Advances in Contraception, 1999; **15**: 191–200.

Comparative study on the acceptability of two modern monophasic oral contraceptive preparations: 30 μg ethinyl estradiol combined with 150 μg desogestrel or 75 μg gestodene

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Abstract

Cycle control and tolerability of two monophasic oral contraceptive pills containing 30 μg ethinyl estradiol (EE) with either 150 μg desogestrel (DSG) or 75 μg gestodene (GSD) were compared in women starting oral contraception.

A minimum of 200 healthy women at risk for pregnancy were to be treated for a total of 6 cycles per patient in a prospective, randomized open parallel-group multicenter trial.

Two hundred and forty-one subjects were randomized, 115 to DSG/EE and 126 to GSD/EE. Compliance to the study preparation was high (around 95%) in both groups and no pregnancies occurred during the study. Cycle control was excellent; there were no differences between the two groups with regard to incidence of spotting and breakthrough bleeding or duration and intensity of withdrawal bleeding. Side-effects were mild and in general comparable in the two groups. Both at baseline and during treatment, a higher proportion of women taking GSD/EE complained about breast tenderness. This resulted in more early withdrawals because of breast tenderness in the GSD/EE group.

It was concluded that monophasic DSG/EE and GSD/EE are equally effective, have similar cycle control and both are generally well tolerated.

Introduction

Ever since oral contraception was introduced in the early 1960s, research has focused on finding the lowest suitable dose of estrogen and progestogen, to avoid serious and troublesome side-effects without losing contraceptive efficacy. Modern oral contraceptives (OCs) combine lower doses of estrogens with small amounts of progestogens with less androgenic effects than older oral contraceptive preparations. Two formulations currently widely used are 30 μg ethinyl estradiol with 150 μg desogestrel (DSG/EE) and 30 μg ethinyl estradiol with 75 μg gestodene (GSD/EE).

Desogestrel and gestodene are modern selective gonane-type progestins, derived from 19-nortestosterone. They were synthesized in an effort to find progestogens with equal efficacy and cycle control but with a better safety and side-effect profile compared with older derivatives like levonorgestrel. In studies performed with OCs containing GSD/EE and DSG/EE, comparable contraceptive efficacy has been shown. Some studies, however, report differences between these two contraceptive preparations with regard to cycle control and tolerability [1–4]. Therefore, we undertook a prospective randomized multicenter trial investigating two monophasic oral contraceptive pills containing 30 μg EE/150 μg DSG or 30 μg EE/75 μg GSD, comparing cycle control and subjective side-effect profiles in women starting oral contraception.

Subjects and methods

Five university centers in Italy agreed to recruit a total of 200 patients (100 in each group), with a follow-up period of 6 cycles per patient. Interim results of this study have been published previously [5]. The study was performed according to accepted ethical standards as well as to local rules and regulations. Informed consent was obtained from all participants.

Medication consisted of packages containing 21 tablets of either 150 μg DSG plus 30 μg EE (Practil-21®, Marvelon®, NV Organon Oss, The Netherlands), or 75 μg GSD plus 30 μg EE (Femodene®, Schering AG, Berlin, Germany). Women were instructed to take one pill per day consecutively for 21 days after which a 7-day pill-free interval was to be followed.

Women between 18 and 40 years of age with a normal cycle length of approximately 28 days and at risk for pregnancy were eligible if no contraindications existed for OC use. Main contraindications to trial participation were: a history of thromboembolic disease, existing thrombophlebitis at first attendance, jaundice or history of jaundice in pregnancy, known or suspected mammary carcinoma or other estrogen-dependent tumors, diabetes mellitus or abnormal glucose tolerance test, and breast feeding. In addition, eligible patients should not have used oral hormonal

contraception for at least the last three months before study entry, i.e. all patients had to be starters.

After a baseline visit, a medical history was taken, a baseline physical examination was performed, subjects were randomized and study medication was dispensed. Patients returned for study visits at the end of cycles 1, 3 and 6. In addition, all patients kept a diary card for cycle control assessment. Spotting was defined as vaginal blood loss during the pill-taking period requiring maximally one sanitary pad/tampon per day; breakthrough bleeding was defined as vaginal blood loss in the pill-taking period requiring two or more sanitary pads/tampons per day; and withdrawal bleeding was defined as bleeding during the 7 tablet-free days. Intensity of withdrawal bleeding was graded according to the following scale: 1 = mild, requiring 1–2 sanitary pads per day; 2 = moderate, requiring 3–4 sanitary pads per day; 3 = severe, requiring 5 or more pads per day. Trial results were analyzed using descriptive statistics.

