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GYNAECOLOGY

Comparative profiles of reliability, cycle control and side effects of two oral contraceptive formulations containing 150 µg desogestrel and either 30 µg or 20 µg ethinyl oestradiol

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ABSTRACT

Objective To compare two oral contraceptive pills, both containing 150 µg desogestrel, but with either 20 µg (Mercilon®) or 30 µg (Marvelon®/Desolett®) ethinyl oestradiol (EE), regarding reliability, cycle control and side effect profile.

Design A double blind, randomised, multicentre study over one year with follow up after three, six and 12 months. The women noted tablet intake and all bleedings on specifically designed diary cards.

Setting University clinics, central hospitals and private gynaecological practices in Norway, Sweden and Denmark.

Subjects One thousand women aged 18 to 40 years requesting oral contraceptive pills.

Main outcome measures Reliability, cycle control, side effects, blood pressure, body weight and haemoglobin.

Results In a total of 4543 cycles with the 20 µg EE dose pill and 4688 cycles with the 30 µg EE dose pill, the number of pregnancies ascribed to method failure were 0 and 2, respectively. Irregular bleeding (breakthrough bleeding or spotting) was signficantly more frequent with the 150/20 combination in about two-thirds of the cycles randomly distributed over the one year of the study. Mean blood pressure decreased slightly, particularly in the group on the 150/20 combination (about 1 mmHg), whereas mean body weight increased approximately 0·5 kg in the group with the 150/30 combination after 12 months. Haemoglobin did not change. Side effects other than bleeding problems were rare, but dizziness and mood changes were more frequent in the group on the 150/20 combination. Due to side effects, more women on the 150/20 combination discontinued the study during the one to three and four to six month periods, and women on this pill were also less positive about continuing the study drug at the end of the trial.

Conclusions Both pills have high contraceptive reliability and are well tolerated, but with the 150/20 combination the cycle control is less effective. However, in view of the potentially increased safety profile of the 150/20 combination, many women can be expected to accept some additional discomfort due to irregular bleeding.

Some epidemiological studies have suggested an association between the use of high oestrogen dose combined oral contraceptive (OC) pills and serious cardiovascular complications, such as myocardial infarction, stroke and venous thromboembolism (Jick *et al.* 1978; Stadel 1981). Furthermore, the risk of developing breast cancer seems to be slightly increased after long use of high oestrogen dose pills by young nulliparous women (Rushton & Jones 1992). By reducing the daily dose of ethinyl oestradiol (EE) to the 30 µg dose in most currently used preparations, the risk of cardiovascular complications has decreased markedly (Böttiger *et al.* 1980; Stampfer *et al.* 1990; Thorogood *et al.* 1991). A further reduction in EE below 30 µg per day has only been described with norethisterone. However, this combination was reported to have poor cycle control (Bounds *et al.* 1979). Furthermore, with norethisterone or levonorgestrel as the progestational agent in a pill with less than 30 µg EE, there would be a

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risk of adverse effects on lipoprotein patterns due to the androgenic properties of these progestogens (Bergink *et al.* 1982; Fotherby 1985).

The search for more potent progestogens resulted in the development of desogestrel which exerts its biological effect after conversion to 3-keto-desogestrel. The main advantage of 3-keto-desogestrel compared with other progestogens used in OCs is that it displays a high ratio between the desired progestational effects and the undesired androgenic effects (Cullberg 1985). This has allowed reduction of the EE dose to 20 μg without risk of unfavourable effects on lipids and liproteins (Kloosterboer *et al.* 1987; Tuimala *et al.* 1987). A monophasic combination of 20 μg EE and 150 μg desogestrel was studied in a large, although open, clinical trial and was found to have an effective cycle control and a Pearl index of 0·2 (Lammers & op ten Berg 1991). We present here the results of a double blind, comparative study of OC pills containing 20 and 30 μg of EE together with 150 μg of desogestrel with special emphasis on reliability and cycle control. The effects on blood pressure, body weight and haemoglobin, as well as side effects, were also studied.

