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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

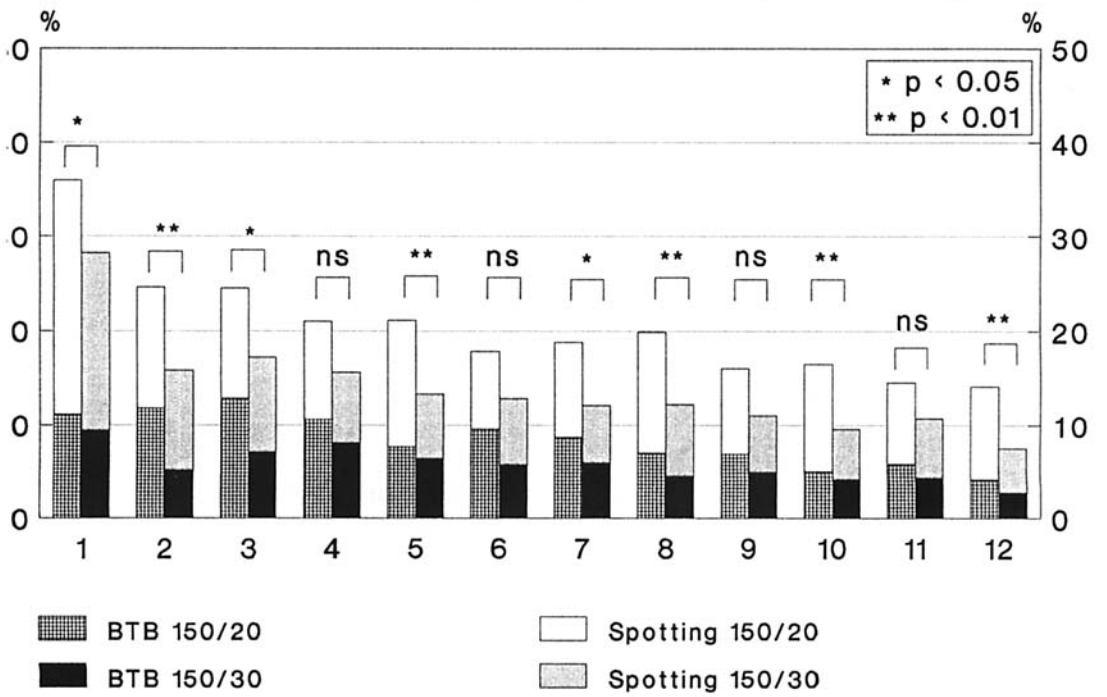

Fig. 1. Irregular bleeding (BTB and/or spotting) in percentage (%) of women per treatment cycle.

was considered to be due to method failure. One subject had prolonged the interval between the taking of two pills and one had had diarrhoea for three days, but did not use additional protection.

Of the three pregnancies on the 150/30 combination (Pearl index 0·6, 95% CI 0·1–1·6), two were ascribed to method failure (Pearl index 0·4, 95% CI 0·04–1·5). The third pregnancy occurred in a woman who had prolonged the interval between two treatment cycles from seven to nine days.

Cycle control

After the study was completed, 8900 cycles were available as recorded on the diary cards. After data validation 8573 cycles could be included in the analysis. The occurrence of irregular bleeding (breakthrough bleeding or spotting) is shown in Fig. 1 for all the study cycles. The absence of withdrawal bleeding is tabulated in Table 2 for the cycles 1, 3, 6, 9 and 12. The duration of irregular bleeding in the women having this event is shown in Table 3. Irregular bleeding was more frequent with the lower EE dose pill than with the higher one. The difference was statistically significant in two-thirds of the cycles randomly distributed over the one year of the study (Fig. 1). The incidence of spotting and breakthrough bleeding decreased with increasing duration of use of both OCs. A similar trend was seen in a subanalysis of those women who completed the study. However, the first six months of the study period showed a lower incidence of irregular bleeding in this group compared with the total study population due to the women having dropped out of the study. There were no significant differences between the two groups regarding absence of withdrawal bleeding (Table 2). The mean duration of irregular bleeding did not show any consistent differences between the two groups, but decreased over time in both of them (Table 3). The two groups did not differ regarding the length of the withdrawal bleeding.