Results

A total of 241 subjects were recruited; 115 patients were randomized to DSG/EE and 126 to GSD/EE. There were no significant differences between the two groups with respect to baseline variables (Table 1). Two hundred and three (203) patients completed 6 cycles, 102 in the DSG/EE group (89%) and 101 in the GSD/EE group (80%). The total number of valid cycles collected was 608 in the DSG/EE group and 613 in the GSD/EE group.

Efficacy and compliance

No pregnancies were reported. Compliance was excellent in both groups; around 95% of the women did not miss one single tablet.

Table 1. Baseline variables and menstrual characteristics (mean ± SD)

Variable	*DSG/EE (n = 115)*	*GSD/EE (n = 126)*
Age (y)	26.4 ± 6.7	27.2 ± 6.8
Weight (kg)	56.7 ± 7.6	57.1 ± 6.8
Systolic BP (mmHg)	116.9 ± 10.4	115.5 ± 9.5
Diastolic BP (mmHg)	74.8 ± 8.2	75.0 ± 8.0
Cycle length (days)	29.8 ± 4.8	29.2 ± 4.6
Duration of withdrawal bleeding (days)	5.2 ± 1.4	5.1 ± 1.7
Irregular bleeding (%)	30	31.7

Cycle control

At enrollment, the mean duration of withdrawal bleeding was 5.2 days for the DSG/EE group and 5.1 days for the GSD/EE group. In the DSG/EE-treated women as well as in the GSD/EE-treated subjects, a progressive reduction in average duration of withdrawal bleeding was noted to be less than 4 days during cycle 6 (Figure 1). When the women were asked to classify the duration of their withdrawal bleeding into 3 classes (<4 days, 4–6 days, >6 days), a similar reduction was seen. At baseline,

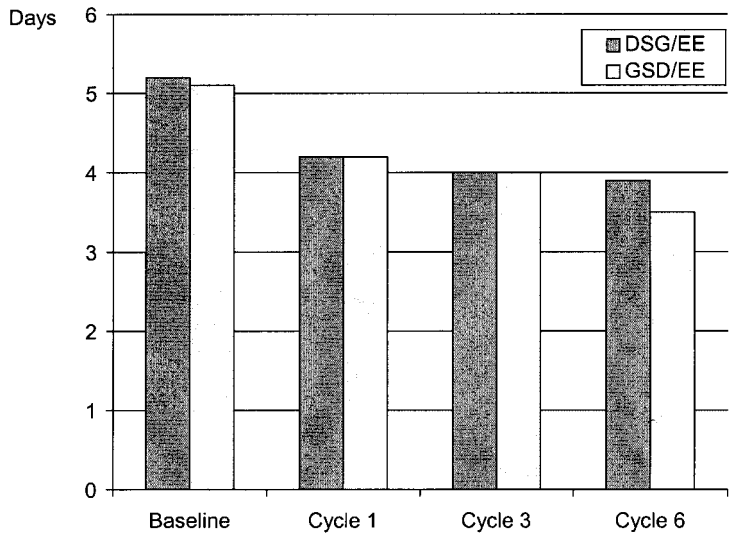

Figure 1. Mean duration of withdrawal bleeding (days)

withdrawal bleeding lasted more than 6 days (prolonged bleeding) in 21.1% of women with DSG/EE and in 15.4% of women in the GSD/EE group. After 6 treatment cycles, the prolonged bleeding figures dropped to 4.1% and 0% in the DSG/EE- and GSD/EE-treated groups, respectively. The percentage of women with less than 4 days of bleeding increased notably: at baseline 6.1% of women randomized to DSG/EE, and 10.8% of women in the GSD/EE group had menstruations of less than 4 days and these figures increased to 33% and 44.1% during the 6th cycle (Table 2). The intensity of the withdrawal bleeding also decreased with continued use of either preparation (Table 3). At baseline, around 30% of women in both groups complained about severe menstrual blood loss. After 6 months of OC use, these numbers had dropped to 7.4% of the GSD/EE users and 4.4% of the women taking the DSG/EE combination. Accordingly, the percentage of women experiencing withdrawal bleeding of mild intensity increased in both groups from

Table 2. Duration of withdrawal bleeding (% of subjects)

