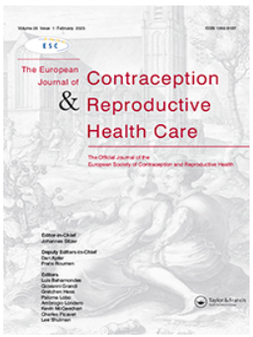


Taylor & Francis
Taylor & Francis Group

The European Journal of Contraception & Reproductive Health Care

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/iejc20

The drospirenone (DRSP)-only pill: clinical implications in the daily use

Ali Kubba, Kristina Gemzell-Danielsson, Santiago Palacios, Inka Wiegratz, Giovanni Grandi, Enrico Colli & Pedro Antonio Regidor

To cite this article: Ali Kubba, Kristina Gemzell-Danielsson, Santiago Palacios, Inka Wiegratz, Giovanni Grandi, Enrico Colli & Pedro Antonio Regidor (2023) The drospirenone (DRSP)-only pill: clinical implications in the daily use, The European Journal of Contraception & Reproductive Health Care, 28:1, 36-43, DOI: 10.1080/13625187.2022.2164186

To link to this article: https://doi.org/10.1080/13625187.2022.2164186

Published online: 01 Feb 2023.

THE EUROPEAN JOURNAL OF CONTRACEPTION & REPRODUCTIVE HEALTH CARE
2023, VOL. 28, NO. 1, 36–43
https://doi.org/10.1080/13625187.2022.2164186

Taylor & Francis
Taylor & Francis Group

REVIEW

The drospirenone (DRSP)-only pill: clinical implications in the daily use

Ali Kubba[a], Kristina Gemzell-Danielsson[b], Santiago Palacios[c], Inka Wiegratz[d], Giovanni Grandi[e], Enrico Colli[f] and Pedro Antonio Regidor[g]

[a]Gynaecology, Guy's Hospital, London, UK; [b]Department of Women's and Children's Health, Karolinska Institutet and WHO-centre, Karolinska University Hospital, Stockholm, Sweden; [c]Salud y Medicina de la Mujer, Instituto Palacios, Madrid, Spain; [d]Frankfurt Hormone and Fertility Center & Goethe University of Frankfurt, Frankfurt, Germany; [e]Department of Medical and Surgical Sciences for Mother, Child and Adult, Obstetrics and Gynecology Unit, university of Modena and Reggio Emilia; Azienda Ospedaliero Universitaria Policlinico, Modena, Italy; [f]Exeltis HealthCare Madrid, Madrid, Spain; [g]Exeltis Europe, Ismaning, Germany

ABSTRACT

Objectives: Progestins used in contraception are either components of combined hormonal contraceptives or are used as a single active ingredient. Progestins are highly effective in long-term contraception and have a very good safety profile with very few contraindications.

Methods: An oestrogen-free ovulation inhibitor POP has been authorised in the USA and the EU. It contains 4 mg of drospirenone (DRSP). The hormone administration regimen of 24 days followed by a 4-day hormone-free period was chosen to improve bleeding control and to maintain oestradiol concentrations at early follicular- phase levels, preventing oestrogen deficiency.

Results: Clinical trials have demonstrated high contraceptive effectiveness, a very low risk of cardiovascular risk events and a favourable bleeding pattern. Due to the long half-life of DRSP (30–34 h), the effectiveness is maintained even in case of a forgotten pill on a single occasion. Studies involving deliberate 4 days in one cycle 24-hour delays in taking a pill have demonstrated that ovulation inhibition is maintained if a single pill is missed.

Conclusions: This review article will describe the clinical impact in the daily use of the 4 mg DRSP only pill and the resulting data on the effectiveness and safety of this hormonal contraceptive.

SHORT CONDENSATION

The 4 mg drospirenone-only pill improves the bleeding profile in comparison to 0.075 mg desogestrel and achieves high contraceptive efficacy even with a 24 h missed pill window.

ARTICLE HISTORY
Received 12 December 2022
Accepted 27 December 2022

KEYWORDS
Drospirenone-only pill; contraception; efficacy; safety

Introduction

Since the advent in 1960 of oral hormonal contraceptives as combined oestrogen/progestogen regimen, combined oral contraceptives (COC) have undergone ongoing developments in the oestrogen and progestogen component with different characteristics aiming to reduce undesirable effects while maintaining inhibition of ovulation [1]. Many steroidal hormone actions translate into non-contraceptive benefits and possibilities of therapeutic impact. The wide range of positive effects besides the primary use as contraceptives include reduction of colorectal, endometrial, and ovarian cancer rates, dysmenorrhoea, and endometriosis symptoms relief and decrease in acne, menstrual flow, and PMS. Awareness of the non-contraceptive benefits of hormonal contraceptives must be appreciated, besides their objective high efficacy and safety, as these effects impact compliance. Moreover, COCs have a very favourable cost/-benefit ratio and a good level of compliance compared to other drugs used therapeutically. Health benefits of COCs represent an essential feature of the overall impact of this class of drugs beyond their primary action [2].

The fact remains that, thirteen percent of women aged between 15 and 19 years become pregnant each year, a ratio that has not changed statistically since the 70 s. Up to eighty-five percent of these pregnancies are unintended. The economic and social impact factors of the one million teenage pregnancies each year in the USA represent an important political factor [3]. According to Bearak et al. the unintended pregnancy rate per 1000 women between 15 and 49 years in North America and Europe remains 35 of 1000 with 49% of them ending in an abortion [4].

