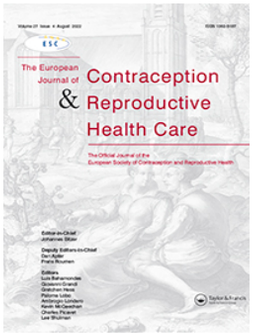

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REVIEW

A novel estetrol-containing combined oral contraceptive: European expert panel review

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ABSTRACT

Purpose: Despite considerable advances in recently developed combined oral contraceptives (COCs), resulting in lower rates of adverse events while maintaining contraceptive efficacy, there is interest in further innovation.

Materials and Methods: Estetrol (E4), a native oestrogen, and progestin drospirenone (DRSP) were combined in a new COC. A European expert panel reviewed the pharmacology, efficacy, and safety and tolerability of this combination. Their findings are presented as a narrative review.

Results: E4 15 mg/DRSP 3 mg in a 24/4 regimen provided effective contraception with good cycle control, characterised by a predictable regular bleeding pattern and minimal unscheduled bleeding, together with a good safety profile. The combination was associated with high user satisfaction, well-being, and minimal changes in body weight. The effects on endocrine and metabolic parameters were limited, and the combination was found to have a limited impact on liver function and lipid and carbohydrate metabolism. Moreover, its effect on several haemostatic parameters was lower than that of comparators containing ethinyl oestradiol (EE) 20 μg/DRSP 3 mg and EE 30 μg/levonorgestrel 150 μg.

Conclusion: E4 15 mg/DRSP 3 mg provides safe and effective contraception, with high user satisfaction and predictable bleeding. Further research will evaluate the long-term safety of the COC.

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Estetrol; drospirenone; combined oral contraceptive; contraceptive efficacy; bleeding pattern; safety profile; satisfaction

Introduction

Combined oral contraceptives (COCs) have been used by women worldwide for more than 60 years; many advances have been made during this time, resulting in fewer adverse events while maintaining contraceptive efficacy [1,2]. Important changes include reductions in oestrogen and progestin doses, replacement with new oestrogens, use of more selective progestins, and adjustment of dosing regimens [1]. Despite these advances, there are still issues associated with the use of COCs, including an increased risk of rare but serious health events, such as venous thromboembolism (VTE) and breast cancer [2], and adverse events that negatively impact women's quality of life, such as headache, mood changes, and unscheduled bleeding, have been reported [2]. However, regulatory authorities such as the European Medicines Agency have concluded that for most women the benefits of COCs continue to outweigh the risks [3], and there is interest in the development of new COCs [1], that might offer satisfactory contraceptive efficacy, together with improved tolerability, good cycle control, and fewer/less serious adverse events. Released in 2009 and in 2011, combinations of oestradiol valerate plus dienogest (E2V/DNG) and oestradiol plus nomegestrol acetate (E2/NOMAC) represent a new class of COCs, since they contain natural oestrogens instead of ethinylestradiol (EE) [4,5], showing favourable results on haemostatic markers [6] and incidence of VTE [7].

This narrative review summarises the discussions amongst international experts from all over Europe in a meeting held in December 2020, on the development of a new COC composed of estetrol (E4), an oestrogen produced exclusively by the foetal liver that is synthetised from a plant source, and the progestin drospirenone (DRSP). The present paper is based on literature search and the knowledge and experience of the authors.

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Estetrol: the first native estrogen with selective tissue activity (NEST)

E4 is a native oestrogen produced during human pregnancy [8] which was discovered in 1965 by Diczfalusy and colleagues at the Karolinska Institute in Stockholm, Sweden [9]. E4 (Figure 1(b)) is primarily present in pregnant humans [10]. It is synthetised by the human foetal liver and crosses the placenta and is detectable in maternal blood and urine from the ninth week of gestation [9,10]. E4 displays a unique mode of action that is distinct from that of other oestrogens. E4 displays a highly selective binding to the human oestrogen receptors (ER) α and β, it has a five times higher affinity for ERα compared to ERβ and its receptor affinity is about 6% compared to oestradiol (E2) [11]. As illustrated in Figure 2, E4 exhibits differential activity on the nuclear and membrane ERα, that is, activation of nuclear ERα and inhibition of membrane ERα, which leads to tissue-specific actions including the breast, and it is therefore termed the first native oestrogen with selective tissue activity (NEST) [10]. As an agonist of nuclear ERα, E4 has been shown *in vitro* and *in vivo* to have potent oestrogenic activity on the vaginal epithelium, endometrium, bone, brain, and blood vessels, where it has beneficial effects [10,12–16]. In a rat osteoporosis model E4 has been shown to have beneficial effect on bone mineral density (BMD), the mineralisation of vertebral bodies from L3 to L5, strength against biomechanical damages, and serum osteocalcin level [15]. In ovarectomized rats treated with E4, the expression of allopregnanolone and β-endorphine increased, and E4 induced changes in certain cerebral areas [17,18]. Following chronic treatment, mice exhibited a prolonged tail-bleeding time and were protected from arterial and venous thrombosis *in vivo*. In addition, E4 treatment decreased *ex vivo* thrombus growth on collagen under arterial flow conditions. The venous and arterial anti-thrombotic properties of E4 is mediated by the ERα present in the haematopoitic cells and was verified in various mouse models [19]. In a phase 1 study in healthy postmenopausal women, E4 improved vaginal cytology, with a clear shift from parabasal to superficial vaginal cells, and decreased the number of hot flushes and sweating [16]. Furthermore, E4 has limited effects on the liver, showing limited impact on liver metabolism and on haemostasis, coagulation, and fibrinolysis parameters [10,13,20–22] (see below in E4 in association with DRSP: Safety profile section). The mode of action of E4 is distinct from that of selective oestrogen receptor modulators (SERMs) [10,12–14,23], and it has been proposed that its features could suggest a future role as a NEST [24], with less adverse effects than tamoxifen (hot flushes, nausea, hypertension, thromboembolic events) [24–28].

