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The benefits of estetrol addition to drospirenone for contraception

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Ethinylestradiol and drospirenone combined oral contraceptive formulations have been marketed for >20 years. Drospirenone has antimineralocorticoid and anti-androgenic effects that may offer several health benefits. Recently, 2 new drospirenone-containing oral contraceptives entered the market, 1 as a progestin-only pill containing 4 mg drospirenone and the other as a combined oral contraceptive containing 15 mg estetrol and 3 mg drospirenone. Estetrol has a unique differential effect on nuclear and membrane estrogen α-receptors when compared with other estrogens, leading to low impact on the liver, breast, and hemostasis parameters and a beneficial effect on the endometrium, vagina, cardiovascular system, bone, and brain. Phase 3 clinical studies demonstrated that the Pearl Index (pregnancies per 100-woman-years) for drospirenone alone is 4.0 in the United States and 0.93 in the European Union and for the estetrol-drospirenone combination it is 2.65 and 0.44, respectively. Drospirenone alone demonstrates high rates of unscheduled bleeding and low rates of scheduled bleeding, whereas the estetrol-drospirenone combination demonstrates a predictable and regular bleeding profile for most users with a high stable rate of scheduled bleeding and a low rate of unscheduled bleeding, reported primarily as spotting only. The adverse event profiles and discontinuation rates owing to adverse events are comparable, and no clinically significant effects were observed on metabolic parameters with either product. Hemostatic assays for drospirenone do not fully evaluate all parameters although the testing that is available suggests negligible effects, whereas validated hemostatic assays demonstrate that the estetrol-drospirenone combination has limited impact on hemostasis. The introduction of 4 mg drospirenone and 15 mg estetrol with 3 mg drospirenone are valuable additions to the contraceptive market. Adding estetrol to 3 mg drospirenone provides advantages of contraceptive efficacy and a regular, predictable bleeding profile with minimal impact on hemostasis parameters.

Key words: contraception, drospirenone, E4, EE, estetrol, ethinylestradiol

Introduction

Since 1956, combined oral contraceptives (COCs) have undergone several improvements, notably dose reductions, alterations in dosing regimen, use of more selective progestins, and replacement of synthetic by natural estrogens.[1] These developments stem from the recognition that COCs need to not only prevent pregnancies, but also be safe, well tolerated, and offer noncontraceptive health benefits and therapeutic roles in gynecologic conditions.[2–4]

COCs with ethinylestradiol (EE) and drospirenone (DRSP) were first marketed in 2000. Two new DRSP-containing contraceptives have been introduced recently, a progestin-only pill (POP) containing 4 mg DRSP and a COC with 15 mg estetrol (E4) and 3 mg DRSP. E4 is a novel estrogen and this COC with E4 and DRSP represents the first COC containing E4. This Clinical Opinion reviews the properties of DRSP and E4, summarizes the 2 new DRSP-containing products, and provides insight on the advantages and disadvantages of both products.

The progestin drospirenone

DRSP is a 17-alpha-spirolactone–derived progestogen with some similarities to spironolactone and a

pharmacologic profile more closely related to endogenous progesterone than that of any other synthetic progestogen, especially in terms of its antimineralocorticoid and anti-androgenic effects.[5,6] The antimineralocorticoid effect of DRSP may compensate for the mineralocorticoid activity of estrogens that enhance the production of angiotensinogen, the substrate of renin. Estrogen activation of the renin-angiotensin-aldosterone system (RAAS), primarily EE, leads to moderate salt and water retention, which can lead to breast fullness and tenderness, abdominal bloating, extremity swelling, and blood pressure (BP) increase, causing moderate hypertension in predisposed users.[7] DRSP counteracts aldosterone, reduces fluid retention, and prevents BP increases observed with COCs containing EE and other progestins.[8,9] Its antiandrogenic effects may reduce acne, oily hair, seborrhea and lipid changes.[9] DRSP has a mostly neutral impact on body weight[10,11] and BP.[12,13] Randomized clinical trials (RCTs) evaluating the clinical impact of the antimineralocorticoid activity of the EE-DRSP combination in normotensive healthy young women (<35 years) showed clinically unimportant small decreases in body weight and BP.[14,15]

However, the clinical impact of DRSP on the RAAS may be important in patients with high normal BP or premenstrual dysphoric disorder (PMDD). Among patients with a baseline systolic BP >130 mm Hg or diastolic BP >85 mm Hg, 4 mg DRSP alone decreased values by 7 mm Hg and 5.5 mm Hg, respectively, whereas no changes occurred among normotensive women.[16] Many progestins in COCs can exacerbate PMDD symptoms.[17] In contrast, the 24/4-day formulation of 20 μg EE with 3 mg DRSP improves PMDD based on pivotal RCTs.[18] In a comparative trial with E4-levonorgestrel (LNG) combination, the E4-DRSP combination conveyed a more predictable bleeding profile, better body weight control, and user acceptability and satisfaction than the combination with LNG.[19,20]

The estrogen estetrol

E4 is produced naturally in the human fetal liver[21] and is manufactured for clinical use from commercially available estrone synthesized from plant sources.[22–24] Extensive studies indicate that in specific cell types, such as breast cancer cells and endothelial cells, E4 presents a profile of estrogen α-receptor (ERα) activation that differs from all other natural synthetic estrogens by inducing only ERα nuclear actions and preventing ERα membrane actions.[24,25] Preclinical data also suggest that E4 has a differential effect on breast epithelial cells and breast cancer cells when compared with other estrogens.[24,25] In addition, E4, compared with other estrogens, has a low estrogenic impact on the liver based on differences in sex hormone-binding globulin (SHBG) and angiotensinogen production, hemostasis parameters, and lipid profiles. These differences between E4 and all other estrogens lead to the classification as the only native estrogen with selective tissue activity (NEST).[24]

