Consensus of the French Endocrine Society on female hyperandrogenism

Anti-androgen Treatments

Traitements anti-androgènes

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Abstract

1. Estrogen plus progestin contraceptives (EPP) are the first-line treatment of moderate hirsutism and acne in women of child bearing age (grade C).
2. CPA, 50 mg/day, 20 days out of 28, associated with estrogen is the first-line treatment of “moderate to severe hirsutism” in women of childbearing age (grade C).
3. Spironolactone, given as a contraceptive, can be proposed as a second-line treatment in case of side effects or counter-indications to CPA in moderate to severe hirsutism (grade C) in women of childbearing age. No market authorization in this indication.
4. Flutamide or Finasteride are “only” to be used under the guise of contraception as a “thirdline therapy” in cases of severe hirsutism, the presence of side effects or counter-indications to EPP, CPA 50 mg/day or spironolactone (grade C). No Market authorization in this indication.
5. There is no indication for GnRH analogs as an anti-androgen treatment in women of childbearing age given the current therapeutic alternatives (grade C)
6. Only long-term hair removal treatments can be proposed (grade C): electrolysis or laser hair removal.

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Keywords: Anti-androgen; Estrogen plus progestin contraceptive; Spironolactone; Cyproterone Acetate; Futamide; Finasteride

1. General methodology

This article is based on original international publications indexed in PubMed that are reviewed and meta-analyzed up through 2008. In some cases, when elements of proof are absent in the literature, we propose consensual attitudes founded on the experience of the members of the work group, which should be completed by expert opinions.

In regards to original studies, only controlled studies evaluating hirsutism scores for a duration of at least 6 months have been retained.

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Treatment for hyperandrogenism is based on several types of medications that aim to either block production of ovarian androgens or their peripheral action, associated with localized treatments. Several problems must be addressed when evaluating the results of published studies: most of the time these studies were carried out on small series of normal weight or overweight patients; they were not always controlled; and etiological diagnoses could be heterogeneous, particularly since the definition of PCOS was ever-changing up through 2003, and the criteria retained were for a long time different in the United States and Europe [1].

Among the significant studies on which this article is based, four “Cochrane” meta-analyses published between 2003 and 2008 [2–5] were retained along with two meta-analyses published recently [6,7].

4. Recommendation No.1

Estrogen plus progestin (EPP) contraceptives are the first-line treatment of moderate hirsutism and acne in women of childbearing age (grade C)

Comments:
- No superiority of one kind of EPP over another.
- Association ethinyl estradiol 35 μg–CPA 2 mg (Diane®) the most studied (not authorized for contraception).
- Attention to metabolic effects and vascular risk with these treatments.

Action: EPP therapies with ethinyl estradiol (EE) have a dual hypothalamic and hypophysial blocking action of gonadotropins and a progestin that also ensures an anti-gonadotropic, hypophysial, and possibly hypophysial effect [8]. LH levels are suppressed, which diminishes thecal production of androgens. Levels of the sex hormone binding globulin (SHBG) increase, which reduces the free fraction of circulating androgens. Progestins have a progestative, androgenic [9] or anti-androgenic action that is variable in vitro [10].

When treating hyperandrogenism, given the high prevalence of PCOS and its related metabolic risks, the in vivo impact of androgenic activity associated with EPP combinations is gaining interest again. The differences between EPP combinations have been widely discussed in terms of metabolic and vascular impact [11–13]. The compositions with the lowest androgenic activity, or the highest anti-androgenic activity, have a more favorable metabolic biological profile. Data in the literature on clinical events in the general population are more nuanced. The risk of stroke or myocardial infarction (MI) is globally increased with EPP, whatever kind of norsteroid progestins is used [12–14]. There is no data in the literature on the onset of clinical vascular events with EPP in women specifically presenting hirsutism. There are also no data on the onset of such events in this population when using an EPP with an anti-androgenic progestin (CPA or drospirenone). The question of venous thrombosis with EPP has been widely debated. It would appear that third-generation EPP carry a higher risk compared to second-generation derivatives [15].

In terms of efficacy against hirsutism, EPP have been evaluated in two randomized studies, one vs placebo [16] and the other vs absence of treatment [17]. These studies have methodological limitations, but did show that EPP reduce hirsutism. They do not give any information on quality of life.

