ORIGINAL RESEARCH ARTICLE

ELSEVIER

Efficacy and Safety of the New Antiandrogenic Oral Contraceptive Belara®

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The aim of this open, noncontrolled phase III study was the assessment of the contraceptive efficacy and the evaluation of the safety of long-term use of Belara® (30 μg ethinyl estradiol plus 2 mg chlormadinone acetate). Furthermore, cycle stability during administration of Belara and the influence of Belara on acne and seborrhea as clinical signs of androgenization were observed. Belara was taken by 1655 women for a total of 22,337 cycles. For the theoretical Pearl index, a value of 0.269 (95% CI [0.109, 0.600]) was calculated. In 1655 of 22,337 cycles (7.4%), no withdrawal bleeding was documented, whereas in 2565 of 22,308 cycles (11.5%), spottings and, in 786 of 22,308 cycles (3.5%), breakthrough bleeding occurred. After the intake of Belara for 12 cycles, acne on the face/neck improved in 64.1% of the women (209 of 326). In 53.4% of the women (175 of 326), acne disappeared completely. Seborrhea improved after 12 cycles in 89 of 131 women (67.9%), of whom 76 women (58.0%) were completely cured. Sixty-two serious adverse events (SAE) occurred in 59 of 1655 women. Accidents and injuries of the musculoskeletal system were the SAE with the highest incidence (0.66%). Two cases of deep venous thrombosis, one pulmonary embolism, and two cases of visual disturbances were observed. Only for the two cases of deep venous thrombosis could a relation to Belara be assumed. Of the adverse events commonly reported for oral contraceptives, headache was observed for the first time under study medication in 37.4%, nausea in 23.1%, breast tenderness in 21.7%, and vaginal discharge in 19.4% of the women. The frequency of adverse events decreased with longer duration of a drug consisting of intake of Belara. In conclusion, Belara can be described as an effective and safe oral contraceptive with marked antiandrogenic properties. CONTRACEPTION 1998;57:103–109 © *1998 Elsevier Science Inc. All rights reserved.*

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Submitted for publication October 6, 1997
Revised December 5, 1997
Accepted for publication December 16, 1997

KEY WORDS: oral contraception, Belara®, cycle control, antiandrogenic efficacy, safety

Introduction

When oral contraceptives were introduced over 30 years ago, the estrogen and progestogen content was high and, consequently, a high incidence of side effects was seen. In order to reduce these side effects, the dosage of the estrogen and progestogen components has been reduced during the last 2 decades. Adverse effects on the metabolism and clotting parameters were reduced and the general tolerability of the pill was improved, without affecting efficacy or cycle stability. The reasons for the reduction of the estrogen fraction are summarized in recommendations made by experts.[1]

In contrast with other progestogens derived from the nortestosterone series, chlormadinone acetate is a progesterone derivative with antiandrogenic properties that reinforces the protective properties of the estrogens on the cardiovascular system. In addition to this positive effect, chlormadinone acetate (CMA) as an antiandrogen can reduce clinical manifestations of androgenization.[2,3]

The aim of the open, noncontrolled phase III study discussed here was the assessment of the contraceptive efficacy of Belara® and the evaluation of safety after long-term intake of Belara (30 μg ethinyl estradiol plus 2 mg chlormadinone acetate). Furthermore, cycle stability during the administration of Belara and the influence of Belara on clinical signs of androgenization (acne and seborrhea) were observed.

Materials and Methods

The study was designed as a multicenter, open, noncontrolled phase III trial. The study protocol was approved by local ethics committees.

