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Safety Data and Beneficial Effects of the Combined Oral Contraceptive Ethinylestradiol 0.03 mg/Chlormadinone Acetate 2 mg (Belara®)

A 13-Cycle, Observational Study in Routine Clinical Practice

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Abstract

Background: The monophasic hormonal combined oral contraceptive (COC) ethinylestradiol (EE) 0.03 mg/chlormadinone acetate (CMA) 2 mg (Belara®) has been shown to have good long-term efficacy and tolerability.

Objectives: The aim of this study was to corroborate the long-term safety of EE 0.03 mg/CMA 2 mg by evaluating the incidence and severity of adverse drug reactions (ADRs) and cycle control over 13 treatment cycles. Additionally, the influence of EE 0.03 mg/CMA 2 mg on dysmenorrhoea, acne and the well-being of subjects was also investigated.

Methods: This observational study was conducted in Spain, France and Italy from April 2006 to August 2008. Subjects of reproductive age, without contraindications mentioned in the current summary of product characteristics, were prescribed EE 0.03 mg/CMA 2 mg in routine clinical practice.

Results: 3771 subjects were analysed and at least one ADR was reported in 833 (22.1%) subjects, with the majority of ADRs (75.6%) being judged as mild or moderate. The most frequently reported ADRs were intermenstrual bleeding (7.7% of all analysed subjects), headache (5.1%) and breast pain (2.7%). Spotting and breakthrough bleeding (defined as slight and heavier intermenstrual bleeding) at baseline were reported by 677 (18.0%) and 268 (7.1%) subjects, but were less frequent in cycles 10–13 (9.6% and 1.7%, respectively).

Before study start, 61.8% of subjects suffered from dysmenorrhea, with the intensity being moderate or severe in 66.9% of these subjects. In cycles 10–13, the corresponding values were noted in 15.0% and 25.6% of subjects. The proportion of subjects who suffered from acne decreased from 46.5% at

study entry to 14.9% after 13 medication cycles. More than 50% of the subjects who had switched from another oral contraceptive (OC) pill stated that the tolerability of EE 0.03 mg/CMA 2 mg and their health-related well-being were much better or better after two cycles of EE 0.03 mg/CMA 2 mg than when they were taking their previous OC, and about 85% of the subjects assessed the tolerability of EE 0.03 mg/CMA 2 mg as very good or good during the study.
Conclusion: These results re-affirmed the favourable ADR profile of the COC EE 0.03 mg/CMA 2 mg, as well as its good cycle control and beneficial effects on dysmenorrhoea, complaints typically occurring during the cycle, acne and well-being.

Introduction

Belara® (Grünenthal GmbH, Aachen, Germany) is a monophasic hormonal combined oral contraceptive (COC) containing ethinylestradiol (EE) 0.03 mg and chlormadinone acetate (CMA) 2 mg per tablet. The special feature of this COC is the combination of the low dose of estrogen with CMA, which is derived from progesterone. EE 0.03 mg/CMA 2 mg has been marketed since 1999, and its safety profile, tolerability and anti-androgenic properties have been explored in several clinical[1,2] and post-marketing surveillance studies.[3-5]

Clinical signs of androgenization such as acne and hair loss[6] may have a pronounced negative impact on the general well-being of a woman. COCs with anti-androgenic properties have proved to be a useful approach in minimizing the effects of androgen-related skin changes.[7,8] CMA is a progestin (progesterone congener) with anti-androgenic activity that can contribute to the reduction of dermal manifestations of androgenization.[9-14] As an anti-androgenic progestin, CMA does not counteract an EE-induced increase in sex hormone-binding globulin and the correlated decrease in free testosterone.[14] Other anti-androgenic mechanisms of CMA result from the down-regulation of androgen receptors and inhibition of 5-α-reductase type I, which in turn reduce the conversion of testosterone into dihydrotestosterone.[10,15-17] Although CMA is like progesterone in that it is anti-estrogenic, it also differs from progesterone in having slight corticosteroid and no anti-mineralocorticoid effects. In humans, CMA has been shown to have no pregnancy-maintaining effects.[15]

A study by Worret et al.[13] evaluated the efficacy of EE 0.03 mg/CMA 2 mg for the treatment of mild to moderate papulopustular acne of the face and acne-related disorders in comparison to an EE/levonorgestrel-containing pill (Microgynon®, Bayer Schering Pharma AG, Berlin, Germany). 199 female subjects with acne were enrolled, and for 59.4% of the women taking EE 0.03 mg/CMA 2 mg and 45.9% taking EE/levonorgestrel the number of papules/pustules present on admission had decreased by at least 50% in the twelfth medication cycle. The relative frequency of women with complete resolution at cycle 12 was 16.5% and 4.3%, respectively. Similarly, in a study of 377 women, there was a significantly higher response in moderate papulopustular acne in women taking EE 0.03 mg/CMA 2 mg (64.1%) compared with placebo (43.7%) after six medication cycles.[1] Improvements in several facial skin disorders were also evaluated during six cycles of treatment of acne-prone skin with EE 0.03 mg/CMA 2 mg in 44 women.[2] Significant reductions in numbers of acne lesions, seborrhoea and pore size were observed.

The acceptance of COCs is also closely related to their cycle stability and occurrences of inconvenient intermenstrual bleeding,[18] which may lead to method discontinuation. It is well documented that spotting and breakthrough bleeding may initially occur either after starting oral contraceptives (OCs) or switching to another preparation.[19,20] In a 6-month study, 19 650 subjects

taking EE 0.03 mg/CMA 2 mg were surveyed.[3] In addition to excellent contraceptive efficacy (adjusted Pearl Index [PI] 0.076), cycle control was good, with beneficial reductions in intermenstrual bleeding, amenorrhoea, severe withdrawal bleeding and dysmenorrhoea. After the six cycles of EE 0.03 mg/CMA 2 mg, which were well tolerated, androgen-related skin disorders were improved in 86.5% of the subjects. After a 12-cycle observation period monitoring 2620 subjects, 61.7% of the subjects with intermenstrual bleeding and 89.3% with amenorrhoea at study entry reported complete relief.[4]

When Schramm and Heckes[5] evaluated 16 781 subjects who switched from another COC to EE 0.03 mg/CMA 2 mg, the most frequently mentioned complaint cited as a reason for switching contraceptives was seborrhoea/acne (41.3%), followed by cycle irregularities (18.8%), headache (15.9%) and breast tenderness (15.1%). After four cycles of EE 0.03 mg/CMA 2 mg, these complaints had either decreased substantially or even disappeared in a large number of women. The vast majority of participants scored both the tolerability of EE 0.03 mg/CMA 2 mg and their well-being as very good or good and 80.5% of the subjects stated they were more or much more satisfied with EE 0.03 mg/CMA 2 mg than with the previously used contraceptive.

