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Bleeding pattern with drospirenone 3 mg+ethinyl estradiol 20 mcg 24/4 combined oral contraceptive compared with desogestrel 150 mcg+ethinyl estradiol 20 mcg 21/7 combined oral contraceptive

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Abstract

Background: The study was conducted to compare cycle control, bleeding pattern and efficacy of two low-dose combined oral contraceptives.

Study Design: Four hundred fifty-three women were randomized to receive a 24/4 regimen of drospirenone 3 mg/ethinyl estradiol 20 mcg (drsp 3 mg/EE 20 mcg; *n*=230) or a 21/7 regimen of desogestrel 150 mcg/EE 20 mcg (DSG 150 mcg/EE 20 mcg; *n*=223), and recorded bleeding daily over 7 treatment cycles.

Results: The duration [mean 4.7 (SD 1.5)–5.2 (SD 2.2) days in the drsp 3 mg/EE 20 mcg 24/4 group and 5.1 (SD 1.5)-5.4 (SD 2.1) days in the DSG 150 mcg/ EE 20 mcg group] and maximum intensity ("normal bleeding" for >50% of all subjects) of scheduled bleeding in Cycles 1–6 was comparable between treatment groups. The incidence of unscheduled bleeding during Cycles 2–6 was also similar between the two groups (drsp 3 mg/EE 20 mcg, 8.8–17.3%; DSG 150 mcg/ EE 20 mcg, 9.4–16.3%).

Conclusion: Drsp 3 mg/EE 20 mcg 24/4 achieved an acceptable bleeding profile with reliable cycle control, comparable with an established formulation.

Keywords: Bleeding pattern; cycle control; Pearl Index; drospirenone; combined oral contraceptive

1. Introduction

Combined oral contraceptives (COCs) are among the most effective reversible forms of contraception available [1,2]. Acceptance of a hormonal contraceptive method depends largely on the degree of cycle control and the side-effects experienced [3]. Concern about estrogen-related adverse effects has led to progressive reductions in the estrogen dose in COCs. However, COCs with low doses of estrogen have previously been associated with more breakthrough bleeding and spotting [4]. Nonetheless, it is generally accepted that women should use COC formulations with the lowest effective hormone dose in order to minimize hormone-related adverse effects.

The type of progestin and dosing regimen may also affect cycle control [5,6]. Drospirenone (drsp) is a novel progestin with a pharmacological profile different from other progestins; in addition to its progestogenic activity, it has both anti-mineralocorticoid and anti-androgenic properties [7]. A new low-dose COC containing drsp 3 mg/ethinyl estradiol (EE) 20 mcg has been developed that comprises a regimen with 24 active pills and 4 inert pills (24/4) regimen. This COC formulation has reliable contraceptive efficacy, a satisfactory safety profile, an acceptable bleeding pattern, and is approved by the FDA for the treatment of the emotional and physical symptoms associated with premenstrual dysphoric disorder [8–10]. Additionally, drsp 3 mg/EE 20 mcg 24/4 has proven benefits in the treatment of acne and has recently been approved by the FDA for the treatment of moderate acne vulgaris in women who desire an OC for birth control [11–14].

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The present study was undertaken to compare the bleeding pattern, cycle control, contraceptive efficacy and safety of drsp 3 mg/EE 20 mcg 24/4 COC regimen with a low-dose 21/7 preparation containing desogestrel (DSG) 150 mcg and EE 20 mcg. Good cycle control, contraceptive reliability and tolerability with the DSG 150 mcg/EE 20 mcg COC has been reported in other studies making this product a good comparison [15,16].

2. Materials and methods

2.1. Study design

This was a randomized, open, parallel group comparison study carried out at 19 study centers in four European countries (six in Austria, five in Finland, five in Lithuania and three in Estonia) between March 2004 and June 2005. The study was conducted in accordance with the Declaration of Helsinki and the International Conference of Harmonization Good Clinical Practice guidelines. Written informed consent was obtained from the study participants prior to enrollment.

2.2. Study population

Healthy women aged 18–35 years were recruited into the study. Smokers over the age of 30 years were precluded due to the age-dependent increased risk of arterial thrombosis among smokers using oral contraceptives. The exclusion criteria were consistent with the accepted contraindications for COC use and included pregnancy, obesity (body mass index >30 kg/m^2), lactation or abortion within the last 3 months before start of treatment; hypersensitivity to any of the study drug ingredients; suspicious cervical smear result within last 6 months prior to start of treatment; use of DSG or drsp-containing COCs or intrauterine device/system within the last cycle before start of treatment; and use of depot contraception within last six cycles before start of treatment.