The tissue-specific properties of E4 are also demonstrated by its limited impact on the proliferation of normal and malignant breast tissues, which has been observed in several models including cell cultures [29–31], animal models of breast cancer [29,32], and patient-derived xenograft mouse models [33], as well as in human patients with end-stage breast cancer [25]. Under these conditions, E4 administered at a therapeutic dose does not seem to enhance tumour growth or metastatic dissemination [25,29–33]. Moreover, a phase IB/IIA clinical study in heavily pretreated patients with progressive, anti-oestrogen resistant advanced breast cancer showed that doses of E4 of 20–60 mg appeared to be safe and were well tolerated, without dose-limiting toxicity; anti-tumour effects were seen in five of nine patients who completed 12 weeks of E4 treatment [25]. In a hormone-dependent breast tumour patient-derived xenograft mouse model, a therapeutic dose (0.3 mg/kg/day) of E4 did not increase tumour growth, but a 10-fold higher dose (3 mg/kg/day) exerted adverse effects similar to that of E2 [33]. E4 may have a lower impact than E2 on risk of breast cancer [23,34]. When investigated in an *in vitro* model of isolated human breast epithelial cells and an *in vivo* model of mouse mammary gland, E4 was found to stimulate breast proliferation with 100-fold weaker efficacy in comparison to E2 [29]. In addition, when co-incubated with E2, E4 was able to partially antagonise the E2-induced proliferation of human breast epithelium cells and mouse mammary gland growth [29]. At present it is not possible to extrapolate these preclinical findings to assess the clinical risk of breast cancer in women using an E4-containing COC [23]. Conflicting data are reported for the risk of breast cancer in women using contemporary hormonal contraception, and even a 20% increase in relative risk, as reported by Mørch and colleagues would translate as approximately 1 additional breast cancer for every 7,690 women using hormonal contraception for one year [35].

The oral bioavailability of E4 is approximately 70% [15]. In addition, no detectable binding to the human sex hormone-binding globulin (SHBG) steroid-binding sites could be shown, and only the non-protein bound ('free') steroids are supposed to have access to the target tissues [36]. After uptake, E4 undergoes extensive phase 2 metabolism to form inactive glucuronide and sulphate conjugates [37]. As a result, E4 is an end-stage product of metabolism which is not converted back into active metabolites and does not produce potentially carcinogenic metabolites [37–39]. As E4 is not further metabolised in the body, no reduced effects from weakly active metabolites can be expected, additionally unlike E2, E4 is not converted into hydroxylated metabolites, precursors of quinone oestrogens that can react and damage the DNA, which has been linked to breast cancer development [28].

The pharmacokinetic parameters of E4 were further evaluated in the first-in-human study, and E4 was found to show high oral bioavailability, slow elimination, and a long half-life of approximately 24 h, indicating that it was likely to be suitable for oral once-daily administration [28,40].

Unlike other oestrogens, cytochrome P450 (CYP450) enzymes do not play a major role in the metabolism of E4, and E4 shows minimal impact on the major CYP450 enzymes [37]. Therefore, E4 might have less potential for drug-drug interactions than other oestrogens.

Drospirenone: a progestin with a specific pharmacodynamic profile

In addition to its progestin activity, DRSP (Figure 1(d)) displays a mixture of anti-mineralocorticoid, anti-androgenic, and anti-oestrogenic effects [41,42]. The anti-mineralocorticoid effect of DRSP may help to alleviate water retention, and its anti-androgenic effect may reduce the risk of side effects that are typically related to androgenic activity [43]. Many progestins are derived from 19-nor-testosterone, and commonly cited side effects of COCs, such as acne, hirsutism,

