No. 444 December 2023 (No. 350, November 2017)

Guideline No. 444: Hirsutism: Evaluation and Treatment

(En français : Directive clinique n^{o} 444 : Hirsutisme : Évaluation et traitement)

The English document is the original version; translation may introduce small differences in the French version.

This clinical practice guideline was prepared by the authors and overseen by the SOGC Reproductive Endocrinology and Infertility committee (this specialized committee has now been regrouped under the Clinical Practice Gynaecology Committee) and reviewed by the Clinical Practice Gynaecology Committee. It was reviewed and approved by the SOGC Guideline Management and Oversight Committee.
This clinical practice guideline supersedes No.350, published in November 2017.

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Acknowledgements: The authors would like to acknowledge and thank Dr. Paul Claman, MD, for his contribution to the original publication.

Disclosures: Statements were received from all authors. No relationships or activities that could involve a conflict of interest were declared. All authors have indicated that they meet the journal's requirements for authorship.

Subject Categories: reproductive endocrinology and infertility

Keywords : hirsutism; polycystic ovary syndrome; disease management; symptom assessment; therapeutics

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RECOMMENDED CHANGES IN PRACTICE

1. Racial differences in modified Ferriman-Gallwey scores should be considered when determining cut-offs for a diagnosis of hirsutism.

J Obstet Gynaecol Can 2023;45(12):102272

https://doi.org/10.1016/j.jogc.2023.102272

This document reflects emerging clinical and scientific advances as of the publication date and is subject to change. The information is not meant to dictate an exclusive course of treatment or procedure. Institutions are free to amend the recommendations. The SOGC suggests, however, that they adequately document any such amendments.

Informed consent: Patients have the right and responsibility to make informed decisions about their care, in partnership with their health care provider. In order to facilitate informed choice, patients should be provided with information and support that is evidence-based, culturally appropriate, and personalized. The values, beliefs, and individual needs of each patient in the context of their personal circumstances should be considered and the final decision about care and treatment options chosen by the patient should be respected.

Language and inclusivity: The SOGC recognizes the importance to be fully inclusive and when context is appropriate, gender-neutral language will be used. In other circumstances, we continue to use gendered language because of our mission to advance women's health. The SOGC recognizes and respects the rights of all people for whom the information in this document may apply, including but not limited to transgender, nonbinary, and intersex people. The SOGC encourages health care providers to engage in respectful conversation with their patients about their gender identity and preferred gender pronouns and to apply these guidelines in a way that is sensitive to each person's needs.

KEY MESSAGES:

1. Hirsutism is a relatively common condition seen across all racial groups.
2. Polycystic ovary syndrome is the most common cause of hirsutism.
3. Hirsutism can be classified into 3 etiologic groups: hyperandrogenic hirsutism, non-androgenic hirsutism, and idiopathic hirsutism.
4. Management of hirsutism involves a 3-pronged approach of mechanical hair removal, suppression of androgen production, and androgen receptor blockade.

ABSTRACT

Objective: This guideline reviews the etiology, diagnosis, evaluation, and treatment of hirsutism.

Target Population: Women with hirsutism.

Options: Three approaches to management include: 1) mechanical hair removal; 2) suppression of androgen production; and 3) androgen receptor blockade.

Outcomes: The main limitations of the management options include the adverse effects, costs, and duration of treatment.

Benefits, Harms, and Costs: Implementation of the recommendations in this guideline may improve the management of hirsutism in women with this condition. Adverse effects and a potential long duration of treatment are the main drawbacks to initiating treatment, as is the possibility of significant financial costs for certain treatments.

Evidence: A comprehensive literature review was updated to April 2022, following the same methods as for the prior Society of Obstetricians and Gynaecologists of Canada (SOGC) Hirsutism guidelines. Results were restricted to systematic reviews, randomized controlled trials, controlled clinical trials, and observational studies. There were no date limits, but results were limited to English- or French-language materials.

Validation Methods: The authors rated the quality of evidence and strength of recommendations using the modified Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, along with the option of designating a recommendation as a "good practice point." See online Appendix A (Tables A1 for definitions and A2 for interpretations of strong and conditional [weak] recommendations).

Intended Audience: Primary care providers, family medicine physicians, obstetricians and gynaecologists, reproductive endocrinologists and others who manage the care of patients with hirsutism.

Tweetable Abstract: Management of hirsutism involves a 3-pronged approach of mechanical hair removal, suppression of androgen production, and androgen receptor blockade.

SUMMARY STATEMENTS:

1. The modified Ferriman-Gallwey score can be used in the assessment of hirsutism to help quantify the problem and assess the response to treatment. Cut-off scores defining hirsutism will vary by racial background. Modified Ferriman-Gallwey scores from 3 to 15 represent mild hirsutism, 16–25 represent moderate hirsutism, and >25 indicate severe hirsutism (*moderate*).
2. Hyperandrogenism in women with polycystic ovary syndrome may result from several mechanisms, including insulin resistance, hyperinsulinemia, elevated luteinizing hormone–related increases in theca cell androgen production, and increased adrenal androgen output. (*high*).
3. Non-classical congenital adrenal hyperplasia often presents with hirsutism and has a similar clinical picture as polycystic ovary syndrome. However, the prevalence of non-classical congenital adrenal hyperplasia is very low outside of specific high-risk ethnic groups (*high*).
4. Hirsutism can be classified into 1 of 3 groups based on etiology: hyperandrogenic hirsutism (including polycystic ovarian syndrome, non-classical congenital adrenal hyperplasia, or androgen-secreting tumours), non-androgenic hirsutism (including medication-induced hirsutism), and idiopathic hirsutism (*moderate*).
5. Polycystic ovary syndrome is the most common cause of hirsutism, with idiopathic hirsutism being the second most common (*high*).
6. Most patients with hirsutism have normal androgen levels. That said, high androgen levels should be investigated immediately, as some impacts will be permanent, such as voice changes and clitoromegaly (*high*).
7. Hirsutism is not a diagnosis, but a symptom or sign, and an underlying etiology should be sought (*high*).
8. The most effective therapy for hirsutism is multimodal and combines physical hair removal techniques with medical therapies. At least six months of medical therapy is required to see a significant improvement in hirsutism. Unfortunately, many permanent physical hair removal procedures are considered cosmetic and the costs can be a barrier to treatment (*moderate*).
9. Hair growth tends to recur after stopping medical therapy, while laser hair removal, intense pulsed light, and electrolysis produce permanent hair reduction (*moderate*).