Women with irregular menstrual cycles, breakthrough bleeding or amenorrhea were not excluded from the study. Moreover, *Chlamydia* screening was not performed; therefore, *Chlamydia* was not included in the exclusion criteria.

2.3. Treatment

Participating subjects were randomized to receive either drsp 3 mg/EE 20 mcg for 24 consecutive days of active treatment followed by 4 days of a daily hormone-free pill (24/4 regimen) or DSG 150 mcg/EE 20 mcg for 21 consecutive days of active treatment followed by a 7-day pill-free period (21/7 regimen) for seven cycles. Computer-generated randomization was performed in blocks balanced for each treatment. The distribution of women to each treatment group was 1:1. Treatment started on the first day of menses for COC starters or scheduled bleeding for switchers.

2.4. Clinical assessments

Subjects were assessed at Visit 1 (initial screening), Visit 2 (admission to treatment and randomization), Visits 3 and 4 (Days 12–19 of the respective cycle) and finally at Visit 5 (10–17 days after last tablet intake). At Visit 1, physical and gynecological examinations (including cervical smear and breast palpation) were performed and medical, surgical and medication history were assessed to ensure study eligibility. At Visit 2, the subjects were assigned their medication and asked to undergo a pregnancy test before first pill intake. Subjects were also given diary cards to record pill intake and intensity of vaginal bleeding. At Visits 3 and 4, completed diary cards and used blister packs were collected and adverse events (AEs) were documented. Vital signs (heart rate and blood pressure) and body weight were assessed at each visit. A final physical and gynecological examination was performed at Visit 5. In order to monitor compliance, the participating women were requested to record tablet intake daily on their diary cards and return all used, partly used, or unused blister packs to the investigator at Visit 5.

The participating women were requested to start their bleeding record with first pill intake at the onset of regular bleeding. Bleeding intensity classifications were defined as follows: none, absence of any vaginal bleeding; spotting, less than associated with normal menstruation relative to the volunteer's experience with no need for sanitary protection (except for panty liners); light, less than associated with normal menstruation relative to the volunteer's experience with need for sanitary protection; normal, like normal menstruation relative to the volunteer's experience; and heavy, more than normal menstruation relative to the volunteer's experience.

2.5. Efficacy assessments

Cycle control, bleeding patterns and unintended pregnancies were the primary variables. For cycle control analysis, time to onset, duration and intensity of scheduled bleeding and unscheduled bleeding episodes were identified. Scheduled bleeding was defined as a bleeding or spotting episode that began during the hormone-free period or started not more than 4 days before the last tablet intake (i.e., not before Day 17 or 20, respectively) in any cycle that continued through into the hormone-free interval. It is possible that scheduled bleeding may start during the hormone-free interval and last until the first few days of the next blister pack of tablets.

All other bleeding episodes besides scheduled bleeding were defined as unscheduled bleeding. Consequently, the bleeding episode at the beginning of the treatment in Cycle 1 was regarded as unscheduled bleeding. A bleeding/spotting episode was defined as a number of days with bleeding/spotting proceeded by at least two bleeding-free days. A bleed-free interval consisted of at least 2 days without bleeding/spotting preceded and followed by at least 1 day of bleeding/spotting.

For bleeding pattern analysis, the mean total number bleeding/spotting days and mean length of all bleeding/spotting episodes were identified. The bleeding pattern was characterized using 90-day reference periods as recom-

mended by the World Health Organization [17]. Reference Period 1 started on the first day of study medication intake.

Contraceptive efficacy was determined using the Pearl Index (PI) with the upper limit of two-sided 95% confidence interval (CI). Kaplan–Meier estimate for the probability of becoming pregnant was calculated supported with the 95% CI.

2.6. Safety and tolerability assessments

Safety was evaluated by clinical laboratory tests, AE reports, physical and gynecological examinations and vital sign measurements. An AE was defined as any untoward medical occurrence in a study participant, which does not necessarily have a causal relationship with this treatment. AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA), version 8.