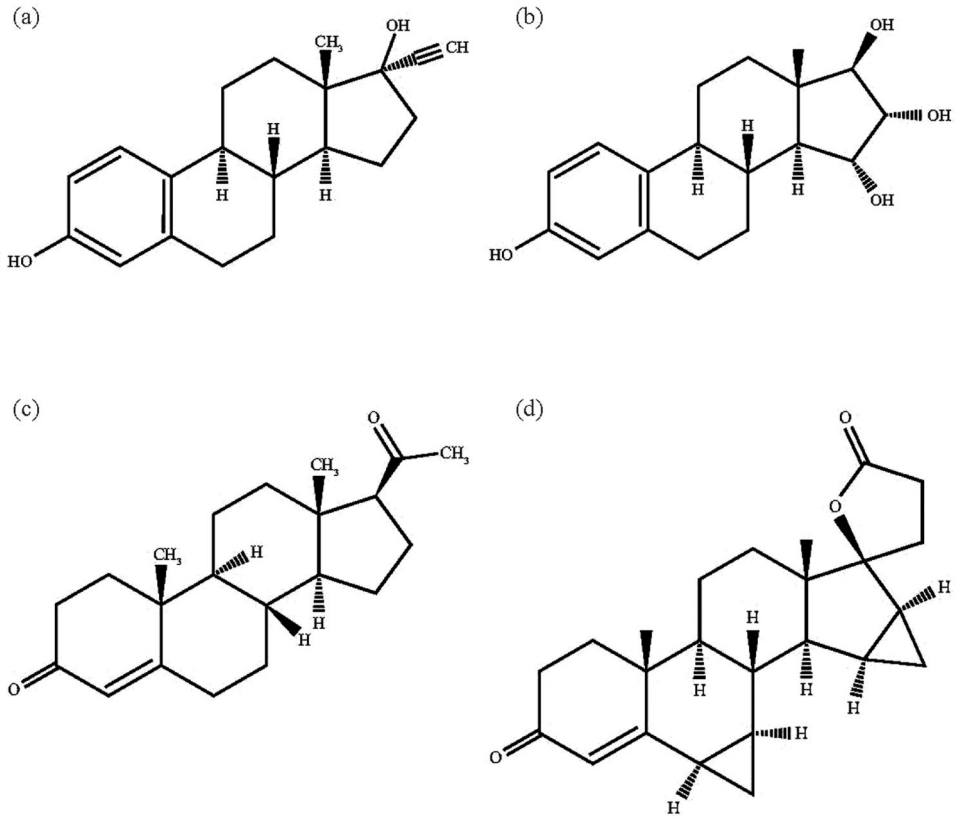

Figure 1. Chemical structures of (a) ethinyl oestradiol, (b) estetrol, (c) progesterone, and (d) drospirenone.

oily hair, lipid changes, and weight gain, are likely related to the androgenic properties or glucocorticoid effects of progestins derived from pregn-4-en-3,20-dion [43]. The overall effect of a COC depends on the type of progestin used, as well as the dose and type of oestrogen [44].

DRSP (Figure 1(d)) is a spironolactone analogue with a pharmacodynamic profile similar to that of endogenous progesterone (Figure 1(c)) [41,43,45]. DRSP has a long terminal half-life of approximately 32 h and bioavailability of approximately 76% [43]. From its pharmacological profile, it seems that DRSP promisingly compares with other progestins, including favourable weight control (due to anti-mineralocorticoid and anti-androgenic activity), mostly neutral impact on blood pressure [45], and improvement of seborrhoea and acne (due to anti-androgenic activity) [41,43]. In addition, a DRSP-only pill has been shown to have no association with any meaningful changes in haemostasis parameters [46], and no case of VTE has been documented in clinical trials of a contraceptive pill containing 4 mg DRSP alone in a 24/4 regime [47].

DRSP is metabolised through the CYP3A4 enzyme [48]. A moderate pharmacokinetic interaction has been observed between DRSP (co-administered with EE or E2) and the CYP3A4 inhibitor ketoconazole, which resulted in increased DRSP exposure but was not associated with any relevant changes of medical concern [48]. Based on *in vitro* inhibition studies and *in vivo* interaction studies in female volunteers using omeprazole, simvastatin and midazolam as marker substrate, an interaction of drospirenone at doses of 3 mg with the metabolism of other active substances is unlikely [40].

E4 in association with DRSP: clinical efficacy, tolerability and bleeding profile

Phase 2 clinical studies

Phase 2 clinical studies evaluated combination treatments containing different doses of E4 (5 mg, 10 mg, 15 mg, 20 mg) with either 3 mg DRSP or 150 μg LNG [20–22,49–53], and a combination of 15 mg of E4 with 3 mg DRSP (E4 15 mg/DRSP 3 mg) administered in a 24-day active/4-day placebo regimen for 3–6 consecutive cycles demonstrated adequate ovulation inhibition and ovarian function suppression, with no identified safety concerns and limited impact on triglycerides and haemostasis parameters [20,22,50,53]. In the second study that compared E4 15 mg/DRSP 3 mg with a marketed COC containing ethinyl oestradiol (EE; Figure 1(a)) 20 μg/DRSP 3 mg for 3 consecutive cycles, none of the participants who received E4/DRSP ovulated and of the participants who received EE/DRSP one ovulated once and one ovulated twice [53].

The bleeding pattern and menstrual cycle control of COCs containing E4 (15 mg or 20 mg) combined with DRSP (3 mg) or LNG (150 μg), administered in a 24/4-day regimen, were assessed in an open-label phase 2 dose-finding study (FIESTA; NCT01221831) [50,51]. In addition, a reference treatment arm of a recently marketed dosing regimen of a natural oestrogen, oestradiol valerate (E2V), combined with the progestin dienogest (Qlaira®, Bayer Healthcare, Germany) was also included [50,51]. By cycle 6, of the treatment modalities studied, the lowest rates of unscheduled bleeding and/or spotting (33.8% vs 47.8% in the E2V/DNG group) and absence of withdrawal bleeding (3.5% vs 27.1%

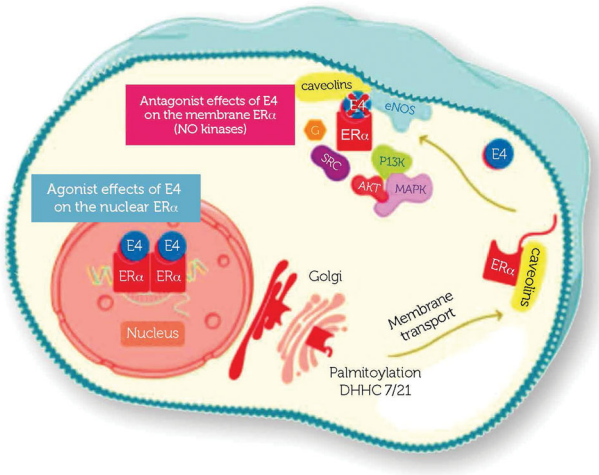

Figure 2. Estetrol (E4) has a distinctive profile of oestrogen receptor alpha (ERα) activation. E4 activates the nuclear ERα and inhibits/antagonises the activity of the membrane ERα. AKT: protein kinase B; eNOS: endothelial nitric oxide synthase; G: G protein; MAPK: mitogen-activated protein kinase; NO: nitric oxide; P13K: phosphoinisitide 3-kinase; SRC: steroid receptor coactivator.

