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Effects of two combined oral contraceptives containing ethinyl estradiol 20 μg combined with either drospirenone or desogestrel on lipids, hemostatic parameters and carbohydrate metabolism

Christine Klipping[a], Joachim Marr[b,*]

[a]Dinox Medical Investigations, Groenewoudseweg 317, NL-6524 TX, Nijmegen, The Netherlands
[b]Clinical Development Gynecology and Andrology, Schering AG, D-13342 Berlin, Germany

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Abstract

Objective: To compare the effect of ethinyl estradiol 20 μg/drospirenone 3 mg (EE 20 μg/DRSP 3 mg) administered according to a 24/4 regimen with ethinyl estradiol 20 μg/desogestrel 150 μg (EE 20 μg/DSG 150 μg) administered according to the conventional 21/7 regimen on lipid, carbohydrate and hemostatic parameters.

Study Design: In this open-label study, healthy women were randomized to EE 20 μg/DRSP 3 mg or EE 20 μg/DSG 150 μg for seven cycles. Mean differences in high-density lipoprotein (HDL)- and low-density lipoprotein (LDL)-cholesterol levels at cycle 7 compared to baseline were assessed. Secondary variables included changes in other lipid, hemostatic and carbohydrate parameters.

Results: Both treatments increased HDL-cholesterol, but decreased LDL-cholesterol by a comparable extent. Although slightly elevated in both groups, blood glucose and C-peptide levels measured during oral glucose tolerance tests were within normal reference ranges at cycle 7. Overall, the differences in lipid, hemostatic or carbohydrate parameters were not significant between the two treatments.

Conclusion: EE 20 μg/DRSP 3 mg has a good safety profile comparable with EE 20 μg/DSG 150 μg.

Keywords: Oral contraceptives; Drospirenone; Lipid metabolism; Carbohydrate metabolism

1. Introduction

Although combined oral contraceptives (OCs) are highly efficacious and have a good safety profile, their hormonal components are known to have various metabolic effects, including effects on lipid and carbohydrate metabolism, and hemostatic variables. For example, it is well known that androgenic progestins exert an adverse influence on lipid metabolism. This is in part due to their ability to counteract the favorable estrogen-induced changes in low-density lipoprotein (LDL)- and high density lipoprotein (HDL)-cholesterol levels [1–4]. Furthermore, the influence on glucose metabolism increases with progesterone dominance [1,5–7]. In contrast, the adverse effects on hemostatic variables and the associated risk of venous thrombosis are most likely to be influenced by the estrogen dose and not by the type of progestin [8].

Recent reviews have suggested that the ideal pharmacological properties of a synthetic progestin should resemble those of progesterone as closely as possible, while reducing or eliminating the undesirable (mainly androgenic and mineralocorticoid) effects [9–11]. Most currently available progestins are 19-nortestosterone derivatives and as such have inherent androgenic potential. Furthermore, of these progestins, none are able to counteract the mineralocorticoid activity of the estrogen component. In contrast, drospirenone has proven antiandrogenic properties and, as an analog of spironolactone, inherent antimineralocorticoid activity [9,12–14].

A new contraceptive formulation and regimen based on drospirenone has been developed. The new formulation, ethinyl estradiol 20 μg/drospirenone 3 mg (EE 20 μg/DRSP 3 mg), is taken daily for an extended treatment period of 24 days followed by four hormone-free days (24/4 regimen).

* Corresponding author. Tel.: +49 0 30 468 17617; fax: +49 0 30 468 15348.
E-mail address: joachim.marr@schering.de (J. Marr).

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The 24/4 regimen was developed in part to accentuate the benefits of drospirenone and to alleviate symptoms such as pelvic pain, headaches, bloating and breast tenderness that are common (particularly during the 7-day hormone-free interval) in most women who adhere to the conventional regimen of 21 days of active treatment followed by seven hormone-free days (21/7 regimen) [15]. Extending the days on active treatment is expected to reduce hormone withdrawal effects.

This open, randomized study was designed to compare the effects of EE 20 μg/DRSP 3 mg administered according to a 24/4 regimen with ethinyl estradiol 20 μg/desogestrel 150 μg (EE 20 μg/DSG 150 μg) administered according to the conventional 21/7 regimen on the lipid profile, hemostatic and carbohydrate metabolism parameters.

