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Review Article

Comparison of estrogenic components used for hormonal contraception☆

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ABSTRACT

Attempts have been made over the years to replace ethinyl estradiol (EE) in combined oral contraceptives (COCs) with the less potent natural estrogen estradiol (E_2), or its prodrug, E_2 valerate (E_2V), to improve their safety and tolerability. Recently, a COC incorporating a novel weak natural estrogen, estetrol (E_4), combined with drospirenone, has become available. We present a comparative analysis of the three prevailing estrogens used in COCs, focusing on their structure-function relationships, receptor-binding affinity, potency, metabolism, pharmacokinetic parameters, and pharmacodynamics. The binding affinity of EE to estrogen receptor (ER)α is twice that of E_2, whereas its affinity for ERβ is about one-half that of E_2. E_4 has a lower binding affinity for the ERs than E_2. The high potency of EE is notable in its dramatic increase in estrogen-sensitive hepatic globulins and coagulation factors. EE and E_2 undergo extensive and comparable metabolism, while E_4 produces only a very limited number of metabolites. E_4 has the highest bioavailability among the three estrogens, with E_2 having < 5%. Studies demonstrate consistent ovulation inhibition, although a higher dose of E_4 (15 mg) in COCs is required to achieve follicular suppression compared to E_2 (1–3 mg) and EE (0.01–0.035 mg). E_2 and E_4 in COCs may be less stimulatory of coagulant proteins than EE. Studies with E_2/dienogest suggest a comparable risk of venous thromboembolism to EE/levonorgestrel, while data assessing risk with an E_4-based COC are insufficient. Nevertheless, the E_4-based formulation shows promise as a potential alternative to EE and E_2 due to its lower potency and possibly fewer side effects.

1. Introduction

The estrogenic component of combined oral and parenteral contraceptives plays an important role in hormonal contraception. It serves three important functions: (1) it exerts negative feedback action on the hypothalamic-pituitary axis, thereby suppressing the gonadotropins involved in follicular maturation and ovulation; (2) it provides stability to the endometrium, preventing irregular shedding and unwanted, unanticipated, and unscheduled bleeding; and (3) it enhances the contraceptive efficacy of the progestational component by its inhibitory action on gonadotropin secretion and the antifertility effects of the progestin on cervical mucus, endometrium, and possibly the fallopian tubes [1]. This stronger ovarian inhibition is associated with a lower risk of follicular cyst formation that is encountered with progestin-only pills and with lower estradiol (E_2) and testosterone production by the ovary [2–4].

Ethinylestradiol (EE) has been the predominant estrogen used in COCs in recent years. Although EE is overall safe at doses of 50 μg or less, concerns regarding some of its adverse and side effects persist. There is a growing need to find an alternative to EE in COCs to mitigate the risk of cardiovascular complications, both arterial events (hypertension, myocardial, and cerebral infarction) and venous events (deep vein thrombosis and pulmonary embolism). EE has been shown to have a dose-dependent risk of thromboembolism, attributed to the activation of coagulation factors and other hemostatic effects [5]. Reductions in the dose of EE (< 50 μg) have resulted in a decreased incidence of venous thromboembolism (VTE),

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ischemic stroke, and myocardial infarction. Additional reduction of the dose to 20 μg may further decrease the VTE incidence, but the evidence for this is limited. Even very low doses of EE in COCs have been shown to adversely affect hemostatic parameters [6]. Although reduction in the dose of EE in currently available COCs has significantly improved COC safety and tolerability, efforts to further reduce EE- and COC-related risks continue.

Attempts have been made over the years to replace EE with the less potent estrogens, estradiol (E_2) or estradiol valerate (E_2V), to improve the safety and tolerability profiles of COCs. Replacement of EE with E_2 by researchers and pharmaceutical companies has proven challenging, primarily due to difficulties in achieving satisfactory cycle control. One significant concern among women is the unanticipated unscheduled bleeding profile of COCs, leading approximately 15% of users to discontinue their usage due to bleeding irregularities, mostly during the first 6 months of use [7].

An alternative approach for achieving satisfactory cycle control in COCs involves using an estrogen with lower potency than E_2. Recently, a COC formulation containing estetrol (E_4) in combination with drospirenone (DRSP) demonstrated effectiveness and tolerability, with a majority of women experiencing predictable bleeding cycles [8–10].

The objective of the present commentary is to compare the different estrogens used in oral hormonal contraception with respect to their structure-function relationships, receptor-binding affinity, potency, metabolism, pharmacokinetic parameters, and pharmacodynamics.

2. Structure-function relationships

The chemical structures of the four estrogens currently used in COCs (EE, E_2, E_2V, E_4) are shown in Figure 1. The most widely used estrogen, EE, differs from E_2 by the presence of an ethinyl group on carbon 17. This group is not removed during the metabolism of EE so that EE is not converted to E_2. In contrast, E_2V differs from E_2 by the presence of a valerate group on carbon 17 and is readily converted to E_2. As for E_4, it contains four hydroxyl groups compared to two hydroxyl groups in E_2, and it is not metabolized back to E_2.

