Effects of 2 mg Chlormadinone Acetate/0.03 mg Ethinylestradiol in Primary Dysmenorrhoea: The BEDY (Belara(R) Evaluation on Dysmenorrhea) Study - an Open Non-Comparative, Non-Interventional Observational Study with 4,842 Women

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Effects of 2 mg Chlormadinone Acetate/0.03 mg Ethinylestradiol in Primary Dysmenorrhoea: The BEDY (Belara® Evaluation on Dysmenorrhoea) Study – an Open, Non-Comparative, Non-Interventional Observational Study with 4,842 Women

G. A. K. Schramm, S. Waldmann-Rex

**Background:** This prospective, non-interventional, observational study designed to reflect the daily medical practice which is very important for the product observation liability investigated the effects of 2.0 mg chlormadinone acetate/0.03 mg ethinylestradiol (CMA/EE) on dysmenorrhoea and related problems. **Study design:** A total of 4,842 patients were observed during a six-cycle period (26,945.5 treatment cycles) in 608 office-based gynaecological centres throughout Germany. **Results:** The administration of CMA/EE significantly reduced the number of patients who suffered from menstrual pain (≤50.4%). Analgesic use and absenteeism from school or work due to dysmenorrhoea was reduced by 74.6% in OC starters and 91.9% in OC switchers. CMA/EE was well tolerated and provided high contraceptive efficacy, with a non-adjusted Pearl index of 0.289 (95% confidence interval 0.11–0.63). Significant reductions (p ≤ 0.001, baseline vs. final visit) were also seen in intermenstrual bleeding, bleeding intensity, premenstrual syndrome, mood swings, breast tenderness, headache, acne-prone skin and greasy hair. **Conclusions:** This evaluation supports previous findings that CMA/EE is an effective, well-tolerated contraceptive, reducing menstrual pain (dysmenorrhoea) significantly. In addition, CMA/EE offers substantial further non-contraceptive benefits. J Reproduktionsmed Endokrinol 2010; 7 (Special Issue 1): 112–18.

**Key words:** dysmenorrhoea; analgesic use; cycle stability; acne; oral contraceptive; chlormadinone acetate

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**Introduction**

Complaints of dysmenorrhoea are widespread among adolescent and young adult women, with population surveys suggesting that up to 90% of reproductive-aged women suffer from some menstrual pain [1–5]. Prevalence rates vary considerably, however, which may be explained by underreporting of symptoms [6]. Although many women self-medicate and never seek medical attention, dysmenorrhoea can profoundly disrupt a sufferer’s personal life [1, 7]. It is frequently associated with time lost from school, work or other activities, compromising the emotional distress brought on by the pain [8]. In view of the adverse impact on a woman’s day-to-day life, the need to minimise this condition is significant and valuable. Treatment is directed at providing relief from the cramping pelvic pain and associated symptoms (e.g., headache, nausea, vomiting, diarrhoea) that typically accompany or immediately precede the onset of menstrual flow. The most commonly used therapeutic modalities for medical management are non-steroidal anti-inflammatory drugs (NSAIDs) and combined oral contraceptives (OCs) [6, 9]. In women with primary dysmenorrhoea, NSAIDs have been found to be significantly more effective for pain relief than placebo [10]. OCs may be an appropriate treatment choice in patients who do not wish to conceive. Research suggests that combination OCs suppress ovulation and endometrial tissue growth, thereby decreasing menstrual fluid volume and prostaglandin secretion with a subsequent decrease in intrauterine pressure and uterine cramping [9, 11]. This generally alleviates primary dysmenorrhoea in most patients.

The more recent application of chlormadinone acetate (CMA) in combination with low-dose ethinylestradiol (EE) as an OC has positive effects on pre-existing dysmenorrhoea and cycle stability [12–16]. Another major benefit is seen in relation to dermatological problems such as acne and acne-prone skin [17, 18]. The aim of this observational non-interventional study, important for the product observation liability, was to shed further light on the significance of changes in dysmenorrhoea and other symptoms during the administration of 2 mg CMA/0.03 mg EE in daily practice. We also present data from a large group of women on the use of analgesics and absence from school or work due to dysmenorrhoea.

