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A prospective study on the effects on hemostasis of two oral contraceptives containing drospirenone in combination with either 30 or 20 μg ethinyl estradiol and a reference containing desogestrel and 30 μg ethinyl estradiol

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Abstract

Purpose: In this open-label, randomized study, we assessed the effects on hemostasis of two combined oral contraceptives containing drospirenone (DRSP) as progestogen component.

Methods: Three milligrams of DRSP, a progestogen with antimineralocorticoid activity, was combined with either 30 or 20 μg ethinyl estradiol (EE) (DRSP/30EE; DRSP/20EE) and compared with a preparation containing 150 μg desogestrel (DSG) and 30 μg ethinyl estradiol (DSG/30EE).

A total of 75 healthy female volunteers aged 18–35 years were enrolled. The hemostasis variables were measured in the medication-free precycle (baseline); in the first, third and sixth treatment cycle; and in the follow-up phase. The target variables for comparison were the relative changes from baseline to Cycle 6.

Results: Data of 25 volunteers in each group were valid for the per-protocol evaluation. Most changes in hemostasis variables were similar in the three treatment groups. All procoagulatory variables and the anticoagulatory variable protein C antigen increased slightly, while protein S antigen and activity decreased. For fibrinogen and protein S activity, the changes were statistically significant: less pronounced with DRSP/20EE compared to DSG/30EE at Cycle 6.

There were no statistically significant differences in the changes of antifibrinolytic variables, the global clotting tests and D-dimer. All pairwise comparisons of DRSP/30EE vs. DSG/30EE yielded nonsignificant results; however, there was a trend of a lower impact of DRSP/20EE on nearly all hemostatic parameters compared to the 30EE products. All three study treatments were safe and well tolerated by the volunteers and provided adequate contraceptive reliability.

Conclusion: The changes in the hemostatic variables for DRSP/20EE were less pronounced compared to DSG/30EE and DRSP/30EE. The results were in accordance with previous reports on effects of similar OCs.

Keywords: Oral contraceptives; Hemostasis; Ethinyl estradiol; Drospirenone; Desogestrel; Dose reduction

1. Introduction

In the year 2000, a novel combined oral contraceptive (COC) containing a combination of 30 μg EE with 3 mg drospirenone (DRSP) (Yasmin TM) was introduced. This preparation is characterized by high contraceptive efficacy in combination with excellent cycle control and low incidence of adverse events [1,2]. The novel progestogen DRSP used in this COC, a 17-α-spirolactone derivative, is of particular interest as it has shown a unique pharmacological profile. In addition to its potent progestogenic activity, it provides antiandrogenic and antimineralocorticoid activity [3–7]. The antimineralocorticoid activity is detectable with contraceptive dosages, which have not yet been described for any other synthetic progestogen, and reduces estrogen-related water retention in women using DRSP in combination with an estrogen [1].

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COCs have been found to modify many variables in the hemostatic system [8]. In the last decades, attempts have been made to minimize the impact on the hemostatic system by introducing new preparations with reduced amounts of estrogen [9]. Estrogens were considered to cause most of the changes induced by COCs, but recently, progestogen-specific effects on hemostasis have also been recorded [8,10–16]. It was postulated that the progestogenic effects may be exercised through modification of the estrogenic effects [17,18].

In order to evaluate progestogen-related effects, we assessed the hemostatic effects of two preparations containing 30 μg ethinyl estradiol (EE) either in combination with DRSP or with desogestrel (DSG). In order to evaluate estrogen dose-related effects, we compared the two 30-μg COCs with a preparation containing DRSP in combination with 20 μg EE.

2. Materials and methods

The study was performed as an open, randomized, prospective study at one center in The Netherlands from October 1992 to July 1993 (report AE91). The aim of the study was to compare the effects of three OCs on hemostatic variables. Two COCs contained 30 μg EE in combination with either DRSP (DRSP/30EE) or DSG (DSG/30EE). The third COC contained 20 μg EE in combination with 3 mg DRSP (DRSP/20EE).