All four of the estrogens are synthesized chemically by multiple chemical reactions for therapeutic use. Two of these, E_2 and E_4, can be considered natural since they are also produced in the body. In premenopausal women, approximately 95% of E_2 is secreted by the ovary, and the remaining 5% is derived from peripheral tissues. As for E_4, it is produced only in pregnancy by the fetoplacental unit [11].

3. Receptor-binding affinity

EE, E_2, and E_4 exert their biologic effects via interactions with the estrogen receptors, alpha and beta (ERα and ERβ). These receptors exhibit tissue-specific biologic actions, as evident from their distinct tissue distribution. ERα is predominantly expressed in organs such as the uterus, ovarian theca cells, Leydig cells in testes, breast, prostate stroma, epididymis, and liver [12]. In contrast, ERβ is highly expressed in bone marrow, brain, ovarian granulosa cells, prostate epithelium, and testes [13]. Moreover, within a single tissue, the expression pattern of each isoform is cell-type specific. For example, in the ovary, ERα is more abundant in the theca cells, whereas ERβ is expressed in the granulosa cells.

A variety of assays have been carried out to study ligand-ER interactions. The widely used isotope-labeled ^3H-E_2 assay determines the IC_{50} of various ligands. The IC_{50} is a quantitative measure that determines how much of a ligand is needed to inhibit a given biological component by 50%. In a study by Zhu and coworkers [14], the IC_{50} values of E_2, EE, and E_4 were determined for recombinant human ERα and ERβ. The data show that EE had a very high binding affinity for both ERα and ERβ but was preferential for ERα (IC_{50} for ERα and ERβ: 5.6 and 15.9 nM, respectively). In contrast, the affinity of E_2 for ERα (11.2 nM) was half that of EE, whereas its affinity for ERβ (8.4 nM) was about twice as high compared to EE. As for E_4, it had a considerably reduced binding affinity for both ERα and ERβ (IC_{50}: 282 and 355 nM, respectively) compared to E_2, with a little greater affinity for ERα than ERβ.

Nuclear immunoreactivity for ERα and ERβ has been demonstrated in both glandular epithelial and stromal cells in the premenopausal endometrium. There are variations in the distribution of both isoforms in endometrial tissue, which suggests that they play

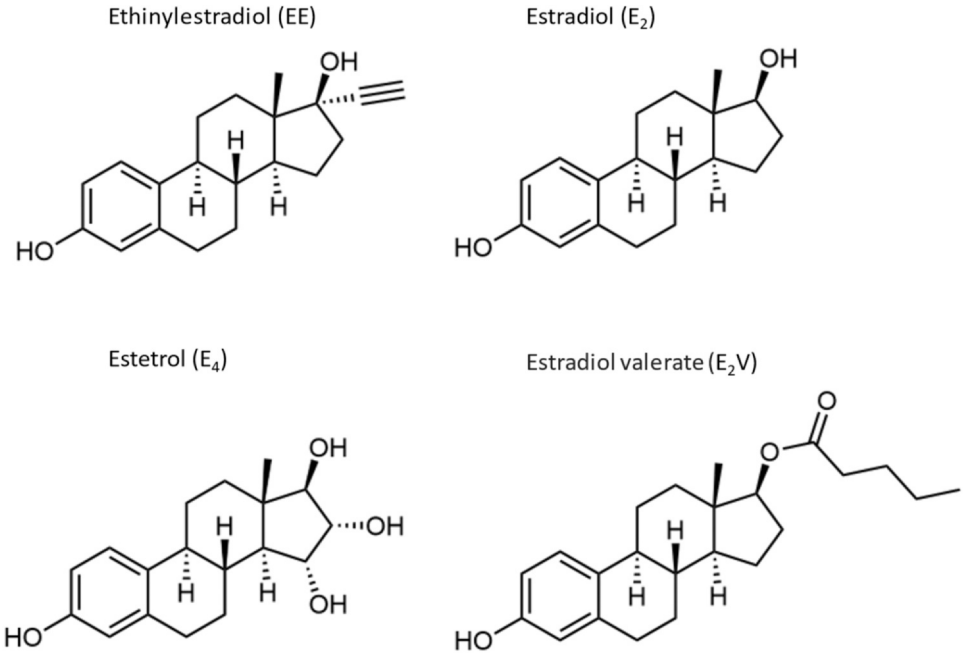

Fig. 1. Chemical structures of estrogens.