With its 4 hydroxyl groups, E4 has a distinct pharmacokinetic and metabolic profile when compared with other estrogens. After oral administration, E4 is rapidly absorbed with high bioavailability (70%) and a long half-life (>24 h),[26,27] which differs from EE[28–30] and estradiol (E2) (Table 1).[29,31] Estetrol metabolism via UDP-glucuronosyltransferases and sulfotransferases lead to inactive glucuronide and sulfate conjugates that are excreted in urine. In contrast with EE and E2, E4 is not metabolized by cytochrome P450 enzymes (CYP450) and shows minimal impact on the major CYP450 enzymes.[32–35] Unlike E2, E4 is not converted into estrone (E1) or hydroxylated metabolites that are known precursors of quinone estrogens that can damage DNA and that are linked to breast cancer development.[36,37] E4 increases SHBG production by hepatic cells much less than other estrogens and minimally binds to SHBG.[35]

Overall, unlike other estrogens, the unique metabolism of E4 leads to a low impact on the liver and breast and on hemostasis parameters[38,39] while maintaining beneficial effects on the endometrium, vagina, cardiovascular system, bone, and brain.[24]

Summary of the 2 new contraceptive products

Drospirenone-alone oral contraceptive

In 2019, 4 mg DRSP (SLYND, SLINDA) was approved for contraceptive use in a cyclic regimen (24 days hormone and 4 days placebo). This regimen was designed with the hope of improving the bleeding profile in comparison with that seen with continuous use of POPs, such as those containing norethindrone or desogestrel (DSG).[40] When combined with EE, DRSP is given at the

TABLE 1
Pharmacokinetic and metabolic properties of E4, EE, and E2 when used in a combined oral contraceptive

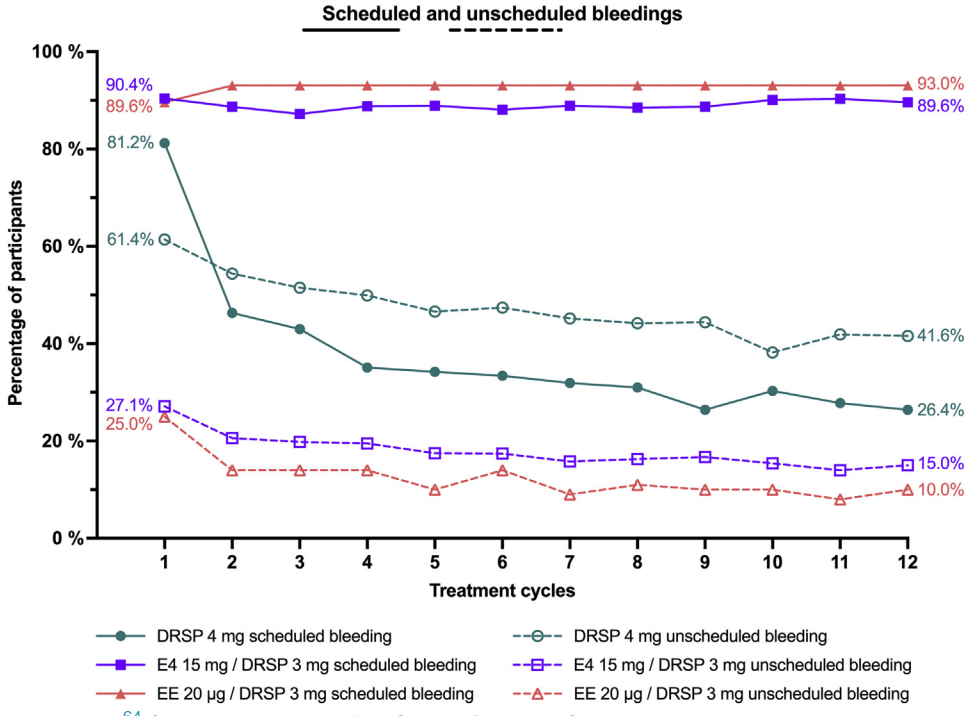
Properties	Estetrol (E4)[26,27]	Ethinylestradiol (EE)[28–30]	Estradiol (E2)[29,31]
Oral bioavailability	70%	45%	<5%
Half-life	>24 h	10–24 h	3.6 h (intravenous) 13–20 h (oral)
Free active fraction	50%	1%–2%	1%–2%
CYP3A4 metabolism	No	Yes	Yes
Active metabolites	No	Yes	Yes[a]

CYP3A4, cytochrome P450 3A4.

[a] Metabolites that can react and damage the DNA——linked to breast cancer development.

Foidart. Combination drospirenone and estetrol for contraception. Am J Obstet Gynecol Glob Rep 2023.

FIGURE 1
Bleeding with 15mgE4/3mgDRSP, 20μgEE/3mgDRSP and 4mgDRSP



E4-DRSP data from Kaunitz et al's[64] Contraception 2022, EE-DRSP data from the US Food and Drug (FDA) assessment report YAZ 2006[52] and DRSP alone data from the FDA assessment report SLYND.[51]

DRSP, drospirenone; *E4*, estetrol; *EE*, ethinylestradiol.

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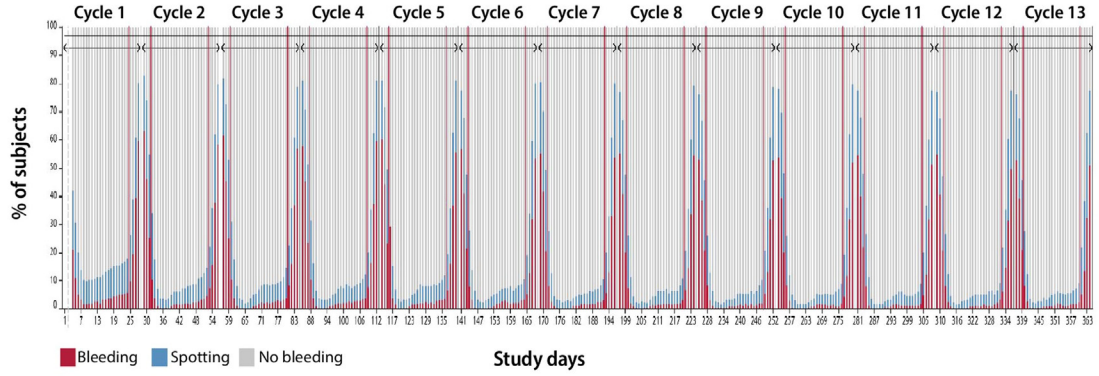
dose of 3 mg, wheras in POP, it is given at the dose of 4 mg despite providing comparable DRSP pharmacokinetic exposure. This difference is explained by the facts that EE inhibits the CYP450 system and because DRSP is micronized when combined with EE, 2 conditions that increase DRSP exposure.[41]

