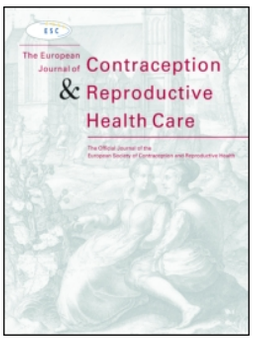

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REVIEW

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Oestrogen-free oral contraception with a 4 mg drospirenone-only pill: new data and a review of the literature

Santiago Palacios[a], Pedro-Antonio Regidor[b], Enrico Colli[c], Sven Olaf Skouby[d,e], Dan Apter[f], Thomas Roemer[g], Christian Egarter[h], Rossella E. Nappi[i], Aleš Skřivánek[j], Artur J. Jakimiuk[k], Steven Weyers[l], Nándor Ács[m], David Elia[n], Kristina Gemzell Danielsson[o] and Johannes Bitzer[p]

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ABSTRACT

Purpose: The contraceptive pill is an effective and safe method of preventing pregnancy. The progestins used for contraception either are components of a combined hormonal contraceptive (tablets, patches or vaginal rings) or are used alone in progestin-only formulations. Progestin-only contraceptives are available as daily oral preparations, subcutaneous or intramuscular injectables (every 1–3 months), subdermal implants (every 3–5 years) and intrauterine systems (every 3–5 years). Long-acting progestins are highly effective in typical use and have a very low risk profile and few contraindications.

Material and Methods: A new progestin-only, oestrogen-free contraceptive, drospirenone, in a dosage of 4 mg/day in a 24/4 regimen, has received regulatory approval in the USA and the EU. The molecule has antigonadotropic, antimineralocorticoid, antiestrogenic and antiandrogenic properties.

Results: The regimen was chosen to improve the bleeding profile; maintain plasma oestradiol levels at those of the early follicular phase, to avoid hypoestrogenism; and preserve efficacy even with a missed pill, as drospirenone has a half-life of 30–34 h.

Conclusions: Clinical studies have shown good efficacy, very low cardiovascular side effects and a favourable bleeding pattern, as well as maintenance of ovulation inhibition after scheduled 24 h delays in pill intake.

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Drospirenone; oestrogen-free contraception; progestins; spirolactone derivative

Introduction

Combined hormonal contraception (CHC) is well accepted, provides effective protection, has a low health risk profile and confers additional health benefits. The main concern from a medical point of view regarding its use is the cardiovascular risk – mainly venous thromboembolism (VTE) – which is in general low but which makes CHC unsuitable for women with risk factors [1].

In addition to this restriction, the increased risk of VTE events in healthy CHC users (6–12/10,000 women per year) compared with non-users (2/10,000 women per year) is of concern and has led to the development of low-dose CHC containing ethinylestradiol (EE) (10–25 μg) or oestradiol (E_2), or to oral contraceptives containing no oestrogen at al. [2]. This development was based on laboratory and epidemiological data indicating that the oestrogen component of CHC was responsible for the increased cardiovascular risk but that there was no increased risk from progestin-only preparations.

Several epidemiological studies have demonstrated that, depending on the dose of oestrogen and the type of progestin, CHC increases the risk of VTE two- to fourfold [1,2]. Except for those with partial glucocorticoid activity, progestins *per se* do not increase the rate of thrombotic events [3].

Oral progestin-only preparations were initially introduced for lactating women, because the highest risk of VTE is during the postpartum period, and because oestrogen may dose-dependently diminish the production of milk. In the last decade, owing to the introduction of an ovulation-inhibiting progestin-only pill (POP) the concept of oestrogen-free contraception has received more interest for a broader population of women.

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Progestin structure and receptor interaction

Depending on the structure, progestins interact differently with the various steroid receptors in the body. Steroid receptors are located intracellularly and on the membrane of target cells and are linked to DNA/RNA and protein production via an increase in transcriptional activity.

The receptors to which progestins bind are:

- Progestin receptor: the most important receptor to induce the desired effect.
- Androgen receptor: activation of androgen receptors mediates androgenic effects on hair growth and activity of the sebaceous glands. Some progestins bind to this receptor and can either block or activate it.
- Oestrogen receptor: this receptor mediates effects in many tissues especially in the endometrial cells.
- Glucocorticoid receptor: the glucocorticoid effect is linked to the activation of the coagulation system.
- Mineralocorticoid receptor: this receptor mediates sodium retention.

