BY DAVID F. ARCHER, MD

Estradiol gel: A new option in hormone replacement therapy

An expert profiles percutaneous gel: easy to use, well tolerated, and available in low doses.

Although the Women's Health Initiative[1] discouraged many menopausal women from using oral estrogen, it failed to address the risks of treatment with other dosages or forms of estrogen and progestin.

Nor has any other trial of similar size and complexity taken up the issue. However, numerous smaller studies have been published.

This article summarizes findings on percutaneous delivery of estradiol gel (EstroGel), the most recently FDA-approved estrogen option for treatment of menopausal symptoms.

It describes the overall safety of estradiol gel, as well as its effects on:

- menopausal symptoms,
- bone,
- metabolism, and
- endometrium.

(In this article, "percutaneous delivery" refers to estradiol gel applied to the skin, and "transdermal estradiol" indicates delivery via a transdermal reservoir or matrix system, otherwise known as "the patch." I have used an arbitrary definition to distinguish the gel from other methods of delivering estradiol across the skin. For example, Estrasorb is a liposomal formulation that is applied to the skin of the thigh. Although it is a percutaneous estradiol similar to the gel, this article focuses only on the latter option.)

KEY POINTS

- Percutaneous estradiol gel can be prescribed at low doses.
- Relief of menopausal symptoms can begin as early as 2 weeks after starting treatment.
- Treatment with estradiol gel maintains or increases bone mineral density.
- No large randomized, controlled trials have explored the effect of estradiol gel on coronary artery disease. It appears to have metabolic effects similar to those of oral estradiol.
- Because percutaneous estradiol stimulates the endometrium, women with an intact uterus should also take a progestogen.

Easy to apply, few skin reactions

Percutaneous estradiol gel formulations have been available for almost 30 years in Europe, where they are utilized by a majority of women on hormone therapy. In the United States, the hydroalcoholic gel is packaged in a

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FIGURE

Estradiol gel: The reservoir is intradermal

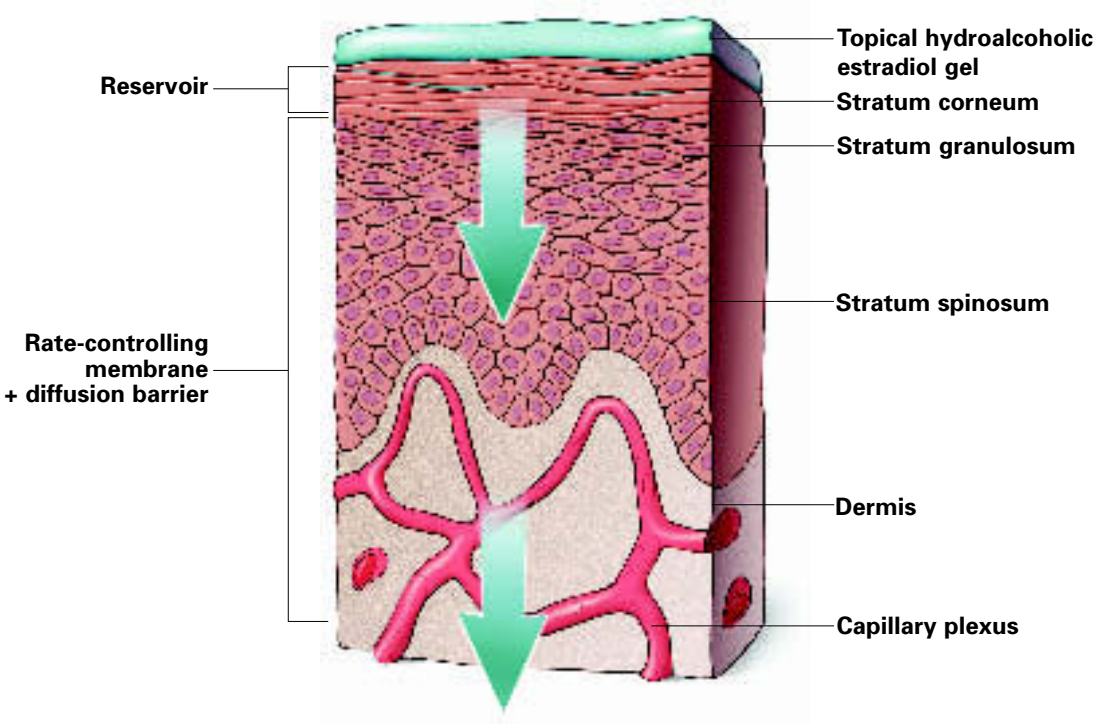

Image: Marcia Hartsock

The hydroalcoholic gel is applied directly to the skin and absorbed into the stratum corneum, which acts as a reservoir. The estradiol then passes through the remaining skin layers, which function as a rate-controlling membrane and diffusion barrier, and enters the systemic circulation in relatively stable physiologic plasma concentrations.

