Endometrial Ablation Safe, Effective in Adolescents

BY MARY ANN MOON
Contributing Writer

WASHINGTON — Endometrial ablation is safe and effective in adolescents who have intractable menorrhagia and for whom future fertility is not a concern, Jon I. Einarsson, M.D., said at the annual meeting of the Central Association of Obstetricians and Gynecologists.

Endometrial ablation for menorrhagia is usually reserved for women who do not desire pregnancy and is used in younger women only when their bleeding is life-threatening, said Dr. Einarsson of Baylor College of Medicine, Houston.

He reviewed the experience at his institution in six adolescents with concomitant severe disorders that ruled out future fertility. These included severe mental retardation, vasculitis, paraplegia, cerebral palsy, and seizure disorder. All patients had failed to respond to nonsurgical therapy.

The patients' mean age at the time of the procedure was 15.6 years. The initial success rate was 66.7% (four out of six).

One patient in whom ablation failed was found to have an arcuate uterus and subsequently underwent hysterectomy. The second patient, found to have a septate uterus, was successfully treated with a second ablation procedure when the uterine horns were more completely accessed.

After treatment, the patients' use of menstrual pads decreased from a mean of 7.7 per day to 1.3 per day. Mean duration of menses decreased from 7.2 days to 1.5 days. When contacted an average of 32 months after the ablation, "all patients and/or guardians were satisfied with the treatment outcome and would recommend the procedure to others," Dr. Einarsson said in a poster presentation at the meeting.

"The use of uterine balloon therapy is especially attractive in teenagers, because the 5-mm device requires minimal cervical dilatation, a procedure that can be challenging in an adolescent nulliparous cervix," he noted.

In addition, the approach is particularly useful because patients typically undergo preablation diagnostic hysteroscopy that allows "identification of possible uterine anomalies that might interfere with the performance of the thermal balloon." ■

ACTIVELLA® 1mg/0.5mg
estradiol/norethindrone acetate tablets

Brief summary of prescribing information.

INDICATIONS AND USAGE

ACTIVELLA therapy is indicated in women with an intact uterus for the:
1. Treatment of moderate to severe vasomotor symptoms associated with the menopause. There is no adequate evidence that estrogens are effective for nervous symptoms or depression that might occur during menopause and they should not be used to treat these conditions.
2. Treatment of vulvar and vaginal atrophy.
3. Prevention of postmenopausal osteoporosis.

Most prospective studies of efficacy for the osteoporosis prevention indication have been carried out in white post-menopausal women, without stratification by other risk factors, and tend to show a universally beneficial effect on bone. Since estrogen administration is associated with risk, patient selection must be individualized based on the balance of risks and benefits.

Case-control studies have shown an approximately 60-percent reduction in hip and wrist fractures in women whose estrogen replacement was begun within a few years after menopause. Studies also suggest that estrogen reduces the rate of vertebral fractures.

When estrogen therapy is discontinued, bone mass declines at a rate comparable to the immediate postmenopausal period.

White and Asian women are at higher risk for osteoporosis than black women, and thin women are at a higher risk than heavier women, who generally have higher endogenous estrogen levels. Early menopause is one of the strongest predictors for the development of osteoporosis. Other factors associated with osteoporosis include genetic factors (small build, family history), lifestyle (cigarette smoking, alcohol abuse, sedentary exercise habits) and nutrition (below average body weight and dietary calcium intake).

The mainstays of prevention and management of osteoporosis are weight-bearing exercise, adequate calcium intake, and, when indicated, estrogen. Postmenopausal women absorb dietary calcium less efficiently than premenopausal women and require an average of 1500 mg/day of elemental calcium to remain in neutral calcium balance. The average calcium intake in the USA is 400-600 mg/day. Therefore, when not contraindicated, calcium supplementation may be helpful for women with suboptimal dietary intake.