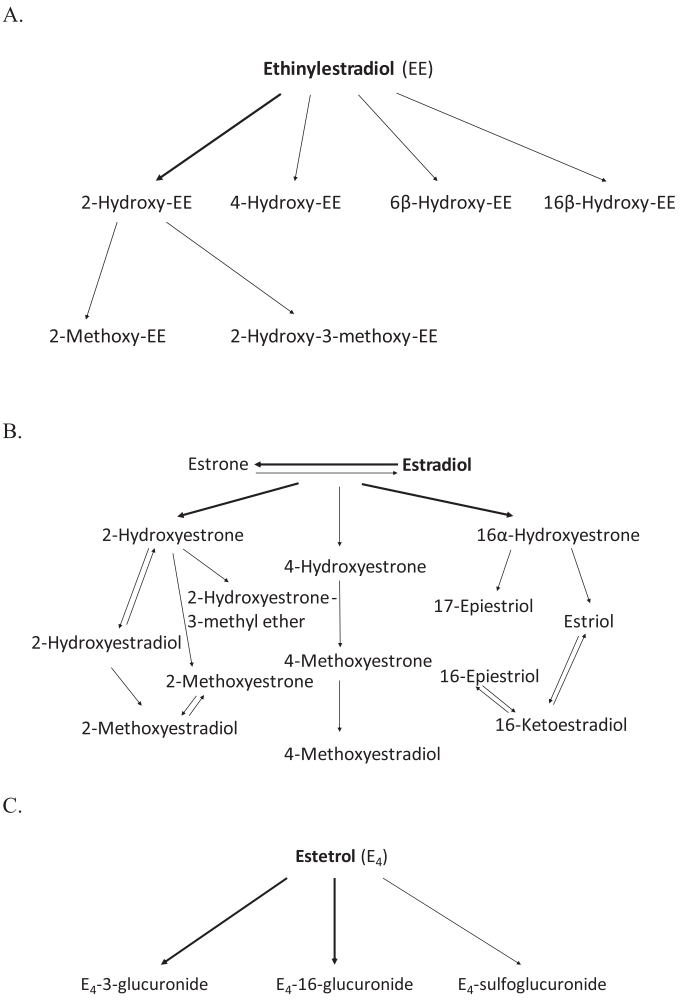

Fig. 2. Metabolism of ethinylestradiol, estradiol, and estetrol.

different roles in the regulation and function of estrogens in the endometrium. Endometrial proliferation is likely dependent on the ratio of ERα to ERβ [15,16].

ERα and ERβ are differentially expressed in endometrial vascular endothelial cells and perivascular cells surrounding endometrial blood vessels. Monoclonal antibodies and immunocytochemistry have shown that ERα is localized to muscle cells of uterine arteries. Analysis of immunostaining confirmed that endometrial endothelial cells only express ERβ, which may be the target of selective agonists or antagonists for the ERβ subtype [17]. This may have important implications for endometrial angiogenesis and for bleeding.

In the classical genomic mechanism of ER action, ERα and ERβ function as ligand-dependent factors that regulate the transcription of target genes. Estrogens bind to the ERs in the cytoplasm, and ER-estrogen complexes then dimerize and translocate to the nucleus, where they interact with estrogen responsive elements of DNA sequences in target cells. However, the nuclear transcriptional actions of ERα do not account for all the biological functions of estrogens. There is a pool of ERα that is associated with the plasma membrane where it can activate rapid, nongenomic signaling (termed membrane-initiated steroid signaling). It has been shown that E_4 activates nuclear ERα, similarly to E_2 and EE, but does not activate the membrane ERα pathway in specific tissues [18,19]. Thus, E_4 appears to be a selective ER modulator.

4. Potency

The potency of an estrogen refers to its strength and can be defined as a measure of the doses of two drugs needed to produce the same pharmacologic effect. The high potency of EE has been demonstrated in several studies. The effect of oral estrogens on follicle-stimulating hormone (FSH) and estrogen-sensitive hepatic proteins was evaluated in postmenopausal women who were treated with different doses of five different estrogen preparations, including EE and E_2 [20]. Each dosage of each formulation was ingested by three women for 2 weeks. Pretreatment and posttreatment serum levels of FSH, luteinizing hormone (LH), sex hormone–binding globulin (SHBG), corticosteroid-binding globulin (CBG), and angiotensinogen were measured by radioimmunoassay. The relative potency of the estrogens was determined by parallel line analyses for each of the parameters that showed dose responses. The results showed that on a weight basis, EE was the most potent estrogen. Compared to E_2, the relative potency of EE was 614 and 331 times greater with regard to the responses of SHBG and angiotensinogen, respectively. The effects on FSH and the hepatic globulins indicate that EE appears to be 200 and 100 to 500 times more potent than E_2, respectively, when the two estrogens are administered orally [21].

The high estrogenic potency of EE is also evident in studies in which EE is administered parenterally. A transdermal delivery system (patch), delivering 20 μg/d of EE and 150 μg/d of norgestimate, was compared to a COC that contains 35 μg of EE and 250 μg of norgestimate with respect to effects on serum levels of SHBG, CBG, thyroid-binding globulin (TBG), and high-sensitivity C-reactive protein (hs-CRP) in 24 women randomized to receive one of the two treatments [22]. The results found that treatment with the patch or COC resulted in significant increases from baseline in SHBG, CBG, TBG, and hs-CRP in both groups. The increases in SHBG and TBG observed with the patch were significantly greater than those associated with the COC. It has also been shown that vaginal delivery of a combined hormonal contraceptive (vaginal ring delivering 150/15 μg of nesterone/EE per day) did not reduce the EE-associated changes in estrogen-sensitive hepatic proteins after the use of a COC (levonorgestrel [LNG]/EE, 150/30 μg) for three treatment cycles [23]. In contrast, studies show that transdermal E_2 treatment in postmenopausal women has negligible effects on SHBG, CBG, and TBG [24]. The profound differences between parenterally administered EE and E_2 regarding their effects on estrogen-sensitive hepatic proteins appear to be due to the one difference in their chemical structures, namely, the ethinyl group on the EE molecule.

