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EDITORIAL

Estetrol (E4): the new estrogenic component of combined oral contraceptives

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1. Introduction

Estetrol (E4) is a natural fetal estrogenic steroid discovered in 1965 at the Karolinska Institutet in Stockholm (Sweden) [1]. It was studied for a period of 20 years originally as a biomarker of fetal well-being during pregnancy [2] before being abandoned as a weak estrogen: research into the potential physiological effects and applications of E4 resumed in 2001. E4 is a steroid hormone with four -OH groups, two more than estradiol (E2), the estrogen physiologically produced by the granulosa cells of human ovaries (Figure 1) [3]. The fetal liver is the exclusive site responsible for 15α- and 16α-hydroxylation [4]: for this reason, E4 is only present during pregnancy from 9 weeks of gestation until only shortly after birth [5] but its physiological role is still unknown. The two additional -OH groups have a crucial impact on the oral pharmacokinetics: the half-life of E4 is 20–28 hours, compared with only 10–20 minutes for estriol (E3), 1–2 hours for natural E2 and 10–12 hours for micronized E2. E4 is minimally, if at all, metabolized and not reconverted to E3 or E2 [6]. Receptor binding and target interaction studies showed E4 to have high selectivity for the estrogen receptors (ER), indicating a potential for low risk of side effects. No specific toxicity for E4 has been observed to date [6].

Combined oral contraceptives (COCs) traditionally contain an estrogen and a progestin component. Estrogens stabilize the endometrium, regulating vaginal bleeding, and they reduce follicle development and the secretion of follicle-stimulating hormone (FSH). Ethinyl estradiol (EE) is the most common estrogen used in COCs because of its demonstrated efficacy and safety over 60 years: it has been associated with a satisfactory bleeding pattern but its impact on liver function and vascular endothelium can produce rare cardiovascular thrombotic complications (arterial and venous) during COC use.

Different strategies have been developed to reduce this effect, such as decreasing the EE dose, improving the progestinic modulation with androgenic progestins and, since 2009, substituting EE with E2 [7], but the optimal combination is yet to be discovered. The introduction of E4 may improve the safety and tolerability of COCs in the near future.

To investigate the potential clinical use of E4 as a safe and well-tolerated estrogenic component of COCs, some dose-finding and comparative studies have begun to emerge in recent years. The complete experimental programme for these studies is reported in Table 1.

2. Hemostatic and metabolic effects

Two publications described the findings of a single-center study, involving 109 women, performed in the Netherlands, regarding the hemostatic and metabolic effects of E4 based COCs [8,9].

Mawet et al., in a dose-finding Phase II study, evaluated the effects of E4/drospirenone (DRSP) and E4/levonorgestrel (LNG) [8] (5 or 10 mg E4/3 mg DRSP; 5, 10 or 20 mg E4/150 µg LNG) versus EE/DRSP COCs on liver function, lipid metabolism and bone and growth markers. E4 acts as a weaker estrogen on lipoprotein and triglyceride levels in comparison to EE but it demonstrated comparable potency with regard to the positive influence on bone turnover markers. Compared with EE/DRSP, combinations E4/DRSP and E4/LNG were associated with a lower effect on sex hormone-binding globulin (SBHG) (–69% to – 44% in E4/LNG, +8% to +44% in E4/DRSP and +306% in EE/DRSP, respectively). In this trial no preferences were made by the Authors between different E4 preparations in association with DRSP or LNG.

In a subgroup of subjects from this study, Kluft et al. [9] evaluated E4 (at two different doses: 5 and 10 mg) with 3 mg DRSP in comparison with 20 µg EE and the same dose of DRSP on plasma levels of SHBG, angiotensinogen and 12 markers of hemostasis. The effects of 10 mg E4/DRSP on SHBG and angiotensinogen levels were only 15–20% that of EE/DRSP. Both E4/DRSP combinations reduced D-dimer levels, and the 5 mg E4/DRSP combination also decreased prothrombin fragments 1 + 2. Because E4/DRSP exerted considerably lower hepatic and vascular estrogenicity than EE/DRSP, the authors suggested that women who take E4-containing COCs may ultimately prove to have a lower risk of venous thromboembolism compared to women who take EE-containing COCs.