Avoiding unintended pregnancies is a primary concern of most sexually active persons, especially adolescents. It is estimated that in 1995, eighty-one percent of the women aged between 15 and 19 years at risk of unintended pregnancy were using contraceptive methods; many of them reported using two methods—one to avoid sexually transmitted diseases (STDs) and the second to prevent pregnancy. The most used contraceptive methods were either oral contraceptives (44% of the cases), male condoms (46% of the cases), or in 8% dual protection. However, the success of these methods depends heavily on user compliance. This becomes evident when comparing typical and perfect use effectiveness data. The discrepancy is most pronounced for adolescents reflecting problems with incorrect intake of tablets or failure to use a condom just before

CONTACT Ali Kubba aliakubba@aol.com Gynaecology, Guy's Hospital, London, UK
This article was originally published with errors, which have now been corrected in the online version. Please see Correction (http://dx.doi.org/10.1080/13625187.2023.2187161)

sexual intercourse. These USA figures are likely to be similar in most settings [5].

Health care providers should also consider the very low but potential risks associated with using COC, e.g., the occurrence of thromboembolic events.

The last referrals of the European Medicine Agency of 2014 [6] rated the risk for drospirenone (DRSP) containing COC at 9-12 cases among 10.000 users (0.1%). They declared in 2016 [8] that this risk for dienogest (DNG) containing COC with ethinyl oestradiol (EE) is still at 8-11 cases among 10.000 users and the risk with oestradiol as unknown.

New developments in oral contraception, such as, oestrogen-free contraceptive, aim to reduce cardiovascular side effects, while maintaining high efficacy. Here the introduction of a new drospirenone-only pill can be a milestone based on the characteristics of this progestogen.

Development and classification of progestins in contraception

The first orally active progestin used in combined hormonal contraceptives were norethynodrel and norethisterone [1,7]. Development of new progestins was introduced to reduce androgenic side effects. The progestins used in Combined Hormonal Contraceptives (CHC) can be classified according to different criteria as follows below.

It has become common practice to apply this 'historical' classification defining 'generations' of COCs based on their introduction to the market; a rather crude categorisation which does not reflect clinical profile:

1st generation: Norethynodrel, Norethisterone Acetate (NET, NETA).
2nd generation: Levonorgestrel (LNG).
3rd generation: Gestodene, Desogestrel, Norgestimate (GEST, DES, NGM).
4th generation: Drospirenone (DRSP).

This classification tends to confuse health care providers and users and should be avoided in counselling as it may be misleading [8].

The classification should instead be focussed on the partial activities of the different progestins.

Cyproterone Acetate (CPA) and Chlormadinone Acetate (CMA) (17α-hydroxyprogesterone derivatives) have never been included in this categorisation. CPA-containing oral contraceptives were initially classified as drugs to treat hyperandrogenism in women who required contraception. CMA was only introduced in some countries and is not internationally available. The same was true for Dienogest (DNG), which was developed in Germany though currently an increasing number of countries are introducing DNG containing COCs, combined with EE or E2 [9].

Classification according to molecular structure

The molecular structure gives an indirect indication of the biological activity of the steroid. Different groups of progestins can be distinguished [9]. These are described in Table 1.

Classification according to interaction with steroid receptors

Depending on the structure, progestins have different interactions with the various steroid receptors in the body (progesterone, androgen, oestrogen, gluco- and mineralocorticoid receptors).

Based on this classification of receptor activities, several groups of progestins can be differentiated.

Androgenic, anti-androgenic, mildly anti-androgenic, or neutral and anti-mineralocorticoid progestins: only drospirenone combines anti-mineralocorticoid and anti-androgen action.

The different binding affinities and the different receptor effects are described in Table 2 [1].

Table 1. Contraceptive progestins and extra-progestogenic effects.

	Progestogen	Anti-gonadotropin	Anti-oestrogen	Oestrogen	Androgen	Anti-androgen	Gluco-corticoid	Anti-mineralo corticoid	Pro Coagulatory
Progesterone	+	+	+	−	−	+/−	+	+	−
Dydrogesterone	+	−	+	−	−	+/−	−	+/−	−
Medrogestone	+	+	+	−	−	+/−	−	−	
17a-Hydroxy-Progesterone Derivates									
Chlormadinonacetate	+	+	+	−	−	+	+	−	−
Cyproterone acetate	+	+	+	−	−	++	+	−	−
19-Nor-Progesteron-Derivates	+	+	+	−	+/−	+	+	−	+
Nomegestrolacetate	+	+	+	−	+/−	−	+	−	
Promegeston									
Trimegeston	+	+	+	−	−	+/−	−	−	−
19-Nortestosterone-Derivates	+	+	+	−	−	−	−	−	−
Norethisterone	+	+	+	−	−	+/−	−	+/−	−
Norethinodrel	+	+	+	+	+	−	−	−	+
Levonorgestrel	+	+	+	+	+	−	−	−	−
Norgestimate	+/−	+	+	+	−	+	−	−	−
Desogestrel	+	+	+	−	+	−	−	−	−
Gestoden	+	+	+	−	-	+	−	−	−
Dienogest	+	+	+	−	+	−	−	−	−
Spironolactone Derivate									
Drospirenone	+	+	+	−	−	+	−	+	−

Table 2. Relative binding affinities of progestins to steroid receptors and serum binding proteins.

