

Acne Resolution Rates: Results of a Single-Blind, Randomized, Controlled, Parallel Phase III Trial with EE/CMA (Belara®) and EE/LNG (Microgynon®)

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Key Words

Ethinylestradiol · Chlormadinone acetate · Levonorgestrel · Oral contraceptive · Acne · Androgenization

Abstract

Background and Objective: Acne in women can often be successfully treated by the intake of oral contraceptives containing gestagens with anti-androgenic properties. This study aimed to evaluate the efficacy of the monophasic oral contraceptive ethinylestradiol/chlormadinone acetate (EE/CMA; Belara®) for the treatment of mild to moderate papulopustular acne of the face and acne-related disorders in comparison to EE/levonorgestrel (LNG; Microgynon®). **Methods:** 199 female acne patients were enrolled in a single-blind, randomized, multicentre phase III study and divided into two groups who received either EE/CMA or EE/LNG. The primary end point was fulfilled if the number of papules/pustules per half of the face present on admission had decreased by at least 50% in the 12th medication cycle. **Results:** 59.4% of the women under EE/CMA and 45.9% under EE/LNG were responders. The relative frequency of women with complete resolution was 16.5% under EE/CMA and 4.3% under EE/LNG at cycle 12. **Conclusion:** EE/CMA is an efficient treatment for women with mild and moderate papulopustular acne of the face and related disorders,

reflecting the well-known anti-androgenic properties of the progestogen CMA.

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Introduction

Acne is a common skin disorder characterized by an overproduction of sebum leading to non-inflammatory (comedones) and inflammatory lesions (papules, pustules, nodulocystic lesions). Its aetiology is multifactorial. Most women with acne may suffer from a hypersensitivity of the sebaceous glands to androgens, but frequently an excess of androgens can also be observed. In the sebaceous gland the enzyme 5 α -reductase type I converts testosterone to its more active component dihydrotestosterone which in turn stimulates the activity of the sebaceous glands. As hormonal balance is a key factor in the aetiology of acne, one possible treatment is systemic hormonal therapy. The use of oral contraceptives with anti-androgenic properties has proven to be a useful approach towards this goal [1, 2].

Belara® (ethinylestradiol/chlormadinone acetate, EE/CMA) is a monophasic oral contraceptive containing 0.03 mg EE and 2 mg CMA which was registered in Germany in 1998. Oestrogens are known to suppress pituitary gonadotropin secretion, thereby inhibiting androgen biosynthesis in ovaries and adrenals [3–5]. Additionally, they

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may have a direct effect on sebum production [6] and raise the sex-hormone-binding globulin (SHBG) levels [7], which in turn lowers circulating testosterone. CMA is a progestogen derivative with anti-androgenic properties. It reduces clinical manifestations of acne by competing with endogenous androgens at their receptors in the sebaceous gland cells and by inhibiting 5 α -reductase type I [8, 9].

The present phase III study compared the efficacy and safety of the combination pill EE/CMA for the treatment of acne of the face, décolleté (i.e. chest) and back, of seborrhoea, alopecia and hirsutism with another commonly used oral contraceptive combining 0.03 mg EE and 0.15 mg levonorgestrel (EE/LNG; Microgynon®).

Methods

This study was designed as a single-blind (investigator), randomized (1:1), controlled, parallel, multicentric phase III trial. It was performed at 32 office-based gynaecological centres in Germany. The participating gynaecologists were instructed and trained in identifying and differentiating as well as in the counting of papules, pustules or comedones according to the definition of Cook et al. [10] and underwent a self-training phase (i.e. interassessment training) prior to the first recruitment of patients to assure consistency and reproducibility in the evaluation of acne lesions. The study was conducted according to the principles of Good Clinical Practice as specified in the Guidelines of the European Community. The study protocol was approved by the local ethics committees.