A separate comparison was made between women starting on the two combinations and women switching to the study medication from their previous pills. It showed that for both preparations in the first three months irregular bleeding was more common in the group of starters (Table 4). There was no difference between the two combinations in the first two cycles of the starters; in the third one, irregular bleeding was more common in this subgroup with the lower EE dose pill. In the group of switchers the percentage of women having irregular bleeding in the first two cycles of use of the 150/30 pill was half that of the women switching to the 150/20 combination. This difference was not reflected in the mean duration of irregular bleeding in these two groups (not shown).

Table 2. Absence of withdrawal bleeding in women using the 150/20 or 150/30 combination. Results are percentages of women per cycle evaluable for cycle analysis. There were no statistically significant differences between study groups.

	Absence of withdrawal bleeding			
Cycle	*n*	150/20	*n*	150/30
1	406	6·4	415	5·1
3	383	5·2	395	3·5
6	354	4·2	367	3·0
9	331	3·9	347	3·2
12	271	3·0	292	1·4

Table 3. Duration of irregular bleeding (breakthrough bleeding and/or spotting) in women using the 150/20 and 150/30 combination. Results are shown as mean (SD) calculated for the women having irregular bleeding.

	Duration of irregular bleeding (days)	
Cycle	150/20	150/30
1	5·2 (3·7)	6·4 (4·5)
3	4·4 (3·1)	3·7 (2·5)
6	3·8 (2·3)	3·9 (2·6)
9	4·3 (2·9)	3·8 (3·0)
12	3·3 (2·4)	2·9 (1·4)

Influence on blood pressure, body weight and haemoglobin

Compared with pretreatment levels, slight decreases (0·5–2 mmHg) in mean systolic blood pressure were seen in the group on the 150/20 combination after three and six months and in mean diastolic pressure at all check-up visits (Table 5). For the 150/30 combination a decrease was only seen with regard to mean systolic pressure after six months. Mean body weight had decreased about 0·2 kg in the group on the 150/20 combination at the three month visit and increased 0·6 kg in the group on the 150/30 combination after 12 months (Table 5). No significant difference between groups in magnitude of blood pressure and weight changes from baseline was seen. Haemoglobin did not vary within or between groups during the study.

Side effects

Side effects with the two preparations reported by 15 women or more in any of the groups or those for which a

Table 4. Frequency of irregular bleeding (breakthrough bleeding and/or spotting) in women using the 150/20 or 150/30 combination including both starters and switchers. Results are percentages of women per cycle evaluable for cycle analysis.

	Irregular bleeding			
Cycle	*n*	150/20	*n*	150/30
Starters				
1	150	48·0	156	51·9
2	148	28·4	154	20·8
3	146	28·8	149	18.8*
Switchers				
1	256	28·9	259	13·9***
2	252	22·2	256	12.9**
3	237	21·9	246	16·3

*$P<0·05$.
**$P<0·01$.
***$P<0·001$.

Table 5. Blood pressure and body weight, mean change from baseline (+ = increase, − = decrease) in women using the 150/20 or 150/30 combination. Significant differences are denoted by asterisks.

	Blood pressure (mmHg)					
	Systolic		Diastolic		Body weight (kg)	
Cycle	150/20	150/30	150/20	150/30	150/20	150/30
3	−1·55**	−0·63	−1·23**	−0·43	−0·23*	−0·04
6	−2·09***	−1·22*	−1·34**	−0·52	−0·02	+0·25
12	−0·66	−0·62	−0·86*	−0·01	+0·21	+0·57***

*$P<0·05$.
**$P<0·01$.
***$P<0·001$.

significant difference in reporting were found between groups are shown in Table 6. More women on the 150/20 than on the 150/30 combination reported dizziness, mood change and irregular bleeding.