CONTRAINDICATIONS

Estrogens/progestins combined should not be used in women under any of the following conditions or circumstances:
1. Known or suspected pregnancy, including use for missed abortions or as a diagnostic test for pregnancy. Estrogen or progestin may cause fetal harm when administered to a pregnant woman.
2. Known or suspected breast cancer, or past history of breast cancer associated with the use of estrogens.
3. Known or suspected estrogen-dependent neoplasia, e.g., endometrial cancer.
4. Abnormal genital bleeding of unknown etiology.
5. Known or suspected active deep venous thrombosis, thromboembolic disorders or stroke or past history of these conditions associated with estrogen use.
6. Liver dysfunction or disease.
7. Hypersensitivity to any of the components of ACTIVELLA (estradiol/norethindrone acetate tablets).

WARNINGS

ALL WARNINGS BELOW PERTAIN TO THE USE OF THIS COMBINATION PRODUCT.

Based on experience with estrogens and/or progestins:

1. Induction of malignant neoplasms.

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. There is no significant increased risk associated with the use of estrogens for less than one year. The greatest risk appears to be associated with prolonged use with increased risks of 15- to 24-fold with five or more years of use. In three studies, persistence of risk was demonstrated for 8 to over 15 years after cessation of estrogen treatment. In one study, a significant decrease in the incidence of endometrial cancer occurred six months after withdrawal. Progestins taken with estrogens have been shown to significantly reduce, but not eliminate, the risk of endometrial cancer associated with estrogen use. In a large clinical trial, the incidence of endometrial hyperplasia with ACTIVELLA was 0.4% (one simple hyperplasia without atypia) compared to 14.6% with 1 mg estradiol unopposed *(see full prescribing information, CLINICAL STUDIES).*

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 "natural" estrogens are more or less hazardous than "synthetic" estrogens at equivalent estrogen doses.

Breast cancer. While the majority of studies have not shown an increased risk of breast cancer in women who have ever used estrogen replacement therapy, some have reported a moderately increased risk (relative risks of 1.3-2.0) in those taking higher doses, or in those taking lower doses for prolonged periods of time, especially in excess of 10 years.

While the effects of added progestins on the risk of breast cancer are also unknown, available epidemiological evidence suggest that progestins do not reduce, and may enhance, the moderately increased breast cancer risk that has been reported with prolonged estrogen replacement therapy.

In a one-year trial among 1,176 women who received either unopposed 1 mg estradiol or a combination of 1 mg estradiol plus one of three different doses of NETA (0.1, 0.25 and 0.5 mg), seven new cases of breast cancer were diagnosed, two of which occurred among the group of 295 women treated with ACTIVELLA.

Women on hormone replacement therapy should have regular breast examinations and should be instructed in breast self-examination, and women over the age of 40 should have regular mammograms.

2. Congenital lesions with malignant potential. Estrogen therapy during pregnancy is associated with an increased risk of fetal congenital reproductive tract disorders, and possible other birth defects. Studies of women who received diethylstilbestrol (DES) during pregnancy have shown that female offspring have an increased risk of vaginal adenosis, squamous cell dysplasia of the uterine cervix, and clear cell vaginal cancer later in life; male offspring with an increased risk of urogenital abnormalities and possibly testicular cancer later in life. Although some of these changes are benign, others are precursors of malignancy.

3. Cardiovascular disease. Large doses of estrogens (5 mg conjugated estrogen 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 risk of nonfatal myocardial infarction, pulmonary embolism, and thrombophlebitis. These risks cannot necessarily be extrapolated from men to women or from unopposed estrogen to combination estrogen/progestin therapy. However, to avoid the theoretical cardiovascular risk to women caused by high estrogen doses, the dose for estrogen replacement therapy should not exceed the lowest effective dose.

4. Hypercalcemia. Administration of estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases. If this occurs, the drugs should be stopped and appropriate measures taken to reduce the serum calcium level.

