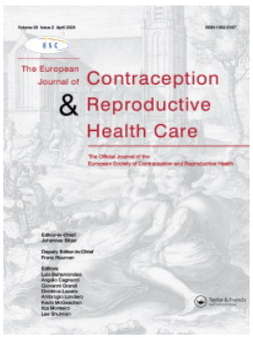

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REVIEW ARTICLE

Oestrogens in oral contraception: considerations for tailoring prescription to women's needs

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ABSTRACT

Background: The oestrogenic component of combined oral contraceptives (COCs) has changed over years with the aim of reducing oestrogen-related side effects and risks, whilst maintaining oestrogen beneficial effects, particularly on cycle control.

Purpose: To describe the pharmacological profiles of different oestrogens commonly used in COCs to provide insights on contraceptive prescription tailored to women's needs.

Results: All COCs ensure a high contraceptive efficacy. COCs containing the natural oestrogens oestradiol (E2), oestradiol valerate (E2V) and estetrol (E4) have limited impact on liver metabolism, lipid and carbohydrate metabolism, haemostasis and sex hormone binding globulin levels, compared with ethinylestradiol (EE). COCs with E2 and E2V appear also to entail a lower elevation of the risk of venous thromboembolism vs. EE-containing pills. No epidemiological data are available for E4-COC. E2- and E2V-containing COCs seem to exert a less stabilising oestrogenic effect on the endometrium compared with EE-COCs. The E4-COC results in a predictable bleeding pattern with a high rate of scheduled bleeding and minimal unscheduled bleeding per cycle. Based on *in vitro* and *in vivo* animal data, E4 seems to be associated with a lower effect on cell breast proliferation.

Conclusion: Today various COCs contain different oestrogens. Prescribers must be familiar with the different properties of each oestrogen for a tailored contraceptive recommendation, considering their safety and contraceptive efficacy, as well as women's needs and preferences.

SHORT CONDENSATION

For contraceptive pills physicians can choose among different oestrogens, besides many progestins. Natural oestrogens have less metabolic impact vs EE, while EE and E4 seem to provide a better cycle control. Knowing the different oestrogen characteristics is crucial for adjusting pill prescription to women's needs and desires.

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Estetrol; oestradiol; oestradiol valerate; ethinylestradiol; combined oral contraceptives; contraceptive tailored prescription; women's needs

Introduction

Since their introduction on the market in the 1960s, combined oral contraceptives (COCs) have become the most common method of reversible hormonal contraception (HC) [1].

The pill contraceptive efficacy mainly depends on the anti-gonadotrophic action of progestins, which leads to the inhibition of ovulation. Progestins suppress the hypothalamic release of gonadotropin-releasing hormone, which inhibits the luteinizing hormone (LH) peak, preventing the dominant follicle development, with a decreased ovarian sensibility to follicle stimulating hormone (FSH), reducing endogenous oestradiol (E2) production. In addition, progestins increase cervical mucus viscosity, inhibiting sperm penetration, and induce morphologic changes in the endometrium, reducing the likelihood of implantation [1–3].

Progestin-only pills (POPs) induce a progressive inhibition of endometrial growth, glandular atrophy, stroma pseudo-decidualization, and vascular changes, characterised by irregular and abnormal angiogenesis, increased vascular density, and superficial vessels becoming thin-walled and dilated. These endometrial changes vary by progestin type, dose, and treatment duration, and may contribute to the high frequency of unscheduled bleeding, spotting and/or amenorrhoea observed with such contraceptives [2,3].

Irregular bleeding is a relevant HC side effect, causing discomfort and premature contraceptive discontinuation [4,5]. In an Italian retrospective cross-sectional study, 20% of women stopped HC due to minor side effects, with irregular bleeding being the most frequent reason of discontinuation (5.3%) [5].

The addition of oestrogens to progestins in contraception was found to balance progestin effects on the endometrium, providing stabilisation and a better cycle control, reducing the occurrence of irregular bleeding [6].

The oestrogenic component of COCs contributes to the inhibition of FSH release and increases progestin receptor concentration, thus reinforcing the progestin-mediated suppressive effect on the hypothalamic–pituitary–ovarian (HPO) axis. This minimises E2 production from the ovary: endogenous E2 concentrations are lower during COC use than POP administration [1,7,8]. Thus, the goal of the ideal oestrogenic component of COCs is to provide endometrial

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stability, avoiding hypoestrogenism signs and symptoms. The ideal oestrogen should ensure endogenous E2 benefits with as few side effects as possible, avoiding any potential risk.

Many types of COCs are available today. Increasing the knowledge and awareness of health care professionals (HCPs) about the characteristics of different COCs is critical for an effective counselling and prescription.

The purpose of this review is to describe the pharmacological profile of different oestrogens used in COCs, to support contraceptive counselling and a prescription tailored to women's individual needs and preferences.

The complex role of oestrogens in women's health

Several types of oestrogens are produced by humans. The predominant oestrogen is E2, which is essential for the reproductive function and women's wellbeing, followed by oestrone (E1) and oestriol (E3). A fourth type of oestrogen, estetrol (E4), is produced only during pregnancy by the foetal liver and placenta [9].