Diseases diagnosed during the time of the study were few, mainly infections, with no differences between preparations. The only serious event emerging during the time of the study was a case of pulmonary embolism. This happened in the third cycle on the 150/30 combination in a woman who had previously been on a triphasic OC for three years. The diagnosis was confirmed by scintigraphy and coagulatory investigation revealed a low antithrombin-III activity. After anticoagulant treatment for four months the patient has recovered completely and she has now gone through an uncomplicated pregnancy with no disturbance in antithrombin-III.

Discontinuation and willingness to continue with study drug

Discontinuation rate amounted in total to 33% with the 150/20 and to 30% with the 150/30 combination, with about half of the drop-outs in the two groups occurring during the first three months of use. The incidence of dropping out was not correlated to age group, whereas more starters on OCs than switchers left the study ($P<0·001$). The respective figures for starters and switchers dropping out were 41·5% and 27·3% for the 150/20 combination and 39·6% and 24·5% for the 150/30 combination.

Reasons given for dropping out of the study by 15 or more women in any of the groups are shown in Table 7. Only regarding irregular bleeding and lack of need of contraceptive were significant differences seen between the 150/20 and 150/30 combination groups. Due to side effects more women on the 150/20 combination had dropped out of the study during both the one to three ($P<0·05$) and four to six ($P<0·01$) month periods. During the months seven to twelve, there was no difference between the remaining women in discontinuation because of side effects. However, women on the 150/20 combination were less positive about continuing with their preparation than those on the 150/30 combination (85·8% *vs* 91·0% wishing to continue, $P<0·05$).

Table 6. Number of women using the 150/20 or 150/30 combination with side effects over one year of use. Symptoms reported by less than 15 women in a group and not differing between groups are not shown. A woman may have reported more than one symptom. Significant differences between study groups are indicated by asterisks.

Side effects	150/20	150/30
Nausea, diarrhoea, vomiting	22	16
Headache	28	17
Dizziness	6	0*
Mood change	28	15*
Painful menstruation	17	12
Prolonged withdrawal bleeding	25	13
Irregular bleeding	48	30*
Increased weight	15	6

*$P<0·05$.

Discussion

This comparative investigation of two OC agents, both containing 150 μg desogestrel per tablet but varying in the content of EE, enabled a specific study of the importance of the oestrogen in the lower dose range for reliability, cycle control and adverse effect profile. Mercilon® was designed to reduce the oestrogen dose while maintaining contraceptive efficacy and acceptability.

The contraceptive reliability of the two preparations was good, with no pregnancy attributed to method failure on the 150/20 combination and two on the 150/30 combination. The low pregnancy rate with the 150/20 combi-

Table 7. Reasons for dropping out of the study over one year of use of women using the 150/20 or 150/30 combination. Reasons given by less than 15 women in a group and not differing between groups are not shown. A women may have given more than one reason for leaving the study. Significant differences between study groups are indicated by asterisks.

	150/20	150/30
Mood changes	15	10
Irregular bleeding	27	10**
No present need for contraception	2	10*
Other social reason	16	30
No reason given	37	39

*$P<0·05$.
**$P<0·01$.

nation was consistent with results from the recent multicentre study on this preparation of about 26 000 cycles in which the pregnancy rate for method failure was 0·05 (Lammers & op ten Berg 1991).

