

# Epidemiology, diagnosis and management of hirsutism: a consensus statement by the Androgen Excess and Polycystic Ovary Syndrome Society

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**BACKGROUND:** Hirsutism, defined by the presence of excessive terminal hair in androgen-sensitive areas of the female body, is one of the most common disorders in women during reproductive age.

**METHODS:** We conducted a systematic review and critical assessment of the available evidence pertaining to the epidemiology, pathophysiology, diagnosis and management of hirsutism.

**RESULTS:** The prevalence of hirsutism is ~10% in most populations, with the important exception of Far-East Asian women who present hirsutism less frequently. Although usually caused by relatively benign functional conditions, with the polycystic ovary syndrome leading the list of the most frequent etiologies, hirsutism may be the presenting symptom of a life-threatening tumor requiring immediate intervention.

**CONCLUSIONS:** Following evidence-based diagnostic and treatment strategies that address not only the amelioration of hirsutism but also the treatment of the underlying etiology is essential for the proper management of affected women, especially considering that hirsutism

is, in most cases, a chronic disorder needing long-term follow-up. Accordingly, we provide evidence-based guidelines for the etiological diagnosis and for the management of this frequent medical complaint.

**Key words:** hirsutism / androgen excess / terminal hair / polycystic ovary syndrome / guidelines

## Introduction

Hirsutism is the medical term that refers to the presence of excessive terminal (coarse) hair in androgen-dependent areas of the female body. Especially among young women, hirsutism negatively influences psychological well-being (Barth *et al.*, 1993; Sonino *et al.*, 1993). This is important because hirsutism is among the most frequent medical complaints (Escobar-Morreale, 2010). Although hirsutism generally reflects hormone imbalances, it can rarely be related to a life-threatening disorder (Escobar-Morreale, 2010).

With the scope of reviewing all published evidence assessing the epidemiology, pathophysiology, diagnosis and treatment of hirsutism, and targeting specialist academic centers in which network-based care involving different subspecialties (i.e. pediatricians, endocrinologists, internists, gynecologists, dermatologists and nutritionists) is provided in collaboration with general practitioners, The Androgen Excess and Polycystic Ovary Syndrome (AE-PCOS) Society appointed a panel of experts. The charge given to this panel of experts was to develop evidence-based guidelines to improve long-term management of hirsutism and the chronic hormonal, reproductive and metabolic disorders frequently associated with hirsutism.

## Methods

### Panel

The AE-PCOS Society Board appointed a panel of experts on hirsutism, selected from those researchers who had authored many original articles in the field. Panel members and Board Directors constituted the Writing Committee.

### Data

Reviews of published peer-reviewed medical literature identified studies evaluating hirsutism. Multiple databases were searched, including MEDLINE, EMBASE, Cochrane, ERIC, EBSCO, dissertation abstracts and Current Contents. Reviews focused on the epidemiology, pathophysiology, diagnosis and treatment of hirsutism. More than 1500 articles were initially available for review. Some studies were eliminated because data were not related to the focus of the guidelines, insufficient for epidemiological analysis or reported in previous publications. All data sources were analyzed recognizing positive publication bias.

### Process

The committee critiqued each review before submitting the manuscript to the AE-PCOS Society Board for approval. Reviews included individual studies, systematic reviews, hand searches, abstracts, and individual databases and expert data. Each review was conducted by at least two investigators, and criteria for inclusion/exclusion were agreed upon by at least two reviewers in each area and arbitrated by a third when necessary. The position statement applied part of the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) group criteria (Atkins *et al.*, 2004; Swiglo *et al.*, 2008a), in which strength of a recommendation was indicated 'recommend' or a weaker recommendation

was indicated 'suggest'. Recommendations were made based on evidence that was considered appropriate in making the recommendation. Institutional Review Board approval was not obtained because the study reviewed publicly available medical literature.

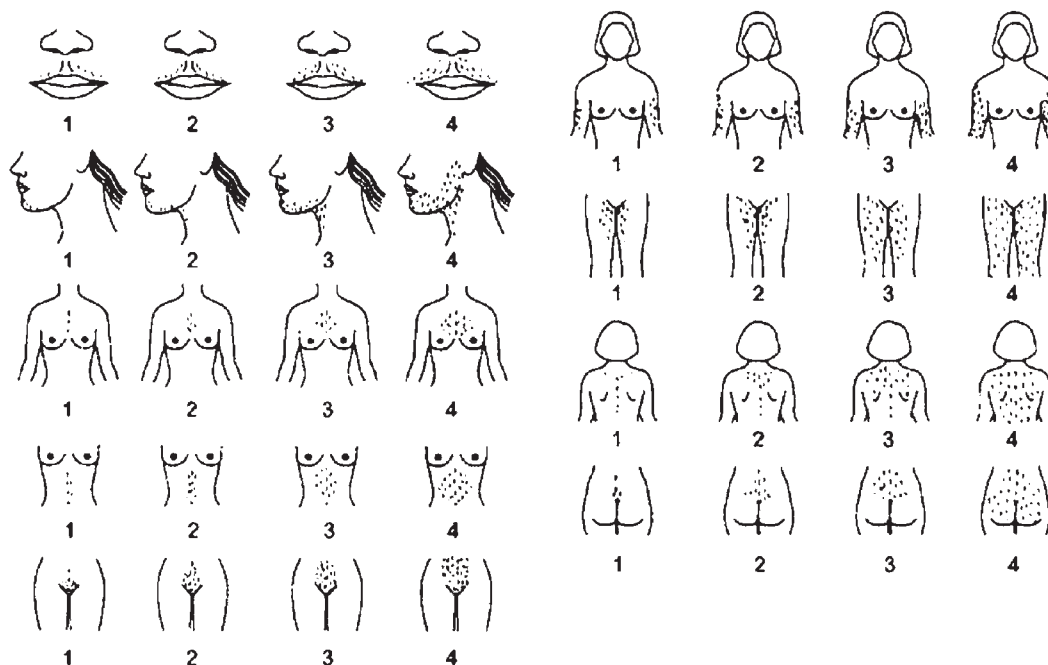
## Quantification and epidemiology of hirsutism

Several methods are available for the evaluation of hirsutism in women, including objective and subjective ones. Objective methods for assessing hair growth (such as photographic evaluations, weighing of shaved or plucked hairs and microscopic measurements) are complex, inconvenient and costly, limiting widespread clinical use (Yildiz *et al.*, 2010). Subjective methods generally refer to visually scoring the body and facial terminal hair growth in specified areas and are potentially subject to inter-observer variation.

Many scoring methods based on visual assessment of hair type and growth have been proposed, the differences between them relate to the area of the body being evaluated and whether or not the characteristics of hair are assessed simultaneously (Yildiz *et al.*, 2010). The landmark study for the visual scoring of hirsutism was conducted in 1951 by Garn (1951); his goal was to assess hairiness in males. He quantified the amount of hair using a five-point scale (0–4) based on the amount of terminal hair in nine body areas (beard and moustache, hypogastric, thoracic, lower arm and leg, upper arm and leg, gluteal, lumbosacral, lower back and upper back).

Several hirsutism scores for women (Shah, 1957; Ferriman and Gallwey, 1961; Moncada, 1970; Hatch *et al.*, 1981; Derksen *et al.*, 1993; Practice Committee of the American Society for Reproductive Medicine, 2006) followed the Garn score for men, and applied a similar 0–4 scale to different areas of the female body that appear to be the most sensitive and specific assessment of the action of androgens on the female pilosebaceous unit (Yildiz *et al.*, 2010).

Of these methods, the modified Ferriman–Gallwey score (mFG) proposed by Hatch *et al.* (1981) has now become the gold standard for the evaluation of hirsutism (Yildiz *et al.*, 2010). This method scores 9 of the 11 body areas (upper lip, chin, chest, upper and lower back, upper and lower abdomen, arm, forearm, thigh and lower leg) originally proposed by Ferriman and Gallwey (1961), excluding the lower legs and forearms, which are areas sensitive to very low androgen concentrations even in healthy women. If terminal hair growth is not present in the examined area, a score of zero is given. Minimally visible terminal hair growth is given a score of 1, a score of 2 is given if hair growth is more than minimal but not equivalent to that of an adult male, and a score of 3 is that of a not very hairy male while a score of 4 is that typically observed in well-virilized healthy adult males (Figs 1 and 2). Total scores range from 0 to 36. Hirsutism has been usually graded as mild up to a score of 15, moderate from 16 to 25, and severe above 25.



**Figure 1** Schematic representation of the mFG score. Nine body areas (upper lip, chin, chest, arm, upper abdomen, lower abdomen, upper back, lower back and thighs) are scored from 1 (minimal terminal hairs present) to 4 (equivalent to a hairy man). If no terminal hairs are observed in the body area being examined the score is zero (left blank). Clinically, terminal hairs can be distinguished from vellus hairs primarily by their length (i.e.  $>0.5$  cm) and the fact that they are usually pigmented. Reproduced with permission from R. Azziz (Yildiz et al., 2010). Copyright Oxford University Press, 2010.

As the mFG score applies a visual and subjective scale, inter-observer variation cannot be completely eliminated. Although the few studies addressing inter-observer variation of the visual scores of hirsutism had conflicting results (Derksen et al., 1993; Wild et al., 2005; Api et al., 2009), if applied by trained physicians, these methods yield a fairly good agreement among independent observers (Derksen et al., 1993; Api et al., 2009). Suggestions to decrease this variability include requesting patients not to use laser or electrolysis for at least 3 months, not to depilate or wax for at least 4 weeks and to avoid shaving for at least 5 days before the examination (Yildiz et al., 2010). Other helpful measures include minimizing the number of examiners (Wild et al., 2005), training the examiners uniformly and using a uniform graphical representation of the scoring system (Yildiz et al., 2010). A photographic representation of the mFG scoring system (Fig. 2) may be helpful in this regard.

An essential aspect for the diagnosis of hirsutism is the cut-off value of the mFG score used for its diagnosis. Currently, many clinicians and researchers choose a mFG score  $\geq 8$  as indicative of hirsutism. This cut-off value was selected by Hatch et al. (1981) because only 4.3% of the reproductive age female population studied by Ferriman and Gallwey in the UK scored 8 or above for the combined nine body areas they termed 'hormonal' (Ferriman and Gallwey, 1961). However, because terminal body hair growth has substantial racial and ethnic variability, the cut-off value of the mFG score should be ideally established for the population to which it is applied. Table I includes suggested mFG score cut-off values for different races and

ethnicities based on the 95th percentile value of unselected women of reproductive age.

However, it must be kept in mind that the mFG scoring system gives an estimation of the total amount of body hair, and not that of the regional distribution of the excessive hair growth. The latter might also occur only in a few areas—particularly the face—without exceeding the cut-off value in the total hirsutism score (Yildiz et al., 2010). Furthermore, a considerable number of women with androgen excess disorders may present with normal body hair; hence the absence of hirsutism does not exclude consideration of such a disorder in women with other features of androgen excess, such as acne, alopecia, infertility or menstrual dysfunction (Yildiz et al., 2010).

In addition to being one of the most frequent medical complaints among young women, hirsutism is also one of the most prevalent health problems in women of reproductive age that can significantly and negatively impact on their quality of life (Sonino et al., 1993). Table II summarizes several studies addressing the prevalence of hirsutism in unselected populations of women worldwide. The actual prevalence of hirsutism ranges from 4.3 to 10.8% in Blacks and Whites, but appears to be somewhat lower in Asians (Table II). The very large prevalence of hirsutism reported by a few studies may represent an overestimation resulting from self-referral bias (Diamanti-Kandarakis et al., 1999; March et al., 2010) and from the fact that the hirsutism score was self-reported by the patients (March et al., 2010).

Accordingly, the committee recommends the routine use of the nine body areas mFG score to quantify hirsutism, and recommends

establishing a cut-off value to define hirsutism as the 95th percentile of the mFG score of the relevant general population ethnicity and age. If this value is unavailable, we suggest that a cut-off value of 8 or above

be applied to White and Black women, while for Far East and South East Asian women this be decreased to three or above.

## Pathophysiology of hirsutism

Hair, especially on the scalp and face among humans, is important for social and sexual communication. There are ~5 million hair follicles covering the human body with ~100 000 located on the scalp (Paus and Foitzik, 2004). Hair covers human skin with the exception of the glabrous skin of lips, palms and soles. Very few new hair follicles are formed after birth, and the number of hair follicles begins to decrease after the age of 40 years (Uno, 1986).