RECOMMENDATIONS:

1. Patients presenting with hirsutism should be evaluated with a focused history taking, physical examination with anthropometric measurements, and appropriate investigations to differentiate between the possible etiologies (*strong, moderate*).
2. Patients with moderate to severe hirsutism should undergo blood testing to determine total testosterone and sex hormone–binding globulin levels; however, the benefit of testing in mild hirsutism is questionable. Additional testing is indicated for patients with irregular cycles and signs of hyperandrogenism or other endocrinopathies (*conditional, low*).
3. Patients with hyperandrogenic hirsutism should have serum levels of dehydroepiandrosterone sulfate and 17-hydroxyprogesterone measured (*strong, moderate*).
4. Referral for evaluation by a medical or reproductive endocrinologist (or another practitioner with similar expertise) is indicated in the presence of 1) virilization; 2) serum testosterone or dehydroepiandrosterone sulfate levels more than twice the upper limit of normal; 3) signs or symptoms of Cushing syndrome; or 4) early follicular phase serum 17-hydroxyprogesterone levels >6 nmol/L (*strong, high*).
5. Therapy should be offered to all patients with hirsutism who desire treatment (*good practice point*).
6. Combined hormonal contraceptives should be offered as first-line therapy if there are no contraindications (*strong, high*).
7. Mechanical hair removal and/or topical treatments can be offered as first-line therapy or as an adjuvant to medical therapy (*strong, high*).

8. Antiandrogens can be considered as monotherapy or in addition to combined hormonal contraceptives to enhance efficacy (*strong, high*).
9. Patients on antiandrogens require an effective method of contraception and should be counselled regarding the risk of feminization of a male fetus if pregnancy were to occur (*good practice point*).

INTRODUCTION

This guideline on hirsutism focuses on patients in their reproductive years. This review is intended as a management guide for family medicine physicians and other primary care providers, obstetricians and gynaecologists, reproductive endocrinologists, and others who manage patients with hirsutism. Because there is a paucity of evidence, guidance for the assessment, classification, and management of hair growth in transgender patients is not specifically addressed in this guideline. This has been identified as an area in need of further research and should be addressed in future updates of this guideline.

DEFINITION AND PATHOGENESIS

Hirsutism is defined as excessive terminal hair growth in androgen-dependent areas of the female body (i.e., face, chest, abdomen, lower back, upper arms, and thighs).[1,2] This common condition affects 5%–15% of reproductive-aged females and is commonly associated with acne and oily skin.[3,4]

The pilosebaceous unit is composed of a hair follicle, arrector pili muscle, and a sebaceous gland.[5] Hair follicles during reproductive life contain either vellus (non-medullated, short, soft, and lightly pigmented) or terminal (medullated, longer, stiff, and pigmented) hair. Vellus hairs, whose growth is mediated by growth and thyroid hormones, cover most of the body, except the lips, palms, soles, and top of the feet .[6] Terminal hair growth in defined body regions can be stimulated by androgens, which drives the development of hirsutism.[7] Specifically, hirsutism results from the effect of androgens on the pilosebaceous unit, as a result of higher circulating free androgen levels, enhanced peripheral metabolism of androgens and/or increased sensitivity of the pilosebaceous unit to androgens.[8]

The modified Ferriman-Gallwey (mFG) score (i.e., upper lip, chin, chest, upper back, lower back, upper abdomen, lower abdomen, upper arms, thighs) is the preferred and most widely used method for scoring excess terminal hair in the assessment of hirsutism (see Figure 1).[2,9] Scores range from 0 to 4 for each body area, with a total score range of 0–36. Typically, scores above the 95th percentile for a population are used to confirm hirsutism; however, because of racial differences in normal hair distribution, cut-off mFG scores for hirsutism vary as follows: >8 (for Black or White patients), >9–10 (for Mexican, Mediterranean, South Asian and Middle Eastern patients), >6 (for Latin American patients), >2–3 (for Chinese, Japanese, Korean, North American Indigenous, and Inuit patients), and >7 (for Southern Chinese patients).[10–13] Classically, mild hirsutism has been defined in patients with a score between 8 and 15, while moderate and severe hirsutism are defined as mFG scores of 16–25 and >25, respectively.[10] Several reports indicate that mFG scores of 3–5 may closer align with patient reported "abnormal" hair growth. Patients with mFG scores >3 had similar complaints of hirsutism and use of hair removal treatments as those with scores >8, suggesting targets for initiation of investigations and management may be lower than traditional mFG scores.[1,13,14]

It is important to distinguish between hirsutism, masculinization, and virilization. Masculinization is the development of male secondary sexual characteristics (facial hair, voice depth, body fat distribution, increased pectoral musculature) in a female. Virilization is an extreme degree of hirsutism and masculinization with male pattern balding, voice deepening, increased muscle bulk, changes in libido, and clitoromegaly (clitoral diameter greater than 4 mm).[15] Virilization is a sign of high and often rapid androgen production, suggesting an androgen-secreting tumour.