Several groups of progestins may be differentiated based on this classification of receptor activity: androgenic, antiandrogenic, mildly antiandrogenic or neutral, and antimineralocorticoid; only drospirenone and its parent compound progesterone have antimineralocorticoid action [4].

Classification of progestins according to market introduction

It has become common to apply the following 'historical' classification. Accordingly, a distinction may be made between first, second, third and fourth generation CHC:

- First generation: norethynodrel, norethisterone acetate;
- Second generation: levonorgestrel;
- Third generation: gestodene, desogestrel, norgestimate;
- Fourth generation: drospirenone.

Cyproterone acetate (CPA) and chlormadinone acetate (CMA) have never been included in this categorisation, as CPA-containing oral contraceptives were originally classified as drugs to treat hyperandrogenism in women who required contraception, and CMA was only introduced in some countries and was and is not internationally available. The same is true for dienogest, which was developed in Germany [5]. The antiandrogenic effects measured in cells and animals [5] are not only caused in combined oral contraceptives (COCs) by the progestin itself but also by the reduction of free testosterone due to the EE-induced rise in sex hormone-binding globulin.

Oral progestin-only oestrogen-free contraception

Levonorgestrel and norethindrone

Levonorgestrel- and norethindrone-only progestins incompletely inhibit ovulation at the usual dosages (with individual components); the contraceptive effect is mainly due to the cervical mucus becoming impenetrable to sperm. An additional action of these POPs is their effect on the endometrium by desynchronising ovulation and endometrial transformation in preparation for implantation. These preparations should be taken at the same time every day when used for regular contraception. The Pearl Index for typical use is between 6 and 8.

Desogestrel

The newer 75 μg desogestrel/day POP is taken continuously without a break. It inhibits ovulation and is as effective as CHC. This POP may be used as an oestrogen-free inhibitor of ovulation. No major health risks are known. Breast cancer, active liver disease, and benign and malignant liver tumours (except nodular hyperplasia) are contraindications to its use.

Owing to the daily intake needed for ovulation suppression, there is no progestin withdrawal phase (which is the reason why bleeding occurs during the pill-free interval when CHC is used in a 21/7 regimen). Irregular bleeding, especially at the beginning of use, is therefore the main complaint leading to discontinuation. In long-term use, unscheduled bleeding is an important clinical problem. Other progestogenic side effects such as acne, weight gain and depressed mood have also been reported. Desogestrel has been reported to alleviate menstrual migraine, reduce pain in women with endometriosis and to lower heavy menstrual bleeding, hypermenorrhoea and dysmenorrhoea [6–8].

New developments and future perspectives

POP treatment has been traditionally associated with strict rules about forgotten pill intake and a suboptimal bleeding pattern [9]. The daily steady intake, particularly with the levonorgestrel formulation, for which the permitted time window is 3 h, and the strict handling of delayed or missed pills demand a high level of user discipline. This can lead to poor adherence to treatment and thus to contraceptive failure [9]. Bleeding irregularities are another disadvantage of traditional POPs and are one of the main reasons for treatment discontinuation [9].

In the search for newer contraceptives, the 75 μg desogestrel oestrogen-free pill (Cerazette; MSD Sharp & Dohme, Haar, Germany) has proven to be a safe and effective alternative [6–8]. However, it has a narrower efficacy margin after 12 h of forgotten intake vs the 24 h margin with 20 μg EE/3 mg drospirenone (Yaz; Bayer HealthCare Pharmaceuticals, Berlin, Germany) [10] and 1.5 mg E_2/2.5 mg nomegestrol acetate (Zoely; Theramex Ireland, Dublin, Ireland) [11] (which are the only pills with a 24 h missed pill intake window) and a higher discontinuation rate due to the irregularities of cycle control [9]. Table 1 lists the progestin-only contraceptives available on the market and their partial activities.

The 4 mg drospirenone-only pill

This new POP is composed of 4 mg non-micronised drospirenone and is used in a 24/4 day intake regimen. This regimen was chosen to improve the bleeding profile, maintain plasma E_2 levels comparable to those of the early follicular phase of the menstrual cycle, and maintain efficacy even when a pill is missed, as drospirenone has a half-life of

Table 1. Partial activities, trade names and dosages of progestin-only contraceptive formulations.

