Review

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Pharmacological and metabolic effects of drospirenone as a progestin-only pill compared to combined formulations with estrogen

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Abstract

The spironolactone derivative drospirenone is combined with ethinylestradiol or estetrol in combined oral contraceptives. Formulations with 17-β-estradiol are used to treat climacteric symptoms. A drospirenone-only formulation has been introduced for contraception. Here, the pharmacological properties of drospirenone, the impact of the different formulations on metabolic and laboratory parameters, and the resulting clinical implications are reviewed. Ethinylestradiol, an inhibitor of CYP metabolic enzymes, changes the pharmacokinetics of drospirenone, leading to a higher drospirenone exposure with ethinylestradiol/drospirenone compared to the drospirenone-only preparation. In addition, several metabolic alterations have been described. The impact of estetrol is less pronounced, and for 17-β-estradiol/drospirenone and drospirenone-only, decreased triglyceride and cholesterol levels were observed. Ethinylestradiol induces various pro-coagulatory factors, leading to hypercoagulability. The effect is significantly reduced with estetrol, and no influence was observed with the drospirenone-only preparation. The anti-mineralocorticoid activity of drospirenone seems to positively counteract the renin-angiotensin-aldosterone-system-activating action of ethinylestradiol. There is no influence on blood pressure with ethinylestradiol/drospirenone and estetrol/drospirenone formulations, while in clinical trials, a reduction has been observed with 17-β-estradiol/drospirenone and drospirenone-only. Anti-aldosterone activity via non-renal mineralocorticoid receptors is associated with cardiovascular health, while interactions with parathyroid hormone signaling impact bone structure and vascular calcification. Though the clinical relevance is unclear for drospirenone, data in this context are reviewed. To sum up, the advantages of drospirenone in hormonal contraception and treatment of menopausal symptoms have been demonstrated for all the formulations described here. Combination with estrogen confers benefits and risks, which must be considered.

Keywords

anti-mineralocorticoid, drospirenone, metabolism, pharmacology

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Introduction

The spironolactone derivative drospirenone (DRSP) was developed as a contraceptive with pharmacological properties comparable to progesterone (P4). The progestogen exerts anti-mineralocorticoid and anti-androgenic activity but shows low affinity to estrogenic or glucocorticoid receptors (GRs).[1] Combined with ethinyl estradiol (EE), it has been used for contraception since 2000.[2] A formulation with DRSP and 17-β-estradiol (E2) is approved to treat climacteric symptoms and osteoporosis prevention in postmenopausal women.[3] Recently, a combined oral contraceptive (COC) with 14.2 mg estetrol (E4)/3 mg DRSP[4]

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and an estrogen-free formulation with 4 mg DRSP, each in a 24/4 regimen, have been approved for hormonal contraception.[5] Here, the pharmacological properties of DRSP are reviewed, including its anti-mineralocorticoid and anti-androgenic effects and potential clinical implications. The metabolic and clinical impact of the DRSP-only contraceptive obtained in recent clinical trials are compared to the preparations containing different kinds of estrogens.

Literature search

A literature search was performed using the MEDLINE database via PubMed, provided by the National Center for Biotechnology Information (NCBI). Also, the Cochrane Database, the Public Library of Science, and Google Scholar were searched.

DRSP in contraception and hormone replacement therapy: an overview

DRSP shows anti-gonadotropic effects and can efficiently transform the endometrium.[6] It prevents the follicular development and reliably suppresses ovulation at a dose of 3 mg per day.[7] This dosage has been used in oral contraception with 0.02 mg EE in a 24/4 intake regimen with four placebos.[8,9] It is also indicated for treating moderate acne and symptoms of the premenstrual dysphoric disorder by US Food & Drug Administration.[9] This preparation is also available in the United States with 0.451 mg levomefolate to raise folate levels.[10] COCs with 0.02 mg EE/3 mg DRSP[11] or 0.03 mg EE/3 mg DRSP[2] in a 21/7 intake regimen (21 active tablets, followed by seven tablet-free days) are marketed as in the US and EU countries. To reduce common EE-induced side effects, a COC was introduced that combines 14.5 mg E4 with 3 mg DRSP in a 24/4 regimen (24 active tablets; 4 placebos). E4 is naturally produced by the fetal liver.[4] Finally, an estrogen-free DRSP-only oral contraceptive (DRSP-POP) has been developed to completely circumvent unwanted estrogenic side effects. This formula contains 4 mg DRSP and is also used in a 24/4 regimen with four placebos.[5]

DRSP is combined with E2 for the treatment of menopausal symptoms (Angeliq®).[3,12] A preparation with 1 mg E2/2 mg DRSP is marketed in the European Union with an additional indication for the prevention of osteoporosis.[3] In comparison, the lower dosed preparations (0.5 mg DRSP/1 mg E2 and 0.25 mg DRSP/0.5 mg E2) available in the United States are indicated for treating vasomotor symptoms and vulvar and vaginal atrophy (only 0.5 mg/1 mg) due to the menopause. Table 1 gives an overview of the available DRSP combinations.

Pharmacological properties of DRSP

In vitro experiments on receptor binding and transactivation have demonstrated a high affinity of DRSP to the progesterone receptor (PR) and mineralocorticoid receptor (MR). Neither does it show relevant binding to the estrogen receptors α and β nor does it activate the androgenic receptor (AR), but DRSP shows anti-androgenic effects that were about one-third of the potency of cyproterone acetate (CPA) in animal models.[13]

The anti-mineralocorticoid activity of DRSP at the MR

DRSP is an aldosterone antagonist at the MR displaying an antagonistic activity while not activating the GR. The anti-MR action of DRSP on the renin-angiotensin-aldosterone system (RAAS) is comparable to the activity of endogenous progesterone observed during the luteal phase of the menstrual cycle when sodium excretion, plasma renin activity, and plasma aldosterone levels are elevated compared to the follicular phase.[1,14]

Bird et al.[15] described that 3 mg of DRSP is equivalent in their anti-mineralocorticoid capacity to 20–25 mg of spironolactone showing the high diuretic efficacy of DRSP.