pump that delivers 64 standardized 1.25-g doses, which contain 0.75 mg of 17ß-estradiol. Once it is applied, the gel is absorbed into an intradermal reservoir (FIGURE) and dries in 2 to 5 minutes, leaving no residue.

Patient selection. Estradiol gel is well-suited for patients who are concerned about the risks of oral estrogen (as portrayed in the mainstream press following the Women's Health Initiative) and want to avoid that route of administration, as well as women who dislike or have difficulty swallowing pills. Percutaneous administration also is appropriate for physically active women who may have adhesion problems or skin irritation with the transdermal patch, or those who have had reactions to local adhesives in the past. The patient should be motivated to apply the gel on a daily basis.

Indications are moderate to severe vasomotor symptoms in menopausal women, and moderate to severe symptoms of vulvar and vaginal atrophy, although topical vaginal products should also be considered for the latter indication.

Contraindications are undiagnosed abnormal vaginal bleeding; history of breast cancer, other estrogen-dependent malignancy, stroke, heart attack, or liver disease or dysfunction; active thrombophlebitis or thromboembolic disorders (or a history of these); and known or suspected pregnancy.

Common side effects include headache, breast pain, irregular vaginal bleeding or

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TABLE 1

Serum estradiol and estrone levels for various routes of estradiol

AUTHOR	THERAPY	ESTRADIOL LEVEL (PG/ML)	ESTRONE LEVEL (PG/ML)
Scott et al[8]	E_2 gel 3 mg/day	102.9 ± 39.9	120.0 ± 50.5
	E_2 gel 1.5 mg/day	68.1 ± 27.4	90.6 ± 45.7
	Transdermal estradiol 50 µg/day	41.1 ± 13.5	45.0 ± 15.9
	Oral micronized estradiol 2 mg/day	114.0 ± 65.2	575.2 ± 279.9
Palacios et al[10]	E_2 gel 1.5 mg/day	75.7 ± 1.0	58.5 ± 2.9
	Oral conjugated estrogen 0.625 mg/day	39.6 ± 4.6	126.0 ± 7.6
Basdevant et al[11]	E_2 gel 3 mg/day	221.0 ± 35.0	146.0 ± 19.0
	Oral micronized estradiol 2 mg/day	121.0 ± 27.0	811.0 ± 370.0
Archer[15]	E_2 gel 0.75 mg/day	33.5*	49.0*
	E_2 gel 1.5 mg/day	65.0*	58.0*
	Placebo	5.0*	23.0*

*Median value
E_2 gel = percutaneous estradiol gel

spotting, stomach cramps or bloating, nausea and vomiting, and hair loss.

▪ **Skin reactions** are infrequent, but should be taken into account when discussing percutaneous or transdermal delivery of any drug. However, estradiol gel appears to cause fewer skin reactions than the patch. In a study over more than 5 years, 0 of 157 women treated with percutaneous estradiol reported skin irritation.[2] Other comparisons found similar outcomes.[3,4]

After the gel dries, other lotions or perfumes can be applied to the site, if desired, and the woman can cover the site with clothing.

Onset of action is rapid, as it is with the transdermal patch.[5] Dose variability is minimized when the gel is applied at the same time every day to a large area of skin, preferably the arm, although all application sites appear to produce similar results: abdomen, shoulders, arms, and inner thigh.[6] The gel should not be applied to the breast or vagina.

Diminished effect with skin washing. In 1 trial, site washing 1/2 hour after application significantly decreased bioavailability and time to reach peak plasma concentrations.[7] For this reason, the gel should be not applied before a bath, shower, or sauna.

