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Contraceptive Efficacy and Tolerability of Chlormadinone Acetate 2mg/ Ethinylestradiol 0.03mg (Belara®)[1]

Results of a Post-Marketing Surveillance Study

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Abstract

Objective: This post-marketing surveillance study aimed to investigate the contraceptive efficacy and tolerability of a combination tablet containing chlormadinone acetate 2mg and ethinylestradiol 0.03mg (Belara®) in daily gynaecological practice. A secondary aim was investigation of the changes in clinical signs of androgenisation.

Design: 21 820 female patients were surveyed during a six-cycle period by 3600 gynaecologists throughout Germany.

Results: Out of 21 820 patients, a total of 19 650 women (90.1%) completed the study. Chlormadinone acetate 2mg/ethinylestradiol 0.03mg had excellent contraceptive efficacy with an adjusted Pearl index of 0.076 (unadjusted Pearl index: 0.344), calculated from 125 634 cycles of exposure. Cycle control was good, with beneficial reductions in intracyclic bleeding (22.9% in cycle 1, 1.6% in cycle 6), amenorrhoea, severe withdrawal bleeding and dysmenorrhoea. At cycle six, only 1.2, 0.4 and 0.5% of all patients complained about spotting, breakthrough bleeding and amenorrhoea, respectively. At baseline, 69.9% of the women showed androgen-related skin disorders. After six cycles of chlormadinone acetate 2mg/ethinylestradiol 0.03mg, these disorders were improved in 86.5% of patients, including 28.5% who had complete resolution. Correspondingly, greasy or very greasy hair condition decreased from 47.0 to 13.6%. Chlormadinone acetate 2mg/ethinylestradiol 0.03mg was well tolerated; a total of two venous thromboembolic events (VTEs) occurred, and both patients recovered with appropriate treatment. Breast pain (3.6%) and migraine/headache (2.6%) were the most frequently reported adverse events. Conversely, these symptoms disappeared in most women (84.5 and 79.9%) who experienced them prior to chlormadinone acetate 2mg/ethinylestradiol 0.03mg treatment.

Conclusions: These results support the reliable contraceptive efficacy, cycle stability and tolerability reported in previous clinical trials and confirm the marked antiandrogenic properties of chlormadinone acetate 2mg/ethinylestradiol 0.03mg.

1 Use of tradenames is for product identification only and does not imply endorsement.

Over the last 40 years, the tolerability of combined oral contraceptives (OCs) has improved via lower dosages of the estrogen and progestogen components. Adverse events related to metabolic and coagulation parameters were reduced without compromising the contraceptive efficacy or cycle stability. A wide range of oral contraceptives is now available with different therapeutic profiles to meet individual needs. Currently, about 80 million women worldwide rely on hormonal contraceptives,[1] all of them expecting optimal contraceptive efficacy, a reliable tolerability profile and additional benefits to their general well-being.

Cycle instability and related symptoms such as hypermenorrhoea, oligomenorrhoea, menorrhagia and dysmenorrhoea are common complaints in daily gynaecological practice. Additionally, many women experience clinical signs of androgenisation such as seborrhoea, acne, hirsutism and alopecia.[2] For a woman, hyperandrogenism may have a pronounced negative impact on general well-being, and may often cause significant emotional and psychological problems.

Modern oral contraceptives differ from older ones primarily with regard to the progestogen component. More recently, progestogens with weak or no androgenic effects, or even with anti-androgenic properties, have been developed. Since hormonal imbalance is a key factor in the aetiology of androgen-related skin and hair changes, oral contraceptives with anti-androgenic properties have proved to be a useful approach to minimise these effects.[3,4]

A monophasic combined low-dose OC containing chlormadinone acetate 2.0mg and ethinylestradiol (EE) 0.03mg per tablet (Belara®) has been developed. In contrast to other progestogens derived from the 19-nor-testosterone series, chlormadinone acetate is a derivative of the naturally secreted hormone progesterone and has marked anti-androgenic properties.[5,6] In addition to its anti-androgenic profile, chlormadinone acetate is not expected to interfere with estrogen-related protective effects on the cardiovascular system.[7]