Above the role in blood pressure regulation via the kidney, aldosterone signaling at non-renal MR is associated with vascular inflammation and the development of atherosclerosis.[16] Interestingly, in animal models, MR antagonists improved endothelial damage induced via aldosterone signaling.[17]

Furthermore, in rat models, MR antagonists, including DRSP, induced the remodeling of white adipose tissue into brown adipose tissue via the MR-antagonistic activity when applied at a high dosage.[18]

In addition, aldosterone signaling also interferes with parathyroid hormone (PTH)-mediated processes. Elevated PTH levels (hyperparathyroidism) lead to side effects like increased fracture risk, coronary microvascular dysfunction, arterial hypertension, and increased stiffness of the aorta.[19] Aldosterone excess leads to increased Ca^{2+} and Mg^{2+} excretion, secondary hyperparathyroidism, and bone resorption. Blocking the MR with spironolactone improved the electrolyte balance and increased bone density and strength.[20] In this context, the klotho protein, involved in regulating phosphate metabolism, also seems to play a role. It has been demonstrated that aldosterone and angiotensin II may reduce klotho expressions, and it has become clear that klotho deficiency is associated with vascular and soft tissue calcification.[21] Interestingly, MR antagonist spironolactone could impede vascular calcification.[22] However, no detailed data are available for the spironolactone analogue DRSP yet.

The anti-androgenic activity of DRSP

The anti-androgenic potency of DRSP was up to tenfold higher than that of progesterone in ovariectomized rats.[1] DRSP, in contrast to other progestins, does not bind to sex

Table 1. Available therapeutic formulations with DRSP.

Active compound	EE/DRSP			EE/DRSP/LVF	E4/DRSP	E2/DRSP	DRSP-only
	Ethinylestradiol/DRSP			EE/DRSP/levomefolate calcium	E4/DRSP	E2/DRSP	DRSP
Amount	0.02 mg/3 mg	0.02 mg/3 mg	0.03 mg/3 mg	0.02 mg/3 mg/0.451 mg	14,2 mg/3 mg	1 mg/2 mg or 1 mg/0.5 mg or 0.5 mg/0.25 mg	4 mg
Regimen	24 active tablets/ 4 placebos	21 active tablets; 7 days tablet-free interval	21 active tablets; 7 days tablet-free interval	24 active tablets with EE/DRS/ LVF; 4 tablets with LVF	24 active tablets/4 placebos	28 active tablets; continuous	24 active tablets/ 4 placebos
Indication[a]	Oral contraception Treat moderate acne[b] Treat symptoms of PMDD[b]	Oral contraception	Oral contraception	Oral contraception Treat symptoms of PMDD Treat moderate acne Raise folate levels	Oral contraception	(1) Hormone replacement therapy (EU) (2) Prevention of osteoporosis (EU) (3) Treatment of vulvar and vaginal atrophy symptoms due to menopause (US) (4) Treatment of vasomotor symptoms due to menopause (US)	Oral contraception
Missed pill window	24 h	12 h	12 h	24 h	24 h	Does not apply	24 h

In the last row, brand names are given. Data are taken from SmPC (Summary of Product Characteristics) as indicated in the first line. DRSP: drospirenone; EE: ethinyl estradiol; E4: estetrol; E2: 17-β-estradiol; EU: European Union; US: United States; PMDD: premenstrual dysphoric disorder; LVF: Levomefolat Calcium.

[a]See SmPC for complete definitions of the indication.

[b]Not in all countries.

Table 2. Pharmacokinetic parameters of DRSP 4 mg compared to DRSP 3 mg/EE 0.02 mg (24/4).

	Variable	4 mg DRSP	0.02 mg EE/3 mg DRSP	Ratio 4 mg DRSP versus 0.02 mg EE/3 mg DRSP
Single dose	$AUC_{(0–24\,h)}$ (ng × h/mL)	543.5	442.0	123.0%
	$AUC_{(0–72\,h)}$ (ng × h/mL)	296.1	264.7	111.9%
	C_{max} (ng/mL)	27.3	37.5	72.7%
	t_{max} (h)	3.5	1.7	–
Repeated dose	$AUC_{(t,ss)}$ (ng × h/mL)	1066.8	1394.5	76.5%
	$AUC_{(0–72\,h)}$ (ng × h/mL)	570.2	732.8	77.8%
	$C_{max,ss}$ (ng/mL)	41.0	61.4	66.8%
	$t_{max,ss}$ (h)	3.2	1.3	2-h delay
	$C_{min,ss}$	17.1	21.7	81.0%
	$R_{AC(AUC)}$	1.9	2.8	–
	$R_{ac(c_{max})}$	1.5	1.6	–

Source: Data taken from Wiesinger et al.[26]
Geometric means; non dose-corrected. DRSP: drospirenone; AUC: area under the curve; c_{max}: maximal plasma concentration; $c_{max,ss}$: maximal plasma concentration in steady state; t_{max}: time to reach maximal plasma concentration; $c_{min,ss}$: lowest plasma concentration during dosing interval in steady state. R_{Ac}: Accumulation ratio calculated from AUC(0–24) (or c_{max} (0–24)) on day 15 compared to AUC(0–24) (or c_{max} (0–24)) on day 1.

hormone-binding globulin (SHBG),[23] and due to its antigonadotropic action, the production of androgens in the ovarian theca cells is reduced. Above that, DRSP inhibits the androgen receptor–mediated transcriptional androgen processes[1,24] and blocks the action of 5-α-reductase in end tissues, reducing testosterone conversion to dihydrotestosterone.[25] Animal studies demonstrated that DRSP has anti-androgenic activity in terms of its effects on the growth of accessory sex glands in androgen-treated juvenile castrated rats. DRSP at dosages ranging from 0.1 to 10 mg/animal/day (s.c.) caused a dose-dependent inhibition of the growth of both seminal vesicles and the prostate upon 7 days' application.[6]