A total of 75 healthy women (25 per group) aged 18–35 years (for smokers, maximum age was 30 years and not more than 10 cigarettes per day) from the outpatient clinic were planned to be evaluated in the efficacy analysis. The study was carried out in accordance with the regulations and recommendations of the Declaration of Helsinki (Hong Kong Amendment, 1989) and was approved by the Medical Ethics Committee of the Leiden University Medical Center before the study started.

2.1. Study population

The women's wish for contraception for at least six 28-day cycles was a prerequisite for their participation in the study. New COC users as well as women who wanted to change their OC (switchers) were eligible. Switchers had to have at least two COC-free cycles, one washout cycle and one pretreatment cycle before start of study medication intake. The exclusion criteria were similar to the known contraindications for COC use. Further exclusion criteria were use of coagulation-relevant preparations, a family history of coagulation disorders, use of parenteral depot-contraceptives during the last 6 months, specified concomitant pathology, diagnostically unclassified genital bleedings and a history of migraine-accompanying menstruation.

2.2. Drug intake schedule

The volunteers had to take the first tablet on the first day of withdrawal bleeding of the precycle. The study medications were supplied in calendar packs of 21 tablets. After the intake phase of 3 weeks, 1 week without tablet intake followed. Thus, all following cycles started on the same weekday as the initial cycle. If a woman missed the scheduled intake time, she was instructed to take the tablet until up to 12 h after the scheduled time and to record the delay in her diary. All deviations from the scheduled tablet intake had to be recorded on a diary.

2.3. Study design

The study consisted of a washout phase of one cycle, one treatment-free precycle, six treatment cycles and a follow-up phase of 28 days without treatment. Before start of treatment, each subject had a thorough medical and gynecological examination, which included a cervical cytology examination by the Papanicolaou method and a pregnancy test. At all study visits, blood pressure and body weight were measured. Adverse events and concomitant medication usage were recorded on the volunteers' diaries and through general questioning by the investigators. In the follow-up period, the volunteers were again asked about their general health, and the examinations of the precycle were repeated. All volunteers gave informed consent before their participation. The allocation of randomization numbers was performed in an ascending order in the sequence of arrival of the volunteers at the study center.

2.4. Blood collection

The hemostasis variables were measured at baseline (at the end of the precycle); in the first, third and sixth treatment cycle between cycle days 17 and 21; and at two time points in the follow-up phase (days 12–14 and 26–28). Blood samples, drawn from the antecubital vein, were collected in Stabilyte tubes (containing citrate, theophylline, adenosine and dipyridamole) and stored at −70°C until analysis.

The hemostasis variables measured were:

- procoagulatory variables (fibrinogen, total factor VII and thrombin–antithrombin complex [TAT]);
- anticoagulatory variables (antithrombin, protein C antigen, protein S antigen and activity);
- fibrinolytic variables [tissue-type plasminogen activator (t-PA) antigen and activity]
- antifibrinolytic variables [plasminogen activator inhibitor 1 (PAI-1) antigen and activity];
- Two global clotting tests (prothrombin time [PT] and activated partial thromboplastin time [APTT]);

Table 1
Demographic characteristics at baseline

	DRSP/30EE	DRSP/20EE	DSG/30EE
Number of subjects	25	25	25
Age (y) (means±SD)	22.4±1.7	24.5±4.0	23.4±2.1
Weight (kg) (means±SD)	62.3±8.3	66.9±9.2	62.4±6.9
Height (cm) (means±SD)	171±6.4	173±6.5	170±6.7
Smokers *n* (%)	7 (28.0)	7 (28.0)	8 (32.0)

Table 2
(A) Procoagulant variables at baseline, treatment cycles and follow-up (median and interquartile ranges)