The long-term efficacy and tolerability of EE 0.03 mg/CMA 2 mg were assessed in 781 women who already had taken EE 0.03 mg/CMA 2 mg for 24 cycles, and were continuing for up to another 45 cycles.[21] Regular withdrawal bleeding in each cycle was reported for approximately 86% of women and only 4% of women reported amenorrhoea. There was a reduction in the incidence of acne (from 13.8% to 5.7%), and rates of hirsutism, alopecia and seborrhoea remained low (≤4%) throughout the study. Lastly, in 45 subjects the effects of two monophasic OCs containing EE, i.e. EE 0.03 mg/CMA 2 mg and EE 0.03 mg/desogestrel 0.15 mg (Marvelon®, N.V. Organon, Oss, the Netherlands), on lipids, hormones and other relevant metabolic parameters were compared.[22] After 6 months of treatment, both of these low-dose monophasic OCs had comparable effects on lipid, hormone and metabolic parameters. A beneficial effect on atherogenic cardiovascular risk markers was apparent and this was slightly more pronounced with EE 0.03 mg/CMA 2 mg.

The aim of the current study was to corroborate the long-term safety of Belara® by evaluating the incidence and severity of adverse drug reactions (ADRs) and the overall cycle stability during long-term use of EE 0.03 mg/CMA 2 mg (13 treatment cycles) in a daily-practice setting. Additionally, the influence of EE 0.03 mg/CMA 2 mg on dysmenorrhoea, androgenic symptoms (e.g. skin and hair disorders), cycle-associated complaints and health-related well-being, as well as the overall tolerability of this COC from the users' perspective, were evaluated.

Subjects and Methods

Study Subjects and Design

This non-interventional study was conducted between April 2006 and August 2008 in 236 gynaecological practices throughout France, Italy and Spain. The study protocol was approved by independent ethics committees and conducted according to the regulations in force in each of the participating countries and the Declaration of Helsinki. All subjects gave written informed consent before enrolment.

Belara® was prescribed according to the clinical judgement of gynaecologists in routine clinical practice to women of reproductive age who were aged ≥18 years. As per conventional use, each woman took one EE 0.03 mg/CMA 2 mg tablet on days 1–21 of the cycle, followed by a 7-day pill-free interval, for up to 13 cycles. The women were classified as 'starters' if they had never used an OC before taking EE 0.03 mg/CMA 2 mg in this study or had at least a 3-month break after the intake of the last previously used hormonal contraceptive. The women were classified as 'switchers' if they had changed directly from another hormonal contraceptive to EE 0.03 mg/CMA 2 mg with a break in administration of less than 3 months.

Evaluation and Efficacy Criteria

At baseline, the following parameters were documented: age, bodyweight, tobacco consumption,

medical history, contraceptive history, dermatological disorders, menstrual cycle history (last three cycles before EE 0.03 mg/CMA 2 mg intake), cycle-associated complaint (e.g. headache, breast pain, tiredness) and health-related well-being.

At each visit, the investigators recorded the ADRs, cycle control (occurrence of intermenstrual bleeding [spotting/breakthrough bleeding], withdrawal bleeding and its intensity, and occurrence of dysmenorrhoea), regular intake and premature withdrawal of EE 0.03 mg/CMA 2 mg, bodyweight change, changes in skin and hair condition, tolerability, health-related well-being and the wish to continue with EE 0.03 mg/CMA 2 mg treatment. Spotting and breakthrough bleeding were defined as slight and heavier intermenstrual bleeding, respectively. Thus, the occurrence of either spotting or breakthrough bleeding separately or both was defined as intermenstrual bleeding.

Dermatological conditions were graded on a four-point scale ranging from 'dry' to 'very greasy' for skin and hair conditions and from 'no' to 'severe' for acne and hair loss. Tolerability and health-related well-being were rated as 'very good', 'good', 'moderate' or 'poor' by both the gynaecologist and the subject.

Subjects were also asked about the occurrence and intensity of any cycle-associated complaints. Investigators asked subjects about breast tenderness, decreased libido, depressed mood, headache, premenstrual syndrome and tiredness. Subjects were required to rate all symptoms as 'not present', 'slight', 'moderate' or 'severe'.

Contraceptive efficacy was evaluated by calculating the PI (PI = [number of pregnancies × 13 × 100]/number of treatment cycles). In the event that a subject stopped taking EE 0.03 mg/CMA 2 mg before the end of the observation period, the investigator recorded the last intake cycle and reason for withdrawal.

As this was a non-interventional study, follow-up examinations of subjects were not anticipated, regardless of whether subjects terminated the study prematurely or at the end of the 13-week observation period. Serious ADRs were followed up until study termination or definite outcome. All pregnancies were documented on a pregnancy reporting form with all available information and followed up to determine the outcome at least 3 months post-parturition.

Statistical Analysis

All data for subjects included in the study were analysed by standard descriptive statistics or by absolute and relative frequencies as appropriate. All analyses were exploratory and no confirmatory statistical analysis was performed.

The unadjusted PI included all pregnancies during the study; pregnancies were excluded from calculation of the adjusted PI if not all active tablets were taken or vomiting or diarrhoea occurred. A two-sided 95% confidence interval (CI) for the PI was calculated assuming a Poisson distribution for the number of pregnancies observed using the formula presented by Sachs[23] and recommended by Gerlinger et al.[24]

Results

Of 3771 subjects who were treated with EE 0.03 mg/CMA 2 mg and were available for evaluation of safety, 979 (26.0%) subjects withdrew or were withdrawn prematurely (see Premature Termination section). Thus, 2792 (74.0%) of 3771 subjects completed 13 cycles of intake. The 3771 treated subjects accounted for 41 149 cycles of exposure.

Baseline Characteristics

The mean ± SD age of the subjects was 27.1 ± 6.7 years, the mean ± SD bodyweight was 59.7 ± 10.1 kg, and the mean ± SD body mass index (BMI) was 22.3 ± 3.6 kg/m^2. A total of 1163 (30.8%) subjects were smokers. At admission, 2785 (73.9%) subjects were defined as starters and 904 (24.0%) as switchers, and information on 82 (2.2%) subjects was missing. The most common previously used contraceptive in all age groups was the OC pill, except in subjects aged 18–20 years, who used alternative forms of contraception (e.g. condom, vaginal cap) more frequently. Reasons for discontinuation of previous OCs were ADRs in 687 (18.2%) of 3771 subjects and common complaints during use of an OC in 347 (9.2%) of 3771 subjects.

At baseline, 677 (18.0%) and 268 (7.1%) of 3771 subjects reported spotting or breakthrough bleeding, respectively (table I). Withdrawal bleeding occurred in 3488 (92.5%) subjects within the last three cycles before taking EE 0.03 mg/CMA 2 mg, and its intensity was moderate or severe in almost 60% of the subjects. More than half of the women with dysmenorrhoea reported the intensity as moderate or severe. Acne and hair loss were reported by 46.5% and 43.3%, respectively, of all subjects at baseline. In addition, subjects also reported premenstrual syndrome (44.3%), breast tenderness (43.1%), tiredness (39.4%), headache (34.0%), depressed mood (26.9%) and decreased libido (17.9%).