Pharmacokinetics of DRSP alone and in combination with estrogens

After oral application, DRSP is metabolized to its primary metabolites 4,5 Dihydrodrospirenone-3-sulfate and the acid form of DRSP. The absolute bioavailability of DRSP is about 76%–85%.[6] The molecule is mainly bound to serum albumin (95%–97%).[23] In a crossover study comparing 0.02 mg EE/3 mg DRSP with 1.5 mg E2/3 mg DRSP,[26] steady state was reached in both groups within 2 weeks, but for EE/DRSP, the mean DRSP exposure was significantly higher compared to E2/DRSP ($p < 0.05$). Adding ketoconazole, a potent CYP3A4 inhibitor, increased DRSP serum concentrations in both groups. Again, a significantly more substantial increase in the EE/DRSP group than the E2/DRSP was observed (2.68-fold vs 2.30-fold). The effect contributed to EE's property as an inhibitor of CYP3A4 itself, while E2 is not.[26] A comparative trial between 0.02 mg EE/3 mg DRSP and 4 mg DRSP alone yielded similar observations[27]: the accumulation ratio of DRSP, as calculated from the area under the curve (AUC) after 15 days of treatment compared to single dose was 1.9 for the 4 mg DRSP-only preparation and 2.8 for 3 mg DRSP combined to EE. Therefore, the exposure to DRSP during steady state was significantly lower after intake of 4 mg DRSP compared to 3 mg in combination with EE (see Table 2 and Figure 1). This was explained by a potential interference of EE with the metabolic enzymes CYP3A4 and sulfotransferase SULT1A1.[27] However, the 4 mg DRSP-only formulation contains non-micronized DRSP, while a micronized form is used in the COC. This also accounts for differences in pharmacokinetics, mirrored by differences in the time until maximal plasma concentration is reached: t_{max} is doubled for the DRSP-POP compared to the COC after a single dose and elevated 2.5 times in steady state (see Table 2).[27]

Pharmacokinetics of the estrogenic compound in the combined preparations is influenced by food, reducing the bioavailability of EE in 25% of the patients after fed conditions[8] and the C_{max} of E4 by 50% also after food intake in comparison to those patients who ingested the drugs under fastened conditions.[4] For E2/DRSP, no influence of food is described.[3] DRSP exposure is not influenced by nutrition in E4/DRSP,[4] EE/DRSP,[8] or E2/DRSP[3] according to their SmPCs (Summary of Product Characteristics).

Metabolic effects of DRSP-containing formulations

Generally, steroids used in hormonal contraception and hormone therapy influence various metabolic parameters, including lipid and glucose metabolism. The effects depend on the kind and quantity of the estrogen compound, with EE being up to 500 times more potent than E2.[28] Therefore, the metabolic effects of E2 compared to EE are generally reduced.[29] Also, the metabolic impact of E4 is markedly reduced compared to EE.[30] For the combination of 0.03 mg EE with 3 mg DRSP in a clinical trial over 13 treatment cycles, an increase in total high-density

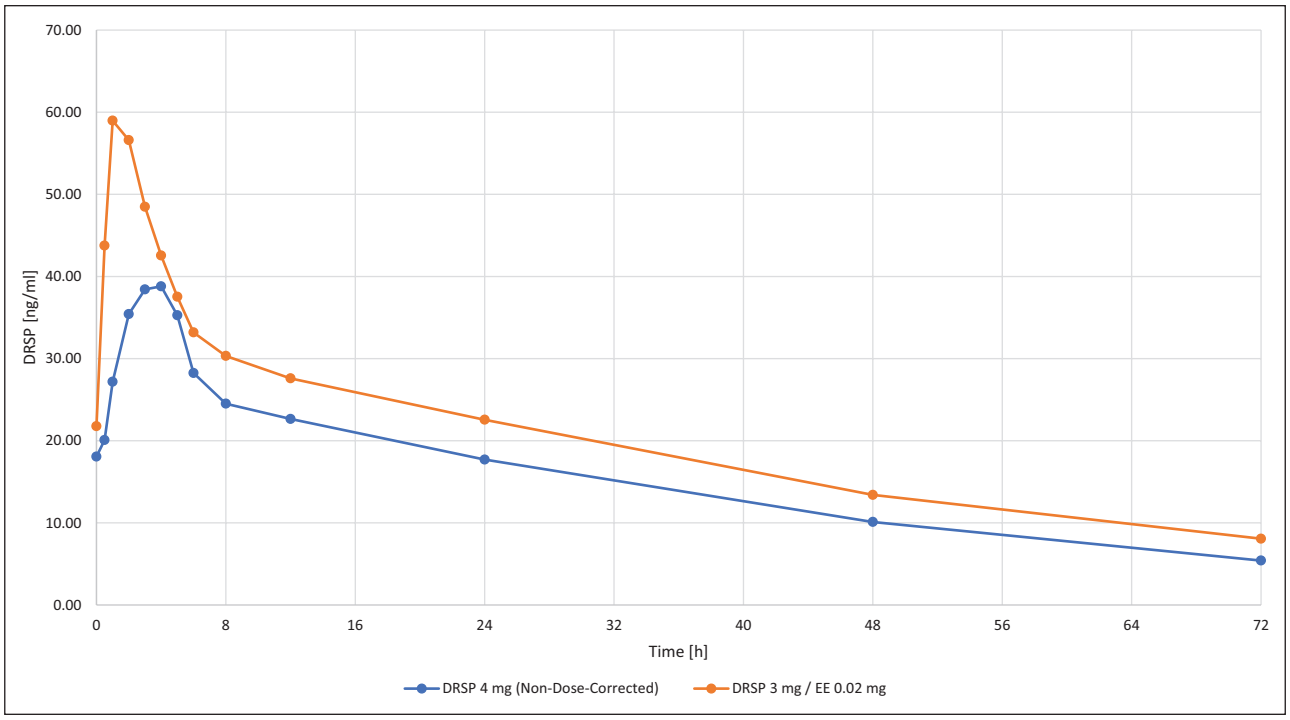

Figure 1. Mean DRSP non-dose-corrected plasma concentration time profile after repeated dosages of two formulations.

