Ethinylestradiol/Chlormadinone Acetate
Dermatological Benefits

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Abstract

Acne vulgaris, hirsutism, seborrhea and female pattern hair loss (FPHL) are common disorders of the pilosebaceous unit (PSU). In some women with hyperandrogenemia, an excess of androgens at the PSU can lead to the development of these dermatological manifestations. These manifestations can cause many psychiatric and psychological implications, such as social fears and anxiety, and can adversely affect quality of life.

High androgen levels at the PSU as a possible underlying cause of acne vulgaris, hirsutism, seborrhea and FPHL supports the rationale for using combined oral contraceptives for the management of these conditions in women. The purpose of this review is to describe these dermatological manifestations of the PSU and the management of these conditions through the use of the oral contraceptive ethinylestradiol/chlormadinone acetate (EE/CMA).

EE/CMA 0.03/2 mg is a combined monophasic contraceptive pill with anti-androgenic properties. It is approved in Europe for contraception and has been investigated in phase III trials for the treatment of acne. EE/CMA was better than placebo and similar to another low-dose oral contraceptive (ethinylestradiol/levonorgestrel) in improving symptoms of acne in two phase III randomized controlled trials in patients with mild to moderate papulopustular acne. In addition, in trials investigating the contraceptive efficacy of EE/CMA, limited data suggest that there were also improvements in hirsutism, FPHL and seborrhea in small subgroups of patients.

EE/CMA has a good safety profile. The most commonly reported adverse events are breast tenderness/pain, headache/migraine and nausea.

Evidence in the literature indicates that the use of EE/CMA for the treatment of dermatological disorders under the control of androgens may be a valid treatment option. Further investigation is warranted.

1. Introduction

Acne vulgaris, hirsutism, seborrhea and female pattern hair loss (FPHL) are common disorders of the pilosebaceous unit (PSU), which consists of a sebaceous gland and a hair follicle. These disorders occur after the onset of puberty and are related to the development of sebaceous glands and terminal hair follicles. This development process is influenced by various factors including androgens; androgens bind to androgen receptors in the PSU and promote the proliferation and differentiation of sebaceous glands and follicular hyperkeratinisation. The response of the PSU to androgens is dependent on their location in the body.

In women, testosterone formation occurs largely in the skin. Dehydroepiandrosterone, dehydroepiandrostosterone sulfate and androstenedione are secreted and then peripherally converted to testosterone. The biological activity of testosterone on the PSU is dependent on the conversion of testosterone to dihydrotestosterone, an androgen that has high potency in the PSU. This is catalyzed by the enzyme 5α-reductase. There are two isozymes of 5α-reductase (types 1 and 2), which are differentially expressed in various tissues such as the sex organs and the skin. In hair follicles and sebaceous glands, a local excess and influence of dihydrotestosterone can lead to the development of acne vulgaris, hirsutism, seborrhea and FPHL. This excess is the result of either a change in the interaction of the androgen/androgen receptor complex genome or as a result of elevated testosterone levels in the PSU.

While there is growing evidence that androgens play a significant role in the pathogenesis of acne vulgaris, hirsutism,
seborrhea and FPHL, other factors such as genetic predisposition are also involved in the development of these PSU disorders.[2] Acne and hirsutism can develop in women with normal serum levels of testosterone, while some women with elevated circulating androgen levels (hyperandrogenemia), may show no symptoms of these PSU disorders (cryptic hyperandrogenemia).[3] Women of childbearing potential, in the peak of their hormonal youth, present to dermatologists in search of solutions for these dermatological disorders of the PSU. Frequently, women who present to their GP or dermatologist have normal androgen levels; however, some of these women present with authentic hyperandrogenemia. In this scenario, women may benefit from concomitant therapy with oral contraceptives with anti-androgen effects in combination with strong anti-androgens or other medications.[3]

The purpose of this review is to describe the dermatological manifestations of androgen-related disorders of the PSU in women and the management of these conditions through the use of the oral contraceptive ethinylestradiol/chlormadinone acetate (EE/CMA).