In contrast to EE-based COCs, E_4 stimulates the production of estrogen-sensitive hepatic proteins to a considerably lesser extent. A study comparing the effect of a COC containing E_4 to other formulations on hepatic proteins and hemostatic parameters in healthy women receiving either E_4 combined with DRSP or EE combined with either DRSP or LNG for six cycles revealed that E_4 combined with DRSP had a significantly lower impact (+55%) on SHBG compared to EE/DRSP (+251%), indicating a lower estrogenic effect on the liver [25]. However, there are no data comparing E_2V/dienogest (DNG) or E_2/nomegestrol acetate (NOMAC) to EE/DRSP.

5. Metabolism

The metabolism of EE and E_2 share similarities but differ significantly from that of E_4 (Fig. 2A–C). Both EE and E_2 undergo extensive hydroxylation through the action of cytochrome P450 by the addition of a single hydroxyl group at one of the carbons on the steroid nucleus. E_2 is readily converted to E_1 by 17β-hydroxysteroid dehydrogenase, type 2. Both E_2 and E_1 undergo major transformations in rings A and D, resulting in mainly 2- and 16α-hydroxylated

metabolites. A hydroxylation reaction also occurs at carbon 4 of E_2 and E_1. The 2- and 4-hydroxylated E_2 and E_1 metabolites are known as catechol estrogens. These estrogens are readily auto-oxidized, by mechanisms that have not yet been elucidated, to semiquinones and quinones, which can bind covalently to DNA and potentially cause DNA damage [26]. Because of this possibility, it has been suggested that catechol estrogens are potentially carcinogenic, particularly in the breast. However, 2-hydroxylated E_2 and E_1 are rapidly converted to 2-methoxy E_2 and 2-methoxy-E_1, respectively [27], by the action of O-methyltransferase, and it has been shown that these metabolites have an anti-proliferative effect on breast cancer cells [28].

Studies have also implicated 16α-hydroxy-E_1 in the oncogenic process due to its covalent interaction with the ER [29]. Because 16α-hydroxy-E_1 has potent hormonal activity for the ER [30], whereas 2-hydroxy-E_1 has a lower affinity for this receptor [31,32], a hypothesis was proposed 25 years ago that the ratio of 2-hydroxy-E_1 to 16α-hydroxy-E_1 measures the balance between two competing pathways (2-hydroxylation vs 16α-hydroxylation) of E_2 metabolism and is a biomarker of breast cancer risk [33]. However, this hypothesis requires further validation [34].

Although EE metabolism also involves extensive hydroxylation, it differs from that of E_2. 2-Hydroxylation is quantitatively the most important pathway of EE metabolism [35]. Hydroxylations at carbons 4 and 16 (16β but not 16α) have also been reported but contribute only to a small extent. Unlike the 16α-hydroxylation of E_2 at carbon 16, this does not occur on the EE molecule, presumably due to blockage of the enzyme, 16α-hydroxylase, by the ethinyl group (steric hindrance).

In contrast to EE and E_2, which are transformed to numerous hydroxylated metabolites, E_4 has a unique metabolism, which is likely due to the presence of four hydroxyl groups on the molecule. Cytochrome P450 enzymes do not play a major role in the metabolism of E_4 [36]. E_4 is metabolized predominantly by conjugation, forming E_4-3-glucuronide, E_4-16-glucuronide, and E_4-sulfoglucuronide.

6. Pharmacokinetics

Two clinically important pharmacokinetic parameters of a drug are its bioavailability and half-life. Bioavailability is the extent to which a drug enters the systemic circulation after undergoing hepatic first-pass metabolism. A high oral bioavailability reduces the amount of an administered drug necessary to achieve a desired pharmacologic effect; therefore, it can reduce the risk of side effects.

The bioavailability of E_4 is high [36], presumably due to its limited metabolism during the hepatic first pass. In contrast, EE has a moderate bioavailability (40%–45% on average) [37]. On the other hand, E_2 is poorly absorbed with very low bioavailability (< 5%), even when its particle size is reduced (micronization) [38], owing to extensive hepatic first-pass metabolism.

Once a steroid hormone is in the circulation, it is rapidly weakly bound to albumin, and depending on its chemical structure, it may also bind with high affinity to SHBG or CBG. A small percentage (< 5%) of each steroid is non-protein-bound (free). Only the free steroid fraction can enter cells and exert biologic effects (“free” hormone hypothesis) [39]. Albumin, SHBG, and CBG transport steroids in blood and also regulate the access of free steroids into target cells. In premenopausal blood, approximately 38% of E_2 is bound with high affinity to SHBG and 62% is loosely bound to albumin; about 2% of E_2 is in a free form [40]. In contrast, EE binds very weakly and E_4 does not bind to SHBG; both are bound predominantly to albumin [41]. The consequence of absence and very low binding of E_4 and EE to SHBG, respectively, is that changes in circulating levels of this protein will not influence access of these estrogens to their target tissues.