Table I. Comparison of clinical characteristics of the study population at baseline and after 13 medication cycles of ethinylestradiol 0.03 mg/chlormadinone acetate 2 mg[a]

Clinical characteristic	At baseline (n = 3771)	After 10–13 medication cycles (n = 3237)
Spotting		
Never	3030 (80.4)	2535 (78.3)
Frequent	221 (5.9)	47 (1.5)
Rare	456 (12.1)	262 (8.1)
Not stated	64 (1.7)	393 (12.1)
Breakthrough bleeding		
Never	3428 (90.9)	2785 (86.0)
Frequent	81 (2.1)	5 (0.2)
Rare	187 (5.0)	50 (1.5)
Not stated	75 (2.0)	397 (12.3)
Intensity of withdrawal bleeding		
Slight	1236 (32.8)	1867 (57.7)
Moderate	2006 (53.2)	918 (28.4)
Severe	246 (6.5)	17 (0.5)
Not stated	283 (7.5)	435 (13.4)
Presence of dysmenorrhoea		
Never	1373 (36.4)	2348 (72.5)
Rare	1117 (29.6)	379 (11.7)
Frequent	1216 (32.2)	107 (3.3)
Missing	65 (1.7)	403 (12.4)
Intensity of dysmenorrhoea		
Slight	773 (33.1)	362 (74.5)
Moderate	944 (40.5)	113 (23.3)
Severe	615 (26.4)	11 (2.3)
Not stated	1 (0.0)	0 (0.0)
Acne		
No	2015 (53.4)	2580 (79.7)
Slight	1122 (29.8)	422 (13.0)
Moderate	553 (14.7)	52 (1.6)
Severe	77 (2.0)	9 (0.3)
Not stated	4 (0.1)	174 (5.4)
Hair loss		
No	2133 (56.6)	2468 (76.2)
Slight	971 (25.7)	482 (14.9)
Moderate	521 (13.8)	99 (3.1)
Severe	143 (3.8)	13 (0.4)
Not stated	3 (0.1)	175 (5.4)

a Data are given as number (%) of subjects.

Adverse Drug Reactions

At least one ADR was reported for 833 (22.1%) of 3771 subjects in this study. The number of subjects with ADRs diminished steadily from 11.1% in cycle 1 to 0.7% in cycle 9. Thereafter, the level of reported ADRs remained almost constant throughout the remaining five medication cycles (0.5–0.8%). This decrease in ADRs over time was also seen in the stratification of results by 'starter' or 'switcher'.

The most frequently reported ADR was intermenstrual bleeding, with 290 (7.7%) of 3771 subjects reporting 404 events (table II). The intensity of 75.6% of ADRs was mild or moderate (1368 of 1809), whilst the intensity of 24.3% (439) was severe. Half of all ADRs did not require any countermeasure (904 [50.0%]). At the final examination, most ADRs (1268 [70.1%]) were reported as having been resolved or as resolving. There were 723 (40.0%) ADRs that led to premature study discontinuation in 382 (10.1%) subjects. During this study, two serious ADRs (one cholelithiasis and one lower limb thrombosis) were reported. In the subject with cholelithiasis, a cholecystectomy was performed and the subject recovered without sequelae. The thrombosis was resolved in the subject with lower limb thrombosis.

Premature Termination

Of the 3771 subjects, 979 (26.0%) stopped taking EE 0.03 mg/CMA 2 mg before the end of the 13-cycle observation period. There were 244 (6.5%) subjects who withdrew prematurely during the first two cycles, 291 (7.7%) who stopped

Table II. Frequency of adverse drug reactions (ADRs) and number of subjects with ADRs (≥0.5% of subjects)[a]

Preferred term	No. (%) of subjects [n = 3771]	No. of events
Any ADR	833 (22.1)	1809
Intermenstrual bleeding	290 (7.7)	404
Headache	193 (5.1)	252
Breast pain	102 (2.7)	130
Breast discomfort	90 (2.4)	95
Weight increased	85 (2.3)	86
Libido decreased	74 (2.0)	78
Nausea	58 (1.5)	72
Acne	56 (1.5)	59
Dysmenorrhoea	56 (1.5)	68
Fatigue	39 (1.0)	40
Premenstrual syndrome	39 (1.0)	40
Depressed mood	35 (0.9)	36
Menstruation irregular	25 (0.7)	26
Menorrhagia	19 (0.5)	21
Withdrawal bleeding irregular	19 (0.5)	25
Vomiting	18 (0.5)	28

a As coded by preferred terms from Medical Dictionary for Regulatory Activities, version 11.0.

treatment during cycles 3–5, and 419 (11.1%) who withdrew during cycles 6–13. For the remaining 25 subjects, no further information was available. EE 0.03 mg/CMA 2 mg was discontinued for non-ADR reasons by 597 (15.8%) of 3771 women, including 82 (8.4%) women who wanted to become pregnant. Of the 382 (10.1%) of 3771 subjects who discontinued treatment due to an ADR, the main reasons were common complaints during use of an OC, i.e. headache (2.1%), intermenstrual bleeding (1.5%) and breast pain (1.3%). The reason for termination of study participation in 180 (4.8%) of 3771 subjects was irregular bleeding.

Cycle Control

There were 867 (23.0%) of 3771 subjects who reported that their cycle was irregular before starting intake of EE 0.03 mg/CMA 2 mg and this number decreased to 39 (1.2%) of 3237 in cycles 10–13. A similar decrease was observed for starters and switchers. Intermenstrual bleeding, both spotting and breakthrough bleeding, was most common during the first treatment cycles; thereafter, its incidence decreased substantially (figure 1). In cycles 10–13, spotting occurred in 309 (9.6%) of 3237 subjects, while breakthrough bleeding was reported by 55 (1.7%) of 3237 subjects.

When analysed by previous use of OCs, the overall frequencies of spotting, breakthrough bleeding and absence of withdrawal bleeding were similar in starters and switchers, with an overall difference of less than 9%.

At baseline, 206 (5.5%) of 3771 subjects reported absence of withdrawal bleeding before starting intake of EE 0.03 mg/CMA 2 mg, and between 91 (2.6%) of 3454 and 64 (2.0%) of 3237 subjects reported absence of withdrawal bleeding at different cycles during intake. Withdrawal bleeding remained similar throughout the study, occurring in 2782 (85.9%) of 3237 subjects in cycles 10–13.

At baseline, the intensity of withdrawal bleeding was slight to moderate for 3242 (86.0%) of the 3771 subjects, and this remained the case in about 90% of subjects during intake of EE 0.03 mg/CMA 2 mg. The number of subjects with severe withdrawal bleeding decreased from 246 (6.5%) of 3771 subjects at baseline to 17 (0.5%) of 3237 subjects after 13 medication cycles. The mean duration of withdrawal bleeding, which was 4.5 days at baseline, decreased during intake of EE 0.03 mg/CMA 2 mg to 3.7 days by the end of the treatment period.