Structurally, there are three types of hair: lanugo is a soft hair densely covering the skin of the fetus, which disappears within the first months of post-partum life; vellus hairs are soft but larger than lanugo hairs, are usually non-pigmented, and are generally <0.03 mm in diameter; and terminal hairs are longer, pigmented and coarser in texture. Eyebrows, eyelashes, scalp hair and pubic and axillary hair in both sexes, and much of the body and facial hair in men, are composed of terminal hairs (Uno, 1986).

Hair arises from the hair follicle, a highly dynamic organ that has the ability to regenerate; the hair cycle consists of rhythmic repetitive growth, regression and tissue-remodeling events (Girman *et al.*, 1998). Clinically relevant hair growth disorders represent undesirable alterations of the hair follicle cycle: prolongation of the hair growth phase (anagen) is observed when vellus hairs evolve into terminal hairs (e.g. in hirsutism), whereas shortening of the anagen phase leads to hair loss.

## Structure of the hair follicle

Hair follicles consist of several components. The most superficial part of the hair follicle extends from the sebaceous duct to the epidermal surface. This portion includes the hair canal and the distal outer root sheath. The tubular connection between the epidermal surface and the distal part contains the hair shaft (Fig. 3). The outer root sheath is contiguous with the basal epithelial layer. The inner root



**Figure 2** Photographs depicting facial and body terminal hair growth scored according to the mFG method. All were taken on women who had not used laser or electrolysis for at least 3 months, not depilated or waxed for at least 4 weeks, not shaved or plucked for at least 5 days before the photograph. The photographs depict scores of 1 through 4 for the upper lip (A), chin (B), chest (C), upper abdomen (D), lower abdomen (E), arm (F), thighs (G) upper back (H) and lower back (I). The areas were photographed with a standard single-lens reflex camera (Nikon N50, Nikon Corp, Melville, NY, USA) equipped with a macro lens (Vivitar 50 or 100 mm Auto Focus Macro, Vivitar Corp, Newbury Park, CA, USA) and ring flash (Vivitar Macroflash 5000, Vivitar Corp). For film, Kodacolor VR 200 ISO film (Eastman Kodak Co, Rochester, NY, USA) was used. Representative areas were selected. All photographs of hair were anonymized and all identifying information removed, meeting current Institutional Review Board for Human Use and Health Insurance Portability and Accountability Act of 1996 standards. Modified with permission from R. Azziz (Yildiz *et al.*, 2010). Copyright Oxford University Press, 2010.

**Table 1** Suggested cut-offs for the mFG hirsutism score according to the 95 percentile in different unselected populations of premenopausal women.

| Author, year                                    | Year | Country  | Race  | Ethnicity              | Sample size | Suggested mFG cut-off <sup>a</sup> |
|---|------|----------|-------|------------------------|-------------|------------------------------------|
| Tellez and Frenkel (1995)                       | 1995 | Chile    | White | Hispanic               | 236         | ≥ 6                                |
| Asuncion et al. (2000)                          | 2000 | Spain    | White | Mediterranean          | 154         | ≥ 8                                |
| Sagsoz et al. (2004)                            | 2004 | Turkey   | White | Middle Eastern         | 204         | ≥ 9                                |
| Cheewadhanaraks et al. (2004)                   | 2004 | Thailand | Asian | Thai and Chinese       | 531         | ≥ 3                                |
| DeUgarte et al. (2006)                          | 2006 | USA      | White | Caucasian and Hispanic | 283         | ≥ 8                                |
|   |      |          | Black | African-American       | 350         | ≥ 8                                |
| Zhao et al. (2007)                              | 2007 | China    | Asian | Chinese Han            | 623         | ≥ 2                                |
| Api et al. (2009)                               | 2009 | Turkey   | White | Middle Eastern         | 121         | ≥ 11                               |
| Moran et al. (2010)                             | 2010 | Mexico   | White | Hispanic               | 150         | ≥ 10                               |
| Noorbala and Kefaei (2010)                      | 2010 | Iran     | White | Middle Eastern         | 900         | ≥ 10                               |
| Kim et al. (2011)                               | 2011 | Korea    | Asian | Chinese                | 1010        | ≥ 6                                |
| Gambineri (2011, personal communication)        | 2011 | Italy    | White | Mediterranean          | 200         | ≥ 9                                |
| Escobar-Morreale (2011, personal communication) | 2011 | Spain    | White | Mediterranean          | 291         | ≥ 10                               |

<sup>a</sup>As defined by the 95th percentile of an unselected population of premenopausal women.

sheath is a multilayered rigid tube that is composed of terminally differentiated hair follicle keratinocytes, surrounded by the outer root sheath. It provides the conduit for the hair to exit at the skin surface, and the hair shaft itself (Headington, 1984; Fuchs et al., 2001). The skin hairs are keratinized epithelial cells organized in a flexible cylinder that differ in color, thickness and length. Keratin proteins form the hair shaft that grows within the outer hair root sheath in the epidermis (Fig. 3).

The sebaceous gland is an acinar gland composed of lipid-filled sebocytes, localized close to the insertion of the arrector pili muscle. The sebaceous gland secretes sebum to the epidermal surface via a holocrine mechanism. Sebum helps to make hair and skin waterproof. The arrector pili muscle is a tiny smooth muscle that connects the hair follicle with the dermis, and causes, when contracted, the raising of the hair. Together with the hair follicle and the arrector pili muscle, the sebaceous gland forms the pilosebaceous unit.

The bulge is a protrusion of the outer root sheath located below the sebaceous gland at the insertion site of the muscle arrector pili. The bulge contains the hair follicle stem cells. The bulb is a thickening of the proximal end of the hair follicle, which contains undifferentiated matrix, melanocytes and outer root sheath cells. The dermal papilla, consisting of closely packed specialized mesenchymal fibroblasts, is a mesodermal signaling system within the hair follicle (Schneider et al., 2009). The dermal papilla produces numerous paracrine factors that influence the size and color of the hair produced.

## Hair follicle morphogenesis

In humans, organization of the primitive epidermis takes place between 9 and 12 weeks of embryonic life. The master switch for hair follicle development involves canonical Wnt/ $\beta$ -catenin signaling that is essential for hair follicle fate at least in mice (Andl et al.,

2002). Communication between the developing epidermis and underlying mesenchyme plays a key role in hair differentiation as well as other ectodermal appendages, such as nails, teeth, feathers and scales. Additional factors modulating this communication include members of the hedgehog protein, transforming growth factor- $\beta$ , bone morphogenetic protein, fibroblast growth factor and tumor necrosis factor families (Andl et al., 2002; Schneider et al., 2009).

## The hair follicle growth cycle

The hair follicle functions as a stem cell repository containing cells of multiple cell lineages (Kligman, 1959; Paus and Foitzik, 2004). To some extent, the molecular oscillator system responsible for hair cycling is autonomous, as demonstrated by persistent hair cycling following transplantation to a different skin site (Ebling, 1988). The presence of these stem cells is crucial to continued hair follicle cycling.

Hair follicles pass through three major growth phases (Fig. 4). These three phases are anagen (a stage of rapid growth), telogen (a stage of relative quiescence) and catagen (apoptosis-mediated regression). Following regression of the epithelial column during catagen, the dermal papilla relocates to lie near the bulge (Schneider et al., 2009). The physical proximity of these two structures promotes stem cell activation and initiation of a new hair cycle. Following activation, the stem cells leave the bulge and proliferate downward to generate the outer root sheath (Hsu et al., 2011). During anagen, rapidly proliferating progenitor cells in the bulb generate the hair shaft and its surrounding inner root sheath, and the distance between the bulge and dermal papilla increases. The duration of the anagen phase governs the hair cycle length in different body regions. Scalp follicles have the longest anagen phase, and most normal scalp follicles are in the anagen phase (Randall, 2008). Although often not obvious, seasonal alterations occur in the human hair cycle with more hair shedding during the autumn months (Randall, 2008).

**Table II** Summary of studies addressing the prevalence of hirsutism in women.

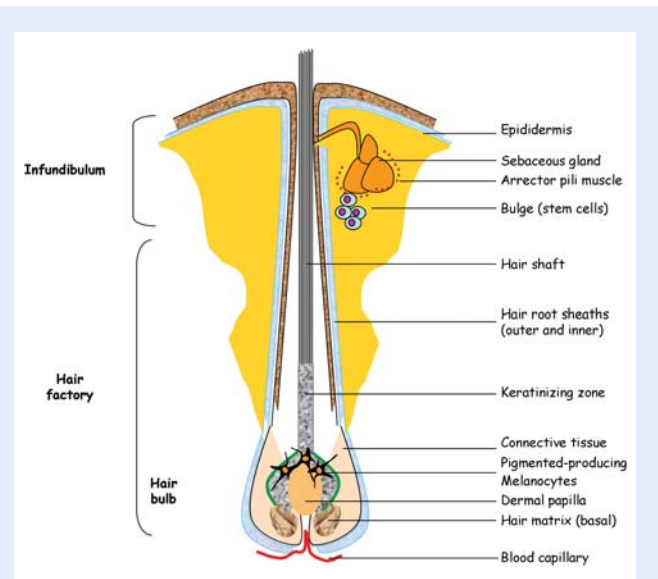
| Author, year                      | Country   | Race  | Ethnicity               | Score | Cut-off | Method of sample selection                                   | Sample size | Prevalence (95% CI) | Comments   |
|-----------------------------------|-----------|-------|-------------------------|-------|---------|--|-------------|---------------------|--|
| Diamanti-Kandarakis et al. (1999) | Greece    | White | Mediterranean           | FG    | ≥ 6     | Invitation of free medical examination                       | 192         | 38% (31–45)         | Possible selection self-referred bias <sup>a</sup> |
| Asuncion et al. (2000)            | Spain     | White | Mediterranean           | mFG   | ≥ 8     | Unselected female blood donors from general population       | 154         | 7.1% (3.0–11.1)     |  |
| Zargar et al. (2002)              | India     | Asian | Kashmir Dardic          | FG    | ≥ 6     | Hospital outpatient clinic                                   | 4780        | 10.5% (9.6–11.4)    | Includes post-menopausal women                     |
| Sagsoz et al. (2004)              | Turkey    | White | Middle Eastern          | mFG   | ≥ 8     | Regular check-up in outpatient clinic                        | 204         | 8.3% (4.5–12.1)     |  |
| Cheewadhanaraks et al. (2004)     | Thailand  | Asian | Thai and Chinese        | mFG   | ≥ 3     | Regular cervical smear check                                 | 531         | 2% (0.8–3.2)        |  |
| DeUgarte et al. (2006)            | USA       | White | Caucasian and Hispanics | mFG   | ≥ 8     | Pre-employment physical exam                                 | 293         | 5.4% (2.8–8.0)      | Possible selection self-referred bias <sup>b</sup> |
| Noorbala and Kefaei (2010)        | Iran      | Black | African-American        | mFG   | ≥ 8     |  | 350         | 4.3% (2.2–6.4)      | 97.5% reproductive age                             |
| March et al. (2010)               | Australia | White | Middle Eastern          | mFG   | ≥ 8     | Randomized cluster sampling proportionate to population size | 900         | 10.8% (8.8–12.8)    | Included only teenagers                            |
|                                   |           | White | Caucasian               | mFG   | 8       | Unselected population cohort                                 | 728         | 21.2% (18.2–24.2)   | Possible selection self-referred bias <sup>c</sup> |
|                                   |           |       |                         |       |         |  |             |                     | 3% were not White                                  |

FG, Ferriman–Gallwey score; mFG, modified Ferriman–Gallwey score, CI, confidence interval.

<sup>a</sup>Invitation of free medical examination.

<sup>b</sup>Only 66% of invited women participated.

<sup>c</sup>Only 53% of invited women participated, and patients self-assessed their hirsutism scores.

