HYPERANDROGENISM AND MENOPAUSE: MANAGEMENT

BMS BRUXELLES 30/11/ 2013

A Pintiaux  Reproductive Endocrinology- Gynaecology ULg
PRESENTING SIGNS AND SYMPTOMS
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- hirsutism on the face and/or trunk
- loss of hair on head.
- detailed history is crucial to differentiate progressive hirsutism from true virilization.
- associated signs
Hirsutism is defined as an increase in terminal hair growth, particularly on chin, upper lip and abdomen. This can be quantified by the Ferriman–Gallwey score which assigns a score of 0–4 to describe hair in nine body areas.
PRESENTING SIGNS AND SYMPTOMS

- **Virilization** includes the combination of **severe hirsutism** together with **male pattern balding**, **anabolic appearance**, lowering of the voice and **clitoromegaly**
- **Virilizing symptoms** suggest severe hyperandrogenism and should trigger an evaluation for an **underlying tumour**.
HISTORY - TIMING - MEDICATIONS

- **The timing** of first menses, of menopause, of hyperandrogenism
- **History** of irregular menses
- **Evidence** of *premenopausal hyperandrogenism*
- **Obesity**: the timing of weight gain and loss must be noted, particularly as it relates to the onset of hirsutism and/or acne.
- **Concomitant medications**
- **Family history** of endocrine disorders or familial hirsutism or balding should be documented.
- **Headaches** and/or **visual symptoms**, galactorrhea, acromegaly or Cushing signs
Hair loss in elderly
MANAGEMENT OF POSTMENOPAUSAL HYPERANDROGENISM

Postmenopausal hyperandrogenism

Clinical history & physical examination
Serum androgen concentrations

Onset of symptoms at puberty
Mild to moderate hyperandrogenemia
Slow progression
Virilization absent
Defeminization absent

Onset of symptoms after menopause
Severe clinical hyperandrogenism
Severe hyperandrogenemia
Rapid progression
Virilization present
Defeminization present

Preexisting functional disorder aggravated by menopause

Conservative management

Adrenal CT or MRI
Transvaginal US scan

Large adrenal tumor
• No tumor found
• Inconclusive results
• Small adrenal adenoma

Adrenalectomy

Combined adrenal & ovarian sampling

Ovarian tumor

Oophorectomy

Macarena Alpanes, J Clin Endocrinol Metab, August 2012
Differential diagnosis and presentation of androgen excess in postmenopausal women

<table>
<thead>
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<th>Diagnosis</th>
<th>Presentation in postmenopausal women</th>
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<td>Polycystic ovarian syndrome</td>
<td>Past history of anovulatory cycles</td>
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<td>Elevated T, dehydroepiandrosterone sulphate (DHEAS)</td>
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<td>Obesity-induced hyperandrogenic anovulation</td>
<td>Past history of regular menses before weight gain, then threshold weight</td>
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<td>Hyperthecosis</td>
<td>Elevated T and/or DHEAS</td>
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<td>Androgen secreting ovarian or adrenal tumor</td>
<td>Past history of anovulatory cycles, Very high T, modest DHEAS</td>
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<td></td>
<td>Pelvic US</td>
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<td>Past history of regular menses</td>
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<td>Rapid onset of virilizing symptoms</td>
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<td>Cushing's syndrome</td>
<td>Very high T, DHEAS</td>
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<td>Elevated urine free cortisol and/or abnormal 1mg dexamethasone suppression</td>
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<td>Pituitary: normal to elevated adrenocorticotropin (ACTH), elevated DHEAS</td>
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<td>Congenital Adrenal Hyperplasia</td>
<td>Adrenal: suppressed ACTH and DHEAS</td>
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<td>Elevated 17 hydroxyprogesterone baseline (classic)</td>
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<td>Elevated 17 hydroxyprogesterone after ACTH stimulation (non classical)</td>
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<td>Iatrogenic</td>
<td>Elevated T, dehydroepiandrosterone, DHEAS, androstenedione</td>
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<td>LH/FSH may or may not be suppressed</td>
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M. Rothman and M. Wierman, Clinical Endocrinology .2011
Any 2 of the following 3 disorders confirmed:
- Oligomenorrhea or amenorrhea
- Hyperandrogenism (e.g., hirsutism, acne, alopecia) or hyperandrogenemia (e.g., elevated levels of total or free testosterone)
- Polycystic ovaries on ultrasonography

All of the following disorders ruled out:
- Hyperprolactinemia
- Nonclassic congenital adrenal hyperplasia
- Cushing’s syndrome
- Androgen-secreting neoplasm
- Acromegaly

Polycystic ovary syndrome

Ancillary studies

Risk assessment for endometrial carcinoma
- Endometrial biopsy if risk increased

Risk assessment for glucose intolerance
- Oral glucose-tolerance test if risk increased