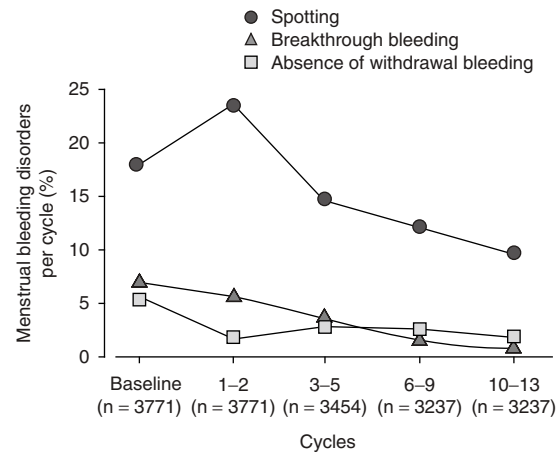

Fig. 1. Menstrual bleeding disorders per cycle during intake of ethinylestradiol 0.03 mg/chlormadinone acetate 2 mg.

Dysmenorrhoea

During the study, the percentage of subjects reporting (rare or frequent) dysmenorrhoea decreased from 2333 (61.8%) of 3771 subjects at baseline to 486 (15.0%) of 3237 of subjects in cycles 10–13. At baseline, the intensity of dysmenorrhoea was slight to moderate in 1717 (73.6%) of 2333 subjects suffering from dysmenorrhea, while at cycles 10–13, the same was reported by 475 (97.8%) of 486 subjects. The percentage of subjects suffering from severe dysmenorrhea decreased from 26.4% (615 of 2333 subjects) to 2.3% (11 of 486 subjects). In parallel, the mean number of subjects who used pain medication for dysmenorrhoea decreased from 1736 (74.4%) of 2333 subjects at baseline to 209 (43.0%) of 486 subjects in cycles 10–13. Additionally, the mean number of subjects who were absent from work or school due to this complaint decreased over time from 25.7% to 3.3%.

At baseline, dysmenorrhoea was reported more frequently for starters than for switchers (66.6% vs 48.2%). In both subgroups, its occurrence decreased during intake of EE 0.03 mg/CMA 2 mg and by the end of the study only 366 (15.1%) of 2421 starters and 139 (18.7%) of 742 switchers suffered from dysmenorrhoea.

Effects on Skin and Hair

At baseline, normal skin type was documented in 1979 (52.5%) of 3771 subjects and in cycles 10–13 after EE 0.03 mg/CMA 2 mg treatment this had increased to 2467 (76.2%) of 3237 subjects. Likewise, the percentage of subjects with greasy or very greasy skin decreased substantially from 1097 (29.1%) of 3771 subjects at baseline to 210 (6.5%) of 3237 subjects taking EE 0.03 mg/CMA 2 mg. After 13 medication cycles, acne was present in only 483 (14.9%) of 3237 women, compared with 46.5% at baseline.

The evaluation of hair condition during EE 0.03 mg/CMA 2 mg intake showed a reduction in seborrhoeic characteristics. Approximately half of the subjects (2070 [54.9%] of 3771) had normal hair condition at baseline, and this fraction increased to three-quarters (2427 [75.0%] of 3237) after 13 medication cycles. Accordingly, the proportion of subjects with greasy and very greasy hair decreased from 30.2% to 9.2%.

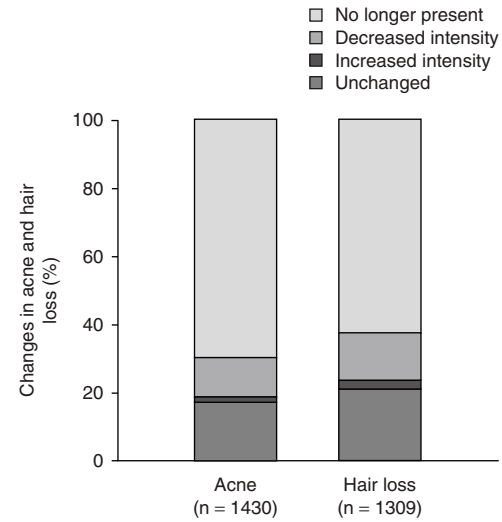

Fig. 2. Changes in acne and hair loss in subjects who had these complaints at baseline and returned after 13 cycles of ethinylestradiol 0.03 mg/chlormadinone acetate 2 mg treatment.

At baseline, 25.7%, 13.8% and 3.8% of subjects reported slight, moderate or severe hair loss, respectively. During intake of EE 0.03 mg/CMA 2 mg, the corresponding proportions in the three groups decreased markedly to 14.9%, 3.1% and 0.4%, respectively. In 69.9% and 63.1% of subjects with acne or hair loss, respectively, at baseline, the problem was no longer present after 13 cycles of EE 0.03 mg/CMA 2 mg treatment (figure 2).

Cycle-Associated Complaints

During the study, the number of subjects with at least one cycle-associated complaint decreased from 2903 (77.0%) of 3771 subjects at baseline to 2401 (63.7%) of 3771 subjects in cycles 1 and 2, and to 1294 (40.0%) of 3237 subjects in cycles 10–13. As before the start of study, the most frequent cycle-associated complaints were breast tenderness, premenstrual syndrome, tiredness and headache.

In cycles 10–13, the majority of cycle-associated complaints were no longer present or were of decreased intensity (figure 3). There were 686

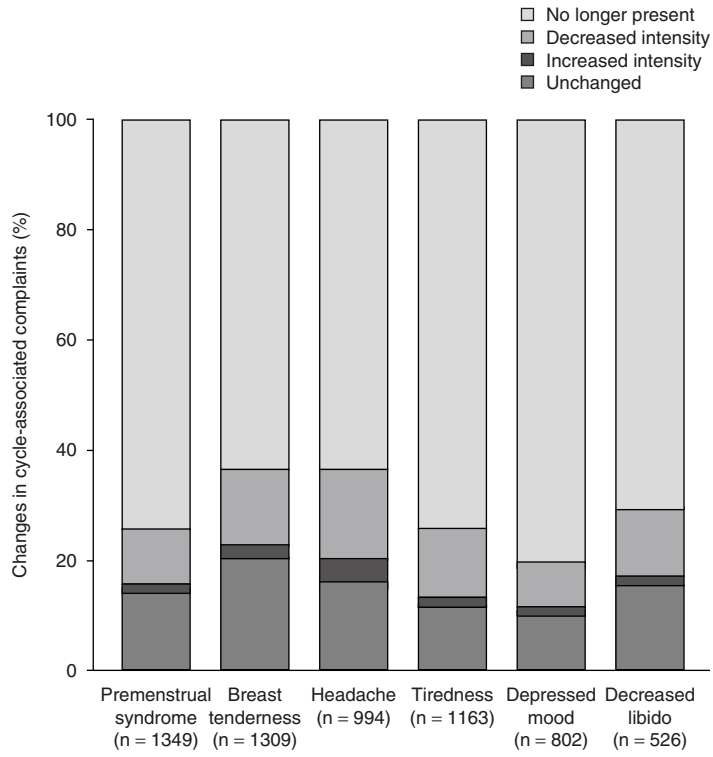

Fig. 3. Changes in cycle-associated complaints in subjects who had these complaints at baseline and returned after 13 cycles of ethinylestradiol 0.03 mg/chlormadinone acetate 2 mg treatment.

