

Oral Progestins in Hormonal Contraception: Importance and Future Perspectives of a New Progestin Only-Pill Containing 4 mg Drospirenone

Orale Gestagene in der hormonellen Kontrazeption: Stellenwert und Zukunftsaussichten eines neuen Gestagen-Monopräparats mit 4 mg Drospirenon



Authors

Thomas Römer¹, Johannes Bitzer², Christian Egarter³, Peyman Hadji^{4,5}, Marion Kiechle⁶, Heike Kramer⁷, Patricia G. Oppelt⁸, Klaus Peters⁹, Petra Stute¹⁰, Katrin Schaudig¹¹, Inka Wiegatz^{12,13}, Pedro-Antonio Regidor¹⁴

Affiliations

- 1 Abteilung für Gynäkologie und Geburtshilfe, Evangelisches Klinikum Köln Weyertal GmbH, Köln, Germany
- 2 Klinik für Geburtshilfe und Gynäkologie, Universitätskrankenhaus Basel, Basel, Switzerland
- 3 Abteilung für Gynäkologische Endokrinologie, Medizinische Universität Wien, Wien, Austria
- 4 Frankfurter Hormon und Osteoporosezentrum, Frankfurt am Main, Germany
- 5 Philipps Universität Marburg, Marburg, Germany
- 6 Direktorin der Frauenklinik, Universitätsklinikum Rechts der Isar der Technischen Universität München (TUM), München, Germany
- 7 Ärztliche Gesellschaft zur Gesundheitsförderung e. V., Spardorf/Erlangen, Germany
- 8 Universitätsfrauenklinik Erlangen, Erlangen, Germany
- 9 Frauenarzt Praxis Hamburg, Hamburg, Germany
- 10 Klinik für Gynäkologie und Geburtshilfe, Universitätsklinikum Inselspital Bern, Bern, Switzerland
- 11 Praxis für gynäkologische Endokrinologie HORMONE HAMBURG, Hamburg, Germany
- 12 Kinderwunsch & Hormonzentrum Frankfurt – Am Palmengarten, Frankfurt am Main, Germany
- 13 Goethe-Universität Frankfurt, Frankfurt am Main, Germany
- 14 Medical Director Exeltis Europe, Ismaning, Germany

Key words

oral progestins, drospirenone, progestin mono-preparations, contraception, control of menstrual bleeding

Schlüsselwörter

orale Gestagene, Drospirenon, Gestagen-Monopräparate, Kontrazeption, Blutungskontrolle

received 4.2.2021
accepted after revision 28.3.2021
published online 14.6.2021

Bibliography

Geburtsh Frauenheilk 2021; 81: 1021–1030

DOI 10.1055/a-1471-4408

ISSN 0016-5751

© 2021. The Author(s).

This is an open access article published by Thieme under the terms of the Creative Commons Attribution-NonDerivative-NonCommercial-License, permitting copying and reproduction so long as the original work is given appropriate credit. Contents may not be used for commercial purposes, or adapted, remixed, transformed or built upon. (<https://creativecommons.org/licenses/by-nc-nd/4.0/>)

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

Correspondence

Prof. Pedro-Antonio Regidor, MD PhD
Medical Director Exeltis Europe
Adalperostraße 84, 85737 Ismaning, Germany
pedro-antonio.regidor@exeltis.com

Deutsche Version unter:
<https://doi.org/10.1055/a-1471-4408>

ABSTRACT

Hormonal contraceptives are an effective and safe method for preventing pregnancy. Progestins used in contraception are either components of combined hormonal contraceptives (tablets, patches or vaginal rings) or are used as a single active ingredient in progestin mono-preparations (the progestin-only pill (POP), implants, intrauterine systems or depot preparations). Progestins are highly effective in long-term contraception when used properly, and have a very good safety profile with very few contraindications. A new oestrogen-free ovulation inhibitor (POP) has recently been authorised in the USA and the EU. This progestin mono-preparation contains 4 mg of drospirenone (DRSP), which has anti-gonadotropic, anti-mineralocorticoidic and anti-androgenic properties. 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. Clinical trials have demonstrated a high contraceptive effectiveness, a very low risk of cardiovascular side effects and a favourable menstrual bleeding pattern. Due to the long half-life of DRSP (30–34 hours), the effectiveness of the preparation is maintained even if a woman forgets to take a pill on a single occasion. Studies involving deliberate 24-hour delays in taking a pill have demonstrated that ovulation inhibition is maintained if a single pill is missed. Following a summary of the current status of oestrogen-free contraception, this review article will describe the clinical development programme of the 4 mg DRSP mono-preparation and the resulting data on the effectiveness and safety of this new oestrogen-free oral hormonal contraceptive.

ZUSAMMENFASSUNG

Hormonelle Kontrazeptiva stellen eine effektive und sichere Methode der Schwangerschaftsverhütung dar. Die Gestagene, die in der Kontrazeption verwendet werden, sind entweder Bestandteil kombinierter hormoneller Kontrazeptiva (Tabletten, Pflaster oder Vaginalringe) oder werden als einzelner Wirkstoff in Gestagen-Monopräparaten (Tabletten [im englischen Sprachgebrauch „POP“ = Progestin-only-Pill], Implantate, Intrauterinsysteme oder Depotpräparate) eingesetzt. Gestagene sind in der Langzeitverhütung bei adäquater An-

wendung höchst effektiv und haben ein sehr gutes Sicherheitsprofil mit nur wenigen Kontraindikationen. Kürzlich wurde ein neuer östrogenfreier Ovulationshemmer (POP) in den USA und der EU zugelassen. Das Gestagen-Monopräparat enthält 4 mg Drospirenon (DRSP), welches antigonadotrope, antimineralokortikoide und antiandrogene Eigenschaften aufweist. Das Einnahmeschema mit 24-tägiger Hormonanwendung, gefolgt von einem 4-tägigen hormonfreien Intervall, wurde gewählt, um die Blutungskontrolle zu verbessern, die Estradiolspiegel auf dem Niveau der frühen Follikelphase zu halten und somit einen Estrogenmangel zu vermeiden. Klinische Studien belegten die hohe kontrazeptive Wirksamkeit, ein sehr geringes Risiko für kardiovaskuläre Nebenwirkungen und ein günstiges Blutungsmuster. Aufgrund der langen Halbwertszeit von DRSP (30–34 Stunden), bleibt die Wirksamkeit des Präparats selbst bei einmaligem Vergessen der Pilleneinnahme erhalten. Die Aufrechterhaltung der Ovulationshemmung bei möglichem Vergessen einer Pilleneinnahme wurde in Studien mit geplanten 24-stündigen Einnahmeverzögerungen gezeigt. Nach einem Überblick über den aktuellen Stand der östrogenfreien Kontrazeption beschreibt die vorliegende Arbeit das klinische Entwicklungsprogramm des 4-mg-DRSP-Monopräparats und die daraus resultierenden Daten zur Wirksamkeit und Sicherheit dieses neuen östrogenfreien oralen hormonellen Kontrazeptivums.