Women of reproductive age with mild to moderate papulopustular acne of the face aged between 18 and 40 years (smokers up to 30 years) were randomly allocated to EE/CMA or EE/LNG. Both study medications were to be taken over 12 treatment cycles. After checking inclusion and exclusion criteria, explanation of the study and obtaining written informed consent both 'pill starters' (first intake of an oral contraceptive or no intake of an oral contraceptive during the last 3 months prior to admission) and 'pill switchers' (change of a previous oral contraceptive to study medication with a break of less than 3 months in-between) received one package of study medication containing 3 blisters with 21 film-coated tablets/drazees of EE/CMA or EE/LNG for the first 3 cycles. Patients were not allowed to take hormonal contraception as well as topical or systemic acne therapy during the study. Systemic acne therapy (e.g. with anti-androgens or retinoids) during the last 6 months prior to study start was also excluded.

The first pill of the study medication was to be taken on the first day of withdrawal bleeding in the first medication cycle and thereafter for 21 days, every day at the same time, preferably in the evening. This phase was followed by a 7-day pill-free interval during which withdrawal bleeding usually occurred. All subsequent cycles began on the same day of the week as the first day of the first cycle, irrespective of whether withdrawal bleeding had occurred or was still present. Each participant received a cycle calendar, where the beginning of study medication, all adverse events, missed pills, bleeding events and concomitant medication, if taken, had to be documented; these entries were transferred into the case report form. General medical, dermatological and gynaecological examinations including Pap

smears and pregnancy tests were performed on admission and at regular intervals during the study course. In addition, blood samples were collected on admission and between the 1st and 8th days of cycles 2, 4, 7, 10 and 12 for safety screening and for determination of hormone parameters [testosterone, free testosterone, dehydroepiandrosterone sulphate (DHEA-S), SHBG, luteinizing hormone, follicle-stimulating hormone, androstenedione, 17- α -OH-progesterone].

Regular dermatological examinations were performed in cycles 4, 7, 10 and 12; these included counting of acne lesions and the assessment of seborrhoea, alopecia and hirsutism. A modified Plewig score [11] assessing the number of inflammatory lesions was used to classify the degree of severity of facial acne at baseline and during the study: acne of grade 0 was defined as consisting of up to 3 papules/pustules per half of the face, grade I acne of 4–10, grade II of 11–20, grade III of 21–30 and grade IV of more than 30 papules/pustules per half of the face. The primary study end point was defined as a decrease by at least 50% in papules/pustules per half of the face in the 12th treatment cycle compared to the number of lesions at admission. If the acne was asymmetric, the more affected half of the face was to be taken at each respective visit. A lesion on the midline of the face was counted to the more affected half of the face. The evaluation of the response rates was performed by a Cochran-Mantel-Haenszel test (CMH test). Drop-outs were defined as non-responders in the intention-to-treat population for the primary end point. Secondary end points were the assessment of comedonal acne of the face, acne of the décolleté and back (number of comedones and papules/pustules), further signs of androgenization such as seborrhoea, alopecia and hirsutism (according to an intensity scale: mild, moderate, severe; for hirsutism the localization was given, data not shown) as well as blood levels of androgens and SHBG, cycle stability and incidence of adverse events.

Results

Participants

In this study 32 gynaecologists in Germany recruited 199 patients. One hundred and one volunteers were randomly allocated to EE/CMA and 98 to EE/LNG. Both treatment groups were comparable to each other concerning demographic data (age, weight, height, Broca index, body mass index), alcohol consumption, smoking habits (47/199 smokers), gynaecological and bleeding history and concomitant diseases. On admission, all patients in both study groups suffered from papulopustular acne of the face; most of the patients were assigned to Plewig grades I and II [11]; 55.4% (56/101) in the EE/CMA and 52% (51/98) in the EE/LNG group had acne of the décolleté, and 52.5% (53/101) in the EE/CMA and 48% (47/98) in the EE/LNG group had acne of the back (all Plewig grade I or II, except 1 patient with grade IV in the EE/LNG group). The number of patients of each study group assigned to each classification was comparable. One hundred and fifty patients (78 on EE/CMA, 72 on EE/LNG) completed all 12 medication cycles, and 148 pa-

tients (78 on EE/CMA and 70 on EE/LNG) finished the study according to protocol. Twenty-three patients on EE/CMA and 26 on EE/LNG terminated the study prematurely, mainly due to adverse events, lack of efficacy of study medication, protocol deviations, non-compliance, wish to conceive and pregnancy.