In addition, chlormadinone acetate differs from other progestogens with regard to its hepatic safety profile; it does not significantly inhibit the enzyme activity of CYP1A2, CYP2C9, CYP2D6 and CYP3A4, and it does not interfere with the hepatic 5-α-reductase.[5,8]

In a multicentre, phase III trial over 24 cycles in 1655 women, chlormadinone acetate 2mg/ethinylestradiol 0.03mg was well tolerated and demonstrated excellent contraceptive efficacy (adjusted Pearl index of 0.27), high-level cycle stability and beneficial anti-androgenic effects on both hair and skin.[9]

Chlormadinone acetate 2mg/ethinylestradiol 0.03mg has been marketed in Germany since 1999, and there is now a great deal of experience with this oral combination contraceptive. Post-marketing surveillance studies are a legal requirement in Germany for newly marketed drugs, in order to confirm the results of premarketing clinical trials. The aim of this six-cycle post-marketing study was to survey the contraceptive efficacy and tolerability of chlormadinone acetate 2mg/ethinylestradiol 0.03mg in a large sample population during routine clinical use. In addition, the influence of this combination OC on clinical signs of androgenisation were evaluated.

Methods

Study Design

This post-marketing study was conducted according to German Drug Law and the quality standards issued by the German Health Authority (1998). The study protocol was approved by the local Ethics Commitees. A non-interventional design was used to reflect daily gynaecological practice.

Chlormadinone acetate 2mg/ethinylestradiol 0.03mg was prescribed according to the discretionary clinical judgement of the gynaecologist, with exclusion criteria limited to the licensed contraindications (as stated in the prescribing information for Belara®). Patients prescribed an OC for the first time ('starters') or switched to chlormadinone

acetate 2mg/ ethinylestradiol 0.03mg ('switchers') were to be included. Patients took one tablet daily for 21 days per cycle, starting on the first day of withdrawal bleeding or menstrual periods, respectively. This phase was followed by a 7-day pill-free interval during which withdrawal bleeding usually occurred before starting the next cycle of treatment. The gynaecologists observed and documented a total of six cycles of chlormadinone acetate 2mg/ ethinylestradiol 0.03mg intake for each woman.

The study was conducted between April 1999 and December 1999, and involved 3600 gynaecologists throughout Germany. Each gynaecologist received files to document data for a maximum of eight patients starting on chlormadinone acetate 2mg/ethinylestradiol 0.03mg. The study design implied a non-selected group of women participating in the survey, with inclusion and exclusion criteria being based on the licensed indications and contraindications.

Evaluation

Data were collected by means of a questionnaire (case record form), which covered age, starter or switcher status at baseline, risk factors (smoking habits, adiposity, family history of thromboembolic events), menstrual cycle history (last two cycles before start of chlormadinone acetate 2mg/ ethinylestradiol 0.03mg), type of skin and hair and changes during treatment, compliance and premature withdrawal, as well as adverse events, complaints and symptoms occurring during treatment.

Type of skin and hair (dry, normal, slightly greasy, greasy or very greasy), occurrence of pustules or acne-like skin disorders and frequency of hairwashing were evaluated at baseline and during six cycles of chlormadinone acetate 2mg/ ethinylestradiol 0.03mg.

All remarks concerning adverse drug reactions, signs and symptoms were recorded. Both investigator and patient assessed the tolerability of study treatment and graded it as 'very good', 'good', 'moderate' or 'poor'.

Every documented sign, symptom or new disease occurring during the study treatment was classified, irrespective of whether it also occurred prior to treatment. Symptoms that increased in intensity during treatment, as well as new symptoms, were considered to be adverse events.

Statistical Methods

The questionnaires were analysed using descriptive statistics. Incomplete information led to exclusion of a questionnaire. The following formula served for evaluating contraceptive efficacy:

Pearl index (PI) =
(no. of pregnancies × 1200)/ (no. of treatment cycles)

A calculation of the venous thromboembolic event (VTE) rate per 10 000 women years was performed on the basis of 13 cycles per year.

The non-interventional design of this survey implied that the statistical significance of any differences was not formally analysed.