2. Acne Vulgaris

Acne vulgaris is a chronic inflammatory dermatological condition characterized by open and/or closed comedones and inflammatory papules, pustules or nodules.[4,5] Factors leading to acne formation include the abnormal desquamation of follicular epithelial cells and an enhanced production of sebum.[1,5] In addition, the proliferation of Propionibacterium acnes in the PSU can also be a causative factor.[5]

In women with acne, not only is there frequent hypersensitivity of the sebaceous glands to androgens but there is also often a systemic excess of androgens.[5] These factors lead to the abnormal cellular development and extra sebum in turn resulting in the comedones, papules, pustules and nodules that characterize acne. Women with conditions that cause androgen excess, such as polycystic ovary disease, regularly show symptoms of acne.[6]

Acne is one of the most common skin disorders.[7] Acne occurs commonly in adolescence; however, in a study examining the prevalence of acne in adults aged 20–49 years, acne was reported in 26.3–50.9% of women.[7] The prevalence of acne decreases with age, with 50.9% of women aged 20–29 years reporting acne compared with 26.3% of women aged 40–49 years.[7] Acne has many psychiatric and psychological implications and can adversely affect quality of life.[8,9] Women with acne may experience clinical depression, anxiety and social anxiety, and often women are more embarrassed by their acne than men.[10]

3. Hirsutism

Hirsutism is defined as excessive androgen-dependent male pattern hair growth in women.[2] An increased density of terminal hairs is observed in hormonally sensitive areas such as the upper lip, chin, midchest, upper and lower back, upper and lower abdomen, arm, forearm, thigh and lower leg.[2]

The transformation of small, fine and unpigmented vellus hair follicles to terminal hair follicles, which are longer, thicker and more pigmented, is stimulated by androgens.[1] Hirsutism is correlated more with plasma levels of free testosterone than levels of total testosterone.[1] Moderate to severe hirsutism is caused by above-normal free plasma testosterone levels, whereas mild hirsutism can occur even when plasma-free testosterone levels are within the normal range. Indeed, half of all women with hirsutism have normal plasma levels of free testosterone.[1] One final factor that is often elevated in hirsute women is the activity of 5α-reductase type 2 in hair follicles.[11]

Hirsutism is prevalent in 5–10% of reproductive women in the general population, and can be associated with a negative effect on a woman’s quality of life.[12] Common causes for hirsutism include polycystic ovary syndrome, idiopathic hirsutism, Cushing’s syndrome, acromegaly, hyperprolactinemia, ovarian or adrenal androgen-secreting tumors, non-classic adrenal hyperplasia and some drugs.[12] Many women with hirsutism report an increase in social fear and anxiety, and hirsutism can lead to psychological distress with an increase in psychotic symptoms.[13]

4. Female Pattern Hair Loss

FPHL is the androgen-dependent thinning of hair that occurs with advancing age but can begin as early as in the teens.[3] FPHL is also referred to as androgenetic alopecia; however, androgenetic alopecia is alopecia that is androgen-independent. FPHL is the result of the transformation of terminal hair follicles to small, fine and unpigmented vellus hair follicles in addition to a reduction of PSUs on the scalp.[2] FPHL develops in a pattern that is distinct from age-related thinning; in women it is demonstrated by a diffuse thinning of hair growth in the frontal and sagittal scalp.[1]

FPHL occurs due to a shortened anagen phase of scalp hair growth: androgens shorten this phase and an increased dihydrotestosterone action on scalp hair follicles can reduce the growth and production of hair.[1] Hair loss in certain regions of the scalp with advancing age can also be attributed to an altered androgen/estrogen ratio.