Effect of Study Medication on Papulopustular Acne of the Face

In total, 60 of the 101 patients (59.4%) on EE/CMA and 45 of the 98 patients (45.9%) on EE/LNG were responders according to the definition of the primary end point (i.e. they showed a reduction of papules/pustules of at least 50% in the 12th treatment cycle). This superiority of EE/CMA over EE/LNG was statistically significant (CMH test, $p = 0.02$).

At admission, both medication groups started with a median number of 8.0 papules/pustules (Q1–Q3 interval: 6–13) per half of the face. A gradual reduction of these numbers from admission until cycle 12 was observable for both medication groups (fig. 1a). Accordingly, the number of women with complete resolution (i.e. no papules/pustules) increased continuously under EE/CMA reaching a relative number of 10.1% (9/89 patients) by cycle 7 and of 16.5% (13/79 patients) by cycle 12. In comparison, in the EE/LNG group only 5% (4/80) of the patients were cured by cycle 7 and 4.3% by cycle 12, respectively. These results point to an earlier onset and a more pronounced improvement of papulopustular acne of the face under EE/CMA. In 98.7% (78 of 79 patients) of the EE/CMA patients and 87.1% (61 of 70 patients) of the EE/LNG patients an improvement of their facial acne was reported after cycle 12. A deterioration (i.e. an increase in the number of pustules/papules) was seen in 11.4% (8 of 70 patients) of the EE/LNG group whereas in the EE/CMA group no exacerbation was observable in the 12th treatment cycle.

Summarizing the results in other words, in cycle 12, 67.1% (53 of 79) of the patients under EE/CMA and 54.3% (38 of 70) of the women of the EE/LNG group could be assigned to Plewig score 0, and 7.6% (6 of 79) under EE/CMA and 17.1% (12 of 70) under EE/LNG still had grade II acne according to Plewig.

In order to investigate whether the previous intake of an oral contraceptive could have an influence on the response rate, a stratification analysis was performed (i.e. pill switcher and pill starter in each treatment group). There were 41.6% (42/101) pill switchers in the EE/CMA group and 40.8% (40/98) in the EE/LNG group, respectively. Response rates for switchers and starters per treat-

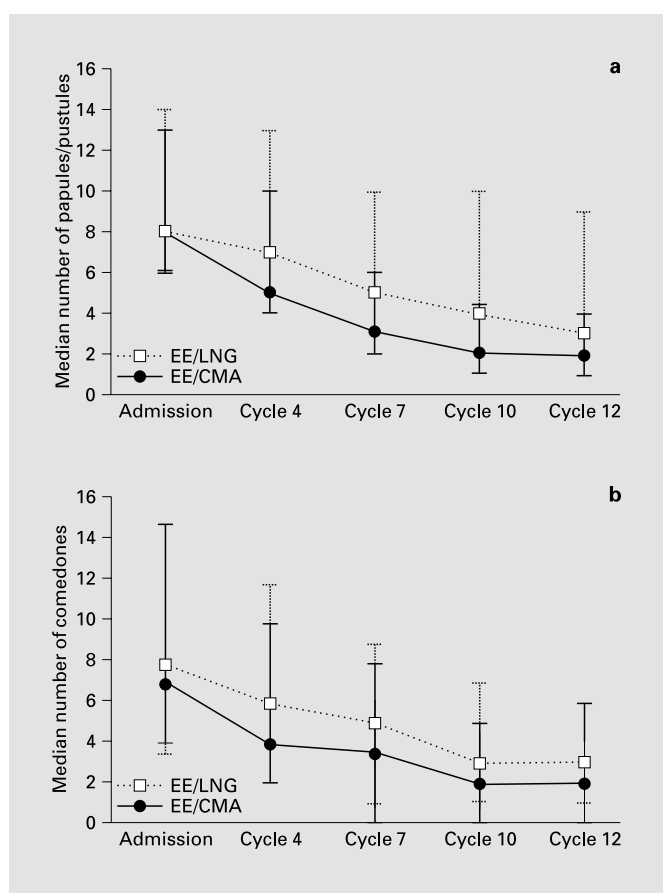


Fig. 1. **a** Median numbers of papules/pustules of the face in women treated with Belara (EE/CMA) and Microgynon (EE/LNG) from cycle 0 (admission) until cycle 12 (end of study). **b** Median numbers of comedones of the face in women treated with Belara (EE/CMA) and Microgynon (EE/LNG) from cycle 0 (admission) until cycle 12 (end of study).

ment group are given in table 1. For both subgroups, again a superiority of EE/CMA was shown, being especially pronounced among pill switchers. This has also been proven statistically by including starters and switchers as an additional stratification variable in the statistical test (CMH test, $p = 0.014$).