Oestrogens exert their tissue-specific biological effects through genomic mechanisms mediated by their interaction with nuclear oestrogen receptors (ERs) alpha (ERα) and beta (ERβ), as well as rapid non-genomic mechanisms through ERs localised at the plasma membrane [10]. These receptors have distinct tissue distribution. ERα are mainly expressed in the uterus, ovarian theca cells, Leydig cells in testes, breast, prostate stroma, epididymis, and liver [10,11]. ERα not only play a key role in reproduction, but exert important functions in many non-reproductive tissues [12]. In contrast, ERβ are highly expressed in the bone marrow, brain, ovarian granulosa cells, prostate epithelium, and testes [10,11].

Beneficial effects of oestradiol

Oestrogens, particularly E2, contribute to the development and maintenance of secondary sexual characteristics, such as breast development and body fat distribution. Moreover, E2 plays a crucial role in regulating the vaginal mucosa function, influencing lubrication and elasticity. Besides, E2 has a stimulating effect on the uterus trophism, contributing to the endometrium growth [13].

In addition, specifically E2 exerts a widespread influence on the overall women's health [14].

First, E2 has a protective effect on the cardiovascular system. It is involved in maintaining healthy blood vessels by promoting vasodilation and influencing blood pressure control [15]. E2 also leads to higher levels of high-density lipoprotein (HDL) and lower levels of low-density lipoprotein (LDL) cholesterol, respectively. This results in a general prevention of atheroma development and neointimal endothelial hyperplasia, with a reduced risk of cardiovascular disease during perimenopause [15,16].

Moreover, E2 entails a major role in bone health and metabolism, contributing to bone formation by stimulating osteoblast activity, and reducing bone resorption by inhibiting osteoclast activity. Therefore, E2 is vital for maintaining bone mineral density, thus preventing osteoporosis [17].

This hormone also plays an important role in mental health, potentially reducing the risk of neurodegenerative diseases [14]. Finally, E2 is involved in the immune response, with a close relationship between hormonal fluctuations during the menstrual cycle, immune cell activity and cytokine production [18].

The natural decline in ovarian E2 production during menopause leads to several metabolic changes, resulting in an increased risk of cardiovascular diseases, osteoporosis, and neurodegenerative diseases [14,19].

Side effects and potential risks of natural and synthetic oestrogens

Oestrogen administration can induce several side effects and lead to some health risks.

Minor side effects, usually related to oral oestrogen administration and its dose, include nausea, vomiting, breast tenderness, water retention/oedema, weight increase (mainly due to water retention), cellulitis and bloating, dizziness, headache and premenstrual tension [13].

The two major oestrogen-related risks pertain to coagulation and the possible augmentation of cancer cell growth.

Oestrogens, particularly ethinylestradiol (EE), increase the activity of several coagulation factors and reduce the activity of naturally occurring anticoagulants such as protein S, which in turn leads to the development of an acquired resistance to activated protein C (APC), thus inducing a prothrombotic phenotype [20,21].

This may lead to an increased stimulation of clot formation. Indeed, COC oestrogenic component is the major contributor of the increased risk of venous thromboembolism (VTE) reported in women using COCs, which encompasses deep venous thrombosis (DVT) and pulmonary embolism (PE). Progestins modulate these oestrogen-mediated procoagulant effects in a variable manner, according to the progestin type in the COC formulation. Progestins with higher androgenic activity, such as levonorgestrel (LNG), norethisterone or norgestimate, are more effective in counteracting these oestrogenic effects on coagulation [20,21].

Furthermore, oestrogens induce endometrial and mammary gland cell proliferation. COC administration has been repeatedly demonstrated to reduce the risk of endometrial hyperplasia and carcinoma, owing to the progestin component. Moreover, a protective effect of COC use against ovarian and colorectal cancers has been documented [22]. On the contrary, there is no consensus on whether an increase in breast cancer risk is associated with COC utilisation [23]. Recent meta-analyses reported a slight but significant increase in breast cancer risk with COC use (odds ratio [OR] = 1.20; 95% confidence interval [CI]:1.00–1.17) [24] and in ever users of HC (pooled OR = 1.33; 95% CI:1.19–1.49) [25].

Characteristics of oestrogens in current combined oral contraceptives

Figure 1 and Table 1 provide an overview of chemical and pharmacokinetic characteristics of oestrogens currently used in COCs.

Ethinylestradiol

EE is the most widely used oestrogen in COCs since the 1970s [1]. EE is a synthetic, orally active oestrogen. After