	PR	AR	ER	GR	MR	SHBG	CBG	Albumin Bound	Free
Progesterone	50	0	0	10		0	36	79.3	2.4
Dydrogesterone	75	0	–	–	–	–	–		
Chlormadinone acetate	67	5	0	8	0	0	0		
Cyproterone acetate	90	6	0	6	8	0	0		
Medroxyprogesterone acetate	115	5	0	29	160	0	0		
Nomegestrol	125	6	0	6	0	0	0		
Drospirenone	35	65	0	6	230	0	0		
Norethisterone	75	15	0	0	0	16	0	60.8	3.7
Levonorgestrel	150	45	0	1	75	50	0	50	2.5
Norgestimate	15	0	0	1	0	0	0		
Desogestrel (Etonogestrel)	150	20	0	14	0	15	0	65.5	2.5
Gestodene	90	85	0	27	290	40	0	24.1	0.6
Dienogest	5	10	0	1	0	0	0		

VTE risk of combined and oestrogen free hormonal contraception

Several studies have shown that CHC have been associated with an increased risk of venous thromboembolism [10], dependent on the dose and type of the oestrogen component [11]. Subsequent studies showed that the risk was significantly reduced by lowering the dose of oestrogen, and this resulted in the introduction of newer preparations containing $<50\,\mu g$ EE [12–14]. The characteristics of the progestogen, when used in combination with EE, may also influence the risk of thrombo-embolism [15]. Some factors may play an essential role in this respect, such as the type and dose of oestrogen with which it is combined, the route of admission; the amount of progestins; the duration of treatment, and the type of progestin [16].

EE has, due to its action on the liver, a procoagulatory effect by enhancing the factors responsible for coagulation and reducing the fibrinolytic factors. It is supposed that oestradiol or oestradiol valerate have less impact on the liver due to faster metabolisation than EE. Oestradiol is metabolised in the liver to oestrone. In turn, oestrone is converted into oestrone sulphate, so a significantly lower biological activity is observed compared to EE [17].

As Winkler [18] has shown, oestrogens modify the dynamic balance of haemostasis by enhancing the coagulatory factors (e.g., Factor VII) and the anti-fibrinolytic factors (e.g., PAI-1). The number of D-dimers rises consecutively due to the higher content of fibrin and its degenerated products in the blood.

This balance is also influenced by the amount of the EE concentration that activates the coagulatory site and the dose of progestogen that activates the anti-fibrinolytic factors, e.g., PAI-1 [16].

During the drospirenone-only pill clinical trial program, laboratory data for the following haemostatic parameters were evaluated: APC resistance, Antithrombin III, D-Dimer, clotting factor VII, Clotting factor VIII, and Protein C reactivity. Data were assessed after randomisation before starting the pill intake and after nine months of treatment and compared to the desogestrel-only pill [19].

At the endpoint, the mean values of factor VII were comparable between the groups, but the change from baseline to endpoint was more pronounced in the DRSP group leading to the statistically significant difference (p 0.0088, 2-sample t-test) between the groups.

The difference in mean Protein C activity change from baseline to endpoint was 0.0332 in the DRSP versus 0.157 in the desogestrel group; p 0.0249, 2-sample t-test. The differences in change of clotting factor VII and Protein C activity during the trial may be attributed to the baseline level differences.

A relevant reduction in the amount of D-Dimer could be observed in the DRSP group. From baseline values of 264.9 ng/mL, they dropped to 215.0 ng/mL, whereas, in the desogestrel group, there was a rise from 201.4 ng/mL to 281.5 ng/mL. The differences in the analysed other parameters (APC resistance, ATIII activity, and clotting factor VIII) were not statistically significant before and after the treatment [19].

Clinical efficacy and safety of the DRSP-only pill

Archer et al. [20], Palacios et al. [21], and Kimble et al. [22] showed in different clinical phase III trials the contraceptive efficacy of drospirenone 4 mg. These trials were performed in the European Union (2 clinical phase III trials) and the USA.

The primary endpoint of all trials was to obtain a satisfactory Pearl Index (PI). The pooled analysis of both European studies showed a total PI of 0.73 [95% CI: 0.3133; 1.4301] (14,329 cycles of drospirenone 4 mg) and an adjusted PI of 0.7898 [95% CI: 0.3410; 1.5562] [21].

In the USA clinical trial, 17 pregnancies occurred (Pearl Index: 4.0 (95% confidence interval [CI], 2.3–6.4, $n = 953$), of which three were unconfirmed, and two were from sites excluded from the primary analysis for significant breaches of FDA regulations were documented. These pregnancies were all detected in non-breastfeeding women aged $\leq$35 years. For confirmed pregnancies among 915 non-breastfeeding women aged $\leq$35 years from sites with no protocol violations, the PI was 2.9 (95% CI: 1.5–5.1) [20]. These PIs obtained with the DRSP-only pill in Europe and USA are in the range of that described for combined formulations.

In a subset of women, a series of cardiovascular risk factors including BMI, age, smoking status, were documented, and a series of clinical and laboratory examinations like RR measurement and electrocardiography (ECG) measurement were evaluated (see Tables 3 and 4) [23].

During the clinical development program of drospirenone 4 mg, there were no reports of venous thromboembolism (VTE) under more than 2500 and 25.000 evaluable cycles. There were also no reports of arterial thromboembolism, myocardial infarcts, or. strokes.