3. Contraceptive efficacy

In the same single-center, dose-finding Phase II pilot study, the inhibition of ovulation with different combinations of E4 with DRSP or LNG was evaluated [10]. E4 in combination with DRSP

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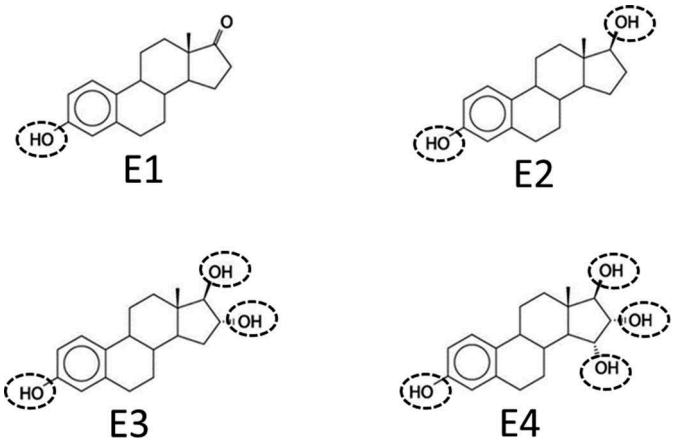

Figure 1. Molecular structures of estrone (E1), estradiol (E2), estriol (E3) and estetrol (E4). The dashed line circles depict -OH groups.

or LNG effectively inhibits ovulation, with no differences between the two progestinic components: ovarian and gonadotropins suppression were most pronounced at the highest E4 doses (20 mg). The effects on endometrial thickness were comparable in all treatment groups: combinations with E4 have a similar effect on endometrial growth to that of EE/DRSP. Ovulation was rapidly restored 17–21 days after the last active treatment in all subjects.

The clinical contraceptive efficacy of these new E4-based COCs in term of the Pearl Index is being studied in two Phase III studies in Europe and the USA (E4 Freedom).

4. Bleeding patterns and cycle control

Two further Finnish publications reported the findings of the FIESTA study, which investigated the effect of E4 combined with either DRSP or LNG on bleeding patterns, cycle control and satisfaction with use of E4 based COCs [11,12]. Apter et al. performed an open-label, multi-center, randomized dose-finding study to select the E4/progestin dosing regimen for Phase III development, based on an optimal vaginal bleeding pattern and cycle control. Four different combinations were evaluated (two different doses of E4 combined with DRSP or LNG) in comparison with quadriphasic E2 valerate and dienogest (E2 V/DNG) as reference. The lowest tested dose of E4 (15 mg) combined with DRSP has been shown to be the most promising in terms of bleeding pattern and cycle control: by cycle 6, the frequencies of unscheduled bleeding and/or spotting and absence of predictable scheduled withdrawal bleeding were the lowest in this treatment group (33.8% and 3.5%, respectively), whereas these frequencies were 47.8% and 27.1%, respectively, in the E2 V/DNG reference group [11]. The FIESTA study also evaluated user acceptability (recording discontinuation rates, reasons for discontinuations and compliance with the study medication), general well-being and satisfaction (using a self-reported Subject Satisfaction and Health-Related Questionnaire) and body weight control when taking these different COCs. Satisfaction depends on the E4 dose and the progestin component: the lowest dose of E4 (15 mg) combined with DRSP has been shown to be the best solution, whereas combined with LNG it was shown to be the worst. Well-being with E4/DRSP combinations was statistically significantly better than with E4/LNG combinations and comparable to E2 V/DNG. A common reason for discontinuation of COCs is weight gain: the proportion of women with 2 kg or more weight loss after 3 and 6 cycles was the highest in the 15 mg E4/DRSP group [12]. For all these reasons (bleeding patterns, acceptability and satisfaction, body weight control) this combination (15 mg E4 and 3 mg DRSP) was chosen for subsequent evaluation in the Phase III studies.

5. Pharmacokinetics, pharmacodynamics and possible additional benefits

E4 is being studied simultaneously for its particular properties in postmenopausal hormone therapy and for the prevention of osteoporosis: these studies on postmenopausal women can help us gain a deeper understanding of the pharmacokinetics, pharmacodynamics and endometrial effects of this estrogen. Coelingh Bennink et al. performed an open-label, multiple-rising-dose, partly-randomized study in postmenopausal healthy

Table 1. Experimental process of E4-containing oral contraceptives.

Phase	Outcomes	Comparator	E4 combinations tested	Sample size	Design	Reference
II	Dose-finding pilot study	Monophasic 20 µg EE/3 mg DRSP 24 + 4 regimen	5 or 10 mg E4/3 mg DRSP; 5, 10 or 20 mg E4/150 mg LNG 24 + 4	*N* = 109	Monocentre, observational	Dujskers et al. [10]
	Hemostatic effect	Monophasic 20 µg EE/3 mg DRSP 24 + 4 regimen	5 or 10 mg E4/3 mg DRSP	*N* = 47	Monocentre, observational	Kluft et al. [9]
	Liver function, lipid metabolism and bone and growth endocrine parameters	Monophasic 20 µg EE/3 mg DRSP 24 + 4 regimen	5 or 10 mg E4/3 mg DRSP; 5, 10 or 20 mg E4/150 mg LNG 24 + 4	*N* = 109	Monocentre, observational	Mawet M et al. [8]
	Cycle control	Quadriphasic E2 V/DNG	15 or 20 mg E4/3 mg DRSP; 15 or 20 mg E4/150 mg LNG	*N* = 396	Open-label, multi-center, randomized	Apter et al. [11]
	Acceptability and satisfaction	Quadriphasic E2 V/DNG	15 or 20 mg E4/3 mg DRSP; 15 or 20 mg E4/150 mg LNG	*N* = 396	Open-label, multi-center, randomized	Apter et al [12].
III	Efficacy and safety	Not applicable				Not yet published