lipoprotein cholesterol (HDL-C) was observed (+12.8%), while the low-density lipoprotein (LDL) values remained stable (+1.6%). Mean triglyceride (TG) levels increased by 73.6%. There was also a slight increase in phospholipids (+13.6%) and apolipoproteins. The increased ratio of HDL/LDL was considered beneficial ($p < 0.05$).[31] The observed changes are in line with a further trial with 100 women using 0.03 mg EE/3 mg DRSP over six cycles: a significant increase in TG levels (+42%) and HDL-C (+25.7%) compared to baseline was accompanied by a decrease in LDL-C (−9.9%) with total cholesterol remaining stable.[31]

Two interesting comparative trials have been performed with E4/DRSP compared to EE/DRSP.[30,32,33] In a dose-finding study over three treatment cycles, total cholesterol increased in a group receiving 10 mg E4/3 mg DRSP (19 participants; 5.0%), which was comparable to 0.02 mg EE/3 mg DRSP (20 participants; +4.9%). However, the increase in TG levels was significantly smaller in the E4/DRSP group compared to women receiving EE/DRSP (+10.0% vs +61.2%). For LDL-C, however, there was an increase in the group receiving 10 mg E4/3 mg DRSP (+6.3%), while a decrease was observed for EE/DRSP (−9.2%).[32] With the currently marketed combination containing 15 mg E4 and 3 mg DRSP, a comparative trial over six cycles was performed with E4/DRSP, EE/DRSP, and 0.03 mg EE/0.150 mg levonorgestrel (LNG).[33] The changes observed were not statistically significant for total cholesterol and HDL-C for E4/DRSP (+4.0% each) before and after treatment, while mean values increased significantly in EE/DRSP users (+6.4% and +8.5%), showing here a significance between baseline and end of the study ($p < 0.05$). LDL-C did not change significantly in both groups. TG levels increased significantly in E4/DRSP (+24%) and EE/DRSP (+65.5%), but also in EE/LNG (+28.0%) between baseline and end of the study and between the three different treatments.[29]

When DRSP is combined with E2, a decrease in total cholesterol and LDL-C, an increase in HDL-C, and decreased or stable TG levels are reported in different clinical trials.[34]

The metabolic impact of the DRSP-only contraceptive pill has been compared to the desogestrel (DSG)-only pill (0.075 mg DSG: continuous intake) in a prospective, randomized, double-blind, and double-dummy clinical trial over nine cycles.[35] Slight mean decreases in total cholesterol, LDL, and HDL were observed for both preparations and were not significantly different from each other. Mean TG level changes were −0.111 nmol/L (DRSP-only) and −0.226 nmol/L ($p > 0.0351$).[34] Thus, the effect of the DRSP-only preparation on lipid parameters was considered as neutral.

Furthermore, steroid hormones may have an impact on carbohydrate metabolism. Namely, EE was associated with increased insulin resistance in some trials.[36,37] However, the overall effect also depends on the properties of the utilized progestin, especially those associated with the androgenic activity, which may negatively impact glucose tolerance.[38] Concerning DRSP, comparative trials did not yield significant differences between 0.03 mg EE/3 mg

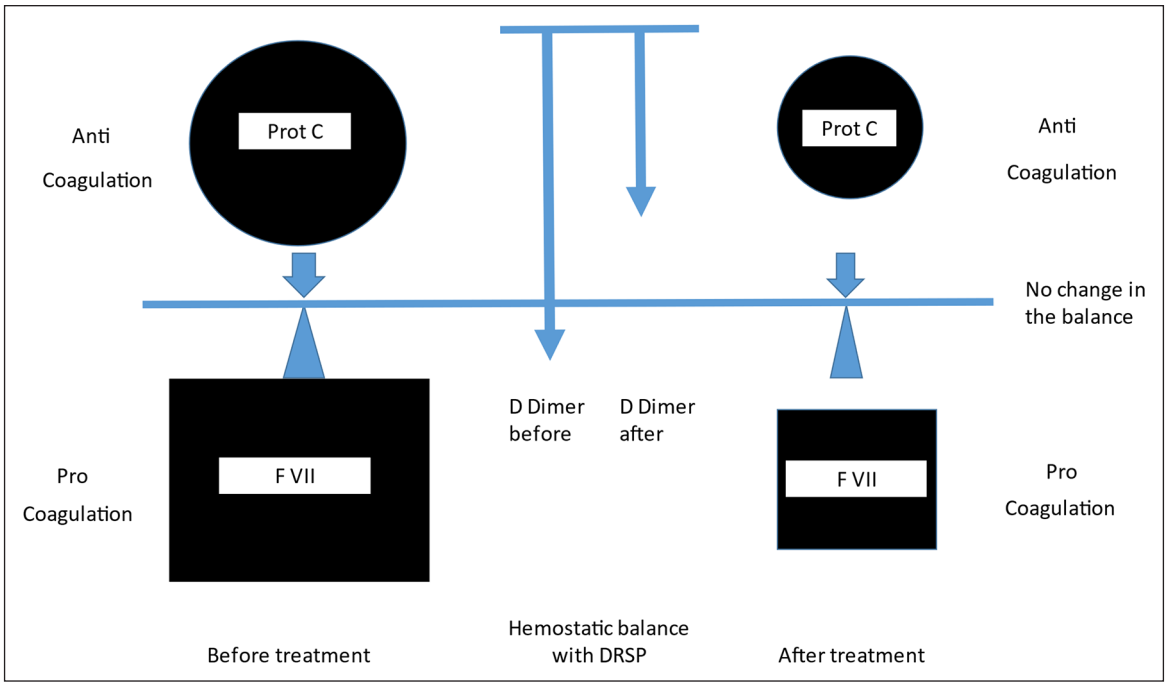

Figure 2. Coagulation balance between pro- and anti-thrombotic factors of the DRSP-only formulation before and after a 9-month treatment.