2. Materials and methods

2.1. Study design

This open-label, randomized, controlled study was conducted in a single center in The Netherlands. The study protocol was approved by an independent ethics committee and was conducted in accordance with both the Declaration of Helsinki (as revised in 1996) and the International Conference on Harmonization for Industry E6-Good Clinical Practice guidelines. All participants gave written and informed consent before enrolment.

2.2. Patients

Healthy women aged 18–35 years (including smokers up to the age of 30 years) requesting oral contraception were eligible to participate in this study. The exclusion criteria included: pregnancy or lactation; contraindications to contraceptive steroids; body mass index >30 kg/m^2; uncontrolled thyroid disorders; clinically significant findings that may worsen with hormonal treatment; depression or a history of depression in the last year; vascular disease or factors that predispose to vascular disease; diabetes mellitus or impaired glucose tolerance; sickle cell anemia; disturbance of lipid metabolism; use of medication that are known to affect the metabolism or pharmacokinetics of combined oral contraceptives such as hydantoins, barbiturates, rifampicin or St. John's wort; use of oral contraceptives (within two cycles from start of the study medication), any sex hormones (within three cycles), any long-acting injectable or implanted preparations (within 6 months); uncontrolled hypertension; and malignant or premalignant tumors.

2.3. Treatment

Patients were randomized according to a computer-generated randomization code to receive seven cycles of either EE 20 μg/DRSP 3 mg administered according to a 24/4 regimen or EE 20 μg/DSG 150 μg (Mercilon®, Organon, Oss, The Netherlands) administered according to the conventional 21/7 regimen. Treatment in cycle 1 began on the first day of menstrual bleeding, which was considered as day 1 of the treatment cycle.

2.4. Clinical assessments

The patients were examined at a baseline screening visit to confirm their eligibility, medical history and general health status. Patients underwent a washout period for sex hormones before the next two clinic visits where blood samples were taken to determine baseline lipid parameters and plasma glucose levels (between cycle days 8 and 15), as well as baseline hemostatic variables, insulin and C-peptide levels (between cycle days 15 and 21). At the latter visit, randomization to study medication was performed and diary cards were issued.

Two clinic visits were scheduled during the treatment phase on days 16–22 of cycles 3 and 7. A final follow-up clinic visit occurred 10–17 days after completing the study or on premature discontinuation.

Treatment compliance was assessed by analyzing patient diary cards of tablet intake along with the return of used, partially used or unused treatment packs.

Blood samples were taken to assess lipid, hemostatic and carbohydrate parameters at baseline and during the clinic visit in cycle 7 from patients in a fasting state before study drug administration. Analysis of the blood samples were performed at a central laboratory.

2.5. Primary target parameters

The primary target variables were relative changes in serum HDL- and LDL-cholesterol (calculated according to Friedewald) levels from baseline to cycle 7 of treatment.

2.6. Secondary target parameters

Other analyses performed at baseline and cycle 7 included serum total cholesterol, lipoprotein (a), triglycerides, HDL_2-cholesterol and VLDL-cholesterol concentrations. Hemostatic parameters such as activation markers (prothrombin fragment 1+2, D-dimer), pro- and anticoagulatory variables (fibrinogen, factor VII and factor VIII activity, antithrombin activity, protein C activity, protein S, APC resistance), and pro- and antifibrinolytic variables [plasminogen, tissue plasminogen activator (t-PA) activity, plasmin–antiplasmin (PAP) complex, plasminogen activator inhibitor-1 (PAI-1) antigen] were also assessed.

Insulin levels (fasting) were determined from blood samples taken at baseline and cycle 7. Total glucose and C-peptide levels were measured during an oral glucose tolerance test (OGTT). Patients were instructed to consume >250 g of carbohydrates on each of the 3 days preceding the test. The test was performed in the morning after an overnight fast (12 h), and food was not allowed during testing. The 75-g standardized OGTT was performed (i.e., patients consumed 75 g glucose for the test). Five 10-mL

Table 1
Baseline characteristics (FAS)

	EE 20 μg/DRSP 3 mg (n=29)	EE 20 μg/DSG 150 μg (n=30)
Age (years)	23.8 ± 4.4	23.7 ± 4.9
Height (cm)	168.76 ± 6.11	172.67 ± 6.06
Weight (kg)	62.73 ± 7.85	64.77 ± 5.95
Body mass index (kg/m2)	21.76 ± 2.86	21.72 ± 1.82
Ethnic origin		
Caucasian	29	29
Other (Asian/Creole)	0	1

blood samples were obtained within 30 min before, and 30, 60, 90 and 120 min (±5 min) after ingestion of the glucose load. The area under the concentration time curve (AUC) of glucose during the OGTT was then determined.