	DSG/EE			*GSD/EE*		
	<4 days	*4–6 days*	*>6 days*	*<4 days*	*4–6 days*	*>6 days*
Baseline	6.1	72.8	21.1	10.8	73.9	15.4
Cycle 1	25.5	71.3	3.2	24.5	73.4	2.1
Cycle 2	24.0	74.0	2.0	30.4	69.6	0.0
Cycle 3	30.7	67.3	2.0	27.6	72.5	0.0
Cycle 4	36.0	61.0	3.0	41.2	58.8	0.0
Cycle 5	34.0	63.0	3.0	42.1	57.9	0.0
Cycle 6	33.0	62.9	4.1	44.1	55.9	0.0

Table 3. Intensity of withdrawal bleeding (% of subjects)

	DSG/EE			*GSD/EE*		
	Mild	*Moderate*	*Severe*	*Mild*	*Moderate*	*Severe*
Baseline	9.7	62.3	28.1	13.2	51.9	34.9
Cycle 1	19.8	67.7	12.5	23.0	60.0	17.0
Cycle 2	26.7	67.3	5.9	26.2	63.6	10.3
Cycle 3	30.4	64.7	4.9	25.0	67.0	8.0
Cycle 4	26.8	68.0	5.2	30.3	62.6	7.1
Cycle 5	27.8	67.0	5.2	29.6	62.2	8.2
Cycle 6	25.3	70.3	4.4	30.5	62.1	7.4

around 10% before treatment, to 25.3% and 30.5% after 6 cycles of OC use in the DSG/EE and the GSD/EE groups, respectively. Amenorrhea occurred in one case in the DSG/EE group (in the first cycle), corresponding to an incidence of 0.2% of all DSG/EE treatment cycles. In women taking GSD/EE, amenorrhea was reported three times (in cycles 2, 3 and 6), an incidence of 0.5%. With regard to irregular bleeding, a progressive decrease over the cycles in both spotting and breakthrough bleeding was observed in both groups (Figure 2). After 6 months, six women reported irregular bleeding in the GSD/EE group (6.2%) and only one in the DSG/EE group (1.0%).

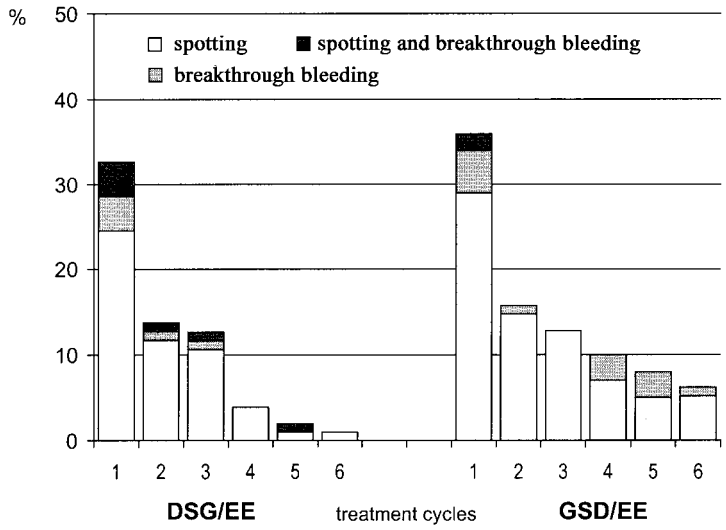

Figure 2. Incidence of irregular bleeding (% of subjects)

Side-effects

Side-effects actively asked for were, among others, the presence or absence of breast tenderness, nausea, and headache. This active search for complaints may explain the relatively high initial percentages of women responding positively, even at the pretreatment visit. The incidence of side-effects declined progressively with continuation of therapy (Table 4). No difference could be detected between the two treatment groups, although the number of women complaining of breast tenderness remained

Table 4. Incidence of side-effects (% of subjects)

	DSG/EE			*GSD/EE*		
	Breast tenderness	*Nausea*	*Headache*	*Breast tenderness*	*Nausea*	*Headache*
Baseline	32.0	7.3	20.4	45.8	12.2	21.4
Cycle 1	36.7	21.1	15.6	41.2	26.5	12.8
Cycle 3	24.1	16.1	14.9	39.8	15.3	12.2
Cycle 6	17.2	9.2	11.5	33.7	6.5	9.8

quite high in the GSD/EE group (33.7% in cycle 6, versus 17.2% with DSG/EE). However, the baseline incidence was also higher in the GSD/EE group than in the DSG/EE group (45.8% vs. 32.0%). Blood pressure and body weight did not differ significantly between treatment groups at any point of the study. There was a small weight increase in both groups during the course of the study, ranging from a mean increase of 0.5 kg in the DSG/EE group to 0.8 kg in the GSD/EE group. Systolic and diastolic blood pressure did not increase in either group compared with baseline.