In the US, 422 participants (41.9%) had a risk factor for VTE, while in the two European studies, 116 patients

Table 3. Patients characteristics of thromboembolic risk factors of the European studies.

n (%)		Study 1 Drospirenone (*N* = 713)	Study 2 Drospirenone (*N* = 858)	Desogestrel (*N* = 332)
Age, mean (SD), years		28.7 (7.1)	28.9 (7.1)	28.9 (7.1)
Age group	≤35 yr	569 (79.8)	682 (79.5)	259 (78.0)
	>35 yr	144 (20.2)	176 (20.5)	73 (22.0)
BMI, mean (SD) (kg/m^2)		23.0 (3.8)	23.0 (3.5)	22.8 (3.9)
BMI group	<30	672 (94.2)	828 (96.5)	316 (95.2)
	≥30	41 (5.8)	30 (3.5)	16 (4.8)
BP group (mm Hg)	SBP <130, DBP <85	571 (80.1)	727 (84.7)	290 (87.3)
	SBP ≥130, DBP ≥85	142 (19.9)	131 (15.3)	42 (12.7)
Presence of ≥1 VTE risk factor		110 (15.4)	142 (16.5)	59 (17.8)
Current smoker		182 (25.5)	237 (27.6)	103 (31.0)
Regular menstrual bleeding during the last 6 cycles		680 (95,4)	786 (91.6)	305 (91.9)
Prior treatment with sex hormones and modulators of genital system		455 (63,8)	704 (82.1)	288 (86.7)
Starters		287 (40.3)	417 (48.6)	

Table 4. Patients characteristics of thromboembolic risk factors of the USA study.

Risk factors		*N* = 1006
Family history of thromboembolic illness, *n* (%)	Yes	12 (1.2%)
	No	993 (98.8%)
	Missing	1
Evidence of predisposing conditions for a vascular or metabolic disease, *n* (%)	Yes	5 (0.5%)
	No	1001 (99.5%)
Current smoker older than 35 years or non-smoker over 40 years old, *n* (%)	Yes	51 (5.1%)
	No	955 (94.9%)
BMI >30 kg/m^2, *n* (%)	Yes	353 (35.1%)
	No	653 (64.9%)
Number of VTE risk factors, *n* (%)	0	611 (60.8%)
	1	367 (36.5%)
	2	27 (2.7%)
	≥3	0
	Missing	1

Table 5. Blood pressure development of study 1 in Europe.

Changes from baseline		SB*p* < 130 and DB*p* < 85 (mmHg) N = 548	SB*p* ≥ 130 and DB*p* ≥ 85 (mmHg) N = 137
SBP (mmHg)	Mean (SD)	1.77 (10.08)	−7.59 (9.19)
	Median	0.0	−8.0
DBP (mmHg)	Mean (SD)	1.06 (8.20)	−4.85 (7.85)
	Median	0.0	−5.0

(16.3%) and 145 (16.9%), respectively had a risk factor. See Tables 3 and 4.

The main risk factors were age >35 years and BMI >30. BMI values over 30 were present in 71 patients in Europe and 388 in the USA. There, 188 women had a BMI >35, and 88 had a BMI >40. In 26% of the participants, smokers were randomised in the EU and 18% % in the US study.

Additional cardiovascular safety factors [blood pressure]

The administration of drospirenone in combination with oestrogens for six months was associated with a slight decrease in systolic (SBP) and diastolic (DBP) blood pressure compared to levonorgestrel in combined formulations in some studies [24,25]. On the other side, studies based on a Holter monitoring of blood pressure (24 h) showed that the association between EE and DRSP had a neutral impact on BP, because of EE impact on the liver [26]. This is not the case for DRSP 24 + 4 alone that gives a slight decrease. This influence on blood pressure in patients with a moderate hypertension was also shown when 4 mg drospirenone was compared with 0.015 mg desogestrel [23]. The anti-mineralocorticoid effect of drospirenone explains these results. Table 5 depicts the data.

The data in study 2 showed that the women with a baseline value of SBP >130 mmHg or DBP >85 mmHg (*n* = 130) had an average decrease of 7.0 mmHg with drospirenone 4 mg for the systolic value and 5.5 mmHg for the diastolic value over time. For participants with average SDP (<130 mmHg) and DBP <85 mmHg, the absolute mean change was 0.00 mmHg for both parameters. The observational period to assess these events was between the first visit at study entry and at day 29 + 2 of the last cycle. Exams were performed at each visit (cycle) during the study.

Finally, no influence on ECG parameters was observed for women treated with drospirenone [23]

Choice of hormonal contraception in high-risk groups

While oestrogen free contraception can be safely used in women with disease risk factors such as high BMI, smoking and being over age 35 the CHC is not an optimal choice

and may be contraindicated when multiple risk factors exist.

Pomp et al. [27] could first describe the impact of the BMI on developing deep vein thrombosis and pulmonary embolism.

They compared 3834 patients with a first venous thrombosis to 4683 control subjects. All were non-pregnant and without active malignancies. Relative to those with a normal BMI (<25 kg/m2), overweight (BMI >= 25 and BMI <30 kg/m2) increased the risk of venous thrombosis 1.7-fold [odds ratio (OR) adj (age and sex) 1.70. 95% confidence interval (CI) 1.55–1.87] and obesity (BMI >30 kg/m2) 2.4-fold (OR adj 2.44, 95% CI 2.15–2.78). Obese women who used oral contraceptives had a 24-fold higher thrombotic risk (OR adj 23.78, 95% CI 13.35–42.34) than women with a normal BMI who did not use oral contraceptives. [27].