Summary Statement 1

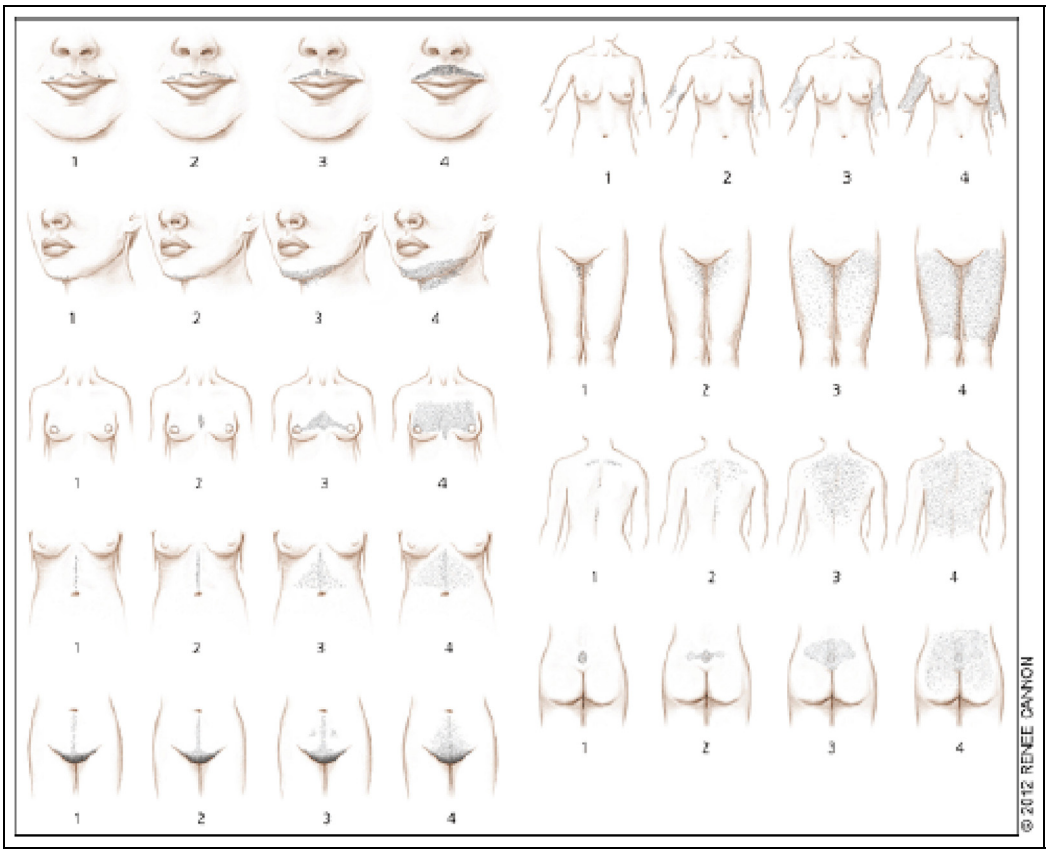
ETIOLOGY

Hirsutism is not a disease or diagnosis; it is a symptom or sign of another (usually benign) condition. It is important to determine the specific etiology of hirsutism as it may be the first sign of a serious underlying disorder.[16] Causes of hirsutism can be divided into the following categories: 1) hyperandrogenic (e.g., polycystic ovary syndrome [PCOS], androgen-secreting tumours), 2) non-androgenic (e.g., medications or anabolic steroids), and 3) idiopathic. The most common cause of hirsutism is PCOS.[17] (See Figure 2 for an overview of all categories of hirsutism).

ABBREVIATIONS

17-OHP	17-hydroxyprogesterone
ACTH	Adrenocorticotropic hormone
CHC	Combined hormonal contraceptives
DHEA-S	Dehydroepiandrosterone sulfate
mFG	Modified Ferriman-Gallwey
NC-CAH	Non-classical congenital adrenal hyperplasia
PCOS	Polycystic ovary syndrome
SHBG	Sex hormone–binding globulin

Figure 1. Ferriman-Gallwey score for hirsutism.



Each of the 9 body areas most sensitive to androgens is assigned a score from 0 (no hair) to 4 (frankly virile), and these separate scores are summed to provide a hormonal hirsutism score. Reproduced with permission from Elsevier (License: 5626631337772), Hatch R, Rosenfield RL, Kim MH, et al. Hirsutism: implications, etiology, and management. Am J Obstet Gynecol 1981;140:815e30. Copyright Elsevier 2023.

Hyperandrogenic Hirsutism

Hyperandrogenic hirsutism is the most common category (>80% of cases) and is usually due to increased androgen production from the ovaries or adrenal glands.[17,18] Elevated levels of dehydroepiandrosterone sulfate (DHEA-S) are almost always of adrenal origin, while high testosterone levels may be of ovarian or adrenal origin (Figure 3).[19] Patients with hyperandrogenism often have irregular menses, anovulation, infertility, hyperinsulinemia, and a risk of endometrial hyperplasia or neoplasia because of unopposed estrogen. The conditions primarily accounting for hyperandrogenic hirsutism are PCOS, nonclassical congenital adrenal hyperplasia (NC-CAH) and androgen-secreting tumours.[3,4]

Polycystic Ovary Syndrome

PCOS is the most common cause of hirsutism, responsible for 72%–82% of all cases and affecting 4%–12% of reproductive age patients.[4] Furthermore, 74% of patients with hirsutism have PCOS, and 76% of patients diagnosed with PCOS have hirsutism. This finding was independent of ethnicity.[3] Although there have been many different definitions of PCOS, the currently accepted Rotterdam Criteria requires at least 2 of the following 3: 1) oligo-anovulation, 2) clinical and or biochemical signs of hyperandrogenism, and 3) polycystic ovaries on ultrasound and the exclusion of other causes of hyperandrogenism and anovulation.[20] PCOS is often, but not always, associated with irregular menses, endometrial hyperplasia, infertility, central obesity, and acanthosis nigricans.[21]

Hyperandrogenism in PCOS is primarily the result of gonadotropin-dependent functional ovarian androgen excess, due to increased theca cell androgen production related to chronic elevations in luteinizing hormone. Adrenocorticotropic hormone (ACTH)-dependent adrenal androgen production also contributes to the hyperandrogenism.[22] Furthermore, hyperinsulinemia also inhibits hepatic synthesis of sex hormone–binding globulin, increasing circulating levels of serum free testosterone.[23] The rare hyperandrogenism, insulin resistance, and acanthosis nigricans syndrome is a severe variant of PCOS,

Figure 2. Common causes of hirsutism.

Cause	History	Physical	Investigations
Hyperandrogenic Hirsutism			
PCOS	• Oligo-ovulation • Infertility	• Acanthosis nigricans • Acne	• Polycystic ovaries on ultrasound
Androgen secreting tumours	• Rapid onset virilization o deepening voice o male pattern o alopecia	• Abdominal or pelvic mass • Clitoromegaly, deepening voice, male pattern alopecia	• Elevated androgens (2 x normal)
NC-CAH	• Oligo-ovulation • Infertility	• Acne	• Elevated follicular 17-OHP
Non-Hyperandrogenic Hirsutism			
Medications	• History of medications associated with hirsutism		
Cushing syndrome	• Fatigue • Muscle weakness	• Central obesity • Striae • Proximal muscle weakness • Moon face • Buffalo hump • Acne	• 24-hour urinary free cortisol, late night salivary cortisol, or dexamethasone suppression
Idiopathic			
Idiopathic	• Regular menses • Family history		• Normal androgens

17-OHP: 17-hydroxyprogesterone; NC-CAH: non-classical congenital adrenal hyperplasia; PCOS: polycystic ovary syndrome.

caused by abnormal number or function of the insulin receptor, or antibodies against the insulin receptor.[24] Patients with PCOS are at risk for metabolic syndrome, hypertension, hyperlipidemia, type 2 diabetes mellitus, and possibly coronary artery disease. Patients diagnosed after first presenting for assessment of hirsutism should be advised of these risks. Appropriate surveillance should be undertaken to identify the early onset of complications, and if possible, efforts should be made to prevent them.[25]

