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Belara® – a reliable oral contraceptive with additional benefits for health and efficacy in dysmenorrhoea

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ABSTRACT Although modern oral contraceptives are safe and have few side-effects, compliance towards them is sometimes less than ideal for various reasons. Compliance, however, can only be achieved when the contraceptive method is accepted by the users, that is, when it is adapted to their individual needs. Consisting of a combination of 2 mg chlormadinone acetate and 0.03 mg ethinylestradiol, Belara® is a modern oral hormonal contraceptive with an unadjusted Pearl index of 0.44 (95% CI, 0.2–0.8) and an adjusted one of 0.04 (95% CI, 0.002–0.2). Its compliance rate in clinical use has been shown to be above 90%. This good acceptance is a consequence of the low rate of intermenstrual bleeding (about 8% up to the 3rd cycle and below 2% from the 12th cycle); its high cycle stability (in approximately 98% from the 6th cycle); the good weight stability (weight is unchanged in about 84% from the 12th cycle); and finally the very low rate of side-effects (below 2% after 12 cycles). In addition, a number of other benefits of using Belara® also contribute to this good compliance rate. These include almost 70% improvement or complete remission of increased seborrhoea after 12 months, almost 90% improvement or cure of acne after 12 months, and improvement or remission of dysmenorrhoea after 12 months in 79% of cases. After 4 months, improvement or remission of dysmenorrhoea associated with the use of another ovulation inhibitor was seen in more than 90% of cases after switching to Belara®. In conclusion, besides being an effective, modern oral hormonal contraceptive Belara® offers a considerable range of additional benefits for a range of symptoms, including primary dysmenorrhea and acne.

KEY WORDS Oral contraceptive, Ethinylestradiol/chlormadinone acetate, Compliance, Menstrual irregularities, Dysmenorrhea, Acne

INTRODUCTION

The WHO has estimated that worldwide 1 million new pregnancies occur each day, 50% of which are unplanned and 25% of which are unwanted. More than 500 women die from abortions each day (WHO 1999), a fact which emphasises the need for effective contraception.

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Modern hormonal oral contraceptives are safe and low in side-effects and only a few contraindications restrict their use. To prevent unwanted pregnancies and insufficient therapeutic outcomes it is absolutely necessary to ensure an acceptable compliance in contraceptive use. In order to promote compliance it is essential for the practitioner to offer a contraceptive adapted to the individual needs of women. Belara®, the combination of 2 mg chlormadinone acetate (CMA) and 0.03 mg ethinylestradiol (EE), is a modern oral hormonal contraceptive with an excellent Pearl index and additional benefits for skin and hair and overall well-being of the woman, and it therefore fulfils these criteria.

CONTRACEPTIVE EFFICACY

Belara® is a modern oral hormonal contraceptive consisting of a monophasic combination of 2 mg chlormadinone acetate and 0.03 mg ethinylestradiol. The efficiency of this micro pill has been demonstrated in a study involving 29,262 cycles in 2620 women, in whom a total of 10 pregnancies occurred during the 12-month observation period. Thus the unadjusted Pearl index was calculated to be 0.4 (95% CI 0.2–0.8). When intake errors were taken into account this resulted in an adjusted Pearl index of 0.04 (95% CI 0.002–0.2)[1]. This high contraceptive efficacy may be explained by the profound modulatory effects of Belara® on the ovaries which result in inhibition of ovulation. In addition, Belara® has an effect on suppression of endometrial growth and increased viscosity of cervical mucus.

TOLERABILITY

A post marketing surveillance study documented the rates of common complaints observed during the use of oral contraceptives[1]. The reported incidence of breast pain, headache, depression, gastrointestinal problems and loss of libido were all reduced during the 12-month study period (Figure 1).

Weight change is a concern for women taking oral contraceptives, particularly those in younger age groups, and can be a major factor affecting compliance. The weight change after 12 cycles with Belara® is shown in Figure 2. In 78.8% of women their weight was unchanged.

The compliance rate for Belara® in clinical use has been shown to be above 90%[1]. In part this is a reflection of the low rate of side-effects, but it may also be due to the additional benefits that Belara® confers on its users. Adequate cycle control is an important factor for the acceptance of an oral contraceptive, and problems with cycle control are probably the most important reason for discontinuing oral contraceptive use.