2.7. Satisfaction and well-being

At the final visit, the women were asked to give their assessments on their well-being while using drsp 3 mg/EE 20 mcg 24/4 or DSG 15 mcg/EE 20 mcg. Women were asked to rate their current overall physical and emotional well-being throughout the study compared with the status before the study using the following rating scale: much better, somewhat better, the same, somewhat worse and much worse. Using a five-point scale (very satisfied, somewhat satisfied, neither satisfied nor dissatisfied, dissatisfied, very dissatisfied), participating women rated their overall satisfaction with study medication. Finally, when asked what their plans for contraceptive use were in the next year, women were asked to choose from the following responses: study treatment, different hormonal contraceptive, different contraceptive method, no contraceptives and undecided.

2.8. Sample size and data analysis

The sample size of 220 women per treatment group was chosen without biometrical consideration. Based on previous experience with other cycle control studies, this sample size was determined sufficient to describe reliably the bleeding patterns of both treatments [18]. The cycle control parameters (time to onset, duration and intensity of scheduled bleeding and unscheduled bleeding episodes) and bleeding patterns (mean total numbers bleeding/spotting days and mean length of all bleeding/spotting episodes) were summarized using descriptive statistics for each treatment and each cycle/reference period. Kaplan–Meier estimate for the probability of pregnancy was calculated supported with the 95% CI. Additionally, the PI and the adjusted PI were also calculated with the upper limit of two-sided 95% CI. Analyses were performed based on the full analysis set, which included all participating women who had taken at least one tablet and for whom at least one observation after dosing was available. Data from Cycle 7 were not included in the evaluation as documentation on this cycle was incomplete and therefore cannot be adequately reported (e.g., bleeding that was ongoing at the end of Cycle 7 was not documented in a subsequent follow-up cycle).

3. Results

3.1. Subject disposition

A total of 453 women were randomized to receive either drsp 3 mg/EE 20 mcg 24/4 (n=230) or DSG 15 mcg/EE 20 mcg regimen (n=223). The full analysis set comprised 229 women in the drsp 3 mg/EE 20 mcg 24/4 group and 220 women in the DSG 150 mcg/EE 20 mcg group. Overall, 29 (12.6%) women in the drsp 3 mg/EE 20 mcg 24/4 group and 26 (11.7%) of the women in the DSG 150 mcg/EE 20 mcg group prematurely discontinued study medication. The reasons for premature discontinuation of the study medication (drsp 3 mg/EE 20 mcg 24/4 vs. DSG 150 mcg/EE 20 mcg) were AEs [18 (7.8%) vs. 9 (4.0%)], protocol deviation [1 (0.4%) vs. 2 (0.9%)], lost to follow-up [3 (1.3%) vs. 2 (0.9%)], pregnancy [0 (0%) vs. 1 (0.4%)] and other [7 (3.0%) vs. 12 (5.4%)]. The baseline characteristics were comparable for both treatment groups, as shown in Table 1.

3.2. Compliance

The mean number of pills taken per cycle ranged from 26.5 to 27.7 in the drsp 3 mg/EE 20 mcg 24/4 group (where accurate dosage is 28 pills) and 20.8 to 21.1 in the DSG 150 mcg/EE 20

Table 1
Baseline characteristics by treatment group in full analysis set at baseline

	drsp/EE (n=229)		DSG/EE (n=220)		Total (n=449)	
	Mean	SD	Mean	SD	Mean	SD
Age (years)	25.2	4.3	24.5	4.0	24.8	4.2
Height (cm)	167.4	5.8	166.6	6.0	167.0	5.9
Weight (kg)	62.4	8.0	61.0	9.2	61.7	8.6
BMI (kg/m^2)	22.3	2.7	21.9	2.9	22.1	2.8
Ethnic group	*n*	%	*n*	%	*n*	%
Caucasian	225	98.3	219	99.5	444	98.9
Hispanic	2	0.9	1	0.5	3	0.7
Asian	2	0.9	0	0	2	0.4
Contraceptive method at screening	*n*	%	*n*	%	*n*	%
Oral contraceptive	133	58.1	115	52.3	248	55.2
Condom	73	31.9	75	34.1	148	33.0
None	17	7.4	14	6.4	31	6.9
Other	6	2.6	16	7.3	22	4.9
Current smoker	*n*	%	*n*	%	*n*	%
Yes	52	22.7	72	32.7	124	27.6
1–5	28	12.2	28	12.7	56	12.5
6–10	17	7.4	29	13.2	46	10.2
11–20	7	3.1	15	6.8	22	4.9
>20	0	0	0	0	0	0

BMI, body mass index.

mcg group (where accurate dosage is 21 pills), suggesting good compliance to treatment in both groups.