The vaginal bleeding pattern was assessed by analyzing the number and type of bleeding episodes recorded on the same diary cards as for tablet intake. Bleeding episodes were rated by the patients as: none, no vaginal bleeding; spotting, no requirement for sanitary protection except panty liners; light, need for sanitary protection but less bleeding than that associated with normal menstruation relative to the patient's experience; normal, like normal menstruation relative to the patient's experience; or heavy, more than normal menstruation relative to the patient's experience. The bleeding episodes were described using the 90-day reference period method recommended by the WHO [16]. The first reference period started on the first day of treatment. According to the day on which each bleeding episode started, it was assigned to the appropriate reference period. Therefore, an episode that started between days 1 and 90 was assigned to the first reference period, and an episode that started during days 91–180 was assigned to the second reference period.

2.7. General safety and tolerability assessments

General safety assessments included monitoring for adverse events, changes in vital signs and changes in laboratory values for hematological variables and blood chemistry. Physical and gynecological examinations (including a cervical smear) were performed at baseline and on study completion. The physician classified the likelihood of a relationship between an adverse event and the study medication as none, unlikely, possible, probable and definite.

2.8. Statistical analyses

All efficacy analyses were performed on the full analysis set (FAS) and on the per protocol set (PPS). For the safety variables, FAS was analyzed only. All randomized volunteers who took at least one tablet of study medication and for whom at least one observation post randomization was available were included in the FAS. A patient was excluded from the PPS if they had a major violation of the inclusion or exclusion criteria; took <26 or >30 EE 20 μg/DRSP 3 mg tablets or <19 or >23 EE 20 μg/DSG 150 μg tablets in any cycle; or had any major protocol deviations.

Assuming a drop-out probability of 30% (including all major deviations from the protocol), 30 patients per group were recruited in order to have a sample size of approximately 20 volunteers per group in the PPS.

All variables were analyzed using descriptive statistical methods. The primary variables were the ratio of HDL-cholesterol levels at cycle 7 compared to baseline and the ratio of LDL-cholesterol at the same time points. The ratios were log-transformed and the 95% confidence intervals (CIs) calculated for the mean differences between the treatment groups on the logarithmic scale. An anti-log transformation yielded primary variables on the original scale.

The ratio of the AUC of glucose (during OGTT) at cycle 7 to baseline was analyzed using the same method as for the primary variables. In addition, the 95% CI of the mean difference between treatments (EE 20 μg/DRSP 3 mg−EE 20 μg/DSG 150 μg) was also calculated for the changes between cycle 7 and baseline for prothrombin fragments