Effect of Study Medication on Comedonal Acne of the Face

Similar trends could be detected for comedonal acne of the face. In each medication group, 88 patients presented with comedones at admission. Throughout the study there was a gradual reduction in numbers of comedones from admission to cycle 12 which was greater with EE/CMA than with EE/LNG (fig. 1b). With EE/CMA, an improvement rate of 70.1% (61/87 patients) was already

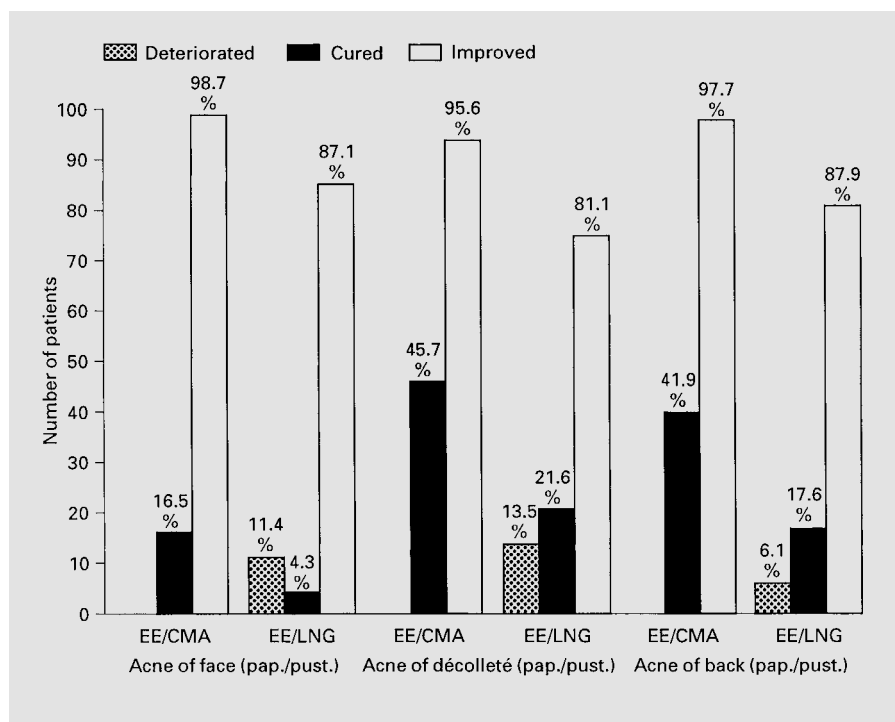


Fig. 2. Improvement, healing and deterioration rates for papulopustular acne of the face, décolleté and back under Belara (EE/CMA) and Microgynon (EE/LNG) after 12 treatment cycles.

Table 1. Absolute and relative numbers of non-responders and responders among pill starters and pill switchers in each study group

Study subgroup	Study group	Non-responders	Responders	Total
Pill starters	EE/CMA	22 (37.3)	37 (62.7)	59 (100)
	EE/LNG	26 (44.8)	32 (55.2)	58 (100)
Pill switchers	EE/CMA	19 (45.2)	23 (54.8)	42 (100)
	EE/LNG	27 (67.5)	13 (32.5)	40 (100)
Total	EE/CMA	41 (40.6)	60 (59.4)	101 (100)
	EE/LNG	53 (54.1)	45 (45.9)	98 (100)

Figures in parentheses indicate percentages.

seen in cycle 4 compared to 56.5% (48/85 patients) in the EE/LNG group, and by cycle 12, 88.9% (64/72) of the patients with facial comedones under EE/CMA and only 77.3% (51/66) under EE/LNG showed improvement of their lesions. Furthermore, deterioration rates of comedonal acne of the face were much lower in the EE/CMA (2.8%) than in the EE/LNG group (9.1%) at the 12th treatment cycle.