Phase 3 clinical trials conducted in the United States and in the European Union demonstrated the contraceptive efficacy of DRSP alone with a Pearl Index (PI) of 4.0 pregnancies per 100 women-years in the United States[42] and of 0.93 pregnancies per 100 women-years in the European Union or 1.27 in cycles with perfect use.[42] The consistent observation of higher PIs in all combined hormonal contraceptive studies in populations largely based in the United States when compared with those conducted in Europe is likely related to population differences, some of which are measurable and some that are not. There were, for instance, differences in previous contraceptive use between populations. Differences that are not measured in these studies may include variance in sexual education and health service provision and socioeconomic and education status among study participants. As classically reported with all OCs recently introduced in the United States, the PIs are higher than those approved decades earlier. Trussell and Portman[43] coined the term "Creeping Pearl" in a 2013 review of increased rates of contraceptive failures in recent vs older hormonal contraceptive trials. More frequent and sensitive pregnancy testing and less adherent participants are also important contributors to the increased PI in recent trials.[43]

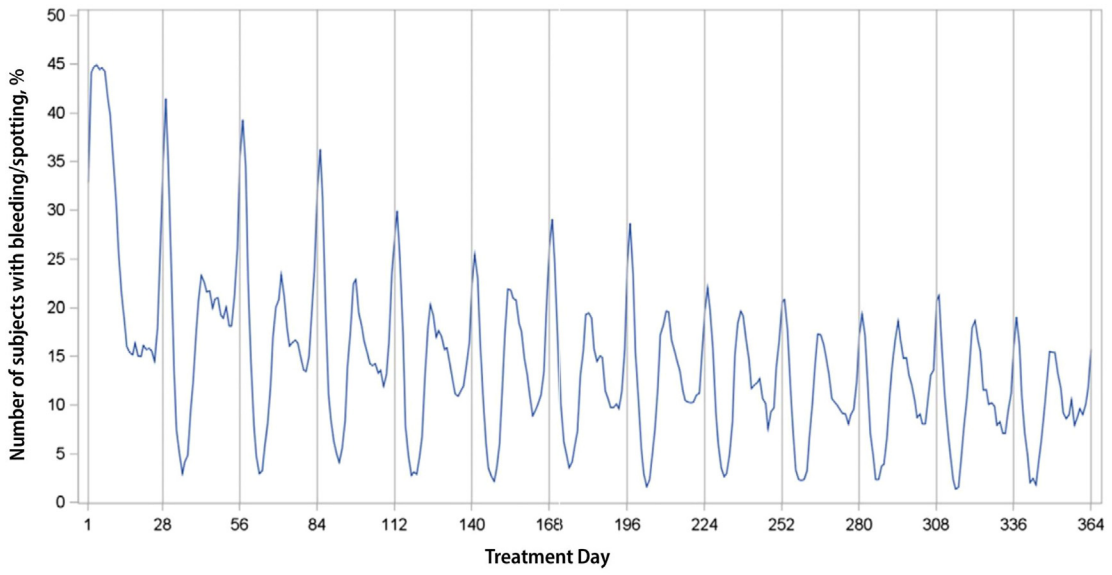
Combined phase 3 data showed a decline in unscheduled bleeding from 54% in cycle 2 to 42% in cycle 12 and in spotting from 87% in cycle 1 to 63% in cycle 6 and 45% in cycle 13 (Table 2 and Figures 1 and 2).[51] However, this decline may be facilitated by a substantial dropout rate occurring from 2178 participants in cycle 1 to 726 in cycle 12.[51] A comparative, randomized, 9-month trial with a 75 μg DSG POP in a continuous 28-day treatment regimen suggested limited differences in the bleeding profiles for the 2 products.[60] The proportion of users with bleeding and spotting by treatment cycle decreased from 70% in cycle 2 to 56% in cycle 9 with DRSP and from 74% to 45% with DSG. The total mean number of bleeding or spotting days in cycles 2 to 9 was 29 in the DRSP group and 35 in the DSG group ($P<.26$). In cycles 2 to 6, the proportion of women with unscheduled bleeding or spotting was significantly lower in the DRSP group (73%) than in the DSG group (88%) ($P=.0001$). However, these calculations are misleading because all bleeding with

FIGURE 2
Bleeding for 15mgE4/3mgDRSP (A) and for 4mgDRSP (B)

Panel A



Panel B



A, E4-DRSP phase 3 trial Euopean Union and Russia, Gemzell-Danielsson et al[46] BJOG 2021. **B,** DRSP phase 3 trial European Union, Archer et al Contraception 2015[12].

DRSP, drospirenone; *E4*, estetrol.

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DSG, which is a continuous regimen, is, by definition, unscheduled. More useful, therefore, is the number of women with any bleeding or spotting during days 29 to 252 (cycles 2−9 in the DRSP cyclic regimen), with no difference (P=.30) between the 2 preparations.[60] Still, DRSP use led to a lower discontinuation rate owing to bleeding complaints than DSG use (4% vs 7%; P<.005).[61]

The most frequently reported adverse events (AEs) during phase 3 DRSP-alone clinical trials (>2% of patients) were bleeding abnormalities, acne, headache, and breast pain.[13,42,44,47] Early discontinuation rates owing to AEs were 11% and 12% in the 13-cycle United States and Euopean Union trials, respectively.[12,13] The discontinuation rate owing to bleeding related AEs was 4% in the European Union trial.[13] This rate was not reported in the US trial, which had a high overall dropout rate of 65% with 27% of participants lost to follow-up.[47]