Summary Statement 2

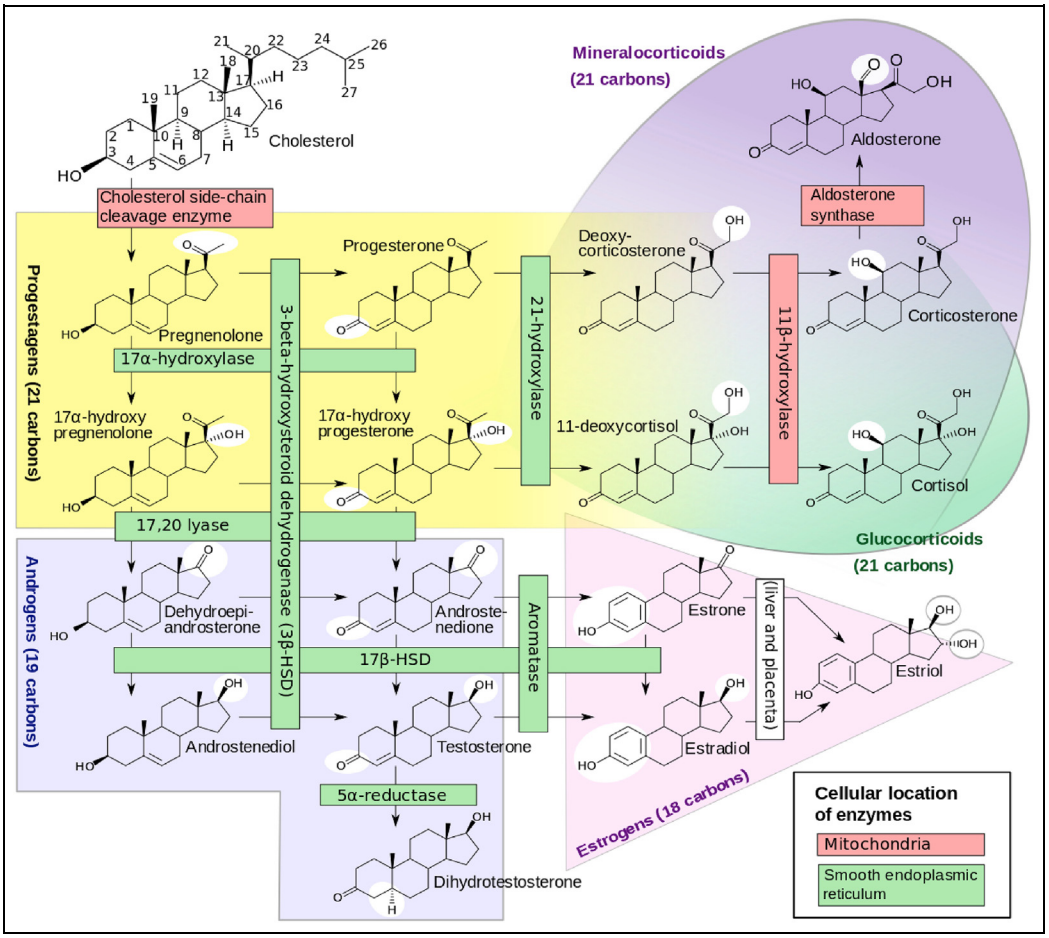
Tumours

Androgen-secreting ovarian and adrenal tumours are rare (0.2% of hirsutism cases).[17] In contrast to PCOS, these tumours function autonomously, without regulatory feedback mechanisms.[26] Luteinizing hormone and follicle-stimulating hormone levels are often suppressed to or below the lower limit of normal, while circulating androgen levels are usually twice the upper limit of normal or higher. Half of all androgen-secreting tumours are malignant.[27] Androgen-secreting tumours present with rapid onset hirsutism, virilization, or an abdominal or pelvic mass.[26,28]

Non-Classical Congenital Adrenal Hyperplasia

Non-classical congenital adrenal hyperplasia (NC-CAH) has an overall prevalence of 0.1% in the White population and 4.2% worldwide. The prevalence in patients with hirsutism varies by population: 1%—2% in White and Latin Americans in the United States, and is rarely reported in African Americans; 3%-6% in Spain, France, Canada, and Italy; and 5%—10% in the Middle East.[29] Ashkenazi Jewish patients are at higher risk, with a 37-fold greater prevalence than the general White population.[3] Patients with NC-CAH remain asymptomatic until after puberty. NC-CAH is the most common adrenal cause of hyperandrogenism and results from a partial deficiency of enzymes leading to cortisol production, most commonly 21-hydroxylase (see Figure 3). It is inherited in an autosomal recessive pattern, and an individual with NC-CAH may be heterozygous for more than one mutation, with variable severity of clinical effect.[30] The clinical picture of NC-CAH is similar to that of PCOS, although there are different manifestations of this disorder depending on the severity of the hormone biosynthesis defect. Presenting symptoms include hirsutism (59%), oligomenorrhea (54%), acne (33%), infertility (13%), alopecia (8%), and primary amenorrhoea (4%).[31] NC-CAH is suspected when an elevated 17-hydroxyprogesterone (17-OHP) level is identified, with confirmation of the diagnosis using an ACTH stimulation test. The diagnosis of NC-CAH does not generally alter the treatment plan for hirsutism, but there may be genetic implications for future pregnancies and a risk of classical CAH in the offspring of affected individuals.[32,33] Hirsutism can also be present in

Figure 3. Steroidogenesis pathway.



Steroidogenesis is the biological process by which steroids are generated from cholesterol and transformed into other steroids. An overview of the pathways wherein these steroids are produced is illustrated in this diagram. From Häggström M, Richfield D. Diagram of the pathways of human steroidogenesis. WikiJournal Med 2014;1(1):4. CC0 1.0 platform, obtained on Wikipedia.

patients with classical CAH if their replacement steroid dose is too low or if they are poorly adherent with their medication.