(18.2%) of 3771 subjects who complained of moderate or severe premenstrual syndrome before entering the study. After 13 medication cycles, the corresponding number of subjects decreased to 45 (1.4%) of 3237. At baseline, breast tenderness in 662 (17.6%) of 3771 subjects was moderate or severe, and during the study, this number decreased to 98 (3.0%) of 3237 subjects. There were 643 (17.1%) subjects with moderate or severe headache at baseline, compared with 146 (4.5%) subjects after 13 medication cycles. Results for tiredness, depressed mood and decreased libido were also comparable, with a similar pattern of decreased incidences.

The results in the subgroups 'starter' and 'switcher' were comparable to the overall results. There were 2101 (75.4%) of 2785 starters and 754 (83.4%) of 904 switchers who reported one or more cycle-associated complaints before starting EE 0.03 mg/CMA 2 mg intake. After 13 medication cycles, the number of subjects suffering from any cycle-related complaint decreased to 951 (39.3%) of 2421 starters and 324 (43.7%) of 742 switchers, respectively.

Health-Related Well-Being and Tolerability

Health-Related Well-Being

At baseline, 3098 (82.2%) of 3771 subjects judged their health-related well-being as very good or good. During intake of EE 0.03 mg/CMA 2 mg, this increased to 3353 (88.9%) of 3771 subjects in cycles 1 and 2, and to 3115 (90.2%) of 3454 subjects in cycles 3–5. After 13 medication cycles, the percentage of subjects (2879 [88.9%] of 3237) with very good or good health-related well-being remained almost unchanged. Correspondingly, the number of subjects with a self-assessment of moderate or poor health-related well-being decreased from 673 (17.8%) of 3771 subjects at baseline to

200 (6.2%) of 3237 subjects at the end of 13 medication cycles.

Assessing the effects in starters and switchers revealed that the latter group received a greater benefit with respect to their well-being. At baseline, 2394 (86.0%) of 2785 starters assessed their health-related well-being as very good or good, while 2191 (90.5%) of 2421 subjects reported the same after 13 cycles of EE 0.03 mg/CMA 2 mg. The corresponding values for switchers were 637 (70.5%) of 904 subjects and 620 (85.6%) of 724 subjects, respectively.

There were 2151 subjects who had taken another OC before entering the study. When these subjects were asked after the first two cycles of EE 0.03 mg/CMA 2 mg intake to assess the tolerability of the medication and their well-being, 1234 (57.4%) subjects stated that both aspects were much better or better in comparison with the previous OC. The proportions of subjects who stated that tolerability and well-being were unchanged and worse were 31.9% and 8.5%, respectively.

After completing the study period of 13 medication cycles, 2395 (63.5%) of 3771 subjects expressed a wish to continue with EE 0.03 mg/CMA 2 mg, while 393 (10.4%) discontinued its use.

Tolerability

When assessed by either investigators or subjects, the tolerability of EE 0.03 mg/CMA 2 mg intake was good throughout the study. There were 3188 (84.5%) of 3771 subjects who reported that the tolerability of EE 0.03 mg/CMA 2 mg was good or very good after two medication cycles, and this proportion remained similar in cycles 6–9 and 10–13 (87.1% and 86.3%, respectively). Similarly, the investigators assessed the tolerability of EE 0.03 mg/CMA 2 mg as good or very good in 87.4% of subjects in cycles 1 and 2, 89.8% of subjects in cycles 6–9, and 88.6% of subjects in cycles 10–13. Stratification by subgroups 'starters' or 'switchers' showed a similar pattern to the overall results.

Contraceptive Efficacy

A total of six pregnancies occurred during these 13 medication cycles in 3771 subjects taking EE 0.03 mg/CMA 2 mg. An unadjusted PI of 0.19 (95% CI 0.07, 0.41) was calculated for 41 149 analysable medication cycles. However, as intake errors were deemed to be responsible for 50% of the undesired pregnancies, only three pregnancies were considered method failures. Thus, an adjusted PI of 0.09 (95% CI 0.02, 0.28) was obtained for 41 130 medication cycles with perfect use.

Vital Signs, Bodyweight and Body Mass Index

At baseline, the mean systolic and diastolic blood pressures were 113.4 mmHg and 68.7 mmHg, respectively. Both remained similar at all visits during the study. The mean heart rate at baseline was 74.0 beats/min, which also remained unchanged during the study. Only minor changes in bodyweight and BMI were observed during the study. At baseline, the mean ± SD bodyweight was 59.7 ± 10.1 kg and the mean ± SD BMI was 22.3 ± 3.6 kg/m^2; after 13 medication cycles, the corresponding values were 60.3 ± 10.2 kg and 22.5 ± 3.7 kg/m^2, respectively.

Discussion

The study population (in terms of age distribution, proportion of smokers/non-smokers and starters/switchers) was considered to be representative of OC users and the non-interventional study design reflected routine gynaecological practice. In the measured parameters, there were no significant differences between overall results for the entire study population and stratification by OC switcher or starter.

The subjective determination of beneficial effect on skin and hair conditions and the recording of data retrospectively could be deemed as weaknesses of this study. However, its major strength is the presentation of long-term results for more than 3000 subjects, a large subject population followed over 13 cycles. In addition, it should be emphasized that this study reflects 'real-life use' as it was set in a routine clinical practice setting.

Adverse Drug Reactions and Tolerability

The profile of reported ADRs during intake of EE 0.03 mg/CMA 2 mg in this study was comparable

with that seen with other COCs[18,19,25-27] and in previous studies of EE 0.03 mg/CMA 2 mg.[4,21] In accordance with these published results, the most frequently reported ADRs in the current study were intermenstrual bleeding, headache and breast pain.

Likewise, as reported for other COCs[28,29] and in previous studies of EE 0.03 mg/CMA 2 mg,[4,5] the incidence of ADRs in this study was highest in the first cycle, decreasing with subsequent cycles during continuous use of EE 0.03 mg/CMA 2 mg. The incidences and intensities of all specifically enquired about cycle-associated complaints (breast tenderness, decreased libido, depressed mood, headache, premenstrual syndrome and tiredness) also decreased during intake of EE 0.03 mg/CMA 2 mg in comparison with those at study entry.

At least one ADR was reported for 22.1% of subjects taking EE 0.03 mg/CMA 2 mg for up to 13 medication cycles. Approximately three-quarters of ADRs reported in this study were of mild or moderate intensity, and 70.1% of all ADRs had been resolved by the end of the study. For various reasons, 26.0% of subjects terminated the study prematurely. Only 10.1% of 3771 subjects discontinued participation because of ADRs, suggesting that the ADR profile of EE 0.03 mg/CMA 2 mg was acceptable to most subjects.

