treatment of non-Hodgkin's lymphoma, rituximab is also used for patients with refractory RA. Although as of yet there are no reports of congenital anomalies associated with this anti-CD20 monoclonal antibody, "there are insufficient data regarding the safety of the drug in animal or human pregnancy," said Dr. Bermas. Two case reports of successful outcomes in women treated with rituximab for non-Hodgkin's lymphoma during pregnancy are promising, but not yet representative, she said. In fact, given the availability of safer alternative medications for pregnant RA patients, along with the possibility of remission during pregnancy, rituximab should probably be avoided unless there's a compelling reason to use it, she said. ■

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 (lowering HDL, raising LDL), and impairment of glucose tolerance.

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.

Hypertriglyceridemia

In patients with preexisting hypertriglyceridemia, estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis and other complications. Consider discontinuation of treatment if pancreatitis or other complications develop.

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.

Hypothyroidism

Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Patients with normal thyroid function can compensate for the increased TBG by making more thyroid hormone, thus maintaining free T_4 and T_3 serum concentrations in the normal range. Patients dependent on thyroid hormone replacement therapy who are also receiving estrogens may require increased doses of their thyroid replacement therapy. These patients should have their thyroid function monitored in order to maintain their free thyroid hormone levels in an acceptable range.

Fluid Retention

Estrogens may cause some degree of fluid retention. Patients who have conditions that might be influenced by this factor, such as a cardiac or renal dysfunction, warrant careful observation when estrogens are prescribed.

Hypocalcemia

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

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-alone therapy. For patients known to have residual endometriosis post-hysterectomy, the addition of progestin should be considered.

Exacerbation of Other Conditions

Estrogens 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.

Alcohol-Based Products are Flammable

Avoid fire, flame or smoking until the spray has dried.

Application of Sunscreen

When sunscreen is applied approximately one hour after application of Evamist™, estradiol absorption was decreased by 11%. When sunscreen is applied approximately one hour before the application of Evamist, no significant change in estradiol absorption was observed.

Laboratory Tests

Serum follicle stimulating hormone and estradiol levels have not been shown to be useful in the management of moderate to severe vasomotor symptoms.

Drug and Laboratory Test Interactions

Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, II-VII-X complex, and beta-thromboglobulin; decreased levels of antifactor Xa and antithrombin III, decreased antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity.

Increased TBG levels leading to increased circulating total thyroid hormone levels, as measured by protein-bound iodine (PBI), T_4 levels (by column or by radioimmunoassay) or T_3 levels by radioimmunoassay. T_3 resin uptake is decreased, reflecting the elevated TBG. Free T_4 and free T_3 concentrations are unaltered. Patients on thyroid replacement therapy may require higher doses of thyroid hormone.

Other binding proteins may be elevated in serum (corticosteroid binding globulin [CBG], SHBG), leading to increased total circulating corticosteroids and sex steroids, respectively. Free hormone concentrations, such as testosterone and estradiol, may be decreased. As with other transdermal estradiol products, a slight increase in SHBG was seen with Evamist™ active drug compared with baseline.

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

Impaired glucose tolerance.

ADVERSE REACTIONS

Clinical Study Experience

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.

In a 12-week, randomized, placebo-controlled trial of Evamist in 454 women, 80–90% of women randomized to active drug received at least 70 days of therapy and 75–85% randomized to placebo received at least 70 days of therapy.

The adverse reactions that occurred in at least 5% of women in any treatment group are shown in Table 1.

Table 1. Frequency of Adverse Reactions ($\geq 5\%$) in Any Treatment Group in a Controlled Study of Evamist

System Organ Class Preferred Term	Frequency n (%)					
	1 Spray Placebo (N=77)	Evamist (N=76)	2 Sprays Placebo (N=76)	Evamist (N=74)	3 Sprays Placebo (N=75)	Evamist (N=76)
Reproductive System and Breast Disorders						
Breast tenderness	0 (0)	4 (5)	4 (5)	5 (7)	0 (0)	4 (5)
Nipple pain	0 (0)	2 (3)	0 (0)	5 (7)	0 (0)	1 (1)
Gastrointestinal Disorders						
Nausea	5 (7)	1 (1)	1 (1)	2 (3)	4 (5)	2 (3)
Infections and Infestations						
Nasopharyngitis	1 (1)	4 (5)	2 (3)	3 (4)	1 (1)	1 (1)
Musculoskeletal and Connective Tissue Disorders						
Back pain	1 (1)	2 (3)	2 (3)	4 (5)	1 (1)	2 (3)
Arthralgia	1 (1)	1 (1)	4 (5)	1 (1)	0 (0)	3 (4)
Nervous system						
Headache	4 (5)	7 (9)	5 (7)	9 (12)	7 (9)	8 (11)

Application site reactions were reported in 3 out of 226 (1.3%) women treated with Evamist.