BENEFITS FOR WOMEN WITH BLEEDING DISORDERS

The post marketing surveillance study further showed that during the first cycle 18.3% of women taking Belara® had spotting and 2.9% had breakthrough bleeding. These figures had decreased to 7.9% and 1.9%, respectively, by cycle 3 and fell further during the 12-month study period[1].

Dysmenorrhoea is a further common menstrual cycle disorder causing discomfort in many women. The incidence of dysmenorrhoea was studied in 531 women, where it was found that between 17.7 and 24.4% (depending on the method of examination) suffered from mild to severe dysmenorrhoea, the younger the women the higher the incidence[2].

In the post marketing surveillance survey, of the 1266 patients who suffered from dysmenorrhoea in the last two cycles before the use of Belara®, the symptoms disappeared in 66% of cases and dysmenorrhoea pain was reduced in a further 13% after 12 cycles of Belara® use[1] (Figure 3).

A further study conducted in Columbia of 742 Latin American mestisse women found that 32% of women reported cycle irregularities such intermenstrual bleeding, oligomenorrhoea and amenorrhoea. After cycle 2 of Belara® intake only 6.6% of women reported cycle abnormalities and this further fell to 4% after the third cycle[3].

This ability of Belara® to decrease blood loss and reduce painful menstruation indicates its potential use as a therapeutic option for anaemia and dysmenorrhoea. Like other ovulation inhibitors, Belara® causes a significant reduction in endometrial thickness. This reduces total endometrial production of the uterine contractile prostaglandin $F_{2\alpha}$, which in turn explains the long familiar therapeutic effect of contraceptive pills and progestins in dysmenorrhoea.

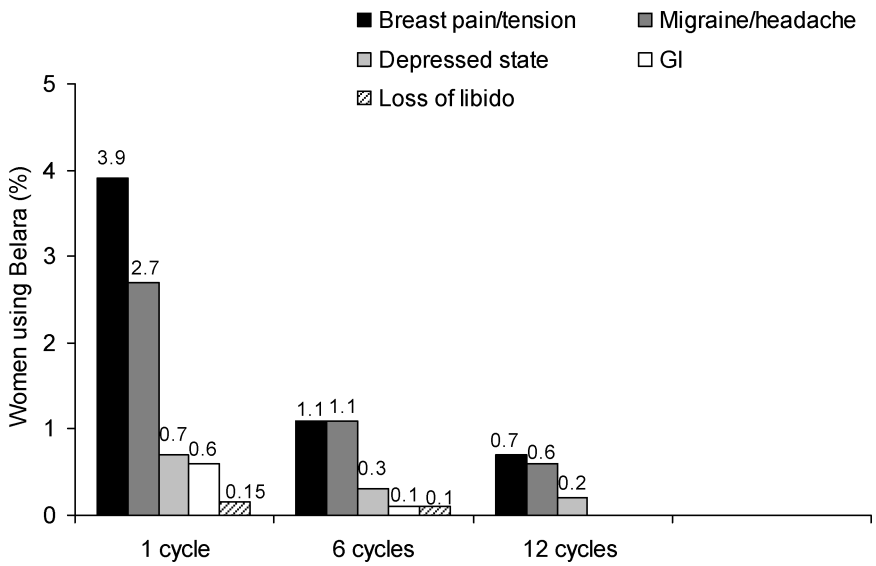

Figure 1 Incidences of breast pain, headache, depression, gastrointestinal problems and loss of libido were reduced during the 12-months of the postmarketing surveillance study[1]

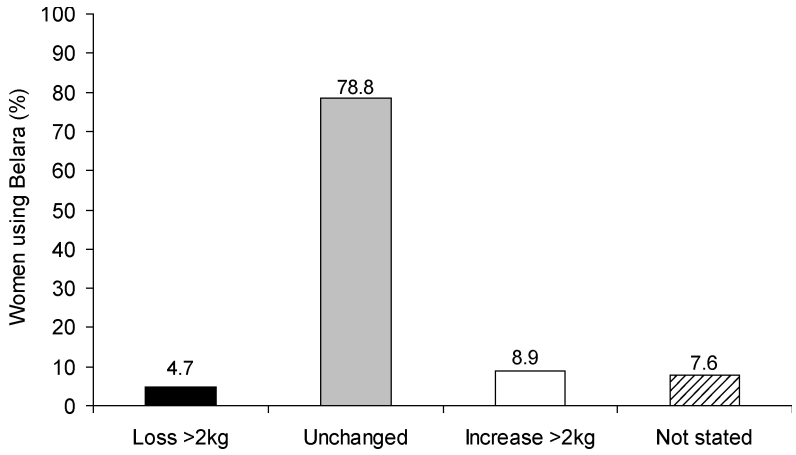

Figure 2 In 78.8% of women weight was unchanged after 12 cycles with Belara®[1]

In a further study of 1939 women with frequent dysmenorrhoea who were using other contraceptives, there was an almost 95% decrease in painful menstruation after 4 cycles of Belara® use[3] (Figure 4).