The same group reported that current and former smoking resulted in a moderately increased risk of deep venous thrombosis (odds ratio (OR) for current smokers = 1.43; 95% confidence interval (CI95) 1.28–1.60. and for former smokers 1.23; CI95 1.09–1.38) compared with non-smoking. Women who were current smokers and used oral contraceptives had an 8.8-fold higher risk (OR 8.79, CI95 5.73–13.49) than non-smoking women who did not use oral contraceptives. Relative to non-smoking non-carriers, the combined effect of factor V Leiden and current smoking led to a 5.0-fold increased risk; for the prothrombin 20210 A mutation, this was a 6.0-fold increased risk [28].

Jick et al. [29] found that age also had a substantial impact on the VTE risk, especially for COC with a higher number of oestrogens or with progestins of the 4th generation.

Whether the women used a combined COC with levonorgestrel or drospirenone, the VTE risk was raised from a basal incidence rate per 100.000 person-years of 24.8 for women using the COC of drospirenone/ethinylestradiol and had an age <30 years to 51.2 cases for women aged 40-44. For those women using a combined contraceptive containing levonorgestrel, these data were 5.39 and 21.3, respectively.

COC users with VTE risk factors should be informed when the method is absolutely [WHO MEC 4] or relatively indicated [WHO MEC 3]. The POP is seen as a safe alternative contraceptive in such cases.

Bleeding profile in pop users with VTE risk

The regimen of 24 + 4 is a real revolution in the evolution of POP: DRSP 24 + 4 is the first POP with a hormone free interval of 4 days in this class of drugs. According to bleeding profiles demonstrated it can be said that it was a 'winning bet' in the field of POP.

Regidor et al. [30] compared 858 women on DRSP (6691 treatment cycles) with 332 women on DSG treatment (2487 treatment cycles), to evaluate the amount of unscheduled bleeding days and/or spotting's between these two progestin-only pills, especially in risk groups. Three groups were considered.

Age >35 years: During cycles 2-4, the mean number of unscheduled bleeding days and spotting was 8.1 (SD10.53) for DRSP and 20.1 (19.41) for DSG; $p = 0.0089$.

BMI >25 kg/m^2: During cycles 2-4 the mean number of unscheduled bleeding days and spotting was 7,8 (SD 12,18) for DRSP and 17,7 for DSG (SD 19, 39); $p = 0.0001$.

Smokers: During cycles 2-4, the mean number of unscheduled bleeding days and spotting was 9,6 (SD 11,69) for DRSP and 17,4 (SD 17, 47); $p = 0.0016$.

These data showed an improvement in the bleeding profile of women with specific cardiovascular risk factors like age >35 years, BMI >25 kg/m^2, and smokers using the DRSP-only oral contraceptive product. Herby, a higher compliance, and thus higher contraceptive efficacy in these patients who benefit from oestrogen-free contraceptive methods are expected [29].

DRSP/DSG adverse events leading to study discontinuation

A double-blind, double-dummy prospective phase III study in healthy women aged 18–45 years evaluated a total of 858 women with 6,691 DRSP and 332 women with 2,487 DSG treatment cycles.

Overall, 82 (9.6%) women in the DRSP group and 44 (13.3%) women in the DSG group experienced TEAEs leading to study discontinuation (see Table 6). The most common individual TEAEs leading to withdrawal were vaginal bleeding (2.6% in the DRSP group vs. 5.4% in the DSG group) and acne (1.0% in the DRSP group vs. 2.7% in the DSG group).

Using the Kaplan–Meier curve estimates and the area under the curve (AUC) for the overall adverse events as a discontinuation reason, the difference between DRSP and DSG was 32.0% in favour of DRSP, with AUC estimates of 0.583 for DRSP and 0.857 for DSG (see Figure 1. The discontinuation rate was 10% for the DRSP group and 14% for the DSG group ($p < .005$).

In total, 48 (5.5%) women in the DRSP group and 33 (9.9%) in the DSG group experienced bleeding related TEAEs. Most of the bleeding related TEAEs were mild or moderate, whereas four (0.4%) women with DRSP and three (0.9%) women with DSG experienced TEAEs of severe intensity. A total of 28 (3.3%) women in the DRSP group and 22 (6.6%) women in the DSG group discontinued the trial due to bleeding related TEAEs ($p < .005$). Using the Kaplan–Meier curve estimates and the AUC for bleeding as a discontinuation reason, the difference between DRSP and DSG was 55.7% in favour of DRSP, with AUC estimates of 0.199 for the DRSP group and 0.449 for the DSG group. The discontinuation rate was 3.7% for the DRSP group and 7.3% for the DSG group [31].

These data support the high acceptability of the DRSP-only formulation.

Summary remarks and conclusions

Contraceptives that combine high efficacy, a safe profile and tolerability as demonstrated by lower discontinuation rates have special attraction for women across the life course. If translated into higher compliance, new formulation may help providers tackle unplanned pregnancy better.

Cardiovascular adverse events remain a concern as demonstrated by The Lancet women and cardiovascular disease Commission statement in 2021 that cardiovascular disease is the leading cause of mortality for women and was

Table 6. Incidence of TEAEs leading to premature discontinuation.