Results

A total of 3600 gynaecologists (87.5% of those agreeing to participate in the survey) returned questionnaires from 21 993 women. Of these, 173 (0.8%) were excluded from the analysis due to lost follow-up and no further tolerability data being available. The analysis thus comprised 125 634 cycles of chlormadinone acetate 2mg/ethinylestradiol 0.03mg exposure in 21 820 women.

Baseline Characteristics

The baseline characteristics of the study population are given in table I.

Age and Previous Intake of Oral Contraceptives

About half of the women (44.8%) were aged 19 to 28 years (figure 1), with a mean age of 24.6 ± 7.4 years. 61.2% of the patients were pill switchers, i.e. they switched directly from another brand at the end of a cycle with the previous OC or

reported that they had previously taken another OC. The remainder were classified as pill starters (38.7%). 15.0% of all pill-switchers had been taking Diane-35®, 13.6% Valette®, 10.4% Neo-Eunomin®, 5.1% Marvelon® and 5.0% Microgynon®. Other OCs represented <5.0%.

Risk Factors

Risk factors for the intake of an oral contraceptive were documented in 8478 women (38.9%)

Table I. Demographic and clinical characteristics of the study population at baseline (n = 21 820)

Mean age (years ± SD)	**24.6 ± 7.4**
Age range (years)	**12–55**
Clinical characteristics	Percentage of patients
Withdrawal bleeding	
Mild	21.9
Normal	62.6
Severe	14.0
Not stated	1.5
Intracyclic bleeding	
Not reported	69.1
Rare	21.9
Frequent	7.6
Not stated	1.4
Amenorrhoea	
Not reported	83.1
Rare	10.4
Frequent	4.4
Not stated	2.1
Dysmenorrhoea	
Not reported	52.1
Mild	33.0
Severe	14.0
Not stated	0.9
Skin condition	
Greasy	59.2
Normal	26.2
Dry	14.3
Not stated	0.3
Hair status	
Greasy	47.0
Normal	43.9
Dry	8.8
Not stated	0.3

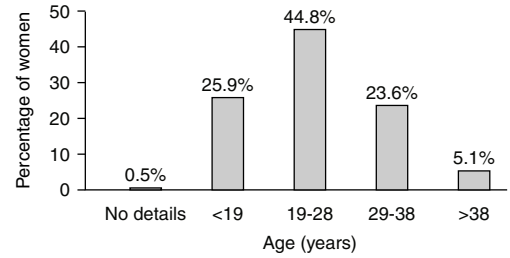

Fig. 1. Age distribution of study participants (n = 21 820).

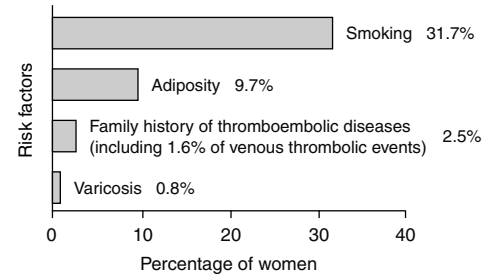

Fig. 2. Risk factors at baseline (n = 8478 women).

at baseline: smoking (31.7%) and adiposity (9.7%) were the most frequent (figure 2). Varicosis was documented in 169 patients (0.8%), and 542 (2.5%) women reported a positive family history with regard to thromboembolic diseases (VTEs 1.6%, varicosis 0.4%, myocardial infarction 0.3%, apoplexy 0.2%). 64.0, 27.0 and 4.4% of smokers stated that they smoked ≤10, 11-20 and >20 cigarettes per day, respectively.

Menstrual Cycle History and Complaints

Investigators were required to assess the last two cycles before starting chlormadinone acetate 2mg/ethinylestradiol 0.03mg administration. Intracyclic bleeding was documented in 6441 women (29.5%), 3047 patients (14.0%) experienced severe withdrawal bleeding, amenorrhoea was reported by 14.8% of all women, and 47.0% of the participants reported mild (33.0%) or severe (14.0%) dysmenorrhoea.

Other complaints prior to study treatment were documented in 6940 (31.8%) patients. Among these, headache/migraine (9.7% of all women), breast pain (9.5%), more serious androgenisation disorders (7.6%), depressed state (4.5%), tiredness (2.0%), weight increase (1.3%) and decreased libido (1.0%) were shown to be the most important.