DRSP and 0.02 mg or 0.03 mg EE combined with DSG, as has been reviewed extensively elsewhere.[39,40] During a recent trial, 0.02 mg EE/3 mg DRSP was compared to 15 mg E4/3 mg DRSP and EE/LNG over six cycles. No relevant difference was observed between the formulations, and although there was a slight increase in insulin resistance, changes were not considered clinically relevant. The neutral effect on glucose metabolism was also confirmed for the DRSP-only preparation in the above-mentioned comparative trial to the DSG-POP.[35]

For the combination of E2/DRSP, a neutral or relatively positive effect on glucose metabolism and insulin resistance was observed in different trials.[41,42]

Effects on coagulation and thromboembolic risk

The use of combined hormonal contraceptives containing EE is generally associated with an elevated risk for venous thromboembolic event (VTE) and arterial thromboembolic event (ATE).[43,44] This is explained by EE's intense hepatic stimulation of coagulation factors.[45] The pro-coagulatory effect is reduced with estradiol valerate (E2V) and E2.[45,46] More androgenic progestins like LNG can counteract the estrogenic stimulation, while anti-androgenic ones are not, which explains the differences in VTE risk depending on the formulation.[45,46] According to epidemiological data, DRSP, combined with EE, belongs to the group with the highest incidence of VTE (together with DSG and gestodene: an estimated incidence of 9–12 cases per 10,000 women and year).[47]

There are no epidemiological data available for the novel COC with E4 or the DRSP-only POP, but clinical trials investigating their effects on haemostatic parameters have been performed. For E4/DRSP, comparative trials with 0.150 mg LNG/0.03 µg EE/ and 0.02 mg EE/3 mg DRSP over six cycles in healthy women showed that the impact of E4/DRSP on the hemostasis parameters was comparable to that observed in the EE/LNG group after 6 months of treatment and generally weaker than in the group that received EE/DRSP. There was an increase in D-Dimer levels by 4% compared to baseline. D-Dimers are fibrin degradation products and therefore represent an important marker for activating the coagulation system[48] (see Figure 2).

For the estrogen-free DRSP-only preparation, no impact on the haemostatic balance was observed in a comparative trial with 0.075 mg DSG over nine cycles. A median reduction in D-Dimer levels by 17.8% has been observed.[35,49] Also, for DRSP-only POP, no case of VTE or ATE has been recorded in phase III clinical trials with more than 25,000 treatment cycles and a high percentage of participants with cardiovascular risk factors.[50]

In contrast, during the full-sized (phase I–phase III trials) clinical development of E4/DRSP with 4219 subjects, two cases of VTE were reported,[51] with one of them occurring in a phase III trial with 1553 participants.[52]

The E2/DRSP preparation is applied by menopausal patients, who generally have an increased risk for cardiovascular disease due to common age-related risk factors. Oral hormone therapy (HRT) is usually associated with a high risk for VTE, attributed to the estrogenic compound.[53] On the contrary, HRT may benefit cardiovascular safety.[54]

Clinical effects of the anti-aldosterone activity of DRSP

Effect on RAAS

While endogenous E2 and low parenteral doses of the steroid hormones have a vasodilatory effect, exogenously administered high-dose estrogen, mainly EE, stimulates the synthesis of angiotensinogen, which leads to an activation of RAAS. Although the effect is small, it may result in elevated blood pressure in susceptible women.[14,55] Due to its anti-mineralocorticoid activity, DRSP was expected to counteract a potentially harmful effect on blood pressure compared to other progestins. Indeed, a positive impact on slightly elevated blood pressure due to its anti-aldosterone activity has been demonstrated in several clinical trials for E2/DRSP. A study with 750 grade 1 or 2 hypertensive postmenopausal women showed a significant reduction in the systolic blood pressure with E2 combined with 2 or 3 mg DRSP without increasing the serum potassium values.[56] The observation was confirmed in several clinical trials.[41,57] When combined with EE, no harmful impact on blood pressure has been observed in a pivotal clinical trial over 13 cycles with 1027 participants who used 0.02 mg EE/3 mg DRSP.[58] This was also confirmed for use in the extended regimen, skipping the hormone-free interval[59] and 0.03 mg EE/3 mg DRSP preparation.[60,61] For E4/DRSP, no relevant effect on blood pressure was reported.[50] With the DRSP-only preparation, a reduction of blood pressure in participants with slight hypertension (baseline values between 130 and 140 mmHg SBP and between 85 and 90 mmHg) was observed during pivotal trials (–8.0/–5.0 mmHg systolic blood pressure (SBP)/diastolic blood pressure (DBP)[62] and –8.5/–4.9 mmHg).[63] At the same time, there was no impact on normotensive women.

Potential benefits of non-renal anti-MR activity on cardiovascular risk factors

Patients with cardiovascular risk factors, like hypertension and type 2 diabetes, benefit from treatment with the MR-antagonist spironolactone, which significantly improved endothelial dysfunction in clinical trials.[64,65] Furthermore, there is an interesting linkage between aldosterone signaling via non-renal MR as well as PTH- and klotho-regulated vascular calcification and bone health. MR-mediated anti-aldosterone signaling might also benefit bone health and counteract vascular calcification via this connection. However, the potential benefits of DRSP signaling via non-renal MR require further investigation to draw any conclusions.

Bone health in HRT

The combination of 1 mg E2 and 2 mg DRSP prevents osteoporosis in postmenopausal women.[3] Clinical trials have demonstrated an increase in the lumbar spine, hip, and total body during 24 months of treatment with E2/DRSP, while bone turnover markers (e.g. bone alkaline phosphatase) decreased significantly compared to baseline.[66] However, due to the potential risks of HRT, osteoporosis prevention by HRT is only recommended for women at increased risk and for whom other therapies are not suitable.[67]

Bone mineral density and contraception

For 0.02 mg EE or 0.03 mg EE combined with DRSP, spinal bone mineral density did not change compared to non-users during 12 months of treatment. In addition, markers for bone degradation at 6, 9, and 12 months were significantly reduced compared to basal values in control groups of non-users.[68,69] In a comparative trial with different doses of E4 combined with DRSP and 0.02 mg EE/3 mg DRSP, a dose-dependent decrease of biomarkers for bone turnover was also observed for the E4-treated patients, and the effect, on the whole, was comparable to that observed with the EE-COC.[33] The DRSP-only preparation alterations in markers for bone turnover did not differ from that observed with DSG in a 9-cycle, comparative trial.[35] Above that, endogenous estradiol levels remained between 30 and 50 pg/mL. Therefore, no harmful effect on bone is expected.[70] However, clinical trials concerning bone mineral density need to be performed.