5. Effects during pregnancy. Use in pregnancy is not recommended.

6. Gallbladder disease. Two studies have reported a 2- to 4-fold increase in the risk of surgically confirmed gallbladder disease in women receiving postmenopausal estrogens. Among the 1,516 women treated in clinical trials with 1 mg estradiol alone or in combination with several doses of NETA, 3 women had surgically confirmed cholelithiasis, none of them on ACTIVELLA treatment.

7. Elevated blood pressure. Occasional blood pressure increases during estrogen replacement therapy have been attributed to idiosyncratic reactions to estrogens. More often, blood pressure has remained the same or has dropped. Postmenopausal estrogen use does not increase the risk of stroke. Nonetheless, blood pressure should be monitored at regular intervals with estrogen use.

8. Thromboembolic disorders. The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism, and retinal thrombosis). Should any of these occur or be suspected, the drugs should be discontinued immediately. In a one-year study where 295 women were exposed to ACTIVELLA, there were two cases of deep vein thromboses reported.

9. Visual abnormalities. Discontinue medication pending examination if there is a sudden partial or complete loss of vision, or a sudden onset of proptosis, diplopia, or migraine. If examinations reveal papilledema or retinal vascular lesions, medication should be withdrawn.

PRECAUTIONS

GENERAL

Based on experience with estrogens and/or progestins:

1. Cardiovascular risk. A causal relationship between estrogen replacement therapy and reduction of cardiovascular disease in postmenopausal women has not been proven. Furthermore, the effect of added progestins on this putative benefit is not yet known.

In recent years, many published studies have suggested that there may be a cause-effect relationship between postmenopausal oral estrogen replacement therapy without added progestins and a decrease in cardiovascular disease in women. Although most of the observational studies that assessed this statistical association have reported a 20% to 50% reduction in coronary heart disease risk and associated mortality in estrogen takers, the following should be considered when interpreting these reports. Because only one of these studies was randomized and it was too small to yield statistically significant results, all relevant studies were subject to selection bias. Thus, the apparently reduced risk of coronary artery disease cannot be attributed with certainty to estrogen replacement therapy. It may instead have been caused by life-style and medical characteristics of the women studied with the result that healthier women were selected for estrogen therapy. In general, treated women were of higher socioeconomic and educational status, more slender, more physically active, more likely to have undergone surgical menopause, and less likely to have diabetes than the untreated women. Although some studies attempted to control for these selection factors, it is common for properly designed randomized trials to fail to confirm benefits suggested by less rigorous study designs. Thus, ongoing and future large-scale randomized trials may fail to confirm this apparent benefit.

Current medical practice often includes the use of concomitant progestin therapy in women with intact uterus. While the effects of added progestins on the risk of ischemic heart disease are not known, all available progestins attenuate at least some of the favorable effects of estrogens on HDL levels, although they maintain the favorable effect of estrogens on LDL levels.

The safety data regarding ACTIVELLA were obtained primarily from clinical trials and epidemiologic studies of postmenopausal Caucasian women, who were at generally low risk of cardiovascular disease and higher than average risk for osteoporosis. The safety profile of ACTIVELLA derived from these study populations cannot necessarily be extrapolated to other populations of diverse racial and/or demographic composition. When considering prescribing ACTIVELLA, physicians are advised to weigh the potential benefits and risks of therapy as applicable to each individual patient.

2. Use in hysterectomized women. Existing data do not support the use of the combination of estrogen and progestin in postmenopausal women without a uterus. Risks that may be associated with the inclusion of progestin in estrogen replacement regimens include deterioration in glucose tolerance, and less favorable effects on lipid metabolism compared to the effects of estrogen alone. The effects of ACTIVELLA on glucose tolerance and lipid metabolism have been studied *(see full prescribing information, CLINICAL PHARMACOLOGY, CLINICAL STUDIES and PRECAUTIONS, DRUG/LABORATORY TEST INTERACTIONS).*

3. Physical examination. A complete medical and family history should be taken prior to the initiation of any estrogen/progestin therapy. The pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen, and pelvic organs, and should include a Papanicolaou smear. As a general rule, estrogen should not be prescribed for longer than one year without another physical examination being performed.