Introduction

Use of oral progestin mono-preparations (progestin-only pills)

Of all the factors influencing a woman's choice of contraceptive method – its effectiveness, personal preferences of the patient, potential additional benefits [1] – most important is the associated risk profile. For several years, the WHO has published a comprehensive set of guidelines on the use of hormonal contraceptive methods, providing advice for and against the use of certain (hormonal) contraceptive methods in a variety of medical scenarios (pre-existing conditions, concomitant medications, etc.) [2]. Its recommendations are grouped into four categories. Methods that on the grounds of a specific medical history fall into category 1 can be recommended without restriction. In contrast, category 4 methods are associated with a high risk to health and should be avoided. Category 2 and 3 methods should only be administered after a rigorous risk-benefit assessment, and while the benefits of category 2 contraceptives generally outweigh the risks, category 3 methods should only be used if no alternative is available [2]. The advantages of the WHO guidelines are evident. They provide very concrete treatment recommendations, ensure a measure of safety from a legal standpoint, and it is relatively easy to employ and document them in consultations. However, even in a set of guidelines as extensive as those published by the WHO it is impossible to cover all specific risk scenarios.

Many potential risks of hormonal contraception can be attributed to the oestrogen component [3, 4], which is why in various scenarios the WHO guidelines classify combined hormonal contraceptives (CHCs) under category 4 and are therefore contraindicated (► **Table 1**). The most important factor in this respect is the increase in the risk of thrombosis due to exogenously administered oestrogens (especially ethinylloestradiol, a constituent of most combined contraceptives), which has been observed for all forms of administration (tablet, patch or vaginal ring) [4–6]. Progestins in CHCs modulate the thromboembolic risk, resulting in estimated incidences of a venous thromboembolic event (VTE) of 5–7 per 10 000 women per year of use for levonorgestrel-containing and norgestimate/norethisterone-containing CHCs and 9–12, for gestodene/desogestrel/drospirenone-containing CHCs [6]. On the other hand, the current state of knowledge suggests that progestin mono-preparations do not increase VTE risk, with the exception of depot injections containing high doses of medroxyprogesterone acetate [5].

Over time, CHCs have been developed with very low doses of ethinylloestradiol (EE) (10–30 µg) or oestradiol (E₂), or ovulation inhibitors with no oestrogen component at all [7].

A recent review by Khialani et al. [3] clearly found that the EE component in CHCs is responsible for the increase in cardiovascular risk and in a dose-dependent manner.

Oral progestin mono-preparations were originally intended for use during breastfeeding, as the highest risk of VTE occurs during the postpartum period and oestrogens can reduce milk production, depending on dosage. Termed the “mini-pill”, they contain

► **Table 1** Extract from the WHO guidelines on the use of combined hormonal contraceptives (CHCs) and POPs in specific medical scenarios. Complete overview: see [2].

Risk factor		CHC	Patch/ring	POP
VTE/pulmonary embolism	Medical history	4	4	2
	Acute	4	4	2
	Anticoagulation discontinued	4	4	2
	Fam. history (grade 1)	2	2	1
VTE and operations	Major surgery, prolonged immobilisation	4	4	2
	Without prolonged immobilisation	2	2	1
	Minor surgery, without immobilisation	1	1	1
Thrombogenic mutation	Factor V Leiden and prothrombin mutations, for instance	4	4	2
Ischaemic heart disease	Acute or in history	4	4	2 (I)/3(C)
Stroke		4	4	2 (I)/3(C)
Multiple risk factors for ATE	Including age, smoking, diabetes, hypertension, dyslipidaemia	3/4	3/4	2
Age	Menarche up to < 18 years old	NDA	NDA	1
	< 40 years old	1	1	1
	> 40 years old	2	2	1
Smoking	< 35 years old	2	2	1
	> 35 years old			
	▪ < 15 cigarettes	3	3	1
	▪ > 15 cigarettes	4	4	1
Hypertension (without other risk factors)	After hypertension (in the absence of measured values)	3	3	2
	Well-controlled hypertension	3	3	1
	140–159/90–99 mmHg	3	3	1
	≥ 160/≥ 100 mmHg	4	4	2
	Vascular disorder	4	4	2
	Non-vascular disorder	2	2	2
	Neuropathy/retinopathy/nephropathy	3/4	3/4	2
	Other vascular disorders or diabetes for > 20 years	3/4	3/4	2

VTE: venous thromboembolic event, ATE: arterial thromboembolic event, I: initiation, C: continuation

very low doses and only inhibit ovulation in about 50% of cycles. The contraceptive action is mainly caused by an increase in cervical mucus viscosity, disruption of tubal motility and premature secretory transformation of the endometrium. The Pearl Index (PI) for these preparations is significantly worse than that for CHCs. The introduction of the higher-dose, and thus much more reliable, ovulation-inhibiting progestin mono-preparation containing desogestrel has made the concept of oestrogen-free contraception attractive to a much larger population of women.

Progestin structure and receptor interaction

Depending on their structure, progestins interact differently with the body's various steroid receptors. Steroid receptors are located both within the cell body and on the membrane of target cells and influence protein biosynthesis at the level of DNA transcription.

The following receptors bind progestins:

- Progesterone receptors (PRs). PR has two isoforms: PR-A and PR-B. PR-A mainly acts by repressing the transcriptional activity of PR-B as well as that of oestrogen, androgen, glucocorticoid and mineralocorticoid receptors. PR-B, in contrast, has an activating effect on transcription.