Progestin-only formulation	Progestogenic	Antigonadotropic	Antiestrogenic	Estrogenic	Androgenic	Antiandrogenic	Glucocorticoid	Antimineralocorticoid	Procoagulatory	Trade name	Dose
Norethisterone	+	+	+	+	+	−	−	−	+	Micronor	0.35 mg
Levonorgestrel	+	+	+	−	+	−	−	−	−	28 Mini	0.30 mg
										Norplant	36 mg/implant
Desogestrel	+	+	+	−	+	−	−	−	−	Cerazette	75 µg
Etonogestrel	+	+	+	−	+	−	−	−	−	Implanon NXT	68 mg/implant
Drospirenone	+	+	+	−	−	+	−	+	−	Slinda	4 mg
										Slynd	4 mg

30–34 h. Its clinical development was based on the medical need for an oestrogen-free contraceptive with the following characteristics:

- Contraceptive effectiveness comparable to that of COCs.
- Improvement of the bleeding profile in comparison with other oestrogen-free formulations; therefore, a regimen of 24 consecutive days of active tablet intake, followed by 4 days of placebo, was established to induce scheduled bleedings and reduce unscheduled bleeding and/or spotting.
- Wide safety window: the new 4 mg drospirenone formulation has a 24 h missed pill safety window. This is an advantage not only over existing POPs but also over almost all COCs.
- Favourable safety profile, especially low to very low cardiovascular risk, i.e. venous and arterial thromboembolic events that are classically associated with EE use.
- Advantage of antimineralocorticoid and antiandrogenic effects.
- Adherence and acceptability thanks to the suitability of its administration.

Efficacy

Preclinical data

Pharmacological properties Drospirenone is a synthetic progestin, chemically belonging to the spirolactone group. Unlike other progestins, drospirenone has antimineralocorticoid, antiestrogenic, antiandrogenic and antigonadotropic partial activities [12]. The biochemical and pharmacological profile of drospirenone therefore closely matches the profile of progesterone.

Pharmacokinetics Since the results of initial preclinical studies indicated that 4 mg drospirenone would provide an area under the curve in the range of that of commercial micronised 3 mg drospirenone plus 20 µg EE, a 4 mg dose was chosen. These results were achieved because drospirenone displays linear pharmacokinetics [13].

Despite the higher drospirenone dose in the new formulation, systemic exposure, after repeated administration, was lower (77% bioavailability relative) compared with Yaz (20 µg EE) [14]. This may be caused by the inhibitory effect of EE on sulfotransferase 1A1. This enzyme is involved in the metabolic axis of drospirenone, which catalyses the formation of the metabolite 4,5-dihydro-drospirenone-3-sulfate [13,15].

Phase II studies

Ovulation inhibition: antigonadotropic effect The antigonadotropic effect of 4 mg drospirenone was demonstrated in phase II studies. Ovulation inhibition (defined as serum progesterone levels below 16 nmol/l) was demonstrated in 100% of healthy young women ($n = 20$) for two cycles. These results were confirmed in a subsequent study which evaluated the ovulation inhibition of 4 mg drospirenone for two cycles in a 24/4 day regimen vs continuous administration of 75 µg desogestrel in healthy women aged 18–35 years [16]. The results showed that 4 mg drospirenone effectively inhibited ovulation.

Table 2. Pearl index data.

Pearl index	Archer et al. [18] Drospirenone 4 mg ($n = 713$)	Palacios et al. [19] Drospirenone 4 mg ($n = 858$)	Palacios et al. [19] Desogestrel 75 µg ($n = 332$)	Pooled analysis Drospirenone 4 mg Total ($n = 1571$)
Overall				
Total no. of exposure cycles	7638	6691	2487	14,329
Pregnancies, *n* (%)	3 (0.4)	5 (0.6)	1 (0.3)	8 (0.5)
Overall Pearl Index				
%	0.5106	0.9715	0.5227	0.7258
95% CI (lower limit, upper limit)	0.1053, 1.4922	0.3154, 2.2671	0.0132, 2.9124	0.3133, 1.4301
After correction for additional contraception and sexual activity status				
Total no. of cycles with sexual activity and without additional contraception	7191	5977	2224	13,168
Pregnancies, *n* (%)	3 (0.4)	5 (0.6)	1 (0.3)	8 (0.5)
Adjusted Pearl Index				
%	0.5423	1.0875	0.5845	0.7898
95% CI (lower limit, upper limit)	0.1118, 1.5850	0.3531, 2.5379	0.0148, 3.2568	0.3410, 1.5562
Method failure				
Total no. of perfect medication cycles	6101	4641	1816	10,742
Pregnancies, *n* (%)	3 (0.4)	5 (0.6)	1 (0.3)	8 (0.5)
Method failure Pearl Index				
%	0.6392	1.4006	0.7159	0.9682
95% CI (lower limit, upper limit)	0.1318, 1.8681	0.4548, 3.2684	0.0181, 3.9885	0.4180, 1.9077
Overall pregnancy rate				
%	0.50	0.70	0.34	0.72
95% CI (lower limit, upper limit)	0.00, 1.07	0.09, 1.31	0.00, 1.01	0.17, 1.27