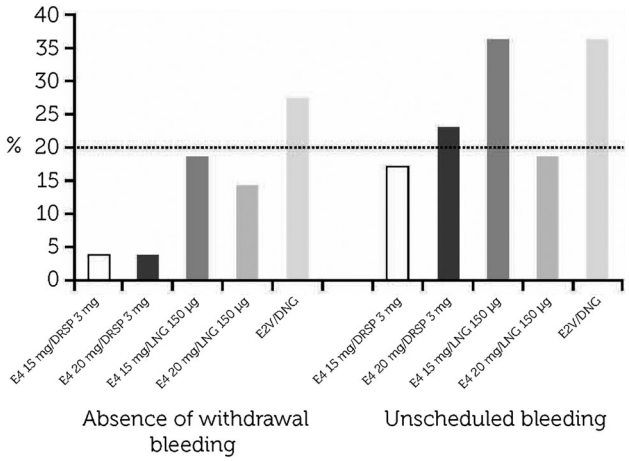

Figure 3. Frequency (%) of women with absence of withdrawal bleeding/spotting and with unscheduled bleeding in each treatment group (per protocol population) in cycle 6 of a phase 2 dose-finding study (FIESTA) [50]. Absence of withdrawal bleeding ≤20% and/or ≤20% unscheduled intracyclic bleeding after 6 treatment cycles was set as a limit (broken line). DNG: dienogest; DRSP: drospirenone; E4: estetrol; E2V: oestradiol valerate; LNG: levonorgestrel. Published with permission from Apter et al. [50].

in the E2V/DNG group) were observed with E4 15 mg/DRSP 3 mg (Figure 3) [50].

In the phase 2 FIESTA study, the E4 15 mg/DRSP 3 mg combination was associated with the highest proportion of treatment satisfaction (73.1%) and E4 20 mg/LNG 150 µg with the lowest (50.6%) [51]. The proportion of women willing to continue with the assigned treatment was also highest in the E4 15 mg/DRSP 3 mg group (82.1%) and the lowest in the E4 20 mg/LNG 150 µg group (58.3%) [51]. E4 15 mg/DRSP 3 mg was associated high user acceptability and satisfaction and favourable body-weight control [51]. The proportion of women who experienced weight loss of 2 kg or more during cycles 3 and 6 was highest in the E4 15 mg/DRSP 3 mg group (30.7% and 36.7%, respectively) and the lowest in the E4 15 mg/LNG 150 µg group (7.7% and 13.0%, respectively) [51]. This may contribute to improved treatment compliance because weight gain is a common reason for discontinuation of COCs in women who desire fertility control [54,55].

From the findings of various phase 2 studies, it was concluded that the E4 15 mg/DRSP 3 mg combination resulted in the most promising bleeding pattern, cycle control, body weight control, user acceptability and satisfaction, and this combination was selected for further development [23,28,50,51].

Phase 3 clinical studies

The E4 15 mg/DRSP 3 mg combination was evaluated in two phase 3 multicentre open-label studies (E4FREEDOM **F**emale **R**esponse Concerning **E**fficacy and Safety of **E**stetrol/**D**rospirenone as **O**ral Contraceptive in a **M**ulticentric Study), which were conducted in Europe/Russia (EU/RUS study; ClinicalTrials.gov Identifier: NCT02817828) and the United States/Canada (US/CAN study; ClinicalTrials.gov Identifier: NCT02817841) [56,57].

The studies enrolled women aged 18 (EU/RUS study) or 16 years (US/CAN study) to 50 years, and the primary objective was to evaluate the contraceptive efficacy of E4 15 mg/DRSP 3 mg, administered in a 24-day active/4-day placebo regimen for up to 13 cycles, in subjects aged 18–35 years (EU/RUS study) or 16–35 years (US/CAN study) by calculating the Pearl Index as the primary efficacy endpoint [56,57]. In both studies, E4 15 mg/DRSP 3 mg use resulted in high contraceptive efficacy in these patient groups (Table 1): the calculated Pearl Index for at-risk cycles (defined according to the US Food and Drug Administration as no other methods of birth control [including condoms] were used by the subject as confirmed in the subject diary, and the subject confirmed that sexual intercourse occurred during the cycle in the subject diary) was 0.47 (95% confidence interval [CI] 0.15–1.11) in the EU/RUS study (5 on-treatment pregnancies) and 2.65 (95% CI 1.73–3.88) in the US/CAN study (26 on-treatment pregnancies) [56,57]. According to the European Medicines Agency definition (no other methods of birth control [including condoms] used), the calculated Pearl Indices were 0.44 (95% CI0.14–1.03) in the EU/RUS study and 2.42 (1.58–3.54) in US/CAN study [56,58].

Bleeding patterns and safety parameters were assessed in the study population aged 18–50 years in the EU/RUS study and 16–50 years in the US/CAN study. The numbers of women included in the bleeding analysis in the EU/RUS study ranged from 1,507 during cycle 1 to 1,183 in cycle 12 (Supplementary material of the primary publication [56]), and the corresponding values in the US/CAN study were 1,758 and 1,006 women [57]. E4 15 mg/DRSP 3 mg use resulted in a predictable vaginal bleeding pattern, with most women having their scheduled bleeding in each cycle without experiencing unscheduled bleeding requiring the use of sanitary protection [56,57]. In the EU/RUS study, unscheduled bleeding decreased from 23.5% in cycle 1 to <16% from cycle 6 onwards [56]; in the US/CAN study, it decreased from 30.3% in cycle 1 to 21.3%–22.1% in cycles 2–4 and remained stable thereafter (15.5%–19.2%) [57].