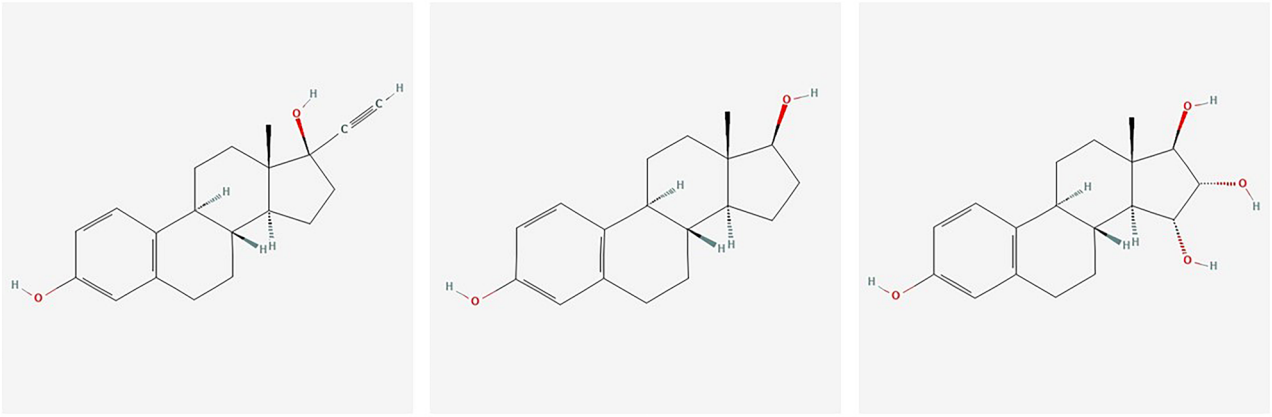

Figure 1. Chemical structure of ethinylestradiol, estradiol and estetrol [PubChem].

Table 1. Pharmacokinetic characteristics of ethinylestradiol (EE), oestradiol (E2), oestradiol valerate (E2V) and estetrol (E4).

	Ethinylestradiol (EE)	Oestradiol (E2, E2V*)	Estetrol (E4)	Data sources
Oral bioavailability	38–48%	2–3%	~90%	Kuhl [10] Stanczyk [39] Hammond [64] Visser [63]
Half-life	26 h	1–2 h (10–12 h for micronized E2)	~28 h	Kuhl [10] Stanczyk [39] Hammond [64] Visser [63]
Protein binding	SHBG (low)	Albumin and SHBG (38%)	No binding to SHBG	Kuhl [10] Stanczyk [39] Hammond [64] Visser [63]
Effects on cytochromes P450	Moderate inhibition of CYP3A4 Strong inhibition of CYP2C19	Moderate inhibition of CYP1A2 Strong inhibition of CYP2C19	No inhibition nor stimulation	Kuhl [10] Stanczyk [39] Visser [65]
Active metabolites	EE sulfates	Oestrone (E1), E1 sulphate, E1 glucuronide, oestriol	No active metabolites	Kuhl [10] Stanczyk [39] Visser [63] Gérard [67]

*E2V is identical to E2 as regards pharmacodynamics and clinical effects as it is rapidly metabolised to E2 after oral administration [38].
SHBG: sex hormone binding globulin.

oral administration, EE is largely absorbed from the upper gastrointestinal tract and undergoes first-pass metabolism in the gastrointestinal mucosa and liver. As opposed to E2, EE is resistant to rapid liver degradation and exerts a prolonged, intense effect on ERs. In fact, unlike E2, EE is not inactivated by 17-hydroxylation due to the presence of the 17α-ethinyl group (Figure 1, Table 1). The reduced inactivation rate of EE, as well as its long half-life and tissue retention, result in a pronounced hepatic effect [10,26], as stimulating the synthesis of sex hormone binding globulin (SHBG), corticotropin binding globulin, angiotensinogen, coagulation factors and HDL cholesterol to a greater extent than E2 [10]. Due to its pharmacological profile, EE remains active in the endometrium, resulting in a better cycle control than progestins alone with a lower rate of irregular bleeding (Table 2) [10,26,27].

To reduce EE metabolic effects and particularly the related VTE risk, the dose of EE in COCs has been gradually reduced over the years from 50 µg to 15 and 10 µg. Indeed, the progressive reduction of EE dose was shown to be associated with a lower impact on liver metabolism, as well as reduced effects on the prothrombotic and fibrinolytic balance. Lowering the dose from 50 to 30 µg has been followed by a decrease of VTE risk [20,28]. However, the risk of VTE in women using COCs with 30 or 20 µg EE is still 2 to 3 times higher if compared with non-users (relative risk 3.5, 95% CI:2.9–4.3), although the absolute risk remains low, ranging from 5 to 12 cases per 10,000 women-years (WY) [20,29].

If a lower dose of EE (especially below 30 µg) results in fewer metabolic side effects, it also leads to a reduced oestrogenic effect on the endometrium, and thus a less favourable bleeding profile [27].

Indeed, COCs containing 20 µg EE combined with different progestins were shown to be associated with a generally low incidence of amenorrhoea and an unscheduled bleeding rate ranging from about 8% to 19% by cycle [30–34]. As a consequence, the discontinuation rate for irregular bleeding is higher for pills with a lower EE content [5]. Notably, considering the vaginal route of administration, 15 µg EE is associated with a lower incidence of irregular bleedings, with a discontinuation rate similar to that of 30 µg EE-containing pills [5,35]. The continuous release of both EE and progestin, resulting in constant serum levels, has been advocated to account for the good cycle control seen with combined vaginal contraception also when very low doses of EE are used [36]. Moreover, because of the extensive vascular connections between the vagina and uterus, a 'first uterine pass effect' has been hypothesised when hormones are administered vaginally [37].

Table 2. Effects on cycle control of ethinylestradiol (EE)-, oestradiol (E2)-, oestradiol valerate (E2V)- and estetrol (E4)-containing COCs.