Approximately 10% of premenopausal women have FPHL. The incidence increases with age and 25–32% of women aged 65 years or older experience FPHL.[14] Women with FPHL...
experience a diminished body image satisfaction and lowered self-esteem.[15,16]

5. Seborrhea

Seborrhea or seborrheic dermatitis is a common chronic inflammatory skin disorder that affects the scalp, face and sebaceous gland-rich areas.[17,18] Seborrhea typically presents with erythematous plaques or patches, but can vary from mild dandruff of the scalp to thick, yellow and greasy areas on the face, head and trunk.[17,18] Seborrhea can be caused by many factors including increased androgen levels, nutritional deficits, neurogenic factors and fungal infections.[19]

There is evidence that human sebocytes respond to androgen stimulation, as reviewed by Zouboulis et al.[20] An increase in free testosterone in women appears to increase sebum production by sebocytes in turn causing seborrhea.

Seborrhea affects 3% of the general population.[17] Seborrhea is most prevalent in adolescents, young adults and adults over 50 years of age.[18] However, most patients (70%) experience mild symptoms.[18,19]

6. Rationale for the Use of Oral Contraceptives for the Treatment of Pilosebaceous Unit Disorders

The use of oral hormonal treatments for acne vulgaris, hirsutism, FPHL and seborrhea has a physiological rationale.[22] Combined oral contraceptives contain an estrogen (such as ethinylestradiol or mestranol) and a progestin (such as desogestrel, drospirenone, levonorgestrel or chlormadinone).[21] Together they reduce the effect of androgens by reducing ovarian and adrenal androgen production and by blocking the action of androgens in the PSU. The ethinylestradiol component inhibits luteinizing hormone[22] and follicle-stimulating hormone (FSH) thus reducing serum androgen levels.[23] In addition, ethinylestradiol increases sex hormone-binding globulin levels, which decrease circulating serum testosterone levels.[23] The progestin component blocks the androgen receptor in the PSU (i.e. is anti-androgenic).[23] Because of these properties, estrogen-containing oral contraceptives are a recommended treatment option in the management of acne vulgaris.[4]

EE/CMA is among the most commonly used combined oral contraceptives, and has an anti-androgenic effect; a review of its potential use for the improvement of dermatological manifestations associated with hyperandrogenemia follows.

7. Ethinylestradiol/Chlormadinone Acetate

EE/CMA 0.03 mg/2 mg is a combined monophasic contraceptive pill with anti-androgenic properties.[24-27] EE/CMA contains the estrogen, ethinylestradiol and the progestin chlormadinone acetate. It is approved in Europe for contraception[28] (Balianca, Belara) where it has also undergone testing in phase III clinical trials for the treatment of acne;[24,29] the combination therapy is not approved for use in the USA.

Ethinylestradiol reduces serum FSH levels, preventing ovarian follicular development and leading to a reduction in circulating estradiol. Estradiol is essential for the pre-ovulatory release of luteinizing hormone, thus reducing circulating estradiol levels and in turn preventing ovulation.[30] Chlormadinone acetate synergistically inhibits follicular growth and maturation by disrupting endogenous gonadotropin secretion.[31,32] In addition, chlormadinone acetate inhibits estrogen and progesterone receptors, in turn inducing a thinning of the endometrium and a reduction in the probability of embryo implantation.[33]

The efficacy of EE/CMA in contraception is well established.[25,26,28,34,35] As described earlier, the ethinylestradiol component reduces serum FSH levels and the chlormadinone acetate component inhibits follicular growth and endogenous gonadotropin secretion, which explains its potential to improve skin disorders that are thought to be attributable to hyperandrogenemia. To evaluate the literature concerning the relationship between EE/CMA and skin disorders a search was conducted and studies used in this review were identified via the MedLine and EMBASE databases using the terms: ethinylestradiol AND chlormadinone AND acne OR seborrhea OR hirsutism OR alopecia. All years of publication were included dating back to 1966. Reference lists of identified publications were also scanned for articles relevant to the topic and some references known to the author were included. Only studies in humans and English language articles were included.

7.1 Ethinylestradiol/Chlormadinone Acetate in Acne

EE/CMA treatment was associated with a clinical response in significantly more patients than with placebo in a randomized phase III trial in 377 patients with moderate papulopustular acne[29] (table I). The study was designed specifically to assess the effect of treatment on acne; clinical response was defined as at least a 50% reduction from baseline in the number of papules/pustules on the face. After six treatment cycles, the median reduction from baseline in the number of papules and/or pustules on the face was greater in women receiving EE/CMA (~63.6% vs −45.3%; p = 0.03) [figure 1].