Variable	Fibrinogen (g/L)			Total factor VII (%)			TAT complex (μg/L)		
	DRSP/30EE	DRSP/20EE	DSG/30EE	DRSP/30EE	DRSP/20EE	DSG/30EE	DRSP/30EE	DRSP/20EE	DSG/30EE
Baseline	1.9 (0.6)	1.9 (0.5)	1.8 (0.2)	83 (25)	90 (27)	85 (22)	2.14 (2.3)	2.09 (1.5)	1.66 (1.2)
Cycle 1	2.3 (0.5)	2.3 (0.4)	2.2 (0.6)	125 (46)	130 (49)	123 (26)	1.85 (1.1)	1.92 (1.6)	1.79 (1.0)
Cycle 3	2.8 (0.5)	2.7 (0.6)	2.7 (0.9)	138 (32)	142 (49)	140 (29)	5.61 (11)	3.74 (5.9)	3.93 (5.3)
Cycle 6	2.7 (0.7)	2.5 (0.3)	2.7 (1.0)	146 (39)	143 (52)	147 (36)	2.85 (2.3)	2.47 (1.8)	2.25 (2.0)
Follow-up, Week 1	2.1 (0.3)	2.0 (0.5)	2.2 (0.5)	102 (22)	105 (39)	113 (31)	1.85 (1.3)	2.17 (1.4)	1.58 (1.6)
Follow-up, Week 3	2.2 (0.6)	2.3 (0.6)	2.2 (0.5)	99 (24)	95 (30)	108 (31)	1.99 (1.4)	2.05 (1.6)	1.95 (1.6)

(B) Anticoagulant variables at baseline, treatment cycles and follow-up (median and interquartile ranges)

Variable	Antithrombin (U/mL)			Protein C antigen (U/mL)			Protein S antigen (U/mL)			Protein S activity		
	DRSP/30EE	DRSP/20EE	DSG/30EE	DRSP/30EE	DRSP/20EE	DSG/30EE	DRSP/30EE	DRSP/20EE	DSG/30EE	DRSP/30EE	DRSP/20EE	DSG/30EE
Baseline	0.93 (0.08)	0.96 (0.09)	0.92 (0.11)	0.88 (0.12)	0.88 (0.16)	0.88 (0.24)	0.86 (0.28)	1.00 (0.38)	0.91 (0.24)	92 (18)	98 (30)	89 (31)
Cycle 1	0.93 (0.11)	0.95 (0.13)	0.93 (0.08)	1.08 (0.30)	1.12 (0.28)	0.96 (0.18)	0.73 (0.22)	0.94 (0.19)	0.71 (0.15)	72 (23)	84 (23)	70 (29)
Cycle 3	0.95 (0.11)	1.00 (0.13)	0.95 (0.10)	1.08 (0.16)	1.08 (0.16)	1.04 (0.18)	0.74 (0.26)	0.86 (0.34)	0.69 (0.17)	59 (17)	75 (18)	57 (20)
Cycle 6	0.96 (0.10)	0.98 (0.14)	0.93 (0.10)	1.08 (0.28)	1.12 (0.26)	1.04 (0.24)	0.68 (0.22)	0.90 (0.24)	0.71 (0.18)	57 (20)	66 (16)	53 (17)
Follow-up, Week 1	1.03 (0.10)	1.00 (0.13)	1.00 (0.09)	1.16 (0.24)	1.00 (0.26)	1.04 (0.20)	0.85 (0.24)	0.96 (0.31)	0.93 (0.18)	82 (17)	84 (23)	79 (22)
Follow-up, Week 3	0.98 (0.06)	0.97 (0.12)	0.95 (0.10)	0.96 (0.20)	0.98 (0.22)	0.92 (0.16)	0.85 (0.25)	0.93 (0.34)	0.94 (0.14)	84 (17)	93 (30)	90 (26)

(C) Fibrinolytic and antifibrinolytic variables at baseline, treatment cycles and follow-up (median and interquartile ranges)

