



100. Vaginal estrogen cream, tablets, and ring

Last Updated: 12/22/2006

Q1: "I'm in a quandary over different medical opinions. I am 67 years old. I had a retinal vein thrombosis 2 years ago while on topical vaginal estrogen cream (Estrace®) and was diagnosed with heterozygous Factor V Leiden. I was told to stop the estrogen cream. Extreme vaginal dryness has exacerbated into atrophy to the extent that in medical examinations visualization of my cervix has become impossible, and a viable sample for a pap smear couldn't be obtained over the past year. After some post menopausal spotting I went for a transvaginal sonogram and the atrophy prevented the procedure so that it was done rectally. Several physicians have differing positions on whether I should go back on estrogen cream in order to facilitate future examinations:

- My surgeon spoke to the head of the hormone division at our university. He said she is the most vigorous advocate of estrogen therapy he has ever met, BUT, in my case, he said she said "absolutely not." He added that a second retinal thrombosis could be very dangerous.
- A hormone specialist from another hospital (who also deals with women's issues) recommends that I go on a light dose of topical vaginal estrogen and have my blood monitored for absorption.
- My internist suggests I go on Estrace® (which I was using when I had the thrombosis) in order to build up the vaginal tissues and then go onto the less potent Vagifem®.
- My gynecologist, in an attempt to avoid estrogen, has prescribed vaginal dilators. I started this therapy over a week ago and I must say there is a Marquis de Sade-ish sense to the exercise. I awoke feeling sore and disheartened.

A1: As always, full details about this person's medical history are needed for a solid assessment. It would be helpful to know (a) whether this patient had other risk factors for retinal vein thrombosis, such as high blood pressure, diabetes, high cholesterol, smoking, overweight, (b) how long she had been on Estrace® (estradiol) cream before the clot happened, (c) whether she has a personal or family history of thrombosis. The Estrace® cream which the patient took may have contributed slightly to the development of the retinal vein thrombosis or may not at all. This is not known. It may be reasonable and safe for her to take a low estrogen vaginal preparation, such as the Estring®, which delivers significantly less estrogen than Estrace®.

Q2: "I am a female, 53 yrs old. Roughly 6 years ago I was diagnosed with a leg DVT (deep vein thrombosis) and found to have homozygous factor V Leiden. I have been on coumadin® since then and have had little complications. I am post-menopausal. My lack of estrogen has caused me extreme vaginal pain and dryness thus making sexual relations with my husband most uncomfortable. I have tried all the prescribed lubricating remedies, but nothing has come close to solving my problem. My gynecologist suggested a type of estrogen that is inserted vaginally and, thus, for the most part confined to the area. I met with a hematologist and he suggested because I was homozygous factor V Leiden that he would not recommend the estrogen therapy. I am wondering if any studies have been conducted on post menopausal women using a suppository type of estrogen for severe vaginal dryness.

A2: Yes, the studies are referenced below [references 1-3]. There is a small amount of estrogen absorption from vaginal estrogen preparations, particularly for the first 7-14 days of therapy. However, any potential minimally increased risk for blood clots due to absorption of estrogen would likely clinically not be relevant in this person, since she is on warfarin

Q3: "I have vaginal dryness. My doctor does not want to prescribe vaginal estrogen cream because I have had a blood clot (DVT in my leg) in the past. I am not on coumadin® any more. What do you think: is the cream safe to take?"