The efficacy of EE/CMA in the treatment of acne was similar to that of another low-dose oral contraceptive, ethinylestradiol/levonorgestrel (EE/LNG) 0.03 mg/0.15 mg (Microgynon).[24] In 199 women with mild-to-moderate papulopustular acne, a
### Table I. Trials investigating the effects of EE/CMA 0.03 mg/2 mg on acne and seborrhea

| Study, year | Trial details | Indication | Duration | No. of patients | Comparative treatments | Results at study end (EE/CMA vs comparator)^a |
|-------------|---------------|------------|----------|----------------|------------------------|-----------------------------------------------|
| Acne        |               |            |          |                |                        |                                               |
| Plewig et al.,[29] 2009 | ph3, r, db, mc | moderate papulopustular acne | 6 cycles | 377 | placebo | % pts with response^b: 64.1 (161/251) vs 43.7 (55/126); p = 0.0001 |
| Worret et al.,[24] 2001 | r, ph3, mc, sb | mild-to-moderate papulopustular acne | 12 cycles | 199; 88 with comedones at baseline | ethinylestradiol/levonorgestrel 0.03 mg/0.15 mg | % pts with response^b: 59.4 (60/101) vs 45.9 (45/98); p = 0.02 % pts with comedonal improvement: 88.9 (64/72) vs 77.3 (51/66) |
| Schramm and Steffens,[26] 2002 | ph4, pms, mc, op | contraception | 6 cycles | 21 820 total; 15 259 with acne-like skin at baseline | N/A | % pts with improvement: 85.5 (13 199/15 259) % pts resolved: 28.5 (4349/15 259) |
| Schramm and Steffens,[25] 2003 | ph4, pms, mc, op | contraception | <12 months | 2620 total; 1628 with slightly greasy, greasy or very greasy skin and 1865 with spots or bad skin at baseline | N/A | % pts slightly greasy skin baseline 35.5 (931/2620) vs study end 19.5 (511/2620) % pts greasy to very greasy skin baseline 26.6 (697/2620) vs study end 2.3 (60/2620) % pts with improvement in spots or bad skin 85.6 (1596/1865) |
| Lello et al.,[36] 2008 | r, ph2, sb | hyperandrogenemic skin-related disorders | 6 cycles | 55 | ethinylestradiol/drospirenone 0.03 mg/3 mg | Acne score from 2.56 to 0.81 vs from 2.63 to 0.66; both p<0.01 vs baseline |
| Zahradnik et al.,[37] 2008 | ph3, pms, mc, nc | contraception | 45 cycles | 781 total; 108 with acne at baseline | N/A | % pts with acne baseline 13.8 (108/781) vs study end 5.7 (13/230) |
| Zahradnik et al.,[24] 1998 | ph3, pms, mc, nc | contraception | ≤24 cycles | 1655 total; 326 with acne at baseline | N/A | % pts with acne (of the face/neck) improved: 64.1 (209/326) and resolved: 53.7 (175/326) % pts with acne (of the trunk) improved: 70.0 (77/110) |
| Anthuber et al.,[38] 2010 | nc, observational, mc | contraception | 6 cycles | 6885 total; 3127 with acne-prone skin at baseline | N/A | % pts with acne/acne-prone skin baseline 53.4 (3127/5858) vs study end 24.1 (1412/5858); p<0.001 |
| Sabatini et al.,[39] 2007 | observational | contraception | 6 cycles | 170 total; 90 with mild, moderate or severe acne at baseline | ethinylestradiol/drospirenone 0.03 mg/3 mg | % pts with mild, moderate and severe acne resolution 75 (21/28), 71.4 (10/14) and 83.8 (5.6) vs 54.1 (13/24), 50.0 (6/12) and 66.7 (4/6), respectively; all p<0.01 |

