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# Introducing the first NEST in contraception (native estrogen with selective tissue activity)

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Estetrol (E4) is a human specific, natural Estrogen (E) with a long half-life, produced only by the fetal liver. In vivo, E4 stimulates uterine gene expression, epithelial proliferation, and prevents atheroma; three recognized nuclear Estrogen receptor ? (ER?) actions. However, E4 fails to promote processes dependent on membrane-initiated steroid signaling (MISS). It antagonizes Estradiol (E2) MISS-dependent effects in endothelium, and in MCF-7 breast cancer cells. Current evidence indicates that in the normal and malignant breast, and in developing brain, E4 has mixed agonist and antagonist estrogenic activities. This profile of ER? activation, uncoupling nuclear and membrane activation, characterizes E4 as a native E with selective tissue activity (NEST). While synthetic SERMs also have mixed agonistic or antagonistic estrogenic activities, their molecular mechanism of action appears distinct. SERMs activity is mainly determined by selective recruitment of corepressors and coactivators to ER? target genes in specific types of tissues and cells. The positioning of the helix 12 in the ligand-binding domain of ER? by the bound SERM determines whether the ligand has an agonistic or antagonistic effect. At variance from SERM- ER? complexes, the E4-ER? ligand binding domain complex has a crystal structure similar to that of the E2-ER?, as well as a similar capacity to activate the two activation functions AF-1 and AF-2 of ER? and to recruit the coactivator SRC3.The differential activity is the consequence of selective nuclear ER? activation and membrane ER? inhibition. Combined oral contraceptives (COC) containing E4, adequately suppress ovarian activity, particularly when given at a dosage above 10 mg E4 /day with a limited effect on liver function, lipid metabolism, bone and growth endocrine parameters. Several E4-LNG or Drospirenone combinations were tested in two phase 2 clinical trials. The 15 mg E4/3 mg DRSP combination had the most favourable bleeding pattern and cycle, body weight and blood pressure control, with a high-user acceptability and satisfaction. It had also a lower impact on plasma levels of SHBG, angiotensinogen and 12 haemostasis markers than EE containing COC. Due to this favourable biological and clinical profile, the 15 mg E4/DRSP combination is the preferred combination for ongoing phase III clinical development.

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