Skin and Hair Condition

More than two-thirds (69.9%) of all patients exhibited pustules and acne-like skin disorders at baseline. Greasy or very greasy hair was documented in 47% of all participants. 23.1% of the women reported the frequency of hair washing as 'daily'. Only 8.1% of the patients preferred hair washing once per week or more rarely.

Contraceptive Efficacy

A total of 36 pregnancies occurred during 125 634 cycles in 21 820 women while taking chlormadinone acetate 2mg/ethinylestradiol 0.03mg. Thus, an unadjusted Pearl index (PI) of 0.344 [95% CI (0.243, 0.466)] was calculated. However, intake errors were considered to be responsible for 27 pregnancies. In one case a possible drug interaction of chlormadinone acetate 2mg/ethinylestradiol 0.03mg with carbamazepine led to contraceptive failure. Further details of the incidence of administration errors are shown in table II. On the basis of eight pregnancies that may have been due to method failure, the adjusted Pearl index was 0.076 [95% CI (0.031, 0.143)].

Table II. Pregnancies occurring during the study

Pregnancies	**36**
No administration errors (n)	**8**[a]
Administration documented (n)	**28**
Type of administration error	No. of patients
Drug interaction	1
Forgot to take tablets once	7
Forgot to take tablets several times	15
No details	5

a 21 820 users and 125 634 cycles gives an adjusted Pearl index of 0.08.

Tolerability

General Assessment of Tolerability

All patients assessed the overall tolerability as 'very good', 'good', 'moderate' or 'poor'. A 'very good' or 'good' tolerability was stated by 86.5% of the women (figure 3). Only 5.7% and 4.0% classed the tolerability of chlormadinone acetate 2mg/ethinylestradiol 0.03mg as moderate or poor, respectively. In terms of rating the tolerability of treatment, patients and gynaecologists agreed unanimously.

Study Discontinuation

A total of 19 650 patients (90.1%) completed the six cycles of treatment. 1980 patients (9.1%) withdrew from the survey for various reasons (table III). For a further 0.8% no information on premature termination was available. 20.6% of the reasons given for discontinuing chlormadinone acetate 2mg/ethinylestradiol 0.03mg turned out to be non-medical. The remaining 79.4% based on medical complaints included intracyclic bleeding (27.3% of withdrawn patients), amenorrhoea (5.2% of withdrawn patients) and dysmenorrhoea (2.4% of withdrawn patients).

About one-third (34.8%) of all women who discontinued the study because of intracyclic bleeding had already complained about these disorders prior to chlormadinone acetate 2mg/ethinylestradiol 0.03mg intake. Similarly, 29.4% and 53.2% of all

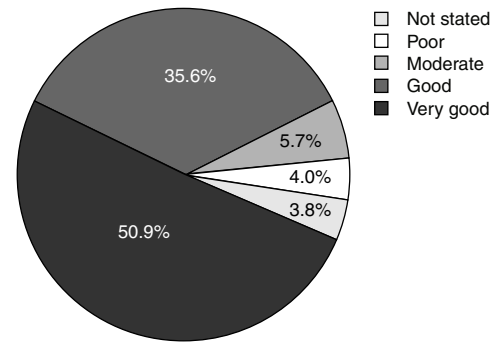

Fig. 3. Patients' overall tolerability rating for chlormadinone acetate 2mg/ethinylestradiol 0.03mg (n = 21 820).

Table III. Reasons for premature discontinuation of chlormadinone acetate 2mg/ethinylestradiol 0.03mg treatment in 1980 women[a]

Reasons	n (% of total no. of participants)
Non-medical reasons	**408 (1.9)**
Wish to get pregnant	144 (0.7)
Tired of taking pills	136 (0.6)
OC no longer required	64 (0.3)
Lost to follow up	64 (0.3)
Intracyclic bleeding	**541 (2.5)**
Amenorrhoea	**102 (0.5)**
Dysmenorrhoea	**47 (0.2)**
Further common complaints during use of OC	**405 (1.9)**
Headache/migraine	194 (0.9)
Weight gain	166 (0.8)
Breast pain	134 (0.6)
Depression/mood swings	77 (0.4)
Other medical reasons	**385 (1.8)**

a Because of multiple citing, the number of reasons for discontinuation is higher than the number of women who stopped prematurely.

