Approach to the management of idiopathic hirsutism

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Case description

A 25-year-old white woman, A.G., presents to a family practice clinic seeking a levonorgestrel intrauterine device (IUD) for contraception. She has only used condoms in the past, but A.G. recently became engaged and wants to avoid pregnancy for several more years while she completes her master's degree. Her medical history is noncontributory; she has no known allergies, is a non-smoker, uses no illicit drugs, and has minimal alcohol intake. She takes a daily multivitamin.

Further history reveals that since puberty A.G. has experienced increased growth of facial hair. It has caused considerable embarrassment for her, and she is reluctant to discuss this issue with her physician. She also has mild acne, but has not tried any prescription therapies. She has heard from friends that contraceptive pills cause increased growth of facial hair, and for this reason she has never used any birth control medication. She has regular monthly menses.

Examination

Examination findings reveal that A.G. is a pleasant woman with appropriate affect. Measurements of her vital signs are normal, with a blood pressure of 110/84 mm Hg. Her body mass index is 26.8 kg/m^2. There is a moderate increase of dark facial hair in the chin area and on the upper lip. Her abdomen is soft and nontender. She declines a pelvic examination because she is menstruating.

The patient is counseled about the causes of hirsutism and agrees to further investigation. She is given a requisition for measurement of complete blood count; thyroid-stimulating hormone, fasting plasma glucose, and lipid levels; a renal panel; and free testosterone, luteinizing hormone, follicle-stimulating hormone, and dehydroepiandrosterone sulfate (DHEA-S) levels. A pelvic ultrasound is ordered as well, and A.G. is asked to follow up in 2 weeks, at which time a suitable contraceptive method will be discussed.

Diagnostic approach

Androgen-excess disorders to consider in A.G.'s case include the following:

- polycystic ovary syndrome (PCOS)—clinical or biochemical hyperandrogenism in addition to ovarian dysfunction or polycystic ovary morphology;
- idiopathic hyperandrogenism—clinical and biochemical hyperandrogenism but regular ovulatory cycles of normal length and normal ovary morphology;
- idiopathic hirsutism—hirsutism with normal androgen concentrations, ovulatory cycles, and ovary morphology;
- nonclassic congenital adrenal hyperplasia;
- androgen-secreting tumours; and
- iatrogenic excess androgen.

Hirsutism should be investigated and treated, not only to determine the underlying cause, but also because it can negatively affect women's psychological well-being.

A detailed history and physical examination are most valuable when determining the cause of hirsutism. Methods for evaluation can be subjective and objective. Visually scoring the body and facial terminal hair growth in specified body areas using the Ferriman-Gallwey score is more convenient and less expensive than more objective scoring with photographic evaluations, microscopic measurements, and weighing of shaved or plucked hair. The Ferriman-Gallwey tool scores 9 of the 11 androgen-sensitive hair growth areas on a scale of 0 to 4 (for a maximum score of 36). A score of 8 to 15 is considered mild hirsutism; a score above 15 is considered moderate to severe hirsutism.[1]

Determination of serum androgen levels should be the first step for establishing the cause of hirsutism. Androgen contributes to the growth of sexual hair in both sexes, as well as to the growth of facial and trunk hair in women with hirsutism. The androgens found in female serum include DHEA-S, DHEA, androstenedione, testosterone, and dihydrotestosterone. The most active androgen, dihydrotestosterone, has low serum levels because it is synthesized in androgen target tissues. For this reason, measurable circulating androgen levels might not reflect androgen activity in the hair follicles of women with hirsutism. Serum levels of DHEA-S and free testosterone are the most sensitive measurements of androgen excess and are considered tumour markers.[2,3]

If PCOS is suspected, a metabolic evaluation (measurement of plasma glucose levels, waist circumference and body mass index, complete lipid profile, and blood pressure) is necessary to evaluate the patient's risk of metabolic and cardiovascular dysfunction. A common finding in PCOS is an increased luteinizing hormone to follicle-stimulating hormone ratio (>2.5). Ultrasound might aid in diagnosing PCOS, as well as nonclassic congenital adrenal hyperplasia or androgen-secreting tumours.