- Androgen receptors. Activation of androgen receptors mediates androgenic effects, for example those that result in hair growth and sebaceous gland activity. Some progestins bind to these receptors and can either block or activate them.
- Oestrogen receptors. These receptors exert an effect in many different tissues; in the context of use of contraceptives, their most important effect is to induce endometrial proliferation.
- Glucocorticoid receptors. Glucocorticoid receptors have been linked with activation of the coagulation system.
- Mineralocorticoid receptors. These receptors modulate sodium retention.

Progestins are grouped on the basis of the differing strength with which they activate these receptors: androgenic, anti-androgenic, slightly anti-androgenic, neutral or anti-mineralocorticoid partial effects. Of the progestins used in treatment, only DRSP and (synthetic) progesterone have anti-mineralocorticoid effects, whereas levonorgestrel, norgestimate and desogestrel have androgenic effects, and DRSP, dienogest, cyproterone acetate (CPA) and chlormadinone acetate (CMA) have anti-androgenic effects [8].

The anti-androgenic effect, which has been demonstrated in cell cultures and animal models [9], is not in CHC solely due to the progestin component, but also to the fact that the EE-induced increase in sex hormone binding globulin (SHBG) reduces the level of free testosterone in the body.

Classification of progestins based on their market introduction

It has become common practice to employ the following “historical” classification scheme. This distinguishes between first, second, third and fourth CHC generations.

- First generation: norethynodrel, norethisterone acetate
- Second generation: levonorgestrel
- Third generation: gestodene, desogestrel, norgestimate
- Fourth generation: DRSP

Cyproterone acetate (CPA) and chlormadinone acetate (CMA) were never incorporated into this categorisation, because oral contraceptives containing CPA were originally classified as drugs to treat hyperandrogenaemia in women requiring contraception. CMA has only been introduced in a small number of European countries and is not available internationally. The same applies to dienogest, which was developed in Germany [9].

Advantages of progestin mono-preparations

Progestin mono-preparations can be recommended in many scenarios where combined contraceptives fall under WHO category 3 or 4.

The German S3 guideline explicitly states that progestin mono-preparations do not significantly increase VTE risk. Only depot medroxyprogesterone acetate (DMPA), which is injected every three months, has been found in one study to increase VTE risk (3.6-fold).

Absolute contraindications (category 4) for the use of CHCs include, acute VTE, a history of VTEs, surgery with prolonged immobilisation or the presence of thrombogenic mutations, such as factor V Leiden. In contrast, POPs fall into category 2 and can generally be recommended after weighing up their risk-benefit ratio (► **Table 1**) [2]. Obesity (BMI > 30 kg/m²) is also classified as a potential risk factor for CHC use, and only falls under category 2 if no further risk factors exist. However, if obesity is additionally associated with hypertension, hyperlipidaemia or diabetes mellitus, oestrogen-free contraceptive methods should be preferred [10]. Even moderate hypertension (140–159/90–99 mmHg) or well-controlled hypertension can be affected by CHCs, making it necessary to carefully consider and monitor their use (category 3) or contraindicate their use in the presence of further risk factors [2]. Severe hypertension (≥ 160/≥ 100 mmHg), as well as vascular disorders in general, are contraindications for oestrogen-containing contraceptives according to the WHO, while POPs can generally be recommended in all these scenarios (category 1 or 2). Diabetes mellitus does not, in itself, restrict CHC use (category 2). However, as soon as it is additionally accompanied by vascular damage, neuropathies or retinopathies, CHCs should only be employed in exceptional cases or are contraindicated, while POPs are considered to be unproblematic (category 2). Smoking is another important VTE risk factor that becomes more pronounced with increasing age and

► **Table 2** VTE risk of combined hormonal contraceptives as per the EMA/BfArM [6, 7].

Progestins in CHC combined with ethinyloestradiol	Relative risk vs. levonorgestrel	Estimated incidence (per 10 000 women and year of usage)
Non-pregnant non-user	–	2
Levonorgestrel	Reference	5–7
Norgestimate/norethisterone	1.0	5–7
Dienogest	1.6	8–11
Gestodene/desogestrel/drospirenone	1.5–2.0	9–12
Etonogestrel/norelgestromin	1.0–2.0	6–12
Chlormadinone/norgestrol acetate (E2)	Still to be verified	Still to be verified

the number of cigarettes smoked. Accordingly, CHC use in women younger than 35 years falls under category 2, while in patients older than 35, CHCs should only be used in exceptional cases and after careful consideration of other risks (category 3) and are contraindicated if more than 15 cigarettes are consumed per day. However, according to the WHO [2], POPs can be used by all women smokers regardless of age or amount of nicotine consumed.

The German S3 guidelines on contraception adopt the same approach as the WHO, likewise the recommendations and risk assessments of the European Medicines Agency (EMA). In the latest version of these (implemented by the BfArM in December 2018), the EMA presents the most recent risk assessment of the occurrence of venous thromboembolism. A new finding is that combination preparations with dienogest also significantly increase the risk of such VTEs (► **Table 2**).

Based on these examples alone, it is clear that CHCs are not an option, or only a very limited option, for a subset of female patients. Consequently, oestrogen-free hormonal contraception is highly important. In addition to oral progestin mono-preparations (the progestin-only pill [POP]), long-term methods based on a levonorgestrel intrauterine system (LNG-IUS), sub-dermal implants (etonogestrel) or injected depot medroxyprogesterone acetate (DMPA) are available. Although the long-term options mentioned are highly effective methods of contraception [11, 12], they are not equally suitable for all patient groups. DMPA, for instance, not only seems to have an adverse effect on thrombosis risk [13], long-term use (> 4 years) also leads to an increased risk of bone fracture, which is attributable to a reduction in bone mineral density [14]. Hence, this method is contraindicated in women under 18 years of age and is not recommended as a first-choice method [14]. Currently available sub-dermal implants with etonogestrel, on the other hand, have no proven adverse effect on bone density and thrombosis risk, but appear to have an unfavourable effect on bleeding patterns [15]. LNG-IUS contraception is highly effective, does not prevent ovulation, has a favourable side-effect profile and is usually well accepted [16]. Problematic, however, is the fact that intrauterine implantation is rejected by some women and is expensive.

In addition, there is increasing evidence of a potential link between LNG IUS and adverse psychiatric side effects such as panic attacks [17].