The study plan was for 1600 healthy women of reproductive age (smokers, 18–30 years; nonsmokers, 18–40 years) to take Belara for a duration of ≤24 cycles. However, only a few women took Belara for this complete period, as the study was terminated

ISSN 0010-7824/98/$19.00
PII S0010-7824(98)00008-0

when a total of 20,000 cycles under medication were collected. After explanation of the study and written informed consent, a detailed medical history, including previous and concomitant diseases and medication, were documented. A general medical examination, a gynecologic examination including a Papanicolaou smear and a pregnancy test, and a dermatologic examination were carried out. At the dermatologic examinations for acne, the stage terms comedonica, papulo-pustulosa, and conglobata were used to reflect the increasingly inflammatory character of the lesions; the intensity of each stage could be further detailed as mild, moderate, or severe. The same intensities were to be used for the description of seborrhea. In addition, blood and urine for laboratory screening were sampled and analyzed by one central laboratory.

After the inclusion and exclusion criteria had been checked, women received one package of study medication containing 3 blisters with 21 film-coated tablets of Belara (30 μg ethinyl estradiol (EE), 2 mg CMA). The first tablet of Belara was to be taken on the first day of withdrawal bleeding. After 21 days of intake, a 7-day pill-free interval followed, after which the intake of Belara was continued. On a cycle calendar, each participant had to document all adverse events as well as missed pills and bleeding events with duration and intensity, and concomitant medication, if taken. Control examinations were planned for cycles 2, 4, 7, 10, 13, 16, 19, 22, and 24; further study medication was then provided. At each examination, a general medical examination was carried out and the volunteer was asked to report on adverse events and bleeding patterns. In cycles 7, 13, 19, and 24, the gynecologic, dermatologic, and laboratory examinations were repeated. In case of premature termination, the same examinations were performed.

For assessment of contraceptive efficacy, the Pearl index (PI)[4] was calculated, and a life table analysis (cumulative rates of pregnancies per number of volunteers) according to Potter[5] was performed.

Results

A total of 1655 women who were patients of 75 office-based gynecologists in Germany participated in the study and were treated with Belara for ≤24 cycles, thus making up a total of 22,337 cycles. A total of 448 of 1655 women (27.1%) were smokers; 1,207 of 1,655 women (72.9%) were non- or ex-smokers. Of all women in the study, 66.9% changed from another oral contraceptive to Belara with a break of <3 cycles (ie, pill switchers), 33.1% took an oral contraceptive for the first time or had a break of >3 cycles between the previous oral contraceptive and Belara (ie, pill starters). Of 1655 women, 972 (58.7%) were analyzable regarding long-term effects of Belara, as these women took the study medication for ≥13 months.

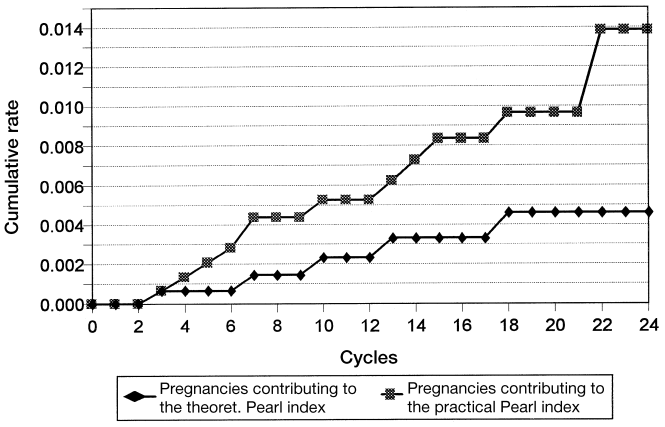

Figure 1. Cumulative rates of pregnancies per number of volunteers during intake of Belara (adjusted for termination process).

The women had a mean age of 25.9 years, a mean height of 168.0 cm, a mean weight of 62.4 kg, and a mean body mass index (BMI) of 22.1 kg/m^2.

Of the 1655 women who participated in the study, 703 terminated the study prematurely. The most common reasons for premature termination were protocol violations, adverse events, bleeding disorders, and the wish to become pregnant.