Variable	t-PA antigen (ng/mL)			t-PA activity (U/mL)			PAI-1 antigen (ng/mL)			PAI-1 activity (IU/mL)		
	DRSP/30EE	DRSP/20EE	DSG/30EE	DRSP/30EE	DRSP/20EE	DSG/30EE	DRSP/30EE	DRSP/20EE	DSG/30EE	DRSP/30EE	DRSP/20EE	DSG/30EE
Baseline	5.4 (6.1)	7.0 (3.6)	6.5 (4.4)	0.24 (0.23)	0.21 (0.12)	0.22 (0.17)	25 (25)	34 (30)	32 (13)	8.1 (2.1)	8.2 (2.4)	8.4 (1.7)
Cycle 1	5.0 (6.7)	5.6 (3.8)	4.5 (3.3)	0.30 (0.18)	0.35 (0.20)	0.34 (0.14)	9.3 (11)	13 (13)	5.2 (7)	7.3 (1.7)	7.2 (2.7)	6.7 (1.9)
Cycle 3	4.5 (5.3)	5.4 (3.7)	4.4 (3.2)	0.33 (0.09)	0.31 (0.17)	0.37 (0.10)	8.8 (6)	12 (35)	5.8 (5)	7.4 (1.3)	8.0 (2.5)	7.0 (2.2)
Cycle 6	4.7 (5.0)	4.7 (4.1)	4.4 (3.6)	0.36 (0.14)	0.31 (0.10)	0.37 (0.13)	7.9 (9)	16 (16)	7.6 (7)	7.3 (1.3)	7.3 (2.5)	7.0 (2.1)
Follow-up, Week 1	6.1 (5.9)	6.4 (4.1)	7.0 (5.7)	0.29 (0.16)	0.23 (0.19)	0.21 (0.10)	36 (28)	43 (43)	47 (26)	9.4 (1.9)	9.3 (3.9)	9.6 (2.4)
Follow-up, Week 3	6.5 (6.4)	5.7 (3.2)	6.4 (4.2)	0.25 (0.18)	0.24 (0.10)	0.26 (0.15)	34 (31)	35 (32)	44 (24)	8.6 (2.6)	8.7 (2.9)	9.0 (1.8)

(D) Global clotting tests and D-dimer at baseline, treatment cycles and follow-up (median and interquartile ranges)

Variable	PT (s)			APTT (s)			D-Dimer (ng/mL)		
	DRSP/30EE	DRSP/20EE	DSG/30EE	DRSP/30EE	DRSP/20EE	DSG/30EE	DRSP/30EE	DRSP/20EE	DSG/30EE
Baseline	11.6 (0.7)	11.4 (0.5)	11.5 (0.7)	25.1 (2.2)	24.9 (2.6)	25.2 (2.3)	69 (85)	106 (173)	94 (66)
Cycle 1	11.1 (0.8)	11.0 (0.8)	11.0 (0.4)	24.7 (1.9)	24.3 (1.5)	24.2 (1.7)	153 (87)	135 (168)	188 (105)
Cycle 3	11.3 (0.8)	11.1 (0.6)	11.1 (0.7)	24.3 (1.6)	24.1 (1.5)	23.7 (1.8)	204 (207)	223 (231)	173 (134)
Cycle 6	11.2 (0.7)	11.1 (0.4)	11.2 (0.5)	25.1 (1.3)	24.7 (1.3)	24.0 (2.1)	199 (267)	187 (271)	213 (161)
Follow-up, Week 1	11.6 (0.8)	11.6 (0.7)	11.6 (0.7)	25.2 (2.4)	24.5 (1.5)	25.1 (1.9)	118 (153)	99 (96)	91 (34)
Follow-up, Week 3	11.5 (0.4)	11.4 (0.9)	11.5 (0.9)	24.7 (1.6)	24.7 (1.4)	24.2 (1.8)	161 (166)	157 (161)	106 (84)

– a variable of fibrin turnover [D-dimeric fibrin cleavage product (D-dimer)].

2.5. Assays for hemostatic variables

Coagulation:

– Fibrinogen (reference range, 2.0–4.5 g/L) was determined using automated methods.
– Total factor VII concentration (76–150% or 0.61–1.63 U/mL) was measured using a chromogenic assay [19].
– TATs (reference range, 1–10 μg/L) were measured using a kit method from Behringwerke (Marburg, Germany) [20].