3.3. Cycle control

Scheduled bleeding and unscheduled bleeding episodes were identified and analyzed (Figs. 1 and 2). Onset of scheduled bleeding ranged, on average, between 2.4 and 2.8 days after last active pill in the drsp 3 mg/EE 20 mcg 24/4 group and between 2.4 and 2.9 days after the last pill in the DSG 150 mcg/EE 20 mcg group. In the first cycle, 29 (14.0%) women in the drsp 3 mg/EE 20 mcg 24/4 group and 22 (12.9%) in the DSG 150 mcg/EE 20 mcg group did not experience scheduled bleeding. In Cycles 2–6, the proportion of women without scheduled bleeding was 4.6–8.9% in the drsp 3 mg/EE 20 mcg 24/4 group and 2.6–6.0% in the DSG 150 mcg/EE 20 mcg group (Fig. 1). The maximum intensity of scheduled bleeding was "normal bleeding" for over 50% of subjects in Cycles 1–6 in both treatment groups. The scheduled bleeding intensity tended to be lighter for the drsp 3 mg/EE 20 mcg 24/4 group than the DSG 150 mcg/EE 20 mcg group. A trend toward a lower proportion of "heavy bleeding" was experienced in the drsp 3 mg/EE 20 μg 24/4 group than in the DSG 150 mcg/EE 20 mcg group in Cycles 1– 6 (Fig. 1).

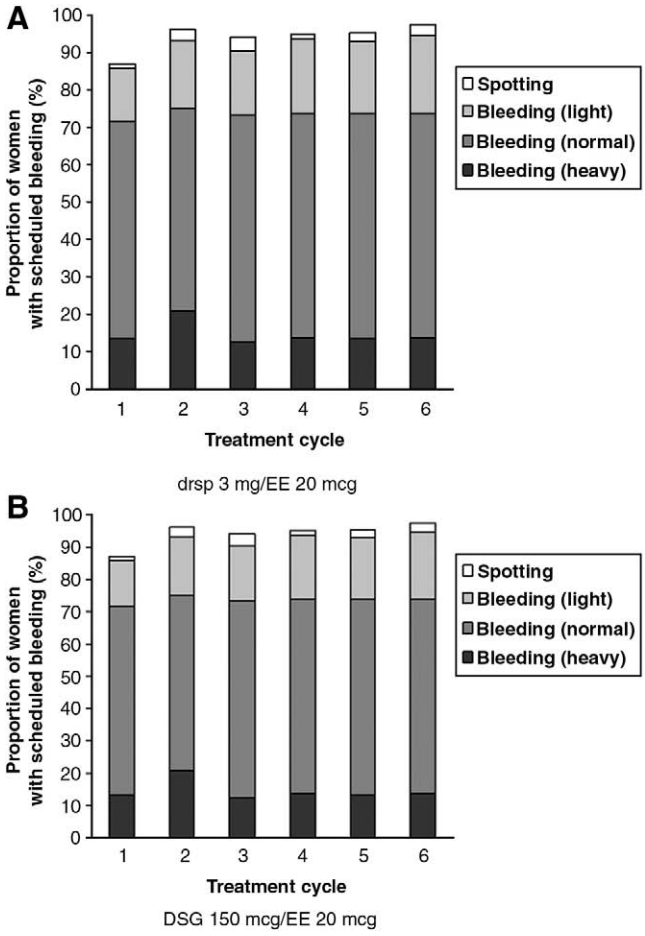

Fig. 1. The proportion of subjects with scheduled bleeding (maximum intensity) in Cycles 1–6 in the (A) drsp 3 mg/EE 20 mcg group and the (B) DSG 150 mcg/EE 20 mcg group.