Discontinuation rates

In total, 13 women (11.3%) discontinued early from the DSG/EE group, and 25 (19.8%) from the GSD/EE group. In the DSG/EE group, 5 women left for non-medical reasons and 8 for medical reasons, whereas, in the GSD/EE group, there were 6 withdrawals on non-medical and 19 on medical grounds (Table 5). As with side-effects, a trend toward a higher number of women suffering from breast

Table 5. Reasons for early withdrawal (number of patients; more than one medical reason could be given)

Reason	*DSG/EE*	*GSD/EE*
Non-medical	5 (4.3%)	6 (4.8%)
Medical	8 (7%)	19 (15.1%)
Hypertension	1	0
Irregular bleeding	2	5
Breast tenderness	0	8
Headache/migraine	3	5
Nausea/vomiting	2	7
Mood change	0	3
Worsening acne	0	1

tenderness was seen with the GSD-containing preparation when looking at the reasons for withdrawal: 8 women left the GSD/EE group for this complaint, whereas no subjects in the DSG/EE group left because of breast tenderness. Two serious adverse events (events involving hospital admission) occurred, one in each group: a woman on DSG/EE was referred to the hospital for menometrorrhagia and one woman taking GSD/EE was referred because of severe headaches. At the end of the trial, 76.9% of doctors prescribing DSG/EE were satisfied or very satisfied with prescribing the preparation, whereas the corresponding figure was 57.4% for the GSD/EE group.

Discussion

An important advantage to women using oral contraception is a general reduction in the duration and intensity of menstrual blood loss. In accordance with earlier studies on gestodene- and desogestrel-containing OCs [1,3,6–9], the average duration and intensity of withdrawal bleeding decreased progressively in both groups from over 5 days before the initiation of the trial medication to less than 4 days at cycle 6. Amenorrhea was reported in only 0.2% (DSG/EE group) and 1.0% (GSD/EE group) of subjects. This is in accordance with previous data as well; figures in the literature vary from 0.3% to 5.1% with both OCs [1,2,8,10–12], with no significant difference between DSG/EE- and GSD/EE-containing contraceptives. In both groups, the incidence of irregular bleeding was comparable. After an initial increase compared with baseline, spotting and breakthrough bleeding occurred only sporadically after the third cycle. Although, in general, all studies show a decline in irregular blood loss from cycle 1 to cycle 3, some authors have reported differences in cycle control between women using DSG/EE vs. GSD/EE in favor of the latter [1–4]. In these studies, it seems that differences between DSG/EE and GSD/EE with regard to irregular bleeding seemed to arise in the first two cycles, whereas, with continued use, these between-group differences disappeared, the incidence dropping to around 4% with both preparations. In contrast, other comparative studies are in line with our findings, and found no differences between DSG/EE and GSD/EE [12,13].

One possible explanation for the different conclusions of comparative studies could be that the incidence of irregular bleeding in the first cycles is highly dependent on previous OC use. The incidence of irregular bleeding in the first cycle has been reported to be higher in starters than in switchers [10,11], probably because continued use has effects on the endometrial vasculature and hemostatic response to vascular bleeding [10]. Although one trial with 461 women using DSG/EE reported the opposite [8], an analysis of bleeding patterns in 2767 women confirmed previous data on the influence of recent OC use on irregular bleeding [4]. In fact, during the first cycle, recent OC use was the strongest predictor of irregular bleeding. Women who had not used oral contraceptives within the last three months before trial initiation (starters) had a more than two-fold higher relative risk (2.2, $p<0.01$) of experiencing irregular blood loss compared with women who had used oral contraceptives within three months of trial initiation (switchers) [4]. Most of the comparative studies did not separately present data on irregular blood loss of starters versus switchers [1,3,4,12,13] or used a different definition of starters [2]. In our study, all patients were starters and therefore the bleeding results obtained in this trial lack the confounding variable of recent OC use that may have led to erroneous conclusions. It thus seems probable that small differences between desogestrel- and gestodene-containing OCs found by others with regard to irregular bleeding are attributable to patient variability. When looking at similar populations, as we did, DSG/EE and GSD/EE can be considered comparable with respect to their effects on irregular bleeding.