	COC	Regimen	Scheduled bleeding	Unscheduled bleeding	Amenorrhoea*	Data sources
Ethinylestradiol (EE)	EE (30 µg)/ DRSP	21/7	100% (cycle 2) – 95.5% (cycle 12)	7.9% (cycle 2) – 3.8% (cycle 13)	/	Marr [30]
			96.6% (cycle 2) – 94.2% (cycle 12)	17.4% (cycle 2) – 10.9% (cycle 12)	/	Mansour [53]
	EE (20 µg)/ DRSP	24/4	91.7% (cycle 2) – 82.0 (cycle 12)[a]	13.8% (cycle 2) – 7.7% (cycle 13)[a]	4.9% (cycle 2) – 6.0% (cycle 6)[b]	[a]Marr [30] [b]Machado [34]
	EE (20 µg)/ LNG	21/7	>95% (cycle 2) – 94%-89% (cycles 12 and 13)	19.3 (cycle 2) – 12.2% (cycle 12)	1.0% (cycle 2) – 2.0%-1.3% (cycles 12 and 13)	Teichmann [32]
	EE (10 µg)/ NETA	24/2/2	43.3 (cycle 1) – 22.8% (cycle 12)[a]	52.7% (cycle 2) – 38.8% (cycle 12)[a]	31.6% (cycle 1) – 49.1% (cycle 13)[b]	[a]Archer [27] [b]Archer [33]
Oestradiol (E2)	E2/NOMAC	24/4	82.4% (cycle 2) – 68.6% (cycle 12)	23.2% (cycle 2) – 15.4% (cycle 12)	15.0% (cycle 2) – 27.5% (cycle 12)	Mansour [53]
Oestradiol valerate (E2V)	E2V/DNG	2/22/2/2	76.5%-79.7% (over cycles 1 to 12)[a,b]	26.4%-28.8% (cycle 2) – 11.2%-12.1% (cycle 11)[a,b]	15.4% (on average over cycles 1 to 7)[c]	[a]Nelson [51] [b]Palacios [52] [c]Ahrendt [31]
Estetrol (E4)	E4/DRSP	24/4	83%-94.4% (over cycles 1 to 12)[a,b]	19.2%-21.8% (cycle 2) – 12.8%-15% (cycle 11)[a,b]	10% at maximum (over cycles 1 to 12)[b]	[a]Gemzell-Danielsson [90] [b]Creinin [91]

*Amenorrhoea is defined as the absence of all bleeding and spotting during a 28-day cycle.
DRSP: drospirenone; LNG: levonorgestrel; NETA: norethindrone acetate; NOMAC: nomegestrol acetate; DNG: dienogest.

Natural oestrogens: 17β oestradiol and oestradiol valerate

The first natural oestrogens being employed in COC formulations are oestradiol valerate (E2V) and micronized 17β oestradiol (E2) (Figure 1, Table 1). E2V is the synthetic 17-pentanoyl ester of E2 and is identical to E2 as regards pharmacodynamics and clinical effects. Indeed, 1 mg E2V has been proven to be equivalent to 0.76 mg E2 [38].

After oral administration, E2 is extensively metabolised in the intestinal mucosa and liver, with a consequent low bioavailability. Notably, the very short half-life of E2 can be prolonged with micronized formulations. After oral administration, E2V is immediately metabolised by cleavage of valeric acid to E2, which is further metabolised by 17β-hydroxysteroid dehydrogenase (HSD) type 2, in a variety of tissues, to the weak oestrogen E1 and the conjugates E1 sulphate and E1 glucuronide [10,26,39]. Progestins indirectly promote the conversion of E2 to E1 in the endometrial epithelium by acting on 17β HSD type 2 [40]. E1 is also metabolised to E3, another weak oestrogen [26,39]. As compared with EE, natural oestrogens entail a lower oestrogenic potency and thus a lower impact on lipid and carbohydrate metabolism, haemostasis and hepatic parameters [10,26,39].

Metabolism, haemostasis and cardiovascular risk

E2V was the first natural oestrogen to be introduced into HC, combined with dienogest (DNG) in a 2/22/2/2-day quadriphasic regime consisting of 2 days of 3 mg E2V, followed by 5 days of 2 mg DNG/2 mg E2V, 17 days of 3 mg DNG/2 mg E2V, 2 days of 1 mg E2V and 2 days of inactive treatment. More recently, micronized E2 (1.5 mg) was combined with 2.5 mg nomegestrol acetate (NOMAC) in a monophasic COC with a 24/4 regimen [1]. Both E2V/DNG and E2/NOMAC have demonstrated a reliable contraceptive efficacy, comparable to or even better than EE/LNG pills [41,42].

Both pills have also demonstrated a lower impact on lipid and carbohydrate metabolism compared with EE-containing COCs [43–45].

As regards hepatic and haemostasis parameters, changes were shown to be less pronounced with E2V/DNG and E2/NOMAC compared with EE-containing pills [38,41], thus indicating a lower activation of coagulation [37,40].

