Leiden University
Medical Center

Interventions for hirsutism

Cochrane review 2015

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NOTTINGHAM

Definition hirsutism

- Excessive amount of terminal hair growth in androgen-sensitive areas in women (male pattern)

- Androgen dependent

- Don't confuse with **hypertrichosis**

  Excessive hair growth localised or generalised on the body (non-sexual pattern)

  Androgen independent

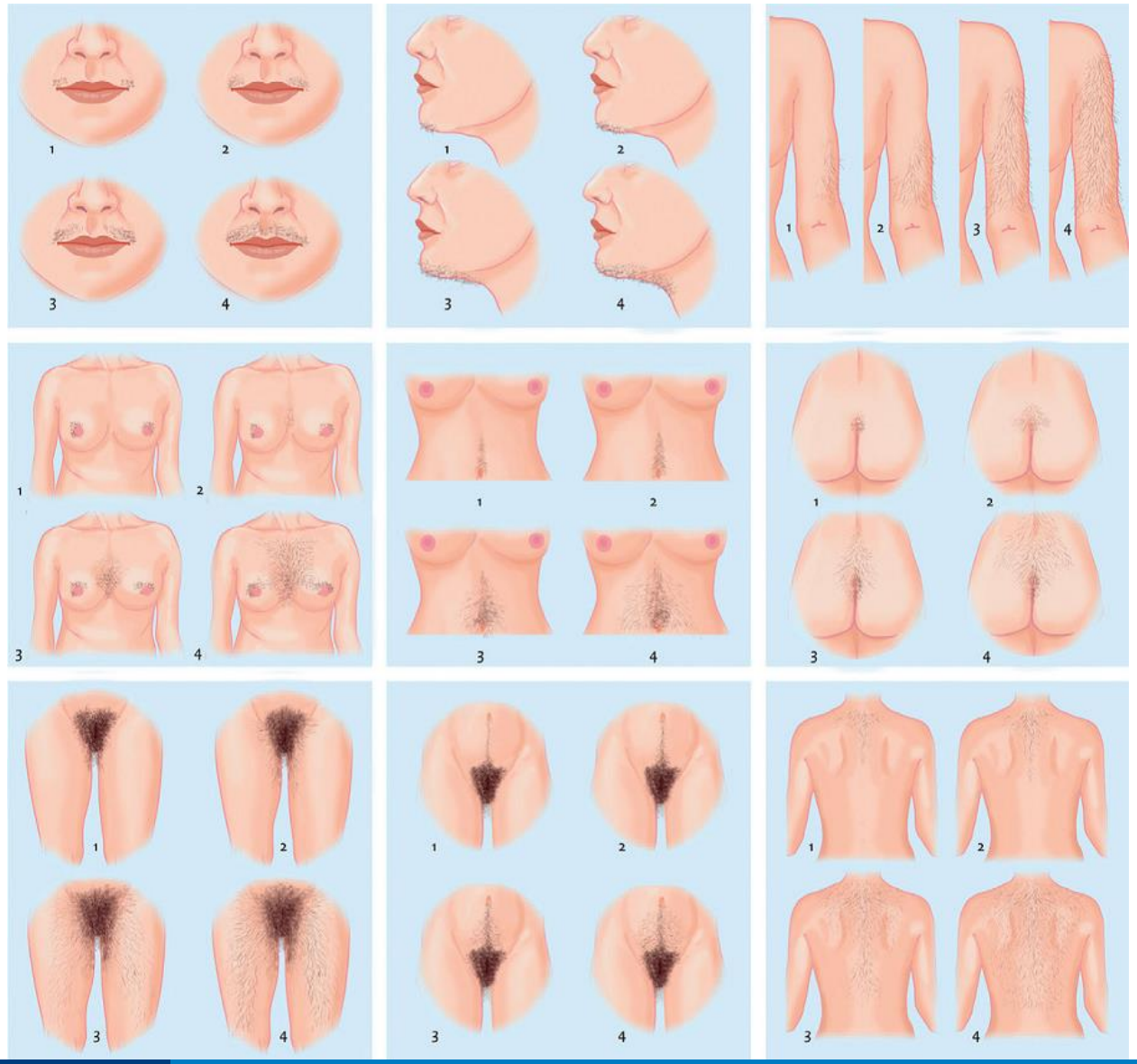
  Might be related to genetic background, to metabolic disorders or medication

Hirsutism

How many women of reproductive age are hirsute?