The EE–CPA combination that has been commercialized the longest has been used for more than 30 years in hirsutism treatment. Only one randomized study vs placebo evaluated a low-dose CPA (Diane® 35) showing a subjective improvement in hirsutism without a rigorous evaluation of hirsutism [16]. However, this treatment is often used as a comparison to other current combinations. Drospirenone is a new progestin available since 1995. It is an analog of spironolactone with low antimineralocorticosteroid and anti-androgenic activity. Pills with drospirenone contain 30 μg or 20 μg ethinyl estradiol and 3 mg drospirenone. Its pharmacological and biochemical profiles are similar to those of progesterone. In terms of treating hirsutism, there is not much data. No randomized vs placebo study has been published and only two prospective studies showing a reduction in hirsutism scores are available [18,19]. The preferential use of one EPP over another has theoretical bases. So-called third-generation progestins such as norgestimate, desogestrel, and gestodene have low androgenic activity compared to the second-generation progestins levonorgestrel and norgestrel. However, the clinical studies available have not shown that progestins with low androgenic activity are more effective in treating hirsutism. Studies of little value have not found a difference in efficacy between EPP with CPA, levonorgestrel, desogestrel or drospirenone [17,19–22].

The role of EE doses (20 vs 30–35 μg) has not been evaluated for effects on hirsutism, but both dosages are effective in treating acne [23].

EPP are the first-line treatment for moderate hirsutism in women of childbearing age (EXPERT OPINIONS).

5. Recommendation No.2

CPIA, 50 mg/day, 20 days out of 28, associated with estrogen is the first-line treatment of “moderate to severe hirsutism” in women of childbearing age (grade C).

Comments:
- Few studies.
- Side effects to be aware of: possible onset of secondary amenorrhea, spotting, metrorrhagia, hematometra, dyspareunia, lowered libido, weight gain.
- Little information known about the treatment’s effect on bone mineralization and remains to be evaluated.
CPA [24] is a powerful progestin that lowers serum concentrations of testosterone and delta-4-androstenedione by inhibiting LH. It also blocks the peripheral effects of androgens by inhibiting their binding with their receptor. Its half-life is long due to an accumulation in fat tissue. It is widely used in France and Europe, and has market authorization for treating hirsutism in women. CPA is not available in the United States, which explains why there are so few studies [4]. Using CPA alone without estrogen does not modify its metabolic parameters or coagulation factors but does expose patients to unpleasant effects due to estrogen deficiency and a long-term risk of bone loss. Currently used doses are 50 mg/day for 20 to 21 days out of 28, associated with estrogen. Most often, due to associated hyperinsulinism, 17β-estradiol is preferred over EE, either orally or via percutaneous route, also administered 20 to 21 days out of 28. In patients at risk for thrombosis, the administration of transdermal estrogen is preferred. An EPP pill with low doses of CPA (cf supra) is also available.

A dual randomized study compared Diane® 35 associated with Diane® 35 (20 mg/day)/high dose CPA (100 mg for 10 days) and did not find any significant difference between the two doses, but this study could be criticized for its methodology and low study population [25]. Other randomized studies, comparing different therapeutic strategies including CPA (12.5 or 25 mg for 10 days) showed a significant reduction in hirsutism in 40 to 60% of cases [2]. Currently, CPA at 50 mg/day, 20 days per month, associated with estrogen is the first-line treatment in moderate to severe hirsutism in women of childbearing age (grade C).

This treatment is generally well tolerated, though the possible onset of secondary amenorrhea should be explained to patients. Irregular bleeding and spotting, metrorrhagia, hematometra, dyspareunia, and lowered libido can be observed and are generally improved with an associated prescription (or increase in dosage) of estradiol. Weight gain is frequent and should be discussed with the patient; monthly weight surveillance must be proposed at the very least. The effect of this therapy on bone mineralization is not well-known. The patient’s risk of hematometra must be known for this therapy.

6. Recommendation No.3

- Spironolactone, given as a contraceptive, can be proposed as a second-line treatment in case of side effects or counter-indications to CPA in moderate to severe hirsutism (grade C) in women of childbearing age.
- No market authorization in this indication

Comments:
- Efficacy is dose-dependent but no rigorous dose-response study is available.

- Initial dose: 100 mg/day, but obese patients may require two doses of 200 to 300 mg/day.
- Side effects: polydipsia, polyuria, nausea, headaches, asthenia, gastritis, spotting...

