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OVERVIEW:

This article traces the evolution of estrogen in contraception, with a special focus on the concept of native estrogen with specific actions in tissues, or NEST. Research surrounding estetrols (E4), receptor binding, and target interactions demonstrate that E4 has high selectivity for the estrogen receptors. Clinical trial data are presented that support the view that E4 – a high NEST activity estrogen – is a safe and effective estrogen for use in combined oral contraceptives. This premise was borne out with the approval of an estetrol/drospirinone combined oral contraceptive by the US Food and Drug Administration in April 2021.

REVIEWERS/CONTENT PLANNERS/AUTHORS:

- Sean T. Barrett has nothing to disclose.
- Barry A. Fiedel, PhD, has nothing to disclose.
- Patricia Geraghty, MSN, FNP-BC, WHNP, receives consulting fees from AbbVie and Mayne Pharma.
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- Lynne Kolton Schneider, PhD has nothing to disclose.
- Robert Schneider, MSW, has nothing to disclose.
- Hugh S. Taylor, MD, is a patent holder of DotLab.

LEARNING OBJECTIVES:

- After completing this CME activity, participants will be better able to:
- Understand the role of estrogens through a woman's reproductive life cycle
 - Compare and contrast the regulatory roles of E1, E2, E3, and E4.
 - Explain the pharmacology supporting the use of estetrol (E4) in combination oral contraceptives.

ACCREDITATION AND CREDIT DESIGNATION STATEMENTS:

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The Next Generation of Oral Contraception: Advances in Estrogens

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Background

There are currently 61 million women of reproductive age (15-44 years) in the United States.¹ Approximately 43 million (70%) are at risk of unintended pregnancy, meaning that they are sexually active and do not want to become pregnant, but they have the potential to become pregnant if they and/or their partner(s) fail to use a contraceptive method correctly and consistently.² Among women who practice contraception, nearly 71% rely on nonpermanent methods, primarily hormonal options administered as contraceptive pills, patches, implants, injectables, or vaginal rings, as well as intrauterine devices/systems (IUD/IUS) and/or condoms. The remaining 29% rely on female (22%) or male (7%) sterilization.³

Combined hormonal contraception (CHC) has been a mainstay of female contraception for the past 60 years, and 80% of sexually experienced women have used a combined oral contraceptive (COC) at some point in their reproductive life. Since 1982, the two most commonly used methods of contraception have been COCs and female sterilization.³⁻⁵

There are three major endogenous estrogens: estrone (E1), estradiol (E2), and estriol (E3). E2 is the most potent and prevalent of these estrogen steroids in the reproductive stage of life.⁶ This journal supplement will present scientific research focused on a little-known fourth estrogen—estetrol, or E4. E4, in combination with the progestin drospirenone (DSP), has been extensively studied over the past several years as a potential contraceptive option. [Editor's note: an OC containing this combination was approved by the US FDA in April 2021]. Data surrounding the E4/DSP COC demonstrate that this agent is highly effective and has favorable vaginal bleeding, safety, and tolerability profiles. Additionally, studies have evaluated the effects of E4/DSP on parameters that are considered surrogate markers for cardiovascular disease risk factors, with promising results.

Reducing Estrogen Dosing in CHC: The Quest to Balance Safety With Tolerability

The optimal COC formulation balances contraceptive efficacy and cycle control while maintaining tolerability and safety and minimizing adverse events. COCs contain an estrogen and a progestin. The role of the progestin is to inhibit ovulation and thicken cervical mucus; progestin-only pills afford effective contraception. The estrogen component stabilizes the endometrium, regulates vaginal bleeding, and reduces follicle development and the secretion of follicle-stimulating hormone (FSH).