DRSP only use showed no clinically relevant effects on carbohydrate metabolism and a nonclinically relevant decrease in cholesterol and triglycerides after 6 months of use (Table 2).[54] Bone markers measured in a subgroup of 64 participants in the European Union phase 3 trial showed a decrease in bone alkaline phosphatase and a small increase in beta-C terminal telopeptide (CTX), markers that both indicate slight bone degradation.[54] The impact of

TABLE 2
Efficacy, bleeding, and safety for E4-DRSP, DRSP and EE-DRSP

Parameters	E4 15 mg with DRSP 3 mg	DRSP 4 mg alone	EE 20 μg with DRSP 3 mg
Contraceptive efficacy[a]	Pearl index US: 2.65 (1.73–3.88)[26] Pearl index EU: 0.44 (upper range 1.03)	Pearl index US: 4.00 (2.30–6.40)[42] Pearl index EU: 0.93 (upper range 1.84)[44]	Pearl index US: 1.41 (0.73–2.47)[28] Pearl index EU: 0.80 (upper range 1.30)
Discontinuations			
Overall	Phase 3 trial US/CAN: 45.5%[45] Phase 3 trial EU/RUS: 21.6%[46]	Phase 3 trial US: 65%[47] Phase 3 trial EU: 27.8%[12]	Phase 3 trial global: 28.9%[48] Phase 3 trial EU: 12.7%[49]
Because of adverse events	Phase 3 trial US/CAN: 9.7%[45] Phase 3 trial EU/RUS: 10.1%[46]	Phase 3 trial US: 11.2%[47] Phase 3 trial EU: 12.3%[12]	Phase 3 trial global: 7.5%[48] Phase 3 trial EU: 6.3%[49]
Because of bleeding-related events	Phase 3 trial US/CAN: 2.7%[45] Phase 3 trial EU/RUS: 3.4%[46]	Phase 3 trial US: not reported Phase 3 trial EU: 4.2%[12]	Not reported
Bleeding profile			
Incidence of scheduled bleeding	Phase 3 trial US/CAN: 82.9% to 87.0% of women per cycle[45] Phase 3 trial EU/RUS: 91.9-94.4% of women over cycles 1 to 12[46]	46.3% in Cycle 2 declining to 26.4% in Cycle 12[50,51]	89.6% in Cycle 1, ranging between 91.7% and 94.4% at Cycles 2 to 13[52]
Incidence of unscheduled bleeding	Phase 3 trial US/CAN: between 15.5% to 19.2% from Cycle 5 onwards[45] Phase 3 trial EU/RUS: <16% from[46] Cycle 6 onwards	54.4% in Cycle 2 declining to 41.6% in Cycle 12[50,51]	14% in Cycle 2, decreasing to 10% in Cycle 12[52]
Safety profile			
Participants reporting AEs	Phase 3 trial US/CAN: 53.8%[45,46] Phase 3 trial EU/RUS: 50.5%	Phase 3 trial US: 61.0%[47] Phase 3 trial EU: 48.5%[51]	Phase 3 trial global: not reported Phase 3 trial EU: 47.8%[49]
Participants reporting ARs	Phase 3 trial US/CAN: 28.9%[45,46] Phase 3 trial EU/RUS: 28.5%	Phase 3 trial US: 33.9%[47] Phase 3 trial EU: 21.0%[12]	Phase 3 trial global: 38.5%[48] Phase 3 trial EU: 21.2%[49]
VTE risk	1 case of VTE in the clinical development program (30,289 cycles)[46]	No cases of VTE in the clinical development program (>20,000 cycles)[53]	2 cases of VTE in the clinical development program (both with the 21/7 treatment regimen) (>28,981 cycles)[52]
Hemostasis parameters	Effects on individual hemostasis parameters were less or similar to those for EE-LNG. Increase in nAPCsr after 6 months of use was 30%.[38] No clinically relevant change in thrombin generation allows to conclude a neutral profile.	No apparent impact on hemostasis parameters but no statistical values (mean ± SD) and inadequate methods to measure the APC resistance preclude definite proof.[54]	Effects on hemostasis parameters higher compared to those for E4-DRSP.[38] Increase in nAPCsr after 6 months of use was 218.5% with EE-DRSP compared to 30% with E4-DRSP.
Endocrine parameters	Decrease in E2 and progesterone levels, indicative for contraceptive efficacy.[55]	No data available	Decrease in E2 and progesterone levels, indicative for contraceptive efficacy.[55]
Liver proteins	Limited increase in CBG (+40%) and SHBG (+55%).[55] Effects were less compared to EE/LNG (CBG+152%, SHBG +74%)	No data available	Increase in CBG (140%) and SHBG (251%).[55] Effects were higher compared to E4/DRSP (CBG+40%, SHBG +55%)
Lipids	Limited changes in lipids: decrease in LDL-C (−2%), increase in HDL-C (+4%), total cholesterol (+4%) and triglycerides (+24%).[55]	Limited decreases in lipid parameters total cholesterol (−5%), HDL-C (−8%), LDL-C (−3%) and triglycerides (−10%).[54]	Limited changes in lipids. Decrease in LDL (−5%), increase in HDL-C (+8.5%), total cholesterol (+6.5%) and triglycerides (+65.5%).[55]

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TABLE 2
Efficacy, bleeding, and safety for E4-DRSP, DRSP and EE-DRSP *(continued)*