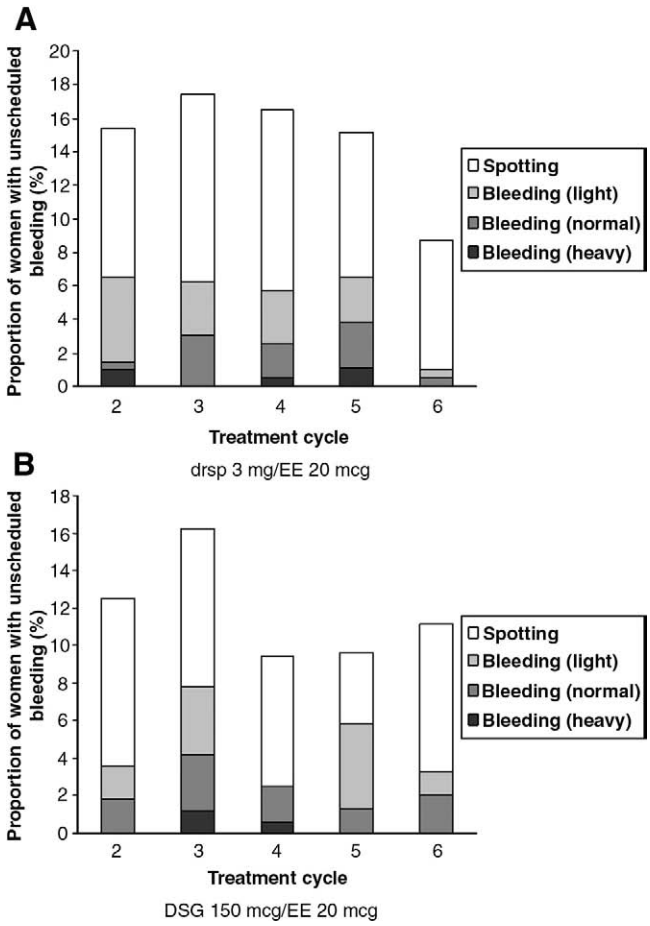

Fig. 2. The proportion of women with unscheduled bleeding in Cycles 2–6 in the (A) drsp 3 mg/EE 20 mcg group and (B) the DSG 150 mcg/EE 20 mcg group.

The length of the scheduled bleeding episode was consistently around 5 days across both treatment groups and throughout Cycles 1–6. The mean length of a scheduled bleeding between Cycles 1 and 6 was 4.7 (SD1.5)–5.2 (SD 2.2) days in the drsp 3 mg/EE 20 mcg 24/4 group and 5.1 (SD 1.5)–5.4 (SD 2.1) days in the DSG 150 mcg/ EE 20 mcg group, respectively.

The mean maximum length of unscheduled bleeding episodes in the drsp 3 mg/EE 20 mcg 24/4 group and DSG 150 mcg/EE 20 mcg group reduced from 7.5 (SD 7.0) and 7.4 (SD 6.0) in Cycle 1 to 3.4 (SD 2.7)–5.4 (SD 6.2) and 3.9 (SD 4.2)–6.1 (5.1) in Cycles 2–6, respectively. The number and proportion of the volunteers reporting unscheduled bleeding was highest in the first cycle in both treatment groups; 200 (96.6%) in the drsp 3 mg/EE 20 mcg group and 165 (97.1%) in the DSG 150 mcg/ EE 20 mcg group. The high incidence of unscheduled bleeding in Cycle 1 is explained by the fact that the bleeding episode at the beginning of the treatment in Cycle 1 was regarded as unscheduled bleeding. In contrast,

the incidence of unscheduled bleeding during Cycles 2–6 was comparable between the two groups; 8.8–17.3% women in the drsp 3 mg/EE 20 mcg group and 9.4–16.3% in the DSG 150 mcg/ EE 20 mcg group (Fig. 2).

In Cycle 1, the maximum intensity of unscheduled bleeding was "normal bleeding" for 128 women (64.0%) in the drsp 3 mg/EE 20 mcg group and 103 women (62.4%) in the DSG 150 mcg/EE 20 mcg group. However, in Cycles 2–6, the maximum intensity was "spotting" for 57.1–87.5% of the drsp 3 mg/EE 20 mcg group and 40.0–73.3% in the DSG 150 mcg/EE 20 mcg group (Fig. 2).