The initial active estrogen component of the first COCs was mestranol at a dose of 75 µg. Safety concerns led to dose reductions to <50 µg of mestranol, which was replaced with ethinyl estradiol (EE) in the early 1960s. Since then, synthetic EE has been the most common estrogen used in COCs because of its demonstrated efficacy, safety, and tolerability. In a study examining the use of COCs in nearly 13,000 American women, Trussell et al reported that while women used 88 different brands of COCs, all of the COC brands contained EE, albeit with different doses and different progestins.⁷

EE (and endogenous estradiol) can impact liver function through increases in the synthesis of various liver proteins, such as lipoproteins, angiotensinogen, sex hormone-binding globulin (SHBG), corticosteroid-binding globulin (CBG), and ceruloplasmin.⁸ They also can impact the vascular endothelium and can produce rare cardiovascular thrombotic complications (arterial and venous) during use.⁹ Higher doses of EE have been associated with an increased risk of cardiovascular disease (CVD), including thromboembolism and myocardial infarction, particularly in women with other predisposing factors such as smoking and obesity.⁹ Strategies to reduce these adverse effects have included decreasing the EE dose, improving the progestogenic modulation with less androgenic progestins, and, since 2009, substituting EE with E2.⁷ E2 has been used in some COCs to minimize the risk of adverse effects. Although the exact mechanism contributing to the increased CVD risk remains unclear, the use of newer low-dose formulations of COC (EE dose ≤35 µg) has resulted in a significant decrease in, but not elimination of, CVD risk. However, the lower doses are also associated with greater incidences of breakthrough bleeding or contraceptive failure, especially in COCs with EE doses ≤20 µg.¹⁰ The optimal combination has yet to be demonstrated.

The Evolution of Estrogen in Contraception—From E1 to E4

Estrogens play a central role in the development and maintenance of the female phenotype, germ cell maturation, and pregnancy. They are also important for many other, non-gender-specific processes, including growth, nervous system maturation, bone metabolism/remodeling, and endothelial responsiveness. There are four endogenous forms of estrogen (**Table 1**). The two

TABLE 1 Estrogen Metabolism^{6,8,11}

	Estrone (E1)	Estradiol (E2)	Estriol (E3)	Estetrol (E4)
Major Biological Production	Nonpregnant female	Nonpregnant female	Pregnant female	Fetal liver
Derivation Process	Peripheral aromatization of androstenedione	Mainly ovaries and testes; adrenals	Synthesized in fetus/placenta	Fetal liver
Biological Potency	1/10 potency of E2	10X potency of E1	1/100 potency of E2	1/5-1/10 potency of E2
Half-Life	10-70 minutes	1-2 hours (17-β) 10-12 hours (micronized)	10-20 minutes	20-28 hours

major biologically active estrogens in nonpregnant females are E1 and E2. There are two fetal estrogens produced almost exclusively in pregnancy. E3 is the main pregnancy estrogen but has no significant role in nonpregnant women; it is produced through a complex multistep pathway involving the mother, fetus, and placenta. E4 is a human-specific native estrogen produced by the fetal liver during pregnancy.

E2 is produced primarily in the ovaries and testes by aromatization of testosterone, with small amounts produced in the adrenal glands and some peripheral (mostly fat) tissues. The majority of E1 is derived from peripheral aromatization of (mainly adrenal) androstenedione. E2 can be converted to E1 and vice versa, and both can be inactivated through hydroxylation and conjugation. However, they have different biological potencies—E2 demonstrates 10 times the biological potency of E1. E2 circulates at 1.5 to 4 times the concentration of E1 in premenopausal, nonpregnant women. The levels of the various types of estrogen vary during the menstrual cycle and depending on a woman's pregnancy and menopausal status. Notably, E2 levels in postmenopausal women are much lower than in reproductive-stage nonpregnant women, while E1 levels differ less, resulting in a reversal of the premenopausal E2:E1 ratio. E2 levels in premenopausal women fluctuate during the menstrual cycle. They are lowest during the early follicular phase. E2 levels then rise gradually until 2 to 3 days before ovulation, at which stage they start to increase much more rapidly. E2 peaks just before the ovulation-inducing luteinizing hormone/FSH surge at levels that are 5 to 10 times those of the early follicu-

lar levels. This is followed by a modest decline during the ovulatory phase. E2 levels then gradually increase again until the midpoint of the luteal phase and then decline to early follicular levels.¹¹