Spironolactone [24] is widely used as an anti-hypertensive due to its anti-aldosterone properties. It also has anti-androgenic effects [5]. The use of spironolactone to treat hirsutism dates back to 1978. It is widely used for this indication in the United States whereas in France it is much less prescribed, particularly given that it does not have market authorization for this indication. It has multiple anti-androgenic effects: inhibiting ovarian and adrenal production of androgens, blocking androgen receptors, elevation of the SHBG, increasing testosterone clearance, and inhibiting the activity of 5α-reductase.

Its efficacy at a dose of 100 mg/day has been evaluated in two randomized vs placebo studies [26,27], but only the most recent one evaluated hirsutism scores in 40 patients and showed a significant decrease in hirsutism (−39% vs +5.4% in the placebo group, over 6 months).

Its efficacy is dose-dependent, but no rigorous dose-response study has been carried out [28]. The usual dose given is 100 mg/day, but obese patients may need to take 200 to 300 mg twice daily. Side effects are common at these doses: polydipsia, polyuria, nausea, headache, asthenia, gastritis, spotting, etc. Cases of hyperkalemia appear to be rare in this age group even though recent studies have highlighted their frequency in elderly people, patients with diabetes or kidney failure or association with other therapies favoring hyperkalemia [29].

This treatment, under the guise of contraception, is effective and can be of interest, particularly in hypertensive patients. It can be proposed as second-line treatment in the presence of side effects or a counter-indication to CPA in moderate to severe hirsutism (EXPERT OPINION).

7. Recommendation No.4

- Flutamide or Finasteride are “only” to be used under the guise of contraception as a “third-line therapy” in cases of severe hirsutism, the presence of side effects or counter-indications to EPP, CPA 50 mg/day or spironolactone (grade C)
- No market authorization in this indication

Comments:
- Flutamide:
  - It appears to be more effective at low doses (125 mg) than at 250 or 375 mg/day, with no hepatic side effects reported.
effective as 250 or 375 mg/day when associated with EPP recently demonstrated that low dose flutamide (125 mg) is as effective for flutamide used at lower doses (125 and 62.5 mg) than doses initially used in men (250 to 500 mg), with no hepatic side effects reported [31]. One study has shown in three randomized studies at a dose of 5 and 7.5 mg/day [33,34]. The efficacy of finasteride vs placebo in hirsutism has been shown in three randomized studies at a dose of 5 and 7.5 mg/day [26,35–36]. Efficacy does not appear to be improved when associated with 2 mg CPA + 35 μg EE in one controlled study [37]. However, its association with this oral contraceptive seems to improve efficacy than just using this type of oral contraceptive alone [38,39]. The differences in efficacy between these anti-androgen treatments are difficult to establish given the few studies and low number of patients included in them. A Cochrane meta-analysis, published in 2003, concluded that spironolactone (100 mg/day) appears to be more effective than CPA (12.5 mg/day) and finasteride (5 mg/day) [2]. However, a more recent meta-analysis [6] did not find any particular anti-androgen treatment better than another when taking into account controlled studies using flutamide, finasteride or spironolactone. As for CPA, the doses used and treatment duration in these studies are not those currently used in France (12.5 mg and 25 mg vs 50 mg and 10 days vs 20 days per month).

The question of the possible advantages to associating several anti-androgens has not been addressed in the literature. Two randomized studies demonstrated the superiority of a spironolactone–finasteride association vs one or the other used alone for treatment. A recent meta-analysis (grouping only five studies) revealed a slight advantage to an EPP (Diane® 35) association with spironolactone or finasteride vs an EPP alone [6].

8. Recommendation No.5

There is no indication for GnRH analogs as an anti-androgen treatment in women of childbearing age given the current therapeutic alternatives (grade C)

Comments:

• Only one controlled study available.
• Side effects: estrogen deficiency with short-term consequences on quality of life and long-term effects on the bones.
• Additional indication (unevaluated): ex: hyperthecosis.

GnRH analogs markedly lower LH more or less rapidly depending on the make-up (agonists produce an initial flare up effect whereas antagonists bring about a rapid drop in just a few hours) and markedly lower FSH. Only one controlled study is available on the treatment of hirsutism with GnRH analogs [40]. GnRH analogs reduce LH and circulating androgen levels, and the Ferriman Gallway score in uncontrolled trials [41–44]. GnRH analogs compared to EPP in controlled studies with few patients had an identical effect on hirsutism [45–47]. The association of GnRH analogs to an add back therapy with estradiol and progesterone were shown to be superior to EPP in two studies [45,47].