Thus, women who were already suffering from dysmenorrhoea while taking other ovulation inhibitors experienced an impressive improvement in the number of painful menstrual cycles when switching to Belara®. Since a further reduction in endometrial thickness is unlikely, the reason for the large difference in effect between Belara® and other contraceptive pills could be presumed to be due to the progestogen component of Belara®. Belara® contains 2 mg of chlormadinone acetate (CMA) which could be responsible for the beneficial effect on dysmenorrhoea. It may be speculated that CMA has a special pharmacological action in relation to endometrial arachidonic acid metabolism (Figure 5).

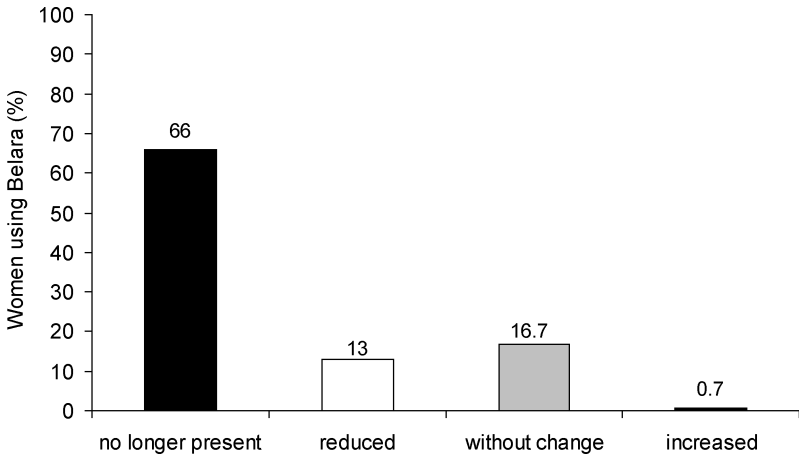

Figure 3 After 12 cycles with Belara (n = 1266), dysmenorrhoea was no longer present in 66% of the women and reduced in 13%[1]

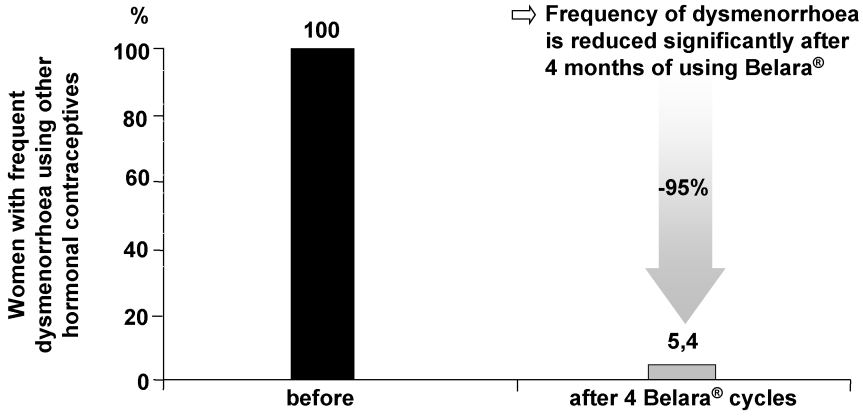

Figure 4 Another post marketing surveillance study showed a decrease in dysmenorrhoea rates by 95% after 4 cycles with Belara in 1939 users[3]

Phospholipase A2 is responsible for the transfer of the substrate to arachidonic acid. Cyclo-oxygenases 1 and 2 are responsible for the production of prostaglandin $F_{2\alpha}$ from arachidonic acid and the consequent stronger uterine contraction in women with dysmenorrhoea. It can be speculated that binding of CMA to glucocorticoid receptors is responsible for blocking phospholipase A2 and this, in combination with the inhibition of cyclo-oxygenases (as with other oral contraceptives) results in specific effects on the prostaglandin levels.

This possible mechanism obviously warrants further investigation, but should it prove to be the case, CMA would be of particular therapeutic relevance not only for dysmenorrhoea but also for a variety of other indications.