OC = oral contraceptive.

patients withdrawing from the study because of amenorrhoea and dysmenorrhoea reported these symptoms at baseline.

Of the 19 650 women who completed the study, 80.6% expressed a definite wish to continue with chlormadinone acetate 2mg/ethinylestradiol 0.03mg treatment after the six cycles were completed.

Cycle Control

During chlormadinone acetate 2mg/ethinylestradiol 0.03mg treatment, 15 187 (69.6%) patients did not experience any bleeding disorder. For 131 (0.6%) participants no data were available. Spotting, breakthrough bleeding and amenorrhoea were documented in 24, 6.0 and 4.3% of the women, respectively. There was no withdrawal bleeding for three or more consecutive cycles in 0.33% of the women. The rate of spotting slightly decreased (<19 years: 27.2%, ≥39 years: 23.5%) and the rate of amenorrhoea slightly increased (<19 years: 3.4%, ≥39 years: 5.5%) with age. When analysed according to previous use of oral contraceptives, the frequencies of bleeding disorders were similar in starters and switchers.

Intracyclic bleeding decreased substantially, from 19.0 and 3.9% of women with spotting and breakthrough bleeding in cycle one to 1.2 and 0.4% in cycle six (figure 4). Figure 5 shows the frequency of intracyclic bleeding and amenorrhoea per treatment cycle in patients who did not suffer from menstrual disorders prior to study treatment.

In women with an initially regular cycle, the rates of menstrual bleeding disorders were always below the average of all patients (spotting: 22.7 *vs* 24.9%, breakthrough bleeding: 5.3 *vs* 6.0%, amenorrhoea: 4.0 *vs* 4.3%). With regard to 125 634 documented cycles of exposure, spotting occurred in 7.8%, breakthrough bleeding in 1.7% and amenorrhoea in 1.0% of all cycles.

Conversely, intracyclic bleeding and amenorrhoea disappeared on chlormadinone acetate 2mg/ethinylestradiol 0.03mg treatment in 62.2 and 92.2% of the women who experienced these symptoms during the last two cycles before study participation.

During study treatment, the intensity of withdrawal bleeding was assessed to be mild in 6977 (32.0 *vs* 21.9% at baseline), normal in 13 457 (61.7 *vs* 62.6% at baseline), and severe in 267 patients (1.2 *vs* 14.0% at baseline). For the remaining 1113 patients, a withdrawal bleeding status had not been

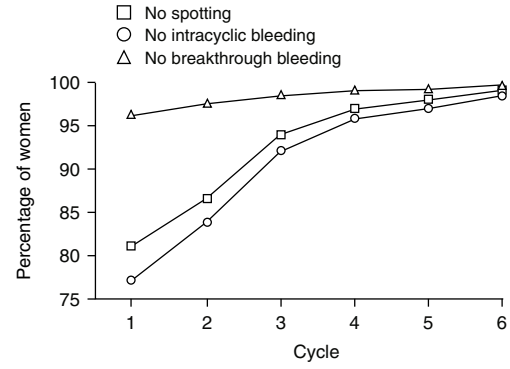

Fig. 4. Proportion of women without menstrual bleeding disorders during treatment with chlormadinone acetate 2mg/ethinylestradiol 0.03mg.

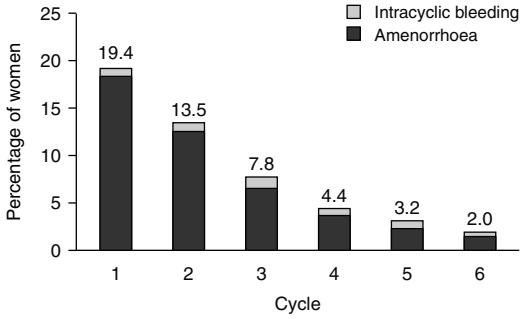

Fig. 5. Frequency of intracyclic bleeding and amenorrhoea per treatment cycle in women who did not have menstrual disorders prior to treatment with chlormadinone acetate 2mg/ethinylestradiol 0.03mg.

documented. In 72.6% of all cases the intensity of severe withdrawal bleeding and severe menstrual periods substantially decreased. 88.1% of the patients without previous dysmenorrhoea also reported being symptom-free during chlormadinone acetate 2mg/ethinylestradiol 0.03mg treatment. In 67.6% of the women who experienced dysmenorrhoea during the last two cycles before study participation, these symptoms were no longer present during chlormadinone acetate 2mg/ethinylestradiol 0.03mg intake.