Parameters	E4 15 mg with DRSP 3 mg	DRSP 4 mg alone	EE 20 μg with DRSP 3 mg
Carbohydrate	No clinically relevant impact on carbohydrate metabolism: glucose (+3%), insulin (+21%), C-peptide (+17%) and HbA1c (0%)[55]	No relevant impact on glucose (-0.4%), insulin (+33%), and C-peptide (+8%)[54]	Limited effects on carbohydrate metabolism: glucose (0%), insulin (+42%), C-peptide (+27%) and HbA1c (+2%)[55]
Cardiovascular safety	No clinically relevant changes in cardiovascular risk parameters such as blood pressure, heart rate, ECG, echocardiography, and coagulation parameters.[38,55,56]	No reports of arterial thromboembolism, myocardial infarcts, strokes, or pulmonary embolisms in clinical development program of DRSP-alone. Slight decreases in systolic and diastolic blood pressure.[53]	Absolute risk of arterial thrombotic stroke and myocardial infarction is increased by a factor of 0.9 to 1.7 with COCs containing EE at a dose of 20 μg.[57]
Bone	Positive effect on bone turnover with a dose-related decrease in C-telopeptide (−8.6% with 5 mg E4 and 3 mg DRSP combination and −13.4 % with 10 mg E4 combined with 3 mg DRSP) and osteocalcin (−10.4% with 5 mg E4 combined with 3 mg DRSP and −16.3% with 10 mg E4 with 3 mg DRSP) after 3 mg of use.[58]	The effect on bone mineral density is unknown. Limited decrease in bone AP (−21.7%) and increase in CTX (3.8%) after 6 months of treatment.[54] Phase IV trial on bone mineral density at 12 months is ongoing (NCT05303636)	At 12 months, no significant effect on spinal bone mineral density.[59]

AP, alkaline phosphatase; *APC*, activated protein C; *CAN*, Canada: *CBG*, cortisol binding globulin; *COC*, combined oral contraceptive; *CTX*, C terminal telopeptide; *DRSP*, drospirenone; *E2*, estradiol; *E4*, estetrol; *ECG*, electrocardiogram; *EE*, ethinylestradiol; *EU*, Europe; *HbA1c*, hemoglobin A1c; *HDL-C*, high density cholesterol; *LDL-C*, low density cholesterol; *LNG*, levonorgestrel; *nAPCsr*, normalized APC sensitivity ratio; *SD*, standard deviation; *SHBG*, sex hormone binding globulin; *RUS*, Russia; *US*, United States; *VTE*, venous thromboembolism.

[a] FDA criteria for Pearl Index: at risk cycles are defined as cycles with no back-up contraception and confirmed vaginal intercourse; pregnancies within 7 days after last use are considered on treatment. EMA criteria for Pearl Index: at risk cycles are defined as cycles with no back-up contraception; pregnancies within 2 days after last use are considered on treatment;

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DRSP only on hemostasis is only weakly documented in the literature by studies reporting individual changes of some selected coagulation factors.[53,54]

Estetrol- drospirenone combined oral contraceptive

Since 2021, E4-DRSP has been approved for pregnancy prevention (NEXTSTELLIS, DROVELIS, ALYSSA, and LYDISILKA).[1,24] E4-DRSP has a cyclic 24/4-day treatment regimen with 24 active tablets containing 15 mg E4 (as monohydrate [14.2 mg anhydrous]) and 3 mg DRSP followed by 4 hormone-free pills.

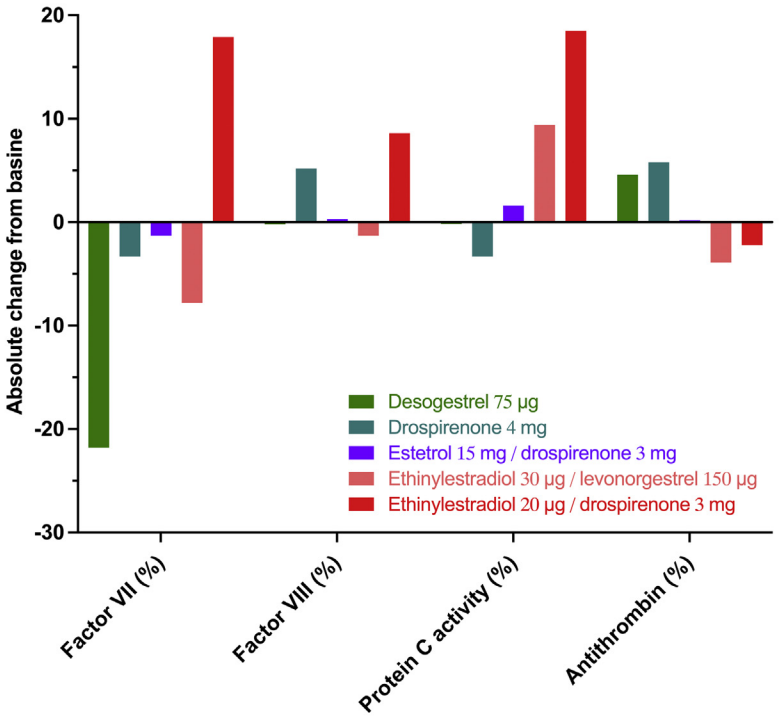
Two 13-cycle phase 3 trials with 15 mg E4 and 3 mg DRSP, one conducted in the United States and Canada (US/CAN) and one in Europe and Russia (EU/RUS), demonstrated a PI of 2.65 pregnancies per 100-women years in the US/CAN trial and 0.44 pregnancies per 100-women years in the EU/RUS trial (Table 2).[62] A recent secondary analysis of the pooled E4-DRSP phase 3 studies further evaluated the 31 on-treatment pregnancies based simply on adherence to remove other confounders, including study location.[63] Pregnancies occurred in 0.09%, 0.25%, 0.83%, and 1.6% of cycles in which participants reported that they took all hormone pills (n=25,613 cycles) or omitted 1 (n=405 cycles), 2 (n=121 cycles), and more than 2 (n=314 cycles) hormone-containing pills ($P<.001$). No pregnancies occurred in 2216 cycles when 1 or more pills were missed and missed-pill instructions were followed. All pregnancies related to not taking pills occurred in the first 3 cycles. Pregnancy rates ranged from 0% to 0.21% per cycle with no significant trend by cycle.[63] Similar data for DRSP only contraception are not available.