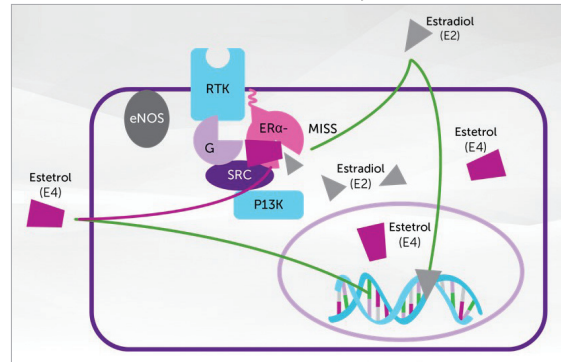
The most abundant of the fetal estrogens is E3. It is produced almost exclusively during pregnancy by a complex pathway that involves maternal precursors that are converted to the androgen dehydroepiandrosterone sulfate (DHEAS) by the fetal adrenal gland and hydroxylated by the fetal liver before being processed to E3 in the placenta. E3 has been thought of as a largely inactive or weak estrogen. Researchers recently reported a potential role for E3 in fetal developmental programming. Because of its production by the fetus, E3 was widely used as a marker of fetal well-being until it was replaced by more sensitive biophysical parameters.

E4 was discovered in 1965 at the Karolinska Institute in Stockholm, Sweden.¹² E4 is a natural fetal steroidal estrogen synthesized from E3 by the fetal liver during pregnancy. Like E3, it was originally studied as a biomarker of fetal well-being during pregnancy. Development for use as a therapeutic agent was subsequently abandoned owing to its weak estrogenic effects.¹³ Research into the potential physiologic effects and applications of E4 resumed in 2001. E4 is a steroid hormone with four hydroxyl (-OH) groups, two more than E2.¹⁴ The two additional -OH groups have a crucial impact on the oral pharmacokinetics of E4, extending its half-life to 20-28 hours. In comparison, the half-life of E3 is 10-20 minutes, natural E2 is 1-2 hours, and micronized E2 is 10-12 hours. E4 is minimally metabolized, if at all, and it is not reconverted to E3 or E2.¹⁵ Studies of E4's receptor binding and target interactions demonstrate that it has high selectivity for the estrogen receptors, indicating the potential for a low risk of side effects from off-target binding. E4 is readily synthesized for commercial production from soy-based starting materials.

New Combined Hormonal Contraceptives—The Concept of Native Estrogen With Specific Activity in Tissues

E4 has been described as a natural human fetal estrogen or native estrogen with a unique and tissue-specific action (NEST). Over the past two decades, evidence has demonstrated that there are two subpopulations of estrogen receptor alpha (ERα). ERα is present in the cell nucleus, but it is also associated with the plasma membrane. Nuclear ERα induces gene transcription while membrane ERα initiates rapid signaling, better known as membrane-initiated steroid signaling (MISS).¹⁶ Similar to other estrogens, E4 activates the nuclear ERα and induces gene transcription (**Figure 1**). However, in contrast to other estrogens, E4 antagonizes (or blocks) the activity of membrane ERα, has a neutral

FIGURE 1 E4 and NEST Activity



Modified from Foidart JM, Gaspard U, Pequeux C, et al. Unique vascular benefits of estetrol, a native fetal estrogen with specific actions in tissues (NEST). In: Diaz Brinton R, Genazzani AR, Simoncini T, Stevenson JC, eds. *Sex Steroids' Effects on Brain, Heart and Vessels*. Volume 6: *Frontiers in Gynecology and Endocrinology*. New York, NY: Springer Nature; 2019:169-195.

eNOS, endothelial nitric oxide synthase; PI3K, phosphatidylinositol 3-kinase; RTK, receptor tyrosine kinase; SRC, steroid receptor coactivator.

effect on the liver, and has a low impact on normal and malignant breast tissue.^{17,18} The nuclear ERα stimulation results in estrogenic activity that has beneficial effects on the vagina, endometrium, bone, and cardiovascular system. These actions of E4 are distinctly different from selective estrogen receptor modulators (SERMs), which induce conformational changes in the estrogen receptor and accordingly recruit co-activators or co-inhibitors in different tissues to allow for varied expression of agonistic or antagonistic activities. The favorable safety profile of E4 results from its distinct effect on both nuclear and membrane estrogen receptors.