Oral progestin mono-preparations are suitable for both short-term and longer-term hormonal contraception. Preparations that do not inhibit ovulation and whose contraceptive effectiveness is based primarily on thickening of the cervical mucus and desynchronisation of endometrial development have the disadvantage that they rely on a very narrow time window (3 h), and their contraceptive effectiveness, consequently, is highly dependent on user compliance. Accordingly, the Pearl Index value for the 30 µg levonorgestrel-only preparation is 4.14 [18].

In contrast, continuous oral POP with 75 µg desogestrel reliably suppresses ovulation, and, hence, requires less strict dosing regimens (12 h time window for a missed pill) and a Pearl Index comparable to that of standard CHCs [12, 19].

Compared to CHC, progestin mono-preparations do not increase the risk of stroke, myocardial infarction and thrombosis [4, 14, 20] (with the exception of DMPA) and are also recommended for breastfeeding women. In addition, oestrogen-related side effects such as nausea, mastodynia and oedema do not occur. In addition, their continuous use makes them well suited for treating cycle-related complaints such as dysmenorrhoea, premenstrual syndrome, hypermenorrhoea and menstrual migraine, which have been shown to improve in many cases [11, 19].

Disadvantages of progestin mono-preparations

Oestrogen-free hormonal contraception, nevertheless, has traditionally also been associated with specific drawbacks. These include bleeding disorders such as bleeding between periods, spotting or prolonged bleeding. The fragility of the superficial vessels in the endometrium plays a role in these, as do local changes in steroid response, structural changes, tissue permeability and local factors contributing to neovascularisation [21, 22]. Bleeding disorders occur in up to 50% of users of the 75 µg desogestrel POP [19] and are a common reason for patients to discontinue treatment [23], which is problematic as poor compliance can reduce contraceptive effectiveness.

Other frequently cited side effects of oestrogen-free contraceptive methods include androgenisation symptoms such as acne. The oestrogen component of combined contraceptives induces SHBG formation in the liver, resulting in increased binding of testosterone and dihydrotestosterone, which can then no longer bind to and activate androgen receptors. Progestins with partial anti-androgenic effects reinforce the anti-androgenic effect of combination preparations. None of the progestin mono-preparations approved to date for contraception use progestins with an anti-androgenic partial effect, and so none of the mentioned anti-androgenic effects are likely to come into play.

The use of hormonal contraceptives can result in mood swings, and even oestrogen-free hormonal contraceptives seem to increase the risk of antidepressant use [24]. However, the extent to which various progestins result in psychobehavioral side effects in various ways or to varying degrees still needs to be investigated [25].

The issue of whether contraceptive use in adolescents is safe is frequently discussed. In particular, in the case of oestrogen-free ovulation inhibitors the concern is that suppressing endogenous

oestradiol synthesis without an exogenous supply of oestrogen could impair attainment of adequate bone density. Long-term use of DMPA does indeed lead to an increased lifetime risk of fracture. In contrast, LNG-IUS, the etonogestrel implant and the 75 µg desogestrel POP are not expected to negatively impact bone density, as oestradiol levels during use of these preparations are within ranges considered safe for bone formation [25]. However, no explicit studies on safety and efficacy in adolescents have been conducted for any of the preparations mentioned.

In the search for new contraceptives, the oestrogen-free 75 µg desogestrel pill has proven to be a safe and effective alternative [18]. However, its 12-hour window to remedy a missed pill still gives it a narrower window than preparations containing 20 µg EE/3 mg DRSP [26] and 1.5 mg E₂/2.5 mg nomegestrol acetate [27], which have a 24-hour window to remedy a missed pill. Also, due to the bleeding irregularities associated with 75 µg desogestrel, the rate of premature discontinuation of treatment is higher [20]. ► **Table 3** lists the oral progestin mono-preparations currently available on the market and their partial effects.

Recent development of the 4 mg drospirenone (DRSP)-only pill

The DRSP-only pill contains 4 mg of non-micronised DRSP (and is hence a progestin mono-preparation) and is administered in a 24/4 regimen. This was selected to improve the bleeding profile and maintain oestradiol levels at a level similar to those during the early follicular phase of the natural menstrual cycle. Furthermore, since DRSP has a half-life of 30–34 hours, effectiveness should be maintained even if a pill is missed. Clinical development was based on the medical necessity to develop an oestrogen-free pill with the following characteristics:

- A contraceptive effectiveness comparable to that of CHC (= doubled ovulation-inhibiting dosage!).
- An improvement in bleeding pattern compared to other oestrogen-free preparations due to a cyclic regimen of 24 consecutive DRSP tablets followed by 4 placebo tablets. This induces planned withdrawal bleeding to reduce bleeding between periods and/or spotting.
- A wide window of effectiveness. The new 4 mg DRSP preparation has a 24-hour window of effectiveness in which a missed pill can be remedied.
- A reduced risk of osteoporosis. Maintaining early follicular oestradiol levels should result in normal bone metabolism without increasing the risk of osteoporosis or fracture.
- An anti-androgenic and anti-mineralocorticoidic partial effect
- Treatment adherence and acceptance of this treatment regimen

Effectiveness

Preclinical data

Pharmacological properties

DRSP is a progestin (a synthetic progestogen) chemical analogue of spironolactone. In addition to its anti-oestrogenic and anti-gonadotropic effects, it also has anti-androgenic and anti-mineralocorticoidic partial effects (► **Table 3**) [28].

► **Table 3** Partial effects of selected progestins that are components of progestin mono-preparations (see also [8]).

Progestin mono-preparations	Pro-gestogenic	Anti-gonadotropic	Anti-oestrogenic	Oestrogenic	Androgenic	Anti-androgenic	Glucocorticoidic	Anti-mineralocorticoidic	Pro-coagulatory
Norethisterone	+	+	+	+	+	–	–	–	+
Levonorgestrel	+	+	+	–	+	–	–	–	–
Desogestrel	+	+	+	–	+	–	–	–	–
Drospirenone	+	+	+	–	–	+	–	+	–

Pharmacokinetics

Results from initial preclinical pharmacokinetic studies revealed that 4 mg of non-micronised DRSP would provide an area under the curve equivalent to that of 3 mg of commercially available micronised DRSP/20 µg EE. Therefore, a dose of 4 mg per tablet was chosen for this progestin mono-preparation. This prediction was based on the knowledge that DRSP's pharmacokinetics are linear in nature [30, 31].