In an open-label, randomised, comparative study with EE 20 µg/DSG 150 µg carried out in four European countries ($n = 230$), the proportion of unscheduled bleeding/spotting during cycles 2–6 ranged between 8.8% and 17.3% [59]. In a pooled analysis of two clinical trials of E2/NOMAC compared to EE 30 µg/DRSP 3 mg, healthy women were taking

Table 1. Efficacy of E4 15 mg/DRSP 3 mg: results from two phase 3 clinical studies [56–58].

	EU/RUS study [56]		US/CAN study [57]
Age range	18–35 years	18–50 years	16–35 years
At-risk cycles[a]			
Subjects (*n*)	1,313	1,510	1,524
Cycles (*n*)	13,692	15,849	12,763
Primary endpoint: PI, according to FDA definition			
On-treatment pregnancies (*n*)	5	5	26
PI (95% CI)	0.47 (0.15; 1.11)	0.41 (0.13; 0.96)	2.65 (1.73; 3.88)
Modified at-risk PI, according to EMA definition	0.44 (0.14–1.03)	0.38 (0.12; 0.89)	2.42 (1.58, 3.54)[58]
Secondary endpoint: Method failure PI[b]			
On-treatment pregnancies (*n*)	3	3	14
PI (95% CI)	0.29 (0.06; 0.83)	0.25 (0.05; 0.72)	1.43 (0.78; 2.39)
Cumulative pregnancy rates at cycle 13 (95% CI)[c]			
On-treatment pregnancies	0.45% (0.19; 1.09)	0.39% (0.16; 0.94)	2.06% (1.40; 3.04)
Method failure pregnancies	0.28% (0.09; 0.86)	0.24% (0.08; 0.74)	1.18% (0.69; 2.01)

CI: confidence interval; COCs: combined oral contraceptives; DSRP: drospirenone; E4: estetrol; EMA: European Medicines Agency; FDA: Food and Drug Administration; PI: Pearl Index (pregnancies/100 women-years).
[a]At-risk cycle: no use of other methods of birth control (including condoms and emergency contraception), and intercourse reported, a pregnancy was considered 'on-treatment' when the estimated date of conception was ≤7 days after the last intake of study treatment; [b]Method failure: excluding pregnancies due to user failure, i.e., not taking study treatment as per protocol during the cycle of conception, or use of co-medication interacting with COCs; [c]Kaplan-Meir estimates.

EE/DRSP in a 21/7-day regimen ($n = 938$) The incidence of unscheduled bleeding/spotting decreased over time from 17.4% in cycle 2 up to 12.8% in cycle 6 and 10.9% in Cycle 12 [60]. In this same analysis, the incidence of unscheduled bleeding/spotting with E2/NOMAC ($n = 2,835$) decreased over time from 23.2% in cycle 2 up to 19.1% in cycle 6 and 15.4% in cycle 12. Healthy women aged between 18 and 50 years ($n = 2,266$) received E2V/DNG, a multiphasic pill, for 7 to 28 cycles in three pivotal trials, one conducted in North America and two in Europe. In the first 13 cycles of treatment, the proportion of women that experienced unscheduled bleeding/spotting between cycles 2 and 13 of treatment ranged between 13% and 23% [61]. Though due to the lack of direct comparative phase 3 trials only indirect comparisons are possible, pooled bleeding analyses of phase 3 trials conducted with other COCs demonstrate the frequency of absence of scheduled bleeding/spotting over cycles of between 8 and 12% with an EE 20 μg/DRSP 3 mg, 24/4 regimen [62], 18–32% with an E2 1.5 mg/NOMAC 2.5 mg, 24/4 regimen [60], and 19–24% with an E2V 1/2/3 mg/DNG 2/3 mg, 26/2 regimen [61]. The absence of scheduled bleeding/spotting with E4/DRSP (5.6–8.1% in the EU/RUS study, and 13.1–18%in the US/CAN study) appears comparable to EE/DRSP and occurs less frequently compared to E2 formulations.

E4 in association with DRSP: Safety profile

Overall, treatment with E4 15 mg/DRSP 3 mg was well tolerated, as indicated by the low rates of treatment-related adverse events. In the phase 3 studies, approximately half of the patients reported experiencing any adverse events (50.5% in the EU/RUS study and 53.8% in the US/CAN study), and approximately 29% of subjects in both studies reported experiencing adverse events that were considered by the site investigator to be treatment-related [56,57]. Treatment-related adverse events reported in at least 2% of subjects in the two phase 3 studies are summarised in Table 2 [56,57]. The most common treatment-related adverse events in both studies included metrorrhagia (bleeding between menstrual periods), acne, headache [56,57]. Discontinuation due to AEs occurred in 9.1% in the EU/RUS study [56] and in 7.1% in the US/CAN study [57]. The adverse event profile observed in these studies was consistent with the use of other COCs [63–65].