Effect on Acne of the Décolleté after 12 Treatment Cycles

On admission, 55.4% (56/101) of the patients on EE/CMA and 52% (51/98) patients on EE/LNG suffered from papulopustular or comedonal acne of the décolleté.

Whereas 45.7% of the patients (21/46) under EE/CMA were completely cured by cycle 12, this was the case for only 21.6% (8/37) patients under EE/LNG. The improvement rate for either papulopustular or comedonal acne of the décolleté was 95.6% (43/45) and 91.9% (34/37) under EE/CMA compared to 81.1% (30/37) and 73.1% (19/26) under EE/LNG. Only 1 woman (2.7%) under EE/CMA had an exacerbation of her comedonal acne on the décolleté reported in cycle 12, but deterioration occurred under EE/LNG in 13.5% of patients with papulopustular acne (fig. 2) and in 15.4% with comedonal acne at cycle 12.

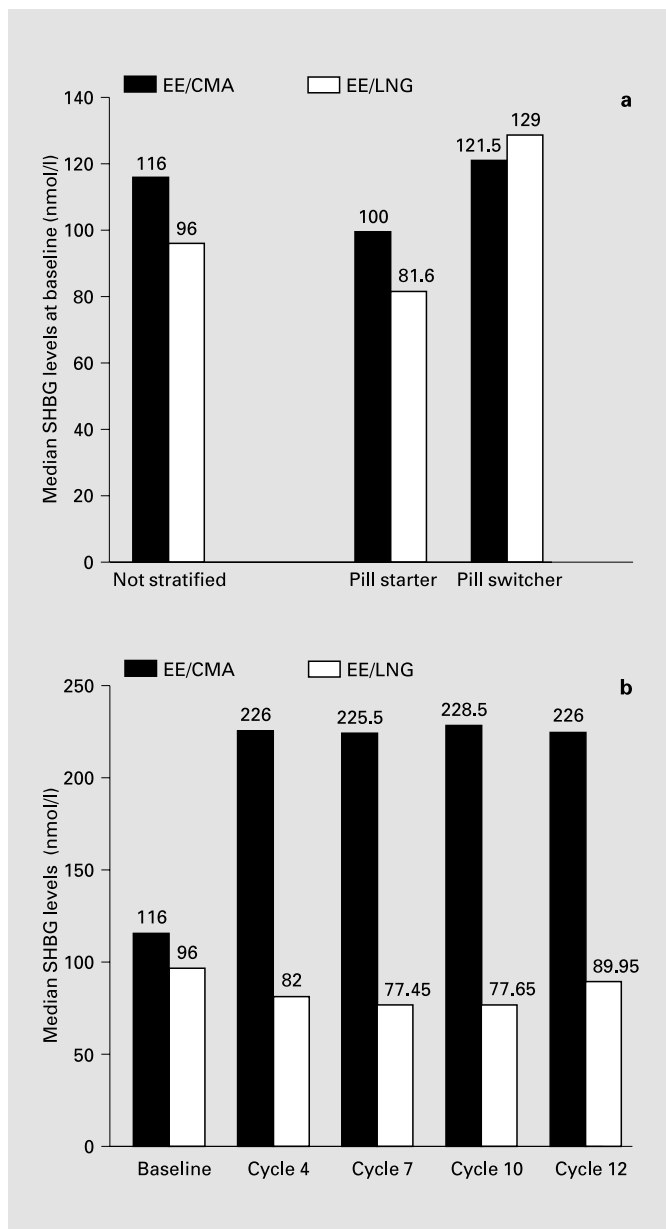


Fig. 3. a Median SHBG levels (nmol/l) at baseline, stratified and not stratified into pill switchers and pill starters for both study groups. **b** SHBG levels during the course of the study in the two medication groups.