General Adverse Events

In addition to menstrual bleeding disorders and dysmenorrhoea, further symptoms and adverse events were reported in 2932 patients (13.4%). They were reported more frequently in pill switchers than in pill starters (symptoms: 15.9% *vs* 9.6%; adverse events: 11.2% *vs* 8.1%). Although the age structure of pill switchers and pill starters is different, increased rates of symptoms/adverse events for pill switchers were also observed in comparable age groups. Most of the women with pre-existing symptoms (e.g. migraine/headache, breast pain, depression, tiredness, decreased libido, gastrointestinal disorder or premenstrual syndrome) reported that these complaints disappeared during treatment with chlormadinone acetate 2mg/ ethinylestradiol 0.03mg (figure 6).

Two thousand one hundred and seventy-four women (10.0%) reported experiencing new symptoms or symptoms with increased intensity during chlormadinone acetate 2mg/ethinylestradiol 0.03mg administration. The most frequently documented adverse events were breast pain (n = 793; 3.6%), migraine/headache (n = 558; 2.6%), weight gain (n = 229; 1.1%), gastrointestinal disorder (n = 202; 0.9%) and depression (n = 174; 0.8%). These symptoms became less frequent during further treatment. The mean bodyweight changed from 61.7 ± 9.1kg at baseline to 62.0 ± 8.0kg after six cycles of treatment. All other adverse events were reported at a rate of less than 0.8% (n = 218; 1.0%).

A total of 13 serious adverse events were documented during the study. Six of them were thought by the investigator to be either possibly or probably related to the use of chlormadinone acetate 2mg/ethinylestradiol 0.03mg; five cases of ovarian cysts (all removed surgically) and one case of palpable unspecified tissue change in the breast (sample excision planned; patient lost to follow up).

Venous Thromboembolic Events

One case of superficial leg vein thrombosis and one case of pulmonary embolism were diagnosed during the six-cycle treatment period; both patients recovered with appropriate treatment. Assuming

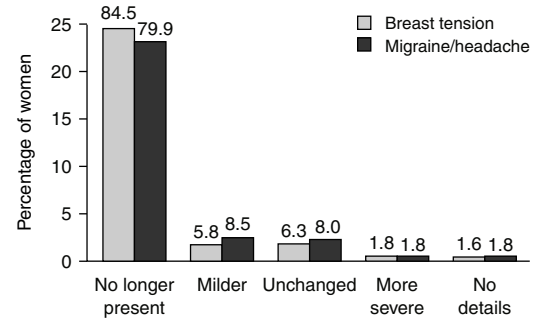

Fig. 6. Changes in breast tension (n = 2076) and migraine/headache symptoms (n = 2127), the two most predominant adverse effects, during treatment with chlormadinone acetate 2mg/ethinylestradiol 0.03mg.

13 menstrual cycles per year, the VTE rate per 10 000 women years was 2.0695 [95% CI (0.2506; 7.4755)].

Effects on Skin and Hair Condition

In women, androgen-related problems such as skin blemishes and greasy hair may considerably impair general psychological well-being. At baseline more than two-thirds of all study participants had pustules or acne-like skin disorders (n = 15 259; 69.9%). These symptoms improved during chlormadinone acetate 2mg/ethinylestradiol 0.03mg treatment in 13 199 patients (86.5%), including 4349 women (28.5%) who experienced complete cure. On the basis of 21 820 study participants, the rate of greasy or very greasy skin conditions decreased from 24.4% at baseline to 2.5% after six cycles of treatment. The number of patients with slightly greasy skin improved from 34.8 to 21.0%, while the rate of dry skin conditions remained nearly unchanged (figure 7).