Preferred term	DRSP ($N = 858$) *n* (%)	DSG ($N = 332$) *n* (%)	Total ($N = 1190$) *n* (%)
Subjects with at least one TEAE leading to premature discontinuation	82 (9.6)	44 (13.3)	126 (10.6)
Abnormal uterine bleeding	27 (3.5)	22 (6.9)	49 (4.2)
Acne	9 (1.0)	9 (2.7)	18 (1.5)
Weight increased	8 (0.9)	3 (0.9)	11 (0.9)
Libido decreased	5 (0.6)	2 (0.6)	7 (0.6)
Headache	2 (0.2)	2 (0.6)	4 (0.3)
Alopecia	2 (0.2)	1 (0.3)	3 (0.3)
Mood swings	3 (0.3)	0	3 (0.3)
Abdominal pain	2 (0.2)	0	2 (0.2)
Depressed mood	2 (0.2)	0	2 (0.2)
Depression	1 (0.1)	1 (0.3)	2 (0.2)
Gamma-glutamyltransferase increased	2 (0.2)	0	2 (0.2)
Nausea	2 (0.2)	0	2 (0.2)
Rash	2 (0.2)	0	2 (0.2)
Abdominal pain lower	1 (0.1)	0	1 (0.1)
Abdominal pain upper	1 (0.1)	0	1 (0.1)
Affective disorder	1 (0.1)	0	1 (0.1)
Alanine aminotransferase increased	1 (0.1)	0	1 (0.1)
Blood thyroid stimulating hormone increased	1 (0.1)	0	1 (0.1)
Constipation	1 (0.1)	0	1 (0.1)
Contact lens intolerance	1 (0.1)	0	1 (0.1)
Dysmenorrhoea	1 (0.1)	0	1 (0.1)
Feeling abnormal	0	1 (0.3)	1 (0.1)
Generalized oedema	0	1 (0.3)	1 (0.1)
Hot flush	1 (0.1)	0	1 (0.1)
Hyperhidrosis	1 (0.1)	0	1 (0.1)
Hyperthyroidism	1 (0.1)	0	1 (0.1)
Hypertrichosis	0	1 (0.3)	1 (0.1)
Malaise	1 (0.1)	0	1 (0.1)
Premenstrual syndrome	1 (0.1)	0	1 (0.1)
Respiratory tract infection	1 (0.1)	0	1 (0.1)
Skin disorder	0	1 (0.3)	1 (0.1)
Vertigo	1 (0.1)	0	1 (0.1)

DRSP: drospirenone; DSG: desogestrel; TEAE: treatment-emergent adverse event.
N = total; n = %.

responsible for 35% of total deaths in women in 2019. In 2019, there were an estimated 275,2 million (95% uncertainty interval [UI] 261,4 million to 289,8 million) cases of cardiovascular disease in women worldwide [32].

Analyses of US National Health and Nutrition Examination Survey data [33] have identified obesity (body-mass index $\geq$30 kg/m^2) as the most important modifiable risk factor for hypertension and pre-hypertension in women of reproductive age. Data suggest that a similar increase in the male or female body mass index is associated with a more significant increase in systolic blood pressure in women than in men [34].

It is estimated that, together with diabetes, obesity contributes substantially to cardiovascular disease prevalence and mortality in women and should be a significant target for health interventions [35]. Data from the Framingham Heart Study showed that the excess risk of cardiovascular disease attributed to obesity was 64% in women versus 46% in men [36].

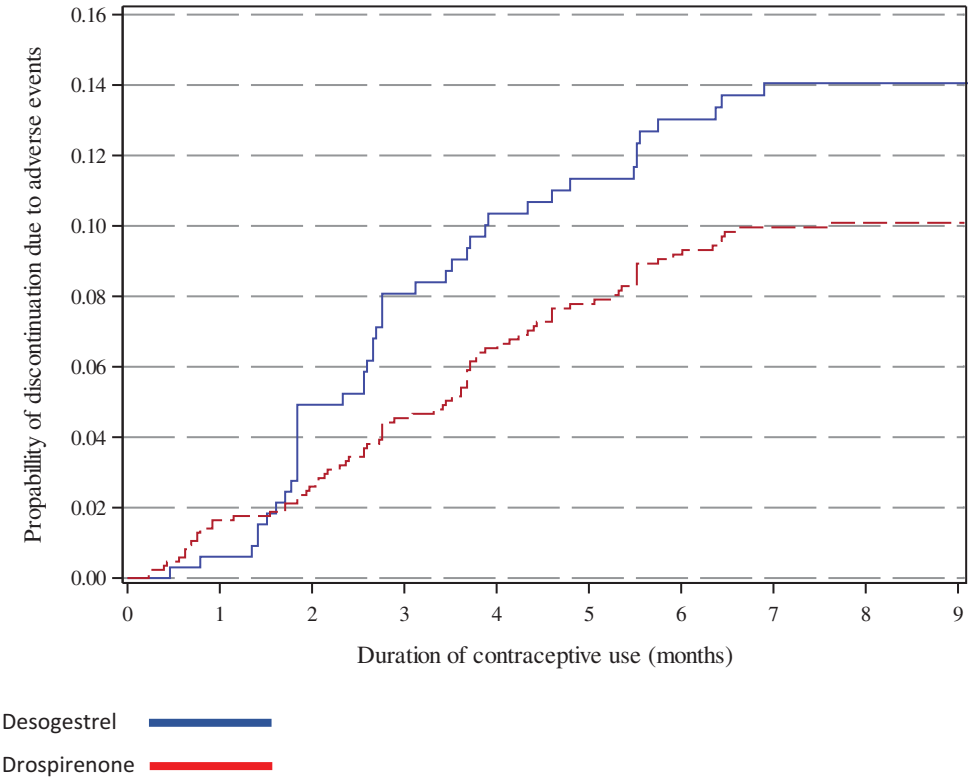
Globally, tobacco smoking and the use of electronic cigarettes (also known as e-cigarettes, vape pens, and vaping devices) are increasing in younger women ($\leq$25 years). A large meta-analysis found that the increased risk of cardiovascular disease associated with smoking was 25% higher in women than men [37]. Further research is warranted to evaluate a potential interaction between sex and smoking concerning cardiovascular disease outcomes.

