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Estetrol is not a SERM but a NEST and has a specific safety profile on coagulation

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Letter to the Editors-in-Chief

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To the Editor,

We read with interest the article of Booyens et al. discussing the risk of venous thromboembolism (VTE) with hormonal replacement therapy (HRT) [1]. This article nicely summarized over 80 years of HRT development for the relief of menopausal symptoms, but we observed some approximations which, in our opinion, need to be highlighted.

The authors wrongly classify estetrol (E4) as a selective estrogen receptor modulator (SERM). E4 has been recognized by the Food and Drug Administration (FDA), the European Medicines Agency (EMA), and the Therapeutic Goods Administration (TGA) as a new chemical entity. It is the only Natural Estrogen with a Selective Action in Tissues (NEST), a distinct classification from SERM. SERMs and estrogens differ in their effects that occur in the ligand-binding domain (LBD) of estrogen receptor (ER) α . The LBD is composed of 12 α helices (H1-H12) and 2 antiparallel β sheets. This helical arrangement creates a scaffold that maintains a ligand-binding cavity. Estrogen binding induces a major structural reorganization of the LBD, which converts the inactive ER to the functionally active form. In contrast, SERMs alter the conformation of the LBD of ERa occluding the coactivator-binding groove, whereas it allows the release of the A domain and possible recruitment of corepressor. E4 is distinct from SERMs as crystallographic studies and kinetics of binding of 154 coregulator motives to the ERa-E4 complexes demonstrate that E4 binds $\text{ER}\alpha$ differently than SERMs and in a manner identical to estrogens forming a complex that permits the binding of a key coactivator protein, the steroid receptor coactivator (SRC3) [2]. It has been demonstrated that E4, like the other estrogens, activates nuclear ER α but in contrast, it antagonizes membrane ER α . In fact, estrogens can act through a membrane pathway to induce a more rapid extracellular signaling pathway via a small pool or $ER\alpha$ located close to the membrane. This pathway has been defined as the membrane-initiated steroid signaling pathway (MISS) and results in the activation of intracellular signaling pathways like PI3K or MAPK, the activation of multiple kinases, and the production of a variety of second messengers like nitric oxide, calcium flux or cyclic adenosine monophosphate. These pathways are known to directly influence cell survival and proliferation. Kinases activated by the MISS pathway can phosphorylate numerous transcription factors, including ERs and coregulators, which are able to influence the transcriptional activity in the nucleus. The discovery of the specific pharmacodynamic profile of E4, i.e. acting as an agonist through ER α located in the nucleus but as an antagonist on the ER α -dependent MISS pathway, permitted to understand its agonist activity in the uterus, in the brain (hot flush, ovulation inhibition, etc.) and in bones, its mixed agonist and antagonist activities in the breast and its almost neutral on the liver [2].

In their manuscript, the authors summarized the effect of different HRT on hemostasis markers [1]. As highlighted by the authors, most studies available on coagulation and the use of HRT have major shortcomings which making difficult to reach definite conclusions on the health and coagulation risk. In addition, the clinical relevance of the magnitude of change induced by individual factors may be questioned since it does not reflect the entire coagulation process but only one parameter which is generally not predictive of the risk of VTE [3]. Nevertheless, in a nested case-control study from the two Women's Health Initiative (WHI) hormone trials which included 27,347 women aged 50-79 who were randomized to conjugated equine estrogen (CEE) with or without medroxyprogesterone acetate or placebo, it was demonstrated that lower protein C, free protein S and higher D-dimer, prothrombin fragment 1 + 2 and plasmin-antiplasmin complex were associated with risk of future thrombosis with odds ratios ranging from 1.9 to 3.2 [4]. Considering a multi-marker score of 8 biomarkers (i.e. factor V Leiden, D-dimer, prothrombin fragment 1-2, protein C, total protein S, free protein S, antithrombin, and plasmin antiplasmin complex), women with 3 or more abnormal markers had 15.5-fold increased odds for VT (95 %: 6.8-35.1) [4]. This clearly highlights that the evaluation of individual biomarkers is insufficient and that a global assessment of the coagulation is needed to identify women at risk of developing VTE while on CEE.