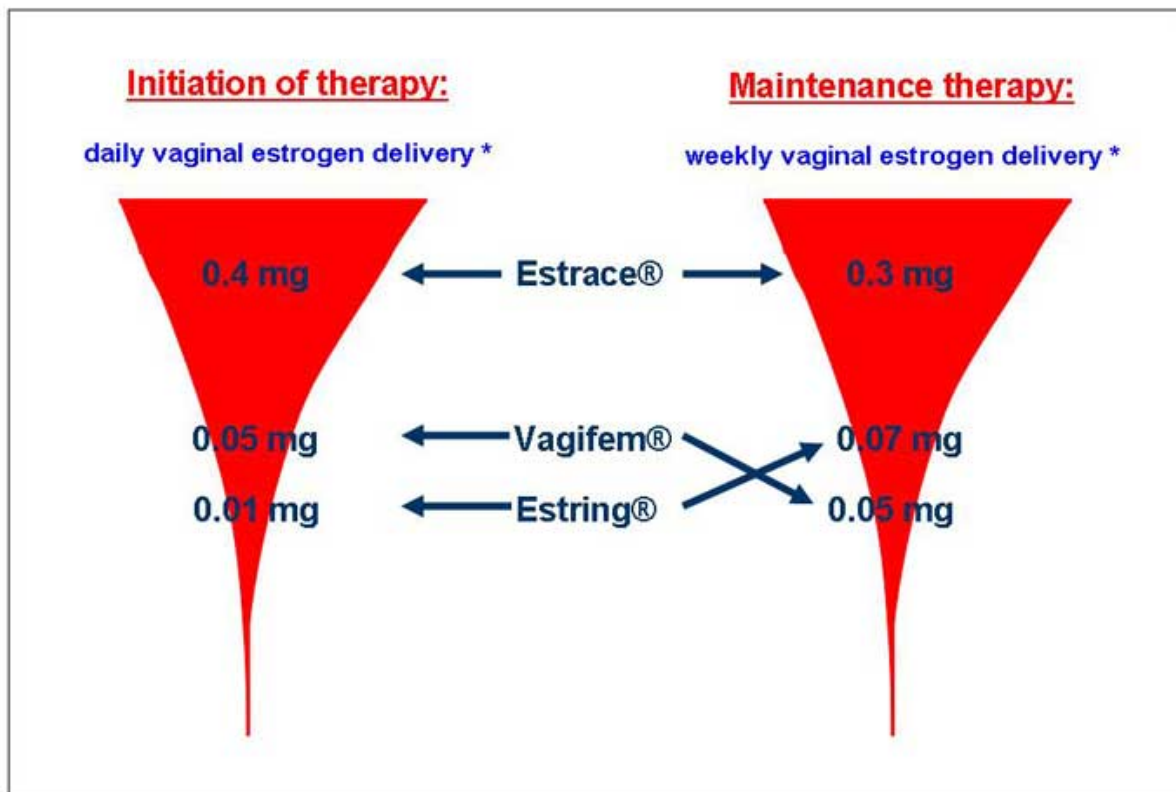
A3: It is not clear whether vaginal estrogen preparations are safe in a person who has had a previous clot but is not on warfarin any more, or the person who has a strong clotting disorder. However, any such potential risk is likely quite low, considering that the low estrogen vaginal preparations lead to only a minimally increase in blood estrogen level. It makes sense to start with the lowest concentration preparation, such as Estring®.

Estrogens can very effectively decrease vaginally dryness, which often occurs after menopause. They can be taken by several different routes:

- a. orally as a tablet,
 - b. transdermally as a skin patch,
 - c. vaginally, as a gel, tablet, or ring.
- A. Oral Estrogens Orally taken estrogens are known to increase the risk for thrombosis (DVT and PE). In women with a history of blood clot or with a known clotting disorder, oral estrogens may, therefore, better be avoided.
- B. Estrogen Patch Recent studies have shown that transdermal estrogen administration does not lead to an increased risk of DVT and PE [references 4 and 5]. Thus, transdermal estrogens may be safe from a clotting point of view. However, because of the scarcity of data one can not make a solid assessment that the transdermal estrogens are really safe. Confirmatory studies are needed. It is clear however, that transdermally delivered estrogen leads to significantly higher blood estrogen levels than vaginally delivered estrogen [reference 2].
- C. Vaginally Delivered Estrogens The doses of vaginally delivered estrogens are small, with only slight absorption into the blood stream. The absorption occurs mostly when treatment begins, because the atrophic vaginal mucosa (= cell layering of the vagina) which is thin and cracked in the absence of estrogens, is a sort of sieve. However, after a relatively short interval of time, such as within 1-2 weeks, the mucosa thickens in response to treatment, and absorption of estrogens into the bloodstream, thus, declines.