Data from the Global Burden Disease (GBD) 2015 study show that the worldwide age-standardized smoking prevalence in 2015 was 5,4% (95% UI 5·1–5·7), although in 34 (17%) of 195 countries analysed, the smoking prevalence in women exceeded 15,0%. Mostly, countries in western and central Europe greatly exceeded the global average in women's smoking prevalence, with an exceptionally high prevalence among women aged 15–19 years [38].

Although the overall risk is low, evidence suggests that CHC are associated with a 12 times increase in the risk of myocardial infarction in women with hypertension [39]. If multiple risk factors exist, CHC could increase a woman's cardiovascular disease risk to an unacceptable extent. There is no robust evidence that past use of hormonal contraceptives significantly affects the risk of subsequent cardiovascular disease, regardless of the duration of use or time since last use [40].

Women should be screened for additional cardiovascular disease risk factors, such as smoking, obesity, diabetes, hypertension, or migraine with aura. Progestogen-only oral contraceptives, subdermal implants, and levonorgestrel-releasing intrauterine devices are options for women with a history or at risk of myocardial infarction or stroke [41].

With the DRSP oestrogen-free pill, the number of unscheduled bleeding days can be reduced due to its cyclic regimen in the application. The efficacy is higher due to ovulation inhibition. The time window for missed pills is narrow for DSG (12 h) versus wider for DRSP (24 h) [42]. In addition, drospirenone's partial anti-androgenic or anti-mineralocorticoid effect may have theoretical advantages in conditions, such as premenstrual syndrome, androgenization symptoms, or polycystic ovarian syndrome. Both desogestrel and drospirenone can be used postpartum including lactating women with no risk of VTE [43,44].



Arm	Treatment duration (months)	AUC
DSG	9	0.8566588
DRSP	9	0.583116

Figure 1. Discontinuation rates due to adverse events. Comparison between drospirenone and desogestrel.

There are also data on drospirenone use in adolescents and contraceptive safety in obese patients [20–22,45].

Every health care provider should know the advantages and disadvantages of the respective oestrogen-free contraceptive methods (oral and non-oral progestin preparations) to carry out an individual contraceptive consultation, especially in known high risk groups.

Disclosure statement

Pedro Antomio egidor and Enrico Colli are employes of Exeltis which markets The DRSP-only pill. The other authors have participated in educational activities sponsored by Exeltis.

ORCID

Ali Kubba http://orcid.org/0000-0001-8693-9964
Pedro Antonio Regidor http://orcid.org/0000-0002-9551-2847

Literature

[1] Schindler AE, Campagnoli C, Druckmann R, et al. Classification and pharmacology of progestins. Maturitas. 2008;61(1-2):171–180.
[2] Schindler AE. Non-contraceptive benefits of oral hormonal contraceptives. Int J Endocrinol Metab. 2013;11(1):41–47.
[3] Trussel J, Card J, Hogue C. Adolescent sexual behavior, pregnancy, and childbearing. In: Hatcher R, editor. Contraceptive technology. 17th rev. edn. New York: Irvington Publishers; 1998.
[4] Bearak J, Popinchalk A, Ganatra B, et al. Unintended pregnancy and abortion by income, region, and the legal status of abortion: estimates from a comprehensive model for 1990–2019. Lancet Glob Health. 2020;8(9):e1152–e1161.
[5] Institute of medicine committee on unintended pregnancies. In: Brown SS, Eisenberg L, editors. The best intentions: unintended pregnancy and the Well-Being of children and families. Washington (DC): National Academies Press (US); 1995.
[6] PRAC referral assessment report. Procedure under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data. Combined hormonal contraceptives containing medicinal products INN: chlormadinone, desogestrel, dienogest, drospirenone, etonogestrel, gestodene, nomegestrol, norelgestromin or norgestimate; 2013. Procedure number: EMEA/H/A-31/1356.
[7] Kuhl H. Pharmacology of progestogens. J Reproduktionsmed Endokrinol. 2011;8(Sonderheft 1):157–177.
[8] Creinin MD, Jensen JT. Oral contraceptive generations – time to stop using a marketing myth to define nomenclature. Contraception. 2020;102(3):143–144.
[9] Regidor PA, Schindler AE. Antiandrogenic and antimineralocorticoid health benefits of COC containing newer progestogens: dienogest and drospirenone. Oncotarget. 2017;8(47):83334–83342.
[10] Jordan WM, Anand JK. Pulmonary embolism. Lancet. 1961; 278(7212):1146–1147.
[11] Stegeman BH, de Bastos M, Rosendaal FR, et al. Different combined oral contraceptives and the risk of venous thrombosis: systematic review and network meta-analysis. BMJ. 2013;347: f5298.
[12] Thorogood M, Villard-Mackintosh L. Combined oral contraceptives: risks and benefits. Br Med Bull. 1993;49(1):124–139.
[13] Wharton C, Blackburn R. Lower dose pills. Population Rep. 1988;16:1–31.
[14] Stolley PD, Tonascia JA, Tockman MS, et al. Thrombosis with low-estrogen oral contraceptives. Am J Epidemiol. 1975;102(3): 197–208.