We recently conducted a multicenter randomized placebocontrolled, dose-finding study with E4 in postmenopausal women for the relief of postmenopausal symptoms ("E4Relief study" (NCT0283431)) [5]. In this study, several hemostasis markers were evaluated at baseline and after 12 weeks of treatment with different doses of E4. This includes the normalized activated protein C sensitivity

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ratio (nAPCsr) as described in detail previously [6], antithrombin, protein C, free protein S, tissue factor pathway inhibitor (TFPI), FVIII activity, prothrombin fragment 1 + 2, and D-dimer [5]. None of these parameters were different compared to placebo, except for nAPCsr which showed a median increase of 42 % after 12 weeks of treatment with E4 15 mg. The observed change from baseline is similar to the increase observed after 3 cycles in women of reproductive age treated with the oral contraceptive E4 15 mg in association with drospirenone (DRSP) 3 mg (i.e. relative increase of 40 %) [7]. Compared to ethinylestradiol (EE)-containing products used in contraception for which the nAPCsr was increased by 165 % (EE 30 µg plus levonorgestrel (LNG) 150 µg) and 229 % (EE 20 µg plus DRSP 3 mg) at cycle 3 (12 weeks), E4, either administered alone in postmenopausal women or in combination with DRSP in contraception, seems to have a neutral profile on this global coagulation marker. In comparison, 2 mg of unopposed 17βestradiol or with 10 mg dydrogesterone or 0.5 mg trimegestone showed a mean nAPCsr increase of 113 %, 118 %, and 107 % after 12 weeks of treatment [8]. Similarly to E4, transdermal E2 at the dose of 50 μ g daily showed a mean change from baseline of 28 % (nAPCsr) which was also statistically and significantly different from placebo [9]. Thus, oral E4 has a similar safety profile to transdermal E2 on APC resistance.

We also investigated the impact of E4 on thrombin generation to assess its possible effect on the entire coagulation process. As highlighted in Fig. 1, E4 at the dose of 15 mg, does not induce changes in the coagulation process which are translated into clinically relevant changes. Indeed, none of the mean thrombograms (±standard deviation) was outside the reference range established for two different populations, i.e. a population of women of reproductive age (Fig. 1 – lower part) and at the age of menopause (Fig. 1 – upper part). On the contrary, treatment with ethinylestradiol associated with LNG or DRSP induced changes in thrombin generation that led to abnormal curves which may suggest an increased risk of thrombosis [10].



* E4 15 mg is the dose as the monohydrate form corresponding the 14.2 mg in the anhydride form.

Fig. 1. Mean [2.5th - 97.5th percentiles] thrombograms of entire baseline cohorts (n = 168 for hormonal replacement therapy (HRT) and n = 86 for combined oral contraceptive (COC)) and mean [\pm standard deviation] thrombograms after 12 weeks of treatment (HRT) or 3 cycles (COC) are presented. The mean thrombogram of the entire baseline cohorts is represented by the yellow lines and the $2.5^{th} - 97.5^{th}$ percentiles, indicating the reference ranges, are represented by yellow dotted lines. For HRT, women treated with placebo or E4 15 mg are represented in blue and in purple, respectively. For COC, women treated with ethinylestradiol (EE) 20 µg/ drospirenone (DRSP) 3 mg are represented in red, EE 30 µg/levonorgestrel (LNG) 150 µg are represented in green, and E4 15 mg/DRSP 3 mg are represented in pink. For E4-containing products and placebo, none of the mean thrombograms \pm standard deviations were outside the reference range established at baseline demonstrating the low impact of E4 on the entire coagulation process.

* E4 15 mg is the dose as the monohydrate form corresponding the 14.2 mg in the anhydride form. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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These data and the evidence of its distinct pharmacological profile support the classification of E4 as a new chemical entity. It is the first NEST on the market and its hemostatic safety profile makes it an attractive alternative to transdermal E2 for women at the age of menopause. Its use in contraception is supported by excellent efficacy and primarily safety data. As for all other new estrogens in contraception, post-authorization safety studies are requested by the regulatory bodies, but the cumulative biochemical data already offer reassurance about its lack of interference in key components of the hemostatic system. Results from the ongoing phase-3 program will tell us if this therapy becomes a game changer in the treatment of complaints linked to menopause.

Declaration of competing interest

J.D. is CEO and founder of QUALIblood s.a. and reports personal fees and honorarium from Daiichi-Sankyo, Diagnostica Stago, DOASense, Gedeon Richter, Mithra Pharmaceuticals, Norgine, Portola, Roche, and Roche Diagnostics. U.G. is a senior consultant at Mithra Pharmaceuticals. W.H·U are members of the Scientific Advisory Board of Mithra Pharmaceuticals. J-M F is co-founder of Mithra Pharmaceuticals, shareholder, and member of the Board.

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