Carmina and Lobo [48] compared GnRH analogs with an add back therapy, Diane® 35, in association with CPA 50 mg/day–EE 50 μg/day from the 5th to 25th cycle day and the Ferriman score was lowered less in the group treated with Diane® than in other groups at 1 year of treatment. When hair began to grow back in the year following treatment cessation, it was slower in the group treated with GnRH analogs. The main side effect of GnRH analogs is an estrogen deficiency with short-term consequences on quality of life and long-term effects on the bones. The impact of GnRH analogs on bone for this specific indication remains to be studied. In a study by Carr et al. [45] an increase in urinary excretion of calcium was observed in the group receiving GnRH analogs alone. Addition of an add back therapy helps to counter balance the short- and long-term effects of GnRH analogs, and is recommended beyond 3 to 6 months of treatment for other indications such as uterine fibroids (Afssaps 2004).


9. Recommendation No.6

Only long-term hair removal treatments can be proposed (grade C): electrolysis or laser hair removal

Comments:

- Shaving and hair removal creams are not recommended for the face.
- Bleaching is possible in cases of mild hirsutism.
- The potential benefits of eflornithine (Vaniqa®), not reimbursed in France, as a supplementary treatment is still under consideration (cost/long-term evaluation).

Hair growth is a slow cyclical phenomenon and the efficacy of treatments needs to be evaluated over a period of several months while using symptomatic treatments in parallel. Studies are nevertheless limited in time and choice of products used.

In electronic hair removal (electrolysis), a needle is inserted into the hair follicle and an electric charge is given off that destroys the root. It is effective albeit fastidious, painful, and costly. It is therefore usually reserved for treating hirsutism of the face. Since 1995 photothermolysis (alexandrite laser neodymium: yttrium-aluminum-garnet [Nd:YAG] and ruby lasers or other IPL sources), where energy targets the pigmented hair and destroys cells of the papillary dermis, has been available. Use of this type of laser is not recommended for dark skin due to the risk of skin burns, and appears to be more effective for those with light skin and dark body hair. Side effects such as redness, hyper- or hypo-pigmentation can be observed in 15–25% of cases. Several sessions are usually necessary over a period of months.

There is some evidence for the efficacy of these local treatments for hirsutism, particularly based on uncontrolled, mid-term studies (6 months). In one retrospective study on 242 patients with hirsutism receiving one to six laser treatments over 4 years, a significant decrease in pilosity for an average period of 8 months was observed; the treatment was generally well tolerated (temporary local irritation) [49]. A systematic review of the literature in 2006 identified 11 controlled randomized studies on laser hair removal on a total of 444 patients [3]. Even if the methodology of these studies can be criticized, what stands out is that laser hair remover was more effective than placebo in the long-term (9 months). Photothermolysis appears to be more effective, less painful, and less costly than electrolysis [6].

Eflornithine (Vaniqa®) – a topical cream that slows hair growth – has been available since 2001, and more recently in Europe and France (not reimbursed in France). It inhibits L-ornithine decarboxylyase, an essential enzyme in polyamine synthesis and cellular division, modulated by androgens and necessary for hair growth. The dosage protocol is one facial application twice daily. Its effect on reducing hair growth appears to peak at 8 to 24 weeks. Two multi-centric, randomized double-blind vs placebo studies in 596 women showed a significant improvement in hirsutism in 58% of women in the treatment group vs 34% in the placebo group [50]. This treatment does not remove existing hair but rather slows and prevents hair growth. Effects can be seen after 2 months of use but are reversible if treatment is stopped, usually after about 2 months. Side effects are mild (irritation, rash, etc.) and rare (10% of cases). It can be used as a supplementary treatment between electrolysis or laser hair removal sessions [51,52]. However, given the cost and reversibility of its efficacy, its therapeutic interest remains questionable.

10. Conclusion

Hirsutism is a common, chronic and sometimes debilitating affliction for which treatment has improved with the combined use of medical and localized treatments.

Our approach relies on few studies with little scientific proof. New studies evaluating the long-term efficacy of these treatments, the potential benefits of the association of treatments, their metabolic impact, and potential cardiovascular impact on morbidity and mortality in higher risk patients (PCOS, obesity, hyperinsulinism) are clearly required.

11. French version

A French version of this article is available at doi:10.1016/j.ando.2009.12.002.

References