### Acne and seborrhea

| Study, year | Trial details | Indication | Duration | No. of patients | Comparative treatments | Results at study end (EE/CMA vs comparator)^a |
|-------------|---------------|------------|----------|----------------|------------------------|-----------------------------------------------|
| Schramm and Heckes,[40] 2007 | ph4, nc, observational | contraception | 4 cycles | 16 781 total; 12 088 with acne or seborrhea at baseline | N/A | % pts with acne/seborrhea improvement 36.5 (4248/11 638) and resolution 45.9 (5342/11 638) |

*Continued next page*
| Study, year | Trial details | Indication | Duration | No. of patients | Comparative treatments | Results at study end (EE/CMA vs comparator)<sup>a</sup> |
|------------|---------------|------------|----------|-----------------|------------------------|--------------------------------------------------|
| **Seborrhea** |               |            |          |                 |                        |                                                  |
| Worret et al.,<sup>[24]</sup> 2001 | r, ph3, mc, sb | mild-to-moderate papulopustular acne | 12 cycles | 199 total; 62 with mild or moderate seborrhea at baseline | ethinylestradiol/levonorgestrel 0.03 mg/0.15 mg | % pts with seborrhea resolution: 80.0 (20.25) vs 76.2 (16.21) |
| Plewig et al.,<sup>[29]</sup> 2009 | ph3, r, db, mc | Moderate papulopustular acne | 6 cycles | 377 total; 276 with mild or moderate seborrhea at baseline | placebo | % pts with seborrhea resolution: 41.5 (78.188) vs 23.9 (21.88) |
| Lello et al.,<sup>[36]</sup> 2008 | r, ph2, sb | contraception | 6 months | 55 | ethinylestradiol/drospirenone 0.03 mg/3 mg | Mean seborrhea distribution from 6321.19–1845.39 to 3461.56–1882.53 mg/cm<sup>2</sup> of skin (p < 0.01 vs baseline) vs from 6479.70–4256.78 to 1797.1–1076.9 mg/cm<sup>2</sup> of skin (p < 0.01 vs baseline); p < 0.05 between groups |
| Kerscher et al.,<sup>[41]</sup> 2008 | ph4, op | acne-prone skin | 6 cycles | 44 | N/A | Clinical sum score<sup>c</sup> 9.5 (in pts aged 18–27 years) and 7.4 (in pts aged 28–37 years) vs 15.1 and 13.4 at baseline, respectively |
| Zahradnik et al.,<sup>[34]</sup> 1998 | ph3, op, mc | contraception | ≤24 menstrual cycles | 1655 total; 131 with seborrhea at baseline | N/A | % pts with improvement 67.9 (89/131) and % pts with resolution: 58.0 (76/131) |
| Schramm and Steffens,<sup>[26]</sup> 2002 | ph4, pms, mc, op | contraception | 6 cycles | 21 820 total; 10 255 with greasy hair at baseline | N/A | % pts greasy or very greasy hair at baseline 47.0 (10 255/21 820) vs study end 13.6 (2968/21 820) |
| Schramm and Steffens,<sup>[25]</sup> 2003 | ph4, pms, mc, op | contraception | <12 months | 2620 total; 1327 with greasy or very greasy hair at baseline | N/A | % pts greasy or very greasy skin baseline 50.6 (1327/2620) vs study end 11.7 (307/2620) |
| Zahradnik et al.,<sup>[37]</sup> 2008 | ph3, op, mc, nc | contraception | 45 cycles | 781 total; 31 with seborrhea at baseline | N/A | % pts with seborrhea baseline 4 (31/781) vs study end 3.0% (7/230) |
| Anthuber et al.,<sup>[38]</sup> 2010 | nc, mc, observational | contraception | 6 months | 6885; 2217 with seborrhea at baseline | N/A | % pts with seborrhea baseline 39.8 (2217/5571) vs study end 17.1 (953/5571); p < 0.001 |

<sup>a</sup> Where data are presented as % pts, patient numbers (n/N) are also provided in parentheses.

<sup>b</sup> Response defined as at least a 50% reduction in the number of papules and/or pustules of the face at study endpoint.