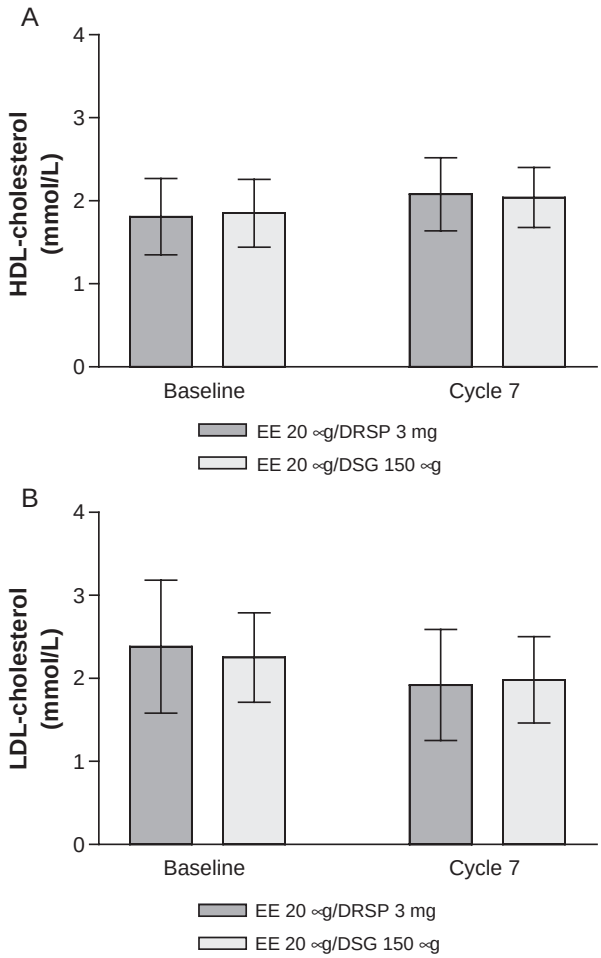

Fig. 1. Changes from baseline to cycle 7 of (A) HDL-cholesterol and (B) LDL-cholesterol, following treatment with EE 20 μg/DRSP 3 mg or EE 20 μg/DSG 150 μg (FAS).

Table 2
Geometric mean ratios (cycle 7/baseline) for changes in HDL- and LDL-cholesterol (FAS)

	EE 20 μg/DRSP 3 mg	EE 20 μg/DSG 150 μg	Ratio of geometric means
	Geometric mean ratio (cycle 7/baseline)	Geometric mean ratio (cycle 7/baseline)	(EE 20 μg/DRSP 3 mg)/ (EE 20 μg/DSG 150 μg) (95% CI)
HDL- cholesterol	1.15	1.10	1.05 (0.97, 1.13)
LDL-cholesterol	0.79	0.88	0.90 (0.79, 1.03)

1+2 and the D-dimer values. The bleeding episodes were described using the 90-day reference period method recommended by the WHO.

3. Results

3.1. Subject disposition

A total of 60 patients were randomized to receive EE 20 μg/DRSP 3 mg ($n=30$) or EE 20 μg/DSG 150 μg ($n=30$). Of these, 29 patients assigned to the EE 20 μg/DRSP 3 mg group and 30 assigned to the EE 20 μg/DSG 150 μg group were included in the FAS. Seven patients discontinued the study prematurely, four in the EE 20 μg/DRSP 3 mg group and three in the EE 20 μg/DSG 150 μg group. Reasons for discontinuation in the EE 20 μg/DRSP 3 mg group included continuous vaginal bleeding, irritable mood, headache and pregnancy before receiving study medication. Reasons for discontinuation in the EE 20 μg/DSG 150 mg group included emotional lability, intracyclic bleeding and finished relationship. There were 13 subjects with major protocol violations in the study, eight subjects in the EE 20 μg/DRSP 3 mg group (pill intake irregularities $n=1$, excluded concomitant medication $n=2$, inclusion/exclusion criteria violations $n=2$, procedure deviations $n=3$) and five subjects in the EE 20/DSG 150 mg with the following G protocol violations. The PPS included 22 patients in the EE 20 μg/DRSP 3 mg group and 25 patients in the EE 20 μg/DSG 150 μg group. There were no relevant differences in patient characteristics at baseline between the two treatment groups (Table 1).

3.2. Primary target variables

Changes in HDL- and LDL-cholesterol levels from baseline to cycle 7 are presented in Fig. 1; both treatments increased HDL-cholesterol levels but decreased LDL-cholesterol levels. The increase in HDL-cholesterol levels was more pronounced in the EE 20 μg/DRSP 3 mg group compared with the EE 20 μg/DSG 150 μg group (16% vs. 11%, respectively), as was the decrease in LDL-cholesterol levels (−18% vs. −10%, respectively). The geometric mean ratios (cycle 7/baseline) for HDL- and LDL-cholesterol are summarized in Table 2. There was no statistically significant difference between the two groups in terms of the HDL- and LDL-cholesterol changes observed after seven cycles. Similar results were obtained for the PPS.

3.3. Secondary target variables

As the data obtained for the secondary variables in the FAS and PPS were similar, data are only presented for the FAS. For both the primary and secondary variables, none of the observed changes were clinically significant.

3.3.1. Additional lipid parameters

Changes in other lipid variables from baseline to cycle 7 of treatment are shown in Table 3. None of the changes between the treatment groups were found to be statistically significant. Furthermore, for the primary variables of HDL- and LDL-cholesterol and all the secondary lipid variables, the majority of volunteers' values were within the reference range at all time points.