Effect on Acne of the Back after 12 Treatment Cycles

On admission, 52.5% (53/101) of the patients in the EE/CMA and 48% (47/98) in the EE/LNG groups reported acne of the back. Of these patients, 41.9% (18/43) on EE/CMA and 17.6% (6/34) on EE/LNG were cured by cycle 12. Papulopustular acne as well as comedonal acne of the back improved in almost 100% of

patients under EE/CMA (97.7%, i.e. 42/43, and 97.3%, i.e. 36/37, respectively) and in a smaller number of patients under EE/LNG (87.9%, i.e. 29/33, and 76.9%, i.e. 20/26, respectively) by the end of the study. No deterioration of acne lesions on the back was reported under EE/CMA in cycle 12, whereas under EE/LNG papulopustular acne deteriorated in 6.1% ($n = 2/33$) and comedonal acne in 11.5% ($n = 3/26$) of the patients at that time point. Figure 2 summarizes the relative frequencies of patients showing effects of both kinds of study medication on acne of the face, décolleté and back after 12 treatment cycles.

Effect on Seborrhoea, Alopecia and Hirsutism after 12 Treatment Cycles

At baseline, 31.7% (32/101) of the women under EE/CMA and 30.6% (30/98) under EE/LNG suffered from seborrhoea mostly of mild (75% in EE/CMA vs. 60% in EE/LNG) or moderate (15.6% in EE/CMA vs. 30% in EE/LNG) intensity. In both medication groups there was a decrease in the number of patients with seborrhoea after 12 treatment cycles: 80% (20/25) of the volunteers in the EE/CMA group showed total resolution versus 76.2% (16/21) in the EE/LNG group.

Similar results were observed among the patients with androgen-dependent alopecia. Resolution rates of 85.7% (6 of 7 patients) in the EE/CMA group and 90.9% (10 of 11 patients) with EE/LNG were achieved. Due to the small number of patients the results give only a hint that the treatments are effective.

Hirsutism, irrespective of the localization, was present in 13.9% of patients under EE/CMA (i.e. 14 women) and in 20.4% (20 patients) under EE/LNG at baseline. It disappeared completely in about one third of patients in each medication group after 12 cycles of treatment: 36.4% of patients on EE/CMA (4/11 women) versus 35.7% on EE/LNG (5/14 women). Again, due to the small patient population these data give only a trend.

Sex Hormones and SHBG

At baseline, median SHBG levels were already positioned at the upper end of the reference range (16–120 nmol/l, fig. 3a). This was probably due to the fact that both study groups contained pill switchers with already elevated SHBG levels at admission. This assumption was confirmed by a stratification analysis of pill switchers and starters concerning baseline SHBG values (fig. 3a).

During the study there was an increase of almost double in the SHBG plasma values under EE/CMA. This increase was already present in cycle 4. In contrast, un-

der EE/LNG, SHBG plasma levels decreased slightly (fig. 3b).

No major changes in androgen levels during treatment were seen.

Tolerability

Both drugs were well tolerated as reflected by the low incidence and intensity of adverse events.

In total, 103 out of 199 patients (51.8%) reported adverse events, most frequently in the first 3–4 cycles for both medication groups. Under EE/CMA, a total of 421 adverse events in 53 patients compared to 568 adverse events in 50 patients under EE/LNG were reported. The most frequently observed adverse events were headache (24/97, 24.7%), breast tension (19/97, 19.6%), dysmenorrhoea (10/97, 10.3%) and nausea (10/97, 10.3%) for the EE/CMA study group and headache (29/94, 30.9%), nausea (16/94, 17%), dysmenorrhoea (15/94, 16%) and breast tension (14/94, 14.9%) for EE/LNG. These are common adverse events of oral contraceptives.

Most adverse events were classified as mild or moderate (72.4% for EE/CMA vs. 64.3% for EE/LNG).

The majority of patients in both medication groups had regular withdrawal bleedings with onset within the medication-free interval lasting 4–5 days.

There was no major difference in incidence and intensity of intracyclic bleeding between the medication groups. Amenorrhoea occurred in only 1.5% of cycles under EE/CMA and in 1.8% of cycles under EE/LNG.