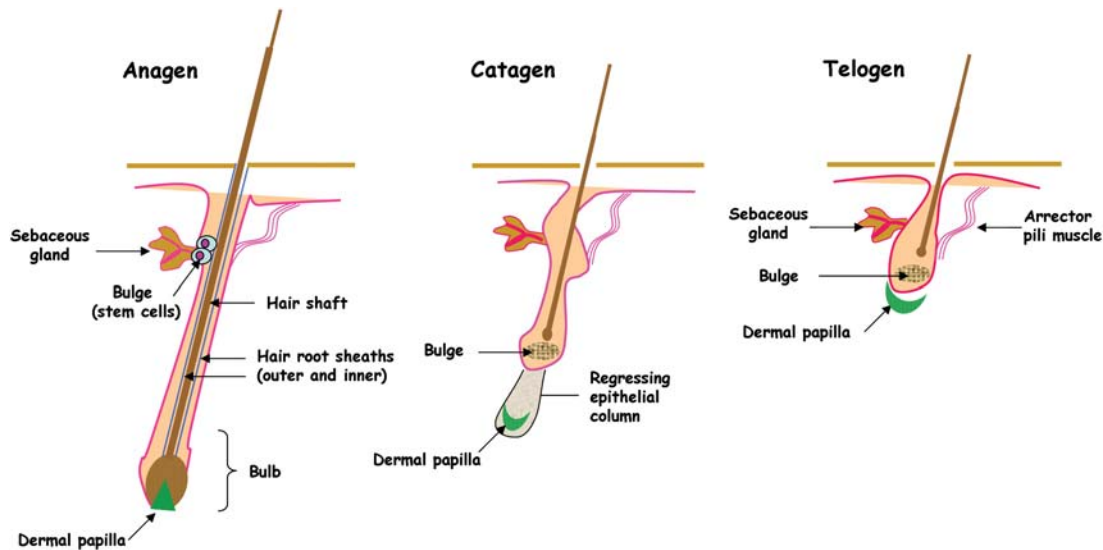


**Figure 3** Schematic histomorphology of the terminal hair follicle. Sagittal section through a human scalp hair follicle showing the infundibulum, the hair shaft and the bulb. Note that bulge is located at a protrusion of the outer root sheath just below the sebaceous gland at the insertion site of the muscle arrector pili, and contains the hair follicle stem cells. Bulb is a thickening of the proximal end of the hair follicle, and encloses proliferating matrix cells, melanocytes and outer root sheath cells surrounding the dermal papilla, which is a mesodermal signaling system of the hair follicle.

The perpetual rhythm of the hair growth cycle is reminiscent of other cyclic biological processes in which distinct clock mechanisms have been studied. CLOCK and BMAL1 are transcription factors that regulate circadian rhythms. RNA microarray data obtained from mouse hair and skin indicated that genes associated with cell cycle and DNA/RNA metabolism were up-regulated in the early anagen phase (Lin et al., 2009). Although no morphological abnormalities were found in hair follicles, delayed anagen progression was found in mice transgenic for mutations in the CLOCK or BMAL1 genes (Lin et al., 2009). Additional details regarding the role of clock genes will likely be elucidated in the future.

## Androgens and hair growth

The growth of sexual hair is mainly dependent on the presence of androgens. Before puberty, vellus hair is small, straight and fair with undeveloped sebaceous glands. In response to the increased levels of androgens during puberty, the vellus follicles in pubic and axillary areas of boys and girls develop into terminal hairs that are larger, curlier and darker (Reynolds, 1951; Marshall and Tanner, 1969). Similarly, the development of facial hair, male pattern pubic hair and trunk hair in men is attributed to androgen stimulation (Hamilton, 1958). In other body areas, such as the forehead and the cheeks, androgens increase the size of the sebaceous glands, but the hair in these areas remains vellus. These specific differentiation patterns remain unexplained, suggesting that androgens have paradoxically different effects on human hair follicles depending on their body site (Randall, 2008).



**Figure 4** The hair follicle growth cycle. Hair follicles possess the ability, unique among mammalian tissues, to be partially regenerated in a process termed the hair follicle growth cycle. Hair follicles go through repeated cycles of development and growth (anagen), regression (catagen) and rest (telogen) to enable the replacement of hairs.

Androgens may be generated via a *de novo* synthetic pathway from cholesterol to testosterone and dihydrotestosterone (DHT), and/or via a shortcut pathway from circulating dehydroepiandrosterone-sulfate (DHEAS). The *de novo* synthesis of androgens requires four 'upstream' proteins, including steroidogenic acute regulatory protein, cytochrome P450 cholesterol side-chain cleavage enzyme, cytochrome P450 17 $\alpha$ -hydroxylase/17,20-lyase and steroid 3 $\beta$ -hydroxysteroid dehydrogenase, which are responsible for the early steps of androgen synthesis from cholesterol to dehydroepiandrosterone. Additional 'downstream' enzymes, including 17 $\beta$ -hydroxysteroid dehydrogenase and 5 $\alpha$ -reductase, catalyze the conversion of androstenedione into testosterone and, subsequently, to DHT, amplifying its androgenic effects (Chen and Zouboulis, 2009).

The major androgens in the serum of normal cycling women are DHEAS, dehydroepiandrosterone, androstenedione, testosterone and DHT, in descending order of serum concentrations (Burger, 2002). Testosterone and DHT bind to the androgen receptor to promote changes in gene transcription. Dehydroepiandrosterone, DHEAS and androstenedione do not bind to the androgen receptor and can be considered to be pro-hormones.

Sulfotransferase, principally sulfotransferase 2A1, catalyzes the conversion of dehydroepiandrosterone to DHEAS in the adrenal cortex. Steroid sulfates can be hydrolyzed to the native steroid by steroid sulfatase. Circulating testosterone in women originates mostly (50%) by peripheral conversion of other steroids, the rest coming in equal parts (25%) from the ovaries and the adrenals (Longcope, 1986). Of note, the most active androgen, DHT, is synthesized locally in androgen target tissues in a step catalyzed by the enzyme 5 $\alpha$ -reductase, and its circulating levels are very low (Longcope, 1986).

Adrenal pubertal maturation, adrenarche, is characterized by increasing DHEAS concentrations. The physical manifestation of

adrenarche is pubarche, the development of sexual hair. Adrenarche, a phenomenon limited to a few higher primate species, is associated with increased 17,20-lyase activity of cytochrome P450 17 $\alpha$ -hydroxylase/17-20 lyase, decreased 3 $\beta$ -hydroxysteroid dehydrogenase type 2 activity and increased expression of cytochrome b5 (Auchus and Rainey, 2004). This change in DHEAS synthesis is independent of the hypothalamic-pituitary-gonadal axis (Sklar et al., 1980; Counts et al., 1987). While adrenocorticotropic hormone (ACTH) plays a permissive role, the molecular events triggering the onset of adrenarche remain uncertain (Miller, 2009). Onset of adrenarche prior to age 8 years in girls, premature adrenarche, can precede the development of PCOS in some, but not all, girls. In addition to the effects of circulating androgens on the growth of sexual hair, human sebaceous glands and hair follicles are equipped with all the necessary enzymes for biosynthesis and metabolism of androgens (Thiboutot et al., 2003). Therefore, circulating androgen levels may not reflect local androgen concentrations at the pilosebaceous unit (Chen and Zouboulis, 2009).

Furthermore, cutaneous androgen effects also depend on the expression of the androgen receptor in the pilosebaceous unit (Chen and Zouboulis, 2009). Androgen receptor expression and activity have been demonstrated mainly in epidermal keratinocytes, sebaceous glands and hair dermal papilla cells, with restricted expression in dermal fibroblasts, sweat gland cells, endothelial cells and genital melanocytes.

In sebaceous glands, androgen receptor immunoreactivity is detected only in the basal, early differentiated sebocytes. Conflicting data exist regarding the exact pattern of androgen receptor expression in human hair follicles, especially concerning expression in occipital scalp. Androgen receptor expression is found mainly in the dermal papilla but is absent in the keratinocytes of outer root sheath (including the bulge regions supposed to contain the hair stem cells) and

those of the inner root sheaths (Fig. 3). On the other hand, higher levels of androgen receptor immunoreactivity are found in the dermal papilla cells from balding hair follicles when compared with non-balding scalp.

Both testosterone and DHT bind to the androgen receptor with high affinity. Polymorphisms in the androgen receptor gene also influence the activity of the receptor. Reports about the association of these polymorphisms with androgen-dependent skin disorders, including hirsutism and male pattern baldness, have been inconsistent (Sawaya and Shalita, 1998; Calvo *et al.*, 2000).

Hirsutism reflects the interaction between circulating androgen concentrations, local androgen concentrations and the sensitivity of the hair follicle to androgens. Yet, the severity of hirsutism does not correlate well with circulating androgen concentrations. Furthermore, the hair follicle response to circulating androgens varies considerably within and between individuals, explaining why some women with clearly elevated androgen levels do not show cutaneous manifestations, or may have seborrhea, acne or alopecia in the absence of clinically relevant hirsutism.

Finally, hirsutism must be distinguished from hypertrichosis, an excessive growth of vellus hair that results from either heredity or from the use of drugs, such as glucocorticoids, phenytoins, minoxidil or cyclosporine, in which hair is distributed in a generalized, non-sexual pattern, and is not caused by excess androgen (although hyperandrogenism may aggravate this condition). Furthermore, although estrogens modulate the hair cycle, they appear to have no direct effects on hair growth.

## Diagnosis of hirsutism

### Etiological diagnosis

After establishing the presence of hirsutism by an increased mFG score, or if a history of hirsutism is strongly suggested by the finding of some evidence of terminal hair in androgen-dependent areas in women successfully treated for this condition, diagnostic studies should focus on identification of the most likely etiology.

The importance of performing an extensive evaluation in women presenting even with mild hirsutism is based on the fact that the severity of hirsutism does not correlate well with the magnitude of androgen excess (Reingold and Rosenfield, 1987; Pfeifer *et al.*, 1989; Carmina and Lobo, 2001; Legro *et al.*, 2010). Minimal unwanted hair growth and mild hirsutism in women can provide important indicators of an underlying androgen excess disorder (Souter *et al.*, 2004; Di Fede *et al.*, 2010). In fact, even severely hyperandrogenemic patients with PCOS or non-classic congenital adrenal hyperplasia (NCCAH) may not have hirsutism and, in contrast, women with severe idiopathic hirsutism may have entirely normal circulating androgen concentrations without evidence of ovarian dysfunction. In some patients, previous treatment of hirsutism may interfere with the current estimation of the mFG score, yielding a falsely low hirsutism score. The occurrence of metabolic disorders and cardiovascular risk markers in women with hirsutism correlates with the severity of hyperandrogenemia (Azziz *et al.*, 2006, 2009; Wild *et al.*, 2010). Finally, specific etiologies, such as NCCAH, are associated with significant heritable risks that entail genetic counseling (Speiser *et al.*, 2000). Therefore, we recommend establishing the etiology of hirsutism in all

patients irrespective of its severity, especially in patients referred for the initial evaluation of this complaint.

Functional causes account for most hirsutism cases. The evolution of the criteria for diagnosis of polycystic ovary syndrome (PCOS) (Zawadzki and Dunaif, 1992; The Rotterdam ESHRE/ASRM-sponsored PCOS consensus workshop group, 2004; Azziz *et al.*, 2006, 2009) has determined important consequences on the classification of the androgen excess disorders. In fact, both European Society of Human Reproduction and Embryology/American Society of Reproductive Medicine (The Rotterdam ESHRE/ASRM-sponsored PCOS consensus workshop group, 2004) and the AE-PCOS Society (Azziz *et al.*, 2006, 2009) diagnostic criteria consider that women with hyperandrogenism and polycystic ovarian morphology but with normal ovulatory cycles have PCOS. These patients need to be separated from the group of hyperandrogenic patients with normal ovulatory cycles and normal ovarian morphology who may be considered to have idiopathic hyperandrogenism (Azziz *et al.*, 2000; Carmina, 2006a, b).

Patients with hirsutism but normal circulating androgens, normal ovulatory cycles and normal ovaries may be considered a separate group, termed idiopathic hirsutism (Azziz *et al.*, 2000). A putative increase in the conversion of testosterone into DHT and/or an increased androgen receptor sensitivity have been proposed as the mechanisms explaining hirsutism in these women (Azziz *et al.*, 2000). However, these women may share mild steroidogenic abnormalities with women presenting with the full hyperandrogenic phenotypes (Escobar-Morreale *et al.*, 1997) that are not detected by the diagnostic tools usually available in clinical practice.

In fact, some experts believe that, because of the many problems in defining the normal androgen range with commercial assays (see below), hirsute patients who have normal ovulatory cycles and normal ovaries should be included in the group of idiopathic hyperandrogenism irrespective of their serum androgen concentrations (Carmina, 2006b). While idiopathic hyperandrogenism and idiopathic hirsutism constitute two separate disorders (Azziz *et al.*, 2000), only accurate testosterone assays may permit differentiation between these two conditions.