[15] Lidegaard Ø, 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; 25343:d6423.
[16] Schindler AE. Differential effects of progestins on hemostasis. Maturitas. 2003;46:31–37.
[17] Fotherby K. Bioavailability of orally administered sex steroids used in oral contraception and hormone replacement therapy. Contraception. 1996;54(2):59–69.
[18] Winkler UH. Hormone replacement therapy and hemostasis: principles of a complex interaction. Maturitas. 1996;24(3):131–145.
[19] Regidor PA, Colli E, 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 μg per day. Gynecol Endocrinol. 2016;32(9):749–751.
[20] Archer DF, Ahrendt HJ, Drouin D. Drospirenone-only oral contraceptive: results from a multicenter noncomparative trial of efficacy, safety and tolerability. Contraception. 2015;92(5): 439–444. contraception.2015.07.014 Epub 2015 July 29.
[21] Palacios S, Colli E, 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.
[22] 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.
[23] Palacios S, Colli E, 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.
[24] Oelkers W, Foidart JM, Dombrovicz N, et al. Effects of a new oral contraceptive containing an antimineralocorticoid progestin, drospirenone, on the renin-aldosterone system, body weight, blood pressure, glucose tolerance, and lipid metabolism. J Clin Endocrinol Metab. 1995;80(6):1816–1821.
[25] 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.
[26] Cagnacci A, Ferrari S, Napolitano A, et al. Combined oral contraceptive containing drospirenone does not modify 24-h ambulatory blood pressure but increases heart rate in healthy young women: prospective study. Contraception. 2013;88(3): 413–417.
[27] Pomp ER, Le Cessie S, Rosendaal FR, et al. Risk of venous thrombosis: obesity and its joint effect with oral contraceptive use and prothrombotic mutations. Br J Haematol. 2007;139(2): 289–296. 06780.x
[28] Pomp ER, Rosendaal FR, Doggen CJM. Smoking increases the risk of venous thrombosis and acts synergistically with oral contraceptive use. Am J Hematol. 2008;83(2):97–102.
[29] Jick SS, Hernandez RK, Risk of non-fatal venous thromboembolism in women using oral contraceptives containing drospirenone compared with women using oral contraceptives containing levonorgestrel: case-control study using United States claims data. BMJ. 2011;342:d2151.
[30] Regidor PA, Palacios S, Colli E. Bleeding profile of women with cardiovascular risk factors using a drospirenone only pill with 4 mg over nine cycles compared to desogestrel 0.075 mg. Gynecol Endocrinol. 2022;38(4):333–338.
[31] Regidor PA, Colli E, Palacios S. Overall and bleeding-related discontinuation rates of a new oral contraceptive containing 4 mg drospirenone only in a 24/4 regimen and comparison to 0.075 mg desogestrel. Gynecol Endocrinol. 2021;37(12): 1121–1127.
[32] Vogel B, Acevedo M, Appelman Y, et al. Jacqueline saw, liesl zühlke, roxana mehran. The lancet women and cardiovascular disease commission: reducing the global burden by 2030. The Lancet Commission. 2021;397(10292):2385–2438.
[33] Bateman BT, Shaw KM, Kuklina EV, et al. Hypertension in women of reproductive age in the United States: NHANES 1999–2008. PLoS One. 2012;7(4):e36171.
[34] Wilsgaard T, Schirmer H, Arnesen E. Impact of body weight on blood pressure with a focus on sex differences: the tromso study, 1986–1995. Arch Intern Med. 2000;160(18):2847–2853.
[35] Bhupathiraju SN, Hu FB. Epidemiology of obesity and diabetes and their cardiovascular complications. Circ Res. 2016;118(11): 1723–1735.
[36] Wilson PWF, D'Agostino RB, Sullivan L, et al. Overweight and obesity as determinants of cardiovascular risk: the framingham experience. Arch Intern Med. 2002;162(16):1867–1872.
[37] Huxley RR, Woodward M. Cigarette smoking as a risk factor for coronary heart disease in women compared with men: a systematic review and meta-analysis of prospective cohort studies. Lancet. 2011;378(9799):1297–1305.
[38] Reitsma MB, Fullman N, Ng M, et al. Smoking prevalence and attributable disease burden in 195 countries and territories, 1990–2015: a systematic analysis from the global burden of disease study 2015. Lancet. 2017;389(10082):1885–1906.
[39] Curtis KM, Mohllajee AP, Martins SL, et al. Combined oral contraceptive use among women with hypertension: a systematic review. Contraception. 2006;73(2):179–188.
[40] Practice Guideline. ACOG practice bulletin no. 206: use of hormonal contraception in women with coexisting medical conditions. Obstet Gynecol. 2019;133:e128–50.
[41] Stampfer MJ, Willett WC, Colditz GA, et al. A prospective study of past use of oral contraceptive agents and risk of cardiovascular diseases. N Engl J Med. 1988;319(20):1313–1317.
[42] Regidor PA, Colli E. Drospirenone 4 mg in a 24/4 regimen maintains inhibition of ovulation even after a 24-h delay pill intake – pharmacological aspects and comparison to other progestin-only pills. Eur Rev Med Pharmacol Sci. 2022;26:1994–1999.
[43] Cerazette® Summary of product characteristics. 2020. https://www.medicines.org.uk/emc/product/1698/smpc#gref
[44] Exeltis. Slynd. 2019. www.drugs.com/pro/slynd.html
[45] Apter D, Colli E, Gemzell-Danielsson K, et al. Multicenter, open-label trial to assess the safety and tolerability of drospirenone 4.0 mg over 6 cycles in female adolescents, with a 7-cycle extension phase. Contraception. 2020;101(6):412–419.