E4-DRSP users experience predictable bleeding episodes with a high stable rate of scheduled bleeding (89% in cycle 2, 90% in cycle 12) and a decreasing rate of unscheduled bleeding (21% in cycle 2 to ≤18% from cycle 5 onwards) (Figures 1 and 2; Table 2); 67% of unscheduled bleeding or spotting episodes included only spotting, 27% included mixed bleeding and spotting, and 6% included only bleeding with a duration of bleeding or spotting of 3 to 4 days.[64] Most frequently (>2%) reported treatment-related AEs during E4-DRSP use were bleeding complaints, breast pain or tenderness, acne, mood disturbance, headache, dysmenorrhea, and increased weight.[56] Discontinuation rates owing to AEs were 10% overall and 3% for AEs specifically related to bleeding in both trials.[45,46]

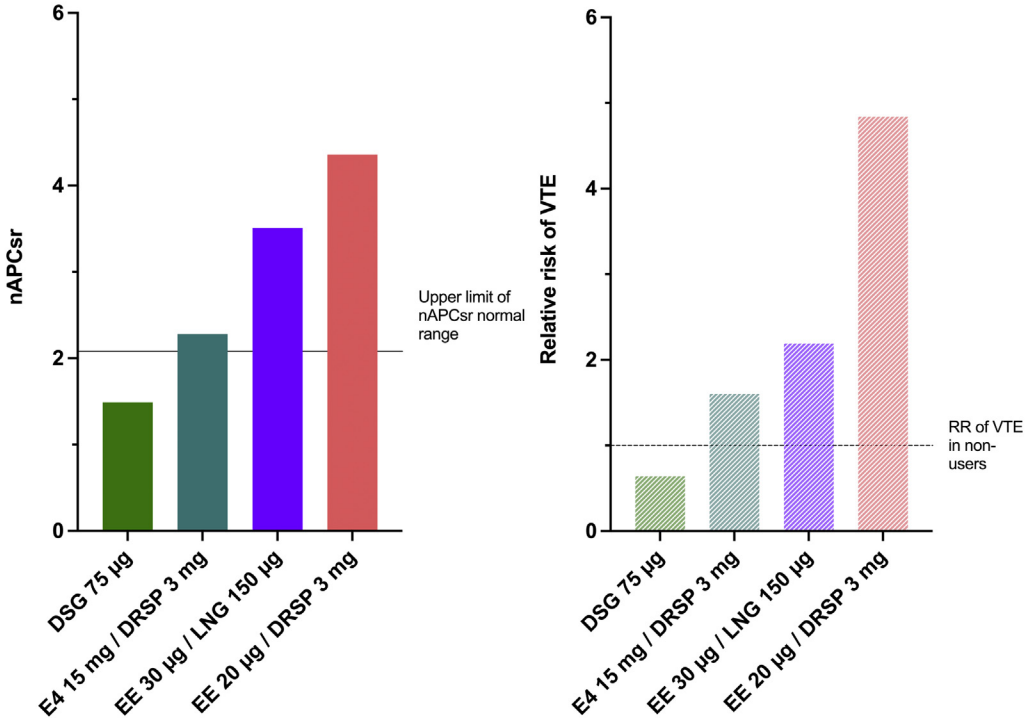
A comparative 6-cycle trial showed that E4-DRSP use had a minimal effect on hemostasis parameters as supported by the impact of E4-DRSP on the endogenous thrombin potential (ETP) −based activated protein C (APC) resistance assay, which was negligible when compared with EE-containing products (Figure 3, B; Table 2).[38] E4-DRSP use also led to minimal effects on

FIGURE 3
Impact of POPs and COCs on coagulation factors, nAPCsr and VTE risk

A. Impact of different POPs and COCs on coagulation factors extracted from phase 2 clinical studies



B. Correlation between nAPCsr values obtained in POPs and COC users and the relative risk of VTE



carbohydrate metabolism and on the lipid profile with only a small but statistically significant effect on apolipoprotein A1, apolipoprotein B, and triglycerides (Table 2).[55]

The E4 effects on bone were first studied in an osteoporosis rat model, which showed dose-dependent bone-sparing effects.[67] In postmenopausal women treated with 15 mg E4, the median osteocalcin and CTX levels decreased respectively by 3.1% and 45.3%.[68] Similar results were obtained with 5 mg E4 with 3 mg DRSP and with 10 mg E4 with 3 mg DRSP (Table 2).[58]

Discussion

Contraceptive efficacy

The progestogen in COCs is primarily responsible for the contraceptive efficacy by suppressing gonadotropin-releasing hormone from the hypothalamus, thus inhibiting follicular development and ovulation.[69,70] Estrogens attenuate follicular development through a pituitary inhibition of follicle stimulating hormone secretion. Although the PIs for 15 mg E4 combined with 3 mg DRSP and for 20 μg EE combined with 3 mg DRSP are lower than for 4 mg DRSP alone (Table 2), the PIs for DRSP alone are in the range of combined formulations because of similar ovulation inhibition.[16]

Bleeding profile

A common drawback of POPs is their effect on endometrial vasculature. Underdevelopment of spiral arterioles and dilated, thin-walled vessels with increased vascular fragility contribute to irregular bleeding.[71,72] Although the number of bleeding days over multiple cycles is similar to DSG only POP, DRSP only contraception has a slightly lower discontinuation rate. Estrogens added to the progestin stabilize the endometrium with uniformly decidualized stroma and only rare, atrophic-appearing glands. The bleeding profile of E4-DRSP demonstrates that 87% to 94% of the cycles had scheduled bleeding vs 26% for DRSP only and lower unscheduled spotting (10% −12%) when compared with 63% for DRSP only users.[50] The bleeding profile of E4-DRSP seems to be comparable with that of EE-DRSP (Figure 1).

Nonbleeding adverse events

The other most frequent AEs that occur during hormonal contraceptive use include breast tenderness, nausea, headache, abdominal pain, increased vaginal discharge, decreased libido, acne, mood changes, and weight gain.[73,74] Most of these AEs are also reported with the use of E4-DRSP, EE-DRSP, or DRSP alone with small differences in frequencies. The overall discontinuation rates and the discontinuation rates owing to AEs (as a proxy for the experienced intensity of the AEs) with the use of E4-DRSP and DRSP alone are comparable (Table 2).