NCCAH caused by 21-hydroxylase or 11 $\beta$ -hydroxylase deficiencies is a less common but still important cause of hirsutism in certain populations. Women with classic congenital adrenal hyperplasia (CAH) may develop hirsutism if their replacement glucocorticoid doses are too low or because of poor adherence. Androgen-secreting tumors are rare but should always be considered in the initial diagnostic approach to hirsutism because of the potential for significant and grave consequences.

Although hirsutism is typically not the major concern, other uncommon disorders associated with hirsutism include gestational hyperandrogenism, drug-induced hirsutism, Cushing's syndrome, glucocorticoid resistance, acromegaly and hyperprolactinemia. Among these disorders, the diagnosis is usually evident from other signs and symptoms (Escobar-Morreale, 2010). In some studies (Azziz *et al.*, 2004), patients with severe insulin resistance and acanthosis nigricans (HAIR-AN) have been considered a separate group, but most authors include these patients within the PCOS spectrum of disorders.

Therefore, we recommend considering five main androgen-excess disorders in the diagnostic approach to patients with hirsutism:



**Table III** Frequencies of the etiologies of androgen excess in large clinical series.

| Author, year                   | Sample size (n) | PCOS (n)         | Idiopathic hyperandrogenism (n) | Idiopathic hirsutism (n) | NCCAH (n) | Tumors (n) | Miscellaneous (n) |
|--------------------------------|-----------------|------------------|---------------------------------|--------------------------|-----------|------------|-------------------|
| Azziz et al. (2004)            | 873             | 749 <sup>a</sup> | 59 <sup>b</sup>                 | 39                       | 18        | 2          | 6                 |
| Glintborg et al. (2004)        | 340             | 134              | 86 <sup>b</sup>                 | 115                      | 2         | 1          | 2                 |
| Unluhizarci et al. (2004)      | 168             | 96               | 29 <sup>b</sup>                 | 27                       | 12        | 3          | 1                 |
| Carmina et al. (2006)          | 950             | 685 <sup>c</sup> | 150                             | 72                       | 41        | 2          | 0                 |
| Escobar-Morreale et al. (2008) | 270             | 171              | 61 <sup>b</sup>                 | 24                       | 6         | 0          | 8                 |
| Total no. (%)                  | 2601 (100)      | 1835 (71)        | 385 (15)                        | 277 (10)                 | 79 (3)    | 8 (0.3)    | 17 (0.7)          |

NCCAH, non-classic congenital adrenal hyperplasia; PCOS, polycystic ovary syndrome.

<sup>a</sup>The original article considered 33 patients with the hyperandrogenism, insulin resistance and acanthosis nigricans (HAIR-AN) syndrome as a separate disorder from PCOS, reducing this figure to 716.

<sup>b</sup>Polycystic ovarian morphology was not considered for the diagnosis of PCOS in these studies, which relied on the 1990 National Institute of Child Health and Human Development criteria (Zawadzki and Dunaif, 1992). Some of these patients might have been diagnosed with PCOS if ovarian morphology had been considered.

<sup>c</sup>This study considered polycystic ovarian morphology for PCOS diagnosis, and 147 of the 685 PCOS patients who had regular ovulatory cycles would have been included in the idiopathic hyperandrogenism subgroup if ovarian morphology had not been considered.

- (i) PCOS, when women present with clinical and/or biochemical hyperandrogenism together with ovulatory dysfunction and/or polycystic ovarian morphology.
- (ii) Idiopathic hyperandrogenism, when women present with clinical and biochemical hyperandrogenism but have regular ovulatory cycles of normal length and normal ovarian morphology.
- (iii) Idiopathic hirsutism, when women present with hirsutism but have normal androgen concentrations, ovulatory cycles and normal ovarian morphology.
- (iv) NCCAH.
- (v) Androgen-secreting tumors.

PCOS is the most common disorder associated with hyperandrogenism. Analysis of large series shows that PCOS is present in about 70% of patients (Table III). Most patients have the classic anovulatory form, while the ovulatory form is relatively less common but still present in almost 20% of PCOS patients (Carmina et al., 2006).

The problem of milder causes of hirsutism, such as idiopathic hyperandrogenism and idiopathic hirsutism, should not be underestimated. In fact, because classic PCOS is present in ~6% of women of reproductive age (Asuncion et al., 2000; Azziz et al., 2004), the prevalence of these milder androgenic disorders may be calculated to occur in approximately another 2% of adult women.

### Clinical history and physical examination

A detailed clinical history including family history and a complete physical examination remain the most valuable tool to determine the etiology of the hirsutism. Functional causes almost always show a peripubertal onset and a slow progression over years, a family history of hyperandrogenism is frequent, and signs of virilization (such as clitoromegaly or balding) or of defeminization (such as mammary atrophy) are extremely rare (Escobar-Morreale, 2010). In contrast, androgen-secreting tumors usually manifest with sudden onset and rapid progression; severe virilization and defeminization usually accompany the hirsutism (Escobar-Morreale, 2010). However, tumors producing only moderately excessive androgen may have indolent presentations (Rosenfield, 2005).

Moreover, clinical evaluation provides valuable clues to discriminate between functional causes of hirsutism: oligo- or amenorrhea and

infertility may indicate the ovarian dysfunction associated with PCOS, NCCAH or even androgen-secreting tumors. Since PCOS is frequently associated with insulin resistance, abdominal obesity and/or acanthosis nigricans are frequent physical findings (Escobar-Morreale, 2010).

### Hormone profile

Although hirsutism is an unequivocal marker of excessive androgen action at the pilosebaceous unit, as stated earlier, the severity of hirsutism correlates poorly with the severity of androgen excess (Reingold and Rosenfield, 1987; Pfeifer et al., 1989; Carmina and Lobo, 2001; Legro et al., 2010). This apparent paradox possibly indicates that hirsutism not only reflects circulating androgen levels but is also influenced by the peripheral metabolism of androgens (Goodarzi et al., 2006), by the sensitivity of target tissues to androgens (Sawaya and Shalita, 1998) and by other hormonal variables, including insulin resistance and compensatory hyperinsulinism (Landay et al., 2009).

Yet this paradox might also result from significant variability among many of the commercial direct immunoassays used for serum androgen measurements. Several Societies have recently questioned the use of direct immunoassays for the measurements of serum androgen levels in children and women in favor of more sensitive methods that couple extraction by liquid chromatography with tandem mass spectrometry (LC/MS) (Rosner et al., 2007; Azziz et al., 2009).

Nevertheless, some total testosterone immunochemiluminescence assays provide reliable values with functional sensitivities similar to that of LC/MS-based methods (Ognibene et al., 2000; Kushnir et al., 2010). Recent data indicate that currently available commercial total testosterone LC/MS-based assays for measuring circulating total testosterone levels in patients with PCOS in a clinical setting may not be superior to a commercial direct radioimmunoassay (Legro et al., 2010).

Until ongoing projects aimed to standardize testosterone testing result in improved cost-effective assays (Rosner and Vesper, 2010), the issue of which serum androgen should be measured in hirsute patients and how these steroids must be assayed remains controversial, to the extreme that some experts suggest not measuring serum

androgens levels at all, at least in women presenting with mild hirsutism (Martin *et al.*, 2008).

Based on our perspective that measuring serum androgens and other steroid concentrations are essential for establishing the etiology of hirsutism and that the magnitude of the increase in serum androgen levels may correlate with the metabolic and cardiovascular associations of functional causes of hyperandrogenism, including PCOS (Wild *et al.*, 2010), while recognizing the limitations of current androgen assays, we suggest to proceed as follows:

- (i) Obtain at least one determination of serum androgen levels in every patient with hirsutism before starting any treatment that might interfere with such measurements.
- (ii) Of all the circulating androgens, assessments of free testosterone levels are much more sensitive than the measurement of total testosterone for the diagnosis of hyperandrogenic disorders (Azziz *et al.*, 2009). Free testosterone measurements ideally require equilibrium dialysis techniques, and should never rely on direct analog radioimmunoassays, which are notoriously inaccurate (Rosner, 2001).
- (iii) A high-quality direct double antibody radioimmunoassay for total testosterone might be useful clinically, as long as the inter-assay coefficients of variation are below 10% as determined by the laboratory conducting the assays, and the normal ranges are determined in-house in a carefully selected healthy non-hyperandrogenic control female population. Alternatively, a greater degree of accuracy, particularly for clinical research, may be possibly obtained by measuring total testosterone concentration using LC/MS techniques (Azziz *et al.*, 2009).
- (iv) The diagnostic performance of measuring serum total testosterone may be enhanced easily by the concomitant measurement of sex hormone-binding globulin (SHBG), permitting the calculation of free testosterone levels that have a fairly good concordance and correlation with free testosterone as measured by the equilibrium dialysis methods (Vermeulen *et al.*, 1999). In this regard, single determinations of serum SHBG and free testosterone levels have a high predictive value for PCOS in epidemiologic studies, with receiver operating characteristic curve values above 0.830 (Escobar-Morreale *et al.*, 2001). Serum SHBG may also provide a surrogate marker of insulin resistance in women (Pugeat *et al.*, 1996) and therefore its measurement may be useful *per se*.
- (v) The value of also measuring serum androstenedione and DHEAS levels in patients with hirsutism is unclear (Azziz *et al.*, 2009). Measuring androstenedione may increase the number of subjects identified as hyperandrogenic by ~10% (Azziz *et al.*, 2009), whereas increased DHEAS concentrations may be the sole abnormality in circulating androgens in ~10% of hyperandrogenic patients. Nonetheless, we should note that DHEAS levels might not always reflect the status of adrenocortical steroidogenesis, and overinterpretation of DHEAS levels should be avoided (Azziz *et al.*, 2009).
- (vi) Less-frequent etiologies of hirsutism must be excluded in order to accurately establish the etiology. All patients presenting with hirsutism should be screened for androgen-secreting tumors, even if screening is primarily clinical as stated earlier. It should be noted that overreliance on androgen levels as a screening tool will lead

to significant false positive rates (Azziz *et al.*, 2009). Hyperprolactinaemia is an uncommon cause of hirsutism but prolactin should be measured if features of menstrual irregularity or galactorrhea are present. NCCAH is more common in certain ethnic groups where its screening may be mandatory, but routine assessment of 17-hydroxyprogesterone or 11-deoxycortisol will depend on the prevalence of the condition in the community, accessibility of the assay and the expense incurred. Accurate serum prolactin determination requires avoidance of stress related to venipuncture and other situations that may falsely increase its serum levels. 17-hydroxyprogesterone measurements should be obtained early in the morning (Azziz *et al.*, 1999). Importantly, the normal ranges for serum markers of these disorders should be established in-house (Escobar-Morreale *et al.*, 2008) and must be followed by further testing in case of doubt, including exclusion of macroprolactinemia by precipitation of serum with polyethylene-glycol before assaying for prolactin (Escobar-Morreale, 2004) or conducting full adrenal stimulation with the synthetic ACTH, cosyntropin (Azziz *et al.*, 2009). Where indicated, identification of women with 21-hydroxylase deficient NCCAH is important because of the benefits of genetic counseling; such women are often heterozygous carriers for at least one *CYP21A2* mutation associated with classic CAH (Speiser *et al.*, 2000; Escobar-Morreale *et al.*, 2008). In addition, the prevalence of having a child with classic CAH is higher than predicted based on population frequency of mutation bearing *CYP21A2* alleles (Moran *et al.*, 2006). Finally, clinical screening is usually adequate to exclude rare causes of hirsutism, such as drugs, gestational hyperandrogenism, acromegaly and Cushing's syndrome.

## Ovulatory function

Assessment of ovulatory function is essential to determine the precise etiology, and is also useful to identify patients with hirsutism who are at risk for metabolic and cardiovascular dysfunction, which is increased in women with PCOS, especially when accompanied by obesity (Wild *et al.*, 2010). We recommend:

- (i) Obtaining a detailed menstrual history dating back to puberty: a chronic history of oligomenorrhea—menstrual cycles longer than 35 days for at least six cycles per year—or amenorrhea—lack of menstrual discharge for three consecutive theoretical menstrual cycles—is suggestive of chronic ovulatory dysfunction.
- (ii) Because as many as 15–40% of patients with hirsutism present with regular but anovulatory menstrual cycles (Azziz *et al.*, 1998), the occurrence of ovulation should be documented using either basal body temperature charts, luteal phase serum progesterone concentrations or both. The cut-off values of serum progesterone levels indicative of ovulation must be established in-house.