4. Fluid retention. Because estrogens/progestins may cause some degree of fluid retention, conditions that might be influenced by this factor, such as asthma, epilepsy, migraine, and cardiac or renal dysfunction, require careful observation.

5. Uterine bleeding. Certain patients may develop abnormal uterine bleeding. In cases of undiagnosed abnormal uterine bleeding, adequate diagnostic measures are indicated *(see WARNINGS).*

6. The pathologist should be advised of estrogen/progestin therapy when relevant specimens are submitted.

Based on experience with estrogens:

1. Familial hyperlipoproteinemia. Estrogen therapy may be associated with massive elevations of plasma triglycerides leading to pancreatitis and other complications in patients with familial defects in lipoprotein metabolism.

2. Hypercoagulability. Some studies have shown that women taking estrogen replacement therapy have hypercoagulability primarily related to decreased antithrombin activity. This effect appears dose- and duration-dependent and is less pronounced than that associated with oral contraceptive use. Also, postmenopausal women tend to have changes in levels of coagulation parameters at baseline compared to premenopausal women. Epidemiological studies have suggested that estrogen use is associated with a higher relative risk of developing venous thromboembolism, i.e., deep vein thrombosis or pulmonary embolism. The studies found a 2- to 3-fold higher risk for estrogen users compared to non-users. There is insufficient information on hypercoagulability in women who have had previous thromboembolic disease. The effects of ACTIVELLA (n=40) compared to placebo (n=40) on selected clotting factors were evaluated in a 12-month study with postmenopausal women. ACTIVELLA decreased factor VII, plasminogen activator inhibitor-1, and, to a lesser extent, antithrombin III activity, compared to placebo. Fibrinogen remained unchanged during ACTIVELLA treatment in comparison with an increase over time in the placebo group.

3. Mastodynia. Certain patients may develop undesirable manifestations of estrogenic stimulation such as mastodynia. In clinical trials, less than one-fifth of the women treated with ACTIVELLA reported breast tenderness or breast pain. The majority of the cases were reported as breast tenderness, primarily during the initial months of the treatment.

Based on experience with progestins:

1. Lipoprotein metabolism. *See full prescribing information, CLINICAL STUDIES.*

2. Impaired glucose tolerance. Diabetic patients should be carefully observed while receiving estrogen/progestin therapy. The effects of ACTIVELLA on glucose tolerance have been studied *(see PRECAUTIONS, DRUG/LABORATORY TEST INTERACTIONS).*

3. Depression. Patients who have a history of depression should be observed and the drugs discontinued if the depression recurs to a serious degree.

INFORMATION FOR PATIENTS

See full prescribing information, Patient Package Insert.

DRUG/LABORATORY TEST INTERACTIONS

The following interactions have been observed with estrogen therapy, and/or ACTIVELLA: ACTIVELLA decreases factor VII, plasminogen activator inhibitor-1, and, to a lesser extent, antithrombin III activity. Estrogen therapy increases thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone, 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. Estrogen therapy may elevate other binding proteins in serum i.e., corticosteroid-binding globulin (CBG), sex-hormone-binding globulin (SHBG), 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). In a 12-month clinical trial, SHBG (sex-hormone-binding globulin) was found to increase with ACTIVELLA. Estrogen therapy increases plasma HDL and HDL-2 subfraction concentrations, reduces LDL cholesterol concentration, and increases triglyceride levels. *(For effects during treatment with ACTIVELLA, see full prescribing information, CLINICAL PHARMACOLOGY, CLINICAL STUDIES.)* ACTIVELLA treatment of healthy postmenopausal women does not decrease glucose tolerance when assessed by an oral glucose tolerance test; the insulin response decreases without any increase in the glucose serum levels. ACTIVELLA treatment does not deteriorate insulin sensitivity in healthy postmenopausal women when assessed by a hyperinsulinemic euglycemic clamp. Estrogen therapy reduces response to metyrapone test. Estrogen therapy reduces serum folate concentration.