Anticoagulation:

– Antithrombin activity (reference range, 0.78–1.29 U/mL) was determined as the capacity of plasma to inactivate bovine thrombin in the presence of heparin, using the synthetic substrate S-2238 from Chromogenix (Mölndal, Sweden) as a substrate for thrombin [21].
– Protein C antigen (reference range, 0.50–1.60 U/mL) was measured using a kit method from Organon Teknika (Turnhout, Belgium).
– Protein S antigen (reference range, 0.55–1.75 U/mL) was measured using a kit method from Organon Teknika.
– Protein S activity (reference range, 45–140%) was measured by a functional PT-based clotting method (Nieuwenhuizen, unpublished information).

Fibrinolysis and antifibrinolysis:

– t-PA antigen (reference range, 0.5–10 ng/mL) was measured using Imulyse-t-PA from Biopool (Umeå, Sweden) [22].
– t-PA activity (0–1.5 IU/mL) was measured using a bioimmunoassay from Chromogenix [23].
– PAI-1 antigen (reference range, 6–250 ng/mL) was measured by Innotest PAI-1 (Chromogenix) [24].
– PAI-1 activity of plasma (reference range, 2–20 IU/mL) was measured by means of titration of purified two-chain t-PA [25].

Global clotting tests:

– The PT (reference range, 10–13 s) was determined by a routine automated method on fresh citrated plasma.
– The activated APTT (reference range, 26–34 s) was determined by a routine automated method on fresh citrated plasma.

Fibrin turnover:

– D-dimeric fibrin cleavage product (reference range, 0–400 ng/mL) was assayed using the kit of Chromogenix.

Table 3
Hemostatic variables: median percentage of change from baseline to treatment cycles and follow-up

Variable	% Change from baseline, Cycle 1			% Change from baseline, Cycle 3			% Change from baseline, Cycle 6			% Change from baseline to follow-up Week 3		
	DRSP/ 30EE	DRSP/ 20EE	DSG/ 30EE	DRSP/ 30EE	DRSP/ 20EE	DSG/ 30EE	DRSP/ 30EE	DRSP/ 20EE	DSG/ 30EE	DRSP/ 30EE	DRSP/ 20EE	DSG/ 30EE
Procoagulatory variables												
Fibrinogen	+25	+14	+21	+47	+42	+47	+40	+31	+50	+19	+17	+23
Factor VII	+56	+44	+45	+57	+56	+55	+68	+59	+54	+15	+7.9	+17
TAT	−13	+1.4	+6.9	+123	+75	+108	+41	+0.2	+72	+5.0	+9.3	+8.5
Anticoagulatory variables												
Antithrombin	+0.5	0.0	−1.1	+3.0	−2.2	+2.0	+6.1	+1.0	+2.3	+3.4	0.0	+3.4
Protein C antigen	+17	+9.7	+10	+21	+14	+14	+28	+17	+16	+15	+8.9	+3.7
Protein S antigen	−18	−5.1	−20	−16	−13	−27	−27	−16	−26	−3.9	−1.6	+1.0
Protein S activity	−21	−9.0	−23	−36	−24	−37	−35	−25	−42	−3.4	−5.0	−6.0
Profibrinolytic variables												
t-PA antigen	−14	−22	−27	−21	−18	−28	−16	−23	−31	+6.8	−9.6	+13
t-PA activity	+54	+45	+61	+47	+49	+25	+81	+35	+57	+9.7	+6.2	+8.6
Antifibrinolytic variables												
PAI-1 antigen	−57	−63	−81	−59	−63	−82	−71	−60	−73	+33	−5.6	+28
PAI-1 activity	−10	−16	−22	−11	−16	−13	−9.0	−12	−19	−0.9	+2.4	+4.4
Global clotting tests												
PT	−4.2	−2.7	−3.6	−3.3	−2.6	−3.3	−4.2	−4.3	−3.4	0.0	0.0	−0.9
APTT	−3.1	−3.2	−2.7	−2.8	−2.0	−4.6	−0.2	−0.6	−1.9	−2.4	−1.6	−0.4
Variable of fibrin turnover												
D-Dimer	+91	+35	+112	+136	+71	+115	+168	+89	+148	+82	+78	+23