Dosing options. The initial dose is 1.25 mg of gel, which is 1 pump of the bottle. The gel is collected in the palm of 1 hand and applied to the skin of the opposite arm from the wrist to the shoulder. The dose can be titrated by adding a second pump of the gel and applying it to the opposite arm. The dose can be lowered by using less than a full depression of the pump.

Stable, physiologic estrogen levels

Estradiol gel produces relatively stable serum estradiol levels, and therapeutic estradiol levels similar to those seen with other formulations, routes of administration, and dosages.

Percutaneous administration produces serum estrone to estradiol ratios close to 1, in contrast to higher ratios (5:1) with oral administration.[8–11] The lower ratio approximates levels during the menstrual cycle of premenopausal women. (TABLE 1 gives estra-

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TABLE 2

Effects of various delivery routes and dosages of estradiol on menopausal symptoms

AUTHOR	ROUTE AND DOSAGE	EFFECTS ON MENOPAUSAL SYMPTOMS
Archer[15]	E_2 gel 0.75 mg/day E_2 gel 1.5 mg/day Placebo	Significant reduction in mean frequency of moderate to severe hot flushes and mean frequency and severity of all hot flushes
Kornafel and March[16]	E_2 gel 1.5 mg/day on days 1-21 Placebo	Vasomotor symptom severity decreased significantly compared with placebo (95% versus 39%) at 3 months
Jensen et al[14]	E_2 gel 3 mg/day on days 1-24, oral micronized progesterone 200 mg/day on days 13-24 added in second year Topical placebo Combination cyclic oral estradiol valerate 2 mg and cyproterone acetate Oral placebo	Hot flushes reduced from 80% to 30% in E_2 gel group after 2 years. Hot flushes reduced from 93% to 22% in oral group
Dupont et al[9]	E_2 gel 1.5 mg/day on days 1-25 CEE 0.625 mg/day on days 1-25 E_2 gel 1.5 mg/day on days 1-25 + oral micronized progesterone 200 mg/day on days 12 to 25 CEE 0.625 mg/day on days 1-25 + oral micronized progesterone 200 mg/day on days 12 to 25	Hot flushes, insomnia, night sweats reduced similarly in all groups Vaginal mucosa returned to normal in 80% to 93% of E_2 gel groups and 73% to 100% in oral groups
Hirvonen et al[17]	E_2 gel 1 mg/day + MPA 20 mg cyclically E_2 gel 2 mg/day + MPA 20 mg cyclically Oral estradiol valerate 2 mg + MPA 10 mg/day cyclically	At 24 months, hot flushes reduced by 82.7% by E_2 gel 1 mg, 80.1% by E_2 gel 2 mg, and 75.9% by oral treatment Night sweats reduced by 63.7% by E_2 gel 1 mg, 67.5% by E_2 gel 2 mg, and 71.2% by oral estradiol Frequency of anxiety/tension, insomnia, depressive symptoms, dizziness, loss of libido, vaginal dryness, and headaches all reduced significantly from baseline in all groups
Hirvonen et al[3]*	E_2 gel 1 mg/day + dydrogesterone 10 mg/day on days 1-12 Transdermal estradiol 50 µg/day + dydrogesterone 10 mg/day on days 1-12 Untreated control	Hot flushes, sweating, dry vagina, and insomnia decreased compared to baseline (P<.001) and depressed mood decreased (P<.05) in both treatment groups after 2 weeks of treatment
Foidart et al[18]	E_2 gel 1.5 mg/day for first 24 days of month (2 different brands) + nomegestrol acetate 5 mg/day from days 11-24	Both gels lowered frequency and intensity of hot flushes and global Kupperman index

*Doses could be adjusted
E_2 gel = percutaneous estradiol gel, CEE = conjugated equine estrogen, MPA = medroxyprogesterone acetate

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diol and estrone levels from different studies following administration of estradiol as a gel, oral formulation, and transdermal patch.)

The percutaneous route also allows for delivery directly to the systemic circulation, avoiding gastrointestinal and first-pass hepatic metabolism and elimination. In contrast, oral micronized estradiol causes large fluctuations in serum estradiol and estrone levels due to absorption and metabolism.[8]

More stable serum levels than with the patch. One study[12] comparing percutaneous and transdermal estradiol found similar interindividual variability but less stable serum levels in women using the transdermal system. A separate study[13] also reported greater fluctuation of serum estradiol levels in women using a transdermal system than in those using the gel.