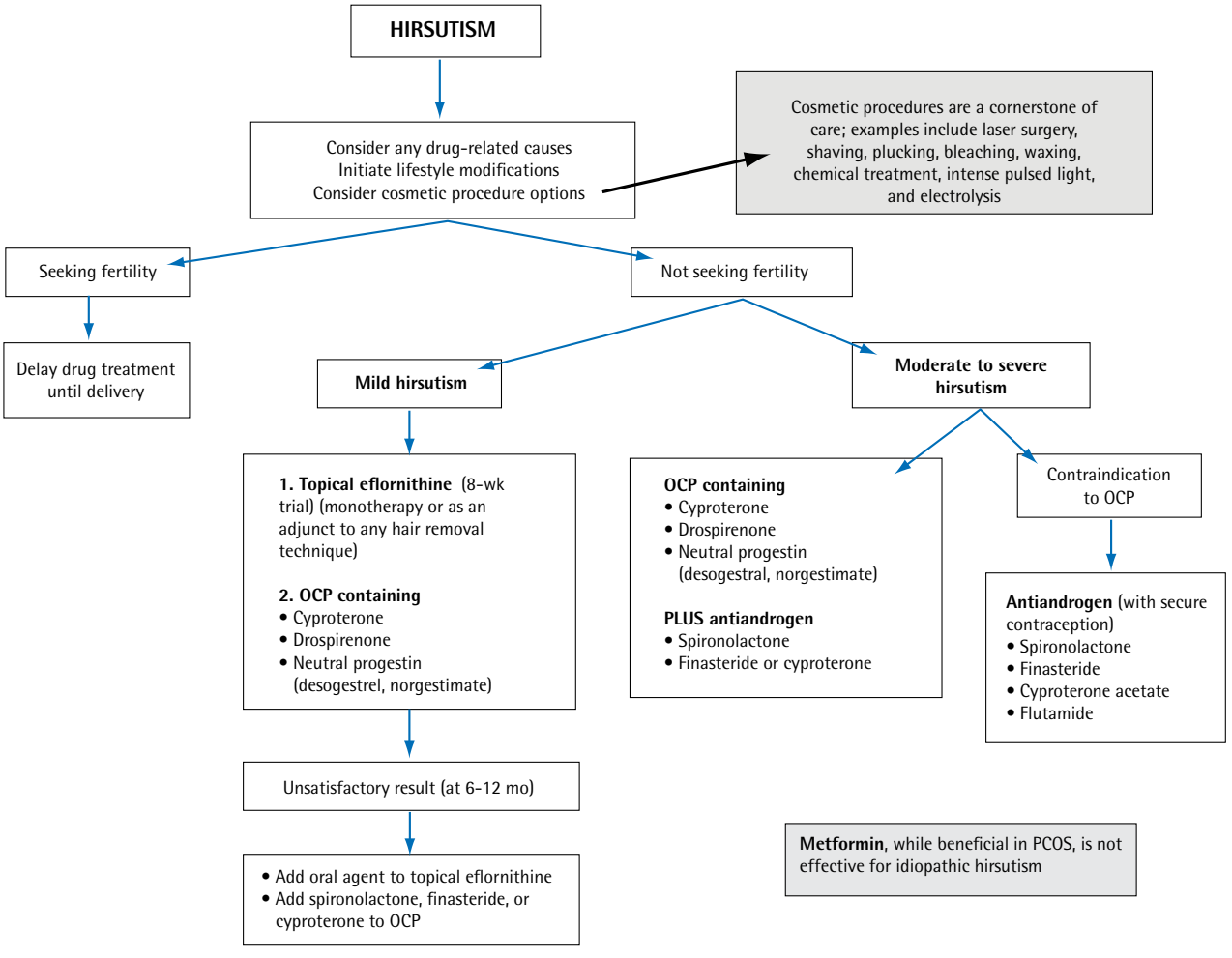
Management of hirsutism

An approach to treatment of hirsutism is outlined in **Figure 1**.[1,2,4]

Rule out potential drug-related causes. Drugs that can cause excessive hair growth (hirsutism or hypertrichosis) include acetazolamide, anabolic steroids (eg, danazol, nandrolone, stanozolol), androgenic progestogens or oral contraceptive pills (OCPs) containing progestogen (eg, norethindrone and levonorgestrel found in first- and second-generation OCPs), cyclosporine, diazoxide, glucocorticoids, drugs containing heavy metals, minoxidil, penicillamine, phenytoin, tamoxifen, and thyroxine.[5,6] Drug-induced excessive hair growth is reversible upon discontinuation of the offending agent. In cases in which the drug cannot be stopped, cosmetic measures might be of value to conceal or remove hair.