2.6. Statistical methods

The primary criteria for statistical evaluation of this study were the hemostatic variables. Two target variables were derived for each criterion calculating absolute and relative changes from baseline to the sixth treatment cycle using the formulas:

Absolute change = value observed in 6th treatment cycle
−value observed at baseline

Relative change
= (absolute change/value observed at baseline)

These relative changes are described in the tables in percentage, that is, multiplied by 100. All other variables were considered as secondary target variables. For all primary target variables, the null hypothesis H0, that the three treatments did not differ with respect to the primary target variables, was tested against the alternative hypothesis H1, that the three treatments did differ with respect to the primary target variables, using the two-sided Kruskal–Wallis test and a significance level of 5%. If a test was significant, further pairwise comparisons were performed by two-sided Wilcoxon rank-sum tests at the significance level of 5%. The significance level was not adjusted for multiple testing, as appropriate for explorative analyses.

In addition, each primary target variable was analyzed by descriptive statistics.

3. Results

A total of 75 women, 25 per group, were randomized and received one of the three treatments. All randomized volunteers were included in the per-protocol analysis. A total of seven cycles from six volunteers were removed from the per-protocol analysis because of major tablet-intake errors.

The demographic characteristics of the three groups at baseline were well matched with the exception of body weight, that was 4.5 kg higher in the DRSP/20EE group compared to DSG/30EE group and 4.6 kg higher compared to DRSP/30EE (Table 1). No significant differences between baseline laboratory values were found (Table 2A–D).

3.1. Hemostatic variables

The results of the procoagulant, anticoagulant, profibrinolytic and antifibrinolytic variables as well as those of the global clotting tests are shown in Table 2A–D. Table 3 illustrates the median percentage of change from baseline to

Table 4
Results of the statistical tests of the percentage of change from baseline to Cycle 6

Variable	DRSP/20EE vs. DRSP/30EE vs. DSG//30EE	DRSP/20EE vs. DRSP/30EE	DRSP/30EE vs. DSG/30EE	DRSP/20EE vs. DSG/30EE
	Two-sided Kruskal–Wallis test (p value)	Two-sided Wilcoxon test (p value)[a]	Two-sided Wilcoxon test (p value)[a]	Two-sided Wilcoxon test (p value)[a]
Procoagulatory variables				
Platelet count	.2500			
Fibrinogen	.0329	.0813	.7113	.0078
Factor VII	.0807			
TAT	.2336			
Anticoagulatory variables				
Antithrombin	.0974			
Protein C antigen	.4173			
Protein S antigen	.2354			
Protein S activity	.0183	.0198	.7949	.0111
Profibrinolytic variables				
t-PA antigen	.4244			
t-PA activity	.7794			
Antifibrinolytic variables				
PAI-1 antigen	.2067			
PAI-1 activity	.2268			
Global clotting tests				
PT	.9138			
APTT	.5085			
Variable of fibrin turnover				
D-Dimer	.6394			

[a] Pairwise Wilcoxon tests were only performed if Kruskal–Wallis test was significant at the 5% level.

treatment cycles 1, 3, 6 and to follow-up (Week 3). The results of the statistical evaluations are shown in Table 4.

All procoagulatory variables increased in all three treatment groups. Only fibrinogen showed a statistically significant higher increase under DSG/30EE compared to DRSP/20EE (p=.0078) at cycle 6.

In the group of anticoagulatory variables, antithrombin and protein C antigen increased slightly, while protein S antigen and activity decreased in all treatment groups. Statistically significant differences were seen for protein S activity for the comparison of DRSP/20EE vs. DSG/30EE (p=.0111) and DRSP/20EE vs. DRSP/30EE (p=.0198). The highest protein S activity reduction was induced by DSG/30EE (−42%) followed by DRSP/30EE (−35%) and DRSP/20EE (−25%).

There were no statistically significant differences in the changes of the profibrinolytic, antifibrinolytic variables and the global clotting tests. While PAI-1 antigen and activity, PT and APTT decreased, D-dimer as indicator for fibrin turnover increased in all three treatment groups.