The number of patients reporting side-effects in this trial was higher than reported in most other trials. This can probably be attributed to the active method of

questioning, illustrated by the high percentage of women complaining about breast tenderness, nausea and headache even before the initiation of treatment. In one previous trial, where standard breast examination was performed as part of the trial, around 35% of women were found to have breast nodularity [11], indicating that active searching increases the number of side-effects reported. The initial increase in cycle 1 and the subsequent sharp decline in number of complaints following continuation of therapy was seen in both groups, and is in accordance with previous data [1,2,7–9,12]. In fact, after 3 cycles, fewer women suffered from side-effects than before initiation of oral contraception.

The prevalence of dropouts in this trial was comparable to that of previous trials. A slightly higher percentage of women withdrew in the GSD/EE group compared with the DSG/EE group. A relatively large number of those women withdrawing from the study complained of breast tenderness (8 in the GSD/EE group vs. none in the DSG/EE group). One previous study also found a higher drop-out rate because of breast tenderness during GSD/EE use compared with DSG/EE [2].

Conclusions

The OC combinations of 150 μg desogestrel plus 30 μg ethinyl estradiol and of 75 μg gestodene plus 30 μg ethinyl estradiol are equally effective, have similar cycle control, and are both generally well tolerated.

Acknowledgements

This study was sponsored by NV Organon, Oss, The Netherlands. The authors would like to thank Moki Vree, Paul Geurts (NV Organon, Oss, The Netherlands) and Jeanine Jaski for their contributions to the manuscript.

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Manuscript received 18 Oct. 99.
Accepted for publication 30 Nov. 99.

Resumé

On a comparé, chez des femmes commençant à recourir à la contraception orale, la maîtrise du cycle et la tolérance pour deux pilules contraceptives orales monophasiques contenant 30 μg d'éthinyl oestradiol (EE) et soit 150 μg de désogestrel (DSG) soit 75 μg de gestodène (GSD).

Lors d'une étude prospective, randomisée, ouverte, et multicentrique en groupes parallèles, un minimum de 200 femmes en bonne santé risquant une grossesse ont été traitées pendant 6 cycles au total par patiente.

Deux cent quarante et une femmes ont été randomisées, 115 pour les essais DSG/EE et 126 pour les essais GSD/EE. Dans les deux groupes, elles ont généralement accepté de poursuivre les essais (environ 95%) et aucune grossesse ne s'est produite durant l'étude. Le cycle était très bien maîtrisé; il n'y avait aucune différence entre les deux groupes en ce qui concerne l'apparition de microrhagies ou pertes sanguines plus importantes, ni du point de vue de la durée et de l'intensité des pertes après l'abandon du traitement. Les effets secondaires ont été bénins et en général comparables pour les deux groupes. Au début et au cours du traitement, une plus forte proportion de femmes dans le groupe GSD/EE se sont plaintes de sensibilité des seins, ce qui a provoqué davantage de cas d'abandon précoce dans ce groupe.

Il en a été conclu que les préparations DSG/EE et GSD/EE sont aussi efficaces l'une que l'autre, qu'elles permettent une maîtrise analogue du cycle et qu'elles sont l'une et l'autre généralement bien tolérées.

Resumen

En mujeres que comenzaban a utilizar anticonceptivos orales se compararon el control del ciclo y la tolerabilidad de dos píldoras anticonceptivas orales monofásicas que contenían 30 μg de etinil estradiol (EE) con 150 μg de desogestrel (DSG) o bien 75 μg de gestodén (GSD).

Un mínimo de 200 mujeres sanas a riesgo de embarazo serían tratadas por un total de 6 ciclos por paciente en un ensayo multicentro prospectivo, aleatorizado, abierto, de grupos paralelos.

Dos cientos cuarenta y un mujeres fueron aleatorizadas, 115 a DSG/EE y 126 a GSD/EE. El cumplimiento con la preparación del estudio fue alto (alrededor del 95%) en los dos grupos y no se registró ningún embarazo durante el estudio. El control del ciclo fue excelente; no hubo diferencias entre los dos grupos con respecto a la frecuencia de microrragias o hemorragias uterinas o con respecto a la duración e intensidad de la hemorragia de retiro. Los efectos secundarios fueron ligeros y, en general, comparables en los dos grupos. Tanto en la línea de base como durante el tratamiento, una mayor proporción de mujeres que tomaban GSD/EE se quejaron de tensión en las mamas. Esto llevó a más retiros tempranos debido a tensión en las mamas en el grupo GSD/EE.

Se llegó a la conclusión de que DSG/EE y GSD/EE monofásicos son igualmente eficaces, tienen un control similar del ciclo y son bien tolerados en general.