The reduction in seborrhoeal conditions was reflected in a change in hair condition. 16 635 (76.2%) reported normal hair condition after six cycles of chlormadinone acetate 2mg/ethinylestradiol 0.03mg treatment, compared with 43.9% at baseline. Correspondingly, the number of women with greasy or very greasy hair improved from 47.0 to 13.6%. The reduction in hair greasiness was also reflected by a decrease of 47% in daily hair washes: at baseline 23.1% of all women preferred to wash their hair once daily; at cycle six, this was still the case for only 12.3% of all study participants.

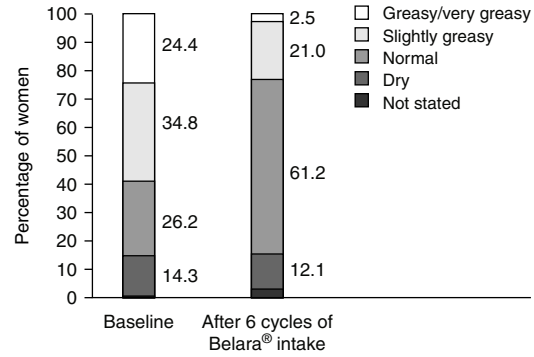

Fig. 7. Skin condition before and after six cycles of chlormadinone acetate 2mg/ethinylestradiol 0.03mg (Belara®).

Discussion

The aim of this post-marketing surveillance study was to examine the contraceptive efficacy and tolerability of chlormadinone acetate 2mg/ethinylestradiol 0.03mg in a large sample of women. In addition the influence of this combination OC on clinical signs of androgenisation was evaluated. The survey involved 3600 gynaecologists and a large study population of more than 21 800 women. A non-interventional design was used, thus reflecting daily gynaecological practice. With regard to the balance of starters and switchers, age ranges and smoking habits, the study population profile appeared to be typical of oral contraceptive users in Germany.

The results confirm that chlormadinone acetate 2mg/ethinylestradiol 0.03mg provides reliable contraceptive efficacy. A total of 36 pregnancies occurred during 125 634 cycles in 21 820 women, resulting in an unadjusted Pearl index of 0.34. However, 27 pregnancies occurred in women who reported intake errors (n = 27) and in one further case a drug interaction could not be ruled out (n = 1), thus leading to an adjusted Pearl index of 0.08. This appears to be an improvement even on the unadjusted Pearl index of 0.65 (adjusted PI: 0.27) found in a phase III study that included 1655 women and 22 337 cycles of chlormadinone acetate 2mg/ethinylestradiol 0.03mg.[9] Runnebaum and Rabe published comparable data for other low-dose combination contraceptives, with a Pearl index based on 12 cycles per woman year ranging from 0.1 to 0.9.[10]

Chlormadinone acetate 2mg/ethinylestradiol 0.03mg was well tolerated, as highlighted by the high percentage of women (80.6%) who chose to remain on the combination after having finished the survey. No clinically relevant differences in terms of cycle control and adverse events were observed between pill switchers and pill starters.

An important factor for the acceptance of an oral contraceptive is sustained cycle stability without intracyclic bleeding or secondary amenorrhoea.[11] Almost two-thirds of all women who previously experienced intracyclic bleeding disorders reported that these symptoms disappeared on chlormadinone acetate 2mg/ethinylestradiol 0.03mg treatment. This was also the case for more than 90% of women with previous amenorrhoea. Furthermore, about one-third of all patients did not experience any spotting or breakthrough bleeding during the course of the study and the rates of cycles without intracyclic bleeding continuously increased with the duration of study treatment. These data are comparable with the published results with other monophasic OCs.[12-14]

Another major concern for oral contraceptive users is missing withdrawal bleeding because there is uncertainty whether contraception has failed. Consequently, preparations with a high incidence of amenorrhoea give rise to non-compliance. In the present survey amenorrhoea was limited to a very low rate of only 1.0% of all cycles during chlormadinone acetate 2mg/ethinylestradiol 0.03mg administration.

Severe withdrawal bleeding and dysmenorrhoea are known to be further common menstrual cycle disturbances causing discomfort. Both symptoms markedly decreased on chlormadinone acetate 2mg/ethinylestradiol 0.03mg intake.