Anti-androgenic efficacy of the DRSP formulations

The 0.02 mg EE/3 mg DRSP is indicated for treating moderate acne vulgaris.[8,10,25] The effect was mainly explained by the increase of SHBG triggered by EE, which reduced free testosterone. At the same time, the impact of the anti-androgenic properties of DRSP has not been clarified.[9,71] In a prospective, randomized, and double-blind phase III trial with 1070 participants that compared 4 mg DRSP to 0.075 mg DSG, acne was more frequent in the group of DSG users than those using DRSP (5.7% vs 3.1%).[72] With the combination of E4/DRSP, the occurrence of acne is in a similar range as with DRSP-only preparation, according to data from the SmPC (3.2%[4] and 3.8%).[5] However, there is a significant increase in SHBG observed with E4.[30]

Limitations

The limitations of this review are especially two:

Comparing analytical findings is always very difficult as each study cited in the text used different analytical systems and reference values.

The second limitation is that all cited studies had a different clinical approach and were sometimes phase I, sometimes phase III or IV. Therefore, it is complicated to drawn comparative conclusions.

Nevertheless, this is one of the first reports describing pharmacokinetics and clinical evidence of the spironolactone DRSP in different pharmaceutical compounds.

Conclusion

DRSP is used for contraception and in HRT. While the combination with an estrogenic compound is mandatory for the treatment of menopausal complaints and prevention of osteoporosis, contraceptive efficacy is achieved by the progestin itself. The addition of estrogen may offer advantages like improved cycle stability or a positive impact on the skin. On the contrary, estrogenic steroids like EE and, to a lower extent, E4 affect metabolic and hemostatic parameters that increase the risk for severe side effects. Therefore, COC can be only used with caution or is an absolute contraindication in women with endogenous risk factors like obesity, elevated age, VTE in anamnesis, diabetes, or pro-thrombotic mutations. At the same time, progestin-only formulations may be recommended for these situations.

The DRSP-only preparation containing 4-mg non-micronized DRSP is neutral concerning metabolic and haemostatic parameters. At the same time, clinical trials have demonstrated a high contraceptive efficacy and an acceptable bleeding pattern.

Future research should also focus on the clinical effects of therapeutic DRSP doses that might derive from anti-MR properties.

Declarations

Ethics approval and consent to participate

An ethics statement is not applicable, because this study is a review and is based exclusively on published literature.

Consent for publication

Not applicable.

Author contribution(s)

Pedro-Antonio Regidor: Conceptualization; Data curation; Project administration.
Anna Mueller: Validation; Writing – original draft; Writing – review & editing.
Manuela Mayr: Formal analysis; Investigation; Methodology; Supervision.

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Availability of data and materials

Not applicable.

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References

1. Fuhrmann U, Krattenmacher R, Slater EP, et al. The novel progestin drospirenone and its natural counterpart progesterone: biochemical profile and anti-androgenic potential. *Contraception* 1996; 54(4): 243–251.
2. Yasmin. *Summary of Product Characteristics*. Berlin: Bayer Ltd., 2021.
3. Angeliq. *Summary of Product Characteristics*. Berlin: Bayer, 2020.
4. Drovelis. *Summary of Product Characteristics*. Budapest: Gedeon Richter, 2021.
5. Slinda. *Summary of Product Characteristics*. Ismaning: Exeltis Germany GmbH, 2021.
6. Krattenmacher R. Drospirenone: pharmacology and pharmacokinetics of a unique progestogen. *Contraception* 2000; 62(1): 29–38.
7. Rosenbaum P, Schmidt W, Helmerhorst FM, et al. Inhibition of ovulation by a novel progestogen (Drospirenone) alone or in combination with ethinylestradiol. *Eur J Contracept Reprod Health Care* 2000; 5(1): 16–24.
8. Yaz. *Summary of Product Characteristics*. Berlin: Bayer HealthCare, 2020.
9. Yaz. *US Prescribing Information*. Berlin: Bayer HealthCare Pharmaceuticals, 2001.
10. Beyaz. *US Prescribing Information*. Berlin: Bayer Ltd., 2012.
11. Yasminelle. *Summary of Product Characteristics*. Berlin: Bayer Ltd., 2021.
12. Angeliq. *US Prescribing Information*. Berlin: Bayer HealthCare Pharmaceuticals, 2012.
13. Muhn P, Fuhrmann U, Fritzemeier KH, et al. Drospirenone: a novel progestogen with antimineralocorticoid and antiandrogenic activity. *Ann N Y Acad Sci* 1995; 761: 311–335.
14. Oelkers W, Helmerhorst FM, Wuttke W, et al. effect of an oral contraceptive containing drospirenone on the renin-angiotensin-aldosterone system in healthy female volunteers. *Gynecol Endocrinol* 2000; 14(3): 204–213.
15. Bird ST, Pepe SR, Etminan M, et al. The association between drospirenone and hyperkalemia: a comparative-safety study. *BMC Clinical Pharmacol* 2011; 11: 23–28.
16. Moss ME and Jaffe IZ. Mineralocorticoid receptors in the pathophysiology of vascular inflammation and atherosclerosis. *Front Endocrinol* 2015; 6: 153.
17. Adel H, Taye A and Khalifa MM. Spironolactone improves endothelial dysfunction in streptozotocin-induced diabetic rats. *Naunyn Schmiedebergs Arch Pharmacol* 2014; 387(12): 1187–1197.