Summary Statement 3

Non-Androgenic Hirsutism

Medications

Hirsutism may develop following the use of medications such as danazol, performance-enhancing anabolic steroids, cyclosporine (treats psoriasis, eczema, arthritis), diazoxide (treats hypoglycemia or hypertension), penicillamine, interferon, phenytoin, cetuximab, glucocorticosteroids, androgen creams or patches, progestins, and estrogen antagonists (e.g., clomiphene, tamoxifen).[34]

Hypertrichosis, excessive vellus hair growth characterized by abnormal hair length and density, should be distinguished from hirsutism. Hypertrichosis can reflect racials variation, non-androgenic endocrine disorders such as anorexia nervosa, thyroid disease or an imbalance in growth hormone, or a side effect of medications.[12] These medications include acetazolamide, streptomycin, latanoprost, psoralen, minoxidil, and cyclosporine, which also causes hirsutism through a different mechanism.[35] Hypertrichosis has no pattern of distribution, and commonly affects the limbs, trunk, back, and occasionally face. Hair growth usually returns to normal after discontinuation of the medication, and unlike hirsutism, hypertrichosis does not respond to antiandrogen therapy.[12,36]

Other Endocrinopathies

Endocrinopathies are an uncommon cause of hirsutism with the diagnosis usually made by recognizing the other signs and symptoms of these disorders.[10] Hypo- or hyperthyroidism are rarely associated with isolated hirsutism. Hyperprolactinaemia (elevated serum prolactin) presents

with galactorrhoea, amenorrhoea, infertility, and, infrequently, hirsutism. Cushing syndrome is characterized by weight gain, obesity, purple stretch marks on breasts, arms, abdomen, and thighs, thinning skin that bruises easily, fat deposition on the abdomen, face (moon-shaped face) and between the shoulders and upper back (buffalo hump), acne, fatigue, muscle weakness, glucose intolerance, polydipsia, polyuria, bone loss, hypertension, headaches, cognitive dysfunction, anxiety, irritability, and depression.[8]

Acromegaly is a rare cause of isolated hirsutism; it more commonly presents with features of frontal bossing, increased hand and foot size, mandibular enlargement, hyperhidrosis, and voice deepening.[17]

Idiopathic Hirsutism

Idiopathic hirsutism is the term used to describe hirsutism that occurs in association with normal ovulatory menstrual cycles and normal androgen concentrations.[35] It is diagnosed by the exclusion of other etiologies, and, when strictly defined, accounts for 5%–15% of all cases of hirsutism.[37] Idiopathic hirsutism may be due to increased sensitivity to androgens in the pilosebaceous unit, a genetic increase in the peripheral conversion of testosterone to dihydrotestosterone by 5α-reductase, or a change in the androgen receptor function. A typical example of idiopathic hirsutism is the familial hirsutism that often affects individuals of Mediterranean or South Asian (Indian) descent.[38]

Summary Statements 4 and 5

DIAGNOSIS AND INVESTIGATIONS

Since hirsutism is a symptom or sign, an underlying etiology should be considered, including systematic evaluation for hyperandrogenism.[16] Clinicians need to be aware that patients often undertake cosmetic therapies, which may minimize the amount of excess hair noted on examination. Diagnostic evaluation is influenced by the severity of hirsutism (mFG score), patient concerns, which may not meet the criteria for hirsutism using the mFG score, and the potential of underlying hyperandrogenism.[39] The severity of hirsutism is associated with the presence of hormonal abnormalities, although the specific level of serum luteinizing hormone, follicle-stimulating hormone, luteinizing hormone/follicle-stimulating hormone, prolactin, thyroid-stimulating hormone, or DHEA-S does not predict severity.[40] A thorough and detailed history should be obtained, including the onset of symptoms, presence of virilization, menstrual history, fertility history, history of weight gain, and medication history prior to the onset of symptoms (Figure 4).

A general physical examination including anthropometric characteristics (i.e., BMI, waist circumference, and blood pressure) will aid in the diagnosis of hyperandrogenism along with a skin assessment looking for acne, striae, or acanthosis nigricans (Figure 5).[41] Signs of virilization must be recognized. Signs of other endocrinopathies should be sought (i.e., breast examination for galactorrhoea), and signs of Cushing syndrome or thyroid dysfunction, should be investigated with serum testing, if needed.[17,42] Particular attention should be paid to symptoms of virilization, including clitoromegaly, deepening voice, male pattern alopecia (fronto-temporal and vertex thinning of scalp hair), and loss of female body contour.[41,43] A family history of hyperandrogenism is common and should be inquired about, while symptoms of virilization are infrequent.[44] A history of sudden onset and rapid progression of hirsutism with severe virilization is frequently associated with androgen-secreting tumours.[44]

Recommendations for laboratory investigations continue to evolve with ongoing research into potential new serum markers. Recent guidelines support measuring total testosterone, DHEA-S, and sex hormone–binding globulin (SHBG) in all patients with an abnormal mFG score, but not in eumenorrheic patients with local hair growth and a normal mFG score <8.[17] There are, however, arguments against testing of testosterone for all patients with hirsutism and irregular cycles.[45] Although some patients have elevated levels of androgens, the majority have normal levels, with research confirming that severity of hirsutism does not correlate with the level of androgen excess.[39,44] Laboratory investigations differentiate hyperandrogenic from idiopathic hirsutism and assist in ruling out other etiologies. A high-quality total testosterone level should be drawn on menstrual cycle days 4–10 when levels are the highest, with a concomitant SHBG measurement.[10,25] Since androgens are small steroidal molecules circulating in low concentrations and differ minimally in structure from other steroid hormones, their assessment requires the highest quality assays. That is, high-quality radioimmunoassay, mass spectrometry and liquid chromatography provide high sensitivity and specificity.[18] Radioimmunoassays are known to have problems with cross-reactivity, especially in steroid hormone measurements with low concentration ranges, making these results less reliable. It may be helpful for practitioners to contact their local laboratory to determine the type and quality of

Figure 4. Diagnosis and investigations of hirsutism.

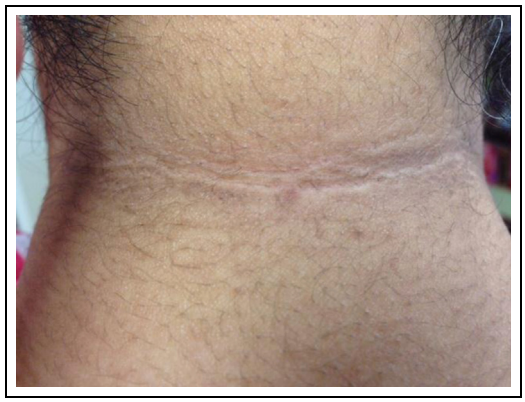
Assessment Categories	Considerations
History	• Onset of hirsutism • Symptoms of virilization: clitoromegaly, deepening voice, male pattern alopecia • Menstrual history • Change in weight • Medication history • Family history of hyperandrogenism and/or hirsutism
Physical Examination	• Severity of hirsutism (modified Ferriman-Gallwey score) • Signs of hyperandrogenism: acne, hair thinning, seborrhoea, acanthosis nigricans • Signs of virilization: clitoromegaly, deepening voice, male pattern alopecia • Signs of Cushing syndrome: (moon faces, central obesity, acne, striae, proximal muscle weakness, thin skin, buffalo hump) • Galactorrhoea • Thyroid examination
Investigations	• Total testosterone • SHBG • DHEA-S • 17-OH progesterone to rule out CAH • TSH • Prolactin if galactorrhoea or menstrual irregularity • Pelvic ultrasound if polycystic ovarian morphology or ovarian neoplasm is suspected • MRI or CT if adrenal neoplasm suspected • Cushing Syndrome screen ONLY if signs and symptoms of Cushing Syndrome