- 0-5%
- 5-10%
- 10-15%

Ferriman-Gallwey scores



9 body sites
Score 0-4
0 = no hair
4 = frankly virile

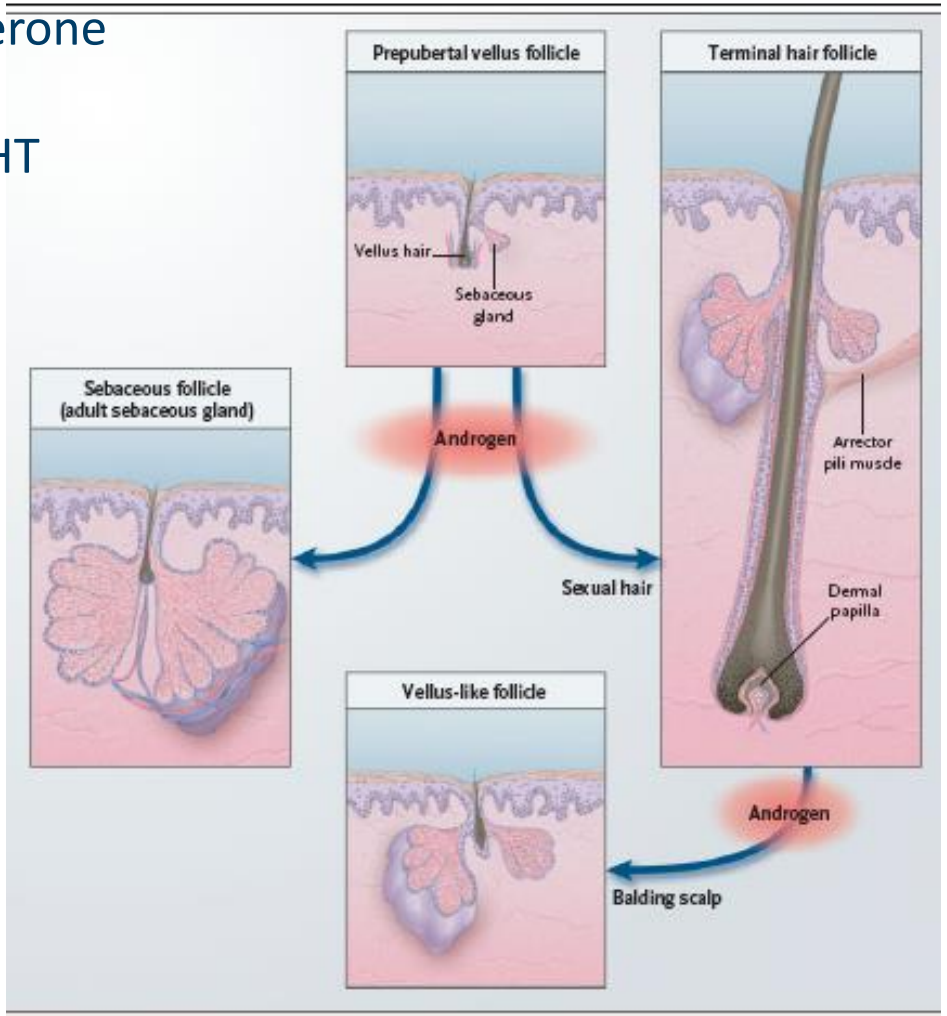
>8 = hirsutism
8-15 = mild
16-25 = moderate
>25 = severe

Physiology of hair growth

- 5 million hair follicles
- Androgens stimulate conversion of vellus hairs into terminal hairs
- Most important androgen is testosterone
  - ovaries and adrenal glands
- In the hair follicle conversion into DHT
  - by 5α reductase

- Bioactive part of testosterone is free testosterone
- Most circulating testosterone bound to SHBG

Obesity increases hyperinsulinemia and this leads to decrease in SHBG



What is most frequent cause of hirsutism?