Nonpharmacologic intervention. Targeted counseling about self-image plays an important role in the treatment of hirsutism. Lifestyle modifications, such as physical exercise and dietary advice, can be recommended. Such modifications might be less effective for idiopathic hirsutism than for hirsutism caused by PCOS; however, they might also be worthwhile for cardiovascular protection.[2] Cosmetic measures, such as bleaching, plucking, shaving, waxing, chemical treatment, electrolysis, laser hair removal, and intense pulsed light are usually effective in controlling mild hirsutism, especially when terminal hair localizes in exposed areas such as the face.

Figure 1. Management of idiopathic hirsutism



OCP—oral contraceptive pill, PCOS—polycystic ovary syndrome.
Adapted from Hirsutism.com,[1] Escobar-Morreale et al,[2] and Harrison et al.[4]

Table 1. Medications used for idiopathic hirsutism[1-8]: *Medications listed are contraindicated in pregnancy and require use of appropriate contraception.*

CLASS AND INGREDIENTS		ROLE IN THERAPY	EFFICACY	DOSE (COST/30 D)
CCI	• Eflornithine 13.9% cream (Vaniqa)	• Monotherapy for mild cases of facial hirsutism or as adjunct to other therapies (complements antiandrogen, laser, or IPL therapy) • Considered first-line in postmenopausal women • Well tolerated: might cause rash, burning, or tingling	• Improvement noted at ≥ 8 wk; effect reverses 8 wk after discontinuation[12-14] • Used alone, treatment is successful about 30% of the time (slows rate of hair growth); variable cosmetic significance[14] • Improves time to effect with laser therapy (up to 95% successful)[12]	Topical; apply twice daily, at least 8 h apart ($64 per 30-g tube; lasts about 3-5 mo for upper lip and 4-6 wk for lower face)
OCPs	• EE with drospirenone (Yasmin, Yaz) • EE with desogestrel (Marvelon, Ortho-Cept, Linessa) • EE with norgestimate (Tri-Cyclen, Tri-Cyclen LO, Cyclen) • See full RxFiles chart[15] for other low-androgen OCP options	• Generalized hirsutism, for women not seeking fertility • All OCPs can help owing to estrogen's effect on SHBG • Risk of VTE, although small, increases with age (especially > 39 y) and possibly choice of OCP -baseline risk: about 5/10 000 -with OCPs: 8-9/10 000 (up to 14/10 000) -possible increased risk with Yasmin, Yaz[16,17]	• Improvement noted at 3 mo; maximum effect at 9-12 mo • Yasmin: FGS 65%-70% lower at 6 mo and 80% lower at 12 mo[18,19] • Marvelon: FGS 40% lower at 6 mo and 35% lower at 12 mo[18] • Tri-Cyclen: no specific evidence	1 tablet, orally, once daily ($17-$23)
	• EE with cyproterone* (Diane-35, CyEstra-35)	• Mild hirsutism, severe acne • Risk of VTE, though small, might be higher compared with some other OCPs[17]	• Diane-35: FGS 55% lower at 6 mo and 80% lower at 12 mo[17,19]	EE 35 µg with CPA 2 mg ($29)
Antiandrogens†	• Spironolactone (Aldactone)	• Moderate to severe hirsutism • Considered first-line antiandrogen	• Superior to metformin, flutamide[20] • Combination of spironolactone with OCPs superior to OCPs alone or flutamide[21,22]	25 mg orally, twice daily, for the first 1 wk; check potassium level in 3-7 d; then 50-100 mg orally, twice daily ($17-$25 for 100-mg tablet; $54-$100 for 25-mg tablet)
	• CPA (Androcur)	• Moderate to severe hirsutism • Considered second-line antiandrogen	• No difference in efficacy between 2-mg and 100-mg doses[23] • Subjectively improves hirsutism and provides a "good clinical response" in 60%-80% of patients[23] • Similar efficacy to spironolactone, finasteride, GnRH analogues; less effective than flutamide[23]	25-100 mg/d, orally, at days 1-10 or 5-15 of cycle ($9-$33 for 50-mg tablet)
	• Finasteride (Proscar)	• Moderate to severe hirsutism • Considered second-line antiandrogen	• No difference in efficacy between 2.5-mg and 5-mg doses[2] • Combination of finasteride with OCPs superior to OCPs alone[21]	5 mg/d orally $35 (5-mg tablet)
	• Flutamide (Euflex)	• Severe hirsutism • Considered third-line antiandrogen (owing to risk of hepatotoxicity[24])	• No difference in efficacy between 125-mg and 375-mg doses[25]	250 mg/d orally $52 (250-mg tablet)

CCI—cell cycle inhibitor, CPA—cyproterone acetate, EE—ethinyl estradiol, FGS—Ferriman-Gallwey score, GnRH—gonadotropin-releasing hormone, IPL—intense pulsed light, OCP—oral contraceptive pill, SHBG—sex hormone–binding globulin, VTE—venous thromboembolism.