Systemic exposure to DRSP was lower (77% relative bioavailability) after taking the 4 mg tablet of non-micronised DRSP than after taking a combination pill containing 3 mg micronised DRSP and 20 µg EE [32]. The higher DRSP exposure after taking the combined pill is presumably due to the superior absorption of micronised versus non-micronised DRSP. In addition, an inhibitory effect of EE on sulphotransferase 1A1 has been discussed. This enzyme is involved in the metabolism of DRSP and catalyses the formation of the metabolite 4,5-dihydrodrospirenone-3-sulphate [32, 33].

Phase II trials

DRSP's anti-gonadotropic effect results in inhibition of ovulation

The anti-gonadotropic effect of 4 mg DRSP has been demonstrated in phase II trials. Inhibition of ovulation (defined as occurring when serum progesterone levels fall below 16 nmol/l) was demonstrated in healthy young women (n = 20) over two administration cycles. This finding was confirmed in another study that investigated the ovulation inhibition of 4 mg DRSP taken in a 24/4 regimen compared with continuous administration of 75 µg desogestrel over two administration cycles in healthy women aged 18–35 years. In this study, ovulation was suppressed just as effectively by the 4 mg DRSP regimen as by the 75 µg desogestrel regimen [34].

Inhibition of ovulation in spite of delayed administration

The ability of 4 mg DRSP to maintain ovulation inhibition even when a pill is delayed was investigated in an open randomised trial in which young healthy women (n = 127) delayed taking the pill for 24 h on pre-determined cycle days [35]. This trial showed that the ovulation rate with 4 mg DRSP was much lower than with traditional POPs (30–40%). It was comparable to, or even slightly lower than, the ovulation rate with CHCs (1.1–2.0%) and lower than the ovulation rate with 75 µg desogestrel after three planned 12-hour delays (1%) [36].

Phase III trials

Effectiveness

The contraceptive effectiveness of 4 mg DRSP has been confirmed by phase III clinical trials, two from Europe [37, 38] and one from the US [39]. A pooled analysis of the two European trials resulted in a Pearl Index of 0.73 (95% confidence interval [CI] 0.3133, 1.4301) (14 329 cycles with 4 mg DRSP) and a corrected Pearl Index (taking into account sexual activity and use of other contraceptive methods) of 0.79 (95% CI 0.3410, 1.5562) [38].

The pooled analysis of a subgroup of 1251 women ≤ 35 years of age yielded similar results: an overall Pearl Index (based on 11 145 cycles) of 0.93 (95% CI 0.4029, 1.8387) and a corrected Pearl Index (based on 10 173 cycles) of 1.02 (95% CI 0.4414, 2.0144) [38]. The findings of both studies show that the contraceptive effectiveness of 4 mg DRSP is comparable to that of currently available CHCs (► **Table 4**). In the US study of 915 non-breastfeeding women ≤ 35 years of age, the Pearl Index was 2.9 (95% CI 1.5, 5.1) [38]. The rate of discontinuation in the three clinical trials (27.8% and 19.8% in the European trials [37, 38] and 65% in the US trial [39]) could potentially bias the results for the primary endpoint and the safety profile, including adverse events.

The higher rate of trial withdrawals in the USA compared to the European pivotal trials is not unusual and the fact that 86% of participants reported being satisfied with the DRSP treatment puts this finding into context. Furthermore, a minimum of 5000 cycles was required to obtain one PI value. This was clearly exceeded [38].

Safety

Haemostaseological parameters

A long-term study investigated the influence of 4 mg DRSP on coagulation factors and potential thromboembolic risks from a haemostaseological perspective [40]. The study included 39 women who took 4 mg DRSP for 9 cycles (24/4 regimen) and 29 subjects who took 75 µg desogestrel daily over the same period. The following haemostaseological parameters were investigated: resistance to activated protein C, antithrombin III, D-dimer, C-reactive protein and coagulation factors VII and VIII [40]. The study revealed that 4 mg DRSP had no effect on haemostaseological parameters and did not affect the balance between pro-coagulatory and anti-coagulatory factors.

Thromboembolic events

Over the period of the entire clinical development programme (> 20 000 cycles), no reports of VTEs in women taking 4 mg DRSP

► **Table 4** Contraceptive effectiveness of the 4 mg DRSP mono-preparation: Pearl Index data from the European pivotal trials.

Pearl Index	Archer et al. [37]	Palacios et al. [38]		Pooled analysis
	Drospirenone 4 mg (n = 713)	Drospirenone 4 mg (n = 858)	Desogestrel 75 µg (n = 332)	Drospirenone 4 mg (n = 1571)
Total				
Total number of treatment cycles	7638	6691	2487	14 329
Pregnancies, n (%)	3 (0.4)	5 (0.6)	1 (0.3)	8 (0.5)
Pearl Index overall, %	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
Post correction (additional contraceptive methods and sexual activity status)				
Total number 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)
Corrected 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 failures				
Total number of perfect medication cycles	6101	4641	1816	10 742
Pregnancies, n (%)	3 (0.4)	5 (0.6)	1 (0.3)	8 (0.5)
Pearl Index method failures, %	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	0.73
95% CI (lower limit, upper limit)	0.00, 1.07	0.09, 1.31	0.00, 1.01	0.17, 1.27

were reported [41]. The documented risk factors included a family history of thromboembolic events, evidence of a predisposition to vascular or metabolic disease, smoking if over 35 years of age, not smoking and over 40 years of age, and a body mass index (BMI) of ≥ 30 kg/m². In the US study, at least 367 participants (36.5%) had a VTE risk factor [39], while in the European studies 139 (16.2%) and 104 (14.6%) of participants, respectively, had a VTE risk factor [37, 38].

These observations are consistent with the fact that 4 mg DRSP was neutral with regard to the haemostaseological parameters examined in the above-mentioned long-term study. Future epidemiological studies will be needed to corroborate the clinical data on cardiovascular safety [41].

Effect on mild hypertension

Previous studies have shown that 6-month use of a drospirenone/oestrogen combination was associated with a modest decrease in systolic blood pressure (SBP) and diastolic blood pressure (DBP) compared with a levonorgestrel/oestrogen combination [42, 43]. This minor effect on blood pressure was also demonstrated in a study that compared the influence of a contraceptive containing 3 mg DRSP and EE with a preparation containing 150 µg desogestrel and EE [43]. The observed effect is most likely attributable to the anti-mineralocorticoid effect of DRSP.