## Metabolic profile

For patients with hirsutism and other signs suggestive of classic PCOS, we recommend following the metabolic evaluation proposed in the AE-PCOS guidelines for the assessment of glucose tolerance (Salley *et al.*, 2007) and cardiovascular risk (Wild *et al.*, 2010) in women with PCOS that include:

- (i) Assessment of waist circumference and BMI.
- (ii) Complete lipid profile, including total cholesterol, low-density lipoprotein-cholesterol, non-high-density lipoprotein (HDL)-cholesterol, HDL-cholesterol and triglycerides.
- (iii) A 2-h post 75-g oral glucose challenge to assess glucose tolerance. A few members of the task force recommend conducting this test only in patients with obesity or in lean patients with additional risk factors such as advanced age (>40 years), personal history of gestational diabetes or family history of type 2 diabetes mellitus.
- (iv) Standard clinical blood pressure determination.

The evidence for an association of metabolic and cardiovascular dysfunction in women with milder forms of hyperandrogenism, such as idiopathic hyperandrogenism or idiopathic hirsutism, remains indeterminate. Current evidence suggests the existence of a graded spectrum of risk depending on the etiology of hirsutism, with higher risk corresponding to women with classic PCOS followed by those with ovulatory PCOS and idiopathic hyperandrogenism, and the lowest risk for women with idiopathic hirsutism (Carmina, 2006a, b; Welt et al., 2006; Barber et al., 2007; Shroff et al., 2007; Goverde et al., 2009).

Until additional data become available, we suggest conducting a limited evaluation of metabolic and cardiovascular dysfunction in women with milder hyperandrogenic disorders, including clinical measurements of obesity, abdominal adiposity and blood pressure. A more complete evaluation, including a lipid profile and indexes of glucose tolerance and insulin resistance, should be restricted to women with obesity, abdominal adiposity or other cardiovascular risk factors (Carmina, 2006a).

## Ultrasound evaluation

Ultrasonography is helpful in the investigation of hirsutism, along with clinical findings and hormonal assays. The main role of ultrasound evaluation is to detect the presence of polycystic ovarian morphology, although this finding may be fortuitously associated with other disorders, such as NCCAH or androgen-secreting tumors.

We recommend using the criteria used in the ESHRE/ASRM (The Rotterdam ESHRE/ASRM-sponsored PCOS consensus workshop group, 2004) and AE-PCOS Society (Azziz et al., 2006, 2009) definitions of polycystic ovarian morphology: presence of either 12 or more follicles measuring 2–9 mm in diameter and/or increased ovarian volume (> 10 ml) (Balen et al., 2003). In developing these criteria, priority was placed on ovarian volume and the follicle number because both are physical entities that can be measured in real-time conditions. Both ovarian volume and follicle number are considered to be key and consistent features of polycystic ovarian morphology.

The consensual threshold to discriminate a normal ovary from a polycystic ovary is 12 or more follicles of 2–9 mm diameter. This threshold was shown as being the best compromise between the most complete studies, up to 2003. With continuing improvement in image resolution, this threshold may need to be redefined since follicles <2 mm in diameter can now be detected and counted with the latest generation of ultrasound equipment.

Recently, when using new ultrasound equipment and applying the 2003 threshold, a major but artificial increase in the prevalence of asymptomatic polycystic ovaries was observed in normal populations, especially in women younger than 30 years (Duijkers and Klipping,

2010; Johnstone et al., 2010; Kristensen et al., 2010). This led some authors to conclude recently that polycystic ovarian morphology has no pathological significance (Johnstone et al., 2010). Furthermore, the consensual volume threshold to discriminate a normal ovary from a polycystic ovary is 10 ml (Balen et al., 2003), but more recent studies (Carmina et al., 2005; Jonard et al., 2005) suggest that decreasing the threshold to 7.0–7.5 ml may be more appropriate in some populations. Until evidence using newer ultrasound techniques leads to an updated consensus, we suggest establishing the threshold values for the antral follicle count and ovarian volume indicative of polycystic ovarian morphology at each center.

Finally, Fig. 5 provides an algorithm for the diagnosis of hirsutism according to the recommendations of the panel of experts.

## Management of hirsutism

Hirsutism is a clinical sign and is not a disease by itself, and its presence does not necessarily require treatment. However, perception of having male-type pattern body hair, irrespective of its objective severity, may have profound adverse effects on the psychological wellbeing of women with even mild hirsutism. Therefore, the subjective perception of the patient, and not only the absolute extent of hair growth, should guide physicians in deciding whether hirsutism should be treated or not.

The goals of the correct management of hirsutism are to ameliorate the hirsutism and reproductive complaints, to prevent and/or treat the possible associated metabolic derangements and, if possible, to treat the underlying cause (Escobar-Morreale, 2010).

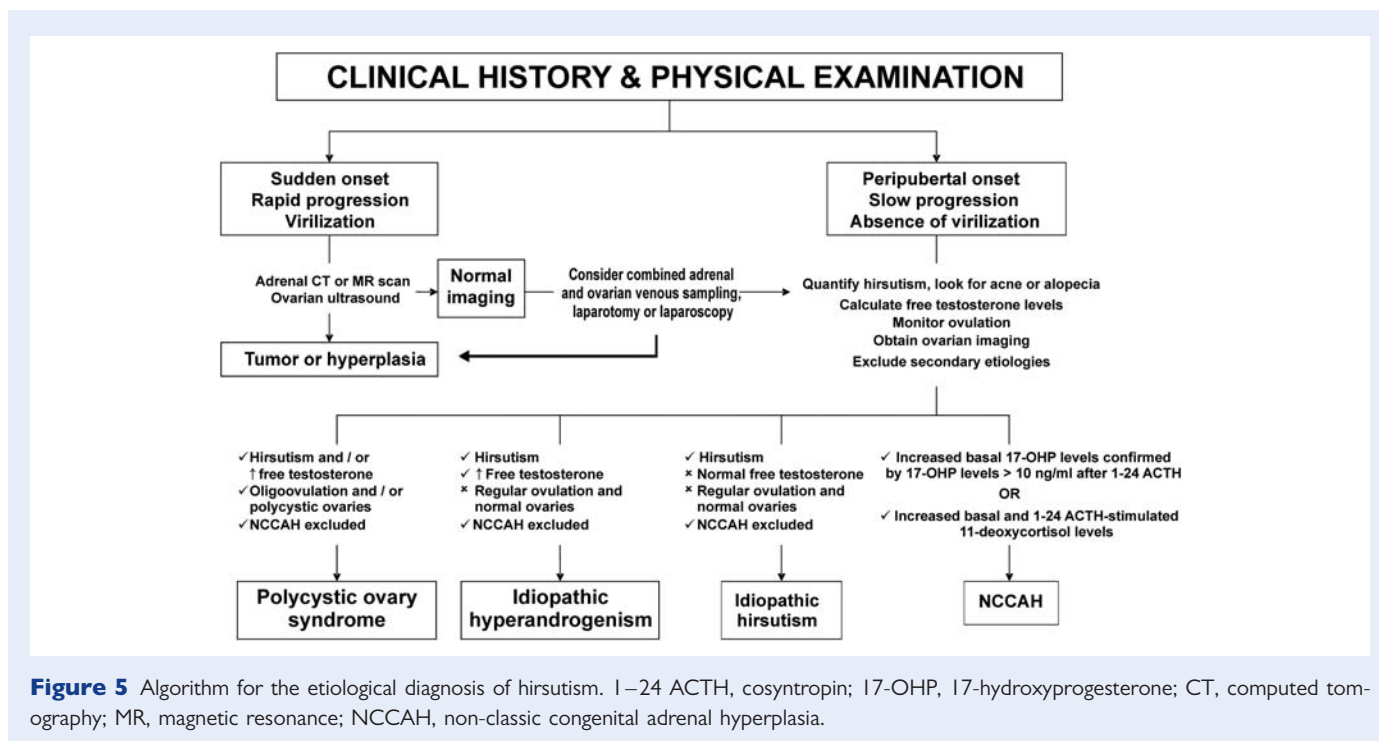
Important principles for the management of hirsutism are listed as follows (Escobar-Morreale, 2010). It may be helpful to discuss these principles with affected women at the onset of therapy.

- (i) Treatment will never be curative and therefore, chronic treatment will likely be necessary.
- (ii) The effects of drugs are not evident before several months of administration.
- (iii) Treatment should take into account the characteristics and expectations of the individual patient.
- (iv) Treatment must be monitored by an expert.

Cosmetic measures are usually effective in controlling mild hirsutism, especially when terminal hair localizes in the most exposed areas such as the face. However, when hirsutism is moderate to severe and/or is widespread in androgen-sensitive areas, a pharmacological approach is usually required. On the other hand, drugs are only partially effective on terminal hairs. Therefore, management of clinically important hirsutism is based upon a dual approach: pharmacological therapy to reduce androgen secretion and/or androgen action, and removal of terminal hair already present.

## Life-style modification

Life-style management, including promotion of physical exercise and dietary advice, is essential for the management of androgen excess and for the cardiovascular protection in women with PCOS (Azziz et al., 2009; Wild et al., 2010). However, even when there is evidence for a reduction in total and free testosterone and an increase in SHBG concentrations after successful life-style modification, no convincing



data support a reduction in hirsutism following such measures (Moran *et al.*, 2011).

Yet because some data suggest that the rate of attenuation of hirsutism may be slower when treatments aim at reducing androgen levels (Spritzer *et al.*, 1990), the effects of life-style changes could have been less noticeable because of the usually short duration of the studies evaluating such effects. On the other hand, lack of substantial effects over an extended period may greatly affect compliance with treatment and cannot be ignored.

Therefore, we suggest offering life-style recommendations to women presenting with hirsutism, especially when PCOS is the most probable underlying etiology but only after explaining that such measures are unlikely to ameliorate hirsutism and will likely need additional approaches. Among life-style recommendations, smoking cessation should be strongly encouraged because this habit exacerbates the undesirable effects of many of the drugs available for hirsutism and related conditions (Luque-Ramirez *et al.*, 2009).

## Cosmetic measures

Cosmetic hair removal complements medical treatment. In mild or localized cases, cosmetic methods may be sufficient as a single therapy.

Traditional cosmetic methods include bleaching, plucking, shaving, waxing, chemical treatment and electrolysis. Of these, only galvanic electrolysis, alone or 'blended' with thermolysis, may destroy the dermal papilla (Kligman and Peters, 1984), resulting in permanent amelioration of hirsutism in the treated area (Richards and Meharg, 1995). If competently performed, electrolysis does not result in scarring or other cosmetic side-effects, although transitory side-effects, such as discomfort, postinflammatory erythema, occasional whealing or even small crusts, may develop (Richards and Meharg, 1995). The application of an eutectic mixture of local anesthetics prior to

the procedures improves tolerance, whereas shaving 1–5 days before electrolysis ensures that only growing anagen hairs are epilated, increasing the efficacy of the procedure (Richards and Meharg, 1995). The other traditional methods are safe and do change the rate of hair growth but should be used ideally in combination with pharmacological intervention. Local discomfort is the common shortcoming of these procedures (Escobar-Morreale, 2010).

Newer methods include laser therapy and intense pulsed light. The available lasers operate in the red or near-infrared wavelengths and rely on selective photothermolysis, in which the melanin pigment in the follicle absorbs the selected wavelength leading to hair follicle destruction (Sanchez *et al.*, 2002). This explains why, in general, laser hair removal is most successful in patients with lighter skin colors and dark colored hairs (Sanchez *et al.*, 2002).

A systematic review (Haedersdal and Gotzsche, 2006) of 11 RCTs comparing laser with control treatments, involving more than 400 patients, noticed long-term hair reduction in only one trial using alexandrite laser therapy (Hussain *et al.*, 2003) while short-term benefits were seen in several others (Haedersdal and Gotzsche, 2006). Several non-randomized studies have suggested the efficacy of laser and intense pulsed light hair removal over the long-term (Haedersdal and Wulf, 2006). Among available photoepilation techniques, alexandrite and diode lasers appear to be more effective than intense pulsed light, neodymium:YAG or ruby lasers (Sanchez *et al.*, 2002; Haedersdal and Wulf, 2006). Laser-based photoepilation is safe, easy to perform and side-effects are rare and transitory (Sanchez *et al.*, 2002; Haedersdal and Wulf, 2006).