*Not approved for contraception in Canada.

†In general, antiandrogens lower FGS by 20%-40% at 6 mo, with maximal effect at 9-12 mo,[6] and are superior to placebo and metformin.[21,26]

This table is an adaptation of the full RxFiles chart, which is available from CFPlus.

Pharmacologic intervention. When hirsutism is cosmetically distressing, moderate to severe, or widespread, a pharmacologic treatment should be offered. As drugs are only partially effective on terminal hairs, management of clinically important hirsutism is based on a dual approach: pharmacologic therapy to reduce androgen secretion and action, and the physical removal of terminal hair already present.[2]

Drug treatment is limited to patients with hirsutism who do not wish to become pregnant in the short term (**Figure 1**).[1,2,4] Oral contraceptives, topical eflornithine, and antiandrogens are common medications used to treat hirsutism[4-11] (**Table 1**).[1-8,12-26]

Bringing evidence to practice

Topical 13.9% eflornithine cream is used as monotherapy for mild facial hirsutism or as an adjunct to other pharmacologic therapies along with nonpharmacologic measures.[2]

The complex interplay of estrogens and progestins contributes to the variable effects of OCPs on hirsutism. Low-dose OCPs containing a neutral (low-androgenicity) progestin, such as desogestrel and norgestimate, or an antiandrogen, such as cyproterone acetate and the spironolactone derivative drospirenone, are considered first-line therapy for hirsutism.

- In a randomized clinical trial of healthy women of childbearing age, 45 women received a third-generation OCP (30 µg ethinyl estradiol plus 150 µg desogestrel) and 46 received a second-generation OCP (30 µg ethinyl estradiol plus 150 µg levonorgestrel). After 6 months of therapy, the group taking the third-generation OCP had significant reduction in the severity of hirsutism and acne without significant weight change compared with those taking the second-generation OCP ($P<.001$).[27]
- Other "contraceptives" that contain cyproterone acetate (eg, Diane-35 and CyEstra-35, which are not officially indicated for contraception in Canada) or drospirenone (eg, Yasmin, Yaz) have similar efficacy in treating hirsutism.[19] There is also some weak, indirect evidence suggesting that they might be slightly more effective than OCPs with neutral progestins.[18,28]

Antiandrogens such as spironolactone, cyproterone acetate, finasteride, and flutamide are recommended for patients with moderate to severe hirsutism. The various antiandrogens have similar efficacy with variations in side effects. Spironolactone, cyproterone acetate, or finasteride are preferred over flutamide because of the increased risk of severe or fatal liver toxicity with flutamide.[2,24]

Other drugs that have been reported to have been used for hirsutism include metformin, prednisone, ketoconazole, and gonadotropin-releasing agonists. These medications are not often recommended for idiopathic hirsutism because their effects are generally limited, they cause adverse effects, or they are more expensive. However, they do have a role in hirsutism with other specific causes,[2,3] as outlined in the chart available from **CFPlus.***

Case resolution

The patient, A.G., is seen at her scheduled follow-up appointment. All laboratory test results are normal and the pelvic ultrasound has not revealed any abnormalities, and A.G. is diagnosed with idiopathic hirsutism. Both contraceptive and hirsutism treatment options are discussed with her. She declines oral treatment, stating that her schedule is hectic and that she will likely forget to take the birth control pill on a regular basis, risking unplanned pregnancy.

Mirena (levonorgestrel-releasing IUD) does not increase or decrease the amount of facial hair in women with idiopathic hirsutism. After considering this information and based on her preference, A.G. decides to proceed with the insertion of the IUD. She is advised to consider cosmetic measures such as bleaching, plucking, waxing, shaving, electrolysis, or laser therapy.

Three months later, A.G.'s facial hair remains unchanged and she wishes to explore additional therapy. A combination of eflornithine cream and laser therapy has been shown to remove unwanted hair on the upper lip of women significantly better than laser therapy alone for up to 6 months ($P=.021$).[12] Thus, A.G. agrees to a trial of eflornithine cream and decides to explore laser therapy options. A switch from Mirena to a drospirenone-containing OCP is also discussed as a future option.

*The full version of the RxFiles chart on the treatment of hirsutism is available at www.cfp.ca. Go to the full text of the article online and click on CFPlus in the menu at the top right-hand side of the page.

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