In this study, the reasons that led to discontinuation of the previous OC given by subjects before starting intake of EE 0.03 mg/CMA 2 mg were similar to those given by subjects for discontinuation of EE 0.03 mg/CMA 2 mg during the period of 13 medication cycles. Comparison of the ADR rate for discontinuation of intake indicated that the tolerability profile of EE 0.03 mg/CMA 2 mg was more favourable (10.1% for EE 0.03 mg/CMA 2 mg vs 18.2% for previous OC). After completing the study period of 13 medication cycles, 10.4% of the subjects discontinued intake of EE 0.03 mg/CMA 2 mg. Comparable overall discontinuation rates can be found with two other COCs: 30% for the combination of EE 0.03 mg/desogestrel 0.15 mg[30] and 33% for the combination containing EE 0.03 mg/drospirenone 3 mg.[20]

Similar to results observed in the study by Schramm and Steffens,[3] a high number of subjects in the current study (approximately two-thirds) expressed a wish to continue intake of EE 0.03 mg/CMA 2 mg after the surveillance period of 13 medication cycles. This correlates with more than 80% of subjects judging their health-related well-being and tolerability of EE 0.03 mg/CMA 2 mg as being very good or good. Correspondingly, investigators assessed the tolerability of EE 0.03 mg/CMA 2 mg in more than 85% of subjects as being very good or good. Even during the first two medication cycles with EE 0.03 mg/CMA 2 mg, more than half of the subjects who had used an OC before study entry judged their health-related well-being and tolerability of EE 0.03 mg/CMA 2 mg as being much better or better than when taking the previous contraceptive pill.

There was a marginal mean bodyweight increase of 0.6 kg during the 13 medication cycles with EE 0.03 mg/CMA 2 mg. However, this mean increase of less than 1 kg, in relation to the length of the study period, may reflect the normal range of bodyweight fluctuations. Additionally, similar bodyweight changes have been observed in other studies of COCs,[19,31,32] and in previous studies investigating EE 0.03 mg/CMA 2 mg during long-term use.[21] There was no relevant influence of EE 0.03 mg/CMA 2 mg on heart rate or blood pressure.

Cycle Control

The intensity of withdrawal bleeding decreased during intake of EE 0.03 mg/CMA 2 mg. There was a 6% and 24.8% decrease in the number of subjects experiencing severe and moderate withdrawal bleeding, respectively, when compared with incidences at baseline and after 13 medication cycles of EE 0.03 mg/CMA 2 mg. During the study, a shortening of duration of withdrawal bleeding was observed, with the mean duration decreasing from 4.5 days at baseline to 3.7 days after 13 medication cycles. Withdrawal bleeding was absent during intake of EE 0.03 mg/CMA 2 mg in less than 3% of subjects (compared with 5.5% at baseline).

As also seen in other studies investigating long-term use of COCs,[19,33] the incidence of spotting and breakthrough bleeding during this study decreased with the continued use of EE

0.03 mg/CMA 2 mg. Spotting was more frequent in the first two medication cycles than at baseline but decreased in the following medication cycles from 23.1% of subjects in cycles 1 and 2 to 9.6% of subjects in cycles 10–13. However, in all 13 medication cycles with EE 0.03 mg/CMA 2 mg the incidence of breakthrough bleeding was less frequent than at baseline. There was a decrease of 5.4% in the number of subjects who reported breakthrough bleeding when incidences at baseline were compared with those in cycles 10–13.

When Parsey and Pong[20] evaluated the cycle control with a COC containing EE 0.03 mg/drospirenone 3 mg during 13 intake cycles, breakthrough bleeding, spotting and missed withdrawal bleeding were observed in 1%, 9.3% and 3.2% of all cycles, respectively, and the mean duration of withdrawal bleeding was 4–7 days. In another study, breakthrough bleeding was observed in 1.6% of all cycles in a study of a COC containing gestodene 0.075 mg/EE 0.03 mg.[26] Furthermore, a review of nine studies of EE 0.03 mg/desogestrel 0.15 mg reported rates between 2.8% and 11% for spotting and 0.1% and 6% for breakthrough bleeding during six medication cycles.[25] As well as being comparable to the results of the above-mentioned studies, the incidences of breakthrough bleeding, spotting and missed withdrawal bleeding in the current study were also comparable to those reported in previous studies of EE 0.03 mg/CMA 2 mg.[3,4]

Overall, a total of 180 (4.8%) of 3771 subjects terminated study participation due to irregular bleeding, suggesting that cycle control during EE 0.03 mg/CMA 2 mg intake was acceptable to most subjects. Thus, EE 0.03 mg/CMA 2 mg provided good cycle control during long-term use, comparable to that of other COCs.[20,25,26]

Dysmenorrhoea

Many women experience cramps and pelvic pain associated with dysmenorrhoea, beginning shortly before or during the onset of menses. The intensity of dysmenorrhoea, especially when severe, can lead to the restriction of activity and absence from school or work.[34,35]

By inducing lipocortin-1 (annexin-1) synthesis, corticosteroids influence inflammatory events and contractility.[36] In this process, phospholipase A_2 is blocked from synthesizing arachidonic acid from precursor phospholipids. In turn, a decrease in the availability of arachidonic acid might have some beneficial effects as it is known to play an influential role in the pathogenesis of dysmenorrhoea.[15,37] CMA exhibits weak, tissue-specific agonistic binding to the corticosteroid receptor, thus inducing partial phospholipase A_2 blockade.[38] This in turn can cause a reduction in prostaglandin (PG) $F_{2\alpha}$ production, which can decrease uterine contractility, as well reducing the incidence and/or severity of dysmenorrhoea. Moreover, a secondary effect of CMA may be to inhibit cyclo-oxygenase (COX)-2 activity and thereby reduce the conversion of arachidonic acid to the contractile uterine $PGF_{2\alpha}$.[39] These reasons might explain the reduction in dysmenorrhoeic symptoms seen in studies of EE 0.03 mg/CMA 2 mg.

During this study, there was a 46.8% decrease in the number of subjects who suffered from dysmenorrhoea when the incidence at baseline was compared with that in cycles 10–13, and the percentage of subjects reporting (rare or frequent) dysmenorrhoea decreased from 61.8% to 15.0%. The intensity of dysmenorrhoea also decreased during the study with the percentage of subjects suffering from severe dysmenorrhoea decreasing from 26.4% to 2.3%.

In parallel, there was a reduction in the number of subjects who required pain medication for treatment of dysmenorrhoea (from 74.4% to 43.0%), and this was also true for the mean number of subjects who were absent from work or school due to this complaint (a decrease in 22.4% of subjects). Thus, the results of this study confirmed previous results of studies investigating EE 0.03 mg/CMA 2 mg in which this COC appeared to have a positive effect on the symptoms of dysmenorrhoea.[4,5,40]

After a 12-cycle clinical evaluation period, in 836 (66.0%) of 1266 women who suffered from dysmenorrhoea in the last two cycles before the use of EE 0.03 mg/CMA 2 mg, this symptom was no longer present during study treatment and the condition was improved in 13.0% of the women.[4] In a separate study, after switching to EE 0.03 mg/CMA 2 mg for four cycles, dysmenorrhoea was

resolved completely in 1184 (61.1%) of 1939 women.[5] In the current study, more starters than switchers presented with dysmenorrhoea at baseline (66.6% vs 48.2%), although after 13 cycles, there was a substantial reduction in the number of subjects reporting the presence of dysmenorrhoea, regardless of whether they were starters (15.1%) or switchers (18.7%).