- Idiopathic hirsutism
- Polycystic ovary syndrome (PCOS)
- Idiopathic hyperandrogenism

She gives me hope that one day I'll find a man who will look past my hirsutism and love me for who I am.

What is most frequent cause of hirsutism?

- Polycystic ovary syndrome 70-80%
  - 2/3 criteria necessary for diagnosis
  - 1 = polycystic ovaries on ultrasound
  - 2 = oligo-ovulation or anovulation
  - 3 = clinical or biochemical signs of hyperandrogenism

- Other signs and symptoms PCOS
  - Obesity
  - Acne
  - Insulin resistance
  - Infertility
  - Acanthosis nigricans
  - Female pattern hair loss

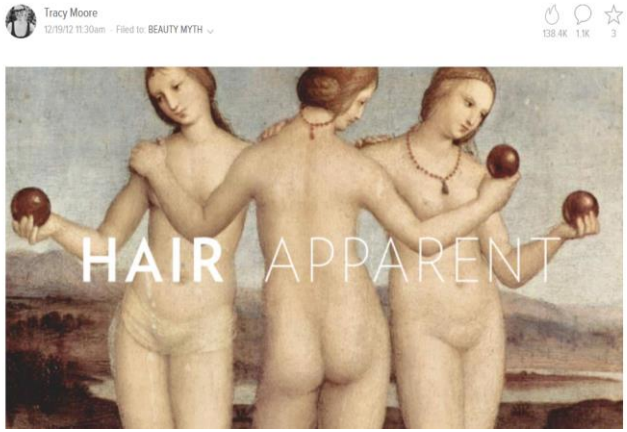
- Sudden onset hirsutism and rapid progression: CAVE ovary or adrenal tumour
- Other causes: Cushing, congenital adrenal hyperplasia, acromegaly, hyperprolactinemia, anabolic steroids, thyroid dysfunction

Impact on quality of life

- A body and face free of hair is nowadays the desired female body image
  - Less is better
  - No hair associated with femininity, beauty, hygienic, sexiness

Yakas, Laura
2009 Femininity, Sexuality, and Body Hair: The Female Body Hair(less) Ideal. Focus Anthro VIII, http://www.focusanthro.org/archive/2008-2009/yakas_0809.pdf, accessed [date accessed].

400 Years of Women Removing Their Body Hair



The last taboo: Women and body hair - Pagina 70

https://books.google.nl/books?isbn... - Vertaal deze pagina
Karin Lesnik-Oberstein - 2011 - Voorbeeld
Kristeva's theory offers an inviting explanation for the 'adult/learned' fear of the **female**/maternal **body**, and for this ... The **hairless female body** also functions as a measure of **feminine** attractiveness, both through its association with youth and ...

- Hirsutism can lead to decreased self image, low self esteem, depression, social phobia etc.

Cochrane review “Interventions for hirsutism”

- Hirsute women
- Randomised controlled trials
- All interventions except laser and intense pulsed light therapy

Primary outcomes – change from baseline

- Participant reported improvement (VAS, Likert scale)
- Quality of life
- Adverse events

Secondary outcomes – change from baseline

- Physician reported improvement (Ferriman-Gallwey, Likert scale)
- Changes in serum androgens and SHBG
- Changes in BMI
- Acne, alopecia, ovulation

Methods

Search:

- 4 electronic databases and 5 ongoing trials registries, contact experts

Twee authors independently:

- Check references for eligibility
- Risk of bias assessment
- Data extraction
- Analyse data
- Rate quality of evidence for each predefined outcome

What is GRADE ???