<sup>c</sup> Clinical sum score of 0–6 = normal skin; 6–12 = mild seborrhea; 12–18 = moderate seborrhea; 18–24 = acne, severe seborrhea.

<sup>db</sup> = double-blind; <sup>EE/CMA</sup> = ethinylestradiol/chlormadinone acetate; <sup>mc</sup> = multicentre; <sup>N/A</sup> = not applicable; <sup>nc</sup> = non-controlled; <sup>op</sup> = open-label; <sup>ph3</sup> = phase III; <sup>ph4</sup> = phase IV; <sup>pms</sup> = post-marketing surveillance; <sup>pts</sup> = patients; <sup>r</sup> = randomized; <sup>sb</sup> = single-blind.
significantly greater proportion of women receiving EE/CMA experienced a clinical response (at least a 50% reduction from baseline) after 12 treatment cycles (59.4% vs 45.9%; p = 0.02; table I). The proportion of women with a complete response in papulopustular acne of the face after 12 cycles of treatment was also greater in the EE/CMA group than the EE/LNG group (16.5% vs 4.3%; between-group significance was not reported). After 12 treatment cycles, papulopustular acne of the face, décolleté and back were improved or resolved in women receiving EE/CMA and EE/LNG (figure 2). Deterioration of acne was not observed in women receiving EE/CMA, whereas very few patients receiving EE/LNG experienced symptom deterioration.

A phase IV, open-label trial of EE/CMA in 44 women further demonstrated the benefits of EE/CMA for the treatment of acne-prone skin. After six menstrual cycles, women receiving EE/CMA reported improvements in multiple skin parameters including facial skin condition, the number of acne lesions and pore size (table I). [41]

Skin condition (secondary endpoint) was improved in more than 80% of women who had acne or other skin conditions in two post-marketing surveillance trials investigating EE/CMA in large patient populations (n = 21,820 and 2620; table I). [25,26]

Many other non-comparative and/or observational studies investigating the contraceptive efficacy ofEE/CMA support data from the previously mentioned well-designed trials. [34,36-40] These clinical trials are summarized in table I.

### 7.2 Ethinylestradiol/Chlormadinone Acetate in Hirsutism

No clinical trials have been conducted to investigate the efficacy of EE/CMA in hirsutism; however; several large phase III trials that investigated the contraceptive effect of EE/CMA and the efficacy of EE/CMA in women with acne also investigated the effects of EE/CMA on other signs of disorders of the PSU (including hirsutism) as a secondary endpoint. [24,29,37] Data from those studies have suggested a potentially favorable effect of EE/CMA on hirsutism in small subgroups (n = 25–92). [24,29,37]

A greater proportion of patients with hirsutism at baseline (n = 92) receiving EE/CMA demonstrated a total resolution of hirsutism symptoms compared with patients receiving placebo in a multicenter, double-blind, placebo-controlled study in 387 women with moderate papulopustular acne. [29]

Furthermore, in a single-blind study comparing the efficacy of EE/CMA and EE/LNG in 199 women with mild-to-moderate papulopustular acne, hirsutism disappeared completely in four out of 11 patients receiving EE/CMA. The improvement observed in EE/CMA recipients was similar to that of EE/LNG (five out of 14 patients). [24] None of the studies mentioned in this section defined how hirsutism was diagnosed and assessed, nor did they report the severity of hirsutism at baseline.

The limited data from other studies also with small subgroups of patients with hirsutism suggest that EE/CMA treatment for six to 12 cycles may improve this disorder; however, further prospective large studies are required better to evaluate the efficacy of the drug in this indication.