We used a non-interventional study design to reflect daily medical practice especially from underaged young women, whom you can prescribe oral contraceptives concerning the German law [19].

**Materials and Methods**

**Study Subjects and Design**

This prospective, observational, non-interventional study – BEDY (Belara® Evaluation on Dysmenorrhoea) – was conducted according to the German Drug Law and quality standards issued by the German Health Authority and was of non-interventional design to reflect daily medical practice which is very important for the product observation liability. Prescription of 2 mg CMA/0.3 mg EE was at the discretionary clinical judgement of the treating gynaecologist, with exclusion criteria limited to the licensed contraindications as stated in the prescribing information for Belara. The single patient inclusion criterion was the wish for contraception. Furthermore,
gynaecologists were asked to preferentially enroll women who complained of dysmenorrhoea. All participating investigators observed and documented the intake of 2.0 mg CMA/0.03 mg EE during a 6-month period, which took place between August 2003 and November 2004. Two investigations were carried out and documented: one at baseline and the other at the end of the 6-month observation period. Beyond the conventional cycle of CMA/EE-intake (21 days of pill intake, followed by a 7-day pill-free interval), an extended-cycle regimen was also documented (2–6 blister strips, followed by a 7-day pill-free interval). During this study, we collected data from 4,824 patients who were enrolled by 608 office-based gynaecologists throughout Germany.

**Efficacy and Tolerability Evaluation**

Demographic and morphometric data were documented at baseline, along with age, weight, risk factors for the administration of hormonal preparations and the reasons for starting or switching to CMA/EE. Primary endpoints were the incidence and intensity of dysmenorrhoea, use of analgesics and absence from school or work. All efficacy parameters (cycle stability, bleeding intensity, premenstrual syndrome, mood swings, breast tenderness, headache and skin and hair condition) were defined as customary in non-interventional studies according the established doctrine [20]. It should be noted that subjective statements of the young women and/or subjective statements of the doctor were made and, because this is a non-interventional trial no results of clinical assessment are available.

Documentation of symptoms referred to the previous 3 months before the baseline visit and to the last 4 weeks before the final visit, as reported by the subjective patient statement. Further parameters included tolerability of CMA/EE and contraceptive efficacy (Pearl index). Adverse drug reactions were recorded using coding from the Medical Dictionary for Regulatory Activities (version 10.0).

**Statistical Analysis**

Data validation and descriptive statistical analysis were performed using SPSS for Windows (release 11.0.1). We calculated descriptive p-values for changes during the observation period using the Wilcoxon signed-rank test and McNemar’s test. These were applied to distribution variables such as cycle stability, dysmenorrhoea and other cycle-related parameters. Metric results were described by mean average value, standard deviation (SD), median and first, 25th, 75th and 99th percentiles. Differences in sample sizes represent missing data. The following formula served for evaluating contraceptive efficacy: Pearl index = (number of pregnancies × 1,300)/(number of cycle equivalents at 28 days).

File analysis was performed by the data-management programme DMSys (release 5.0). Validation methods were used to improve the quality of data (e.g., date specification, consistency checks, simultaneous plausibility testing and extreme-value checking). Retrospectively collected data were excluded from all efficacy analyses and used only for the tolerability assessment.

**Results**

**Baseline Characteristics**

A total of 4,824 girls and women participated in this non-interventional study (safety population). A total of 310 patients were excluded from the efficacy evaluation (efficacy population, n = 4,514) because only retrospective data were available, but were included in the safety analysis. The efficacy population comprised 25,166 treatment cycles and 1,936 woman-years. The safety population comprised 26,945.50 treatment cycles and 2,073 woman-years.

**Age, Occupation and Risk Factors**

The median age of the efficacy population was 20.9 years. More than two-thirds of women (n = 3,082; 68.3 %) were aged ≤ 24 years and 8.5 % (n = 384 were aged > 34 years (Fig. 1). The youngest patient was 13 years, while the oldest was 51 years.