Grading of **R**ecommendations, **A**ssessment, **D**evelopment and **E**valuation

- Systematic and explicit approach to make judgements about *quality of evidence* and strength of recommendations
- Includes: methodological limitations, consistency of results, efficacy of interventions

GRADE used by WHO, Cochrane, NICE, and > 70 other organisations for making guidelines

- Quality of evidence: high, moderate, low or very low

Results

- 157 randomised controlled trials (RCTs), 10.550 women
- 133 comparisons (Cochrane review = 600 pages !!)
- 123/157 RCTs high risk of bias mainly due to no blinding
- Study duration between 6-12 months
- Participant assessed improvement and quality of life hardly addressed in the studies
- Assessments physician, adverse events and serum androgens reported most
- Quality of evidence **moderate to very low** for most outcomes

Results

- Lot of studies did not intend to treat hirsutism but e.g. infertility or insulin resistance

  Studies with insulin-sensitizers, gonadotropin-releasing analogues, statins, clomiphene, ovary drilling

- No studies assessed cosmetic measures such as waxing, plucking, shaving, electrolysis, bleaching, etc.

- Pooling of data limited

- Sports and diet reduced BMI and improved ovulation but did not result in clinical relevant improvement of hirsutism

Results topical treatments

Eflornithine 13.9% cream versus vehicle

- 126/395 (32%) experienced treatment success (clear, almost clear, marked improvement) versus 18/201 (9%) RR 3.56 (95% CI 2.24 - 5.66; P < 0.001)
- Also significant improvement of quality of life

Finasteride cream (0.25%-0.5%) versus vehicle

- 0.5% was not effective, 0.25% might be effective but just 8 patients included

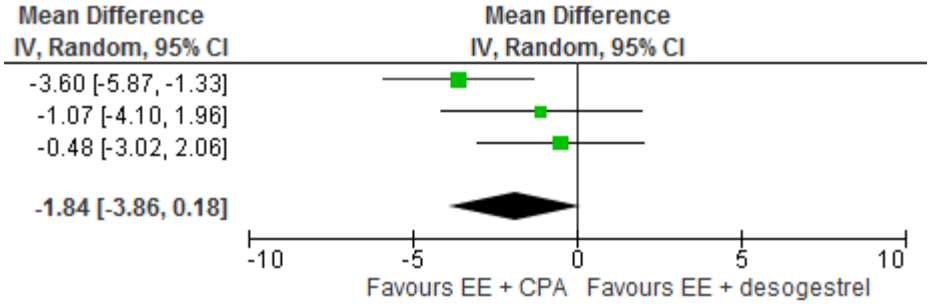
Fennel cream (1 and 2%)

- Forget it, does not work

Results oral contraceptive pills (OCPs)

- Almost all OCPs reduced Ferriman-Gallwey (FG) scores
  - However extent of reduction varied

- Only data of 3 studies (164 women) could be pooled
  - ethinyl estradiol 35 µg + cyproterone acetate 2 mg versus ethinyl estradiol 30 µg + desogestrel 0.15 mg
  - Both arms showed clinically important reductions (>7 in FG score), but difference not statistically significant

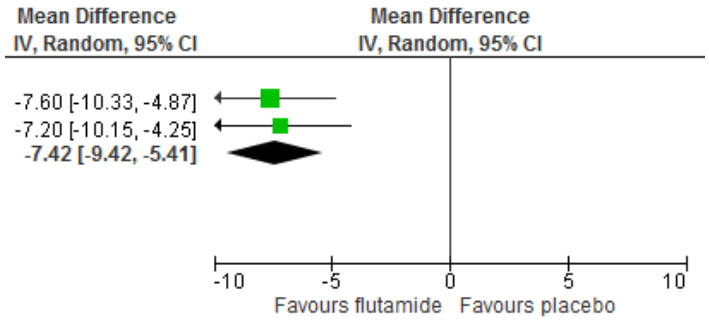


Low quality of evidence mainly due to risk of bias (no blinding) and imprecision

Results anti-androgens

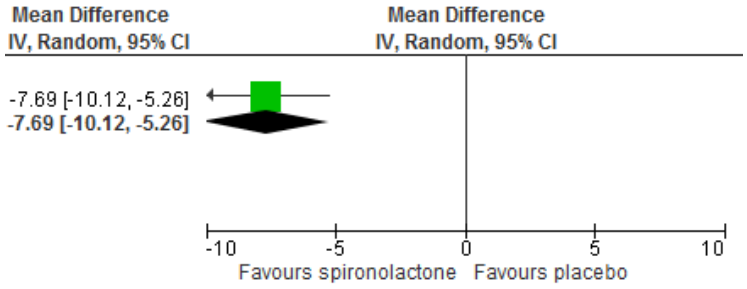
Flutamide 250 mg versus placebo

- Quality of evidence very low
  (risk of bias and very serious imprecision)