Discussion

As acne is mainly characterized by the overproduction of sebum in response to the stimulation of the sebaceous glands by androgens, it can often be successfully improved by the intake of oral contraceptives with anti-androgenic properties [1]. The present study was focused on the comparison of the effects of two low-dose oestrogen-progestogen combinations, EE/CMA (Belara) and EE/LNG (Microgynon), on mild to moderate papulopustular acne of the face.

Efficacy on Acne of the Face, Décolleté and Back

EE/CMA was superior to EE/LNG ($p = 0.02$, CMH test) in reducing the clinical symptoms papules/pustules of facial acne. After 12 treatment cycles, response rates of 59.4% under EE/CMA and 45.9% under EE/LNG were reached. This difference between the two study medications was even more pronounced for acne of the décolleté

and the back. For both localizations, an earlier improvement and fewer cases with exacerbation under EE/CMA were observed.

Sansone and Reisner [12] noted that the majority of women suffering from acne show a 2- to 3-fold elevated activity of 5- α -reductase type I, the enzyme that converts testosterone into its active component dihydrotestosterone which stimulates the sebaceous glands. The CMA presented in Belara is a competitive inhibitor of the androgen receptor (e.g. of the sebaceous gland cells). Several publications have also documented positive effects of anti-androgens, such as CMA and cyproterone acetate (CPA) on clinical manifestations of acne, seborrhoea, alopecia and hirsutism [1, 8, 9, 13]. Kaiser [1] using a CMA-containing biphasic oral contraceptive observed resolution rates of 14.5% in patients with facial papulopustular acne after 12 treatment cycles. Similar resolution rates (16.5%) were seen in the present study.

The effects of the CMA in Belara on clinical signs of acne and related disorders are additionally enhanced by the oestrogen component of the pill, EE. EE raises the levels of SHBG leading to a lower level of circulating testosterone. Other 'anti-androgenic' effects of EE, which were proven in animal models, are the inhibition of 5- α -reductase type I [14, 15] as well as a direct effect on sebum production [6]. Finally, both CMA and EE suppress the secretion of gonadotropins of the pituitary gland. This leads to an associated reduction in androgen secretion of the ovary and adrenal cortex. The marked treatment success in women on EE/CMA which occurred already in the 4th treatment cycle exceeded the effect seen with Microgynon by far. This indicates that the anti-androgenic activity of CMA adds to the oestrogen effect of EE, thus underlining that the combination of both components seems to be responsible for the considerably better total treatment success of Belara in acne and other androgen-related symptoms. These results are further supported by the results of a comparative study where an LNG-containing contraceptive (Neovletta® with 0.03 mg EE and 0.15 mg LNG, which is identical with the contents of Microgynon) was compared to two hormonal combinations containing 2 mg CPA and different amounts of EE (Dianette® and Diane®, 35 and 50 μ g, respectively) for the treatment of acne over 6 cycles [2]. After 4 cycles under CPA, the patients had a significantly higher reduction in the number of acne lesions compared to those on EE/LNG. Women taking EE/LNG showed an average reduction of acne lesions by 35%; this is of the same order of magnitude as determined for patients on placebo by Lucky et al. [7] and Redmond et al. [5]. In contrast, in women who took an

anti-androgenic oral contraceptive (EE/CPA) the average reduction of acne lesions reached 70%, again confirming the assumed superiority of anti-androgenic oral contraceptives for the treatment of this skin disorder.

SHBG and Androgen Levels

There was no noteworthy change in the levels of testosterone, free testosterone, dihydrotestosterone or DHEA-S under EE/CMA and EE/LNG. The SHBG levels rose strikingly under EE/CMA to almost double the baseline values as early as after 4 treatment cycles. This points to the oestrogenic influence not being counteracted by CMA. In the EE/LNG group, SHBG decreased slightly, most probably due to the anti-oestrogenic effect of LNG on EE.

As the ovarian activity increases during a pill-free interval, this leads to a raised androgen synthesis which is only reduced after several days of a continuous pill intake [16]. Therefore, in the present study no decrease could be observed (in the current trial blood samples were taken during days 1–8). In another clinical trial in which EE/

CMA (Belara) was compared to EE/desogestrel (Grünenthal, data on file) and blood samples were collected on later days of the cycle (days 18–21), a more pronounced suppression of androgen levels could be seen.