BENEFITS FOR THE SKIN AND HAIR

The benefits of Belara® on the skin are in part a consequence of the moderate anti-androgenic properties of CMA.

Many women with seborrhea and acne suffer from hypersensitivity of the sebaceaous glands to androgens. In the sebaceous gland the enzyme 5α-reductase type 1 converts testosterone to its more active component

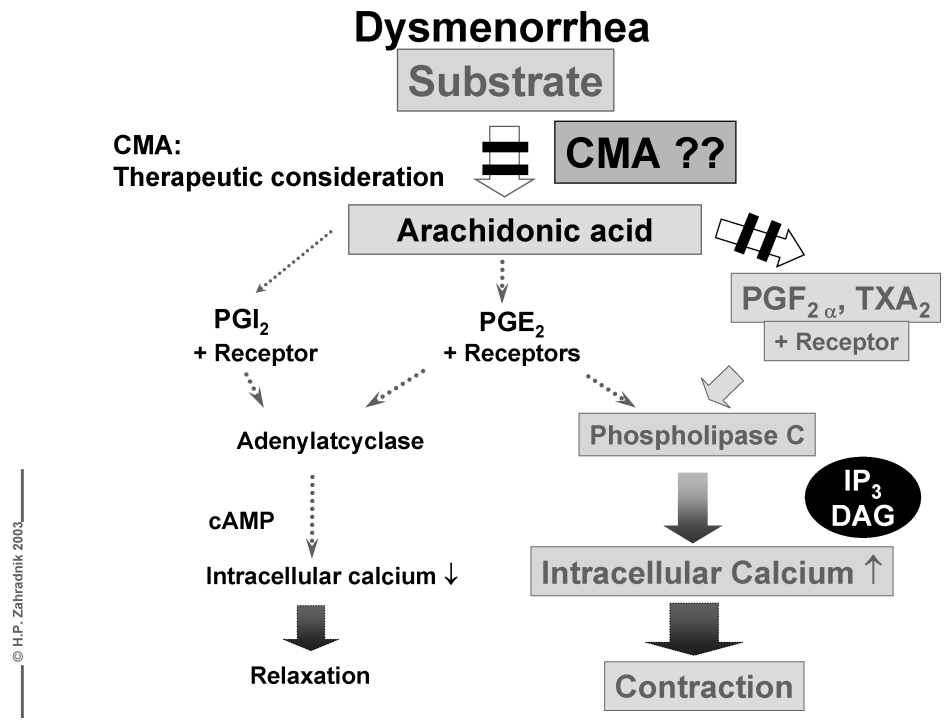

Figure 5 The possible intracellular pathways leading to dysmenorrhea. Chlormadinone acetate – binding to glucocorticoid receptor might be responsible for blocking phospholipase A2 and this, in combination with the inhibition of cyclo-oxygenases (as with other oral contraceptives) results in specific effects on the prostaglandin levels. IP_3 = Inositol-1,4,5-triphospate, DAG = Diacylglycerol, PGE_2 = prostaglandin PG E_2, PG $F_{2\alpha}$ = Prostaglandin $F_{2\alpha}$, TXA_2 = ThromboxaneA2

dihydrotestosterone (DHT). In contrast to many other progestins used in oral contraceptives, CMA competes with androgens at the level of the androgen receptor, displacing natural androgens so that they cannot act. In addition, CMA may also inhibit 5α-reductase type 1 resulting in lower levels of circulating DHT. This leads to a down-regulation of the number of androgen receptors.

CMA inhibits the secretion of androgens from both the woman's ovaries and adrenal cortex. In addition, the estrogenic component of Belara®, ethinylestradiol (EE) induces the liver to synthesize increased amounts of sex hormone binding globulin (SHBG). About 98% of sex hormones travel in the blood, half loosely bound to albumin and tightly bound to SHBG. The extra SHBG increases the quantity of tightly bound testosterone and reduces the amount that is biologically available. The free testosterone levels stay within the normal range.

The combined effects of CMA and EE, as found in Belara®, on levels of SHBG have been shown in a comparative study with another oral contraceptive (0.03 mg EE/ 0.15 mg levonorgestrel)[5]. By cycle 4 of Belara® administration the plasma level of SHBG had almost doubled (Figure 6).

CLINICAL CONSEQUENCES

The benefits conferred by Belara® intake in terms of skin problems have been demonstrated in a phase III study, where it was found that after six cycles of Belara®, there was a 60–70% improvement in acne[6]. After 12 cycles acne was either cured or improved in 90% of cases (Figure 7).