Efficacy

A total of 12 pregnancies occurred during 22,337 cycles in 1655 women on study medication. The practical Pearl index was 0.645 (95% CI [0.359, 1.092]). For the theoretical Pearl index in this study, a value of 0.269 (95% CI [0.109, 0.600]) was calculated. The cumulative 12-cycle pregnancy rate was 0.00232 (95% CI [0.0, 0.0049]) considering only the pregnancies contributing to the theoretical Pearl index and 0.00525 (95% CI [0.00135, 0.00914]) considering all pregnancies. After 24 cycles, the cumulative pregnancy rate was 0.0046 (95% CI [0.00047, 0.00873]) and 0.01385 (95% CI [0.0038, 0.0239]), respectively (Figure 1).

For the assessment of cycle control, 1655 women were evaluated. In 92.0% of the cycles (20,543 of 22,337 cycles), regular withdrawal bleeding was observed. Only in 1655 of 22,337 cycles (7.4%; 0.6% missing values) was no withdrawal bleeding documented. The highest frequency of absence of withdrawal bleeding was observed in the first cycle (216 of 1628 women/13.3%), with a higher frequency in the subgroup of pill starters (86 of 535 women/16.1%) than in the group of pill switchers (130 of 1093

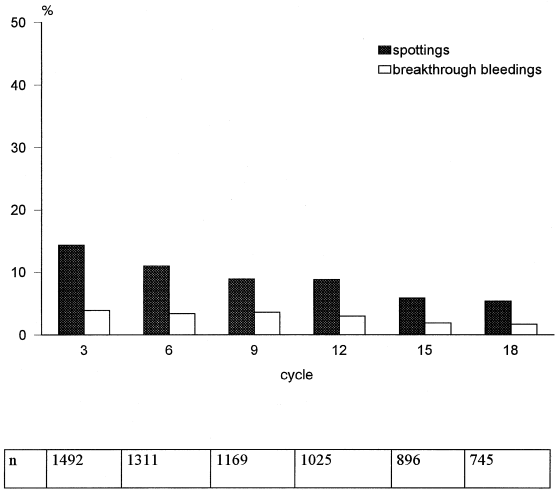

Figure 2. Percentage of women with spotting and breakthrough bleeding during intake of Belara.

women/11.9%). The proportion of women without withdrawal bleeding decreased with duration of intake of Belara, and the early difference in absence of withdrawal bleeding between pill starters and pill switchers tended to disappear with duration of intake.

In 2565 of 22,308 cycles (11.5%) spotting and in 786 of 22,308 cycles (3.5%) breakthrough bleeding were documented. The frequency of spotting and breakthrough bleeding decreased with longer duration of intake of study medication. In the third medication cycle, 215 of 1492 women (14.4%) reported spottings, 144 of 1311 (11.0%) in cycle 6, 104 of 1169 (8.9%) in cycle 9, 90 of 1025 (8.8%) in cycle 12, 53 of 896 (5.9%) in cycle 15, and 40 of 745 women (5.4%) in cycle 18. The frequency of breakthrough bleeding dropped comparably (Figure 2).

A total of 439 of 999 women (43.0%) who were analyzable regarding dermatologic findings had acne at the beginning of the study. Acne was found both on the face/neck and the trunk, but the face was by far the most frequently affected area. A total of 326 of the women with acne on the face at the beginning of the study took Belara for ≥13 cycles and were, therefore, analyzable in terms of long-term intake of study medication. All types of acne (comedonica, papulopustulosa, and conglobata) were seen at baseline. Sixty-seven of 326 women (20.6%) suffered from the more severe types of acne on the face that may lead to scarring (moderate or severe acne papulo-pustulosa and all intensities of acne conglobata). After 12 cycles of Belara, all types of acne on the face/neck improved in 64.1% of the women (209 of 326 women with an intake of ≥13 cycles); improvement defined as either a decrease in intensity of the type of acne, or a change to the less severe type (acne comedonica the least

