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EDITORIAL

Estetrol for menopause symptoms: the Cinderella of estrogens or just another fairy tale?

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Despite the advent of lower dosing, transdermal delivery, and targeted use in younger age groups, safety concerns persist regarding the potential for estrogen-based menopause hormone therapy (MHT) to raise breast cancer and thromboembolism risk. In the last few decades a wealth of scientific advances has revealed the molecular biology of the estrogen receptors (ERs) α and β, opening up new directions for their pharmaceutical manipulation and promise to improve hormone therapies. With the help of the ER knockout mouse model, an array of estrogen-mediated actions in tissues throughout the body was elucidated, followed by the emergence of new compounds with tissue-dependent, ER agonistic, antagonistic, and mixed actions.[1] Although several of the first- and second-generation compounds, known as selective ER modulators or SERMs, have proven to be important therapies in the treatment of breast cancer and osteoporosis, no SERM to date has achieved a profile conducive to managing the full spectrum of menopausal symptoms. In fact, most SERMs tend to exacerbate rather than alleviate vasomotor symptoms (VMS) and exhibit agonistic actions on the liver, raising concerns about stroke and cardiovascular disease risk similar to those associated with conventional MHT.[2] Now comes a breakthrough compound that demonstrates unique ER-binding activity, distinct from SERMs, with potential for enhanced safety. Surprisingly, this super ligand, purported to have all the attributes of estradiol and few of its flaws, did not originate in a sophisticated steroid biochemistry laboratory. Instead, scientists had to look no further than the urine of pregnant women for the next exciting innovation.

Estetrol is the lesser-known, understudied ''stepsister'' of estradiol (E2), estriol (E3), and estrone (E1), produced in nature only during human pregnancy and only by the fetal liver where enzymes needed to convert E2 and E3 into E4 are exclusively found. Although first described in the late 1960s by Diczfalusy and proposed as a marker of fetal well-being (still under study), it was abandoned by the pharmaceutical industry as a possible contraceptive due to its much lower ER affinity (<5%) compared to E2.[3] Interest was, however, renewed in the 2000s when preclinical and pharmacokinetic studies showed that estetrol elicits considerable estrogenic effects in rat models for both hot flashes and bone loss, but with minimal stimulation of liver and breast.[4] More recent translational studies[5] showed that E4 was bestowed with an intriguing ER pharmacology, unique from SERMs, thus pushing it to center stage for its potential as the first native estrogen with selective action in tissues (NEST).

Unlike other estrogens, which interact with both α and β receptors at the cell surface and in the nucleus, E4 not only preferentially binds to the ERα subtype, but does so in a distinct non-SERM way. Estetrol is endowed with a unique capability to uncouple ERα modulation: activating the *nuclear* ERα to induce genomic transcription while blocking *membrane* ERα at the cell surface that normally triggers rapid downstream signal transduction in the cytoplasm.[6] This property of E4 is the basis for its tissue-specific action and unusual pharmacodynamic profile. As the final product of human steroid metabolism, estetrol has been shown in pharmacokinetic studies to have essentially no active metabolic end products, minimal first-pass metabolism, a high oral availability, an elimination half-life of approximately 28 hours, and reduced estrogenic impact on hepatic synthesis of hemostasis parameters[7,8] – all important attributes of an oral, liver-friendly candidate for MHT.

Now under development by Mithra Pharmaceuticals (Liege, Belgium, www.mithra.com) as an oral contraceptive (in combination with drospirenone) and MHT products, these attributes of E4 have been mostly supported in phase 1 and early phase 2 clinical studies. In a 4-week, multiple- rising dose study in 49 postmenopausal women, even the lowest doses studied (2 and 10 mg) improved VMS and vaginal cytology.[9] Although a placebo control was lacking, effects in a comparator group treated with 2 mg estradiol valerate (EV) were similar. In the safety portion of that study a dose-dependent estrogenic effect (dose range of 2-40 mg) was observed on endocrine parameters, bone turnover markers, lipids, and lipoproteins, but with only modest detriment to triglycerides and hemostatic values.[10] At the same time, endometrial proliferation at the 10 mg dose was pronounced and similar to that seen in the EV group, prompting reviewers to note that perhaps the best indication for E4 use might be as an estetrol-only therapy for vaginal atrophy at a dose low enough to avoid endometrial effects.[11]