In an open-label non-comparative study of EE 20 μg/DRSP 3 mg (13 cycles in 24/4 regimen), drug-related TEAE frequency was 38.5% and the discontinuation frequency due to TEAEs was 7.5%. Five serious adverse events (SAE) in three women were reported as possibly or probably related to treatment [66]. In 3 clinical trials where EE30/DRSP was a reference COC in the clinical development program of E2/NOMAC, TEAEs frequency with was 69.0%, drug-related TEAEs frequency was 37.3% and the discontinuation frequency due to TEAEs was 10.1% with EE30/DRSP [67]. The safety of E2V/DNG as a COC was evaluated in three large multi-centre studies. Sixty-two percent of women exposed to E2V/DNG reported at least one TEAE, SAEs considered related to study medication were recorded in 0.3% of women, and 10% of women discontinued the study due to AEs [61]. In 6 clinical trials of E2/NOMAC, TEAEs frequency was 75.3%, drug-related TEAEs frequency was 49.1% and the discontinuation frequency due to TEAEs was 17.1% [67].

An increased risk of thromboembolic events is a major safety concern associated with existing COCs [44,68–70]. However, because the absolute incidence of events is low, prospective clinical trials with high number of women/exposed cycles are required to obtain reliable estimates for the thromboembolic risk associated with a particular COC – this may take up to 5–10 years [10]. However, biological variables that may reflect different pharmacological effects, possibly related to VTE risk, are investigated in the development of a new combined contraceptive product [71]. Therefore, to obtain some advanced knowledge of the likely incidence of this adverse event in women using E4/DRSP as a COC, the haemostatic effects of E4 combined with DRSP were examined [20,52,70]. In a 6-cycle randomised study, the haemostatic effects of E4 15 mg/DRSP 3 mg were compared with the effects of EE 20 μg/DRSP 3 mg and EE 30 μg/LNG 150 μg [20]. After 6 cycles, APCr was increased (relative to baseline) by 30% in the E4/DRSP group, by 165% in the EE/LNG group and by 219% in the EE/DRSP group [20]. Both EE/LNG and EE/DRSP increased prothrombin fragment 1 + 2 and EE/DRSP increased SHBG significantly more than E4/DRSP ($p < .05$),

Table 2. Treatment-related adverse events reported in at least 2% of subjects in the phase 3 studies of E4 15 mg/DRSP 3 mg use for up to 13 cycles (12 months) [56,57].

	EU/RUS study [56] ($n = 1,553$)	US/CAN study [57] ($n = 1,864$)
Any treatment-related AEs[†]	442 (28.5)	539 (28.9)
Treatment-related AEs reported by ≥2% of participants		
Metrorrhagia	77 (5.0)	82 (4.4)
Vaginal haemorrhage	67 (4.3)	NA
Acne	59 (3.8)	53 (2.8)
Headache	44 (2.8)	65 (3.5)
Breast tenderness	NA	51 (2.7)
Weight increased	NA	46 (2.5)
Breast pain	37 (2.4)	NA
Libido decreased	34 (2.2)	NA
Dysmenorrhoea	33 (2.1)	52 (2.8)
Nausea	NA	40 (2.1)

Data presented as *n* (%).
Safety population: all enrolled subjects who received at least one dose of study treatment.
AE: adverse events; DRSP: drospirenone; E4: estetrol; NA: data are not available.
[†]Relatedness established by site investigator.

and other haemostasis parameters, including anticoagulant proteins and fibrinolytic proteins, were similar or smaller for E4/DRSP than those for EE/LNG and EE/DRSP [20]. Those results confirmed previous data obtained in women receiving either E4 5 mg/DRSP 3 mg, E4 10 mg/DRSP 3 mg or EE 20 μg/DRSP 3 mg [52]. At the end of treatment cycle 3, neither of the E4/DRSP treatments had affected antithrombin, protein S activity or activated protein C resistance (APCr), and they had only a minor effect on free tissue factor pathway inhibitor (TFPI), whereas EE/DRSP had a significant effect on all four markers of coagulation inhibition, effects that would promote coagulation [52]. No cases of VTE were observed in the US/CAN phase 3 study among the 1864 users of whom 23% had a BMI > 30 kg/m^2, a risk factor for VTE [57], and in the EU/RUS phase 3 study, one case of VTE was reported among the 1553 users [56].

The effect of different COCs on haemostasis depends on the type of oestrogen and their association with progestin, and even if individual COC-induced changes in coagulation factors remain within the normal range, the synergistic effects tend to increase thrombogenicity [72]. The findings of these two studies suggest that E4/DRSP has a lower impact on the coagulation and fibrinolytic systems compared with EE/LNG or EE/DRSP, and may be less likely to cause VTE. However, this will need to be confirmed in large post-authorisation safety studies.

The difference in the coagulation parameters and the fibrinolytic systems seen with EE/DRSP and E4/DRSP also implies that the effect of COCs on haemostasis parameters is mainly mediated by the type of oestrogen [20].

A crossover study of Klipping et al. comparing E2V/DNG to EE 30 μg/LNG 150 μg showed no intra-individual change in the levels of prothrombin fragment 1 + 2, whereas a slight increase was observed with EE/LNG, but the differences between the two treatments were not statistically significant [73]. Meanwhile, there was a smaller increase in D-dimer in E2V/DNG (intraindividual relative change: 37.3%–69.3%) than in EE/LNG group (intraindividual relative change: 88.1%–99.3%) [73].

In a randomised, open-label study comparing E2V/DNG or EE/LNG [74], prothrombin fragment 1 + 2 and D-dimer levels remained essentially stable in the E2V/DNG group but increased in the EE/LNG group (by 117.3% ± 358.0% for prothrombin fragment 1 + 2 and 62.9% ± 99.5% for D-dimer). Effects of E2V/DNG in other hepatic-induced parameters (SHBG, cortisol-binding globulin [CBG]) were less pronounced than those observed with EE/LNG.