Applying Clinical Trial Data on Newer CHCs to Real-World Patient Care

E4's use in oral contraceptives has been extensively studied. Phase 1 and 2 clinical studies of COCs containing E4/DSP demonstrate that E4 has a minimal impact on hemostasis, coagulation factors, coagulation inhibitors, fibrinolysis, angiotensinogen, triglycerides, and cholesterol.¹⁹ Several phase 2 clinical trials have evaluated the efficacy of different dosages of E4 combined with either of two progestins (DSP or levonorgestrel [LNG]) in suppressing the pituitary-ovarian axis and ovulation in healthy premenopausal women. No ovulation occurred in any treatment group. Endometrial thickness was suppressed to the same extent in all groups.²⁰ Another phase 2 clinical trial of E4 combined with either DSP or LNG evaluated acceptability, user satisfaction, body weight control, and general well-being encompassing general feeling, mood, sexual life, premenstrual complaints, and overall effect. This study demonstrated that a combination of 15 mg of E4 and 3 mg of DSP is associated with high user acceptability and satisfaction and positive body weight control.²¹

Two phase 3 trials of the E4/DSP COC have been conducted, one in the United States and Canada and the other in Europe and Russia.^{22,23} The two trials were part of the Female Response Concerning Efficacy and Safety of Estetrol/Drospirenone as Oral Contraceptive in a Multicentric Study (FREEDOM) and evaluated contraceptive efficacy (in a 24-day active agent/4-day placebo regimen), vaginal bleeding pattern (cycle control), and general safety and acceptability profiles associated with the E4 (15 mg)/DSP (3 mg) COC in healthy women aged 16 (US/Canada)/18 (Europe/Russia) to 50 years. Over 3,600 women participated in these studies (divided nearly equally between the two continents).

Recently, results of the US/Canada and Europe/Russia studies were presented as abstracts at the 19th Congress of the International Society of Gynecologic Endocrinology (ISGE) in December 2020.²⁴ The main outcome measure was the on-treatment pregnancy rate as measured by the Pearl Index. In the US/Canada trial, 26 on-treatment pregnancies occurred, of which 12 were user failures, for a Pearl Index of 2.65, and 14 were method failures, for a Pearl Index of 1.43. In the EU/Russia trial, five on-treatment pregnancies occurred, for a Pearl Index of 0.44, and two of the pregnancies were method failures, for a Pearl Index of 0.26. Secondary outcomes included bleeding patterns and safety. In the US/Canada trial, unscheduled bleeding/spotting occurred over 12 cycles in 19.5% of women. In the EU/Russia trial, unscheduled bleeding/spotting episodes decreased from 23.5% in Cycle 1 to 12.8% at Cycle 11. Safety information has only been reported for the EU/Russia trial; no relevant changes were observed in any physical examinations or laboratory parameters, including hematology, biochemistry, and lipid profile. The most common treatment-related adverse events were metrorrhagia (5.0%), vaginal hemorrhage (4.3%), acne (3.8%), and headache (2.8%); the discontinuation rate for these events was 9.1%.

Conclusion

Phase 1 and 2 clinical studies of COCs containing E4/DSP demonstrate that E4 has a minimal impact on hemostasis, coagulation factors, coagulation inhibitors, fibrinolysis, angiotensinogen, triglycerides, and cholesterol.¹⁹ Data from these studies indicate that E4 could provide a better safety/efficacy profile than other estrogens currently used in COCs. The two multinational phase 3 studies supported the earlier findings. E4, in combination with DSP, has been shown to have an acceptable level of contraceptive efficacy, along with a very favorable bleeding and safety profile. The use of this unique estrogen will lead to highly promising new contraceptive formulations.

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