In Cycle 1, the mean number of unscheduled bleeding days was 8.4 days (SD 8.3) in the drsp 3 mg/EE 20 mcg 24/4 group and 8.1 days (SD 6.7) in the DSG 150 mcg/EE 20 mcg group. In Cycles 2–6, this number dropped to below 1 in both treatment groups, except for Cycle 3 in the DSG 150 mcg/EE 20 mcg group where the mean number of unscheduled bleeding days was 1.1 (SD 3.4). Similarly, the number of unscheduled bleeding episodes reduced from 1.3 (SD 0.6) and 1.2 (SD 0.5) in Cycle 1 to 0.1 (SD 0.3)–0.2 (SD 0.5) and 0.1 (SD 0.3)–0.2 (SD 0.4) for Cycles 2–6 in the drsp 3 mg/EE 20 mcg 24/4 group and DSG 150 mcg/EE 20 mcg group, respectively.

3.4. Bleeding pattern

Overall, the number and mean length of bleeding/spotting days per reference period were lower for the drsp 3 mg/EE 20 mcg 24/4 group. The mean total number of bleeding/ spotting days in the drsp 3 mg/EE 20 mcg 24/4 group and DSG 150 mcg/EE 20 mcg group were 23.6 and 24 days in Reference Period 1 and 16.1 and 16.6 days in Reference Period 2, respectively. Moreover, the mean length of all bleeding/spotting episodes (scheduled bleeding episodes and/ or the unscheduled bleeding episodes) was 5.6 in Reference Period 1 and 4.8 in Reference Period 2 in the drsp 3 mg/EE 20 mcg 24/4 group, and 5.7 in Reference Period 1 and 5.1 in Reference Period 2 in the DSG 150 mcg/EE 20 mcg group.

3.5. Contraceptive efficacy

The PIs for on-treatment pregnancies in the full analysis set were 0 (no pregnancies) with an upper two-sided 95% CI of 3.40 in the drsp 3 mg/EE 20 mcg 24/4 group and 0.93 (one pregnancy) with an upper two-sided 95% CI of 5.16 in the DSG 150 mcg/EE 20 mcg group. The adjusted PI was similar, 0.93, with the upper two-sided 95% CI of 5.18. This pregnancy was assessed as method failure. The Kaplan–Meier estimate for the probability of becoming pregnant in the DSG 150 mcg/EE 20 mcg group was 0.0045 (95% CI, 0.0006–0.0318) and 0 in the drsp 3 mg/EE mcg 24/4 group. The CI for the drsp 3 mg/EE 20 mcg 24/4 group could not be determined as there were no pregnancies.

3.6. Safety and tolerability

AEs were similar between the treatment groups and were typical of those associated with hormonal contraceptive use. The most frequently reported AEs (reported by ≥1% of women in the full analysis set) considered "possibly" or "probably" related to treatment are presented in Table 2. AEs that occurred more than once and that led to premature discontinuation from the study in both treatment groups were headache, metrorrhagia, mood swings and loss of/decreased libido. No women in this study died. A total of 8 (1.8%) women experienced nonfatal serious AEs [3 in the drsp 3 mg/EE 20 mcg 24/4 group (limb injury, cervical smear result abnormal, peritonsillar abscess and tonsillitis) and 5 in the DSG 150 mcg/EE 20 mcg group (abscess, enteritis, gastroenteritis, ovarian cyst, optic neuritis, cervical smear result abnormal)], but they were assessed as not being treatment related.

Clinical laboratory findings and physical and gynecological examination assessments gave no reasons for any safety concerns.

3.7. Subject satisfaction with study treatment

The majority of women were satisfied or very satisfied with the study treatment in the drsp 3 mg/EE 20 mcg 24/4 group (86.9%) and the DSG 150 mcg/EE 20 mcg group (85.4%) (Fig. 3). When comparing their physical and emotional well-being during the treatment compared to the time before the study, the majority of women assessed it as "the same" for both physical (drsp 3 mg/EE 20 mcg 24/4 group, 61.1%; DSG 150 mcg/EE 20 mcg group, 63.6%) and

Table 2
Most frequently reported AEs (reported by ≥1% of women in the full analysis set) considered "possibly" or "probably" related to treatment

AE	drsp 3 mg/EE 20 mcg (*n*=229)		DSG 150 mcg/EE 20 mcg (*n*=220)		Overall (*n*=449)	
	n	%	*n*	%	*n*	%
Acne	1	0.4	5	2.2	6	1.3
Breast pain	3	1.3	0	0	3	0.7
Breast tenderness	6	2.6	1	0.5	7	1.6
Dysmenorrhea	3	1.3	2	0.9	5	1.1
Headache	7	3.1	6	2.7	13	2.9
Metrorrhagia	6	2.6	6	2.7	12	2.7
Mood swings	3	1.3	1	0.5	4	0.9
Nausea	4	1.7	3	1.4	7	1.6