Table 3. Thromboembolic events and changes from baseline in blood pressure and body weight in the European studies' patient populations.

Variable	Archer et al. [18]			Palacios et al. [19]		
	n	Change from baseline		*n*	Change from baseline	
		SBP (mmHg)	DBP (mmHg)		SBP (mmHg)	DBP (mmHg)
SBP <130/DBP <85 mmHg	548			723		
Mean (SD)		1.77 (10.08)	1.06 (8.20)		−0.3 (10.0)	−0.8 (7.7)
Median		0	0		0	0
SBP ≥130/DBP ≥85 mmHg	137			130		
Mean (SD)		−7.59 (9.19)	−4.85 (7.85)		−8.3 (8.6)	−7.2 (8.4)
Median		−8	−5		−7	−5.5
BMI <30 kg/m^2	644			823		
Mean (SD)		0.14 (1.22)			0.04 (1.11)	
Median		0			0	
Range		−4.5 to 6.7			−5.0 to 5.2	
BMI ≥30 kg/m^2	41			30		
Mean (SD)		−0.77 (3.00)			−0.07 (2.41)	
Median		−0.4			0	
Range		−8.4 to 8.6			−8.9 to 4.8	
Thromboembolic events						
Sample size	713			858		
Cases	0			0		

SD, standard deviation.

Ovulation inhibition despite delayed intake An open randomised study was designed to evaluate the potential of 4 mg drospirenone to maintain ovulation inhibition in young healthy women ($n = 127$) despite several 24 h pill intake delays [17]. It was shown that the ovulation rate with 4 mg drospirenone was much lower than that with traditional POPs (30–40%); it was comparable or even slightly lower than the ovulation rate with COCs (1.1–2.0%) and the ovulation rate with 75 µg desogestrel after three programmed delays of 12 h (1.0%) [17].

Phase III studies

Efficacy The contraceptive efficacy of 4 mg drospirenone is supported by clinical phase III trials, which included two pivotal European studies [18,19] and one US study [20]. A pooled analysis of the two European studies showed an overall Pearl Index of 0.73 (95% confidence interval [CI] 0.3133, 1.4301) (14,329 cycles of 4 mg drospirenone) and an adjusted Pearl Index of 0.79 (95% CI 0.3410, 1.5562) [19]. A pooled analysis of a subgroup of 1251 women aged ≤35 years showed similar results: an overall Pearl Index (based on 11,145 cycles) of 0.9332 (95% CI 0.4029, 1.8387) and an adjusted Pearl Index (based on 10,173 cycles) of 1.0223 (95% CI 0.4414, 2.0144) [19]. The results of both studies reveal that the contraceptive effectiveness of 4 mg drospirenone is similar to that of currently available COCs (Table 2). In the US study among 915 non-breastfeeding women aged ≤35 years the Pearl Index was 2.9 (95% CI 1.5, 5.1) [20]. A possible bias for the primary endpoint and the safety aspect including adverse events for all data obtained from the three clinical trials is the discontinuation rate, which was 27.8% and 19.8%, respectively, in the two European studies [18,19] and 65% in the US study [20].

Safety

Haemostatic variables. A long-term study assessed the impact of 4 mg drospirenone on coagulation factors and possible thrombotic risks from a haemostatic point of view [21]. The study comprised 39 women who took the 4 mg drospirenone POP (24/4) and 29 women who took

desogestrel 75 μg daily for nine continuous cycles. The haemostatic variables evaluated were activated protein C resistance, antithrombin III, D-dimer, C-reactive protein and coagulation factors VII and VIII [21]. The study results showed that 4 mg drospirenone did not influence the haemostatic variables and did not affect the balance between procoagulant and anticoagulant factors.