Studies compared relief of menopausal symptoms

Estradiol gel effectively relieved meno-pausal symptoms in randomized, double-blind studies, open label comparisons, and observational trials in postmenopausal women, with and without the addition of various progestins.

Symptom relief in comparison with baseline values is statistically significant as early as 2 weeks after initiating treatment. Relief of up to 2 years' duration has been reported.[3,14]

Several studies have compared symptom relief achieved with estradiol gel, oral estrogen, transdermal delivery systems, and placebo[3,9,14–18]; findings are summarized in **TABLE 2.**

Same efficacy when progestogen is added. The following studies, and other studies,[14] demonstrated that estradiol gel relieves menopausal symptoms whether it is administered alone or in combination with a progestogen, with efficacy similar to other estrogen formulations:

Climacteric symptoms decreased to the same extent when estradiol gel was combined with a levonorgestrel-releasing intrauterine device, oral micronized progesterone, or vaginal micronized progesterone.[19]

A study[20] that added lynestrenol decreased the frequency of hot flushes and night sweats more than in women using estradiol gel alone. However, negative mood symptoms were more pronounced in the progestin-treated group.

Estradiol gel 1 mg/day in combination with monthly or quarterly oral medroxyprogesterone acetate reduced the severity of hot flushes, sweating, and vaginal dryness, according to a 12-month trial.[21]

Symptoms decreased the same whether a levonorgestrel-releasing IUD or oral or vaginal progesterone was added.

Bone mineral density maintained or increased

Several randomized, controlled trials have documented the effects of estradiol gel on bone mineral density (BMD) and various markers of bone metabolism. In these studies, BMD remained steady[22,23] or increased[10,24,25] following treatment, and estradiol gel remained effective for up to 4 years.[25] Estradiol gel maintained or increased BMD with or without addition of progestins.[22,23,26]

These investigations involved measurement of BMD at the lumbar spine, forearms, or hip, as well as biologic markers of bone turnover such as urinary hydroxyproline/creatinine ratio, serum alkaline phosphatase, and serum osteocalcin.

Serum estradiol and skeletal uptake of a bone-seeking agent also were determined. Estradiol gel regimens ranged from 0.75 mg/day to 3 mg/day, and populations included both surgical and natural menopausal subjects in several countries.

Effects comparable to oral estrogen. Compared with oral conjugated estrogen, which increased BMD at the lumbar spine by 4.3% (± 3.2%), estradiol gel produced increases of 5.6% (± 2.9%) at 24 months and 4.7% (± 3.2%) at 36 months.[10]

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Proper patient selection leads to good compliance and relief

The case. A 52-year-old woman with no menses for 8 months presents for management complaining of disabling hot flushes. Although she is moderately obese, with a body mass index of 29, she is normotensive without any other significant medical history except for hysterectomy at age 44 for excessive bleeding.

Counseling. During her 20s, the patient tried to use oral contraceptives on 3 separate occasions, but was unable to continue them because of nausea. Although she is interested in estrogen therapy for her vasomotor symptoms, she is concerned about the possibility of experiencing nausea again. You explain that one of the benefits of percutaneous estradiol is that it avoids the gastrointestinal tract.

Physical findings. Her physical examination is within normal limits, and gynecologic examination confirms no uterus and finds no palpable adnexal masses.

Outcome. After weighing the pros and cons, she elects to use estradiol gel. At her 3-month follow-up, she reports effective relief and good compliance.

Minimum level of protection achieved. Following a comparison of oral and percutaneous estradiol, Reginster et al[27] suggested that a minimum estradiol level of 60 pg/mL is necessary to prevent postmenopausal bone loss. Mean serum estradiol levels in women receiving 1.5 mg/day estradiol gel were 75.7 pg/mL and 78.4 pg/mL at 24 and 36 months, respectively, in a study by Palacios et al,[10] and 85.8 pg/mL in a study by Devogelaer and colleagues.[24] In these trials, BMD increased, and it remained steady in other investigations.[28,29]

More recent trials suggest that lower serum estradiol levels secondary to smaller estrogen doses have the capacity to maintain BMD.[30,31] A 1.9% mean increase of BMD at the lumbar spine was reported in women with a mean serum concentration of 17 pg/mL in a 2-year study[30] of a transdermal estradiol delivery system. The percutaneous route does not appear to limit these beneficial effects.