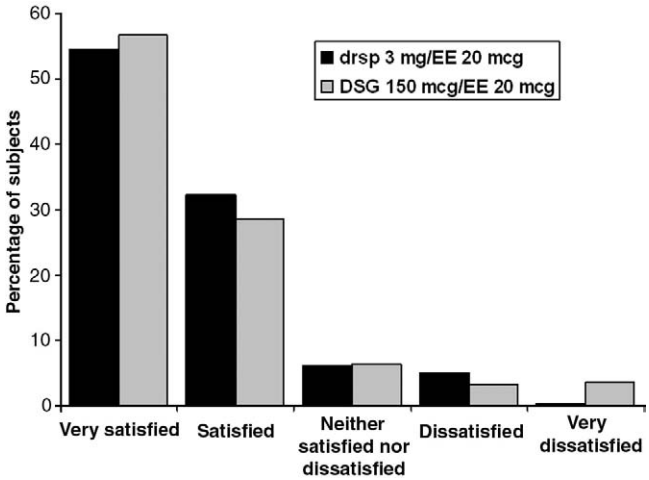

Fig. 3. Overall satisfaction with the drsp 3 mg/EE 20 mcg and the DSG 150 mcg/EE 20 mcg COC following seven treatment cycles.

emotional (drsp 3 mg/EE 20 mcg group, 62.4%; DSG 150 mcg/EE 20 mcg group, 65.5%) aspects of well-being. Slightly more women in the drsp 3 mg/EE 20 mcg 24/4 group (28.8%) than in the DSG 150 mcg/EE 20 mcg group (25.4%) assessed their emotional well-being during the study as "better" or "much better" compared to the time before the study.

4. Discussion

The present study shows that the drsp 3 mg/EE 20 mcg 24/4 COC is comparable to the established DSG 150 mcg/EE 20 mcg COC in terms of cycle control, contraceptive efficacy and tolerance. There was a trend toward a progressive decrease in the incidence of unscheduled bleeding throughout the study period in both treatment groups. Although cycle control data may not be directly comparable between studies because of the inherent variability in the definitions used [19], our study is consistent with the general trend reported for other low-dose COCs [18,20–23]. Using the reference period analysis, again the decrease in bleeding/spotting days and the shorter mean length of bleeding/spotting episodes with continued use (i.e., from Reference Period 1 to 2) observed in our study are consistent with that reported with other COCs containing higher EE doses (30–40 mcg) [24].

The contraceptive reliability of the two contraceptive preparations were comparable to each other, with no pregnancies occurring in the drsp 3 mg/EE 20 mcg group and one pregnancy occurring in the DSG 150 mcg/EE 20 mcg group. Moreover, the contraceptive efficacy of these two formulations was similar to those reported of other 20-mcg-containing COCs with different progestins [20–23].

AEs reported in this study were similar between the two treatment groups except breast symptoms and consistent with those experienced with other low-dose COCs [21,22]. Discontinuation from the study due to AEs was low in both treatment groups (5.7% of all women overall), suggesting that both treatment medications were well tolerated.

The majority of women were satisfied or very satisfied with study treatment in both groups; 86.9% in the drsp 3 mg/EE 20 mcg 24/4 group and 85.4% in the DSG 150 mcg/EE 20 mcg group. Accordingly, the majority of women rated their emotional and physical well being as "the same" as before they started medication in both treatment groups. A slightly larger proportion of women in the drsp 3 mg/EE 20 mcg 24/4 group (28.8%) assessed their emotional well-being as "better" or "much better" than before treatment started compared with women in the DSG 150 mcg/EE 20 mcg group (25.4%).

In conclusion, treatment with both formulations offered good and comparable cycle control. The occurrence of unscheduled bleeding was highest in the first treatment cycle and diminished throughout the study in both groups. The total mean number of bleeding/spotting days and the mean length of all bleeding/spotting episodes were slightly lower, and the maximum scheduled bleeding intensity lighter with drsp 3 mg/EE 20 mcg COC treatment than DSG/EE, but these differences were not statistically different. Overall, both drsp 3 mg/EE 20 mcg 24/4 and DSG 150 mcg/EE 20 mcg demonstrated good contraceptive efficacy and tolerability.

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