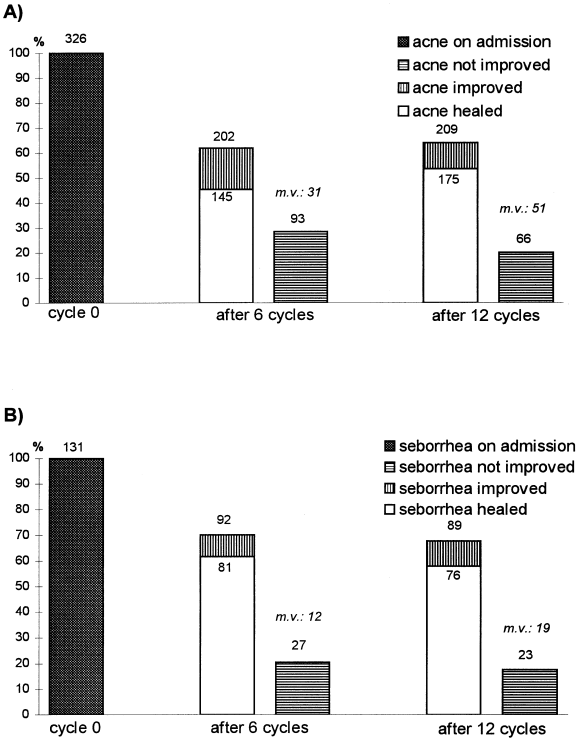

Figure 3. Percentage of women with changes in **A**) acne findings and **B**) seborrhea findings (women with intake of Belara for ≥13 cycles and with acne or seborrhea on admission). Only women with an examination at the appropriate time are shown. *m.v.:* missing value.

severe and acne conglobata the most severe type) or the disappearance of symptoms. For acne on the trunk, an improvement was seen in 77 of 110 women (70.0%). About 3% of the women with acne at baseline experienced a deterioration of acne. Of the women without acne at baseline, <4% developed acne during the use of Belara. A disappearance of symptoms on the face after 12 cycles was observed in 175 of 326 women (53.7%) who were taking Belara for ≥13 cycles (Figure 3A).

Seborrhea was found in 167 of 999 women (16.7%). Assessing the effect of the long-term intake of Belara for 12 cycles, 89 of 131 women with seborrhea at baseline (67.9%) experienced an improvement of seborrhea. Seventy-six of these women (58.0%) were completely cured of seborrhea. Comparable effects were already seen after seven cycles of Belara (Figure 3B).

Safety

For the safety analysis, data for 1631 women were evaluated. Twenty-four women who received study medication on admission did not return for any examination; therefore, no further information on use of Belara or on adverse events was available.

Table 1. Absolute and relative frequencies of women with symptoms in selected cycles (first occurrence during intake of study medication)

	Cycle 3		Cycle 9		Cycle 15	
Symptoms	n/total n	%	n/total n	%	n/total n	%
Headache	156/1257	12.4	97/987	9.8	51/754	6.8
Breast tenderness	67/1263	5.3	31/1006	3.1	13/771	1.7
Vaginal discharge	66/1294	5.1	29/1013	2.9	14/769	1.8
Nausea	65/1440	4.5	25/1128	2.2	13/869	1.5
Tiredness	54/1324	4.1	25/1040	2.4	9/793	1.1
Excitability	45/1270	3.5	15/1017	1.5	4/770	0.5
Depressed state	39/1380	2.8	16/1095	1.5	6/840	0.7
Dysmenorrhea	29/1300	2.2	16/1034	1.5	8/799	1.0
Dizziness	30/1432	2.1	11/1129	1.0	4/871	0.5
Nervousness	24/1359	1.8	6/1081	0.6	5/822	0.6
Vomiting	25/1476	1.7	8/1155	0.7	3/888	0.3
Heaviness in limbs	23/1427	1.6	6/1116	0.5	4/857	0.5
Edema, legs	9/1445	0.6	9/1135	0.2	1/873	0.1
Visual disturbance	5/1470	0.3	3/1151	0.3	2/885	0.2
Pigmentation abnormality	4/1469	0.3	0/1154	0	2/885	0.2
Other	126/1469	8.6	87/1153	7.5	50/885	5.6

In general, the reported adverse events reflect the spectrum of complaints usually observed during use of oral contraceptives. The most frequently reported adverse events, observed for the first time with study medication were headache in 37.4% of the women, nausea in 23.1%, breast tenderness in 21.7%, and vaginal discharge in 19.4%.