Notably, the use of these COCs for their lesser effects on angiotensinogen is not expected to lead to elevated blood pressure. Indeed, the administration of E2-based COCs was reported not to alter systolic and diastolic blood pressure over 24 h. Furthermore, the use of E2V/DNG or E2/NOMAC did not increase the heart rate in normotensive women, suggesting a neutral impact of natural oestrogens on independent risk factors for cardiovascular diseases [46].

The lower activation of coagulation elicited by natural oestrogens suggests that E2V and E2 could have a more favourable cardiovascular risk profile than EE combined with LNG, which is considered to entail the lowest elevation of VTE risk [47,48].

VTE risk in users of COCs containing natural oestrogens compared with EE-containing pills was recently investigated in two international, large, prospective, non-interventional cohort studies. In the INAS-SCORE study, E2V/DNG users showed a similar elevation of VTE risk compared with users of EE-containing COCs (including EE/LNG pills), with a crude hazard ratio (HR) of 0.9 (95% CI:0.4–1.8). E2V/DNG use was associated with a significant reduction of 60% of VTE risk vs. EE-containing COCs after adjusting for age, body mass index (BMI), family history of VTE and current duration of HC use (adjusted HR of 0.4; 95% CI:0.2–1.0) [49]. The PRO-E2 study showed that E2/NOMAC use was associated with a similar VTE risk compared with EE/LNG-containing COCs (crude HR of 0.65 [95% CI:0.28–1.48] and adjusted HR of 0.59 [95% CI:0.25–1.35] after adjusting for the abovementioned potential confounding variables). Moreover, the risk of DVT of lower extremities and PE was slightly but significantly lower in E2/NOMAC vs. 20 µg EE/LNG users (crude HR of 0.41 [95% CI:0.17–0.99] and adjusted HR of 0.31 [95% CI:0.13–0.75]) [50]. Thus, pills with natural oestrogens and non-androgenic progestins appear to entail a lower elevation of VTE risk compared with EE-containing COCs, and a similar risk as EE/LNG pills.

Cycle control

Despite the fact that many confounders may influence cycle control [27,40], making difficult to draw conclusions when different COCs are compared, COCs containing natural oestrogens seem to exert a less stabilising effect on the

endometrium compared with EE-containing pills, given the rapid conversion of E2 to E1 after oral administration, especially in the progestin presence.

The administration of E2V/DNG, using an oestrogen step-down and progestin step-up approach, was associated with scheduled bleeding in 76.5%-79.7% of participants in the two phase III trials, while the incidence of unscheduled bleeding ranged from 28.8%-26.4% to 11.2%-12.1% over cycles 2 to 11 [51,52]. A comparative, prospective trial showed similar results, demonstrating that the occurrence of unscheduled bleeding with E2V/DNG use was similar to that of 20 µg EE/100 mg LNG, even though a significantly higher incidence of amenorrhoea was observed with E2V/DNG [31].

As regards E2/NOMAC, regular bleeding was reported by 82.4%-68.6% of E2/NOMAC users, while irregular bleeding incidence ranged from 23.2% to 15.4% over cycles 2 to 12, as shown by the pooled analysis of the two comparative phase III trials. Moreover, the occurrence of amenorrhoea and unscheduled bleeding was significantly higher in women using E2/NOMAC compared with COCs containing EE and drospirenone (DRSP) [53].

The discontinuation rate for unacceptable bleeding seems to be higher with natural oestrogens compared with EE-containing COCs (5.3%, [5]). In the abovementioned pooled analysis of the two phase III study performed by Mansour and colleagues on 3,773 women, the discontinuation rate due to irregular bleeding of E2/NOMAC and 30 µg EE/DRSP was 3.9% vs. 1.3%, respectively [53]. No other comparative study is available. In a large-scale non-interventional study, 27.7% of users interrupted E2V/DNG use due to unacceptable bleeding pattern [54]. Another observational real-world study on E2V/DNG reported a discontinuation rate for irregular bleedings of 15%, with a shorter time to interruption for adolescents [55].

Estetrol

Estetrol (E4) is a natural oestrogen discovered in 1965. It is synthesised exclusively during pregnancy by the foetal liver from maternal E2 or E3 through 15α- and 16α-hydroxylation [56]. E4 is transferred into maternal circulation through the placenta, reaching high concentrations in maternal plasma (i.e., approximately 1,200 pg/ml at term), with about 12–19-fold higher levels in foetal plasma [57,58].

E4 has four hydroxyl groups, i.e., two additional groups at the 15α and 16α positions compared with E2 (Figure 1, Table 1) [57].

E4 has a high selectivity showing a four-to-five-fold preference for ERα. The affinity for ERα is low-to-moderate [57], resulting 100-fold lower vs. E2 [57,59]. Moreover, E4 shows a unique uncoupled profile of nuclear and membrane ERα activation. Indeed, E4 behaves as a membrane ERα antagonist in some tissues, in contrast to other oestrogens, while it acts as agonist on nuclear ERα. Thus, E4 is considered a natural oestrogen with selective tissue activity (NEST) [59]. The unique structural features of E4 compared with other oestrogens entail important clinical implications resulting in tissue-specific actions [60–62].

The pharmacokinetic profile of estetrol

E4 also differs from other oestrogens by exhibiting in humans a high oral bioavailability with a long plasma half-life, as shown in Table 1. Additionally, E4 does not bind to SHBG and has no inhibitory nor stimulatory effects on cytochrome P450 liver enzymes, which may result in fewer drug–drug interactions, as opposed to EE and E2 [63–66].