All three estrogens display a high dose-response relationship and exhibit a pharmacokinetic pattern suggestive of enterohepatic recirculation. Reported half-lives for EE, E_2, and E_4 are 5 to 30 hours [42], 13 to 20 hours [43], and 28 hours [44], respectively.

7. Ovarian function

COCs inhibit ovulation by disrupting the hypothalamic-pituitary-ovarian axis, mainly through suppression of pituitary gonadotropin secretion and inhibition of pituitary LH and its midcycle surge. It has also been shown that the EE dose in a COC has a significant effect on follicular ovarian activity [45]. Reducing the dose from 30 to 20 μg is associated with a significant increase in follicular size. In a study that compared E_2V (2 mg)/DNG (2–3 mg) with EE (30 μg)/DNG (2 mg), the suppression of FSH by the E_2V formulation (median, −27%) was significantly lower than that of the EE formulation (median, −64%) [46]. However, both formulations displayed a similar decrease in LH levels.

In a randomized, open-label parallel study in 82 premenopausal women, the effects of E_4 (15 mg)/DRSP (3 mg) on ovarian function were compared to those of EE (20 μg)/DRSP (3 mg) during treatment for three consecutive cycles [47]. The results show that ovulation inhibition was generally comparable with the two formulations. No ovulations occurred with E_4/DRSP, which is due to the major contraceptive effect of DRSP. However, three ovulations occurred in two women treated with the comparator. Most participants in both groups had a Hoogland score of 1 (no ovarian activity) in cycle 3 (65.8% and 83.8% of participants treated with E_4/DRSP and EE/DRSP, respectively) [48]. Also, in cycle 3, 21.1% of the participants (8/38) using E_4/DRSP had an active follicle-like structure (FLS; Hoogland score 4) compared with 5.4% of participants (2/37) using EE/DRSP. None of the participants had a luteinized unruptured follicle (Hoogland score 5). Both treatments suppressed follicular growth; the mean diameter of the largest FLS remained below 10 mm throughout cycles 1 and 3. FSH and LH were suppressed with both formulations, but the concentrations were less pronounced with the E_4/DRSP formulation. These data show that the E_4-based COC appears to be associated with more follicular activity compared to the EE-containing formulation. This is likely due to the higher level of FSH achieved with the E_4-based preparation. Further clinical studies are needed to clarify the effect of E_4 alone on FSH suppression and the degree of inhibition of folliculogenesis in menarchal women.

Given the low estrogenic potency of E_4, the current E_4/DRSP formulation requires a relatively high E_4 dose of 15 mg. In contrast, EE doses in COCs vary from 0.01 to 0.035 mg, which is 428 to 1500 times lower than the E_4 dose. Also, E_2 or E_2V doses in COCs range between 1 and 3 mg, which is 5 to 15 times lower than the E_4 dose. Thus, as an example, a 15 mg E_4 dose would correspond to 0.02 mg EE and 1.5 mg E_2 doses in COCs.

8. Cycle control

Lower EE doses in COCs are associated with higher rates of bleeding. COCs with EE doses of 20 μg result in a less favorable bleeding profile than COCs with higher EE doses [49]. Additionally, in a noncomparator phase 3 trial with 10 μg of EE combined with 1 mg of norethindrone acetate, there was a relatively high incidence of unscheduled bleeding and absence of scheduled bleeding [50].

Attempts to replace EE with E_2 or E_2V have been problematic, primarily due to bleeding outcomes. A review of studies of E_2-based COCs shows that despite good ovulation inhibition, bleeding irregularities affected most women, often resulting in high discontinuation rates

Table 1
Summary of studies showing the effects of ethinylestradiol-, estradiol-, and estetrol-based combined oral contraceptives on the coagulation and fibrinolytic systems in premenopausal women

