Estriol

Estrriol (E3) is one of the three physiologic estrogens found in the human body. The unique biochemical and biologic effects of estriol distinguish it among alternative FDA-approved chemical entities. Estriol, oestra-1, 3,5 (10)- triene- 3,16 α, 17 β-triol, is widely used as hormone replacement therapy in Europe and Japan since it obviates the need for progestin administration. There is extensive, peer-reviewed data that supports the use of vaginal and, to a lesser extend, oral estriol.

Estriol has been used in Europe for over 60 years (Puck 57, 60). Vaginal estriol's safety profile is well established. Vaginal estriol is currently available over the counter in Finland. Prior to that, it was the most widely prescribed therapy to treat vaginal and urinary symptoms.

Efficacy & Safety of Vaginal Estriol

Local and systemic effects of vaginally administered estriol

Relative Binding affinities (RBA) and differential effects
Vaginal estriol has been shown to relieve local, vaginal and urinary symptoms without stimulating the breast tissue or endometrium. Estriol has a high relative binding affinity (RBA) for estrogen receptors in the bladder and vaginal tissue and a relatively low RBA for estrogen receptors in the uterus (myometrium) and breast tissue, figure 1, figure 2, (Bergink 84).

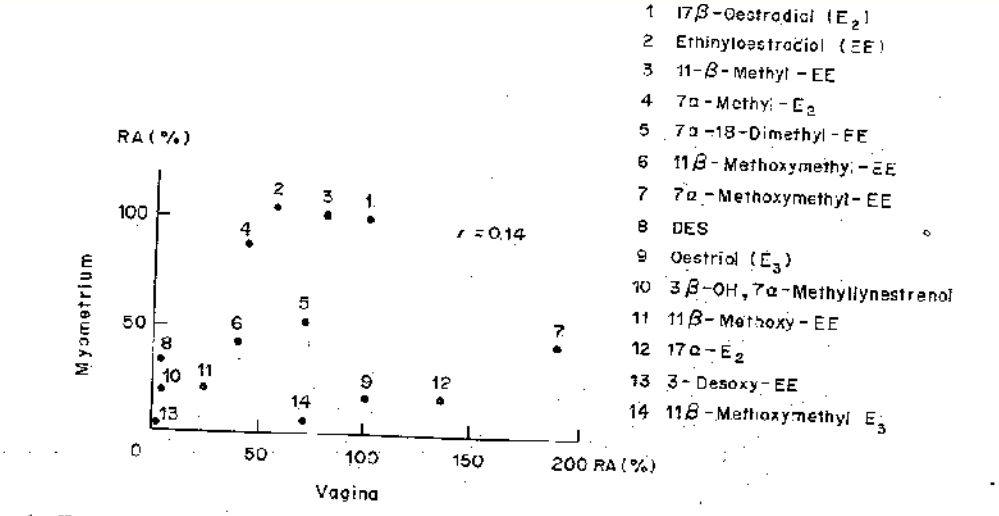

Fig. 1. Comparison of relative affinities for oestrogen binding proteins in human myometrium and vagina.

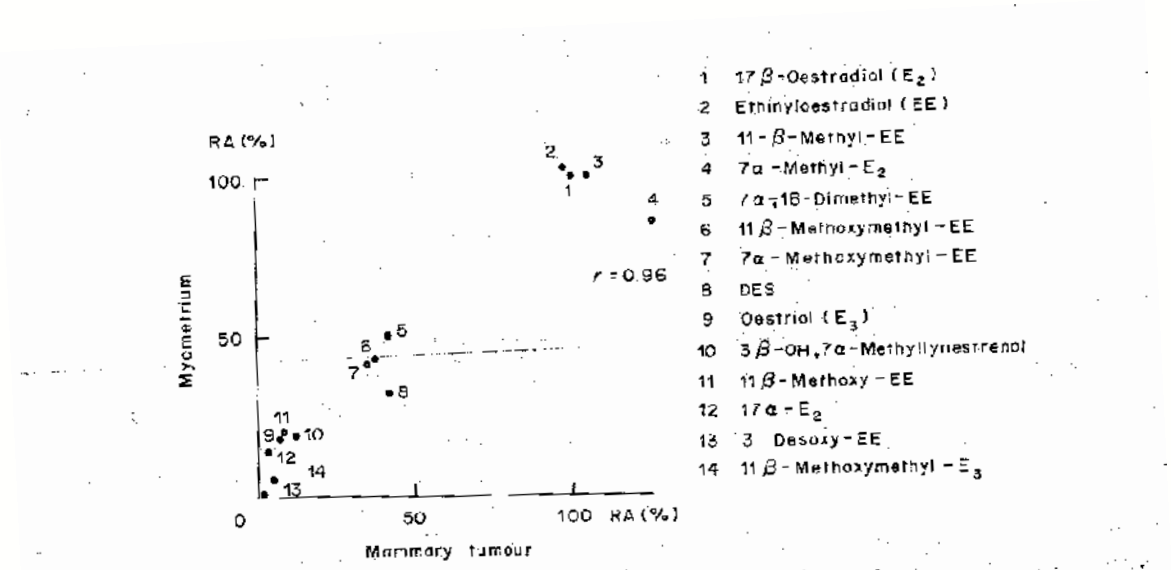

Fig. 2. Comparison of relative affinities for oestrogen binding proteins in human myometrium and mammary tumour.

Because of the high RBA for the ER in the vaginal tissue and bladder, estriol will have a strong/beneficial effect in these tissues. Because of the low RBA for the ER in the myometrium and breast, estriol exerts only a weak effect in these tissues. Estriol is much less stimulatory to the breast and endometrial tissue than 'strong' estrogens like estradiol, which have much higher RBA in these tissues. Estriol acts as a selective estrogen receptor modulator, binding strongly to the ER in the bladder and vaginal tissue and weakly to the breast and endometrial tissue.