The description of symptoms showed maximum occurrence at the beginning of the study, with a decrease in all symptoms in the following cycles (Table 1).

No adverse event was judged by the investigators to be definitely caused by the study medication. No uniform trend toward an increase in the observed adverse events within the categories ''probable'' and ''possible'' were observed in smokers or nonsmokers.

In total, 62 serious adverse events (SAE) occurred in 59 of 1655 women. In most cases, the SAE were not related to the intake of Belara. Accidents and injuries of the musculoskeletal system were the SAE with the highest incidence (n = 11; 0.66%), followed by surgery due to ovarian cysts (n = 7; 0.42%), hearing impairments (n = 3; 0.18%) and goiter (n = 3; 0.18%). The other SAE were single events. No indications of a remarkable frequency of any given event were found.

Two diagnostically proved cases of deep venous thrombosis (DVT) and one case of pulmonary embolism occurred during the study. Furthermore, two cases of visual disturbances in combination with headache were observed that might be suspected of being thromboembolic in origin, but that were not classified as serious adverse events.

No clinically relevant influences of Belara on laboratory parameters such as coagulation, liver and renal function, carbohydrate metabolism, electrolyte balance, thyroid function, or hematological parameters were found. The median total cholesterol values were at the upper limit of the reference range (200 mg/dL) on admission and during the entire study period. Total triglycerides and VLDL values increased during the study. On the other hand, an increase in median HDL cholesterol and a corresponding marked decrease in median LDL values led to a decreased LDL/HDL ratio. Thus, a beneficial effect of Belara on the risk of developing atherogenic diseases can be assumed.

The systolic and diastolic blood pressure remained unchanged in all cycles during the course of the entire study. No relevant changes were observed either in heart rate or in body weight during Belara use. The mean change in weight was 0.8% in cycle 2, 0.7% in cycle 4, 1.0% in cycle 10, and 0.6% in cycle 22. The majority of the women had a body mass index of 22 kg/m^2 and did not experience major weight changes. From the data collected, no negative influence of long-term administration of Belara on libido, mood, or appetite could be assumed.

Discussion

Efficacy

A total of 12 pregnancies occurred during intake of Belara. The practical Pearl index was 0.642 (95% CI [0.359, 1.092]). In 7 of these 12 pregnancies, conception occurred because of intake errors, concomitant administration of antibiotics, diarrhea, or vomiting. Thus, the theoretical Pearl index was 0.269 (95% CI

[0.109, 0.600]). These results are in accordance with Runnebaum and Rabe, who published a range of 0.1–0.9 for the Pearl index of combination oral contraceptives.[6]

Missed withdrawal bleeding is a sign of poor cycle control that may cause discomfort in women. The relative frequency of cycles without withdrawal bleeding was low and decreased with prolonged intake of Belara. In cycle 1, 13.3% of all women did not show a withdrawal bleeding; this rate was 8.1% in cycle 3 and 5.8% in cycle 13. The relative frequencies of cycles without withdrawal bleeding during treatment with desogestrel 150 μg plus 30 μg EE were 12.1% in cycle 1, 7.9% in cycle 3, and 6.4% in cycle 12.[7] The results of the current study are in accordance with these data.

Although bleeding disturbances are not major side effects of oral contraceptives, they are a major concern for oral contraceptive users.[8] In a study of an oral contraceptive containing 30 μg EE and 150 μg desogestrel, breakthrough bleeding was found in 2.5% of the cycles and intermenstrual bleeding and spotting were found in 5.6% of the cycles.[9] These results are comparable with the effects seen in women using Belara. The relative frequencies of spottings and breakthrough bleedings in the previously mentioned study with 30 μg EE and 150 μg desogestrel decreased from 10% and 3.5% in cycle 3 to 8% and 2% in cycle 12, respectively, which is in accordance with the data observed during Belara use. In summary, the current study demonstrated that during Belara use, good cycle control was achieved, which compares well with the cycle control during intake of other combined, low-dose oral contraceptives.