	Percentage change from baseline (%)						
	Agren et al. [59] (median change)		Junge et al. [61] (intraindividual change)		Douxfils et al. [62] (median change)		
Coagulation & fibrinolytic parameters	E_2/NOMAC	EE/LNG	E_2V/DNG	EE/LNG	E_4/DRSP	EE/LNG	EE/DRSP
Anticoagulant proteins							
Antithrombin III	3.9	−3.6[a]	0.8	−3.0	−1.0	−5.0	−3.5
Protein S activity			1.8	−11.7[a]	−4.0	−5.0	−30.5[a]
Protein S free	13.3	11.9			5.0	−3.0	−22.5[a]
Total protein S	4.7	−3.6[a]					
Protein C	−3.1	8.2[a]			2.0	7.0	17.5[a]
Protein C activity			8.3	14.5			
TFPI free					−8.5	1.0	−20.0
Fibrinolytic proteins							
Plasminogen					12.0	40.0[a]	35.5[a]
PAI-1			−10.6	−36.2	20.0	0.0	0.0
t-PA			−3.7	−5.1	−7.0	−33.0[a]	−39.5[a]
Marker for ongoing coagulation							
D-dimer	0.0	0.0	−2.1	62.9[a]	4.0	7.0	0.0
Prothrombin fragment 1 + 2	−1.7	13.5	−0.6	117.3	23.0	71.0[a]	64.0[a]
Procoagulant factors							
Fibrinogen			7.9	28.1[a]	10.0	5.0	16.0
Prothrombin/factor II	−0.9	3.0			7.0	13.0	7.0
Factor VII					−3.0	−5.0	20.0[a]
Factor VIIa	8.8	14.4					
Factor VIIc	1.0	−12.7[a]					
Factor VII activity			13.5	24.4[a]			
Factor VIII	4.8	6.8			5.0	3.0	9.0
Factor VIII activity			6.9	7.5			
Von Willebrand factor					5.0	−2.0	13.0
Functional coagulation tests							
nAPCsr					30.0	164.5[a]	218.5[a]
APC resistance (aPTT)	3.3	2.0	−5.3	−7.0			
ETP-based APCr	60.0	146.4[a]					

APC, activated protein C; DNG, dienogest; DRSP, drospirenone; E_2, estradiol; E_2V, estradiol valerate; ETP, endogenous thrombin potential; LNG, levonorgestrel; nAPCr, normalized APC sensitivity ratio; NOMAC, nomegestrol acetate; PAI-1, plasminogen activator inhibitor-1; TFPI, tissue factor pathway inhibitor; t-PA, tissue plasminogen activator.
[a] Statistically significant difference ($p < 0.005$) from the reference product (reference products are E2/NOMAC for Agren et al. [59]; E2V/DNG for Junge et al. [61]; E4/DRSP for Douxfils et al. [62]).

[9,51]. E_2 or E_2V were combined with norethindrone, desogestrel, or cyproterone acetate using different doses and regimens. All these formulations were associated with poor cycle control.

Suggested reasons for the bleeding irregularities observed with E_2-based estrogen/progestin preparations include suboptimal doses of estrogen and an inappropriate estrogen/progestin ratio. In addition, the progestin used in those formulations may have affected the overall bleeding profile. It is known that progestins stimulate endometrial 17β-HSD type 2, which converts E_2 to its less potent metabolite, E_1 [52]. In addition, progestins reduce nuclear ER concentrations and thereby decrease nuclear estrogen bioavailability, resulting in an antimitotic effect on the endometrium. Therefore, it appears that the decrease of endometrial proliferation depends on the antiestrogenic effect of the progestin component. The actual cause of unscheduled bleeding is unknown but is probably related to the progestin component of the COC acting on the endometrial vasculature [53,54]. Increasing the dose of EE has not been found to reduce unscheduled bleeding, which appears to be progestin related [49].

In recent years, two E_2-based COCs were developed and are in clinical use at present. One formulation contains E_2V/DNG (Natazia, Qlaira) in a quadraphasic regimen, which is available in and outside the United States, and the other contains monophasic E_2/NOMAC in a 24/4-day regimen (Zoely, Naemis), which is only available outside the United States. Two phase III trials with E_2V/DNG showed that the incidence of unscheduled bleeding diminished from 28.8% in cycle 2 to 11.2% in cycle 11 in the North American trial [55] and from 26.4% in cycle 2 to 12.1% in cycle 11 in the European trial [56]. In a 7-month comparative trial, the incidence of unscheduled bleeding was similar for E_2V/DNG (range, 10.5%–18.6%) and EE/LNG (range, 9.9%–17.1%). As for E_2/NOMAC, in a pooled phase III analysis, it was shown that unscheduled bleeding incidence ranged from 15.4% to 24.1% over cycles 2 to 12 [57,58] and was significantly higher compared to EE/DRSP [58]. Based on limited recent clinical contraceptive studies, E_4-containing COCs may have less unscheduled bleeding than other low-dose COCs [9], which may be due to the lower estrogenic potency of E_4 at the receptor level. However, this has not been confirmed by head-to-head studies.

9. Hemostasis

Studies involving the effects of EE, E_2, and E_4 on the coagulation and fibrinolytic systems in premenopausal women have been carried out predominantly in combination with a progestin. Most of the studies have involved EE-based COCs. Considerably fewer studies with E_2-based COCs exist, and the novel estrogen, E_4, has been studied only recently. Nevertheless, some conclusions can be drawn from comparisons of the three estrogens regarding their effects on coagulation and fibrinolysis.