17-OHP: 17-hydroxyprogesteron; CAH: congenital adrenal hyperplasia; DHEA-S: dehydroepiandrosterone sulfate; SHBG: sex hormone–binding globulin; TSH: thyroid-stimulating hormone.

androgen assay being used in their centre. A low SHBG level is associated with insulin resistance and an increased risk of developing type 2 diabetes mellitus in the future. Free testosterone measurement is not recommended, as it does not provide additional information beyond total testosterone measurement; in addition, the free testosterone test is less reliable and is often not available in many laboratories. Serum androstenedione should not be measured in patients with hirsutism.[46] To screen for adrenal hyperandrogenism, serum DHEA-S levels should be measured.[17] In severe DHEA-S elevation, an adrenal or ovarian neoplasm should be suspected, and an MRI or CT scan ordered to identify lesions and guide treatment.[41,43] Importantly, treatment response to hirsutism is based on clinical signs, not laboratory values, so repeat testosterone or DHEA-S measurements (regardless of assay quality) to monitor treatment "success" are both unnecessary and wasteful.

A serum assessment of 17-OHP should be routinely performed for all patients with hyperandrogenic hirsutism to screen for NC-CAH.[8,47–49] 17- OHP should be measured between 7 and 9 AM in the early follicular phase of the menstrual cycle or at any time if the patient is anovulatory. In patients with hyperandrogenic hirsutism who also have oligomenorrhea (and in whom determining the early follicular phase may be challenging), a serum progesterone level should also be measured simultaneously as elevated progesterone can lead to a compensatory rise in 17-OHP, leading to misdiagnosis. A morning early follicular serum 17-OHP level <6 nmol/L effectively rules out congenital adrenal hyperplasia, while a level >30 nmol/L

Figure 5. Acanthosis nigricans.



Acanthosis nigricans is a condition that causes areas of dark, thick velvety skin in body folds and creases. It typically affects the armpits, groin and neck. Figure courtesy Dr. Paul Claman. Patient consent was obtained for publication of this photograph.

confirms the diagnosis of NC-CAH without need for further testing. Levels between 6 and 30 nmol/L warrant an ACTH stimulation test.[50]

Screening for Cushing syndrome (24-hour urinary free cortisol measurement or dexamethasone suppression test) should only be done when signs and symptoms of Cushing syndrome are present (see in the section Other Endocrinopathies in this guideline). Elevated serum prolactin is an uncommon cause of hirsutism and should be measured if galactorrhoea or menstrual irregularity are present. A raised thyroid-stimulating hormone level (hypothyroidism), which can lead to elevated prolactin levels, can also be associated with hirsutism. A pregnancy test should be done in all patients with amenorrhea.

A pelvic ultrasound can detect the presence of an ovarian neoplasm (androgen-secreting tumour) or polycystic ovarian morphology.[41] An ultrasound examination may be helpful in the evaluation of the endometrium in hirsute patients with menstrual cycle irregularity or amenorrhoea. Individuals with a thickened endometrium may have associated anovulation, while those with a thin endometrium are more likely have oligomenorrhea caused by hyperandrogenism. Therefore, an endometrial biopsy to rule out endometrial hyperplasia or malignancy may be warranted.

In patients with hirsutism, the diagnosis of PCOS can be made if there is concomitant ovulatory dysfunction and/or polycystic ovary morphology on ultrasound with the exclusion of other etiologies.[20] The diagnosis of PCOS in adolescence is controversial, as the diagnostic features (i.e., acne, irregular menses, and polycystic ovary morphology) may be normal pubertal physiologic events.[51] Patients with PCOS will benefit from an assessment of glucose tolerance and cardiovascular risk. This includes measurement of waist circumference, body mass index, serum lipids, and blood pressure and an oral glucose tolerance test in patients with obesity, advanced reproductive age (greater than 35 years), a history of gestational diabetes, or a family history of type 2 diabetes mellitus.[52] Based on a study of 135 patients with PCOS and hirsutism, the investigators suggested that insulin resistance should be assessed in patients with PCOS and hirsutism regardless of their BMI.[53]

Summary Statements 6, 7 & Recommendations 1, 2, 3, 4

TREATMENT

Treatment for hirsutism depends upon the severity and the patient's desired outcomes. Patients often rate their hirsutism worse than their physicians, and treatment should be offered for patients who are bothered by their hirsutism and not based solely on hirsutism scoring.[54] The stigma associated with hirsutism can lead to depression and effect quality of life.[55,56] Treatment for hirsutism can provide cosmetic and psychological benefits. We acknowledge that much of the available literature involves study of hirsutism in White individuals. Those providers caring for non-White people with hirsutism may consider referral to a practitioner with experience in management of hirsutism in the relevant population, if possible.

After ruling out other treatable causes, the most effective therapy for hirsutism may involve a combination of modalities, including physical hair removal techniques, topical agents, and medical therapies. Medical therapy involves androgen suppression or antiandrogens and is most beneficial in hyperandrogenic hirsutism but may also be useful in idiopathic hirsutism.[19] Given the lifespan of terminal hair, at least 6 months of medical therapy is required before slower and finer regrowth of hair is noted.[57] Hair growth tends to recur after cessation of medical therapy.[58–60] Concomitant physical hair removal may be used for temporary results and may hasten the effects of medical therapy. Laser hair removal and electrolysis can produce permanent hair reduction, although periodic retreatment may be required.[58,61] Important considerations in choosing treatment should include side effects, concurrent need for contraception, costs, and patient preference.

Figure 6. Physical methods of hair removal.

Method	Advantages	Disadvantages	Cost	Effect
Shaving	• Easily available • Can be done at home	• Less acceptable to some patients • Early "stubble" during initial days following shaving	$	Temporary
Bleaching	• Easily available • Can be done at home • Good for moustache and sideburn areas	• Can cause severe skin irritation	$	Temporary
Chemical Depilation	• Easily available • Can be done at home • Pain-free	• Can cause skin irritation	$	Temporary (lasts about 10 days)
Plucking	• Easily available • Can be done at home • Good for individual long hairs	• Can cause ingrown hairs, folliculitis, and scarring	$	Temporary
Waxing	• Easily available • Can be done at home • Can be used for larger areas	• May cause skin irritation, especially on the face	$	Temporary (lasts 3 - 6 weeks)
Threading	• Can be done at home • Mainly used for face	• Requires skill	$	Temporary (lasts 3 - 6 weeks)
Laser	• Can be used for larger areas	• Requires qualified operator • Painful • Time-consuming - usually 6 treatments (more if PCOS) and possible maintenance therapy • Best for darker hair	$$-$$$	Permanent hair reduction
IPL	• Can be used for larger areas	• Requires qualified operator • Painful • Time consuming - usually 6 treatments (more if PCOS) and possible maintenance therapy	$$-$$$	Permanent hair reduction
Electrolysis	• All hair and skin types	• Requires qualified operator • Painful • Time consuming - targets one hair follicle at a time; impractical for large areas	$$-$$$	Permanent hair reduction

IPL: intense pulse light; PCOS: polycystic ovary syndrome.