Chlormadinone acetate as an antiandrogen reduces dermal manifestations of androgenization.[10] Antiandrogenic substances compete with androgens at the receptor of the target cell, thus improving seborrhea, acne, alopecia and hirsutism.[2,3] Furthermore, the estrogen component (ethinylestradiol) of combination oral contraceptives induces increased sex hormone binding globulin (SHBG) plasma levels due to increased hepatic synthesis. These increased SHBG plasma levels reduce the free testosterone plasma levels through an increased binding rate of plasma testosterone. By suppression of the production of androgens in the ovaries and the adrenal cortex, an additional antiandrogenic effect has to be assumed.[11]

As expected, the results of the current study showed that Belara had a positive effect on clinical signs of androgenization. Regarding the women with acne at baseline who took Belara for ≥13 cycles, an improvement of acne on the face/neck was found in 62.0% and in 64.1% of the women after cycles 6 and 12, whereas 18.4% showed unchanged acne and, in 1.8% of the women, the acne on the face/neck deteriorated after 12 cycles of Belara. Complete healing of the acne was observed in 45.4% and 53.4% of the women with ≥13 cycles on Belara after 6 and 12 cycles, respectively. Kaiser investigated the effect of a two-phase oral contraceptive containing 1 or 2 mg of chlormadinone acetate and 50 μg of EE on signs of androgenization and compared it with an oral contraceptive (OC) containing norethisterone and 50 μg EE.[10] Improvement rates after 12 months of use of the CMA-containing OC resulted in 61.5%, whereas improvement rates of about 20% were achieved with the norethisterone combinations. Although (due to the higher EE content of these preparations) a more pronounced effect on clinical signs of androgenization could be expected, the improvement rate during intake of the CMA-containing OC is comparable with that achieved with Belara. Furthermore, the results indicate a more marked effect of OC containing CMA than that of OC containing norethisterone.

The effect of Belara on seborrhea was pronounced and could be observed earlier than the effect on acne. Comparable results were obtained during intake of the CMA-containing OC in the previously mentioned study of Kaiser, irrespective of a higher EE content.[10]

Safety

Two thromboembolic events related to the study medication were observed. In both cases, no activated protein C resistance was found. Nevertheless, in one case a positive family case history with varicosis and, in the other case, a protein C deficiency and a predominantly sedentary lifestyle are to be regarded as predisposing factors. Pabinger et al showed that the incidence of deep vein thrombosis/volunteer year in protein C-deficient women on OC was doubled in comparison with that of control women.[12] The pulmonary embolism occurred after surgery for a broken lower leg, 18 days after stopping the intake of Belara. It is well known that the combination of surgery and immobilization is a high risk factor for developing a thromboembolic event.[13] So, although the event was chronologically connected to the study, in agreement with the physician concerned, it was considered as being not related to use of Belara. Furthermore, two cases of visual disturbances that were not regarded as SAE were observed during the study. For both events, no evidence of a thromboembolic process could be found. In one case, the volunteer had suffered from hyperthyroidism since age 15. Hyperthyroidism at this age is accompanied in 40% of cases by ocular disorders. The other volunteer already suffered from visual disturbances before admission. Therefore, a relation to Belara is improbable.

Although this study was performed according to

the current guidelines, thromboembolic events are so rare that, from these cases, no calculation of epidemiologic risk is possible. Nevertheless, combining the results of the epidemiologic studies of Poulter et al.[14] and Farley et al.,[15] no higher frequency of thromboembolic events for OC containing CPA or CMA can be assumed in comparison with those containing progestogens of the first and second generation, whereas for the progestogens of the third generation, a twofold elevation of risk was found.