The two European pivotal trials also investigated the effect of 4 mg DRSP on blood pressure. The first study demonstrated a median decrease of 8 mmHg (SBP) and 5 mmHg (DBP) in participants with a baseline SBP of ≥ 130 mmHg and a baseline DBP of ≥ 85 mmHg (n = 137) [36, 37]. In participants with a baseline SBP

of < 130 mmHg and a baseline DBP of < 85 mmHg (n = 548), the absolute median change was 0 mmHg for both SBP and DBP [41].

Oestradiol levels and bones

A study of 64 volunteers [26] revealed that the E₂ level on day 24 of the second administration cycle was just below 51 pg/ml (187 pmol/l), higher than the levels on day 3 of the first cycle, which can be considered to be baseline levels. Thus, 24 days of treatment with 4 mg DRSP did not reduce E₂ levels below the baseline levels of day 3. The difference in E₂ levels compared to the control group (75 µg desogestrel) was not statistically significant. Under the recommended regimen (24/4), endogenous E₂ production can occur in the ovaries, as the 4-day break should be sufficient to increase FSH levels. This was confirmed with the values from day 3 of the second administration cycle, which were higher than the values on day 27 of the first administration cycle. The new dosing regimen (24/4 regimen of 4 mg DRSP compared to a 28-day regimen of 75 µg desogestrel) resulted in higher E₂ levels at the end of administration cycle 2 than those on day 3 of the first administration cycle [26].

During the 4 mg DRSP 24/4 regimen, mean E₂ levels do not fall below 30 pg/ml (110.1 pmol/l) [25]. This value is considered a potential limit for the onset of osteoclast activity in bone, as demonstrated in the study by Doran et al. [44].

Changes in body weight

No significant changes in mean body weight occurred among users of 4 mg DRSP during the various short and long-term studies [36–38, 40]. This confirms data from the literature indicating

► **Table 5** Median number of planned and unplanned bleeding or spotting days and premature study withdrawals associated with AUB (abnormal uterine bleeding) in specified reference periods.

Variable	Archer et al. [37]	Palacios et al. [[38,39]]	
	Drospirenone 4 mg (n = 713)	Drospirenone 4 mg (n = 858)	Desogestrel 75 µg (n = 332)
Total bleeding and spotting days			
Cycles 2–4	11	10*	12
Cycles 5–7	8	6	7
Cycles 8–10/7–9 ^a	6	6	7
Cycles 11–13	5		
Unplanned bleeding and spotting days			
Cycles 2–4	6	5**	12
Cycles 5–7	5	4*	7
Cycles 8–10/7–9 ^a	3	4*	7
Cycles 11–13	3		
Premature withdrawal from the trial due to bleeding disorders	30 (4.2)	28 (3.3)	22 (6.6)

Data are shown as n (%)

^a 8–10 for study 301, 7–9 for study 302

* $p < 0.05$ drospirenone vs. desogestrel

** $p < 0.001$ drospirenone vs. desogestrel

that use of DRSP is not associated with weight gain or significant changes in body fat percentage [44].

Tolerance

Bleeding pattern: control of bleeding profile with 4 mg DRSP in comparison to 75 µg desogestrel.

A phase III clinical trial over 9 administration cycles compared bleeding profiles of women treated with 4 mg DRSP and women treated with 75 µg desogestrel [46,47]. The percentage of women with bleeding and spotting decreased in the 4 mg DRSP group from 69.2% in administration cycle 2 to 56.3% in administration cycle 9, and in the 75 µg desogestrel group from 74.05% to 45.3%. The median number of bleeding and spotting days decreased from 10 days in the 4 mg DRSP group in the first reference period (administration cycles 2–4) to 6 days in the last reference period (administration cycles 7–9), and from 12 to 7 days in the 75 µg desogestrel group. Most of these days were days with spotting rather than bleeding. The differences were statistically significant.

In addition, during administration cycles 5–9, the proportion of women with prolonged bleeding (> 10 days) was significantly lower in the 4 mg DRSP group than in the 75 µg desogestrel group ($p < 0.001$). Premature study withdrawal due to abnormal uterine bleeding (AUB) occurred in 3.3% of DRSP and 6.6% of 75 µg desogestrel users ($p < 0.001$) [46,47]. In summary, the results of the clinical trials revealed that 4 mg DRSP controlled bleeding patterns better than did 75 µg desogestrel. ► **Table 5** presents data on bleeding patterns from the trials.

Endometrial safety

Endometrial thickness was assessed in a dedicated endometrial safety study [48]. The mean maximum double endometrial thickness was 5.5 mm, and after 13 administration cycles it was reduced by an average of 2.6 mm. Biopsies were taken to assess changes in the endometrium. After one year of treatment with 4 mg DRSP, not a single case of hyperplasia occurred [48].

Use in Special Groups

Adolescents

A study was designed to prospectively assess the safety and tolerability of 4 mg DRSP (24/4) in 111 adolescent females aged 12–17 years [48]. The study consisted of six 28-day administration cycles and a further optional extension phase of 7 administration cycles. The number of participants reporting dysmenorrhoea decreased from 47 (46.1%) before screening to 14 (29.8%) after administration cycle 6, and to 8 (17%) after administration cycle 13. At the same time, the percentage of women who used painkillers to treat dysmenorrhoea decreased. Only five participants (4.9%) withdrew prematurely from the study due to irregular bleeding and one (1%) due to amenorrhoea. No treatment-related serious adverse events and no pregnancies occurred. At the conclusion of the study, 82.4% of the participants rated the tolerability of 4 mg DRSP as excellent or good [49].

Overweight and obese women

Obesity leads to physiological changes, such as increased cardiac output or changes in liver enzyme function, compared to individuals of normal weight. Some liver changes have the potential to alter the absorption, distribution, metabolism and elimination of drugs, reducing their efficacy [50].

The contraceptive effectiveness of DRSP in overweight and obese women has been confirmed in a pooled analysis of European studies from the clinical development programme of the 4 mg DRSP preparation [37,38]. Four reported pregnancies ($PI = 1.89$) occurred in women with a BMI of 25–30 kg/m² ($n = 301$), while no pregnancies occurred in participants with a BMI ≥ 30 kg/m² ($n = 71$) ($PI = 0.0$).