How are metabolic factors affected?

In general, oral estrogens produce beneficial changes in lipid metabolism, particularly higher levels of high-density lipoprotein (HDL) cholesterol. However, they also elevate triglyceride and glucose levels. How this plays out clinically is unclear. Both the Women's Health Initiative and the Heart and Estrogen/Progestin Replacement Study (HERS) found no cardioprotective effects of oral estrogen despite increases in HDL and decreases in low-density lipoprotein (LDL) levels.[1,32]

Oral versus percutaneous estradiol. No long-term studies of this magnitude have investigated the effect of percutaneous estradiol on coronary artery disease, although numerous clinical trials have shown that the route of estrogen delivery affects many of the metabolic variables used to estimate the risk of negative cardiac outcomes. It remains to be determined whether percutaneous estradiol affects these metabolic factors in ways that influence morbidity and mortality.

In 1 trial,[33] oral conjugated estrogen led to the following significant changes in lipids:

- increase in very low density lipoprotein (VLDL) cholesterol,
- decrease in LDL cholesterol (but not the LDL apoprotein B),
- increase in HDL and apoprotein A1, and
- significant increase in HDL2 cholesterol.

In contrast, percutaneous administration increased only HDL2 and the triglyceride and cholesterol content of the whole HDL fraction.

In a separate study,[9] oral conjugated estrogen had a 2.5-fold increase in serum angiotensin, and percutaneous estradiol gel, no effect.

Same effects when progestin is added. Beneficial effects were not diminished when

oral micronized progesterone was added to percutaneous estradiol.[34] Estradiol gel significantly reduced total serum cholesterol and LDL cholesterol in the first year of treatment, compared with placebo.

Coagulation effects. Percutaneous estradiol has fewer negative effects on coagulation factors than its oral counterpart. One study[35] investigating combination therapy with micronized progesterone compared the effects of percutaneous estradiol and oral estradiol valerate. The group receiving percutaneous estradiol gel/micronized progesterone had no significant changes in plasminogen activator inhibitor, tissue-type plasminogen concentration, and global fibrinolytic capacity. The other group had a significant decrease in mean tissue-type plasminogen concentration and plasminogen activator inhibitor activity and a significant rise in global fibrinolytic capacity.

The oral estradiol—but not the percutaneous formulation—significantly increased the mean value of prothrombin activation peptide and decreased mean antithrombin activity compared with no treatment.

Poor glycemic control may increase the risk of cardiovascular disease, but oral and percutaneous estradiol appear to have similar glycemic effects. A comparative trial[36] of oral estradiol valerate 2 mg/day and percutaneous estradiol 1 mg/day found no differences in glycosylated hemoglobin A1c levels (declined in both groups) or in fasting and 2-hour postprandial blood glucose levels (constant in both groups) or insulin sensitivity.

Treatment duration may also influence how percutaneous estradiol affects metabolic factors. An open-label longitudinal prospective study[37] of 30 women receiving estradiol gel 1.5 mg/day for 6 months found a significant decrease in lipoprotein (a), apoprotein A-I, apoprotein B, HDL cholesterol, and HDL3 cholesterol. At 1 year, however, these changes were not significant.

No association with venous thromboembolism. Transdermal estradiol administered

as a patch or percutaneous gel had no effect on the risk of venous thromboembolism in a multicenter case-control investigation.[38]

In contrast, a recent retrospective study found a risk of venous thromboembolism that was at least 4 times greater with oral estrogen than with transdermal estradiol.[38]

Use a progestogen to prevent endometrial hyperplasia

Like other forms of estrogen, percutaneous estradiol stimulates the endometrium. For this reason, women who have an intact uterus should use a progestogen in an adequate dose to prevent hyperplastic changes.[39] Although numerous regimens appear to be effective, the optimal route, dose, and duration of progestin in women using percutaneous estrogen remain to be determined.