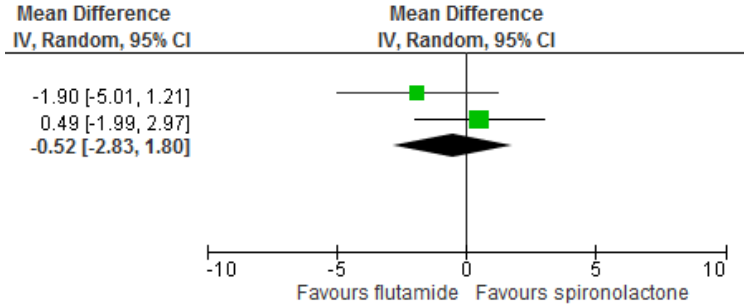
Spironolactone 100 mg versus placebo

- Quality of evidence low
  (very serious imprecision)



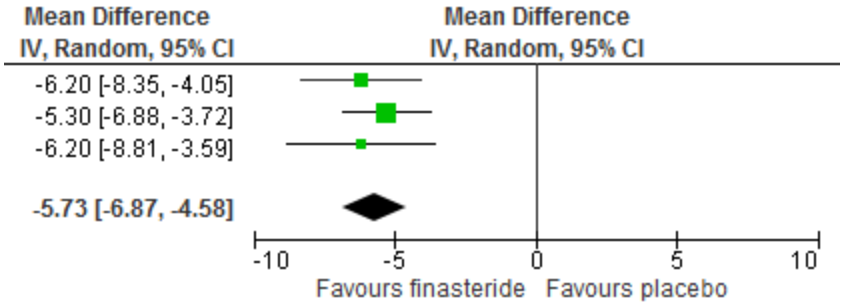
Flutamide versus spironolactone

- Quality of evidence very low
  (not blinded and very serious imprecision)



Results 5α reductase inhibitor

Finasteride 5-7.5 mg versus placebo

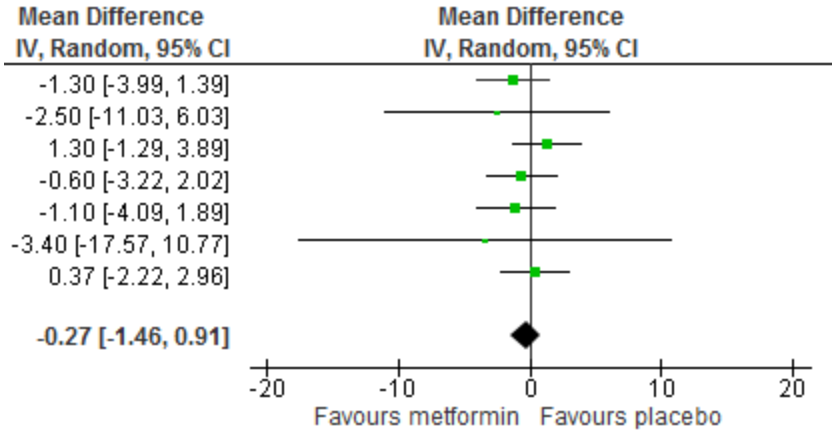


- Difference <6 in FG score not clinically relevant. Confirmed by judgements patients and in other comparisons inconsistent results
- Quality of evidence very low (risk of bias, and very serious imprecision)
- Studies that combined OCPs with cyproterone acetate 20-100 mg showed greater improvements than OCPs 'only' but studies to heterogeneous to pool