CARCINOGENESIS, MUTAGENESIS, and IMPAIRMENT OF FERTILITY

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 *(see CONTRAINDICATIONS and WARNINGS).*

PREGNANCY: CATEGORY X

Estrogens/progestins should not be used during pregnancy *(see CONTRAINDICATIONS and WARNINGS).*

NURSING MOTHERS

Detectable amounts of estradiol and norethindrone acetate have been identified in the milk of mothers receiving these products and has been reported to decrease the quantity and the quality of the milk. The administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

GERIATRIC USE

Clinical studies of ACTIVELLA did not include sufficient number of subjects aged 65 and over to determine if they responded differently from younger subjects. Other reported clinical experience has not identified differences in responses between elderly and younger subjects. Dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

(See WARNINGS regarding induction of neoplasia, adverse effects on the fetus, increased incidence of gallbladder disease, elevated blood pressure, thromboembolic disorders, cardiovascular disease, visual abnormalities, and hypercalcemia and PRECAUTIONS regarding cardiovascular disease.)

Adverse events reported by investigators in the Phase 3 studies regardless of causality assessment are shown in the following table.

ALL TREATMENT-EMERGENT ADVERSE EVENTS REGARDLESS OF RELATIONSHIP REPORTED AT A FREQUENCY OF ≥ 5% WITH ACTIVELLA®

	Endometrial Hyperplasia Study (12-Months)		Vasomotor Symptoms Study (3-Months)		Osteoporosis Study (2 Years)	
	Activella (n=295)	1 mg E2 (n=296)	Activella (n=29)	Placebo (n=34)	Activella (n=47)	Placebo (n=48)
Body as a Whole						
Back Pain	6%	5%	3%	3%	6%	4%
Headache	16%	16%	17%	18%	11%	6%
Digestive System						
Nausea	3%	5%	10%	0%	11%	0%
Gastroenteritis	2%	2%	0%	0%	6%	4%
Nervous System						
Insomnia	6%	4%	3%	3%	0%	8%
Emotional Lability	1%	1%	0%	0%	6%	0%
Respiratory System						
Upper Respiratory Tract Infection	18%	15%	10%	6%	15%	19%
Sinusitis	7%	11%	7%	0%	15%	10%
Metabolic and Nutritional						
Weight Increase	0%	0%	0%	0%	9%	6%
Urogenital System						
Breast Pain	24%	10%	21%	0%	17%	8%
Post-Menopausal Bleeding	5%	15%	10%	3%	11%	0%
Uterine Fibroid	5%	4%	0%	0%	4%	8%
Ovarian Cyst	3%	2%	7%	0%	0%	8%
Resistance Mechanism						
Infection Viral	4%	6%	0%	3%	6%	6%
Moniliasis Genital	4%	7%	0%	0%	6%	0%
Secondary Terms						
Injury Accidental	4%	3%	3%	0%	17%*	4%*
Other Events	2%	3%	3%	0%	6%	4%

*including one upper extremity fracture in each group

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

Genitourinary system: changes in vaginal bleeding pattern and abnormal withdrawal bleeding or flow, breakthrough bleeding, spotting, increase in size of uterine leiomyomata, vaginal candidiasis, changes in amount of cervical secretion, pre-menstrual-like syndrome, cystitis-like syndrome.

Breasts: tenderness, enlargement.

Gastrointestinal: nausea, vomiting, changes in appetite, cholestatic jaundice, abdominal pain, flatulence, bloating, increased incidence of gallbladder disease.

Skin: chloasma or melasma that may persist when drug is discontinued, erythema multiforme, erythema nodosum, hemorrhagic eruption, loss of scalp hair, hirsutism, itching, skin rash and pruritus.