Hemostasis parameters and venous thromboembolism

The impact of DRSP alone has only been investigated in a small series of selected coagulation proteins, making it difficult to draw conclusions about its influence on hemostasis.[54] For example, the effect of DRSP alone on protein C activity and factor VII levels has been reported to be different than that of DSG. Comparatively, the level of factor VII decreases to a similar extent with E4-DRSP use (ie, −3%), and the levels of protein C, factor VIII, and antithrombin are also not influenced by E4-DRSP use (Figure 3).[38,54] The use of inappropriate methodologies for assessing activated protein C resistance[53,54,75] precludes conclusions on the impact of DRSP alone on the entire coagulation process.[76] Therefore, until the evaluation of hemostasis using appropriate techniques is completed for DRSP alone, it is difficult to infer any differential impacts on hemostasis in comparison with COCs containing DRSP.

The characterization of the hemostatic profile of E4-DRSP is well documented.[1,38,39,66,77,78] Its impact on the entire coagulation process has been determined using the endogenous thrombin potential−based APC resistance assay, the thrombin generation assay, and several hemostasis markers, suggesting the absence of a clinically relevant impact on hemostasis when compared with EE-containing products (Figures 3 and 4). EE-containing products increase the production of procoagulant factors and decrease the production of anticoagulants to a level that favors clot formation.[25,38,39,79] E4-DRSP has less impact on thrombin generation than EE-containing OCs associated with LNG or DRSP, which either increase the production of procoagulant factors or decrease the production of anticoagulant ones, shifting the patient to a prothrombotic state. EE-containing OCs thus generate prothrombotic environments, whereas the E4 containing OCs demonstrate a neutral profile on these hemostasis markers.[39]

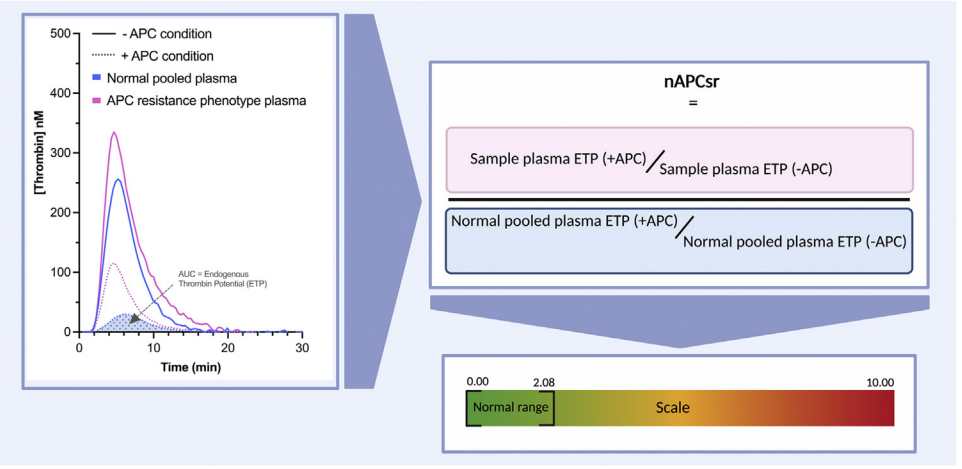
During clinical development with E4-DRSP, 1 venous thromboembolism (VTE) event was reported among 3574 women (35,677 cycles), giving an estimated incidence of 3.7 per 10,000 woman-years, which is in line with rates observed among reproductive-age women who do not use COCs (1−5/10,000 woman-years).[80,81] For comparison, 2 participants in the 20 μg EE with 3 mg DRSP clinical trials experienced a VTE in 42,338 treatment cycles (6.1 per 10,000 women-years of use), whereas similar phase 3 clinical studies with other combined hormonal

The impact of POPs and COCs on some individual coagulation factors has been extracted from Palacios et al[54] and Douxfils et al[38] (**A**). The correlation between nAPCsr results and relative risk for VTE was extracted from Douxfils et al,[38] whereas desogestrel data are extracted from QUALIblood s.a. (unpublished data). The VTE risk was either extracted from Lidegaard et al[65] or recovered by the in silico model of Morimont et al.[66]

COCs, combined oral contraceptive; *nAPCsr*, endogenous thrombin potential-based activated protein C resistance (ETP-based APC), expressed as normalized APC sensitivity ratio; *POP*, progestin-only pill; *VTE*, venous thromboembolism.

Foidart. Combination drospirenone and estetrol for contraception. Am J Obstet Gynecol Glob Rep 2023.

FIGURE 4
Endogenous thrombin potential(ETP)-based activated protein C(APC) resistance assay



The ETP-based APC resistance assay permits the evaluation of congenital and acquired APC resistance by using data from thrombin generation curves. Thrombin generation curves (thrombograms) reflect the amount of thrombin produced over time in a measurement well. Several parameters can be extracted from this curve but for the sake of the ETP-based APC resistance assay, only the area under the curve of the thrombograms, reflecting the endogenous thrombin potential (ETP), was used.

In the ETP-based APC resistance assay, thrombograms are generated in the absence (——— *continuous line*) and in presence (——- *dotted lines*) of APC. The resistance towards APC in a subject's plasma, for example, with an APC resistant phenotype (continuous and dotted pink lines), is compared with the resistance obtained in a pool of plasma from normal subjects (continuous and dotted blue lines). This method of calculation permits to express the results in terms of normalized activated protein C sensitivity ratio (nAPCsr).

nAPCsr results scale from 0 to 10, which ease its interpretation. Therefore, the higher the nAPCsr, the higher the resistance toward APC. The normal range in a young and healthy population not taking combined hormonal contraceptives (CHCs) is from 0.00 to 2.08. Women taking EE/LNG COCs usually express nAPCsr results around 3.50.

