Best practice in the treatment of hyperandrogenic skin symptoms

Educational Slide Kit
Module 3
1. What do you think is the **most important** goal of treatment of hyperandrogenic skin symptoms?

A. Improve clinical symptoms i.e. reduce hair growth or number and severity of acne lesions
B. Restore menstrual function
C. Minimize psychological and QoL impairment
D. It depends on the individual patient’s needs and goals of treatment
2. What is the aim of pharmacological treatment for the skin symptoms of androgen excess?

A. Reducing amount of androgens produced
B. Controlling androgen effects at tissue level
C. Reducing the level of free testosterone
D. All of the above
Testing your knowledge

3. Which of the following statements is true about antiandrogenic potential of EE/progestogen combinations?

A. EE/progestogen combinations have no antiandrogenic potential
B. Different combinations of EE/progestogen have varied antiandrogenic potential
C. All EE/progestogen combinations have the same antiandrogenic potential
D. None of the above
4. A patient with androgen excess should always be referred if you suspect an androgen-secreting tumour. What other circumstances might you refer a patient with androgen excess?

A. Undiagnosed bleeding
B. Severe psychological morbidity for example, severe anxiety and/or depression
C. Scarring acne
D. Fertility problems
Module content

• Aims of treatment for hyperandrogenic skin symptoms
• Treatment options
• Rationale for antiandrogen treatment
• Role of antiandrogens as combined hormone treatment
• The AWARE treatment proposal
Aims of treatment for androgen excess
Goals of treatment for androgen excess\textsuperscript{1-4}

- In women with \textbf{clinical hyperandrogenism}:
  - Improve clinical symptoms i.e. reduce hair growth or number and severity of acne lesions
  - Restore menstrual function (if needed)
  - Minimize psychological and QoL impairment

- In women with \textbf{biochemical hyperandrogenism}:
  - Reduce the risk of long-term metabolic and reproductive complications

Treatment options for hyperandrogenic skin symptoms
Overview of treatment options

• **Lifestyle management**
  – Aimed at reducing the risk of long-term metabolic consequences\(^1,2\)

• **Topical or cosmetic options\(^1\)**
  – Targets hyperandrogenic skin symptoms such as hirsutism and acne

• **Pharmacological treatment\(^1\)**
  – Aimed at reducing the level of circulating androgens and controlling their effect at tissue level

Lifestyle management should be a core part of treatment to improve metabolic and psychological consequences associated with this condition\(^1-^3\)

*Where necessary to reduce weight/BMI\(^1\)
Topical or cosmetic treatments options

**Cosmetic options for treatment of hirsutism mainly involve hair removal**
- Shaving, plucking, or waxing
- Use of depilatory creams or epilators
- Electrolysis or laser hair removal
- Eflornithine cream

**Topical options for treatment of acne mainly involve use of:**
- Topical retinoids, such as isoretinoin or adapalene
- Azaleic acid
- Benzoyl peroxide
- Topical antibiotics such as tetracyclines

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Pharmacological treatment options

Treatment is aimed at reducing the level of circulating androgens and controlling their effect at tissue level\(^1\)

- Antiandrogens, such as cyproterone acetate and spironolactone
- Finasteride
- Insulin-sensitizers, such as metformin and pioglitazone
- GnRH* analogues, such as goserelin and leuprolelin

*Gonadotrophin-releasing hormone

Rationale for antiandrogen treatment
Antiandrogens in the treatment of skin symptoms such as hirsutism and acne\textsuperscript{1-5}

Treatment is focused on:

- Reducing androgen production
- Decreasing the fraction of circulating free testosterone
- Limiting androgen bioactivity to sebaceous gland and hair follicles

Cyproterone Acetate (CPA): a steroidal antiandrogen

CPA is a steroid compound with potent...

...Antigonadotropic properties

...Antiandrogenic activities

...Progestogenic activities

CPA targets hyperandrogenic skin symptoms via two mechanisms

CPA also affects synthesis and secretion of ovarian androgens\textsuperscript{1-3}

CPA interacts with GnRH receptors in the pituitary gland blocking the release of LH and FSH

Inhibition of FSH and LH leads to a decline in ovarian androgen production and a reduction in free testosterone

\textbf{CPA}, cyproterone acetate; \textbf{FSH}, follicle stimulating hormone; \textbf{GnRH}, gonadotropin-releasing hormone; \textbf{LH}, luteinizing hormone

Role of antiandrogens as combined hormone treatment
Different combinations of EE/progestogen have varied antiandrogenic potential\textsuperscript{1-3}

- CPA/EE has the greatest antiandrogen potential of hormonal treatments containing a combination of progestogens and EE\textsuperscript{4-5}

Combination CPA/EE* treatment effectively treats hyperandrogenic skin symptoms and menstrual dysfunction$^{1,2}$

- Significant reduction in:$^1$
  - Acne lesions count and severity at 6 months
  - Hirsutism score (mF-G) and use of cosmetic treatments at 6 months
  - Sebum production and seborrhea at 9 months

- Additional benefits of menstrual regularity and effective contraception$^2$

- Reduction in long-term risk of endometrial hyperplasia and endometrial cancer$^2$

*CPA/EE, 0.035mg ethinylestradiol/2mg cyproterone acetate

Cardiovascular safety with EE/progestogen combinations

Use of estrogen/progestogen combinations is associated with an increased risk for VTE (DVT or PE)\(^1,2\)

The use of CPA/EE carries an increased risk of VTE/ATE compared with no use or LNG/EE use

Highest during the 1\(^{st}\) year of use

Highest when restarting or switching from another OC\(^*\)

However, the risk of VTE during COC use remains lower than that during pregnancy and childbirth\(^3,4\)

ATE, Arterial thromboembolism; LNG, levonorgestrel; COC, Combined oral contraceptive; DVT, Deep vein thrombosis; PE, Pulmonary embolism; OC, Oral contraceptive; VTE, Venous thromboembolism; CPA/EE, 0.035mg ethinylestradiol/2mg cyproterone acetate

Due to its labeled indication, CPA/EE may channel use towards women with an inherently higher cardiovascular risk\textsuperscript{1,2}

Observational studies of VTE risk with CPA/EE compared to LNG-containing and other COCs (low-estrogen <0.05mg) yield varying findings.

