

OPINION

Cyproterone acetate/ethinyl estradiol for acne and hirsutism: time to revise prescribing policy

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Clinical manifestations of androgen excess—hirsutism, acne and alopecia—are very common and distressing symptoms in women of reproductive age. These symptoms are frequently associated with polycystic ovary syndrome, in which condition menstrual disturbances are also common. The combination of the anti-androgen cyproterone acetate (2 mg) and ethinyl estradiol (35 µg) (co-cyprindiol) is of proven efficacy in management of symptoms of both hyperandrogenism and menstrual abnormalities but its long-term use has been discouraged because of concern about increased risk of venous thromboembolism. In this article, we review the evidence for efficacy and adverse effects and conclude that its benefits are clear and that the risks of venous thromboembolism are no more common than with the use of third generation combined oral contraceptives.

Keywords: anti-androgen; oral contraceptive; venous thromboembolism; polycystic ovary syndrome

Co-cyprindiol [ethinyl estradiol 35 µg + cyproterone acetate 2 mg (CPE/EE), commonly prescribed as Dianette[®] in the UK] is an approved and effective treatment for severe acne and hirsutism which has been used in clinical practice for more than 30 years. It is particularly useful in the management of women with polycystic ovary syndrome (PCOS) for whom it has the added benefit of regulating erratic periods. Although not licensed for contraception in the UK, Dianette is as effective in preventing pregnancy as combined oral contraceptive pills and is widely used as such in other European countries. Indeed, a recent study from Spain has shown that CPA/EE is not only effective in regulating menses and treating hirsutism in women with PCOS but is also superior to metformin in management of symptoms of PCOS, without any adverse effect on cardiovascular risk factors (Luque-Ramirez *et al.*, 2007).

PCOS is the most common endocrine disorder in women, is estimated to affect more than 5% of the population and is associated with chronically elevated serum androgen concentrations (Franks, 1995; Knochenhauer *et al.*, 1998). The current recommendation of the Committee for the Safety of Medicines and the Medicines Control Agency (UK) (CSM, 2002) is that the use of Dianette is restricted to women with symptoms of androgen excess and that it 'should be withdrawn

3–4 cycles after the treated condition has completely resolved'. This recommendation [which, not surprisingly, also features in the British National Formulary (BNF) and in the online General Practitioner (GP) notebook (www.gpnotebook.co.uk)] is founded on reports of a significantly increased risk of venous thromboembolism compared with other combined oral contraceptives.

The evidence cited by the Committee for the Safety of Medicines was based on four epidemiological studies (WHO, 1995; Pini *et al.*, 1996; Parkin *et al.*, 2000; Vasilakis-Scaramozza and Jick, 2001) (reports of the two smaller series appeared as letters in the *Lancet*) in which the number of cases of venous thromboembolism in women taking CPA/EE was very small. One of the largest and most authoritative studies [the General Practice Research database (GPRD) case–control study; not cited in the Committee for the Safety of Medicines article] did show a small but significant increase in risk of venous thromboembolism, but the crude rate of venous thromboembolism during CPA/EE use was 2.2 per 10,000 exposed woman-years, which was similar to that in comparable 'third generation' combined oral contraceptives (Farmer *et al.*, 1999). Importantly, the report of a more recent study from the same GPRD survey concluded that: 'the risk of venous

thromboembolism associated with CPE/EE use does not differ significantly from that associated with the use of conventional other combined oral contraceptives'. These data are reassuring and together with the risks associated with other treatments for acne, in particular, should influence prescribing practice' (Seaman *et al.*, 2004).

Acne is often self-limiting; however, the mean duration is frequently between 8 and 14 years. Recurrent and/or persistent acne are not uncommon and all forms of acne may cause permanent scarring and significant psychosocial morbidity. Hirsutism is also a highly distressing chronic complaint which has a significant negative impact on self-esteem. Although consideration of other therapeutic options (including cosmetic measures) is important, the long-term use of anti-androgens is often the most effective means of control. Unfortunately, like acne, hirsutism usually recurs when treatment is stopped and certainly recurs if it is stopped only after 4 months. In the vast majority of cases, these symptoms are the consequence of chronically elevated concentrations and/or increased action of circulating androgens (as in PCOS). The ability of CPA/EE to suppress ovarian androgen secretion as well as blocking androgen action makes it particularly suitable for management of chronic androgen excess. Thus, the current recommendation that 'CPA/EE should be discontinued 3–4 cycles after the treated condition has resolved' is not very practical. A further consideration is that PCOS usually presents during adolescence and symptoms of androgen excess are particularly distressing for teenagers. Early and effective treatment is important and CPA/EE is of proven benefit but clearly long-term treatment may need to be considered. In weighing up risks and benefits of such treatment, it is important for primary care physicians and specialists to be aware that there is no clear evidence that CPA/EE carries a higher risk of adverse effects than third generation combined oral contraceptives.

CSM (2002) allows women to use third-generation progestogen containing combined oral contraceptive pills provided they accept the increased risk of venous thromboembolism. The

duration of use is not restricted. Women with chronic acne and hirsutism surely have a much stronger case for expressing a preference for a certain type of treatment provided they understand the similar level of risk of venous thromboembolism. We therefore submit that these recommendations should be updated to remove unnecessary restrictions on the use of drug that has proved effective in treating hirsutism and acne and is of particular usefulness in management of women with PCOS who may have associated menstrual disorders.

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