Thromboembolic events. Throughout the clinical development programme (>20,000 cycles) there were no reports of VTE with 4 mg drospirenone. There were also no reports of arterial thromboembolism, myocardial infarction, stroke or pulmonary embolism (Table 3).

It is important to point out that the phase III clinical trials included a significant number of participants with risk factors for VTE [18–20]. The recorded risk factors were family history of thromboembolic illness, evidence of predisposing conditions for a vascular or metabolic disease, current smoker >35 years or non-smoker >40 years, and body mass index (BMI) ≥30 kg/m^2. In the USA, at least 367 participants (36.5%) had a risk factor for VTE [20], while in the European studies, 139 (16.2%) and 104 (14.6%) participants, respectively, had a VTE risk factor [18,19].

These data agree with the neutral effects of 4 mg drospirenone on haemostatic variables reported in a long-term study [21]. Thus, 4 mg drospirenone may be considered a safe contraceptive option that may be used in women with a thromboembolic risk factor, without increasing the risk of a venous or arterial thromboembolic event.

Effects on mild hypertension. It was reported that the administration of drospirenone in combination with oestrogens for 6 months was associated with a slight decrease in systolic (SBP) and diastolic (DBP) blood pressure compared with levonorgestrel combined with oestrogens [22]. This slight impact on blood pressure was also demonstrated when 3 mg drospirenone was compared with 150 μg desogestrel [23]. These findings are associated with the antimineralocorticoid action of drospirenone.

The effects of 4 mg drospirenone on blood pressure were analysed in the two Pearl Index studies [18,19]. In the first study a median decrease of 8 mmHg in SBP and 5 mmHg in DBP in participants with basal values of SBP ≥130 mmHg or DBP ≥85 mmHg was observed ($n = 137$) [18]. In participants with basal SBP <130 mmHg and DBP <85 mmHg ($n = 548$), the absolute median change was 0 mmHg for SBP and DBP (Table 3) [18].

E_2 levels and bone. A study with 64 volunteers [16] showed that E_2 levels on day 24 of the second cycle were just below 51 pg/ml (187.2 pmol/l) and were higher than those on day 3 of the first cycle, which may be considered starting values. That means that a treatment of 24 days with 4 mg drospirenone had no impact on decreasing the E_2 level below the starting level of day 3. The difference in terms of E_2 levels vs the control group (75 μg desogestrel) on day 24 of the second cycle was not statistically significant.

With this recommended dosing regimen (24/4) the ovary can again produce endogenous E_2, as 4 days should be enough to raise levels of follicle-stimulating hormone. This was observed in the values on day 3 of the second cycle, which were higher than the values on day 27 of the first cycle. This different dosing regimen (a 24/4 day regimen of 4 mg drospirenone vs a 28 day regimen of 75 μg desogestrel) led to higher values of E_2 at the end of cycle 2 in comparison with values on day 3 of the second cycle [16].

E_2 levels are not suppressed below 30 pg/ml (110.1 pmol/l) with 4 mg drospirenone in a 24/4 dosing regimen [24]. This is considered as the cut-off for the start of osteoblastic activity in the bone, as shown in the study of Doran et al. [25], where the selective oestrogen receptor modulator raloxifene in elderly men pre-treated with a gonadotropin-releasing hormone agonist created an agonist effect on the bone only if the mean baseline values were below 26 pg/ml (95.5 pmol/l). If the values were higher than 26 pg/ml (95.5 pmol/l), raloxifene acted as an antagonist.

Body weight changes. There were no significant changes in average body weight during short- and long-term studies in participants who received 4 mg drospirenone [16–18], confirming the data in the literature which have established no association with weight gain or significant changes in percent body fat with drospirenone [26].

Tolerability

Bleeding profile: cycle control with 4 mg drospirenone vs 75 μg desogestrel.