Additional Adverse Reactions Reported With Estrogen and/or Progestin Therapy

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

Genitourinary System

Abnormal uterine bleeding/spotting, dysmenorrhea/pelvic pain, increase in size of uterine leiomyomata, vaginitis including vaginal candidiasis, change in amount of cervical secretion, changes in cervical ectropion, ovarian cancer, endometrial hyperplasia, endometrial cancer.

Breasts

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

Cardiovascular

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

Gastrointestinal

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

Skin

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

Eyes

Retinal vascular thrombosis, intolerance to contact lenses.

Central Nervous System

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

Miscellaneous

Increase or decrease in weight, glucose intolerance, aggravation of porphyria, edema, arthralgias, leg cramps, changes in libido, urticaria, angioedema, anaphylactoid/anaphylactic reactions, hypocalcemia (preexisting condition), exacerbation of asthma, increased triglycerides.

DRUG INTERACTIONS

No formal drug interaction studies have been conducted for Evamist™.

Metabolic Interactions

In vitro and in vivo studies have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4 such as St. John's Wort preparations (Hypericum perforatum), phenobarbital, carbamazepine, and rifampin may reduce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effects and/or changes in the uterine bleeding profile. Inhibitors of CYP3A4 such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir, and grapefruit juice may increase plasma concentrations of estrogens and may result in side effects.

USE IN SPECIFIC POPULATIONS

Pregnancy

Evamist™ should not be used during pregnancy [see Contraindications]. There appears to be little or no increased risk of birth defects in children born to women who have used estrogens

and progestins as an oral contraceptive inadvertently during early pregnancy.

Nursing Mothers

Evamist should not be used during lactation. 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.

Pediatric Use

Evamist is not intended for pediatric use and no clinical data have been collected in children.

Geriatric Use

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

In the estrogen-alone substudy of the Women's Health Initiative (WHI) study, 46 percent (n = 4,943) of subjects were 65 years and older, while 7.1 percent (n = 767) of subjects were 75 years and older. There was a higher relative risk (daily CE 0.625 mg versus placebo) of stroke in women less than 75 years of age compared to women 75 years and older.

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 receive daily conjugated estrogens (CE 0.625 mg) or placebo. After an average follow-up of 5.2 years, the relative risk (CE versus placebo) of probable dementia was 1.49 (95 percent CI, 0.83–2.66). The absolute risk of developing probable dementia with estrogen alone was 37 versus 25 cases per 10,000 women-years compared with placebo.

Of the total number of subjects in the estrogen plus progestin substudy of WHI, 44 percent (n = 7,320) were 65 years and older, while 6.6 percent (n = 1,095) were 75 years and older. In women 75 years of age and older compared to women less than 75 years of age, there was a higher relative risk of non-fatal stroke and invasive breast cancer in the estrogen plus progestin group versus placebo. In women greater than 75, the increased risk of non-fatal stroke and invasive breast cancer observed in the estrogen plus progestin group compared to placebo was 75 versus 24 per 10,000 women-years and 52 versus 12 per 10,000 women-years, respectively.

In the estrogen plus progestin WHIMS substudy, a population of 4,532 postmenopausal women, aged 65 to 70 years, was randomized to receive daily CE 0.625 mg/MPA 2.5 mg or placebo. In the estrogen plus progestin group, after an average follow-up of 4 years, the relative risk (CE/MPA versus placebo) of probable dementia was 2.05 (95 percent CI, 1.21–3.48). The absolute risk of developing probable dementia with CE/MPA was 45 versus 22 cases per 10,000 women-years compared with placebo.

Seventy-nine percent of the cases of probable dementia occurred in women that were older than 70 for the CE alone group, and 82 percent of the cases of probable dementia occurred in women who were older than 70 in the CE/MPA group. The most common classification of probable dementia in both the treatment groups 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 percent 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 Warnings and Precautions].

OVERDOSAGE

Overdosage of estrogen may cause nausea and vomiting, breast tenderness, dizziness, abdominal pain, drowsiness/fatigue and withdrawal bleeding may occur in women. Treatment of overdose consists of discontinuation of Evamist™ together with institution of appropriate symptomatic care.

Marketed by

Ther-Rx Corporation

St. Louis, MO 63044

U.S. Patent Nos.: 6,299,900; 6,818,226; 6,923,983; 6,978,945.

Other U.S. Patents pending.

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References: 1. Evamist™ (estradiol transdermal spray) prescribing information, Ther-Rx Corporation, January 2008. 2. Data on file, Ther-Rx Corporation.

Evamist™
(estradiol transdermal spray)