Estriol also binds to the estrogen receptor in the breast tissue for a shorter period of time, 6 hours, thus causing less of an effect than the more stimulatory estradiol and estrone which bind to the ER for a longer period of time, 24 hours. Estriol acts as a weak estrogen in the breast, endometrium and liver while having full estrogenic responses in the vaginal and bladder epithelium (Kuhl 05).

Dosage and Pharmacokinetics

The doses and pharmacokinetics of *vaginally* applied estriol are well known. Estriol is delivered as a vaginal cream in a 0.5 to 1.0 mg dose. Unlike oral estriol, which may accumulate, vaginal estriol *does NOT accumulate* (Haspels 81, Trevoux 82). Vaginal estriol, like other hormones administered vaginally, shows *consistent absorption* without adverse effects on estrone and estradiol levels (Trevoux 82, Fink 85, Shiff 78, Keller 80, Bottiglione 95, Kesim 94).

Vaginal estriol, commonly delivered 0.5 mg daily for 14 days then 3 times weekly, has been shown to *consistently* relieve vaginal dryness, vaginal atrophy and dsypareunia, normalize vaginal flora and improve the vaginal maturation index. Vaginal estriol also relieves urinary

symptoms: stress incontinence, dysuria, urgency and reduces the incidence of urinary tract infections (Barentsen 96, Ishiko 01, Kesim 94, Melis 96, Yoshimura 00, Trevoux 82, Luisi 80).

There is substantial peer reviewed data which supports that vaginal estriol *relieves systemic menopausal symptoms* including: hot flashes, night sweats and symptoms reflected by the Kupperman index (Fink 85, Bottigione 95, Melis 96, Luisi 80). Vaginal estriol has been shown to be superior to Premarin vaginal cream (Luisi 80). Vaginal estriol does not affect clotting factors, cause fluid retention or weight gain.

Vaginal estriol has also been shown to prevent bone loss and increase *bone* density (Blum 85, Michaelssom 02, Melis 96). Estriol also has been shown to have a beneficial effect on the *heart*. Vaginal estriol has been shown to increase serum HDL, lower LDL, activate the NO (nitrous oxide) system, improve endothelial function and have a vaso-relaxing effect (vaso-dilator). Estriol had been shown to be atheroprotective. (Kano 02, Hayashi 00, Kesim 94, Kilkuchi 00, Sheardown 97, Mishra 05). Vaginal estriol has also been shown to lower or have no adverse effect on blood pressure (Fink 85, Sheardown 97, Utian 80).

A recent study in the US has shown vaginal estriol to be protective in the transmission of HIV (Smith 04).

Breast and endometrial safety of estriol

Vaginal estriol, delivered in the *correct doses*, does not stimulate the uterine lining. Estriol does not cause uterine hyperplasia (Blum 85, Minaguchi 96, Melis 96, Nishibe 98, Takashi 00, Granberg 02, Vooijs 95 review). There is also no increase in the incidence of uterine cancer with *vaginal* estriol therapy (Salmi 79, Persson 89, Weiderpass 99). However, oral synthetic estriol succinate (Synapause®) and continuous, high dose oral estriol, administered 2-3 times daily, have been shown to induce endometrial hyperplasia (Punnonen 83, Englund 80) and possibly increase the risk of uterine cancer (Wiederpass 99).

As mentioned above, estriol has a low RBA (Relative Binding Affinity) for the ER in breast tissue and a rapid dissociation, 6h, from the Estrogen receptor (6h). Estriol does not increase breast density (Valdivia 00, Minaguchi 96, Takahashi 00).

Major, large, peer reviewed trials have repeatedly shown that **vaginal estriol does NOT increase the risk of breast cancer**:

- Million Women's Trial 03 RR 0.67
- Fournier 04 RR 0.7
- Fournier 07
- Rosenberg 06
- Lyntinen 02
- Bergvist 89

There is **no** data to the contrary.

Studies are mixed in regards to oral estriol and breast cancer, with he majority of trials showing *no increase* in the risk of breast cancer. One exception is Olsson's study from 2003, which showed an increased risk of breast cancer with oral estriol therapy. It was unclear whether Synapause®, oral estriol succinate, or estriol had been used in the study. Rosenberg 06, showed that oral estriol (Ovesterin ®, estriol) did not increase the risk of ductal carcinoma, but *did* increase the risk of lobular carcinoma, but only if used less than 5 years. There was no increase in the risk of lobular carcinoma if oral estriol had been used more than five years.

Vaginal estriol has also been safely used in breast cancer survivors (Dew 03). There was a decrease in' recurrence of disease' in vaginal estriol users (RR 0.57) vs. non-users and no adverse affect on mortality.

Conclusion

Peer reviewed data clearly demonstrates that vaginal estriol is efficacious for both local vaginal urinary symptoms and systemic menopausal symptoms. Vaginal estriol, delivered in the correct dosage, has a proven safety profile. There are no adverse affects of *vaginal estriol* to the vascular system, liver, endometrium or breast tissue. It has safely been used to treat symptoms in breast cancer patients.

There is a lack of data supporting the use of topical estriol on skin. There is also a lack of data supporting the claim that topical 'Bi-estrogen', applied to the skin, is safer than conventional estrogen therapy. However, this is not to be confused with the large amount of data supporting the use and safety of vaginal estriol and in some cases, lower dose oral estriol (vs. oral estriol succinate). Full text articles are available upon request.

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