Some studies reported a greater VTE risk, comparable to so-called 3rd generation COCs\textsuperscript{3–5}

Other studies showed no differences in VTE risk\textsuperscript{1,6,7}

Studies that addressed the issue of confounding or duration of use concluded that the VTE risk is not significantly higher\textsuperscript{1,7}

COC, Combined oral contraceptive; LNG, Levonorgestrel; PCOS, Polycystic ovary syndrome; VTE, Venous thromboembolism; CPA/EE, 0.035mg ethinylestradiol/2mg cyproterone acetate.

The AWARE treatment proposal
Challenges in the management of androgen excess

- Identifying different presenting symptoms and their pathophysiology
- Understanding the role of non-hormonal and hormonal treatment
- Effective treatment of presenting clinical symptoms e.g. skin manifestations and menstrual dysfunction
- Identifying and managing associated syndromes e.g. polycystic ovary syndrome
- Managing patient expectations of treatment outcomes
- Balancing risks and benefits of long-term treatment through life stages
- Managing long-term metabolic syndrome and reproductive consequences

The AWARE treatment proposal addresses these challenges

5. EXPLAIN
What to explain?
- The pathophysiology of symptoms in simple, patient-focused language
- How the treatments work
- The need for a follow-up plan

Why?
- Increasing patient knowledge helps to empower patients
- To help patients understand the importance of correct and consistent treatment, especially in long-term conditions
- Skin symptoms such as acne and hirsutism often require long-term treatment

6. TREAT
What to treat?
- Bothersome symptoms of clinical hyperandrogenism i.e. acne, hirsutism, seborrhea and alopecia
- Symptoms of biochemical hyperandrogenism such as endometrial or metabolic complications

- Use established treatment combinations for androgen excess and follow clinical guidelines and relevant criteria for use
- Patients must be carefully screened before using any estrogen/progestogen combinations, and pregnancy must be excluded
- Further guidance on contraindications is available in the "WHO MEC for contraceptive use" [16]

Why?
- To help to improve the symptom-related quality of life and psychological impairment
- To help reduce the risk of both reproductive and metabolic/cardiovascular consequences associated with long-term androgen excess disorders [19]

7. REFER IF
When to refer?
- Suspicion of androgen-secreting tumour
- Undiagnosed bleeding
- Severe psychological morbidity for example, severe anxiety and/or depression
- Scarring acne
- Fertility problems

Why?
- An androgen-secreting tumour requires urgent confirmation of diagnosis and treatment
- Menstrual dysfunction and irregular bleeding can have multiple, different etiologies; the possibility of endometrial abnormality should be excluded with use of ultrasound (if available)
- For effective treatment of depression, anxiety or other symptom of psychological morbidity due to symptoms of androgen excess
- Severe, scarring acne requires specialist treatment from a dermatologist
- Referral for assisted reproduction techniques and counselling may be needed for women who still have difficulty conceiving due to androgen excess

References:
Important elements of patient communication when discussing treatment\textsuperscript{1-3}

5. EXPLAIN

What to explain?

- The pathophysiology of symptoms in simple, patient-focused language
- How the treatments work
- The need for a follow-up plan

Effective treatment of seborrhea, acne, hirsutism and alopecia can help to improve quality of life and psychological impairment associated with clinical hyperandrogenism. Hyperandrogenic skin symptoms can arise due to biochemical hyperandrogenism, treatment of which can help reduce the risk of both reproductive and metabolic/cardiovascular consequences associated with long-term androgen excess disorders.

References:
Factors to consider before prescribing combined hormonal treatment

• Use established treatment combinations for androgen excess

• EE in combination with progestogens with antiandrogenic potential (CPA, CMA, DNG or DRSP) are preferred treatment options.  
  1,3

• CPA combined with EE, is indicated for the treatment of moderate to severe acne related to androgen-sensitivity (with or without seborrhea) and/or hirsutism, in women of reproductive age.  
  1,2

• Screen patients using WHO MEC for guidance in the prescribing of estrogen/progestogen combinations  

When to refer women with androgen excess\textsuperscript{1,2}

\begin{itemize}
  \item Suspicion of androgen-secreting tumour
  \item Undiagnosed bleeding
  \item Severe psychological morbidity for example, severe anxiety and/or depression
  \item Scarring acne
  \item Fertility problems
\end{itemize}

Conclusions

• **Treatment of androgen excess aims to:**¹⁻⁵
  – Reduce the level of circulating androgens and control their effect at tissue level
  – Improve clinical hyperandrogenic skin symptoms and associated psychological impairment⁶ and restore menstrual regularity where needed
  – Reduce the risk of long-term reproductive and metabolic consequences of biochemical hyperandrogenism

• Options include cosmetic or topical treatments, pharmacological therapy and lifestyle management¹,⁷

• **CPA/EE offers effective treatment of hyperandrogenic skin symptoms and menstrual dysfunction**⁸

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Find The Global AWARE Group educational materials on the European Menopause & Andropause Society website

https://www.emas-online.org/nonemaseducationalmaterials/

FREE resources to download

The AWARE group is a panel of independent physicians with an expert interest in androgen excess in women. Formation of the AWARE group and its ongoing work is supported and funded by Bayer AG.