The prevalence of seborrhoea after 6 cycles was reduced to 23% in comparison the first cycle without Belara®.

CONCLUSIONS

Belara® has been demonstrated to be a reliable and effective oral contraceptive. Its proven anti-androgenic

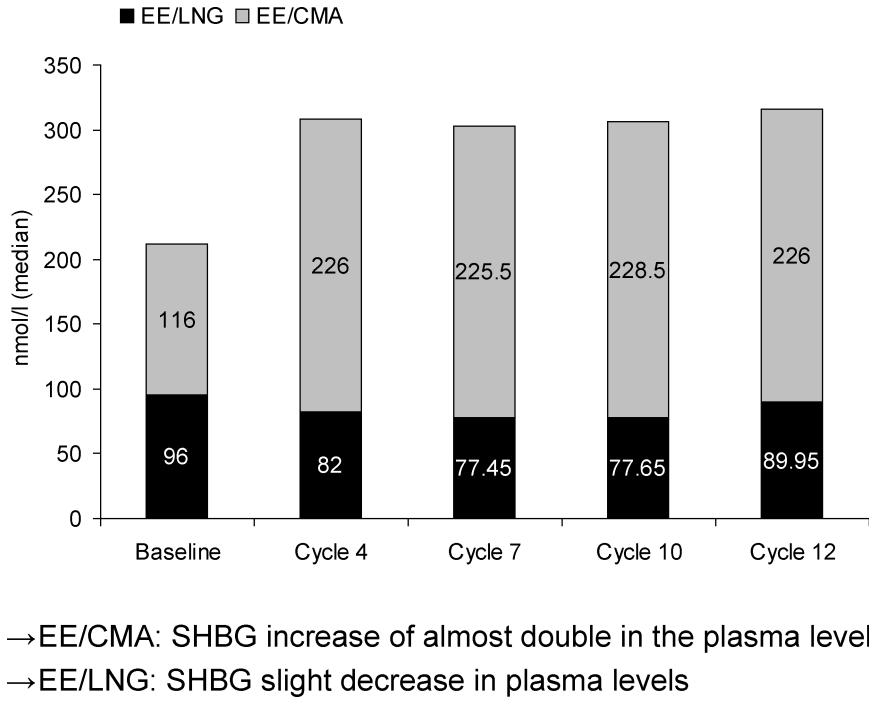

Figure 6 SHBG-levels have doubled after 4 cycles with Belara as shown in a comparative study with another oral contraceptive (0.03 mg EE/ 0.15 mg levonorgestrel)[5]

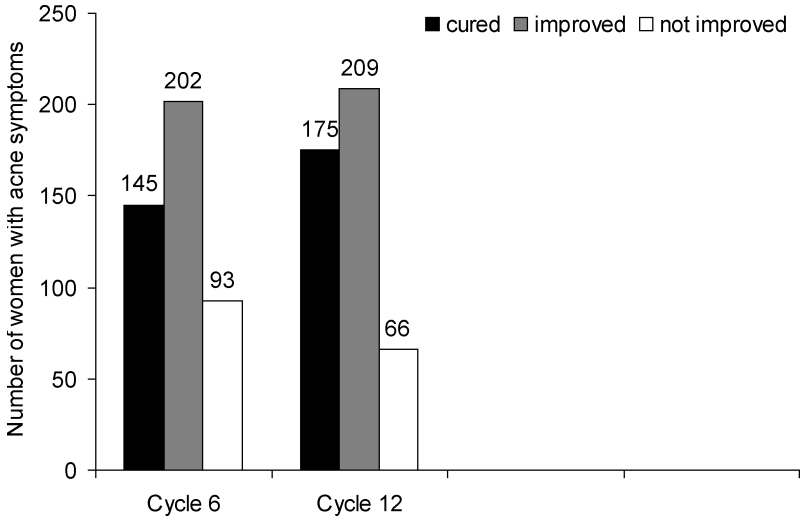

Figure 7 A phase III study showed that after six cycles of Belara®, there was a 60–70% improvement of acne in 326 women who suffered from it at study start, and after 12 cycles acne was either cured or improved in 90% of cases[6]

profile results in beneficial effects on the hair and skin both in terms of reduction of seborrhea and also acne. These advantages when combined with a lack of weight gain, a low rate of adverse events and significant improvements in bleeding disorders, ensure a high rate of compliance. Belara® is a product which is suitable for all age groups.

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