Total cholesterol concentration did not vary significantly with treatment in both groups. Lipoprotein (a) concentration decreased slightly (−5%) from baseline to study end in both treatment groups. Triglycerides, HDL_2- and VLDL-cholesterol concentrations increased by a greater extent from baseline to cycle 7 in the EE 20 μg/DRSP 3 mg group (triglycerides, 78%; HDL_2, 20%; VLDL, 78%) compared with the EE 20 μg/DSG 150 μg group (triglycerides, 40%; HDL_2, 4%; VLDL, 41%).

Table 3
Changes in the lipid profile from baseline to cycle 7 (FAS)

	EE 20 μg/DRSP 3 mg ($n=29$)		EE 20 μg/DSG 150 μg ($n=30$)	
	Absolute change	Ratio (post/pre)	Absolute change	Ratio (post/pre)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Total cholesterol (mmol/L)	0 (0.61)	1.01 (0.14)	0.02 (0.48)	1.01 (0.11)
Triglycerides (mmol/L)	0.53 (0.44)	1.78 (0.76)	0.27 (0.38)	1.40 (0.46)
HDL_2 (mmol/L)	0.09 (0.23)	1.20 (0.37)	0 (0.18)	1.04 (0.27)
VLDL (mmol/L)	0.24 (0.20)	1.78 (0.79)	0.12 (0.17)	1.41 (0.46)
Lp(a) (g/L)	−0.03 (0.06)	0.95 (0.12)	−0.03 (0.08)	0.95 (0.20)

Lp(a), lipoprotein (a).

Table 4
Changes in hemostatic parameters from baseline to cycle 7 (FAS)

	EE 20 μg/DRSP 3 mg (n=29)		EE 20 μg/DSG 150 μg (n=30)	
	Absolute change	Ratio (post/pre)	Absolute change	Ratio (post/pre)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
(Pro)coagulatory factors				
Factor VII activity (%)	64.27 (25.50)	1.56 (0.23)	46.44 (22.71)	1.36 (0.16)
Factor VIII activity (%)	21.00 (24.23)	1.21 (0.25)	11.11 (20.59)	1.10 (0.17)
Fibrinogen (mg/dL)	42.42 (36.37)	1.18 (0.16)	34.63 (32.65)	1.14 (0.12)
Anticoagulation variables				
Antithrombin activity (%)	−3.58 (8.73)	0.97 (0.09)	−7.22 (7.40)	0.93 (0.07)
Protein C activity (%)	29.62 (17.24)	1.30 (0.19)	16.89 (13.84)	1.17 (0.15)
Protein S, free (%)	−8.65 (12.43)	0.90 (0.15)	−0.85 (15.26)	1.00 (0.20)
Protein S, total (%)	−13.58 (12.57)	0.82 (0.15)	−9.30 (16.27)	0.88 (0.29)
(Pro)fibrinolytic parameters				
Plasminogen (%)	40.23 (15.47)	1.37 (0.13)	34.07 (11.81)	1.31 (0.10)
t-PA activity (U/mL)	0.38 (0.48)	8.02 (8.54)	0.33 (0.53)	6.31 (7.62)
PAP complex (μg/mL)	128.46 (102.07)	1.72 (0.62)	96.19 (79.82)	1.54 (0.53)
Antifibrinolytic parameters				
PAI-I antigen (ng/mL)	−22.38 (14.89)	0.32 (0.23)	−27.15 (22.28)	0.28 (0.16)

3.3.2. Hemostatic parameters

Both treatments caused increases in the levels of the activation markers of thrombin and fibrin turnover (i.e., prothrombin fragments 1+2 and D-dimers). However, the mean increase (cycle 7−baseline) in prothrombin fragments 1+2 was less pronounced in the EE 20 μg/DRSP 3 mg group compared with the EE 20 μg/DSG 150 μg group [0.25 nmol/L (SD 0.23) vs. 0.19 nmol/L (SD 0.19), respectively]. The difference in means between the two treatments (EE 20 μg/DRSP 3 mg−EE 20 μg/DSG 150 μg) was not statistically significant (−0.06 nmol/L; 95% CI −0.18, 0.06). In contrast, for D-dimer, the mean increase was greater in the EE 20 μg/DRSP 3 mg group than in the EE 20 μg/DSG 150 μg group [96.00 ng/mL (SD 13.36) vs. 80.74 ng/mL (SD 83.77)]. Again, the difference in mean change between the two treatments was not significant (15.26 ng/mL; 95% CI −45.91, 76.43).