18. Armani A, Cinti F, Marzolla V, et al. Mineralocorticoid receptor antagonism induces browning of white adipose tissue through impairment of autophagy and prevents adipocyte dysfunction in high-fat-diet-fed mice. *FASEB J* 2014; 28(8): 3745–3757.
19. Silverberg SJ, Lewiecki EM, Mosekilde L, et al. Presentation of asymptomatic primary hyperparathyroidism: proceedings of the third international workshop. *J Clin Endocrinol Metab* 2009; 94(2): 351–365.
20. Chhokar VS, Sun Y, Bhattacharya SK, et al. Hyperparathyroidism and the calcium paradox of aldosteronism. *Circulation* 2005; 111(7): 871–878.
21. Tomaschitz A, Ritz E, Pieske B, et al. Aldosterone and parathyroid hormone interactions as mediators of metabolic and cardiovascular disease. *Metabolism* 2014; 63(1): 20–31.
22. Lang F, Leibrock C, Pelzl L, et al. Therapeutic interference with vascular calcification-lessons from Klotho-Hypomorphic mice and beyond. *Front Endocrinol* 2018; 9: 207.
23. Kuhl H. Pharmacology of progestogens. *J Reproduktionsmed Endokrinol* 2011; 8(Sonderheft 1): 157–177.
24. Louw-du Toit R, Perkins MS, Hapgood JP, et al. Comparing the androgenic and estrogenic properties of progestins used in contraception and hormone therapy. *Biochem Biophys Res Commun* 2017; 491(1): 140–146.
25. Tan JK and Ediriweera C. Efficacy and safety of combined ethinyl estradiol/drospirenone oral contraceptives in the treatment of acne. *Int J Womens Health* 2010; 91: 213–221.
26. Wiesinger H, Berse M, Klein S, et al. Pharmacokinetic interaction between the CYP3A4 inhibitor ketoconazole and the hormone drospirenone in combination with ethinylestradiol or estradiol. *Br J Clin Pharmacol* 2015; 80(6): 1399–1410.
27. Richter WH, Koytchev R, Kirkov V, et al. Comparative pharmacokinetic estimates of drospirenone alone and in combination with ethinyl estradiol after single and repeated oral administration in healthy females. *Contraception* 2020; 101(2): 137–143.
28. Helgason S, Damber MG, von Schoultz B, et al. Estrogenic potency of oral replacement therapy estimated by the induction of pregnancy zone protein. *Acta Obstet Gynecol Scand* 1982; 61(1): 75–79.
29. Grandi G, Napolitano A and Cagnacci A. Metabolic impact of combined hormonal contraceptives containing estradiol. *Expert Opin Drug Metab Toxicol* 2016; 12(7): 779–787.
30. Klipping C, Duijkers I, Mawet M, et al. Endocrine and metabolic effects of an oral contraceptive containing estetrol and drospirenone. *Contraception* 2021; 103(4): 213–221.
31. Gaspard U, Endrikat J, Desager JP, et al. A randomized study on the influence of oral contraceptives containing ethinylestradiol combined with drospirenone or desogestrel on lipid and lipoprotein metabolism over a period of 13 cycles. *Contraception* 2004; 69(4): 271–278.
32. Taneepanichskul S and Phupong V. Influence of a new oral contraceptive with drospirenone on lipid metabolism. *Gynecol Endocrinol* 2007; 23(6): 347–350.
33. Mawet M, Maillard C, Klipping C, et al. Unique effects on hepatic function, lipid metabolism, bone and growth endocrine parameters of estetrol in combined oral contraceptives. *Eur J Contracept Reprod Health Care* 2015; 20(6): 463–475.
34. Archer DF. Drospirenone and estradiol: a new option for the postmenopausal woman. *Climacteric* 2007; 10(Suppl. 1): 3–10.
35. Palacios S, Colli E and Regidor PA. Metabolic and laboratory effects of a progestin-only pill containing Drospirenone 4 mg in comparison to desogestrel 75 μg: a double-blind, double-dummy, prospective, randomised study. *Eur J Contracept Reprod Health Care* 2021; 4: 1–8.
36. Godsland IF, Walton C, Felton C, et al. Insulin resistance, secretion, and metabolism in users of oral contraceptives. *J Clin Endocrinol Metab* 1992; 74(1): 64–70.
37. Kojima T, Lindheim SR, Duffy DM, et al. Insulin sensitivity is decreased in normal women by doses of ethinyl estradiol used in oral contraceptives. *Am J Obstet Gynecol* 1993; 169(6): 1540–1544.
38. Bastianelli C, Farris M, Rosato E, et al. Pharmacodynamics of combined estrogen-progestin oral contraceptives: 1. Effects on metabolism. *Expert Rev Clin Pharmacol* 2017; 10(3): 315–326.
39. Klipping C and Marr J. Effects of two combined oral contraceptives containing ethinyl estradiol 20 μg combined with either drospirenone or desogestrel on lipids, hemostatic parameters and carbohydrate metabolism. *Contraception* 2005; 71(6): 409–416.
40. Gaspard U, Scheen A, Endrikat J, et al. A randomized study over 13 cycles to assess the influence of oral contraceptives containing ethinylestradiol combined with drospirenone or desogestrel on carbohydrate metabolism. *Contraception* 2003; 67(6): 423–429.
41. Gambacciani M, Rosano G, Cappagli B, et al. Clinical and metabolic effects of drospirenone-estradiol in menopausal women: a prospective study. *Climacteric* 2011; 14(1): 18–24.
42. Paoletti AM, Cagnacci A, Di Carlo C, et al. Clinical effect of hormonal replacement therapy with estradiol associated with norethisterone or drospirenone. A prospective randomized placebo-controlled study. *Gynecol Endocrinol* 2015; 31(5): 384–387.
43. Lidegaard O, Nielsen LH, Skovlund CW, et al. risk of venous thromboembolism from use of oral contraceptives containing different progestogens and oestrogen doses: Danish cohort study, 2001-9. *BMJ* 2011; 343: d6423.
44. Lidegaard O, Lokkegaard E, Jensen A, et al. Thrombotic stroke and myocardial infarction with hormonal contraception. *N Engl J Med* 2012; 366(24): 2257–2266.
45. Khialani D, Rosendaal F and Vlieg AVH. Hormonal contraceptives and the risk of venous thrombosis. *Semin Thromb Hemost* 2020; 46(8): 865–871.
46. Farris M, Bastianelli C, Rosato E, et al. Pharmacodynamics of combined estrogen-progestin oral contraceptives: 2 effects on hemostasis. *Expert Rev Clin Pharmacol* 2017; 10(10): 1129–1144.
47. Benefits of combined hormonal contraceptives (CHCs) continue to outweigh risks—CHMP endorses PRAC recommendation, 2013, https://www.ema.europa.eu/en/news/benefits-combined-hormonal-contraceptives-chcs-continue-outweigh-risks-chmp-endorses-prac
48. Douxfils J, Klipping C, Duijkers I, et al. Evaluation of the effect of a new oral contraceptive containing estetrol and drospirenone on hemostasis parameters. *Contraception* 2020; 102(6): 396–402.