Subjects and methods

Oral contraceptives containing 150 μg desogestrel and 20 or 30μg of EE per tablet (Mercilon® and Marvelon®/Desolett®, respectively) were compared in 1000 women over a treatment period of one year. The sample size of the study (2 × 500 participants) was determined so that it would be possible to demonstrate that there was a minimal difference with respect to presence of irregular bleeding. With 500 women in each group the upper limit of a 95% confidence interval (CI) for the difference between the proportions would be less than 6% with the probability 80% provided that the two treatments did not differ.

Women asking for oral contraception were recruited for the study. In Norway 300 women were recruited for the study (six centres, all private gynaecological practices), in Sweden 500 woman (two university clinics, two central hospitals, one private practice) and in Denmark 200 women (one university clinic). The participating women were aged 18 to 35 (Norway) or 18 to 40 years (Sweden, Denmark). Informed consent was obtained from each participant, and the study was performed according to the Helsinki declaration with permissions obtained from the ethics committees and from the national boards for health and welfare.

Criteria for exclusion of women from the study were heavy smoking (>15/day) in women over the age of 35 years, risk factor for or history of thromboembolic processes of the participant or a close relative, hypertension, liver disorders, systemic lupus erythematosus, undiagnosed vaginal bleeding, sickle cell anaemia, porphyria, hyperlipidaemia, otosclerosis, use of certain antibiotics and breast feeding. If a woman started using rifampicin, griseofulvin or anticonvulsants, or used other antibiotics for more than 14 days, she was excluded from the study.

At the first visit inclusion and exclusion check lists were completed, the medical history was recorded and physical examination was performed, including gynaecological examination and measurement of blood pressure (after 5 min of seated rest), body weight and haemoglobin concentration. The women were randomly allocated to the study medication according to a list computed by simple randomisation and provided by Organon International bv (Oss, The Netherlands): 485 women on the 150/20 and 497 on the 150/30 combination. The tablets were supplied by Organon International bv in standard, unmarked 21 day blister packs. Women either changed from another OC formulation to the study medication (switchers) or had not used any hormonal contraceptive medication for at least two months (starters).

The women started to take the study medication on the first day of menstruation or of withdrawal bleeding after previous OC pill use. The tablets were taken for 21 consecutive days followed by a seven-day, tablet-free period. Follow up visits were done after three, six and 12 months of OC-treatment with recording of blood pressure and body weight. Furthermore, throughout the study the women noted all vaginal bleeding on specifically designed diary cards, on which each tablet intake and all side effects also were recorded. Completed diary cards were collected, and new cards, as well as new study medication, were distributed at follow up visits. At the final visit gynaecological examination was again performed and haemoglobin concentration measured.

Bleeding was defined as normal withdrawal bleeding if it started within the tablet-free interval and lasted no more than eight days. Any other bleeding during the tablet-taking period was defined as irregular bleeding. Bleeding was further subdivided into spotting (requiring at the most one sanitary pad or tampon a day) or breakthrough bleeding (requiring more than one sanitary pad or tampon a day). The occurrence and duration of these two types of bleeding irregularities were calculated. Days of breakthrough bleeding and spotting within the same bleeding episode was all counted as breakthrough bleeding. For the analysis, all information on bleeding and tablet intake was taken directly from the diary cards. Cycles in which the pill-taking period was less than 18 days or greater than 33 days of treatment were not included in the analysis nor were those cycles with a pill-free period of less than five days or greater than nine days. The same accounts for cycles for which no information was obtained on the pill-free period. Bleeding during the first eight days of the first treatment cycle was not included in the calculations.

The occurrence of side effects was recorded at each follow up visit. If these side effects were reasons for drop-out from the study this was also noted. At the final visit each participating woman was asked whether or not she would have liked to continue with the preparation used.

The χ^2 test was used for the comparison of occurrence of bleeding irregularities. Otherwise comparisons between the treatment groups were performed by Fisher's permutation test (Bradley 1968), which includes Fisher's exact test as a special case. Fisher's test for paired comparisons (Bradley 1968) as applied for comparisons within treatment groups. All tests were two-sided.