![Fig. 1. Median number of papules and/or pustules of the face over six medication cycles with ethinylestradiol/chlormadinone acetate (n = 251) or placebo (n = 126). *p < 0.05 vs placebo. (Adapted from Plewig et al.[29], with permission.)](image1)

![Fig. 2. Improvement, healing and deterioration rates for papulopustular acne of the face, décolleté and back under ethinylestradiol/chlormadinone acetate (EE/CMA) and ethinylestradiol/levonorgestrel (EE/LNG) after 12 treatment cycles.[24] Reproduced with permission from Worret et al.[24]](image2)
7.3 Ethinylestradiol/Chlormadinone Acetate in Female Pattern Hair Loss

Like hirsutism, there have been no clinical trials investigating the effects of EE/CMA in FPHL. However, a phase III trial suggested that EE/CMA may be effective in this patient population and worth investigation.[24] In the very small number of patients who had FPHL (n = 18) in the large trial (n = 199), resolution rates of 85.7% (six out of seven) and 90.9% (10/11) were observed in the EE/CMA and EE/LNG groups, respectively, following 12 cycles of treatment. The rating scale to assess alopecia was not defined in the study and the severity of alopecia at baseline was not reported. The efficacy of EE/CMA in this condition cannot be concluded on this basis; however, these limited data suggest that further investigation of EE/CMA in FPHL is warranted.

7.4 Ethinylestradiol/Chlormadinone Acetate in Seborrhea

Several large clinical studies have indicated that EE/CMA could possibly be a treatment for seborrhea; however, none of the trials investigated EE/CMA in a seborrheic-specific population. In one of the studies, seborrhea resolved in a large proportion of patients receiving EE/CMA after 12 treatment cycles; this resolution was similar to improvements observed in patients receiving EE/LNG (table I).[24] The phase III, randomized controlled trial compared the efficacy of EE/CMA and EE/LNG in 199 women with mild-to-moderate papulopustular acne; 62 of these women had mostly mild or moderate seborrhea at baseline. Furthermore, in another phase III trial, a greater proportion of patients with seborrhea at baseline (n = 276) receiving EE/CMA demonstrated total symptom resolution compared with patients receiving placebo (table I).[29]

Data from uncontrolled clinical trials investigating the contraceptive efficacy of EE/CMA in women that support the possible effect of EE/CMA in patients with seborrhea are presented in table I.[25,26,34,37,38,40]

Taken together, these limited data suggest that EE/CMA may be effective for the management of seborrhea; however, further examination of EE/CMA in seborrhea is required.

8. Tolerability

EE/CMA is generally well tolerated. The most commonly reported adverse events in two post-marketing trials investigating EE/CMA in large patient populations (n = 21 820 and 2620) were breast pain and headache/migraine (figure 3).[25,26] A small effect of EE/CMA on average body weight was observed in those studies, with an increase of 0.9–1.1% observed with EE/CMA administration.[25,26] It is well known that oral contraceptives are associated with a small increased risk of cardiovascular events. In the two post-marketing trials, there was one case of thrombosis in the thigh in the smaller trial, and in the larger study there was one case each of superficial leg vein thrombosis and pulmonary embolism, i.e., an incidence rate of 2.1 per 10 000 women years.

When administered for the treatment of acne, no unexpected adverse events were experienced in women receiving EE/CMA.[24,29] The toxicity profile was as expected; discontinuations from study treatment occurred as a result of menstrual bleeding, irritability and nausea.[29]

The tolerability profile of EE/CMA is broadly similar to most low-dose combined oral contraceptives.[24,39] The most common adverse events associated with these oral contraceptives are weight gain, mood changes, loss of libido, migraine, breast tenderness and intermenstrual bleeding.[1,29,37]

9. Conclusions

The dermatological conditions associated with hyperandrogenemia are often a cause of major cosmetic concern in women. EE/CMA is a combined monophasic contraceptive pill with anti-androgenic properties that was better than placebo in improving the symptoms of acne and similar to that of other low-dose oral contraceptives in several large, well controlled studies in patients with mild-to-moderate papulopustular acne. EE/CMA also appeared to improve hirsutism, FPHL and seborrhea in small
subgroups of women enrolled in several large trials investigating the contraceptive efficacy of EE/CMA. EE/CMA is well tolerated in clinical trials; adverse events reported with EE/CMA use were those commonly reported with oral contraceptives. Evidence in the literature indicates that the use of EE/CMA for the treatment of dermatological disorders under the control of androgens may be a valid treatment option. Further investigation is warranted.

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