A randomized, six-cycle study involving 121 premenopausal women by Agren and coworkers [59] compared the effects of E_2 (1.5 mg)/NOMAC (2.5 mg) vs EE (30 μg)/LNG (150 μg) on hemostatic parameters (Table 1). Both formulations induced minimal changes from baseline to the end of treatment in procoagulant prothrombin,

activated factor VII, coagulated activated factor VII, and factor VIII. The results of the anticoagulatory indices also showed relatively small changes from baseline in each group, with significant differences in antithrombin III, protein C, and total protein S, but not in the activated partial thromboplastin time–based activated protein C (APC) sensitivity ratio and free protein S. However, a substantial significant increase from baseline with EE/LNG was observed in the endogenous thrombin potential (ETP)-based APC sensitivity ratio. As for markers of thrombin turnover, the percent change from baseline to end of treatment showed a small increase in the prothrombin fragment 1 + 2 (F1 +2) in the EE/LNG group but not in the E_2/NOMAC group; however, D-dimer was unchanged in both groups. In the same study, the percent change from baseline on CRP was considerably greater in the EE/LNG group, although the CRP levels in this group were within the normal range of values for premenopausal women.

A similar study [60] compared the hemostatic effects of E2/NOMAC with those of EE/LNG using a lower dose of the latter formulation, EE (20 μg)/LNG (100 μg) and three consecutive cycles instead of six. The results show that although some of the changes from baseline to end of treatment in measured coagulation and fibrinolysis parameters differed between the two groups, most of the changes were relatively small, and the end-of-treatment values were within the normal range.

In another study [61], the hemostatic effects of the multiphasic formulation consisting of E_2V (1–3 mg) combined with DNG (2–3 mg) were compared with those of a triphasic formulation containing EE (30–40 μg) combined with LNG (50–125 μg) during a treatment period of seven cycles (Table 1). Changes in coagulation and fibrinolytic parameter values from baseline to end of treatment were relatively small and remained within the range of normal values.

Based on the limited data available from the short-term studies that compared E_2 with EE, each combined with a different progestin, on hemostatic parameters, it appears that the effects of the E_2- and EE-based formulations are similar.

A recent randomized open-label exploratory study by Douxfils and coworkers [62] assessed the effect of an E_4-based COC on hemostatic parameters (Table 1). In the study, premenopausal women received either E_4 (15 mg)/DRSP (3 mg; $n = 39$), EE (30 μg)/LNG (150 μg; $n = 30$), or EE (20 μg)/DRSP (3 mg; $n = 32$) for six 28-day cycles. The median change from baseline was evaluated for procoagulant, anticoagulant, and fibrinolytic parameters. Changes in the coagulation factors, fibrinogen, prothrombin, factor VII, factor VIII, and Von Willebrand factor following treatment with the three formations for six cycles were generally small, with no significant differences for the different parameters, except for factor VII, which was significantly different between EE/DRSP and the other two formulations. However, the median change in the ETP-based APC sensitivity resistance at cycle 6 was 30% for E_4/DRSP, which was significantly different from that of EE/LNG (105%) and EE/DRSP (219%). The coagulation studies infer that a laboratory-based screener for "coagulation status" incorporating several markers, such as the ETP-based APC sensitivity resistance test, is a potential marker for VTE risk assessment [63]. There are no data that indicate a correlation between changes in hemostatic factors and the clinical finding of VTE.

Small changes from baseline to end of treatment were observed for E_4/DRSP and EE/LNG in the anticoagulant parameters, antithrombin, protein S activity, free protein S, protein C, and the tissue factor pathway inhibitor. The changes were significantly greater in protein S activity, free protein S, and protein C compared to the E_4/DRSP and EE/LNG groups.

E_4/DRSP showed a weak impact on fibrinolytic markers (plasminogen, plasminogen activator inhibitor, tissue plasminogen activator). However, the data do not allow any conclusions regarding a potential hypofibrinolytic or hyperfibrinolytic profile of E_4/DRSP. There is little evidence supporting the importance of changes in serum fibrinolysis factors for VTE.

In another recent study, Morimont and coworkers [64] showed that E_4 (15 mg)/DRSP (3 mg) does not have an impact on thrombin generation compared to EE (20 μg)/DRSP (3 mg) and EE (30 μg)/LNG (150 μg) in a cohort of women treated for six cycles. Based on their findings, they concluded that EE-containing COCs are associated with a shift to a prothrombotic state, in contrast to E_4/DRSP, which demonstrates a neutral profile on hemostasis.

10. Venous thromboembolism

EE has been associated with increased procoagulant factors and decreased anticoagulatory mechanisms, with a risk of VTE appearing to be dose dependent [65,66]. Development of low-dose COCs containing < 50 μg of EE led to a reduced risk of VTE but remained consistent even with very low EE doses or with the use of parenteral routes of administration. VTE risk from COC use is highest in women with known cardiovascular risk factors, including smoking, high blood pressure, diabetes, obesity, age, history of thrombosis, or other coagulation abnormalities [67–70].

Some studies have shown that androgenic progestins such as LNG and norethindrone antagonize the risk of VTE associated with EE more than nonandrogenic progestins such as desogestrel [71–74]. However, in studies that corrected for various confounding factors, such as weight, smoking status, alcohol use, age, and duration of use, no difference in VTE risk was observed between androgenic and nonandrogenic progestins [75–79].