In a study by Sabatini et al.,[40] the effects of two formulations containing EE 0.03 mg/CMA 2 mg or EE 0.03 mg/drosperinone 3 mg were compared. Six-month data were obtained from 156 sexually active adolescents requiring contraception. After three cycles with either of the two contraceptives, there was a significant improvement in mild and moderate dysmenorrhoea, although a progressive and significant reduction continued only in the EE 0.03 mg/CMA 2 mg group until the end of the observation period (EE 0.03 mg/CMA 2 mg vs EE 0.03 mg/drosperinone 3 mg: $p < 0.01$). In addition to thinning of the endometrial lining, the close similarity of CMA to progesterone and its effects on corticosteroid receptors and COX-2 activity may explain the beneficial effects of EE 0.03 mg/CMA 2 mg on dysmenorrhoea.

Effects on Skin and Hair

In previous studies, EE 0.03 mg/CMA 2 mg demonstrated remarkably positive effects on acne, seborrhoea and hirsutism.[1,2,5,13,21,41] During the current study, in comparison with 46.5% of subjects at study entry, only 14.9% suffered from acne (including 13.0% with slight acne) after 13 medication cycles. Likewise, there was a 22.6% decrease in the number of subjects with greasy and very greasy skin from baseline to after 13 medication cycles. These findings are similar to results from a post-marketing surveillance study of 21 820 women taking six cycles of EE 0.03 mg/CMA 2 mg treatment.[3] At baseline, more than two-thirds of all study participants had androgen-related skin disorders (15 259 [69.9%]) and these symptoms improved during EE 0.03 mg/CMA 2 mg intake in 13 199 (86.5%) of these women, including 4349 (28.5%) women in whom this condition was no longer present. The proportion of women with greasy or very greasy skin decreased from 24.4% at baseline to 2.5%, and the proportion of women with slightly greasy skin decreased from 34.8% to 21.0%.

In the current study, the number of subjects with normal hair condition increased by 20% from baseline to after 13 medication cycles. In 63.1% of subjects with hair loss at baseline, this problem was no longer present after 13 cycles of EE 0.03 mg/CMA 2 mg treatment. In the study by Schramm and Steffens,[3] after six cycles of EE 0.03 mg/CMA 2 mg treatment, 16 635 (76.2%) subjects reported normal hair condition compared with 43.9% at baseline. The proportion of women with greasy or very greasy hair in parallel improved from 47.0% to 13.6%.

A study with longer follow-up data (12 cycles in 2620 women) demonstrated even greater improvement and normalization of skin and hair conditions.[4] In this study, 85.6% of subjects who previously suffered from papules and pustules and/or seborrhoeic skin conditions showed significant improvement during the observation period. A normal hair type was documented in 76.7% of the women (compared with 41.3% at baseline), and the percentage of women with greasy or very greasy hair decreased from 50.6% at baseline to 11.7% after 12 cycles of EE 0.03 mg/CMA 2 mg.

Acne lesions are known to be caused by increased sebum production and disturbances in hormonal levels. The activity of dermal sebaceous glands can be inhibited by the anti-androgenic CMA as it competes with the body's androgens at androgen receptors.[2] There is an eventual reduction in androgenic secretions caused by suppression of the secretion of gonadotropins from the pituitary gland by CMA and EE.[13,15] This synergistic effect, in turn, could contribute to the improvement in androgen-related symptoms observed during EE 0.03 mg/CMA 2 mg treatment.

Contraceptive Efficacy

This long-term study confirms the reliable contraceptive efficacy of EE 0.03 mg/CMA 2 mg. Six pregnancies occurred during a total of 41 149 medication cycles in 3771 women taking EE 0.03 mg/CMA 2 mg, leading to an unadjusted PI

of 0.19 (95% CI 0.07, 0.41). In three of these six pregnancies, conception occurred at time-points during which the efficacy of EE 0.03 mg/CMA 2 mg was reduced because of intake errors, resulting in an adjusted PI of 0.09 (95% CI 0.02, 0.28).

These results for the adjusted and unadjusted PI for EE 0.03 mg/CMA 2 mg compare favourably with those of other COCs containing EE 0.03 mg, which have reported PIs between 0 and 1.2.[19,29,42-44] In addition, they support the reliable contraceptive efficacy of EE 0.03 mg/CMA 2 mg, as already shown in previous studies.[1,3,21,41]

Conclusion

The results of this non-interventional study investigating EE 0.03 mg/CMA 2 mg (Belara®) in 3771 subjects during long-term use demonstrated that this COC has a favourable ADR profile, provides highly effective contraception and has a good bleeding profile. Additionally, EE 0.03 mg/CMA 2 mg was well tolerated and had beneficial effects on dysmenorrhoea, acne and hair loss as well as complaints associated with the cycle.

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References

1. Plewig G, Cunliffe WJ, Binder N, et al. Efficacy of an oral contraceptive containing EE 0.03 mg and CMA 2 mg (Belara®) in moderate acne resolution: a randomized, double-blind, placebo-controlled phase III trial. Contraception 2009; 80 (1): 25-33
2. Kerscher M, Reuther T, Bayrhammer J, et al. Effects of an oral contraceptive containing chlormadinone and ethinylestradiol on acne-prone skin of women of different age groups: an open-label, single-centre, phase IV study. Clin Drug Investig 2008; 28 (11): 703-11
3. Schramm G, Steffens D. Contraceptive efficacy and tolerability on chlormadinone acetate 2 mg/ethinyl estradiol 0.03 mg (Belara®): results of a post-marketing surveillance trial. Clin Drug Invest 2002; 22 (4): 221-31
4. Schramm G, Steffens D. A 12-month evaluation of the CMA-containing oral contraceptive Belara®: efficacy, tolerability and anti-androgenic properties. Contraception 2003; 67 (4): 305-12
5. Schramm G, Heckes B. Switching hormonal contraceptives to a chlormadinone acetate-containing oral contraceptive. The Contraceptive Switch Study. Contraception 2007; 76 (2): 84-90
6. Mall-Haefeli M. Die Wirkung der Androgene auf das Zyklusgeschehen. In: Loch EG, Schramm G, editors. Chlormadinonacetat bei Androgenisierungserscheinungen. Stuttgart: Schattauer, 1995: 42-55
7. Kaiser E. Action of a new hormonal contraceptive (Neo-Eunomin®) on androgenisation of the skin in women. Geburtshilfe Frauenheilkd 1984; 44: 651-5
8. Carlborg L. Cyproterone acetate versus levonorgestrel combined with ethinyl estradiol in the treatment of acne. Acta Obstet Gynecol Scand 1986; 134 Suppl.: 29-32
9. Breckwoldt M, Zahradnik HP, Wiecker P. Hirsutismus. In: Orfanos CE, Happle R, editors. Hair and hair diseases. Berlin: Springer, 1990: 777-89
10. Luderschmidt C. Akne der Frau: eine interdisziplinäre Herausforderung. In: Loch EG, Schramm G, editors. Chlormadinonacetat bei Androgenisierungserscheinungen. Stuttgart: Schattauer, 1995: 57-76
11. Kuhl H. Comparative pharmacology of newer progestogens. Drugs 1996; 51 (2): 188-215
12. Rabe T, Kowald A, Ortmann J, et al. Inhibition of skin 5 alpha-reductase by oral contraceptive progestins in vitro. Gynecol Endocrinol 2000; 14 (4): 223-30
13. Worret I, Arp W, Zahradnik HP, et al. Acne resolution rates: results of a single-blind, randomized, controlled, parallel phase III trials with EE/CMA (Belara®), EE/LNG (Microgynon). Dermatology 2001; 203 (1): 38-44
14. Raudrant D, Rabe T. Progestogens with antiandrogenic properties. Drugs 2003; 63 (5): 463-92
15. Druckmann R. Profile of the progesterone derivative chlormadinone acetate: pharmacodynamic properties and therapeutic applications. Contraception 2009; 79(4): 272-81
16. Gerstmann BB, Piper JM, Tomita DK, et al. Oral contraceptive estrogen dose and the risk of deep venous thromboembolic disease. Am J Epidemiol 1991; 133 (1): 32-7
17. Kuhl H. Chemie und Pharmakologie von Chlormadinonacetat. In: Loch EG, Schramm G, editors. Chlormadinonacetat bei Androgenisierungserscheinungen. Stuttgart: Schattauer, 1995: 1-12
18. Rosenberg MJ, Waugh MS. Oral contraceptive discontinuation: a prospective evaluation of frequency and reasons. Am J Obstet Gynecol 1998; 179: 577-82
19. Akerlund M, Rode A, Westergaard J. Comparative profiles of reliability: cycle control and side effects of two oral contraceptive formulations containing 150 micrograms desogestrel and either 30 micrograms or 20 micrograms ethinyl oestradiol. Br J Obstet Gynaecol 1993; 100 (9): 832-8
20. Parsey KS, Pong A. An open-label, multicenter study to evaluate Yasmin, a low-dose combination oral contraceptive containing drospirenone, a new progestogen. Contraception 2000; 61 (2): 105-11