After oral administration, E4 undergoes phase II metabolism, with E4-16-glucuronide, E4-3-glucuronide and E4-glucuronide-sulphate as main inactive conjugated metabolites [67]. E4 is not converted into active metabolites, including E1, E2 or E3, either in the liver nor in the endometrium, in contrast with E2 and EE (Table 1) [63].

The absence of E4 conversion to E1, as opposed to natural oestrogens, entails important implications as regards coagulation and endometrial stability. Indeed, E1 was shown to be involved in the prothrombotic state development [68]. Therefore, E4 may be characterised by reduced procoagulant effects compared with other oestrogens. Moreover, E4, at the dose used in contraception, may exert a greater oestrogenic effect on the endometrium vs. natural oestrogens [57,61].

The pharmacological profile of estetrol

Preclinical studies demonstrated that E4 exerts oestrogenic effects on the vagina, uterus and bone. E4 oestrogenic action on the uterus has been confirmed in several studies. E4 administration increased the uterine weight both in immature rats [69], and ovariectomized rats [70]. Comparing the potency of E4 vs. other oestrogens, E4 showed a potency 20-fold lower than EE [70]. In another study in rats, E4 exerted the same stimulatory effect of E2 but using a 100-times higher dose [59]. E4 was shown to increase vaginal epithelial proliferation and vaginal lubrication, through nuclear ERα activation, in ovariectomized mice [71]. Furthermore, E4 was proven to exert a beneficial effect on bone metabolism by preventing the increase of osteocalcin and bone demineralisation in ovariectomized rats [72].

An oestrogenic agonist activity was also demonstrated in the central nervous system (CNS), as E4 increased the serum levels of allopregnanolone and β-endorphin in ovariectomized rats [73]. Moreover, E4 effectively reduced menopausal vasomotor symptoms in a rat model [74].

E4 also exerts beneficial effects on the vascular system. E4 exhibited an atheroprotective effect *in vivo*, preventing neointimal hyperplasia and atheroma formation in a mouse model [75]. In contrast to E2, E4 is not able to elicit an activation of endothelial nitric oxide (NO) synthase, which is known to depend upon membrane ERα activation [59]. However, E4 was shown to prevent hypertension in ovariectomized mice, suggesting that it may induce vasodilation by a specific mechanism distinct from NO production [76]. As other oestrogens, E4 induced endothelial cell migration *in vitro*, presumably indicating a comparable vascular remodelling and regeneration capacity [77].

At present, only some E4 oestrogenic effects have been evaluated in humans. A multiple-rising-dose study in postmenopausal women showed that E4 (at 2, 10, 20, and 40 mg) reduces FSH and LH levels in a dose-dependent manner, indicating an oestrogenic action on the HPO axis [60]. In another study in postmenopausal women, E4 improved vaginal cytology and decreased the number of hot flushes and sweating [78]. However, clinical data on the effects of E4 administration on bone health and osteoporosis prevention, CNS and cardiovascular system, are missing.

Additional properly designed clinical studies are needed to further evaluate E4 clinical effects.

E4 does not activate membrane ERα in the mammary gland. E4 showed a reduced impact on breast cell proliferation *in vitro* (human breast epithelial cells) and in a mammary gland mouse model. E4 demonstrated oestrogen-antagonistic effects in the breast in the E2 presence. Similar effects were observed in human ER + breast cancer cells: E4 reduced E2 stimulatory effects, when co-administered both *in vitro* and *in vivo* [79,80]. In a rat model, E4 dose-dependently prevented breast tumour development and promoted regression of existing tumours, while E2 and EE stimulated mammary tumour formation [81]. In women with ER + early breast cancer who received 20 mg E4 for 14 days before surgery, apoptotic cells in breast tumour tissue were more numerous compared with placebo-treated women [82]. Moreover, in a recent phase Ib/IIa, dose-escalation study, E4 at high daily doses (20, 40, and 60 mg) was well tolerated and demonstrated anti-tumour effects in 5/9 women with progressive, advanced breast cancer treated for 12 weeks [83].

E4 has no or minimal impact on the liver by acting on ERα only. E4 exerts minimal effects on SHBG, lipids, lipoproteins, angiotensinogen, coagulation and fibrinolytic factors and carbohydrate parameters, thus demonstrating a neutral metabolic profile [84–87].

Thus, E4 seems to represent another valid option for COCs, with many potential advantages related to its dual effect on ERs and its pharmacokinetics properties.

Estetrol in oral contraception: the estetrol/drospirenone pill

In clinical practice, 15 mg E4 associated with 3 mg DRSP (an antiandrogenic progestin) in a 24/4 regimen COC has been recently approved in different Countries, including the United States (US), Canada, the European Union (EU), Russia and Australia [61,62,66].

E4/DRSP demonstrated a high and adequate contraceptive efficacy, similar to other DRSP-containing COCs [62,66].

