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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)