The clinical programme demonstrated the favourable thromboembolic safety profile of 4 mg DRSP, also for women with VTE risk factors. Cigarette smoking in women > 35 years of age was the most common risk factor in the European studies (10.1% and 12%, respectively) [37,38,41]. In the US study [39,41], this incidence was 5.1%. The most common risk factor in the US study was a BMI of > 30 kg/m², accounting for 35% of the participants. In the European studies, only 5.8% and 3.5%, respectively, of the participants had a BMI above 30 kg/m².

The incidence of women with a family history of thromboembolic events or of women with predisposing factors for cardiovascular or metabolic disease was lower in all studies.

In conclusion, even in women with risk factors for venous thromboembolic events (VTEs), such as being over 35 years of age, tobacco use and obesity, no venous or arterial thromboembolic events occurred [40].

Breastfeeding women

A prospective study investigated the amount of DRSP transferred to breast milk after reaching a steady state [51]. DRSP 4 mg per day was administered for 7 days to reach this steady-state concentration. The mean AUC (0–24 h) of DRSP in plasma 24 h after administration of the last dose was 635.33 ng h/ml. The mean C_{\max} was 48.64 ng/ml. The mean AUC (0–24 h) of DRSP in the mother's milk 24 h after administration of the last dose was 134.35 ng h/ml. The mean C_{\max} was 10.34 ng/ml. On average, 18.13% of plasma DRSP entered breast milk and the highest concentration measured in breast milk was 17.55% of plasma DRSP. The mean total quantity of DRSP that passed into breast milk was 4478 ng during a 24-hour period, equivalent to 0.11% of the maternal daily dose. Hence, no effects on breastfed newborns/infants are expected with the DRSP 4 mg preparation at the recommended dosages, as these amounts are considered to be negligible [52].

Summary

Progestins play an essential and independent role in contraception, with or without oestrogens. Although they differ in structure and effect profile, they have a multimodal mode of action in contraception. In addition to its progestogenic effect, each progestin has an inherent partial effect profile that is highly relevant in clinical use. This can influence or determine effects and possible side effects.

In view of the available data, it may be concluded that the introduction of a new oestrogen-free contraceptive containing 4 mg of non-micronised DRSP in a 24/4-day regimen expands contraceptive options for women and represents an innovation in modern contraception for the following reasons:

- clinical trials have shown DRSP to be highly effective (Pearl Index = 0.73),
- no relevant safety concerns were identified in the clinical trials (0 thromboembolic cases in more than 20 000 cycles in more than 2000 women), and
- a high acceptance rate (96.5%) among users with a low discontinuation rate due to unacceptable bleeding disorders (91 of 2593 women (3.5%) during all phase III trials) has been documented [52].

Conflict of Interest

Pedro-Antonio Regidor is an employee of Exeltis.

References

- [1] Schindler AE. Non-contraceptive benefits of oral hormonal contraceptives. *Int J Endocrinol Metab* 2013; 11: 41–47. doi:10.5812/ijem.4158
- [2] World Health Organization. Medical eligibility criteria for contraceptive use. 5th ed. Geneva: WHO; 2015. Accessed March 08, 2021 at: <https://www.who.int/publications/i/item/9789241549158>
- [3] Khialani D, Rosendaal F, van Hylckama Vlieg A. Hormonal Contraceptives and the Risk of Venous Thrombosis. *Semin Thromb Hemost* 2020; 46: 865–871. doi:10.1055/s-0040-1715793
- [4] Lidegaard Ø, Nielsen LH, Skovlund CW et al. Risk of venous thromboembolism from use of oral contraceptives containing different progestogens and oestrogen doses. *BMJ* 2011; 343: d6423. doi:10.1136/bmj.d6423
- [5] Lidegaard Ø, Nielsen LH, Skovlund CW et al. Venous thrombosis in users of non-oral hormonal contraception: follow-up study, Denmark 2001–10. *BMJ* 2012; 344: e2990. doi:10.1136/bmj.e2990
- [6] Bundesinstitut für Arzneimittel und Medizinprodukte. Rote-Hand-Brief zu den kombinierten hormonalen Kontrazeptiva. Accessed December 13, 2020 at: www.bfarm.de/SharedDocs/Risikoinformationen/Pharmakovigilanz/DE/RHB/2014/rhb-khk.html
- [7] European Medicines Agency. Combined hormonal contraceptives. Accessed May 31, 2021 at: www.ema.europa.eu/en/medicines/human/referrals/combined-hormonal-contraceptives
- [8] Schindler AE, Campagnoli C, Druckmann R et al. Classification and pharmacology of progestins. *Maturitas* 2008; 61: 171–180. doi:10.1016/j.maturitas.2008.11.013
- [9] Regidor PA, Schindler AE. Antiandrogenic and antimineralocorticoid health benefits of COC containing newer progestins: dienogest and drospirenone. *Oncotarget* 2017; 8: 83334–83342. doi:10.18632/oncotarget.19833
- [10] Römer T, Göretzlehner G. Kontrazeption mit OC in 238 Problemsituationen. 3rd ed. Berlin: De Gruyter; 2017: 3–320
- [11] Ahrendt HJ, Böhling KJ. Estrogen Free Contraception: progestin-only systems. *J Reprod Med Endocrinol* 2010; 7 (Sonderheft 1): 97–105
- [12] World Health Organization; Johns Hopkins Bloomberg School of Public Health. Family Planning: A Global Handbook for Providers. 3rd ed. 2018. Accessed May 31, 2021 at: <https://apps.who.int/iris/bitstream/handle/10665/260156/9780999203705-eng.pdf?ts>
- [13] van Hylckama Vlieg A, Helmerhorst FM, Rosendaal FR. The risk of deep venous thrombosis associated with injectable depot-medroxyprogesterone acetate contraceptives or a levonorgestrel intrauterine device. *Arterioscler Thromb Vasc Biol* 2010; 30: 2297–2300. doi:10.1161/ATVBAHA.110.211482
- [14] AWMF. AWMF guideline hormonal contraception 2020. Accessed July 06, 2020 at: <https://www.awmf.org/leitlinien/detail/ll/015-015.html>
- [15] Bachmann G, Korner P. Bleeding patterns associated with non-oral hormonal contraceptives: a review of the literature. *Contraception* 2009; 7: 247–58. doi:10.1016/j.contraception.2008.10.012
- [16] Hsia JK, Creinin MD. Intrauterine Contraception. *Semin Reprod Med* 2016; 34: 175–182. doi:10.1055/s-0036-1571438
- [17] World Health Organization. WHO Pharmaceuticals Newsletter No. 6, 2019. Licence: CC BY-NC-SA 3.0 IGO. Geneva: World Health Organization; 2019
- [18] Fachinformation 28 mini®; November 2019
- [19] Cerazette® Summary of product characteristics 2020. May 2020. Accessed May 31, 2021 at: <https://www.medicines.org.uk/emc/product/1698/smpc#gref>
- [20] Lidegaard Ø, Løkkegaard E, Jensen A et al. Thrombotic stroke and myocardial infarction with hormonal contraception. *N Engl J Med* 2012; 366: 2257–2266. doi:10.1056/NEJMoa1111840
- [21] de Melo NR. Estrogen-free oral hormonal contraception: benefits of the progestin-only pill. *Womens Health (Lond)* 2010; 6: 721–735. doi:10.2217/whe.10.36
- [22] Smith OP, Critchley HO. Progestogen only contraception and endometrial break through bleeding. *Angiogenesis* 2005; 8: 117–126. doi:10.1007/s10456-005-9003-z
- [23] Villavicencio J, Allen RH. Unscheduled bleeding and contraceptive choice: increasing satisfaction and continuation rates. *Open Access J Contracept* 2016; 7: 43–52. doi:10.2147/OAJC.S85565
- [24] Skovlund CW, Mørch LS, Kessing LV et al. Association of Hormonal Contraception With Depression. *JAMA Psychiatry* 2016; 73: 1154–1162. doi:10.1001/jamapsychiatry.2016.2387. Erratum in: *JAMA Psychiatry* 2017; 74: 764