According to age distribution, 2,571 patients (57.0 %) were students or in professional training. The remaining women reported being employed (n = 1,394; 30.9 %) or housewives (n = 479; 10.6 %). For 70 women (1.6 %), another occupation was stated or details were missing.

Pre-existing risk factors for OC administration included smoking (1,478 patients; 32.7 %), a positive family history of thromboembolic disease (86 patients; 1.9 %), being overweight with a body mass index of > 25 kg/m² (712 patients; 15.8 %) or other (e.g., varicosis, hypertension, diabetes or migraine, 53 patients; 1.2 %).

**Previous Contraception and Reasons for Administration of CMA/EE**

At study entry, 2,914 participants (64.6 %) were taking an OC for the first time or had used hormonal contraception > 3 months ago (“OC starters”); 1,170 patients (25.9 %) were switching from another OC preparation to CMA/EE (“OC switchers”). No details were avail-
Effects of CMA/EE in Primary Dysmenorrhoea

Dysmenorrhoea

Incidence and Intensity of Symptoms
The intensity and incidence of dysmenorrhoea was documented as a primary endpoint of this non-interventional study. A total of 3,089 patients (78.6 %) suffered from menstrual pain during the last 3 months prior to study entry. After 6 cycles/blister packs of CMA/EE treatment, only 1,531 participants reported such pain (39.0 %; change vs. baseline, p ≤ 0.001). In OC switchers, the incidence of symptoms was reduced from 75.3 % (n = 756) at baseline to 38.7 % (n = 388) at final visit (p ≤ 0.001). The number of patients (starters and switchers) who self-reported moderate to severe symptoms decreased from 2,402 women (62.2 %) at study entry to 248 women (6.4 %) following 6 cycles/blister packs of CMA/EE (Fig. 2).

Administration of Analgesics
Patients suffering from moderate to severe dysmenorrhoea require medication. Treatment is usually with NSAIDs and minor analgesics, based on studies that have implicated prostaglandins in the pathogenesis of dysmenorrhoea [15]. In the present study, relief from pain due to CMA/EE intake was accompanied by a significant reduction in analgesic treatment.

The use of analgesics due to dysmenorrhoea during the last 3 months before study entry was documented in 2,211 cases (57.3 %). From these, 902 patients (23.4 %) reported taking NSAIDs or other analgesics at every menstruation. After 6 cycles/blister packs of CMA/EE treatment, the percentage of women who needed analgesics decreased to 14.5 % (n = 561). Only 39 women (1.0 %) still stated they took analgesics frequently or at every menstruation (Fig. 3). Conversely, the number of patients who did not require pain medication grew from 1,649 (42.7 %) at baseline to 3,299 (85.5 %) at the final visit (change vs. baseline, p ≤ 0.001).

Absenteeism from School or Work
Dysmenorrhoea interferes with daily living and is a common reason for absence from school or work. Before study entry, 1,079 participants (29.0 %) disclosed absenteeism from school or work due to menstrual pain occasionally or during every menses. This number was reduced to 87 patients (2.3 %) after 6 cycles/blis-

The observation period on CMA/EE treatment averaged 6.01 months. Tablets were usually administered for 21 days, followed by a 7-day pill-free interval (n = 4,263; 94.4%). A minority of patients (n = 180; 4.0%) used CMA/EE in an extended-cycle regimen, with the onset of a pill-free interval most commonly after three blister strips (n = 102; 56.7 %).

Contraceptive Efficacy
A total of six pregnancies occurred during 26,945.50 treatment cycles (the safety population). This resulted in an unadjusted Pearl index of 0.289 (95 % confidence interval [CI]: 0.11–0.63). However, all of the pregnant women admitted CMA/EE administration irregularities.

Available for 430 participants (9.5 %). In the subgroup of OC switchers, 44.8 %, 19.2 % and 10.3 % of participants had previously taken an OC with a second-generation progestogen, a third-generation progestogen or dienogest, respectively.