Women using the 150/20 combination generally had a higher incidence of irregular bleeding (spotting and breakthrough bleeding) than women using the 150/30 combination. This difference was seen in all cycles and reached statistical significance in two-thirds of them. Absence of withdrawal bleeding was consistently about 1% higher in the 150/20 combination compared with the 150/30 pill, but this difference never reached statistical significance. The finding that the percentages of irregular bleeding in starters were higher than in switchers is consistent with earlier observations (Edgren *et al.* 1989). The difference between the lower EE dose and the higher EE dose OC in treatment cycle 1 was almost entirely caused by the group of switchers. Taking into account that the majority of the switchers used OCs containing at least 30 μg EE or more, prior to the study, it might be assumed that a part of this bleeding was due to the adaptation of the target organs to daily administration of a lower EE dose (an EE withdrawal phenomenon). However, the difference between the preparations cannot be explained by an EE withdrawal phenomenon only, since it was observed in various cycles throughout the whole year of the study and was seen also in starters on OC. The increase in irregular bleeding with the lower EE dose pill is not surprising since the steroid dose is one of the factors that have been recognised to influence cycle control. Increased irregular bleeding was also reported when the EE content of OC pills was reduced to below 50 μg (Gray 1980).

The incidence of irregular bleeding both with the 150/20 and with the 150/30 combination was higher than has been reported in other European studies with these OCs using almost the same definitions for breakthrough bleeding and spotting (Rekers 1988; Lammers & op ten Berg 1991). The present study was performed in a homogenous Scandinavian population, whereas women from 12 European countries participated in these earlier studies. Therefore, the data obtained on the 150/30 combination in the current study have been compared with data on this same combination from studies also performed in Scandinavian women (Borglin *et al.* 1982; Cullberg *et al.* 1982). The incidence of bleeding irregularities in these studies was indeed comparable to that of irregular bleeding reported in our study.

The incidence and duration of breakthrough bleeding and spotting decreased in both groups during the study period, particularly after the first cycle. This finding is in agreement with results of previous trials of these pills (Rekers 1988; Lammers & op ten Berg 1991), and can be explained by an effect of longstanding OC treatment on endometrial vasculature (Johannisson 1982; Ludwig 1982) and its haemostatic response to endometrial bleeding (Casslén & Åstedt 1983). An effect of the dropping out of the study of women with a particular tendency to bleed irregularly could also have contributed to the decrease.

Side effects other than bleeding problems were few in this study. Although overall a slight decrease in blood pressure was observed, this finding is probably fortuitous, an assumption supported by previous findings with these two OCs in larger studies (Rekers 1988; Lammers & op ten Berg 1991). The recorded weight changes were small and divergent, which suggests that they were coincidental. Of the side effects other than irregular bleeding, a statistically significant difference between the groups was only seen regarding dizziness and mood changes. Whether these differences reflect a real difference between the two preparations or chance observations related to the multiple testing remains to be assessed.

With both OCs the main reason given for dropping out of the study was insufficient cycle control. This is in agreement with other observations that bleeding problems constitute an important reason for discontinuation of OCs (Belsey *et al.* 1988). The number of drop-outs among starters was greater than among switchers and a significantly higher number of women taking the 150/20 combination terminated the study prematurely. When the women were asked whether they would like to continue using the study drug at the end of the trial period if that were possible, the women who had used the 150/20 combination were less positive. The reasons for discontinuing the use of any contraceptive method are complex and may be physical as well as psychological. The finding that haemoglobin concentration did not vary between the groups suggests that it was not the amount of blood loss, but the discomfort of unpredictable bleeding that caused discontinuation. On the other hand, cycle disturbances such as breakthrough bleeding and absence of withdrawal bleeding may have increased anxiety and affected some women's confidence in the method (Hillard 1989).

Our study demonstrated low pregnancy rates of the 150/20 and 150/30 combinations and very little difference between them in general side effects. A difference which was demonstrated in this randomised, double blind, comparative investigation was the less effective cycle control with the 150/20 combination, leading to more drop-outs for that reason. The increase in irregular bleeding with the lower EE dose, while the pregnancy rate remained low is in agreement with the well-established fact that the threshold EE dose for cycle control is higher than the dose for inhibiting conception. However, in view of the potentially better safety profile of the 150/20 combination, many women can be expected to accept some additional discomfort due to irregular bleeding. In addition, for the large majority of women who have perfect cycle control with the 150/20 combination there is no reason to revert to a higher EE dose preparation.

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