A comparison of cycle control between 4 mg drospirenone and 75 μg desogestrel was performed in a study of nine cycles [27]. The proportion of women with bleeding and spotting decreased from 69.7% in cycle 2 to 56.3% in cycle 9 in the 4 mg drospirenone group and from 74.0% to 45.3% in the 75 μg desogestrel group; the overall median number of bleeding and spotting days decreased from 10 days (first reference period: cycles 2–4) to 6 days (last reference period: cycles 7–9) in the 4 mg drospirenone group and from 12 to 7 days in the 75 μg desogestrel group. Among these, spotting days prevailed. The differences were statistically significant. Moreover, the rate of patients with prolonged bleeding (>10 days) was significantly lower in the 4 mg drospirenone group compared with the 75 μg desogestrel group for cycles 5–9 ($p < 0.001$). Early study withdrawal related to abnormal uterine bleeding (AUB) was reported for 3.3% of participants who received 4 mg drospirenone against 6.6% who took 75 μg desogestrel ($p < 0.001$) [27]. The results demonstrated that cycle control with 4 mg drospirenone was superior to that with 75 μg desogestrel. Table 4 shows some of the bleeding profile results [19].

Endometrial safety. Endometrial thickness was assessed in a specific study evaluating endometrial safety [28]. The maximum average thickness was 5.5 cm; after 13 cycles of treatment there was a mean reduction of 2.5 cm. Biopsies were performed and endometrial changes evaluated; no hyperplasia was detected after 1 year of treatment [28].

Use in special groups

Adolescents

A study was designed to assess prospectively the safety and tolerability of 4 mg drospirenone (24/4) in 111

Table 4. Median number of scheduled and unscheduled bleeding or spotting days, and early study withdrawal associated with AUB, by reference period.

Variable	Archer et al. [18] Drospirenone 4 mg ($n = 713$)	Palacios et al. [19] Drospirenone 4 mg ($n = 858$)	Palacios et al. [19] Desogestrel 75 µg ($n = 332$)
Scheduled bleeding days			
Cycles 2–4	11 (1.5)	10 (1.2)*	12 (3.6)
Cycles 5–7	8 (1.1)	6 (0.7)	7 (2.1)
Cycles 8-10/7-9[a]	6.0 (0.8)	6 (0.7)	7 (2.1)
Cycles 11–13	5 (0.7)		
Unscheduled bleeding days			
Cycles 2–4	6 (0.8)	5 (0.6)***	12 (3.6)
Cycles 5–7	5 (0.7)	4 (0.5)*	7 (2.1)
Cycles 8-10/7-9[a]	3 (0.4)	4 (0.5)*	7 (2.1)
Cycles 11–13	3 (0.4)		
Early study withdrawal associated with AUB	30 (4.2)	28 (3.3)	22 (6.6)

Data are presented as *n* (%).
[a]8–10 for 301 study; 7–9 for 302 study.
*$p < 0.05$ drospirenone vs desogestrel.
***$p < 0.001$ drospirenone vs desogestrel.

adolescents aged 12–17 years [29]. The study consisted of six 28 day treatment cycles and an optional seven cycle extension. The number of participants reporting dysmenorrhoea decreased from 47 (46.1%) prior to screening to 14 (29.8%) at the end of cycle 6, and to eight (17.0%) at the end of cycle 13. The number of participants using pain medication for dysmenorrhoea similarly declined. Only five participants (4.9%) prematurely terminated the trial because of irregular bleeding and one (1.0%) because of amenorrhoea. There were no treatment-related serious adverse events and no pregnancies. At the endpoint, 82.4% of participants rated the tolerability of drospirenone as excellent or good [29].

Obese women

Obese individuals have some physiological changes compared with normal weight individuals, such as increased cardiac output or alterations of liver enzyme functions. Some of these changes have the potential to affect the absorption, distribution, metabolism and elimination of drugs, which may affect their effectiveness [30].

The contraceptive efficacy of drospirenone in overweight and obese women was confirmed in a pooled analysis of the European studies [18,19] of the 4 mg drospirenone clinical development programme analysis [30]. In women with BMI 25–30 kg/m^2 ($n = 301$), four pregnancies were reported (Pearl Index 1.89), whereas in women with BMI >30 kg/m^2 ($n = 71$), no pregnancies were recorded (Pearl Index 0.0).

The favourable thromboembolic safety profile of 4 mg drospirenone, even for participants with VTE risk factors, was demonstrated during the clinical development programme. Cigarette use in women >35 years old was the most common risk factor in the European studies(10.1% and 12%, respectively) [18,19]. In the US study [20], the incidence of this risk factor was 5.1%. BMI >30 kg/m^2 was the most common risk factor in the US study, representing 35% of participants [20]. The percentages recorded in the European studies were 5.8% and 3.5%, respectively [18,19].