For all other hemostatic parameters, the majority of patients' values were within the reference range at cycle 7 (Table 4). Anticoagulatory variables (AT-III antigen, free and total protein S and APC resistance) all decreased slightly, except for protein C antigen, which increased in both treatment groups. The profibrinolytic variables of plasminogen and PAP complex increased from baseline to cycle 7 in both treatment groups. Although the increase in plasminogen was similar in both treatment groups, the increase in the level of PAP complex was slightly greater in the EE 20 μg/DRSP 3 mg group. In contrast, t-PA antigen levels decreased in both treatment groups, while t-PA activity strongly increased in both treatment groups, with the increase observed in the EE 20 μg/DRSP 3 mg group being greater than that in the EE 20 μg/DSG 150 μg group (702% vs. 531%, respectively). The levels of the antifibrinolytic variable, PAI-1 antigen, decreased considerably in both treatment groups (−68% vs. −72%, respectively).

3.3.3. Carbohydrate metabolism parameters

The mean levels of glucose during OGTT at baseline and at cycle 7 for both treatments are shown in Fig. 2. There were slight increases in the AUC for glucose for both contraceptive preparations (Table 5); the geometric mean ratios (cycle 7/baseline) for AUC during OGTT were 1.13 and 1.10 for the EE 20 μg/DRSP 3 mg and EE 20 μg/DSG 150 μg groups, respectively. The observed difference between the two treatments was not significant as indicated by the 1.03 (95% CI 0.93, 1.13) ratio of geometric means [(EE 20 μg/DRSP 3 mg)/(EE 20 μg/DSG 150 μg)].

C-peptide values also increased from baseline to cycle 7 in both treatment groups; (Table 5), however, the increase was more pronounced in the EE 20 μg/DRSP 3 mg group

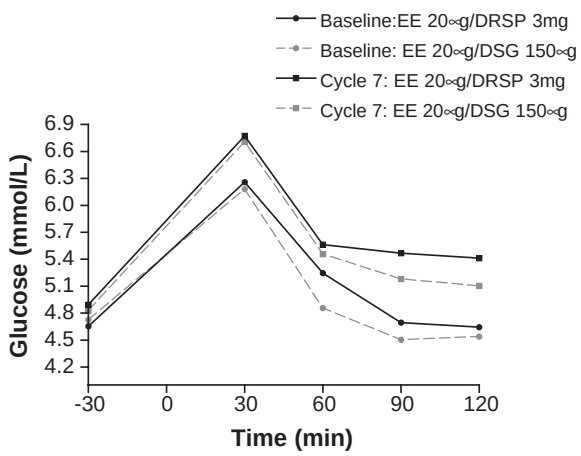

Fig. 2. The time course of glucose (mmol/L) at baseline and cycle 7 (FAS).

Table 5
Changes in carbohydrate metabolism parameters from baseline to cycle 7 (FAS)

	EE 20 μg/DRSP 3 mg (n=26)		EE 20 μg/DSG 150 μg (n=27)	
	Absolute change	Ratio (post/pre)	Absolute change	Ratio (post/pre)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
AUC glucose [(h mg)/L]	1.54 (2.89)	1.15 (0.24)	1.31 (2.02)	1.11 (0.17)
C-peptide (ng/mL)				
−30 min	0.12 (0.42)	1.12 (0.29)	0.03 (0.53)	1.05 (0.31)
30 min	0.17 (1.68)	1.05 (0.24)	−0.28 (1.51)	0.98 (0.22)
60 min	0.40 (2.97)[a]	1.19 (0.42)[a]	−0.28 (1.45)	0.99 (0.21)
90 min	1.40 (2.54)	1.33 (0.40)	0.61 (1.67)	1.13 (0.30)
120 min	1.23 (1.73)	1.30 (0.37)	0.47 (2.07)	1.16 (0.39)
Insulin (mU/L)	1.61 (2.40)[a]	1.58 (0.88)[a]	0.51 (4.19)	1.55 (1.27)[b]

[a] n=25.
[b] n=26.