Cardiovascular: changes in blood pressure, cerebrovascular accidents, deep venous thrombosis and pulmonary embolism.

CNS: headache, migraine, dizziness, depression, chorea, insomnia, nervousness.

Eyes: steepening of corneal curvature, intolerance to contact lenses.

Miscellaneous: increase or decrease in weight, aggravation of porphyria, edema, changes in libido, fatigue, allergic reactions, back pain, arthralgia, myalgia.

OVERDOSAGE

Acute Overdose: Serious ill effects have not been reported following acute ingestion of large doses of estrogen/progestin-containing oral contraceptives by young children. Overdosage may cause nausea and vomiting, and withdrawal bleeding may occur in females.

DOSAGE AND ADMINISTRATION

ACTIVELLA therapy consists of a single tablet to be taken once daily. For the treatment of moderate to severe vasomotor symptoms associated with the menopause, treatment of vulvar and vaginal atrophy, and the prevention of postmenopausal osteoporosis - **ACTIVELLA** 1 mg E_2/0.5 mg NETA daily. The doses of 17β-estradiol and norethindrone acetate in ACTIVELLA may not be the lowest effective dose-combination for the prevention of osteoporosis. Treated patients with an intact uterus should be monitored closely for signs of endometrial cancer, and appropriate diagnostic measures should be taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.

HOW SUPPLIED

ACTIVELLA, 1 mg estradiol and 0.5 mg norethindrone acetate, is a white, film-coated tablet, engraved with "NOVO 288" on one side and the APIS bull on the other. It is round, 6 mm in diameter and bi-convex. ACTIVELLA is supplied as:

28 tablets in a calendar dial pack dispenser NDC # 0169-5174-02

Store in a dry place protected from light. Store at 25ºC (77ºF); excursions permitted to 15-30ºC (59-86ºF) *[see USP Controlled Room Temperature].*

Rx only

ACTIVELLA® is a trademark owned by Novo Nordisk A/S.
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1-866-668-6336
www.novonordisk-us.com
Manufactured by Novo Nordisk A/S, 2880 Bagsvaerd, Denmark

Reference: 1. ACTIVELLA [package insert]. Princeton, NJ: Novo Nordisk Pharmaceuticals Inc; 2003.

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Satisfaction Rate For MEA Is 87% After 6 Years

SAN FRANCISCO — A retrospective study involving 6 years of experience with microwave endometrial ablation revealed that almost 87% of 660 women were satisfied with the outcome of the procedure.

Overall, 80% of the women avoided hysterectomy over the long term, and 41% achieved amenorrhea, said Sherif Tawfeek, M.D., who acknowledged receiving grant support from Microsulis Americas Inc., which manufactures equipment for microwave endometrial ablation (MEA).

All patients were treated at Dr. Tawfeek's institution, Royal United Hospital in Bath, England, he said at the annual meeting of the American Association of Gynecologic Laparoscopists.

When the endometrial ablation clinic at the hospital began performing MEA in 1994, all patients underwent general anesthesia. But by 2000, about half the patients were undergoing the procedure under local anesthesia.

The mean patient age was 43 years, with a range of 25-57 years. Cavity length averaged 87 mm, with a range of 50-130 mm. The average treatment time was 246 seconds, with a range of 47-810 seconds.

The treatment time was directly correlated with the cavity length, with 111- to 115-mm cavities taking more than 7 minutes, 91- to 95-mm cavities taking a bit less than 4 minutes, and 60- to 70-mm cavities taking less than 2 minutes.

Of the original group of 660 patients, 641 (97%) were followed for at least 6 months. Of those patients, five underwent incidental hysterectomy, mostly for reasons related to cancer. Of the remainder, 78% were satisfied with their first microwave endometrial ablation.

Of the patients who were dissatisfied, about half were satisfied by a second MEA procedure, for a total satisfaction rate of 87%. The remaining 13% of patients underwent hysterectomy.

—Robert Finn