Summary Statement 8

Physical Hair Removal Treatment

Various physical methods of hair removal can be used safely and effectively (Figure 6). The choice will be dictated by cost, patient tolerance, and efficacy. Bleaching, shaving, and chemical depilatories are inexpensive and painless, but entirely cosmetic in nature, with no change in the underlying hair or follicle. Plucking, waxing, threading, laser hair removal, and electrolysis are more uncomfortable and costly, and can reduce regrowth of hair, especially if combined with concomitant medical therapy.[58–60]

Laser and intense pulsed light (often referred to as IPL) devices have been shown to result in long-term hair reduction.[60] Several laser devices are commercially available: long-pulsed ruby (694 nm), long-pulsed alexandrite (755 nm), diode (800– 980 nm), and long-pulsed Nd:YAG (1064 nm) are the most widely studied. Lasers have better results in patients with light skin and dark hair. Patients with darker skin benefit from Nd:Yag and Diode-based lasers for optimal safety.[62–64] There are several laser hair removal devices available for home use which are weaker than in-office professional devices yet may be effective with frequent use.

Electrolysis requires a trained electrologist inserting a thin wire into the hair follicle under the surface of the skin. An electric current moves down the wire to the bottom of the follicle, destroying the hair root. Electrolysis can lead to permanent hair reduction and can be used for all skin types. However, it often requires more sessions for larger areas and may be more painful than laser.[58]

Summary Statement 9

Medical Therapy

Topical Therapy

Eflornithine hydrochloride cream (Vaniqa), an ornithine decarboxylase inhibitor, has been shown to reduce facial hirsutism over placebo after 8 weeks of use.[65] Two randomized double-blind studies involving 594 patients treated for 24 weeks found a significant reduction in unwanted facial hair.[66] Treatment is intended to be indefinite, as hair growth recurs after cessation of therapy. Eflornithine may also be used as an adjuvant to laser to improve

Figure 7. Medical therapy for hirsutism.

Treatment	Usage	Side effects/adverse effects
Topical therapy		
Eflornithine hydrochloride	• For facial hirsutism • Thin layer applied twice daily at least 8 hours apart	• Acne, local irritation, pruritus, and stinging
Combined hormonal contraceptives		
CHC	Multiple formulations	• Breakthrough bleeding, amenorrhea • Nausea, bloating • Weight gain • Headache • Breast tenderness • Venous thromboembolism
Antiandrogens		
Spironolactone	• 50–200 mg once daily • Can be combined with CHC	• Irregular menses • Transient diuresis • Fatigue • Headache • Gastric upset • Breast tenderness • Feminization of a male fetus if taken during pregnancy
Cyproterone acetate	Cyproterone acetate 2 mg combined with ethinyl estradiol 0.035 mg (Diane 35)	• Irregular menses, breakthrough bleeding, amenorrhea • Nausea, bloating • Headache • Breast tenderness • Venous thromboembolism • Decreased libido • Liver toxicity • Feminization of a male foetus if taken during pregnancy
Finasteride	• 5 mg once daily • Can be combined with CHC	• Minimal • Feminization of a male fetus if taken during pregnancy
Flutamide	• 250–500 mg once daily • Can be combined with CHC • Monitor serum transaminase levels before treatment, monthly x 4 months then annually	• Hepatotoxicity, liver failure • Hot flashes • Decreased libido • Diarrhea • Feminization of a male fetus if taken during pregnancy

CHC: Combined hormonal contraception.

results and prevent hair regrowth.[67] A thin layer should be applied twice daily at least 8 hours apart. In Canada, eflornithine is only indicated for the management of unwanted facial hair and should not be used for larger areas. Adverse effects of eflornithine include acne, local irritation, pruritus, and stinging.[61] (See Figure 7).

Combined Hormonal Contraceptives

Combined hormonal contraceptives (CHCs) contain both estrogen and progestin components, and include oral, transdermal, and vaginal ring options. In the absence of contraindications to CHCs, first-line suppressive therapy involves the use of a CHC to suppress gonadotropins, decrease ovarian androgen production, and augment hepatic production of SHBG, effectively decreasing free testosterone levels.[68] Multiple studies have shown the benefits of CHCs for hirsutism. Oral CHCs with non-androgenic (i.e., desogestrel, norgestimate) or anti-androgenic progestins (i.e., cyproterone acetate, drospirenone) may be more effective in treating hirsutism compared to CHC with more androgenic progestins.[69] However, there is conflicting evidence as to whether these newer generation CHCs carry an increased risk of venous thromboembolism.[70–73] It is important to note that patients with PCOS may also have an increased risk of venous thromboembolism.[74–76] (See Figure 7).

Antiandrogens

Antiandrogens are especially useful for idiopathic hirsutism or as adjuncts to androgen suppressive therapies.[77,78] Patients who may become pregnant require a reliable form of contraception if using an antiandrogen because of the risk of feminization of a male fetus. For moderate and severe hirsutism, the addition of antiandrogens can enhance the effect of a CHC and should be considered if there is no improvement after 6 months of therapy.[10,78–80] In addition, CHCs provide contraception, which is required in some patients using antiandrogen therapies.

Spironolactone competes for the androgen receptor in skin fibroblasts and produces limited suppression of gonadal and adrenal androgen biosynthesis. Monotherapy can be used in doses staring at 50 mg with doses of 100—200 mg daily often required, especially for PCOS.[81–84] Spironolactone can also be used in combination with a CHC.[78,85] There may be a dose-related increase in irregular menses, which is controlled by concomitant CHC use. Adverse effects such as transient diuresis, fatigue, headache, gastric upset, and breast tenderness can be minimized by gradual dose increases.[86] Periodic assessment of serum electrolytes to detect electrolyte imbalance should be done at appropriate intervals (3 months after starting and annually thereafter) in patients

with significant renal or hepatic impairment or on other medications that may affect potassium balance. There is a theoretical risk of feminizing a male fetus if pregnancy occurs while on spironolactone.