Based on these considerations we recommend:

- (i) Using bleaching and temporary methods of hair removal, such as shaving, plucking, waxing or the use of chemical depilatory agents, in the first months of treatment while waiting for drug treatment

to be noticed, or even as single treatment in milder cases. The patient must be assured that shaving does not increase the growth and thickness of hair, which is a common misbelief among patients because the blunt tip of shaved hair is more visible than the tapered tip of uncut hair.

- (ii) Using galvanic or blended electrolysis for localized areas, such as the face, as single procedure or as an adjuvant to pharmacological intervention but only if an experienced operator is available because inexperienced electrolysis may cause considerable local side-effects or even scarring.
- (iii) Using alexandrite or diode laser photoepilation for generalized hirsutism, as the single procedure in mild cases, or as an adjuvant to pharmacological intervention in patients presenting with moderate or severe hirsutism, or in those requiring such treatment for associated conditions.

### Pharmacological intervention

Drug treatment of hirsutism is limited to patients with hirsutism who are not seeking immediate fertility. Evidence-based information regarding the pharmacological treatment of hirsutism is scarce. The vast majority of available literature on the issue is constrained by several major limitations, in particular by the lack of blinded and objective assessment of effects of treatments, small sample sizes and short duration of trials in relation to the physiology of hair growth. In addition, the individual response to treatment may be variable. These limitations make it difficult to establish a scale of relative efficacy of different drugs and even to prove the real efficacy of these medications.

#### Topical eflornithine

A 13.9% eflornithine cream is licensed for use in the topical treatment of unwanted facial hair (Barman Balfour and McClellan, 2001). Eflornithine, a drug initially developed for the treatment of trypanosomal sleeping sickness, is an irreversible inhibitor of L-ornithine decarboxylase, an enzyme that catalyzes the conversion of ornithine to putrescine, a polyamine that is critical to the regulation of cell growth and differentiation within the hair follicle (Barman Balfour and McClellan, 2001). Continuous topical administration of eflornithine cream reversibly slows facial hair growth in up to 70% of patients treated, significantly improving and reducing the psychological burden of facial hirsutism (Jackson et al., 2007; Wolf et al., 2007; Lapidot et al., 2010). However, eflornithine is not approved for the treatment of unwanted terminal hair in areas other than the face, and its cost is relatively high. The problem that limits the possibility of using eflornithine cream in larger skin areas is linked to the possibility of undesirable effects in the case of significant systemic absorption.

We suggest the use of topical eflornithine for facial hirsutism as a single procedure only in mild cases, or as an adjuvant to permanent or long-term depilation (Hamzavi et al., 2007) or to medical treatment with oral drugs (Escobar-Morreale, 2001).

#### Oral contraceptive pills

Oral contraceptive pills (OCPs) contain estrogen plus progestin and have been the mainstay for hirsutism therapy for decades. OCPs suppress ovarian androgen synthesis via inhibition of gonadotrophin secretion from the pituitary, and the estrogen compound increases SHBG concentrations markedly, thereby suppressing free testosterone

levels to values that—in some cases—may fall even below the lower limit of the normal range for adult women (Luque-Ramirez et al., 2007).

The decrease in circulating free androgens results in an improvement in the hirsutism, provided that OCPs are administered chronically (Porcile and Gallardo, 1991). Even if large long-term placebo-controlled RCTs assessing the actual efficacy of OCPs for hirsutism are lacking, subjective improvement in hirsutism with OCPs ranges from 60 to 100% (Raj et al., 1982; Dewis et al., 1985; Guido et al., 2004). Such an improvement may decrease hirsutism scores to within the normal range in women presenting with mild hirsutism, supporting the use of an OCP as the single drug in these cases. Moreover, several studies documented improvement in hair growth using objective measures (Casey et al., 1966; Cullberg et al., 1985; Dewis et al., 1985; Venturoli et al., 1999; Guido et al., 2004; Batukan and Muderris, 2006).

Among the different formulations, low-dose OCPs containing a neutral (low androgenicity) progestin, such as desogestrel or gestodene, or an antiandrogen, such as cyproterone acetate, chlormadinone acetate or the spironolactone-derivative drospirenone, are of choice for the treatment of hirsutism because all of these drugs provide adequate normalization of testosterone levels (Sobbrio et al., 1990; Porcile and Gallardo, 1991; Coenen et al., 1996). If the clinical response to OCPs containing a neutral progestin is unsatisfactory, changing the OCP formulation to include an antiandrogenic progestin may be useful.

Of note, these low-dose third-generation OCP formulations are not associated with the unfavorable metabolic profile of older formulations, and may even have beneficial effects on the lipid profile (Vermeulen and Rubens, 1988) even among obese insulin-resistant patients with PCOS (Lemay et al., 2006; Luque-Ramirez et al., 2007).

However, a mild increase in blood pressure might occur with some of these newer OCP formulations (Luque-Ramirez et al., 2007; Kriplani et al., 2010). Especially among smokers, the third-generation OCPs may have deleterious effects on coagulation (Luque-Ramirez et al., 2009) and may increase the risk of non-fatal venous thromboembolism compared with second-generation OCPs containing the androgenic progestin levonorgestrel (Kemmeren et al., 2001; van Hylckama Vlieg et al., 2009; Jick and Hernandez, 2011; Parkin et al., 2011). Although the increased risk of venous thromboembolism with third-generation OCPs is small, it must be noted that even older formulations containing androgenic progestins may also ameliorate hirsutism (Breitkopf et al., 2003). However, these older OCPs may be less effective on hirsutism and might increase BMI, compared with OCPs containing neutral progestins (Sanam and Ziba, 2011). Therefore, the choice of an OCP for the treatment of hirsutism must balance carefully the greater efficacy of third-generation pills against the safer coagulation profile of second-generation OCP, especially in adolescents, hypertensive women and smokers.

Aside from the amelioration of hirsutism, OCPs provide the effective contraception recommended for the concomitant use of antiandrogens, and are quite useful for the regularization of menstrual bleeding in women with PCOS (Escobar-Morreale, 2010), which will also reduce the risk of endometrial hyperplasia.

Based on these considerations, we recommend prescribing a low-dose neutral or antiandrogenic OCP as first-line therapy for hirsutism:

- (i) As a single drug in women with mild hirsutism.
- (ii) As an adjuvant to antiandrogen administration in women with moderate or severe hirsutism and to provide adequate contraception to these patients.
- (iii) To guarantee regular menstrual bleeding in hirsute patients with PCOS presenting with oligo- or amenorrhoea.

### Antiandrogens

Antiandrogens (androgen receptor blockers and 5 $\alpha$ -reductase inhibitors) are possibly the most effective drugs for hirsutism, although the evidence supporting this statement is relatively weak (Swiglo *et al.*, 2008b).

Several RCTs, summarized in Table IV, support the use of antiandrogens for hirsutism. All these drugs ameliorate hirsutism compared with placebo. In a 6 month double-blind, placebo-controlled study carried out in 40 women with PCOS or idiopathic hirsutism, flutamide 250 mg/day, finasteride 5 mg/day or spironolactone 100 mg/day were all more effective than placebo on hirsutism, as assessed by changes in hair shaft diameter, hirsutism score and self-evaluation by the patients (Moggetti *et al.*, 2000a). Furthermore, the combination of a triphasic oral contraceptive and flutamide was more effective than the oral contraceptive alone in a 1 year double-blind, placebo-controlled multicentre trial, carried out in 119 hirsute women (Calaf *et al.*, 2007). Similarly, the combination of an oral contraceptive containing 2 mg of cyproterone acetate and either spironolactone 100 mg, finasteride 5 mg or cyproterone acetate 100 mg was better than the oral contraceptive alone in three 1 year double-blind studies (Belisle and Love, 1986; Kelestimur and Sahin, 1998; Sahin *et al.*, 1998).

However, at present there is not enough information to establish a scale of efficacy for these drugs. Some comparative studies did not find differences in efficacy between antiandrogen drugs (Wong *et al.*, 1995; Grigoriou *et al.*, 1996; Falsetti *et al.*, 1997; Fruzzetti *et al.*, 1999; Moggetti *et al.*, 2000a; Spritzer *et al.*, 2000; Beigi *et al.*, 2004), whereas in other studies flutamide appeared to have the greatest efficacy, and finasteride the lowest, of antiandrogens (Cusan *et al.*, 1994; Erenus *et al.*, 1997; Sahin *et al.*, 1998; Falsetti *et al.*, 1999; Pazos *et al.*, 1999; Venturoli *et al.*, 1999). Furthermore, these drugs do not appear to exert dose-dependent effects against hirsutism (Barth *et al.*, 1991; Muderris *et al.*, 1997; Bayram *et al.*, 2002; Tartagni *et al.*, 2004; Calaf *et al.*, 2007).

Among approaches combining several antiandrogens, the combination of spironolactone with finasteride was more effective than spironolactone alone in two small 6-month studies carried out in women with PCOS or idiopathic hirsutism (Unluhizarci *et al.*, 2002; Kelestimur *et al.*, 2004).

It must be stressed that antiandrogens cannot be given to pregnant women for the risk of feminization of male fetuses and should only be prescribed to women using secure contraception. Unless oral or transdermal (Henzl and Loomba, 2003) contraceptives are contraindicated, antiandrogens should be given in combination with these drugs (Kuttann *et al.*, 1980), especially cyproterone acetate and spironolactone. These medications may cause menstrual disturbances or even amenorrhoea when given alone because of their strong progestin effects. If hormonal contraception is contraindicated, for instance in women at risk for thrombophilia or in heavy smokers older than 35 years, contraception must be assured by use of an intrauterine

device or by surgical sterilization (Escobar-Morreale, 2010) before using antiandrogens.

Another consideration for antiandrogens is the potential for significant side-effects. In particular, the non-steroidal antiandrogen flutamide (Castelo-Branco *et al.*, 2009) is associated with an increased risk for severe or even fatal liver toxicity; this risk was below 0.5% in large populations of male subjects with prostate cancer, given the higher amounts of the drug than those used for hirsutism (Wysowski *et al.*, 1993; Manso *et al.*, 2006). In hirsute women, severe liver toxicity is anecdotal but has been reported to occur with doses as low as 250 mg/day (Manso *et al.*, 2006; Castelo-Branco and Del Pino, 2009). Finally, with the exception of cyproterone acetate and spironolactone in some countries, antiandrogens are not approved for the treatment of hirsutism and are used off-label after adequate informed consent.

In summary, we recommend prescribing an antiandrogen:

- (i) Combined with OCPs in women presenting with moderate or severe hirsutism, or in those with a milder hirsutism who do not reach a satisfactory control of hair growth using OCPs alone after 1 year of treatment.
- (ii) As single drugs in women in whom OCPs are contraindicated, warranted that a reliable contraceptive method is used.

Considering their similar efficacy and potential for side-effects, we suggest prescribing finasteride, cyproterone acetate or spironolactone instead of flutamide when an antiandrogen is needed, although the latter is apparently safe at doses below 250 mg/day (Ibanez *et al.*, 2005).

### Insulin sensitizers

Insulin sensitizers are widely used for PCOS because insulin resistance contributes to the pathogenesis of this disorder (Azziz *et al.*, 2009). Insulin sensitizers improve insulin resistance and menstrual dysfunction and may decrease serum androgen concentrations (Lord *et al.*, 2003); their effects on hirsutism are much less clear.

In recent years, several placebo-controlled comparisons of insulin sensitizer drugs for the treatment of hirsutism were published: nine used metformin (Moggetti *et al.*, 2000b; Pasquali *et al.*, 2000; Kelly and Gordon, 2002; Gambineri *et al.*, 2004; Hoeger *et al.*, 2004; Maciel *et al.*, 2004; Onalan *et al.*, 2005; Gambineri *et al.*, 2006; Romualdi *et al.*, 2010), whereas one involved pioglitazone (Aroda *et al.*, 2009) and another used troglitazone (Azziz *et al.*, 2001), a thiazolidinedione that is no longer available in the market because of its hepatic side-effects. Of note, hirsutism was not the main outcome measure in any of these studies. Most of the studies with metformin found effects on hirsutism that were similar to placebo, whereas troglitazone (Azziz *et al.*, 2001) and pioglitazone (Aroda *et al.*, 2009) induced small but statistically significant decreases in the hirsutism score compared with placebo (Table V).