The incidence of a family history of thromboembolic disease and predisposing evidence for cardiovascular or metabolic disease was lower in all studies. In summary, even in women with risk factors for thromboembolism (VTE) such as age >35 years, tobacco use and obesity, no venous thromboembolic or arterial events were reported.

Conclusions

Progestins play an essential and independent role in contraception, whether used with or without oestrogens. Even though they differ in structure and in action profile, they exhibit a multifocal mode of action in contraception. Besides the common progestogenic effect, each progestin has a partial effect pattern, which has utmost relevance when clinically used. Effects and possible side effects can be influenced or determined by this.

Considering the available evidence, it may be stated that the introduction of a new oestrogen-free contraceptive containing 4 mg non-micronised drospirenone in a 24/4 day regimen broadens the contraceptive options for women and health care practitioners and represents a step forward in modern contraception, as:

- A high efficacy was achieved in clinical trials;
- No relevant safety aspects were documented in clinical trials (0 cases of thromboembolic events in more than 20,000 cycles);
- A high acceptability rate of 96.5% and a discontinuation rate of only 3.5% (91 out of 2593 women during the whole clinical trial programme, owing to unacceptable bleeding patterns) was documented [31].

Disclosure statement

SP has received honoraria from Pfizer, Amgen, Gedeon Richter, Exeltis Healthcare, Bayer HealthCare Pharmaceuticals, Novo Nordisk, Servier, MSD, Procare Health, Shionogi, Teva, Sérélys Pharma and Mylan.

PAR and EC are employees of Exeltis Healthcare.

SOS has received honoraria for consulting and sponsored symposia from Mithra Pharmaceuticals, Exeltis Healthcare, Pfizer, Gedeon Richter and Bayer HealthCare Pharmaceuticals.

DA has been a lecturer, member of advisory board or consultant with Bayer HealthCare Pharmaceuticals, Exeltis Healthcare, GSK, MSD and Mithra Pharmaceuticals.

TR has received honoraria for lectures and advisory board membership from Bayer HealthCare Pharmaceuticals, Aristo Pharma, Gedeon Richter, Exeltis Healthcare, Hexal, Theramex and Mylan.

CE has received honoraria and reimbursements of expenses for attendance at advisory boards, lectures and sponsored symposia from Exeltis Healthcare.

REN had a financial relationship (lecturer, member of advisory boards and/or consultant) with Bayer HealthCare Pharmaceuticals, Endoceutics, Exeltis Healthcare, Gedeon Richter, MSD, Novo Nordisk, Palatin Technologies, Pfizer, Shionogi, Teva and Theramex.

AJJ is a lecturer, member of an advisory board or consultant with Exeltis Healthcare, NutroPharma, Verco, Olympus and Johnson & Johnson. He was the local principal investigator for trials sponsored by PregLem and Myovant Sciences.

KGD's institution has received support for clinical trials from Bayer HealthCare Pharmaceuticals, MSD/Merck, Exeltis Healthcare, Mithra Pharmaceuticals and Myovant Sciences. She was the local principal investigator for a study of drospirenone in adolescents.

JB has worked as an adviser for and received honoraria from Bayer HealthCare Pharmaceuticals, MSD, Teva, Exeltis Healthcare, Eli Lilly, Boehringer-Ingelheim, Vifor Pharma, Gedeon Richter and Mithra Pharmaceuticals. He has also given invited lectures and received honoraria from Bayer HealthCare Pharmaceuticals, MSD, Johnson & Johnson, Teva, Mylan, Allergan, Abbott Laboratories, Eli Lilly and Pfizer.

AS, SW, DE and NA declare no conflicts of interest.