women not older than 70 years old (mean age 59–63) to investigate safety, tolerability, pharmacokinetic and pharmacodynamic properties of E4. Subjects with an intact uterus were randomized to receive 2 mg E4 or E2 V for 28 days with subsequent dose-escalation groups (non-randomized) to 10 mg E4 (intact uterus and ≥ 35 hot flushes per week) and 20 and 40 mg E4 (hysterectomized subjects). In all the groups there was a clear shift from parabasal to superficial vaginal cells, indicating an estrogenic vaginal effect and the potential for vulvovaginal atrophy treatment. The endometrial thickness remained stable in the 2 mg E4 group but it starts to increase with 10 mg E4, as it does with 2 mg E2 V. A decrease in the mean number of hot flushes and sweating was seen with 2 and 10 mg E4 and 2 mg E2 V. This Phase I safety study reported no possible concerns due to laboratory or vital sign assessments. The majority of the subjects experienced at least one adverse event during the treatment period but none stopped treatment: the most frequent drug-related adverse events were nipple tenderness, headache, abdominal pain and vaginal discharge, but only nipple tenderness showed a relation with E4 dose [13].

The other kinetic study [14] demonstrated an extremely fast absorption and distribution phase of E4 followed by a gradual terminal elimination phase, with steady state mean plasma concentrations reached during the second week, suggesting the possibility of a single daily administration.

In addition, E4 may have a lower impact on the risk of breast cancer: estrogens are usually considered dangerous for mammary tissue due to their mitogenic activity. Gérard et al. investigated the impact of E4 on normal breast tissue by an *in vitro* model of isolated human breast epithelial cells and an *in vivo* model of mouse mammary gland [15]. The study concluded that E4 stimulated breast proliferation with 100-fold weaker efficacy in comparison to E2, both *in vitro* and *in vivo*, ERα mediated. In addition, when E4 and E2 are co-incubated, E4 seems to be able to partially antagonize the E2-induced proliferation of human breast epithelium cells and mouse mammary gland growth.

Moreover, Pluchino et al. evaluated the activity of E4 and E2 V on the central nervous system (CNS) regarding the neurosteroidogenesis of allopregnanolone (AP) [15] and beta-endorphin (β-END) [16]. AP is a 3,5-reduced metabolite of progesterone produced by the CNS, adrenals and ovaries that interact with the excitability of neurons and glial cells and with the neurotrophic/neuroprotective CNS cells. The study [15] demonstrated that E4 increased the AP levels both in the CNS and peripheral tissues, suggesting a weak estrogen-agonistic effect for E4 in a rat model of reproductive age, but in the presence of E2 V it showed an estrogen-antagonistic effect on brain and serum levels of AP. E4 induces the same changes in β-END [17], which is a crucial molecule for brain development and regulation: E4 induces estrogenic-agonist changes in plasma and CNS β-END levels but if co-incubated with E2 V it exerts antagonistic effects.

6. Expert opinion

The estrogen dose in COCs has gone from micrograms (50 to 15) in the age of EE, to a few milligrams (1.5–3) in the E2 era, to several milligrams (15) in the age of E4, as the estrogenic component became weaker and weaker: during evolution the emphasis has shifted from the crude mass of steroids administered to their real biological activity. In terms of safety, mainly the lowest E4 doses seems to be associated to a favorable hemostatic profile and impact on lipids, low drug-drug interaction and a limited stimulation of breast tissue. The 10 mg E4 dose potency at endometrial level seems similar to that of the 2 mg E2 V dose: for this reason it seems that at the highest doses of E4 used and studied (≥ 15 mg), E4 COCs can guarantee more satisfactory cycle control in comparison to E2-based COCs (i.e. low rate of unscheduled bleeding and/or spotting and the absence of withdrawal bleeding). Unfortunately, at these E4 doses (≥ 15 mg) the hemostatic and metabolic effects of this combination have not been deeply studied and it has not been clearly demonstrated to be weaker than during traditional EE-based COCs. However, this third estrogenic generation of COCs could provide additional benefits to women's health and in the coming years will be a topic for great interest and further personalization in hormonal contraception technology.

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