In the present survey, the documented adverse events reflect the spectrum of complaints usually observed with OCs. As expected, their frequency decreased with further treatment. However, there was no report of an adverse event considered definitely related to chlormadinone acetate 2mg/ethinylestradiol 0.03mg. Many women already experienced symptoms such as breast pain and migraine/headache prior to the commencement of the study. It is noteworthy that these symptoms substantially improved during treatment.

Weight gain is another frequent complaint of women on OCs. Cachrimanidou et al.[15] reported that 1% of all women using a combination contraceptive of EE and desogestrel discontinued use because of weight gain. A negligible effect on bodyweight has been found for chlormadinone acetate 2mg/ethinylestradiol 0.03mg, with only a very slight tendency for average bodyweight to increase.

Thromboembolic events are critical aspects for the tolerabilty of any oral contraceptive.[16] More than one-third of all women showed risk factors for the intake of an OC at baseline, including smoking, varicosis and a family history of thromboembolic disease. Nevertheless, only two VTEs occurred during the course of the study: one case of superficial leg vein thrombosis and one case of pulmonary embolism. These results are similar to those of a post-marketing study with dienogest 2.0mg and EE 0.03mg in which two cases of thrombosis and one case of suspected pulmonary embolism were reported in 92 146 cycles of exposure.[17] In the present survey pulmonary embolism was diagnosed in a 20-year-old woman who was admitted to hospital because of breathing problems. Smoking 1 to 10 cigarettes per day was the only risk factor for developing a thromboembolic event. However, the breathing problems had been evident for 3 years. Thrombolytic therapy was given and the patient soon recovered.

In this large post-marketing survey, the incidence of venous thrombosis was approximately 2.1 per 10 000 women-years at risk, which appears to be low. The results found with chlormadinone acetate 2mg/ethinylestradiol 0.03mg are comparable with the published data for the incidence of VTEs on the intake of low-dose OCs, ranging from 1.5 to 4 per 10 000 women-years at risk.[18-21]

Chlormadinone acetate is a progestogen derivative with anti-androgenic properties. It reduces dermal manifestations of androgenisation by competing with endogenous androgens at their receptors in the sebaceous gland cells, thus improving acne, seborrhoea, alopecia and hirsutism.[6,23] Other anti-androgenic mechanisms shown in several studies are the downregulation of androgen receptors and the inhibition of 5α-reductase type I, which converts testosterone into the far more potent dihydrotestosterone.[5,6,22,23] Estrogens are

known to suppress pituitary gonadotropin secretion, thereby inhibiting androgen biosynthesis in ovaries and adrenals.[24-26] Furthermore, they may have a direct effect on sebum production[27] and they raise the plasma levels of sex hormone binding globulin,[28] which in turn lowers circulating testosterone. In contrast to progestogens derived from the 19-nortestosterone series, chlormadinone acetate is not expected to interfere with these estrogen-related anti-androgenic effects.

The results of the present study confirm the pronounced anti-androgenic properties of chlormadinone acetate 2mg/ethinylestradiol 0.03mg. At baseline, pre-existing androgen-related skin and hair conditions were seen in about two-thirds of all patients. More than 80% of these women experienced substantial improvement or even complete resolution during chlormadinone acetate 2mg/ethinylestradiol 0.03mg administration. In parallel, the decrease in seborrhoeal conditions was reflected by a nearly 50% reduction in daily hair washes. These results correspond well with the anti-androgenic effects shown in various investigations of combined preparations containing chlormadinone acetate and EE.[3,9,29]

Conclusion

Overall, chlormadinone acetate 2mg/ethinylestradiol 0.03mg was shown to provide both a reliable contraceptive efficacy and an excellent tolerability profile comparable with other low-dose contraceptives. This was highlighted by the high number of women who chose to remain on treatment after completion of the study. Furthermore, the results of this post-marketing survey demonstrated high cycle stability and substantiated the well-known major benefits of chlormadinone acetate 2mg/ethinylestradiol 0.03mg on androgen-related conditions such as greasy skin and hair disorders. OCs with anti-androgenic properties such as chlormadinone acetate 2mg/ethinylestradiol 0.03mg may represent a preferred option for women wanting effective contraception combined with beneficial effects on dermatological manifestations of hyperandrogenaemia.

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