Cyproterone acetate is a progestational agent which inhibits gonadotropin release (thereby decreasing androgen production) and binds competitively to androgen receptors. For mild hirsutism, cyproterone acetate is most conveniently administered as a combined pill with ethinyl estradiol (35 μg ethinyl estradiol and 2 mg cyproterone acetate), which is effective in controlling acne and hirsutism alone or in combination with spironolactone 100 mg daily.[69] The benefit of combining high-dose cyproterone acetate (100 mg daily) with a CHC over monotherapy CHC is less clear, as the only study showed no significant differences between the treatment regimens.[87,88] Cyproterone acetate has been associated with liver toxicity, irregular menstrual bleeding, nausea, decreased libido, and depression.[87,89]

Finasteride 5 mg daily blocks the 5α-reductase enzyme responsible for converting testosterone to dihydrotestosterone (see Figure 3) and is useful in the treatment of idiopathic hirsutism.[90,91] It may be less effective on its own than other antiandrogens.[92–94] However, it has a low side-effect profile and can also be used in combination with a CHC to improve treatment effects.[78,90,95] It should not be used in individuals who may become pregnant because of its significant teratogenic potential.

Flutamide is the first nonsteroidal antiandrogen available that is devoid of any other hormonal activity. Flutamide 250–500 mg daily, alone or in combination with a CHC, appears as or more effective than other antiandrogens.[82,83] However, flutamide is associated with hepatotoxicity and risk of liver failure.[92,94,96] Adverse effects can also include hot flashes, decreased libido, and diarrhea. Flutamide should not be used as a first-line therapy and careful monitoring of serum transaminase levels is required. (See Figure 7).

Additional Therapies

Glucocorticoids can be used to suppress adrenal androgen production and may be used in NC-CAH; however, its use for other causes of hirsutism is not proven and can be associated with significant adverse effects.[33,61,97,98]

Gonadotropin-releasing hormone analog can induce a medical oophorectomy effect to treat refractory hirsutism due to ovarian hyperandrogenism.[99] However, hypoestrogenic side effects frequently necessitate the use of an oral contraceptive pill or estrogen/progestin add-back therapy.[100,101] Most studies did not find a benefit to the addition of gonadotropin-releasing hormone analog over CHC monotherapy.[83]

Insulin sensitizers such as metformin or thiazolidinediones may improve several clinical parameters in PCOS, but to date there is insufficient evidence to determine the effectiveness of this approach for hirsutism.[102,103]

Medroxyprogesterone acetate has been recommended for use in patients with contraindications to estrogen-containing therapies (i.e., CHCs). Although short courses of oral medroxyprogesterone acetate (to induce a withdrawal bleed in individuals with PCOS) have been shown to reduce androgen levels, there are no studies assessing efficacy of long-term therapy.[104] Subcutaneous medroxyprogesterone acetate was studied over 26 weeks and was found to decrease SHBG levels ($p = 0.002$), but no significant decrease in total testosterone or free testosterone was observed; however, significant weight gain was noted ($p = 0.02$).[105]

Lifestyle Interventions

Lifestyle interventions and weight loss through dietary, exercise, or behavioural interventions have been shown to lower total testosterone, increase SHBG, and improve hirsutism scores.[106] There is insufficient data on the impact of bariatric surgery on hirsutism.

Recommendations 5–9

OTHER HEALTH IMPLICATIONS

Comprehensive assessment for other health conditions and risk factors is important for patients with hirsutism, especially patients with hyperandrogenism and/or PCOS. Patients with hyperandrogenism and oligomenorrhea will benefit from regular withdrawal bleeds to reduce their risk of endometrial hyperplasia and cancer due to prolonged unopposed estrogen exposure in the context of oligo/anovulation.[107] This can be accomplished with a CHC, continuous progestogen use, or cyclical progestogen-induced withdrawal bleeding. These patients may also require ovulation induction therapy to facilitate conception.[108] For patients with PCOS and associated obesity, assessment for metabolic syndrome and lifestyle modifications may reduce the long-term risk of medical complications.[17,21,25] Identification of other causes of hirsutism, such as Cushing syndrome and NC-CAH will allow appropriate management of associated risks.

SUMMARY

Investigating hirsutism requires medical history taking, physical examination, minimal laboratory investigations, and appropriate imaging, as required. Although hirsutism may be idiopathic, it may also be associated with hyperandrogenism and, in rare cases, NC-CAH or an androgen-secreting tumour. Health problems or long-term medical consequences of hyperandrogenism include obesity, irregular menses, anovulation, infertility, gestational hypertension, diabetes mellitus, hyperlipidemia, hypertension, and heart disease. Supportive counselling, lifestyle modifications, mechanical hair removal, and selected medical therapies can be used to reduce a patient's degree of hirsutism and improve their self-esteem and general health.

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APPENDIX A

Table A1. Key to Grading of Recommendations, Assessment, Development and Evaluation

Strength of recommendation	Definition
Strong	High level of confidence that the desirable effects outweigh the undesirable effects (strong recommendation for) or that the undesirable effects outweigh the desirable effects (strong recommendation against)
Conditional (weak)*	Desirable effects probably outweigh the undesirable effects (weak recommendation for) or that the undesirable effects probably outweigh the desirable effects (weak recommendation against)
Quality of evidence	**Definition**
High	High level of confidence that the true effect lies close to that of the estimate of the effect
Moderate	Moderate confidence in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Limited confidence in the effect estimate: The true effect may be substantially different from the estimate of the effect
Very low	Very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

*Do not interpret conditional (weak) recommendations to mean weak evidence or uncertainty of the recommendation. Adapated from GRADE Handbook (2013), Table 5.1, available at gdt.gradepro.org/app/handbook/handbook.html.

Table A2. Implications of Strong and Conditional (Weak) Recommendations

Perspective	Strong recommendation • "We recommend…" • "We recommend to not…"	Conditional (weak) recommendation • "We suggest…" • "We suggest to not…"
Authors	The net desirable effects of a course of action outweigh the effects of the alternative course of action.	It is less clear whether the net desirable consequences of a strategy outweigh the alternative strategy.
Patients	Most patients in the situation would want the recommended course of action, while only a small proportion would not.	The majority of patients in the situation would choose the suggested course of action, but many would not.
Clinicians	Most patients should receive the course of action.	Recognize that patient choices will vary by individual and that they must ensure care is consistent with a patient's values and preferences.
Policy makers	The recommendation can be adapted as policy in most settings. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	The recommendation can serve as a starting point for debate with the involvement of many stakeholders.