21. Zahradnik HP, Hanjalic-Beck A. Efficacy, safety and sustainability of treatment continuation and results of an oral contraceptive containing 30 mcg ethinyl estradiol and 2 mg chlormadinone acetate, in long-term usage (up to 45 cycles): an open-label, prospective, noncontrolled, office-based phase III study. Contraception 2008; 77 (5): 337-43
22. Winkler UH, Sudik R. The effects of two monophasic oral contraceptives containing 30 mcg of ethinyl estradiol and either 2 mg of chlormadinone acetate or 0.15 mg of desogestrel on lipid, hormone and metabolic parameters. Contraception 2009; 79 (1): 15-23
23. Sachs L. Angewandte Statistik: Statistische Methoden und ihre Anwendung. Berlin, Heidelberg, New York: Springer, 1978
24. Gerlinger C, Endrikat J, van der Meulen EA, et al. Recommendation for confidence interval and sample size calculation for the Pearl Index. Eur J Contracept Reprod Health Care 2003; 8 (2): 87-92
25. Fotherby K. Twelve years of clinical experience with an oral contraceptive containing 30 micrograms ethinyloestradiol and 150 micrograms desogestrel. Contraception 1995; 51 (1): 3-12
26. Endrikat J, Müller U, Düsterberg B. A twelve-month comparative clinical investigation of two low dose oral contraceptives containing 20 micrograms ethinyl estradiol/75 micrograms gestodene and 30 micrograms ethinyl estradiol/75 micrograms gestodene, with respect to efficacy, cycle control, and tolerance. Contraception 1997; 55 (3): 131-7
27. Foidart JM, Wuttke W, Bouw GM, et al. A comparative investigation of contraceptive reliability, cycle control and tolerance of two monophasic oral contraceptives containing either drospirenone or desogestrel. Eur J Contracept Reprod Health Care 2000 Jun; 5 (2): 124-34
28. Gollnick H, Albring M, Brill K. The efficacy of oral cyproterone acetate in combination with ethinyloestradiol in acne tarda of the facial type. Ann Endocrinol (Paris) 1999 Sep; 60 (3): 157-66
29. Huber J, Foidart JM, Wuttke W, et al. Efficacy and tolerability of a monophasic oral contraceptive containing ethinyl estradiol and drospirenone. Eur J Contracept Reprod Health Care 2000; 5 (1): 25-34
30. Akerlund M. Clinical experience of a combined oral contraceptive with very low dose ethinyl estradiol. Acta Obstet Gynecol Scand Suppl. 1997; 164: 63-5
31. Vartiainen M, de Gezelle H, Broekmeulen CJ. Comparison of the effect on acne with a combiphasic desogestrel-containing oral contraceptive and a preparation containing cyproterone acetate. Eur J Contracept Reprod Health Care 2001; 6 (1): 46-53
32. Gallo MF, Lopez LM, Grimes DA, et al. Combination contraceptives: effects on weight (review). Cochrane Database Syst Rev 2006; (2): 1-72
33. Rosenberg MJ, Long SC. Oral contraceptives and cycle control: a critical review of the literature. Adv Contracept 1992; 8 Suppl. 1: 35-45
34. Archer DF. Menstrual-cycle related symptoms: a review of the rationale for continuous use of oral contraceptives. Contraception 2006; 74: 359-66
35. Proctor M, Farquhar C. Diagnosis and management of dysmenorrhoea. BMJ 2006; 332 (7550): 1134-8
36. Goppelt-Struebe M, Wolter D, Resch K. Glucocorticoids inhibit prostaglandin synthesis not only at the level of phospholipase A2 but also at the level of cyclo-oxygenase/PGE isomerase. Br J Pharmacol 1989; 98 (4): 1287-95
37. Hanjalic-Beck A, Schäfer WR, Fischer L, et al. Ex vivo and in vitro assays for testing progestogenic effects on endometrial phospholipid-/arachidonic-acid metabolism [abstract]. Presented at the 8th Congress of the European Society of Gynecology, Rome; 2009 Sep 10-13
38. Zahradnik HP. Progestogen and endometrial regulation: theoretical and clinical considerations [abstract]. Presented at the 13th World Congress of Gynecological Endocrinology, Florence; 2008 Feb 28–Mar 2
39. Zahradnik HP. Symposium Grunenthal, Gynovatoins 2008. Monaco 1998; 57 (2): 103-9
40. Sabatini R, Orsini G, Cagniano R, et al. Noncontraceptive benefits of two combined oral contraceptives with antiandrogenic properties among adolescents. Contraception 2007; 76 (5): 342-7
41. Zahradnik HP, Goldberg J, Andreas JE. Efficacy and safety of new antiandrogenic oral contraceptive Belara®. Contraception 1998; 57 (2): 103-9
42. Corson SL. Efficacy and clinical profile of a new oral contraceptive containing norgestimate. Acta Obstet Gynecol Scand 1990; 152 Suppl.: 25-31
43. Speroff L, DeCherny A, Advisory board for the new progestin. Evaluation of a new generation of oral contraceptives. Obstet Gynecol 1993; 81: 1034-47
44. Runnebaum B, Rabe T. In: Gynäkologische endokrinologie. Berlin, Heidelberg, New York: Springer, 1994: 412-53

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