All pairwise comparisons of DRSP/30EE vs. DSG/30EE yielded nonsignificant results; however, there was a trend of a lower impact of DRSP/20EE on nearly all hemostatic parameters compared to the 30EE products (Table 3).

3.2. Contraceptive efficacy

None of the women became pregnant in this study.

3.3. Tolerability

No serious adverse event and no death occurred during the study. Physical and gynecological examinations showed only clinically irrelevant abnormal findings. Mean body weight and blood pressure remained constant or fell slightly under the DRSP preparations, while both parameters slightly increased under DSG/30EE. The general clinico-chemical parameters remained virtually unchanged.

4. Discussion

Our results indicate that all three preparations have similar effects on hemostatic variables. After three and six treatment cycles, the hemostatic variables, that is, pro- and anticoagulatory as well as pro- and antifibrinolytic variables, established a new status at a higher level of turnover that was comparable across all three treatment groups. The changes of all variables were in agreement with the effects published for similar low-dose COC preparations [8,26–29]. However, a test method for one parameter of interest, the APC resistance [30], was not yet available at the time when the study was performed. A recent cross-sectional evaluation showed a closely similar result for this test for DRSP and desogestrel [31].

With special regard to DRSP, so far, no effects of aldosterone on hemostasis are known except for a recent report of Brown et al. [32] who described a stimulating effect of the combination of aldosterone and angiotensin II on PAI-1 production in smooth muscle cells. They hypothesized that aldosterone antagonists might have a beneficial effect on cardiovascular diseases through the decrease in PAI-1 expression.

All pairwise comparisons of DRSP/30EE vs. DSG/30EE yielded nonsignificant results. Thus, in contrast to the results with other oral contraceptives [15,16,33,34], we were not able to show any progestogen-related differential effect on hemostasis between DSG and DRSP. Even D-dimer, the parameter for fibrin turnover that was regarded as one of the most relevant indicators for changes in the hemostatic system by The Oral Contraceptive and Hemostasis Study Group [33,34], did not show any differential effect.

Combining the vast amount of single results into a more meaningful general assessment, we saw a trend of a lower impact of DRSP/20EE on nearly all hemostatic parameters compared to the two 30EE products. However, the level of statistical significance was reached only for fibrinogen and protein S activity. Our observation is in accordance with the findings of The Oral Contraceptive and Hemostasis Study Group that prospectively investigated seven COCs in 707 healthy women for six cycles [34]. Preparations with different EE content and different progestogens were assessed with regard to their impact on hemostasis variables. Lower changes were found with lower EE content of the brands. The group showed significant differences for prothrombin fragment 1+2 after six treatment cycles with 30 μg EE+150 μg DSG vs. 20 μg EE+150 μg DSG. Additionally, weak positive associations between D-dimer and factor VII and estrogen dose were reported. Decreases in protein S were larger with increasing estrogen dose, although not reaching statistical significance. The clinical relevance of these changes still remains subject for further investigations.

We conclude that, in general, reduction of estrogen in COCs results in smaller changes of hemostatic variables yielding a more favorable hemostatic profile. However, the clinical relevance remains to be investigated. The extent of correlation between the EE dose and the incidence of thrombotic diseases has been under discussion, particularly with low-dose COCs. Gerstman et al. [35] showed in a retrospective analysis of epidemiological data that vascular diseases were more frequent in users of COCs containing 50 μg EE than in users of COCs containing 30 μg EE. This estrogen dose-related association with fewer cases of venous thromboembolism in women using 30 μg EE COCs was also reported by Lidegaard [36]. However, valid epidemiological data for COCs containing 20 μg EE are currently not available. The pitfall for future large epidemiological studies will be that estrogen and progestogens interact at many levels, and it might be difficult to assign a separate risk to either component [37].

The results of the safety laboratory examinations did not suggest any influence of the study preparations on the general laboratory variables. None of the other safety variables examined in the study gave rise to safety concerns.

In conclusion, the changes in the hemostatic variables for DRSP/20EE were less pronounced compared to DSG/30EE and DRSP/30EE. The results were in accordance with previous reports on effects of similar OCs.

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