(30% at 120 min of OGTT) as compared with the EE 20 μg/DSG 150 μg group (16% at 120 min of OGTT). Insulin levels increased from baseline to cycle 7 (Table 5) in the EE 20 μg/DRSP 3 mg and EE 20 μg/DSG 150 μg groups by a similar extent (58% vs. 55%, respectively).

3.3.4. Bleeding profile

In both treatment groups, the mean number of bleeding/spotting episodes and days, as well as the mean duration of these bleeding episodes, decreased from reference period 1 to 2 (Fig. 3). The mean number of spotting-only episodes was low in both groups occurring at an incidence of <1 episode per reference period. In addition, the mean length of spotting-only episodes decreased from reference period 1 to 2 in both groups [from 3.02 days (SD 1.60) to 2.36 days (SD 0.97) in the EE 20 μg/DRSP 3 mg group and from 3.33 days (SD 1.60) to 2.08 days (SD 1.07) in the EE 20 μg/DSG 150 μg group].

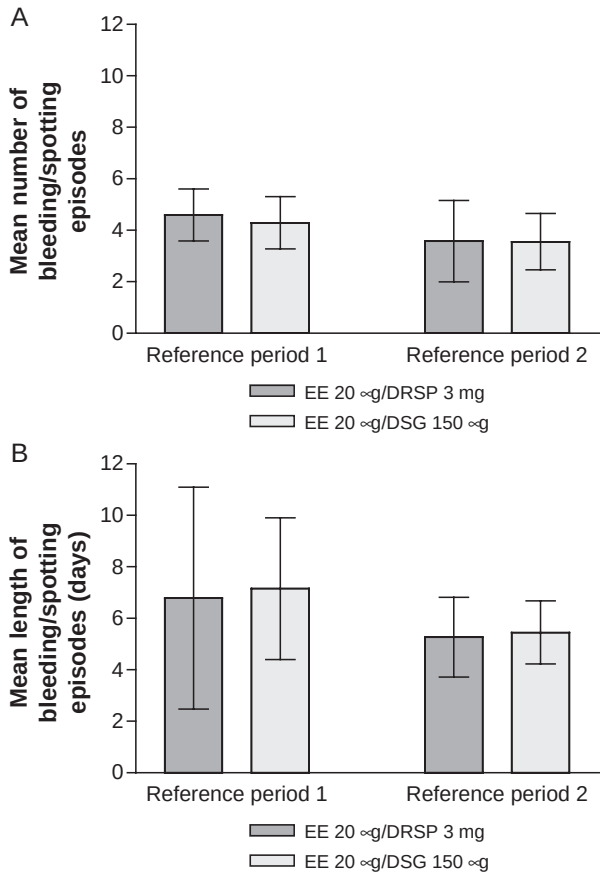

Fig. 3. Bleeding pattern: (A) mean number and (B) mean length of bleeding/spotting episodes during the 90-day reference periods, after treatment with EE 20 μg/DRSP 3 mg or EE 20 μg/DSG 150 μg (FAS).

3.3.5. Contraceptive efficacy

No pregnancies occurred while on study medication.

3.4. Safety and tolerability

Both treatments were well tolerated and none of the other laboratory assessments or physical medical assessments gave rise to any safety concerns. Treatment-related (possibly, probably, definitely related to treatment) adverse events occurred in 17 (58.6%) patients in the EE 20 μg/DRSP 3 mg group and in 13 (43.4%) patients in the EE 20 μg/DSG 150 μg group. Overall, the four most frequent treatment-related adverse events were headache (n=5: EE 20 μg/DRSP 3 mg, n=2: EE 20 μg/DSG 150 μg), emotional lability (n=2: EE 20 μg/DRSP 3 mg, n=4: EE 20 0 μg/DSG 150 μg), acne (n=2: EE 20 μg/DRSP 3 mg, n=2: EE 20 μg/DSG 150 μg) and dysmenorrhea (n=2: EE 20 μg/DRSP 3 mg, n=2: EE 20 μg/DSG 150 μg). No deaths or serious adverse events occurred in the course of the study.

4. Discussion

This study showed that both EE 20 μg/DRSP 3 mg and EE 20 μg/DSG 150 μg have similar effects on lipid, hemostatic and carbohydrate parameters. Overall, these results suggest that extending the period of active treatment by 3 days per treatment cycle (24/4 regimen) does not have any negative influence on these parameters compared with the conventional 21/7 regimen. Furthermore, EE 20 μg/DRSP 3 mg demonstrated a safety profile comparable to other combined OCs with no reasons for any safety concerns [4,17–19].