The most frequently reported reasons for prescribing CMA/EE were for contraception (2,799 patients; 62.0 %), to improve dysmenorrhoea (2,995 patients; 66.3 %) and to reduce skin or hair problems (2,150 patients; 47.6 %). The percentage of patients who gave dysmenorrhoea as a reason for starting CMA/EE was nearly identical in both the starter and switcher groups (68.5 % and 66.0 %, respectively).

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Effects of CMA/EE in Primary Dysmenorrhoea

According our experiences with Belara®, we found benefits for women with bleeding disorders, skin and hair problems and other cycle related disorders. As usual in non-interventional studies, subjective statements were made by the participants and/or their doctors. Because this was a non-interventional trial, no clinical assessment results are available.

Cycle Stability
- CMA/EE treatment reduced the number of patients who complained of intermenstrual bleeding by approximately half, from 1,232 (32.0 %) at baseline to 585 (15.2 %) after 6 cycles/blister packs (change vs. baseline, \( p \leq 0.001 \)) (Fig. 4).
- On CMA/EE administration, very severe withdrawal bleeding intensity was reported by only 36 patients (0.9 %), with participants who experienced slight to moderate menstruation increasing from 74.0 % (\( n = 2,836 \)) to 99.1 % (\( n = 3,797 \); change vs. baseline; \( p \leq 0.001 \)).
- The number of patients with Amenorrhoea (846 study participants (22.1 %) at baseline) decreased to 265 (6.9 %) patients during CMA/EE intake (change vs. baseline; \( p \leq 0.001 \)).

Skin and Hair Problems
Skin and hair problems decreased during CMA/EE intake. At the end of the 6 cycles/blister packs, the number of affected women declined by half to 1,339 (33.9 %) for skin problems and by more than half to 991 (25.2 %) for greasy hair (change vs. baseline for both; \( p \leq 0.001 \)) (Fig. 5).

Other Cycle-Related Disorders
Other cycle-related disorders investigated in this study (premenstrual syndrome, mood swings, breast tenderness, headache) decreased statistically significant decrease in number and intensity at the final visit following CMA/EE treatment (\( p \leq 0.001 \)) (Fig. 6).

Tolerability
In the safety population (\( n = 4,824 \)), 284 adverse drug reactions were documented in 223 patients (4.6 %). These reactions most commonly concerned the reproductive system and breast disorders.

Figure 4: Absence from school or work due to dysmenorrhoea, before and after the administration of 2 mg chlormadinone acetate/0.03 mg ethinylestradiol (CMA/EE). Results from patients with valid ratings at baseline and after 6 cycles/blister packs of CMA/EE treatment are shown (\( n = 3722 \)).

Figure 5: Incidence and intensity of skin and hair symptoms, before and after the administration of 2 mg chlormadinone acetate/0.03 mg ethinylestradiol (CMA/EE). Results from patients with valid ratings at baseline and after 6 cycles/blister packs of CMA/EE treatment are shown (\( n = 3951 \), Acne Prone Skin; \( n = 3934 \), Greasy Hair).

Figure 6: Incidence of moderate to severe symptoms in other cycle-related disorders, before and after the administration of 2 mg chlormadinone acetate/0.03 mg ethinylestradiol (CMA/EE). Results from patients with valid ratings at baseline and after 6 cycles/blister packs of CMA/EE treatment are shown.
Discussion

The aim of this prospective, non-interventional study was to examine the influence of CMA/EE on cycle-related disorders and dermatological problems, with a main focus on primary dysmenorrhoea in daily practice. Analysis of the present data confirms that CMA/EE provides reliable contraceptive efficacy and good tolerability. Incidences of adverse drug reactions were low (4.6%) and in line with the known tolerability profile of OC treatment. Previous findings have highlighted several non-contraceptive benefits for the CMA-containing OC, such as anti-androgenic properties, sustained cycle stability, substantial relief of dysmenorrhoea and improvement of well-being [12–18]. The present non-interventional study supports those results. The effects were particularly pronounced for symptoms of moderate to severe intensity.

CMA/EE Treatment Provides Substantial Relief of Dysmenorrhoea

Primary dysmenorrhoea usually begins in adolescence after the establishment of ovulatory cycles [21, 22]. The incidence is between 43 and 91% [9].