As stated in by the plasma coagulation inhibitors subcommittee of the International Society on Thrombosis and Haemostasis (ISTH) Scientific and Standardisation Committee (SSC), the ETP-based APC resistance assay[77] has to be used for assessment of hormone-induced APC resistance since clotting (ie, aPTT-based) APC resistance assays are insensitive to this acquired APC resistance condition.[75]

Foidart. Combination drospirenone and estetrol for contraception. Am J Obstet Gynecol Glob Rep 2023.

contraceptives containing EE reported 3 events among 1683 participants for oral 10 μg EE with 1 mg norethisterone acetate,[82] 4 events among 1188 participants for vaginal 13 μg EE with 150 μg segesterone,[83] and 4 events over 2031 participants for transdermal 20 μg EE with 120 μg LNG.[84]

Altogether, the limited comparison of DRSP only vs E4-DRSP and the exhaustive evaluation of E4-DRSP in comparison with other EE-containing products support the observation that E4-DRSP has minimal impact on hemostasis[66] and confirm that the effect of COCs on hemostasis is mainly driven by the estrogen component of the pill. E4 can thus be viewed as having a minimal effect on hemostasis. The conclusions from the surrogate markers of hemostasis must be confirmed by a phase 4 postauthorization safety study.

Metabolic effects

Estrogens in a COC typically increase high density lipoprotein cholesterol, decrease low density lipoprotein cholesterol, and increase triglyceride blood concentrations. The magnitude of these effects depends on the potency of the estrogen impact on liver cells. E4 selectivity with relative liver neutrality is reflected in the lack of clinically relevant effects on lipids observed in the clinical trials with E4-DRSP, which comparable with the lack of effects of DRSP alone on plasma lipids levels.[54,55] Current low-dose COCs rarely impair glucose metabolism in healthy women. DRSP has only a minimal effect on this metabolism.[9,85,86] No clinically relevant effects on carbohydrate metabolism were observed with E4-DRSP, DRSP alone, or EE-DRSP.[54,55]

Drug-drug interaction

E4 is not metabolized by CYP450 and shows minimal impact on this enzyme system,[32–35] which leads to less interference with the many drugs metabolized by CYP450. The inhibition or induction of CYP450 by EE or E2 alter the metabolism of at least 200 drugs. Reciprocally, these drugs may increase or decrease EE and E2 plasma levels but will not modify E4 levels. However, because DRSP interferes with CYP450, concomitant use of other drugs might reduce contraceptive efficacy.[87] Finally, unlike E2, E4 is not converted into estrone (E1), which increases thrombin generation.[88] Interestingly, the VTE risk is increased

30-fold among patients who use oral estrogen and who express the CYP450 3A5*1 allele, a cytochrome mutation that enhances the conversion of E2 into E1.[89] These observations add weight to the epidemiologic data demonstrating an increased VTE risk among women who use oral E2 treatment.

Bone

Because of the suppression of follicular development, the use of progestin-only contraceptives leads to a decrease in E2 levels, which may affect bone mineral density (BMD).[90] In a COC, the decrease in endogenous E2 levels is compensated for by the exogenous estrogen that maintains a favorable effect on bone. In the phase 3 trial with DRSP alone, bone alkaline phosphatase, a marker for bone formation, decreased and CTX, a marker for bone resorption, modestly increased after 6 months of use, suggesting a moderate increase in bone turnover.[4,54] A phase 4 trial is in progress to evaluate the effect of DRSP alone on BMD after 12 months of treatment (ClinicalTrials.gov, NCT05303636). The combination of E4 and DRSP led to an E4 dose-related decrease in bone turnover, which is indicative of a positive influence of E4 on bone turnover in young, postadolescent women.[58] For EE-DRSP, no changes in BMD were observed after 12 months of use.[59]

Cardiovascular and cardiometabolic thromboembolic safety

Cardiometabolic disorders encompass a cluster of metabolic disorders including insulin resistance, hyperglycemia, hypertriglyceridemia, dyslipidemia, and more.[91] The incidence of these disorders, together with smoking and high blood pressure, predispose users from 35 years of age to a higher risk for cardiovascular disease.[92] Preclinical studies suggest that COCs containing DRSP are likely safer than those with LNG because of less insulin resistance, pancreatic β-cell dysfunction, glucose deregulation, dyslipidemia, and circulating corticosterone.[93] Clinical studies with DRSP alone or with E4-DRSP have demonstrated a good cardiovascular safety profile.[53,56] DRSP alone and E4-DRSP also showed limited impact on lipid parameters,[54,55] whereas with the addition of EE to DRSP, lipid parameters, such as triglycerides, increased by 66% from baseline after 6 cycles of usage.[55]

Conclusion

Many factors determine the preferred individual choice of contraception, including the characteristics of the user, contraindications, the AE profile of different products, costs, availability, and the user's preferences. Healthy users should be free to choose the most acceptable method.

From its introduction to the market in 2000, DRSP held great promise as the progestin that could prevent increases in blood pressure, maintain stable body weight, and have a beneficial impact on health-related quality of life. Unfortunately, DRSP is devoid of anti-estrogenic activity to counteract the estrogenic properties of EE, which leads to a negative impact on hemostasis and VTE risk. The beneficial properties of DRSP may be expressed much better when DRSP is given alone or in combination with a selective estrogen that does have a minimal impact on the breast, liver, and coagulation. The introduction of 4 mg DRSP alone and of 15 mg E4 with 3 mg DRSP are therefore valuable additions to the contraceptive market. Because of the absence of a strong estrogen component, such as EE, DRSP alone offers the advantage of no or a low additional VTE risk like with other POPs.[53] However, DRSP alone provides a suboptimal bleeding profile even if somewhat better than other POPs thanks to the 24/4 regimen.[60] Indeed, it is associated with a high level of discontinuation, a higher rate of unscheduled bleeding, and a lower rate of scheduled bleeding than combined products.[16,47,50,51,60] Adding 15 mg E4 to 3 mg DRSP concurs with the contraceptive efficacy and stabilizes the endometrium, leading to a COC with a robust contraceptive efficacy and a regular and predictable bleeding profile with a high rate of scheduled bleeding and lower rates of unwanted, unscheduled bleeding. Because of its unique pharmacologic profile, the impact of E4 on hemostasis remains minimal even when compared with DRSP alone.[1,38,56] If phase 4 population-based studies confirm the expected low VTE incidence with E4-DRSP, the EE COC may be obsolete in the near future. ■

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