The increase in HDL-cholesterol levels and the decrease in LDL-cholesterol levels observed with both study medi-

cations in our study have been understood to be favorable effects of estrogen. Although there were no significant differences in HDL- and LDL-cholesterol levels between the two treatment groups, the greater increase in HDL-cholesterol (16% vs. 11%) and the greater decrease in LDL-cholesterol (−18% vs. −10%) observed with EE 20 μg/DRSP 3 mg treatment may reflect the lack of androgenic activity with DRSP compared with DSG. In a recently published study looking at lipid metabolism over 13 cycles, EE 30 μg/DRSP 3 mg also increased HDL-cholesterol levels by 12.8% compared with an increase of 11.8% with EE 30 μg/DSG 150 μg [20]. Similarly, in a study by Oelkers et al. [12], HDL-cholesterol rose by 9 and 23% in patients treated with EE 30 and 20 μg/DRSP 3 mg, respectively, whereas it fell by 12% in patients treated with EE 30 μg/levonorgestrel. Furthermore, the authors found that LDL-cholesterol levels fell by similar rates to our findings (−12% EE 20 μg/DRSP 3 mg). Studies with other contraceptive preparations have also shown similar increases in HDL-cholesterol and reductions in LDL-cholesterol [21–25].

In our study, total cholesterol levels did not alter but there was an increase with both EE 20 μg/DRSP 3 mg and EE 20 μg/DSG 150 μg in the levels of triglycerides (+78%, +40%), HDL_2 (+20%, +4%) and VLDL-cholesterol (+78%, +41%). A similar rise in triglyceride levels was observed after 13 cycles of treatment with the higher EE (30 μg) dose of these contraceptives (+73.6% in the DRSP group and +61.3% in DSG group). This rise in triglyceride levels have also been observed with contraceptives containing EE combined with gestodene or norgestimate (24–100% increase) [21,22,24,25]. However, from the literature, it seems that an EE-induced rise in triglyceride levels does not appear to increase atherosclerotic risk if LDL levels are not increased and HDL levels remain high [26].

The observed changes in hemostatic parameters in this study, the increase in activation markers for thrombin (clotting activation) and fibrin (fibrinolytic activation) turnover, in (pro)coagulatory parameters, and in (pro)fibrinolytic parameters as well as the decrease in PAI-1 antigen levels, suggest that the overall balance between factors influencing hemostasis were maintained on an up-regulated level in both treatment groups. Overall, the changes in hemostatic profiles observed with EE 20 μg/DRSP 3 mg treatment in our study are consistent with those observed with other OCs containing gestodene, levonorgestrel or desogestrel [18,27–29].

Blood glucose and C-peptide levels measured during OGTT remained within reference range at cycle 7 for both treatments, despite small increases in AUC for glucose and levels of C-peptide in both groups. In addition, although insulin levels increased from baseline to cycle 7 by a similar extent in both groups, these also remained in the reference range for the majority of patients. Overall, the changes in these carbohydrate parameters are consistent with those reported for combinations of EE with DRSP [12,17] or DSG [17]. Although, DSG has been demonstrated to have generally less effects on carbohydrate metabolism than older progestins [6,19], all progestins derived from 19-nortestosterone have the potential to impair glucose tolerance and increase insulin resistance.

Overall, our results confirm that extending active treatment with EE 20 μg/DRSP 3 mg to 24 days (24/4 regimen) does not make any difference in the safety profile compared with other combined OCs administered according to the conventional 21/7 regimen. The extended period of active treatment is expected to benefit women who suffer from hormonal withdrawal symptoms that are particularly common during the 7-day hormone-free interval associated with the conventional regimen [15].

In conclusion, treatment with EE 20 μg/DRSP 3 mg following a 24/4 regimen is well tolerated and has a good safety profile that is comparable with EE 20 μg/DSG 150 μg treatment following the conventional 21/7 regimen. The observed favorable changes in HDL-cholesterol and LDL-cholesterol suggest a potential cardioprotective benefit, and the changes in the hemostatic parameters are comparable to those observed with other OCs. The carbohydrate parameters in both treatment groups are not suggestive of clinically meaningful deteriorations.

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