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Building on this preliminary work, Gaspard et al[12] report in this issue of *Menopause* the first round of results on VMS and overall safety from the *E4Relief* trial – a phase 2b multicenter, randomized, placebo-controlled, double-blind, dose-finding study designed to determine the minimally effective oral dose of estetrol for VMS relief in postmenopausal women. (Data on biomarkers of hemostasis, lipids and glucose metabolism, and vaginal symptoms and quality of life will be published in later reports). Recruited from six European countries, a total of 257 participants, ages 40 to 65 years, were randomized to placebo or treatment groups (approximately 45 per group) of E4 (2.5, 5, 10, or 15 mg), and compared at baseline, 4, and 12 weeks on VMS features (daily electronic diaries) and safety measures including endometrial thickness and bleeding patterns. Women qualified to participate in the trial if they had not had a period for at least 6 months either due to hormonally-defined natural menopause or hysterectomy, had 7 or more moderate to severe hot flushes per day, or 50 or more moderate to severe hot flushes in the week before baseline; and for those with natural menopause, had findings on transvaginal ultrasound of a bilayer endometrial thickness of 5 mm or lesser. At study completion, nonhysterectomized participants received 2 weeks of progestin therapy (dydrogesterone 10 mg).

Study results were somewhat surprising in that the minimum efficacy dose for VMS relief also carried notable estrogenic effects on the endometrium. In this larger and longer controlled trial, only the highest E4 dose (15 mg) demonstrated a significantly greater reduction in VMS frequency and severity compared to placebo. At this dose, the improvement in VMS over placebo at week 4 was already marked, and by week 12, a highly significant response was demonstrated (>80% of participants achieved at least 75% lower frequency) similar to that seen in studies of estradiol therapy. Although there were no unexpected adverse events and no endometrial hyperplasia, safety profiles indicated a clear dose-dependent, stimulatory effect on the endometrium, with endometrial biopsy required in 13% of volunteers, mostly in the highest dose groups, due to abnormal bleeding.

But as pointed out by the investigators, the failure of lower E4 doses (eg, 10 mg) to achieve superior VMS effects over placebo may in part be due *not* to the failure of the drug, but to the success of the placebo, which demonstrated a mean percentage decline in VMS frequency from baseline of 65% by week 12. Notably excessive, even for hot flash studies,[13] the investigators attribute the large placebo-induced VMS improvement in part to elevated E2 values in controls (as high as 180 pg/mL), suggesting the possibility of serendipitous follicular development or the undisclosed use of estrogenic compounds during study. (The inclusion of participants who met the weaker eligibility criteria for postmenopause as 6 months amenorrhea in the presence of a single measure of E2 of <20 pg/mL may have also contributed.) To their credit, the authors demonstrated in post hoc analyses that neither study site nor country of residence was associated with response rates, but acknowledge that other possible contributing factors were not systematically assessed.

Although investigators acknowledge that part of the problem may have been due to the small sample size, another study limitation might be the failure to adequately exclude placebo responders during screening. It has been estimated that in the last decade, a rising placebo response rate may be contributing to a 15% increase in failed phase 2 clinical trials.[14] One well-established approach for reducing placebo effects in drug trials is to include a run-in period, where every eligible volunteer is blinded and receives a placebo for a week or so, to identify and exclude placebo responders before randomization. In a recent meta-analysis of hot flash intervention trials, Li et al[15] concluded that the intertrial variability of the placebo response was significantly lower in trials with a run-in period versus those without, leading them to recommend the incorporation of a run-in period into study design to improve the sensitivity and accuracy of the efficacy measures. Had such an approach been used in this trial, it is possible that lower doses may have also shown efficacy.

Building on these *E4Relief* findings as well as other preliminary reports of favorable secondary outcomes and safety measures for cardiovascular risk,[16,17] two world-wide phase 3 trials (study I in Europe, Russia, and South America; study II in North America), already in the recruitment phase (ClinicalTrials.gov NCT04209543), should better define the appropriate balance between E4 efficacy for VMS relief and safety. It is, however, noteworthy that the lower doses used in the study reported here will not be tested in the *E4 Comfort* trial; only oral doses of 15 and 20 mg will be compared against placebo for up to 1 year in large cohorts of postmenopausal women ($n = 1{,}200$ in study I; $n = 1{,}000$ in study II). Changes in frequency and severity of moderate to severe VMS in postmenopausal women will be monitored at 4 and 12 weeks, and then followed for an additional 40 weeks, along with vaginal symptoms, multiple safety parameters, and quality of life measures.[18]

How these higher doses of longer duration will impinge on the promising benefit/risk profile remains to be seen. Happy ever-after-endings to such trials are seldom realistic. (Already recruitment is temporarily on hold as of April 1, 2020 due to the Covid 19 pandemic). But if the study aims are met, and results indicate improved outcomes with a lower impact on hemostatic and metabolic factors, then estetrol is likely to emerge as the chosen princess from the dingy cellar of forgotten compounds, to be crowned the first NEST molecule for safer hot flash relief. Only time will tell whether the shoe fits.

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