The most frequently documented adverse events were found in the predefined list of complaints that are known to be most common during use of OC. Adverse events were documented on the volunteer's cycle calendar and the investigator made inquiries at each control visit. The fact that the volunteer's attention was especially directed towards these adverse events could have increased the proportion of reports regarding these adverse events in comparison with those not mentioned on the cycle calendar. The incidences of the most frequent adverse events decreased with the duration of Belara use.

Goldzieher et al. investigated the side effects attributed to OC in a double-blind, placebo-controlled, cross-over study.[16] These results demonstrated that, during intake of placebo, the incidence of the most frequent complaints correlated with the incidence during intake of OC. The authors found that, during intake of placebo, headache in 14.5% of the women in cycle 1, 12.7% in cycle 2, 7.3% in cycle 3, and 9.8% in cycle 4; breast tenderness in 6.6% of the women in cycle 1, 11.1% of the women in cycle 2, and 1.8% and 2.4% of the women in cycles 3 and 4, respectively; nausea in 9.2% of the women in cycle 1, 4.8% in cycle 2, 9.1% in cycle 3, and 2.4% in cycle 4.

Dunson et al. compared the efficacy and safety of a triphasic and a monophasic oral contraceptive.[17] The triphasic OC contained 0.05 mg levonorgestrel and 30 μg EE, 0.075 mg levonorgestrel and 40 μg EE, and 0.125 mg levonorgestrel and 30 μg EE (Triquilar®); the monophasic OC contained 0.15 mg levonorgestrel and 30 μg EE (Lo-Femenal®). During the Dunson study, 40.4% of women experienced headache on Triquilar® and 36.3% of women on Lo-Femenal®. These incidences are comparable with those reported in the current study. Furthermore, Dunson et al. found incidences of nausea in 19.8% of women in both medication groups and of breast discomfort in 14.3% of women on Triquilar® and 12.8% of women on Lo-Femenal®.[17] However, the women investigated by Dunson et al. took the study medication for only 12 months.

In conclusion, Belara can be described as a well-tolerated, low-dose oral contraceptive with minor side effects comparable with those of other low-dose oral contraceptives.

Acknowledgments

Participating centers and investigators: *Aachen*: Bärtling/Theres, Gerick A, Jankovic E, Kehren S, Molitor D, Neumann J, Seibel H; *Aschaffenburg*: Hild A, Keller K; *Berlin*: Berger H-D, Eisinger A, Heinemann R, Heinze S, Kabisch-Jüpner S, Kaufmann H, Klebe U, Lampe G, Lorbach H, Müller B, Mund-Hoym A, Shönegg W, Steinert W, Ufer S, Vogel H; *Bonn*: Brökelmann K, Paus P, Stathakis K; *Düsseldorf*: Vrinssen D; *Hamburg*: Albrecht M, Brandes/Sprotte, Kimmich-Laux/Ehni, Koos L, Korthals D, Kuhl/Bonk, Nachtigäller/Firnrohr, Schreiber R, Zsuffa M, Züllich/Schulz-Züllich; *Kiel*: Arp W-D, Fischer W, Habura-Flüh O, Herbold H, Schilling R; *Köln*: Berendes R, Blatzheim K, Horbach G, Horstmann W, Merzenich M, Meyer, Freund, Orth, Michel R, Nasse-Neuhaus S, Palkovich/Winnen, Speeter D; *Krefeld*: Flohr A, Meinhold H; *Mönchengladbach*: Büren K, Hack-Werdier/Bäumer, Wysocki S; *München*: Hartmann D, Herrmann H, Horváth P, Ihm K, Koch S, Krause H, Krings U, Kruesmann/Friedrich, Prinz W, Rebhan K, Rothhaas W, Sasse H, Schuster W, Wolf V; *Saarbrücken*: Emmrich J; *Speyer*: Arbogast R, Laubscher M.

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