Fasting cholesterol, HDL cholesterol, triglycerides, LDL cholesterol

Risk assessment for obstructive sleep apnea
- Polysomnography if risk increased

**Figure 1. Diagnostic Algorithm for the Polycystic Ovary Syndrome.**

Single measurements of serum prolactin and 17-hydroxyprogesterone are usually sufficient to rule out hyperprolactinemia and nonclassic congenital adrenal hyperplasia due to deficiency of 21-hydroxylase. It is important to measure the 17-hydroxyprogesterone level in a blood sample taken in the early morning, when endogenous corticotropin levels peak. As an alternate test, 17-hydroxyprogesterone can be measured in response to a single dose of exogenously administered corticotropin. Risks for glucose intolerance include an elevated body-mass index, an increased waist circumference, a history of gestational diabetes, a family history of type 2 diabetes, and certain racial or ethnic backgrounds (including black, Caribbean Hispanic, and Mexican American). HDL denotes high-density lipoprotein, and LDL low-density lipoprotein.
PCOS: changing women’s health paradigm

Metabolic disease

- Reproductive disorders
  - (young age)
    - menstrual disorders
    - hirsutism
    - contraception
    - sexual health
    - infertility
  - (older age)
    - pregnancy complications
    - quality of life
    - type 2 diabetes
    - cardiovascular disease
    - cancer risk?

Multi-disciplinary approaches

- pediatrics
- dermatology
- gynecology
- endocrinology
- diabetology
- cardiology
- geriary
Hormonal changes

Genetics

Lifestyle/obesity

Androgens

Insulin

Ovarian follicles/
anovulation/estrogen

Diabetes

Hirsuitism/
acne

Menstrual
disturbances

Cardiovascular
risk/metabolic
syndrome

Psychosocial issues: body image, self esteem, depression, anxiety
Treatment

- **Diet** (low glycaemic index) and physical activity

Insulin-sensitizers improve insulin resistance may decrease serum androgen concentrations (Lord et al., 2003); their effects on hirsutism are much less clear.
PCOS is associated with increased risk of impaired glucose tolerance (IGT), GDM and T2D (Dunaif, 1997; Boomsma et al., 2006; Moran et al., 2010).

Risk of IGT or diabetes is highest in women who have both oligo/anovulation and hyperandrogenism, and the risk is further amplified by obesity (Barber et al., 2007).

Management of women at risk for T2D should include diet and lifestyle improvement as first-line treatment. Metformin treatment is indicated in those with IGT who do not respond adequately to calorie restriction and lifestyle changes. In those with frank diabetes, metformin is safe and effective (Franks, 2011).
Treatment

- Estradiol - Progestin (SHBG increase, LH inhibition)
- Anti-androgens
- Cosmetic
TREATMENT

• Cosmetic measures are usually effective in controlling mild hirsutism, especially when terminal hair localizes in the most exposed areas such as the face.

• When hirsutism is moderate to severe and/or is widespread in androgen-sensitive areas, a pharmacological approach is usually required.
HIRSUTISM/ACNE/ ALOPECIA

• Treatment is focused
  I. on reduction in androgen production,  
  II. decreasing the fraction of circulating free testosterone  
  III. limiting androgen bioactivity to hair follicles
HIRSUTISM/ACNE/ ALOPECIA

- Treatment is focused
  
  I. On reduction in androgen production, decreasing the fraction of circulating free testosterone and limiting androgen bioactivity to hair follicles through augmentation of sex hormone-binding globulin (SHBG) levels

  II. Anti-androgens
    1. spironolactone (an aldosterone-antagonist diuretic),
    2. flutamide (an androgen receptor antagonist)
    3. finasteride (a 5α-reductase type 2 inhibitor)
    4. cyproterone acetate

The Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS Consensus Workshop Group 2012
HIRSUTISM/ACNE/ALOPECIA

• **Prolonged** (6 months) medical therapy for hirsutism is necessary to document effectiveness (Level B).
• Many drugs used for the treatment of hirsutism are **not FDA approved** for this indication (GPP).
• No effective treatment for alopecia is known (Level B).
• Flutamide is of limited value because of its dose-dependent **hepatotoxicity** (Level B).
• Drospirenone in the dosage used in some combination is not anti-androgenic (Level B).

The Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS Consensus Workshop Group 2012
• Physical approaches, to remove unwanted hair, including **electrolysis and laser**, may be acceptable to many patients..

• Topical treatment with **eflornithine** hydrochloride, an inhibitor of ornithine decarboxylase limits cell division, has been shown effective for decreasing the development of new unwanted facial hair (Balfour and McClellan, 2001).

• In severe acne, **isotretinoin** can be beneficial, but individual responses vary. It is not effective for hirsutism and occasionally may lead to alopecia.
• 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).
CONCLUSIONS

• A careful history, examination, selected laboratories and radiologic tests will clarify the diagnosis
• Appropriate medical, surgical and lifestyle interventions
• Few data on hyperandrogenism management in postmenopausal women