Results

The number of women starting on oral contraceptives or switching to the study drugs from whom data was avail-

Table 1. Number of women (*n*) starting on oral contraceptives or switching to the 150/20 or 150/30 μg desogestrel/ethinyl oestradiol combination is shown. A total of 18 women agreed to participate and were randomised to one of the treatment groups but never started with their contraceptive pill. The age distribution at the start of the study is also indicated.

	150/20			150/30		
	Starters	Switchers	Total	Starters	Switchers	Total
Cycle						
Start	188	297	485	197	298	497*
1	163	279	442	168	282	452
3	161	275	436	163	279	444
6	136	252	388	138	258	398
9	122	228	350	122	235	359
12	110	216	326	119	225	346
Age distribution						
<20	41	51	92	59	59	118
20–24	76	139	215	81	145	228
25–29	50	59	109	34	56	90
30–34	19	37	56	20	33	53
35–39	1	11	12	3	5	8
>39	1	0	1	0	0	0

*Information about previous use of contraceptives was not obtained from two women.

able for analyses, as well as the distribution in age groups for the two preparations, are shown in Table 1. Data on 4543 cycles with the 150/20 and 4688 cycles with the 150/30 combination were obtained. The decrease in number of subjects from start of the study to cycle 1 was due to women electing to participate and receiving a study drug, but thereafter not commencing the medication.

The mean age of women on the 150/20 combination (23·8 years) was significantly higher ($P<0·05$) than that of subjects on the pill with the higher EE dose (23·1 years). The percentage of starters did not differ between the two treatment groups, 38·8 in the 150/20 and 39·8 in the 150/30 group. No difference between study groups was seen regarding previous pregnancies, parity, previous OC use, smoking, use of medication, pattern of menstrual cycles, blood pressure, weight, length, body mass index, haemoglobin and findings at gynaecological examination.

Reliability

Two pregnancies occurred on the 150/20 combination (Pearl index 0·41; 95% CI 0·04–1·5), but neither of them

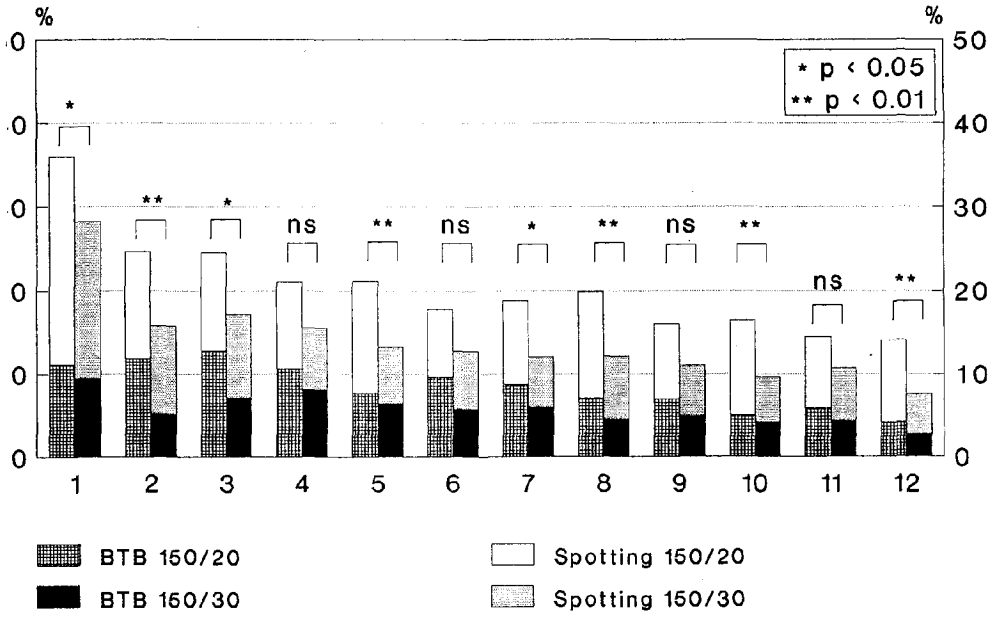

Fig. 1. Irregular bleeding (BTB and/or spotting) in percentage (%) of women per treatment cycle.

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