Additionally, it has to be mentioned that both pill starters and pill switchers were allowed to enter the study so that the baseline values had most probably already been influenced by the previous intake of another oral contraceptive.

Despite the minimal observed changes in the androgen levels over the course of the study, the clinical signs of androgenization decreased strikingly under EE/CMA.

Thus, Belara can be recommended as a treatment for women with mild to moderate clinical signs of acne and/or other androgen-related disorders and the wish for efficient and safe contraception.

Acknowledgement

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References

- 1 Kaiser E: Action of a new hormonal contraceptive (Neo-Eunomin®) on androgenisation of the skin in women. *Geburtsh Frauenheilkd* 1984;44:651–655.
- 2 Carlborg L: Cyproterone acetate versus levonorgestrel combined with ethinylestradiol in the treatment of acne. *Acta Obstet Gynecol Scand* 1986;134:29–32.
- 3 McKenna TJ: The use of anti-androgens in the treatment of hirsutism. *Clin Endocrinol* 1991; 35:1–3.
- 4 Dieben T, Vromans L, Theeuwes C, Bennink HJT: The effects of CRT-24, a biphasic oral contraceptive combination, compared to Diane-35 in women with acne. *Contraception* 1994;50:373–382.
- 5 Redmond GP, Olson WH, Lippman JS, Kafirissen ME, Jones TM, Jorizzo JL: Norgestimate and ethinylestradiol in the treatment of acne vulgaris: A randomized, placebo-controlled trial. *Obstet Gynecol* 1997;89:615–622.
- 6 Ebling FJ: Hormonal control of sebaceous glands in experimental animals; in Montagna W, Ellis RA, Silver AF (eds): *Advances in the Biology of Skin: The Sebaceous Gland*. Oxford, Pergamon Press, 1963, vol 4, pp 200–219.
- 7 Lucky AW, Henderson TA, Olson WH, Robisch DM, Leibold M, Swinyer LJ: Effectiveness of norgestimate and ethinylestradiol in treating moderate acne vulgaris. *J Am Acad Dermatol* 1997;37:746–754.
- 8 Breckwoldt M, Wieacker P: Hirsutismus; in Bettendorf G, Breckwoldt M (eds): *Reproduktionsmedizin*. Stuttgart, Fischer, 1989, pp 483–487.
- 9 Breckwoldt M, Zahradnik HP, Wieacker P: Hirsutism; in Orfanos CE, Happle R (eds): *Hair and Hair Diseases*. Berlin, Springer, 1990, pp 777–789.
- 10 Cook H, Centner RL, Michael SE: An acne grading method using photographic standards. *Arch Dermatol* 1979;115:571–575.
- 11 Plewig G: Klassifikation und Ätiopathogenese der Akne; in Braun-Falco O, Marghescu S (eds): *Fortschr Prakt Dermatol Venerol* 1976;8: 1279–1288.
- 12 Sansone G, Reischer RM: Differential rates of conversion of testosterone to dihydrotestosterone in acne and in normal human skin – Possible pathogenetic factors in acne. *J Invest Dermatol* 1971;56:366–372.
- 13 Fugère P, Robin KL, Lussier-Cacan S, Davignon J, Farquhar D: Cyproterone acetate/ethinylestradiol in the treatment of acne: A comparative dose-response study of the estrogen component. *Contraception* 1990;42:225–234.
- 14 Dubé JY, Ngo-Thi NH, Tremblay RR: In vivo effects on steroid hormones on the testosterone 5- α -reductase in rat skin. *Endocrinology* 1975; 97:211–214.
- 15 Frost P, Gomez EC: Inhibitors of sex hormones: Development of experimental models; in Montagna W, van Scott EJ, Stoughton RB (eds): *Advantages in Biology of Skin*. Pharmacology and Skin. New York, Meredith Corp, 1972, vol XII, pp 403–442.
- 16 Dericks-Tan JSE, Gudacker V, Taubert HD: Influence of oral contraceptives on integrated secretion of gonadotropins. *Contraception* 1992;46:369–377.