Table 3 shows the effects of natural oestrogen-containing COC on different haemostatis parameters [72].

Activated protein C resistance (APCr) is considered to be an important factor in the aetiology of VTE [70,75]. A link between acquired resistance to APC and the risk of thrombosis in women on COCs has been reported for more than two decades, and recent work undertaken to standardise the evaluation of APC resistance induced by COCs have shown the link between the relative risk of VTE with the normalised activated protein C sensitivity ratio [72,76,77], however, further studies are needed to characterise and eventually strengthen this correlation between APC resistance and VTE risk. Figure 4 shows the correlation between the normalised activated protein C sensitivity ratio (nAPCsr) and the relative risk of VTE as observed in the Cochrane meta-analysis of De Bastos et al. [78]. The low impact of E4 on nAPCsr and other haemostasis parameters is in line with the assumption that risk is driven by the presence of EE [72], and that the choice of the oestrogenic component modulates the effects of COCs in this regard [20]. The relative risk of VTE that can be retrieved from the model for EE/DNG or E2/NOMAC are very close to the adjusted relative risk observed in epidemiological studies [7,79] reinforcing the findings that E4/DRSP should be associated with a lower or similar risk of VTE compared to the reference EE/LNG.

More recently, COCs containing the natural oestrogen, oestradiol (E2), or its ester derivative oestradiol valerate (E2V), have been developed with the aim of reducing cardiovascular risk. Data are now available from large observational studies of COCs containing E2 or E2V. In the 'International Active Surveillance Study – Safety of Contraceptives: Role of Estrogens' (INAS-SCORE), a post-authorisation safety study (PASS) [7,80], the final results showed that the risk of VTE associated with use of a COC containing E2V and dienogest was significantly lower compared to all EE-COCs (hazard ratio 0.4, 95% CI 0.2–0.9), but not in comparison to EE/LNG COCs [80,81]. The authors concluded that there was no suggestion of a higher risk of VTE or ATE in users of a COC containing E2V and dienogest compared with users of other COCs [80]. Another PASS was conducted to assess cardiovascular

Table 3. Changes in haemostasis parameters according to the type of natural oestrogen-containing combined oral contraceptives.

	E2V-DNG	E2-NOMAC	E4-DRSP
Coagulation factors			
Fibrinogen	↑	=	
Prothrombin		= / ↑	↑
Factor VII	= / ↑	=	
Factor VIII	=	=	
Anticoagulant factors			
Antithrombin (antigen/activity)	=	=	=
Protein C	= / ↑	=	=
Protein S (total and free/activity)	=	= / ↑	=
Tissue factor pathyway inhibitor		= / ↓	↓
APCsr (aPTT-based)	=	=	=
APCsr (ETP-based)	= / ↑	↑	=
Fibrinolytic markers/system			
Tissue plasminogen activator (activity/antigen)			=
Plasminogen		↑	
Plasminogen activator inhibitor 1 (antigen/activity)	↓	↓	
Coagulation activation markers			
D-dimer	=	= / ↓	↓
Prothrombin fragment 1 + 2	=	=	=

Adapted with permission from Douxfils et al. [72]
aPTT: activated partial thromboplastin time; DNG: dienogest; DRSP: drospirenone; ETP: endogenous thrombin potential; E2: oestradiol; E2V: oestradiol valerate; E4: estetrol; NOMAC: nomegestrol acetate.

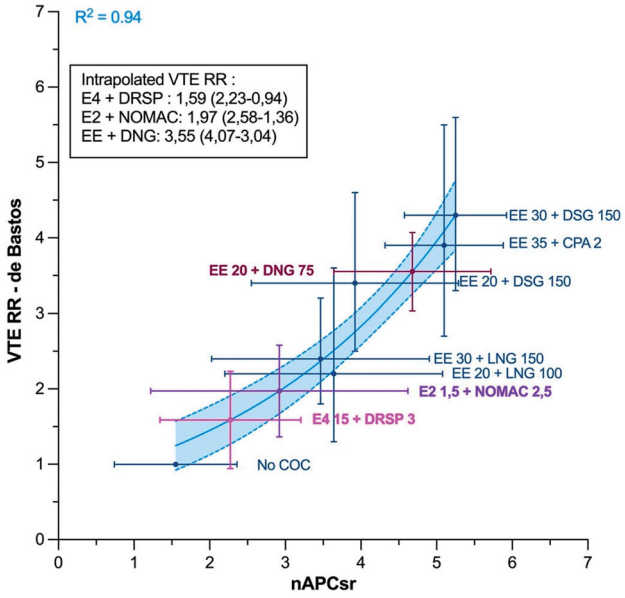

Figure 4. The nAPCsr has been computed against the relative risk of VTE as extracted from the publication of De Bastos et al. [78]. Based on this mathematical model, the relative risk of combined oral contraceptives not included in the initial meta-analysis has been intrapolated, i.e. EE/DNG, E2/NOMAC and E4/DRSP. For EE/DNG and E2/NOMAC, the intrapolated relative risk corresponds to the adjusted relative risk observe in the meta-analysis of Dinger et al. [7] and in the PRO-E2 study for E2/NOMAC [79].

and other health risks in users of E2 in association with nomegestrol acetate (NOMAC-E2) or COCs containing LNG (COC-LNG) [79]. According to the results of this study, NOMAC-E2 use was not associated with a higher risk of VTE or ATE compared with COC LNG [79]. Together, the findings of these large observational studies suggest that the risk of VTE may be lower in COCs containing E2 or E2V than in other COCs. The risk for E4 15 mg/DRSP 3 mg is unknown and needs to be obtained from post-marketing surveillance program [40].