- [25] Mitchell VE, Welling LLM. Not All Progestins are Created Equally: Considering Unique Progestins Individually in Psychobehavioral Research. *Adaptive Human Behavior and Physiology* 2020; 6: 381–412. doi:10.1007/s40750-020-00137-1
- [26] Hadji P, Colli E, Regidor PA. Bone health in estrogen-free contraception. *Osteoporos Int* 2019; 30: 2391–2400. doi:10.1007/s00198-019-05103-6
- [27] Jenapharm GmbH & Co KG. Yaz. Summary of product characteristics. July 2020. Accessed May 31, 2021 at: <https://db.cbg-meb.nl/mri/spc/nlh-1269-001.pdf>
- [28] Theramex Ireland Limited. Zoely. Summary of product characteristics. June 2020. Accessed May 31, 2021 at: www.medicines.org.uk/emc/product/3038/smpc
- [29] Regidor PA. The clinical relevance of progestins in hormonal contraception: present status and future developments. *Oncotarget* 2018; 9: 34628–34638. doi:10.18632/oncotarget.26015
- [30] Fuhrmann U, Krattenmacher R, Slater EP et al. The novel progestin drospirenone and its natural counterpart progesterone: biochemical profile and antiandrogenic potential. *Contraception* 1996; 54: 243–251. doi:10.1016/s0010-7824(96)00195-3
- [31] Krattenmacher R. Drospirenone: pharmacology and pharmacokinetics of a unique progestin. *Contraception* 2000; 62: 29–38. doi:10.1016/s0010-7824(00)00133-5
- [32] 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. doi:10.1016/j.contraception.2019.10.005
- [33] Rohn KJ, Cook IT, Leyh TS et al. Potent inhibition of human sulfotransferase 1A1 by 17 α -ethinylestradiol: role of 3'-phosphoadenosine 5'-phosphosulfate binding and structural rearrangements in regulating inhibition and activity. *Drug Metab Dispos* 2012; 40: 1588–1595. doi:10.1124/dmd.112.045583
- [34] Duijkers IJ, Heger-Mahn D, Drouin D et al. 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. doi:10.3109/13625187.2015.1044082
- [35] 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. doi:10.1016/j.contraception.2015.12.007
- [36] Rice CF, Killick SR, Dieben T et al. A comparison of the inhibition of ovulation achieved by desogestrel 75 mg and levonorgestrel 30 mg daily. *Hum Reprod* 1999; 14: 982–985. doi:10.1093/humrep/14.4.982
- [37] 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
- [38] 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. doi:10.1016/j.contraception.2015.07.014
- [39] 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* 2020; 2: 100020. doi:10.1016/j.conx.2020.100020
- [40] 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 μ g per day. *Gynecol Endocrinol* 2016; 32: 749–751. doi:10.3109/09513590.2016.1161743
- [41] 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: 218. doi:10.1186/s12905-020-01080-9
- [42] 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. doi:10.1210/jcem.80.6.7775629
- [43] 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. doi:10.1016/s0010-7824(02)00537-1
- [44] Doran PM, Riggs BL, Atkinson EJ et al. 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: 2118–2125. doi:10.1359/jbmr.2001.16.11.2118
- [45] Foidart JM, Faustmann T. Advances in hormone replacement therapy: weight benefits of drospirenone, a 17 α -spiroactone- derived progestogen. *Gynecol Endocrinol* 2007; 23: 692–699. doi:10.1080/09513590701582323
- [46] 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. doi:10.1007/s00404-019-05340-4
- [47] Palacios S, Colli E, Regidor PA. Bleeding profile of women using a drospirenone-only pill 4 mg over nine cycles in comparison with desogestrel 0.075 mg. *PLoS One* 2020; 15: e0231856. doi:10.1371/journal.pone.0231856
- [48] 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
- [49] 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: 412–419. doi:10.1016/j.contraception.2020.02.004
- [50] 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. doi:10.1016/S0140-6736(14)60460-8
- [51] Melka D, Kask K, Colli E et al. A single-arm study to evaluate the transfer of drospirenone to breast milk after reaching steady state, following oral administration of 4 mg drospirenone in healthy lactating female volunteers. *Womens Health (Lond)* 2020; 16: 1745506520957192. doi:10.1177/1745506520957192
- [52] Exeltis. Slynd. 2019. Accessed at: www.drugs.com/pro/slynd.html

Correction

Oral Progestins in Hormonal Contraception: Importance and Future Perspectives of a New Progestin Only-Pill Containing 4 mg Drospirenone

Thomas Römer, Johannes Bitzer, Christian Egarter et al. *Geburtsh Frauenheilk*. doi:10.1055/a-1471-4408

In the e-first version of this article the name of the co-author was incorrect. Correct is: Katrin Schaudig.