Compared with OCPs and antiandrogens, metformin does not appear to be more effective for the treatment of hirsutism. Mixed results were observed when comparing metformin with OCPs (Morin-Papunen *et al.*, 2000; Harborne *et al.*, 2003; Morin-Papunen *et al.*, 2003; Allen *et al.*, 2005; Lemay *et al.*, 2006; Luque-Ramirez *et al.*, 2007; Meyer *et al.*, 2007; Hoeger *et al.*, 2008). Most studies used a combination of ethinylestradiol and low-dose cyproterone acetate, and in approximately half of them the OCP was more effective compared with the insulin-sensitizer (Table V). However, the short length

**Table IV** Summary of RCTs comparing the efficacy of different antiandrogen drugs on hirsutism.

| Author, year                | Blinding | Months | Sample size | Disorders                                   | Regimens compared <sup>a</sup>                             | Outcome                                 | Efficacy on hirsutism                  |
|-----------------------------|----------|--------|-------------|---|--|---|--|
| Belisle and Love (1986)     | Double   | 12     | 158         | Hirsutism<br>(mFG > 14)                     | (1) Diane<br>(2) Diane + CPA 100                           | mFG                                     | Diane + CPA > Diane                    |
| McLellan et al. (1989)      | Double   | 9      | 22          | Hirsutism                                   | (1) Spironolactone 100<br>(2) Placebo                      | Diameter<br>Self-evaluation             | No difference                          |
| Barth et al. (1991)         | Double   | 12     | 38          | Hirsutism                                   | (1) Diane<br>(2) Diane + CPA 20<br>(3) Diane + CPA 100     | mFG<br>Hair diameter<br>Linear growth   | No difference                          |
| Cusan et al. (1994)         | Single   | 9      | 53          | Hirsutism<br>(mFG > 13)                     | (1) Flutamide 500 mg + OCP<br>(2) Spironolactone 100 + OCP | mFG                                     | Flutamide + OCP > Spironolactone + OCP |
| Ciotta et al. (1995)        | Single   | 9      | 18          | PCOS<br>Idiopathic hirsutism                | (1) Finasteride 7.5<br>(2) Placebo                         | mFG                                     | Finasteride > Placebo                  |
| Wong et al. (1995)          | None     | 6      | 14          | Hirsutism<br>(mFG > 11)                     | (1) Spironolactone 100<br>(2) Finasteride 5                | mFG<br>Hair diameter<br>Self-evaluation | No difference                          |
| Grigoriou et al. (1996)     | None     | 9      | 22          | Idiopathic hirsutism                        | (1) CPA 100<br>(2) Flutamide 500                           | mFG                                     | No difference                          |
| Erenus et al. (1997)        | Single   | 9      | 40          | Idiopathic hirsutism<br>(mFG > 10)          | (1) Spironolactone 100<br>(2) Finasteride 5                | mFG                                     | Spironolactone > Finasteride           |
| Falsetti et al. (1997)      | None     | 6      | 44          | PCOS<br>(mFG 11–24)                         | (1) Finasteride 5<br>(2) Flutamide 500                     | mFG<br>Hair diameter                    | No difference                          |
| Muderris et al. (1997)      | Single   | 12     | 65          | Hirsutism                                   | (1) Flutamide 250<br>(2) Flutamide 500                     | mFG                                     | No difference                          |
| Kelestimur and Sahin (1998) | Single   | 12     | 50          | Hirsutism<br>(mFG > 8)                      | (1) Diane<br>(2) Diane + Spironolactone 100                | mFG                                     | Diane + Spironolactone > Diane         |
| Sahin et al. (1998)         | Single   | 9      | 42          | PCOS<br>Idiopathic hirsutism                | (1) Diane<br>(2) Finasteride 5                             | mFG                                     | Diane > Finasteride                    |
| Falsetti et al. (1999)      | None     | 12     | 110         | PCOS<br>Idiopathic hirsutism<br>(mFG 11–23) | (1) Finasteride 5<br>(2) Flutamide 500                     | mFG<br>Hair diameter                    | Flutamide > Finasteride                |

|                                  |        |    |    |   |  |   |   |
|----------------------------------|--------|----|----|---|--|---|---|
| Fruzzetti <i>et al.</i> (1999)   | Single | 12 | 45 | Hirsutism   | (1) Finasteride 5<br>(2) CPA 25 + EE 0.020<br>(3) Flutamide 500                                    | mFG                                     | No difference   |
| Pazos <i>et al.</i> (1999)       | None   | 9  | 33 | Functional ovarian hyperandrogenism<br>Idiopathic hirsutism | (1) GnRHa + OCP<br>(2) CPA 100 + OCP<br>(3) Flutamide 500 + OCP                                    | mFG                                     | Flutamide > (CPA = GnRHa)   |
| Venturoli <i>et al.</i> (1999)   | None   | 12 | 66 | PCOS<br>Idiopathic hirsutism<br>NCCAH                       | (1) Flutamide 250<br>(2) Finasteride 5<br>(3) Ketoconazole 300<br>(4) 3) CPA 12.5 + EE 0.010–0.020 | mFG<br>Hair diameter<br>Linear growth   | (CPA = Flutamide) > Finasteride<br>Ketoconazole 50% drop out rate |
| De Leo <i>et al.</i> (2000)      | None   | 6  | 35 | PCOS  | (1) GnRHa<br>(2) GnRHa + Diane<br>(3) GnRHa + Flutamide 250  | mFG                                     | No difference   |
| Moggetti <i>et al.</i> (2000a)   | Double | 6  | 40 | Hirsutism   | (1) Spironolactone 100<br>(2) Finasteride 5<br>(3) Flutamide 250<br>(4) Placebo                    | mFG<br>Hair diameter<br>Self-evaluation | (Spironolactone = Finasteride = Flutamide) > Placebo              |
| Muderris <i>et al.</i> (2000)    | Single | 12 | 70 | Hirsutism<br>(mFG > 8)                                      | (1) Flutamide 250<br>(2) Finasteride 5   | mFG                                     | Flutamide > Finasteride   |
| Spritzer <i>et al.</i> (2000)    | None   | 12 | 44 | PCOS<br>Idiopathic hirsutism<br>(mFG 11–35)                 | (1) Spironolactone 200<br>(2) CPA 50 + EE 0.035  | mFG                                     | No difference   |
| Tartagni <i>et al.</i> (2000)    | Single | 6  | 50 | PCOS<br>Idiopathic hirsutism                                | (1) Diane<br>(2) Diane + Finasteride 5   | mFG<br>Self-evaluation                  | Diane + Finasteride > Diane                                       |
| Sahin <i>et al.</i> (2001)       | Single | 12 | 40 | Hirsutism   | (1) Diane<br>(2) Diane + Finasteride 5   | mFG                                     | Diane + Finasteride > Diane                                       |
| Bayram <i>et al.</i> (2002)      | None   | 12 | 46 | PCOS<br>Idiopathic hirsutism<br>(mFG > 12)                  | (1) Finasteride 2.5<br>(2) Finasteride 5   | mFG                                     | No difference   |
| Taner <i>et al.</i> (2002)       | None   | 6  | 84 | Hirsutism   | (1) Flutamide 250<br>(2) Flutamide 250 + Diane   | mFG                                     | No difference   |
| Unluhizarci <i>et al.</i> (2002) | Single | 6  | 34 | PCOS<br>Idiopathic hirsutism                                | (1) Spironolactone 100<br>(2) Spironolactone 100 + Finasteride 5                                   | mFG                                     | Spironolactone + Finasteride > Spironolactone                     |

Continued



**Table IV** Continued

| Author, year                    | Blinding | Months | Sample size | Disorders                               | Regimens compared <sup>a</sup>  | Outcome                | Efficacy on hirsutism   |
|---------------------------------|----------|--------|-------------|---|---|------------------------|---|
| Lakryc <i>et al.</i> (2003)     | Double   | 6      | 24          | PCOS<br>Idiopathic hirsutism            | (1) Finasteride 5<br>(2) Placebo  | mFG<br>Self-evaluation | Finasteride > Placebo   |
| Beigi <i>et al.</i> (2004)      | None     | 9      | 40          | PCOS<br>Idiopathic hirsutism            | (1) Finasteride 5<br>(2) CPA 25 + EE 0.020  | mFG                    | No difference   |
| Ganie <i>et al.</i> (2004)      | None     | 6      | 69          | PCOS                                    | (1) Spironolactone 50<br>(2) Metformin 1000   | mFG                    | Spironolactone > Metformin                                      |
| Kelestimur <i>et al.</i> (2004) | Single   | 12     | 65          | PCOS<br>Idiopathic hirsutism            | (1) Spironolactone 100<br>(2) Spironolactone 100 + Finasteride 5  | mFG                    | Spironolactone + Finasteride > Spironolactone                   |
| Tartagni <i>et al.</i> (2004)   | Single   | 10     | 38          | PCOS<br>Idiopathic hirsutism (mFG > 10) | (1) Finasteride 2.5 once daily<br>(2) Finasteride 2.5 every 3 days                                      | mFG                    | No difference   |
| Gambineri <i>et al.</i> (2006)  | Single   | 12     | 76          | PCOS                                    | (1) Diet<br>(2) Diet + Metformin 1700<br>(3) Flutamide 500<br>(4) Diet + Metformin 1700 + Flutamide 500 | mFG                    | (Flutamide = Flutamide + Metformin) > (metformin + diet = diet) |
| Calaf <i>et al.</i> (2007)      | Double   | 12     | 119         | PCOS<br>Idiopathic hirsutism (mFG > 15) | (1) OCP<br>(2) Flutamide 125 + OCP<br>(3) Flutamide 250 + OCP<br>(4) Flutamide 375 + OCP                | mFG                    | Flutamide (125 = 250 = 375) + OCP > OCP                         |

CPA, cyproterone acetate; Diane, cyproterone acetate 2 mg plus ethinylestradiol 35 µg; EE, ethinylestradiol; mFG, modified Ferriman–Gallwey score; GnRHa, GnRH analog; OCP, oral contraceptive pill.

<sup>a</sup>Doses are mg per day unless stated otherwise.