Age is a determinant of menstrual pain, with symptoms being more pronounced in adolescents than in older women [1, 7, 23]. Accordingly, the present study encompassed a relatively young population with an average age of 21 years. Gynaecologists were specifically instructed to focus on dysmenorrhoea for inclusion in this study. This resulted in a study population in which almost eight out of 10 participants (78.6%) suffered from painful menstruation at study entry.

CMA/EE administration substantially reduced the intensity and incidence of dysmenorrhoea symptoms. This was shown for both OC starters and OC switchers, indicating a pronounced effect of the gestagen component CMA on dysmenorrhoea. Women with no contraindications who suffer from painful menstruation should be offered NSAIDs as a first-line treatment for pain relief. NSAIDs were found to be an effective treatment for dysmenorrhoea in a review of 63 randomized controlled trials, although overall adverse effects were significantly more common with NSAIDs compared to placebo (odds ratio 1.52, 95%-CI: 1.09–2.12) [10]. Adverse effects include gastrointestinal intolerance, headaches and drowsiness [6]. In the present study, 57.3% of patients used analgesics for their dysmenorrhoea. This fraction was reduced to 14.5% during CMA/EE intake. The distinct menstrual pain reduction also resulted in a dramatic decline in current school or job absenteeism – a common problem for many adolescent and young women with dysmenorrhoea.

Although several mechanisms for the dysmenorrhoea pain relief attained with OC have been suggested, suppression of prostaglandin synthesis, leading to reduced uterine contractions, represents one of the most probable pathways [9]. Beyond this pathophysiological background, multiple other factors may also play a role in the perception and severity of pain [6].

Current evidence suggests that the pathogenesis of primary dysmenorrhoea is due to the action of prostaglandin F2α, a potent myometrial stimulant and vasoconstrictor, in the secretory endometrium [24]. Elevated prostaglandin levels have been found in the endometrial fluid of women with dysmenorrhoea, and correlated well with the degree of pain [25]. A 3-fold increase in endometrial prostaglandins occurs from the follicular to the luteal phase of the menstrual cycle, with a further increase during menstruation [26]. Progesterone inhibits prostaglandin synthesis and has a relaxing influence on the myometrium via the α-adrenergic receptor. The fall in progesterone in the late luteal phase results in increased prostaglandins in the endometrium, followed by rising myometrial tone and excessive uterine contraction [27, 28].

CMA (17α-acetoxy-6-chloro-4,6-pregnadiene-3,20-dione) has a similar structure to progesterone and a strong pro-

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<th>Table 1: Gynecologists’ assessment of CMA/EE treatment after 6 cycles/blisters.</th>
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<td><strong>Effects on</strong></td>
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<td>Dysmenorrhoea (n = 4514)</td>
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<tr>
<td>Very good</td>
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<td>66.4%</td>
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<td>Skin/hair condition (n = 4514)</td>
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<td>57.4%</td>
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<td>Overall assessment (n = 1887)</td>
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| * compared to the last contraceptive: subgroup of OC switchers.
gestogenic effect – about one-third higher than that of naturally produced progesterone [29]. The high intrinsic activity of CMA at progesterone receptors and possible further pharmacological effects may provide a rationale for its marked beneficial effects on dysmenorrhoea in women of reproductive age [30].

The data from OC starters and OC switchers were not analysed separately in this study. We acknowledge that the different OC formulations previously taken by subjects may impart a bias on the results. This, in turn, limits the conclusions.

Conclusions

The results of this 6-month prospective study provide strong evidence for a substantial improvement in dysmenorrhoea and related problems following the administration of 2 mg CMA/0.03 mg EE. The high efficacy in terms of menstrual pain reduction may be due to the distinct prostogenetic effect of CMA, a derivative of naturally produced progesterone.

Furthermore, this study supports earlier findings that CMA/EE offers reliable contraceptive efficacy and an excellent tolerability profile, and produces major benefits on bleeding intensity, cycle stability and skin or hair problems.

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