Based on phase III studies, E4/DRSP is expected to have a good tolerability profile. The following were reported as severe treatment-related adverse events (AEs): dysmenorrhoea (0.26%), headache (0.23%), mood disturbance (0.23%), breast pain or tenderness (0.09%), bleeding complaints (0.12%), increased weight (0.06%) [88]. Discontinuation due to treatment-related AEs was low (8.0%), most commonly consisting of bleeding complaints (2.8%) and mood disturbance (1.1%) [88].

Metabolism, haemostasis and cardiovascular risk

In a dose-finding phase II study, E4-containing COCs exerted lower effects on HDL, LDL, triglycerides and SHBG compared with 20 µg EE/DRSP [85]. In another phase II study, E4/DRSP was reported to have no effect on carbohydrate metabolism and minimal impact on lipid parameters. The largest effect was observed for triglycerides (+24.0%), which nonetheless was lower as compared with EE/LNG (+28.0%) and EE/DRSP (+65.5%). Moreover, E4/DRSP increased SHBG and angiotensinogen levels, even if at a lower extent compared with EE-containing COCs. Taken together, these data suggest that E4/DRSP exerts a low oestrogenic effect on the liver, despite the antiandrogenic properties of the progestin [86].

This was further confirmed by a randomised trial comparing the haemostatic effects of E4/DRSP with EE/DRSP and EE/LNG. E4/DRSP had significantly less impact on SHBG production (+55%) and increase of APC resistance (+30%) vs. EE/DRSP (+251% and +219%, respectively) and EE/LNG (+74% and +165%, respectively), as well as on prothrombin fragment 1 + 2 levels. Changes in other haemostasis parameters after E4/DRSP treatment were smaller or similar to those observed for EE/LNG [84].

Furthermore, E4/DRSP was shown to have minimal impact on thrombin generation, as opposed to EE/DRSP and EE/LNG, which induce a shift towards a prothrombotic state by increasing the production of procoagulant factors and reducing the synthesis of anticoagulant ones [87]. Thus, to date, E4/DRSP has demonstrated a more neutral profile on haemostasis parameters, compared with EE-containing COCs [62,67].

In a pooled analysis of phase III trials, including over 3,417 participants, only one VTE event was reported [88]. Overall, these data, although quite favourable, are not sufficient to draw any conclusion about the VTE risk associated with E4/DRSP vs. other COCs. At present, studies focusing on clinical endpoints for VTE and cardiovascular risks, as well as CNS and bone density and metabolism, are still missing, and larger post-authorization safety study/ies (PASS) are needed to evaluate the impact of E4/DRSP use on VTE risk vs. other COCs [62,67,87], and understand the full benefits of E4-COC.

Cycle control

An overview of the effects exerted on cycle control by E4/DRSP and COCs containing EE and natural oestrogens is provided in Table 2. Due to the lack of direct comparative phase III trials only indirect comparisons are possible.

A dose-finding phase II trial showed that frequencies of unscheduled bleeding/spotting and absence of scheduled bleeding were lower in users of 15 mg E4/DRSP (33.8% and 3.5%, respectively) vs. E2V/DNG (47.8% and 27.1%, respectively) after six treatment cycles [89].

In the two comparable pivotal phase III clinical studies, stable regular bleeding was reported in 91.9–94.4% (EU/Russia trial) [90] and more than 83% (US/Canada trial) [91] of participants. The incidence of irregular bleeding (mostly spotting-only episodes) decreased from 19.2% in cycle 2 to 12.8% in cycle 11 in the EU/Russia trial [90], and from 21.8% in cycle 2 to 15–20% from cycle 5 onwards in the US/Canada study [91].

Moreover, the absence of scheduled bleeding with E4/DRSP (5.6–8.1% in the EU/Russia study, and 13.1–18% in the US/Canada study) seems comparable to EE/DRSP and lower than E2 formulations (about 20–23% for E2V/DNG and 18–31% for E2/NOMAC, respectively) [27,62]. Besides, irregular bleeding appears to occur at a slightly lower rate with E4/DRSP vs. E2V/DNG and E2/NOMAC (Table 2) [27]. Notably, the incidences of scheduled bleeding and unscheduled bleeding for DRSP-only pill were reported to range from 46.3% to 26.4% and 54.4% to 41.6%, respectively, over 12 cycles [27].

Table 3. Pharmacological properties of ethinylestradiol (EE)-, oestradiol/oestradiol valerate (E2/E2V)- and estetrol (E4)-containing COCs with insights for tailoring prescription to women's needs.

	Ethinylestradiol (EE)	Oestradiol (E2, E2V*)	Estetrol (E4)	Considerations for a tailor-made choice of COC
Effect on SHBG	↑↑ [10,26]	↑ [26,43,44]	↑ [64,84–86]	EE may be a better option in case of hyperandrogenism
Effects on metabolism and coagulation	↑↑ [10,20,26]	↑ [26,43–45]	↑ [62,67,84–87	E2, E2V and E4 may be a better option in terms of favourable metabolic and coagulation profile
Effect on endometrium (cycle control)	+ Stabilisation [27]	- Stabilisation [27,31,51–53]	+ Stabilisation [27,62,89–91]	EE (30–35 µg oral, 15 µg vaginal) and E4 may be a better option in terms of regular bleeding
Other oestrogenic effects (e.g., breast tenderness, water retention)	↑↑ [10,26]	↑ [10,26]	↑ [59,60,88]	E2, E2V and E4 may be a better option in cases of hyperestrogenism symptoms with EE-COC use or water retention and bloating in spontaneous menstrual cycle

*E2V is identical to E2 as regards pharmacodynamics and clinical effects as it is rapidly metabolised to E2 after oral administration [38].
SHBG: sex hormone binding globulin.