**Table V** Summary of RCTs of interventions with insulin sensitizers for hirsutism.

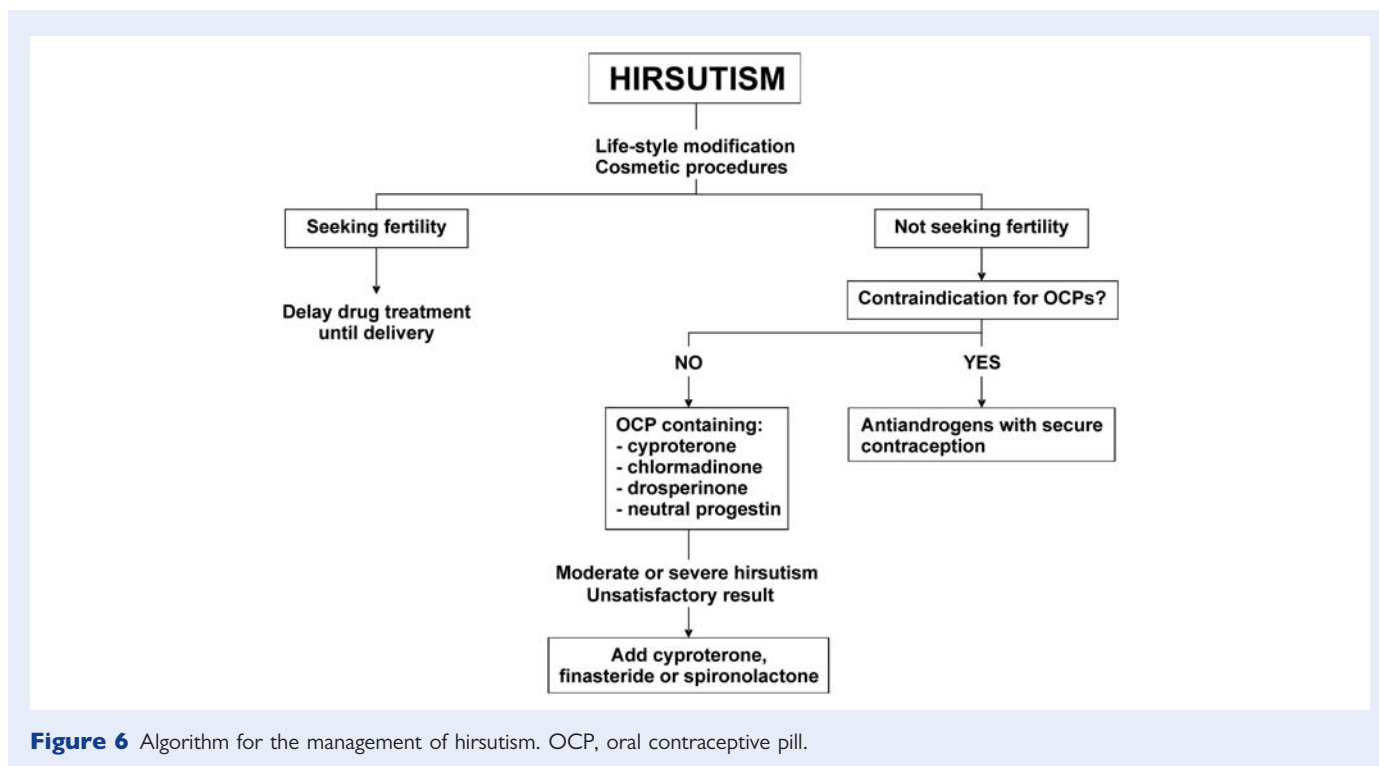
| Author, year                       | Blinding | Months | Sample size | Disorders | Regimens compared <sup>a</sup>                   | Outcome                                | Efficacy on hirsutism   |
|------------------------------------|----------|--------|-------------|-----------|--|--|---|
| Insulin sensitizers versus placebo |          |        |             |           |  |  |   |
| Moggetti <i>et al.</i> (2000b)     | Double   | 6      | 23          | PCOS      | (1) Metformin 1500<br>(2) Placebo                | mFG                                    | No difference   |
| Pasquali <i>et al.</i> (2000)      | Double   | 6      | 20          | PCOS      | (1) Diet + Metformin 1700<br>(2) Diet + Placebo  | FG                                     | Metformin > placebo   |
| Azziz <i>et al.</i> (2001)         | Double   | 11     | 410         | PCOS      | (1) Troglitazone 150, 300 and 600<br>(2) Placebo | mFG                                    | Troglitazone 600 > placebo  |
| Kelly and Gordon (2002)            | Double   | 6      | 16          | PCOS      | (1) Metformin 1500<br>(2) Placebo                | FG<br>Hair growth<br>Self-assessment   | Metformin > placebo<br>Metformin > placebo<br>Metformin > placebo |
| Gambineri <i>et al.</i> (2004)     | Single   | 6      | 20          | PCOS      | (1) Diet + Metformin 1700<br>(2) Diet + Placebo  | FG                                     | No difference   |
| Hoeger <i>et al.</i> (2004)        | Double   | 11     | 18          | PCOS      | (1) Metformin 1700<br>(2) Placebo                | mFG                                    | No difference   |
| Maciel <i>et al.</i> (2004)        | Double   | 6      | 34          | PCOS      | (1) Metformin 1500<br>(2) Placebo                | FG                                     | No difference   |
| Onalan <i>et al.</i> (2005)        | Double   | 6      | 139         | PCOS      | (1) Metformin 1700<br>(2) Placebo                | FG                                     | No difference   |
| Gambineri <i>et al.</i> (2006)     | Single   | 12     | 40          | PCOS      | (1) Diet + Metformin 1700<br>(2) Diet + Placebo  | FG                                     | No difference   |
| Aroda <i>et al.</i> (2009)         | Unclear  | 6      | 28          | PCOS      | (1) Pioglitazone 45<br>(2) Placebo               | FG                                     | Pioglitazone > placebo  |
| Romualdi <i>et al.</i> (2010)      | Double   | 6      | 28          | PCOS      | (1) Metformin 1000<br>(2) Placebo                | FG                                     | Metformin > placebo   |
| Insulin sensitizers versus OCPs    |          |        |             |           |  |  |   |
| Morin-Papunen <i>et al.</i> (2000) | None     | 6      | 18          | PCOS      | (1) Metformin 1000 → 2000<br>(2) Diane           | FG                                     | Diane > Metformin   |
| Harborne <i>et al.</i> (2003)      | Unclear  | 12     | 52          | PCOS      | (1) Metformin 1500<br>(2) Diane                  | FG<br>Hair diameter<br>Self-assessment | Metformin > Diane<br>No difference<br>Metformin > Diane           |
| Morin-Papunen <i>et al.</i> (2003) | None     | 6      | 20          | PCOS      | (1) Metformin 1000 → 2000<br>(2) Diane           | FG                                     | Diane > Metformin   |

Continued

Table V Continued

| Author, year                     | Blinding | Months | Sample size | Disorders | Regimens compared <sup>a</sup>   | Outcome | Efficacy on hirsutism   |
|----------------------------------|----------|--------|-------------|-----------|--|---------|---|
| Allen et al. (2005)              | None     | 6      | 35          | PCOS      | (1) Metformin 1000<br>(2) Norgestimate 0.25 + EE 0.035   | mFG     | No difference   |
| Lemay et al. (2006)              | None     | 6      | 28          | PCOS      | (1) Rosiglitazone 4<br>(2) Diane   | FG      | Diane > Rosiglitazone   |
| Luque-Ramirez et al. (2007)      | None     | 6      | 34          | PCOS      | (1) Metformin 1700<br>(2) Diane  | mFG     | Diane > Metformin   |
| Meyer et al. (2007)              | None     | 6      | 110         | PCOS      | (1) Metformin 2000<br>(2) Diane<br>(3) Levonorgestrel 0.100 + EE 0.020 + Spironolactone 100                    | FG      | No difference   |
| Hoeger et al. (2008)             | Double   | 6      | 43          | PCOS      | (1) Metformin 1700<br>(2) Desogestrel 0.15 + EE 0.030<br>(3) Life-style modification<br>(4) Placebo            | FG      | No difference   |
| Metformin and thiazolidinediones |          |        |             |           |  |         |   |
| Yilmaz et al. (2005)             | Single   | 6      | 96          | PCOS      | (1) Metformin 1700<br>(2) Rosiglitazone 4  | FG      | Rosiglitazone > Metformin   |
| Ortega-Gonzalez et al. (2005)    | None     | 6      | 52          | PCOS      | (1) Metformin 2550<br>(2) Pioglitazone 30  | FG      | No difference   |
| Dereli et al. (2005)             | None     | 8      | 40          | PCOS      | (1) Rosiglitazone 2<br>(2) Rosiglitazone 4   | mFG     | Rosiglitazone 4 > Rosiglitazone 2                                     |
| Metformin versus antiandrogens   |          |        |             |           |  |         |   |
| Ganie et al. (2004)              | None     | 6      | 69          | PCOS      | (1) Spironolactone 50<br>(2) Metformin 1000  | mFG     | Spironolactone > Metformin  |
| Gambineri et al. (2004)          | Single   | 6      | 20          | PCOS      | (1) Metformin 1700<br>(2) Flutamide 500  | FG      | Flutamide > Metformin   |
| Gambineri et al. (2006)          | Single   | 12     | 76          | PCOS      | (1) Diet<br>(2) Diet + Metformin 1700<br>(3) Diet + Flutamide 500<br>(4) Diet + Metformin 1700 + Flutamide 500 | mFG     | (Flutamide =<br>Flutamide + Metformin) ><br>(metformin + diet = diet) |

<sup>a</sup>Doses are mg per day unless stated otherwise.



**Figure 6** Algorithm for the management of hirsutism. OCP, oral contraceptive pill.

of these studies precludes reaching any definite conclusion on the possible long-term effects of both families of drugs.

A few trials compared antiandrogens with metformin for hirsutism (Table V). Overall, metformin was less effective compared with flutamide and spironolactone (Ibanez *et al.*, 2002; Gambineri *et al.*, 2004, 2006; Ganie *et al.*, 2004). Also, compared with antiandrogens, the effect of metformin on hirsutism may require longer periods of therapy to be noticeable (Gambineri *et al.*, 2006). Very few studies (Dereli *et al.*, 2005; Ortega-Gonzalez *et al.*, 2005; Yilmaz *et al.*, 2005) compared the effects on hirsutism of the different insulin sensitizers available.

Therefore, we recommend against the use of metformin or other insulin sensitizers as therapy for hirsutism as its possible effects are unconvincing and possibly not superior to placebo.

#### Other drugs

There are inconsistent reports regarding the role of glucocorticoids in the treatment of hirsutism and concerns about their safety (Steinberger *et al.*, 1990). In addition, there is considerable controversy about the regimen and the most appropriate dosage (Horrocks and London, 1987; Rittmaster and Givner, 1988; Steinberger *et al.*, 1990). The studies currently available in patients with adrenal (Frank-Raue *et al.*, 1990; Spritzer *et al.*, 1990) or unselected hyperandrogenism (Emsans *et al.*, 1988; Prezelj *et al.*, 1989; Carmina and Lobo, 1998) and in women with idiopathic hirsutism (Devoto *et al.*, 2000) suggest that glucocorticoids are less effective on hirsutism compared with OCPs or antiandrogens. However, in women with NCCAH, prolonged remission after withdrawal of antiandrogen therapy may be obtained by the addition of glucocorticoids (Carmina and Lobo, 1998).

The adrenal enzyme inhibitor ketoconazole ameliorates hirsutism (Martikainen *et al.*, 1988; Akalin, 1991) but its frequent side-effects

limit its use (Venturoli *et al.*, 1999) to subjects with Cushing's syndrome while waiting for definite therapy.

GnRH analogs are potent inhibitors of ovarian steroidogenesis but experience with these drugs in the management of hirsutism is quite limited (van der Spuy and Tregoning, 2008). Considering that these drugs induce a reversible menopause requiring combined use with OCPs and its very high economic cost, this class of drugs should be restricted, if used at all, to the very selected patients with severe hyperandrogenism of ovarian origin that do not respond to other drugs.

We therefore recommend against the use of glucocorticoids, ketoconazole and GnRH analogs for first-line therapy of hirsutism because their effects are generally limited. In addition, other drugs are safer and/or more cost-effective.

#### Follow-up

As stated earlier, treatment of hirsutism must be monitored by an experienced physician. The assessment of treatment efficacy is mostly clinical and should include an objective measure of the amelioration of hirsutism by repeating the mFG score as well as considering patient's satisfaction.

The usefulness of measuring serum androgen levels is less clear, albeit confirming a decrease in serum androgen levels may increase patient's confidence with the efficacy of treatment in women with hyperandrogenemia, especially while waiting for the clinical response to be evident. When using OCPs, it is important to measure not only total testosterone but also SHBG, as these drugs induce a marked increase in SHBG concentrations that may increase serum total testosterone levels (Escobar-Morreale, 2010). Measuring serum androgen levels is not useful in patients treated with antiandrogens as single drugs.

Any change in treatment in response to an unsatisfactory result must consider the length of the terminal hair cycle; the effects of drug treatment must only be assessed after at least 6 months of continuous therapy and, ideally, assessment of the clinical response should ideally wait for at least 1 year after any change in drug treatment.

Finally, Fig. 6 provides an algorithm for the management of hirsutism according to the recommendations of the panel of experts.

## Concluding remarks

Hirsutism is one of the most common disorders affecting women during the reproductive years. Although often caused by relatively benign functional conditions, hirsutism may be the presenting symptom of a life-threatening tumor requiring immediate intervention. In contrast to the previous guidelines (Martin et al., 2008), we recommend applying the diagnostic and therapeutic strategies described here even to patients with mild hirsutism, because the severity of hirsutism does not correlate well with the magnitude of androgen excess and because PCOS and NCCAH may be found in a significant number of such patients (Di Fede et al., 2010). In most cases, hirsutism is a chronic disorder benefiting from long-term follow-up. The use of evidence-based strategies to improve the hirsutism and to treat the underlying disorder is essential for the proper management of women with hirsutism.

## Authors' roles

H.F.E.-M. contributed to data acquisition, revision and interpretation, drafted and revised critically the article for important intellectual content, wrote and approved the final version of the manuscript. E.C., D.D., A.G., F.K., P.M., M.P., J.Q., C.N.W., S.F.W. and R.J.N. contributed to data acquisition, revision and interpretation, drafted and revised critically the article for important intellectual content and approved the final version of the manuscript.

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## Disclaimer

These guidelines are not inclusive of all recommended approaches or methods or exclusive of others and do not guarantee outcome or establish standards of care. They do not dictate treatment, which depends upon independent judgment for each patient. The AE-PCOS Society makes no warranty, expressed or implied, regarding the guidelines and excludes any warranties of merchantability and fitness for particular use, and shall not be liable for damages from use of information contained herein.

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