49. Regidor PA, Colli E and Schindler AE. Drospirenone as estrogen-free pill and hemostasis: coagulatory study results comparing a novel 4 mg formulation in a 24 + 4 cycle with desogestrel 75 mg per day. *Gynecol Endocrinol* 2016; 32(9): 749–751.
50. Palacios S, Colli E and Regidor PA. Efficacy and cardiovascular safety of the new estrogen-free contraceptive pill containing 4 mg drospirenone alone in a 24/4 regime. *BMC Womens Health* 2020; 20(1): 218.
51. EMA. Assessment Report Drovelis, 2021.
52. Gemzell-Danielsson K, Apter D, Zatik J, et al. Estetrol-Drospirenone combination oral contraceptive: a clinical study of contraceptive efficacy, bleeding pattern and safety in Europe and Russia. *BJOG* 2021; 129: 63–71.
53. Vinogradova Y, Coupland C and Hippisley-Cox J. Use of hormone replacement therapy and risk of venous thromboembolism: nested case-control studies using the QResearch and CPRD databases. *BMJ* 2019; 9364: k4810.
54. Manson JE, Bassuk SS, Kaunitz AM, et al. The Women's Health Initiative trials of menopausal hormone therapy: lessons learned. *Menopause* 2020; 27(8): 918–928.
55. Kang AK, Duncan JA, Cattran DC, et al. effect of oral contraceptives on the renin-angiotensin system and renal function. *Am J Physiol Regul Integr Comp Physiol* 2001; 280(3): R807–R813.
56. White WB, Hanes V, Chauhan V, et al. Effects of a new hormone therapy, drospirenone and 17-beta-estradiol, in postmenopausal women with hypertension. *Hypertension* 2006; 48(2): 246–253.
57. Archer DF, Thorneycroft IH, Foegh M, et al. Long-term safety of drospirenone-estradiol for hormone therapy: a randomized, double-blind, multicenter trial. *Menopause* 2005; 12(6): 716–727.
58. Bachmann G, Sulak PJ, Sampson-Landers C, et al. Efficacy and safety of a low-dose 24-day combined oral contraceptive containing 20 micrograms ethinylestradiol and 3 mg drospirenone. *Contraception* 2004; 70(3): 191–198.
59. Klipping C, Duijkers I, Fortier MP, et al. Contraceptive efficacy and tolerability of ethinylestradiol 20 mug/drospirenone 3 mg in a flexible extended regimen: an open-label, multicentre, randomised, controlled study. *J Fam Plann Reprod Health Care* 2012; 38(2): 73–83.
60. Yildizhan R, Yildizhan B, Adali E, et al. Effects of two combined oral contraceptives containing ethinyl estradiol 30 μg combined with either gestodene or drospirenone on hemostatic parameters, lipid profiles and blood pressure. *Arch Gynecol Obstet* 2009; 280(2): 255–261.
61. Parsey KS and Pong A. An open-label, multicenter study to evaluate Yasmin, a low-dose combination oral contraceptive containing drospirenone, a new progestogen. *Contraception* 2000; 61(2): 105–111.
62. Archer DF, Ahrendt HJ and Drouin D. Drospirenone-only oral contraceptive: results from a multicenter noncomparative trial of efficacy, safety and tolerability. *Contraception* 2015; 92(5): 439–444.
63. Kimble T, Burke AE, Barnhart KT, et al. A 1-year prospective, open-label, single-arm, multicenter, phase 3 trial of the contraceptive efficacy and safety of the oral progestin-only pill drospirenone 4 mg using a 24/4-day regimen. *Contracept X* 2020; 2: 100020.
64. Mohandas A, Suboc TB, Wang J, et al. Mineralocorticoid exposure and receptor activity modulate microvascular endothelial function in African Americans with and without hypertension. *Vasc Med* 2015; 20(5): 401–408.
65. Garg R, Rao AD, Baimas-George M, et al. Mineralocorticoid receptor blockade improves coronary microvascular function in individuals with type 2 diabetes. *Diabetes* 2015; 64(1): 236–242.
66. Christiansen C. Effects of drospirenone/estrogen combinations on bone metabolism. *Climacteric* 2005; 8(Suppl. 3): 35–41.
67. Marjoribanks J, Farquhar C, Roberts H, et al. Long-term hormone therapy for perimenopausal and postmenopausal women. *Cochrane Database Syst Rev* 2017; 1(1): CD004143.
68. Nappi C, Di Spiezio Sardo A, Greco E, et al. Effects of an oral contraceptive containing drospirenone on bone turnover and bone mineral density. *Obstet Gynecol* 2005; 105(1): 53–60.
69. Gargano V, Massaro M, Morra I, et al. Effects of two low-dose combined oral contraceptives containing drospirenone on bone turnover and bone mineral density in young fertile women: a prospective controlled randomized study. *Contraception* 2008; 78(1): 10–15.
70. Hadji P, Colli E and Regidor PA. Bone health in estrogen-free contraception. *Osteoporos Int* 2019; 30(12): 2391–2400.
71. O'Connell K and Westhoff C. Pharmacology of hormonal contraceptives and acne. *Cutis* 2008; 81(Suppl. 1): 8–12.
72. Palacios S, Colli E and Regidor PA. Multicenter, phase III trials on the contraceptive efficacy, tolerability and safety of a new drospirenone only pill. *Acta Obstet Gynecol Scand* 2019; 98(12): 1549–1557.