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References

[1] World Health Organization. Medical eligibility criteria for contraceptive use. 5th ed. Geneva: WHO; 2015.
[2] European Medicines Agency. Combined hormonal contraceptives. Available from: www.ema.europa.eu/en/medicines/human/referrals/combined-hormonal-contraceptives.
[3] Schindler AE. Non-contraceptive benefits of oral hormonal contraceptives. Int J Endocrinol Metab. 2013;11:41–47.
[4] Schindler AE, Campagnoli C, Druckmann R, et al. Classification and pharmacology of progestins. Maturitas. 2008;61:171–180.
[5] Regidor PA, Schindler AE. Antiandrogenic and antimineralocorticoid health benefits of COC containing newer progestins: dienogest and drospirenone. Oncotarget. 2017;8:83334–83342.
[6] Rice CF, Killick SR, Dieben T, Bennink HC. A comparison of the inhibition of ovulation achieved by desogestrel 75 mg and levonorgestrel 30 mg daily. Hum Reprod 1999;14:982–985.
[7] Sarfati J, de Vernejoul MC. Impact of combined and progestin-only contraceptives on bone mineral density. Joint Bone Spine. 2009;76;134–138.
[8] Rice C, Killick S, Hickling D, Bennink HC. Ovarian activity and vaginal bleeding patterns with a desogestrel-only preparation at three different doses. Hum Reprod. 1996;11:737–740.
[9] de Melo NR. Estrogen-free oral hormonal contraception: benefits of the progestin-only pill. Women's Health (Lond). 2010;6:721–735.
[10] Bayer HealthCare Pharmaceuticals. (2015). Yaz. Summary of product characteristics. Available from: https://db.cbg-meb.nl/mri/spc/nlh-1269-001.pdf.
[11] MSD. (2011). Zoely. Summary of product characteristics. Available from: www.medicines.org.uk/emc/product/3038/smpc.
[12] Regidor PA. The clinical relevance of progestins in hormonal contraception: present status and future developments. Oncotarget. 2018;9:34628–34638.
[13] Krattenmacher R. Drospirenone: pharmacology and pharmacokinetics of a unique progestin. Contraception. 2000;62:29–38.
[14] 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;101:137–143.
[15] Rohn KJ, Cook IT, Leyh TS, et al. Potent inhibition of human sulfotransferase 1A1 by 17α-ethinylestradiol: role of 3′-phosphoadenosine 5′-phosphosulfate binding and structural rearrangements in regulating inhibition and activity. Drug Metab Dispos. 2012;40:1588–1595.
[16] Duijkers IJ, Heger-Mahn D, Drouin D, Skouby S. A randomised study comparing the effect on ovarian activity of a progestogen-only pill (POP) containing desogestrel and a new POP containing drospirenone in a 24/4 regimen. Eur J Contracept Reprod Health Care. 2015;20:419–427.
[17] Duijkers IJM, Heger-Mahn D, Drouin D, et al. Maintenance of ovulation inhibition with a new progestogen-only pill containing drospirenone after scheduled 24-h delays in pill intake. Contraception. 2016;93:303–309.
[18] Archer DF, Ahrendt HJ, Drouin D. Drospirenone-only oral contraceptive: results from a multicenter noncomparative trial of efficacy, safety and tolerability. Contraception. 2015;92:439–444.
[19] 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;98:1549–1557.
[20] 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. Contraception. 2:100020.
[21] 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;32:749–751.
[22] 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;80:1816–1821.
[23] 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;67:423–429.
[24] Hadji P, Colli E, Regidor PA. Bone health in estrogen-free contraception. Osteoporos Int. 2019;30:2391–2400.
[25] Doran PM, Riggs BL, Atkinson EJ, Khosla S. Effects of raloxifene, a selective estrogen receptor modulator, on bone turnover markers and serum sex steroid and lipid levels in elderly men. J Bone Miner Res. 2001;16:2118–21125.
[26] Foidart JM, Faustmann T. Advances in hormone replacement therapy: weight benefits of drospirenone, a 17α-spirolactone-derived progestogen. Gynecol Endocrinol. 2007;23:692–699.
[27] Palacios S, Colli E, Regidor PA. A multicenter, double-blind, randomized trial on the bleeding profile of a drospirenone-only pill 4 mg over nine cycles in comparison with desogestrel 0.075 mg. Arch Gynecol Obstet. 2019;300:1805–1812.
[28] Regidor PA, Colli E, Georgiev D, et al. Safety, influence on the endometrium, sonographic changes and bleeding profile after 13 cycles with the new drospirenone only pill (DOP) for contraception. Horm Mol Biol Clin Investig. 2020. doi: 10.1515/hmbci-2019-0061
[29] Apter D, Enrico E, Gemzell Danielsson K, Klaus Peters K. *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*. Presented at 19th FIGIJ World Congress of Paediatric and Adolescent Gynecology, Melbourne, VIC, 2019; 176.
[30] Ng M, Fleming T, Robinson M, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980–2013: a systematic analysis for the Global Burden of Disease Study 2013.Lancet. 2014;384:766–781.
[31] Exeltis. (2019). Slynd. Available from: www.drugs.com/pro/slynd.html.