As discussed earlier, both E_2 and E_4 have less of a stimulatory effect than EE on the hepatic system to increase the production of procoagulant proteins. Two large international surveillance studies, the INAS-SCORE and PRO-E_2, were initiated to assess the risk of short- and long-term use of E_2V/DNG and E_2/NOMAC, respectively [80,81]. In comparison to LNG-based COC users, the VTE risk was slightly lower with the E_2-based formulations, suggesting that these products are as safe as EE-based COCs containing LNG [63,82]. As for the E_4-based COC, it is presently being evaluated in postmarketing VTE studies.

11. Conclusions

There are significant differences among the various estrogens used in COCs, which are summarized in Table 2. One striking difference is the profound potency of EE, evident in its greater effects on estrogen-sensitive hepatic proteins, including coagulation and anticoagulation factors, which surpass those of E_2 and E_4. Dose-dependent effects of EE on VTE risk are well established. Limited data suggest that E_2-based COCs may pose a lesser VTE risk, whereas the VTE risk of E_4 remains to be determined. Of interest is that E_4 has a limited impact on hemostatic parameters, which theoretically may translate into a lower clinical risk of VTE.

Replacement of EE with the weaker natural estrogen, E_2, has been problematic due to poor cycle control. Studies with currently used E_2-based COCs show that the incidence of unscheduled bleeding with the quadriphasic E_2V/DNG formulation is similar to that of EE/LNG; however, the bleeding incidence with E_2/NOMAC is significantly higher compared to EE/DRSP. In contrast, recent data show that the E_4/DRSP formulation may offer improved cycle control.

Table 2
Comprehensive overview of pharmacologic characteristics of estrogenic components used for hormonal contraception

Characteristics	Ethinylestradiol (EE)	Estradiol (E_2)	Estetrol (E_4)
Origin	Synthetic	Premenopausal women ovaries	Fetoplacental unit during pregnancy
Receptor-binding affinity (IC_{50}*)	Very high affinity for ERα (preferential). ERα 5.6 nM ERβ 15.9 nM	Slightly higher affinity for ERβ than ERα; affinity for ERα two times lower compared to EE. ERα 11.2 nM ERβ 8.4 nM	Reduced affinity for ERα and ERβ compared to E_2. ERα 282 nM ERβ 355 nM
Potency	Increases estrogen-sensitive hepatic proteins dramatically.	Has less of an effect on hepatic proteins than EE.	Lower potency compared to EE and E_2, with reduced estrogenic effect on the liver.
Metabolism	2-hydroxylation and limited 4-hydroxylation, but not 16α-hydroxylation due to the presence of the ethinyl group on carbon 17.	Extensive metabolism, with the formation of 2- and 4-hydroxylated catechol estrogens, and 16α-hydroxylated metabolites.	Limited metabolism with formation of glucuronidated metabolites.
Bioavailability	Moderate, ~40%–45%	Poorly absorbed; very low bioavailability (< 5%)	High bioavailability.
Half-life	~5–30 h	~ 13–20 h	~ 28 h
Ovarian function	In combination with a progestin, effectively inhibits ovulation by disrupting pituitary gonadotropin secretion.	In combination with DNG or NOMAC, inhibits ovulation by disrupting pituitary gonadotropin secretion.	In combination with $DRSP_{,}$ effectively inhibits ovulation, despite exhibiting lower estrogenic potency.
Cycle control	Doses below 20 μg EE may lead to a less favorable bleeding profile.	When combined with various progestins, it is associated with problematic bleeding outcomes.	Shows less unscheduled bleeding than with other COCs, but head-to-head comparisons are needed.
Hemostasis	Increases procoagulatory factors and decreases anticoagulatory mechanisms.	E_2V/DNG and E_2/NOMAC show minimal changes in coagulation and fibrinolytic parameters and similar effects on hemostasis as EE/LNG.	Demonstrated relatively small changes in hemostatic parameters, with weak impact on fibrinolytic markers; no impact on thrombin generation.
Venous thromboembolism	Increases the risk of VTE due to its effect on procoagulatory factors and decreased anticoagulatory mechanisms. At low-dose or parenteral routes of administration, VTE risk remains consistent and is highest in women with cardiovascular risk factors.	E_2-based formulations have slightly lower VTE risk compared to EE-based COCs, indicating that they are as safe.	Insufficient data available on long-term effects of E_4 on VTE risk.

DNG, dienogest; NOMAC, nomegestrol acetate; DRSP, drospirenone; LNG, levonorgestrel; E_2V, estradiol valerate.
IC_{50}, concentration of a ligand (estrogen) required to inhibit the binding to the estrogen receptor by 50%. Lower IC_{50} values indicate higher receptor-binding affinity. EE exhibits the highest binding affinity, followed by E_2, while E_4 has a considerably reduced binding affinity for both ERα and ERβ compared to E_2.

Although all COCs containing EE, E_2, E_2V, or E_4 inhibit ovulation, their effects on ovarian activity differ, with the E_2- and E_4-based COCs showing a less pronounced effect on gonadotropins. Also, the estrogen dosing varies widely in the COCs, with E_4 requiring a relatively high dose due to its low estrogenic potency. E_4 is a unique estrogen with potential clinical benefits suggested by its profile.

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