Percutaneous estradiol versus other routes of administration. Endometrial thickness and amenorrhea rates over 6 months were not statistically different among 54 women treated with estradiol gel 1.5 mg/day, transdermal estradiol 50 μg/day, or oral estradiol valerate 2 mg/day—all in combination with nomegestrol acetate 2.5 mg/day.[40] The overall rates of no bleeding or spotting over 6 cycles of treatment were 78% in the percutaneous estradiol group, 48% in the transdermal group, and 60% in the oral group.

Although the percutaneous estradiol group had a lower overall incidence of no bleeding or spotting than the other groups, the difference was not significant. Nor were there significant differences in the variation of endometrial thickness from baseline: A mean increase of 1.5 mm (± 0.4 mm) was reported in the percutaneous group, compared with 1.5 mm (± 0.7 mm) and 1.7 mm (± 0.6 mm) in the transdermal and oral estrogen groups, respectively.

Estrogenic and progestogenic effects were similar for transdermal and percutaneous estradiol (with dydrogesterone 10 mg/day for days 1 to 12) after a baseline atropic endometrium was identified.[3]

The most effective progestogen dosage and duration are unknown, although many regimens have been studied:

- Percutaneous estradiol 1.5 mg/day for the first 24 days of the month in combination with nomegestrol acetate 5 mg/day for days 11 to 24: Over 6 months, researchers found a secretory pattern in the majority of women and no evidence of hyperplasia.[18]

Estradiol gel produces stable, physiologic serum estradiol levels and has a serum estrone to estradiol ratio close to 1.

- Percutaneous estradiol 3 mg/day for 3 of every 4 weeks in combination with nomegestrol acetate 5 mg/day for 10 days: No reduction in estrogenic endometrial effects.[41,42]
- Estradiol gel 3 mg/day for 3 of every 4 weeks in combination with 200 mg or 300 mg oral micronized progesterone for the last 10 days of treatment: Dose was too low or treatment too short to produce a complete secretory transformation of the endometrium.[43] However, the Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial[44] found no increased occurrence of hyperplasia in women using micronized progesterone 200 mg for 12 days of each cycle for more than 3 years in combination with oral conjugated estrogen 0.625 mg.
- Percutaneous estradiol 1.5 mg/day combined with micronized progesterone 100 mg daily (orally or vaginally) for the first 25 days of the month: Fully inhibited mitoses and induced amenorrhea in most of the women studied, with amenorrhea rates of 93.3% at 3 months and 91.6% at 6 months.[45]
- Estradiol gel 1.5 mg/day with 100 mg vaginal micronized progesterone for 21 days per cycle: Stable endometrial thickness and no endometrial hyperplasia over 12 months.[46] However, breakthrough bleeding was reported in up to 30% of subjects, principally in the second 3 months of treatment.

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• Percutaneous estradiol 1 mg/day for 3 months with oral medroxyprogesterone acetate 20 mg/day for the last 14 days, followed by a 7-day free interval: No reports of endometrial hyperplasia or suspect changes at 12 and 24 months.[17]
• Estradiol gel 2 mg/day for 21 days with 10 mg oral medroxyprogesterone acetate for the last 14 days, followed by a 7-day free interval: No endometrial hyperplasia or suspect changes at 12 and 24 months.[17]
• Estradiol gel 1 mg/day with medroxyprogesterone acetate 10 mg on days 1-12 every month or every 3 months: Endometrial hyperplasia was found in 1 woman (0.3%) in the group receiving the progestogen every 3 months. Endometrial histology did not differ between women taking medroxyprogesterone monthly and those taking it every 3 months.[21]
• Estradiol gel 3 mg/day with oral micronized progesterone 200 mg for 12 days of each cycle: Regular withdrawal bleeding in 70% of women.[34]
• Percutaneous estradiol 1.5 mg/day in combination with a levonorgestrel-releasing intrauterine device: 80% of women were amenorrheic at 1 year, with a mean endometrial thickness 3 mm; at 5 years, 100% of women had epithelial atrophy.[47]
• Estradiol gel 1.5 mg for 21 days with 200 mg oral progesterone for 14 days (126 women); 3 mg percutaneous estradiol for 21 days with 300 mg oral progesterone for 10 days (23 women); 1.5 mg estradiol gel with 300 mg oral progesterone (3 women); or 3 mg estradiol gel for 28 days with 200 mg progesterone for 14 days (5 women): No evidence of hyperplasia after 5 years of treatment.[2] ■

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