Several preparations exist, Estring®, Vagifem®, Estrace®, and Premarin®. Estring®, Vagifem®, and Estrace® contain the same type of estrogen and comparison of the strength between these preparations is, therefore, somewhat possible (see figure below). Estring® appears to lead to the lowest daily exposure, followed closely by Vagifem®. Estrace®, on the other hand, appears to lead to a significantly higher daily exposure. However, even Estring® leads to some absorption into the blood stream of estrogens, as evidenced by the fact that it does not only improve vaginal dryness, but also decreases hot flushes and other perimenopausal symptoms.

Premarin® contains a mixture of different types of estrogen, called conjugated estrogens. It is difficult, if not impossible, to compare its strength to estradiol (because it depends on what biological measure of estrogen action one uses in the comparison). When Premarin® is delivered into the vagina at lower doses (0.3 mg per day or less) no detectable absorption into the blood stream was seen [reference 1].



* depends on what dosing the woman uses

The preparations for women with vaginal dryness are:

1. Name: Estring® [references 2 and 3]

Content: 2 mg estradiol. Releases 6.5-9.5 µg/24 hours (1000 µg = 1 mg)

Dosing: exchange every 3 months.

Comment: After an initial 3-4 day peak of blood estrogen levels, the ring maintains a continuous plasma estradiol concentration of 20-30 pmol/L for 3 months - a level that is slightly higher (ca. 3 pmol/L, i.e. ca. 10 % higher) than the level in women not having the ring.

2. Name: Vagifem® vaginal

Content: 1 tabl = 0.025 mg estradiol

Dosing: Start 1-2 tabl per day for 2 weeks. Then 1 tab 2x/week

3. Name: Estrace vaginal® 0.01 % cream

Content: 1 g cream = 0.1 mg estradiol

Dosing: Start 2-4 g per day for 1-2 weeks, then 1 g 1-3x/wk)

Comment: This is a higher estrogen dose preparation than Estring® and Vagifem®: vaginal estrogen delivery is approximately 10x higher.

4. Name: Premarin vaginal® cream.

Content: 1 g cream = 0.625 g conjugated estrogen.

Dosing: Start 0.5 - 2 g per day for 1-2 weeks, then 1-2 g 1-2 times per week.

Comment: Difficult, if not impossible to compare to the other 3 products, since Premarin® contains a different type of estrogen.

Personal Comment:

Although there is some systemic absorption of vaginally delivered estrogens, these levels are very low. For the woman with vaginal dryness and a history of blood clots or a thrombophilia it appears very reasonable to take a vaginal estrogen preparation, starting with the lowest concentration preparation. Doses can then be slowly increased if the low

dose does not alleviate the symptoms. The Estring® (a) is a very low estrogen preparation, (b) is less hassle than creams and gels, (c) results in more stable vaginal and blood estrogen concentrations, and (d) is very effective. For all these reasons, it appears to be a good choice in the woman with vaginal dryness and a history of thrombosis or thrombophilia.

References:

1. Deutsch S et al.: Comparison between degree of systemic absorption of vaginally and orally administered estrogens at different dose levels in postmenopausal women. *Am J Obstet Gynecol* 1981;139:967-968.
2. Gabrielsson J et al.: Pharmacokinetic data on estradiol in light of the Estring® concept. *Acta Obstet Gynecol Scand* 1996;Suppl 163;75:26-31.
3. Sarkar NN: Low-dose intravaginal estradiol delivery using a Silastic vaginal ring for estrogen replacement therapy in postmenopausal women: a review. *The European Journal of Contraception and Reproductive Health Care* 2003;8:217-224.
4. Scarabin PY et al. Differential association of oral and transdermal oestrogen-replacement therapy with venous thromboembolism risk. *Lancet* 2003;362:428-432.
5. Straczek C et al. Prothrombotic mutations, hormone therapy, and venous thromboembolism among postmenopausal women. Impact of the route of estrogen administration. *Circulation* 2005;112:3495-3500.