In phase 2 trials, E4-containing COCs (5 mg or 10 mg E4/3 mg DRSP; 5 mg, 10 mg or 20 mg E4/150 mg LNG) showed limited impact on hepatic and lipid metabolism [21], and E4 15 mg/DRSP 3 mg also exhibited limited effects on endocrine and metabolic parameters, with minimal impact on lipid parameters (the effects on triglycerides were less than those seen with EE/DRSP) and no effect on carbohydrate metabolism [22].

Potential future merits of estetrol plus drospirenone in combination

Long-term safety

The overall incidence of thromboembolic events reported in phase 3 studies of E4 15 mg/DRSP 3 mg was low, and the phase 2 haemostasis data were reassuring [20,56,57]. These findings suggest that E4/DRSP may have a similar or even lesser likelihood to cause VTE than EE/LNG [20,70,77]. However, large phase 4 studies are needed to confirm the phase 3 findings that E4/DRSP use is associated with low clinical thrombosis risk [58].

E4 has limited impact on the proliferation of normal and malignant breast tissue [25,29–33] and may have lower impact than E2 on risk of breast cancer [23,33,34]. In addition, unlike some androgenic progestins, DRSP does not stimulate breast cell proliferation in animal xenograft models [82]. However, how this translates to the combined use of E4 and DRSP in long-term use in humans needs to be further investigated.

Sexual well-being

Although the use of COCs is linked to the quality of sexual life, the effect is complex: a small percentage of women experience an increase or a decrease in sexual function, while the majority remain unaffected [83]. Current COCs are thought to be able to negatively modify the sexual activity of women by increasing the androgen-binding protein and producing hypoandrogenism [84].

Some studies reported negative changes in sexual desire [85,86] or reduced vaginal lubrication [87], while others showed no detrimental effects [88,89], or found increased frequency of sexual intercourse and intensity of orgasm [90–92], improved sexual outcomes and arousal [93], improvement in oral contraception-associated female sexual dysfunction [4].

Switching to an E2V/DNG or EE/LNG contraceptive in women affected by COC associated female sexual

dysfunction (FSD) improved the symptoms of FSD [94]. In women who wanted to discontinue their contraception use due to low sexual desire, E2/NOMAC use improved sexual desire [84], while in a clinical follow-up feasibility study of women with premenstrual dysphoric disorder, arousal scores worsened with E2/NOMAC but not with EE/DRSP [95]. EE 30 μg/LNG 150 μg compared to placebo exhibited no negative effect on overall sexual function, though the domains of desire, arousal, and pleasure of the Profile of Female Sexual Function were significantly reduced [96]. In an open-label, multi-centre, dose-finding, 6-cycle study, direct comparison of 15 mg E4/DRSP and E2V/DNG showed a comparable favourable overall outcome including sexual function [51].

In a meta-analysis of 36 studies of COC users ($n = 8,422$), 85% reported an increase ($n = 1,826$) or no change ($n = 5,358$) in libido, and 15% reported a decrease ($n = 1,238$), primarily in users of COCs with a low oestrogen dose (EE <20 μg) [97]. Though in the US/CAN and EU/RUS phase 3 studies, >97% of women did not report decreased libido as an adverse event when using E4 15 mg/DRSP 3 mg [56,57], real-life experience is needed to tell whether the E4 15 mg/DRPS 3 mg combination may indeed not affect sexual well-being.

Ecotoxicology

Oestrogens in oral contraceptives are widely released into the environment, and there is growing concern about the environmental impact of endocrine disruptors [98,99]. Standard environmental tests, applied to aquatic species to examine their growth, reproduction, and life-cycle, have indicated that the predicted concentration of E4 in the aquatic environment is unlikely to have negative effects [100]. European environmental risk assessment studies with E4, including the Japanese medaka extended one generation reproduction test, indicated that the predicted environmental exposure to E4 did not affect the aquatic ecosystem [40].

However, environmental risk assessment studies have shown that the combination of ethinylestradiol and drospirenone have the potential of posing a risk to the aquatic environment [101–103].

Conclusion

In contrast to other oestrogens, E4 is an activator of the nuclear ERα, but an antagonist of the membrane ERα. Its effects on bone, vaginal epithelium, central nervous system, uterus, and – though less known – on breast holds the implication that E4 may be a useful and safe addition in hormonal therapy. An important application of E4 is its use in combined oral contraceptives [24].

E4 15 mg/DRSP 3 mg in a 24/4 regimen provides effective contraception with satisfactory cycle control, characterised by a predictable and regular bleeding pattern and minimal unscheduled bleeding, together with a good tolerability/safety profile [56,57]. The combination of an oestrogen that has selective effects on tissues and the progestin DRSP has several characteristics, including anti-mineralocorticoid and anti-androgenic activity [41,42] and a long half-life [43]. In phase 2 clinical trials, E4 15 mg combined with DRSP 3 mg demonstrated significantly lower impact than EE 20 μg/DRSP 3 mg on several haemostatic parameters and was associated with favourable effect on well-being, including minimal changes in body weight [20,51]. It also exhibited a favourable metabolic profile, with limited impact on lipid metabolism (including minimal impact on triglycerides), and glucose tolerance [22].

Ecotoxicological studies have suggested that the use of E4 in the E4/DRSP combination is unlikely to have negative effects on the environment [40].

The combination of E4 15 mg/DRSP 3 mg showed high contraceptive efficacy, a predictable bleeding pattern, low rates of treatment-related adverse events, and a favourable safety profile [56,57]. Further investigations are planned to understand the full benefits of this combination.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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