Overall, E4/DRSP COC is deemed effective at preventing unintended pregnancies with a satisfactory bleeding pattern and cycle control.

Selection of COC in clinical practice

The recent rapid growth in the range of available COCs offers a wider choice to HCPs and women, but also increases the complexity of such choice. The ideal pill for all women does not exist. HCPs should be familiar with the efficacy, safety and non-contraceptive benefits profiles of different contraceptive methods. HCPs should also be able to support women in making informed decision, based on their preferences and reproductive goals. A tailored choice must be recommended. In general, the selection of the most appropriate COC formulation should be based on its capability to provide an effective contraception, along with good cycle control, safety, and tolerability profile. Notably, a decision based on cycle control alone sometimes may be not recommended, as differences in unscheduled bleeding and discontinuation rates reported in most trials were not always statistically different and occasionally cannot be easily interpreted. Moreover, all above aspects should be paired with patient's characteristics, health conditions, needs and preferences. Physicians should also consider the possible additional non-contraceptive benefits offered by the pill and, finally, its costs [92].

Many women may value other COC features, such as a regular and predictable bleeding profile or a particular non-contraceptive effect. Consideration of the potential user's preferences can have a positive impact on contraceptive compliance.

Today, COCs containing different oestrogens are available. The question is: which oestrogen to choose? The main pharmacological properties of EE-, E2-/E2V- and E4-containing COCs described in this review are summarised in Table 3 with final considerations for a patient-tailored prescription, bearing in mind that all the above mentioned COCs have an adequate contraceptive efficacy.

Considering the oestrogenic effects on metabolism and haemostasis, E2, E2V and E4 have a minimal impact on lipid and carbohydrate metabolism, liver and haemostasis, including SHBG increase, in comparison with EE [67]. Therefore, when metabolism and haemostasis are of concern, as in case of smoking, obesity, or women over 40 years, E2-/E2V- and E4-containing COCs may be a better choice. However, at present, no clinical data are available regarding VTE incidence of the E4-containing pill vs. other COCs. The use of natural oestrogens may also be recommended in women referring symptoms of hyperestrogenism with EE formulations use or, in general, suffering from water retention and bloating in spontaneous menstrual cycle.

Conversely, considering that the oestrogen-mediated increase of SHBG reduces free testosterone and improves androgen-sensitive conditions, such as acne and hirsutism [93], EE-containing COCs may be more indicated in women with signs of hyperandrogenism.

As regards cycle control, despite the difficulty to compare data from different studies, pills containing natural oestrogens seem to exert a less stabilising oestrogenic effect on the endometrium compared with COCs with EE [27,61]. Thus, a combined contraceptive containing 30–35 µg EE (oral) or 15 µg EE (vaginal) may be the most appropriate choice to ensure regular bleeding and cycle stability. The use of the E4-COC may also be appropriate because of the high percentage of scheduled bleedings. Nonetheless, women should be informed that all COCs may induce unscheduled bleedings and can reduce the amount of blood loss, as well as other factors may increase the likelihood of bleeding irregularities. Of note, E2V/DNG is currently the only COC indicated for heavy menstrual bleeding (blood loss of at least 80 mL per menstrual cycle) treatment [94].

The effects of hormones on the mammary gland are of concern for both women and HCPs. As regards oestrogens, both genomic and non-genomic activation of nuclear and membrane ERα play pivotal roles and act in concert to promote breast cell proliferation and cancer growth. Given its peculiar mode of action on ERs and differential effects on the breast [67], E4 is associated *in vitro* with a different effect on breast normal and cancer cell cultures compared with other oestrogens. The lower stimulation of breast tissue with E4 could be of interest. However, as the augmented risk of breast cancer associated with COC use mainly depends on the progestin component, and no comparative clinical data on breast cancer risk are available for the E4/DRSP pill, no speculations can be made on E4/DRSP being associated with a different risk of breast cancer compared with other COCs.

Conclusions

HCPs should be familiar with the safety and efficacy profiles of each contraceptive method. Nowadays, besides numerous progestins with different pharmacological profiles, HCPs face the choice between different types of oestrogens.

Natural oestrogens appear to overcome the unwanted metabolic effects exerted by EE. E4 seems to offer metabolic advantages similar to E2 and E2V, while providing a better cycle control, although we are still awaiting studies on relevant clinical endpoints.

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Franca Fruzzetti has served as speaker and advisory board member for Theramex, Gedeon-Richeter, Bayer, Organon, Exeltis, Italfarmaco. Tiziana Fidecicchi has no conflict of interest to declare. Marco Gambacciani has served as speaker and advisory board member for Theramex, Gedeon-Richter, Fotona, Organon.

Ethics statement

The authors report that ethics approval was not required for this narrative review.

Data availability statement

Data sharing is not applicable to this article as no new data were created or analysed in this review.

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