Results metformin

Metformin versus placebo

- No difference in reduction of Ferriman-Gallwey score

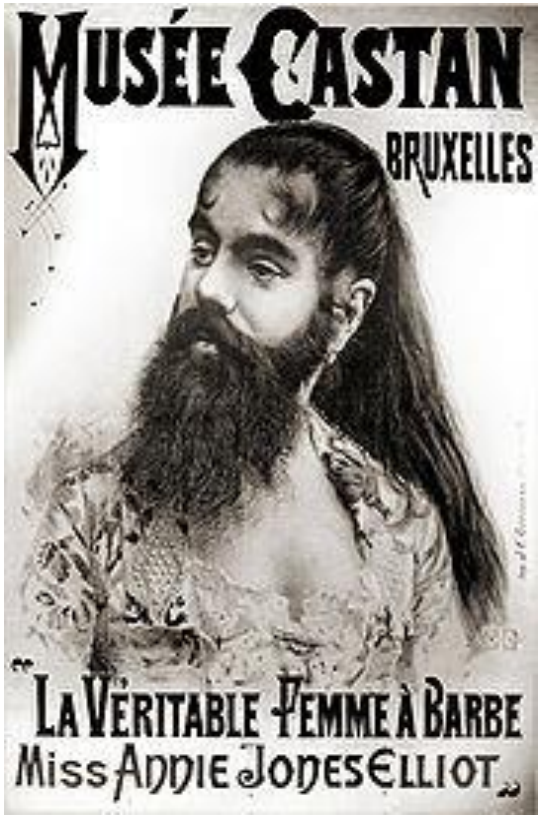


- Quality of evidence low (risk of bias, selection bias and attrition bias)

- Inconsistent results gonadotropin releasing hormone analogues, but these have serious adverse events (premature menopause)

Results of treatments with no or minimal effect

- Statins
- Arcabose, myo-inositol
- Acupuncture
- Cimetidine
- Bromocriptine
- Sibutramine
- Spearmint tea



Adverse events of treatments

-spironolactone: metrorrhagia

-flutamide, cyproterone acetate and finasteride:

reduced libido, gastro-intestinal complaints, mastalgia, dry skin, depression)

Conclusions

Treatment is never curative, chronic treatment is necessary

Results take 6-9 months before visible, therefore cosmetic measures remain necessary

Very mild hirsutism can be treated with only cosmetic measures

Otherwise treatment of hirsutism consist of ‘dual approach’:

1 reduce androgen secretion/androgen activity

2 remove hair that is already there

Conclusions regarding treatment

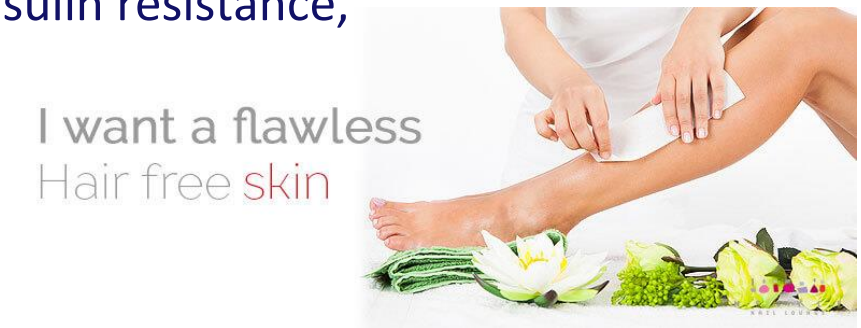
Mild hirsutism: cosmetic measures and OCPs (maybe eflornithine cream)

Moderate to severe hirsutism: cosmetic measures and OCPs + spironolactone/flutamide/cyproterone acetate (maybe finasteride)

Unclear if combination treatments are more effective than ‘mono therapy’

Only Dianette and cyproterone acetate are registered for treatment of hirsutism

By the way with 5% weight reduction, less insulin resistance, SHBG↑ and free testosterone↓ resulting in hirsutism↓



What should you do in the clinic?

- Good history taking: including family history, cycle, acne, alopecia, virilisation, kids?, drugs, weight gain?
- Physical: FG score, signs of virilisation, BMI, Cushing?
- Lab: when FG > 8, OCPs need to be stopped 3 months!
  - DHEAS (exclude production androgens by adrenal glands)
  - 17-OH progesterone (to exclude congenital adrenal hyperplasia)
  - Testosterone (excluding tumour and increased in PCOS)
  - Estradiol (E2)(increased in PCOS)
  - Progesterone (low in PCOS)
  - SHBG (low in PCOS)
  - Prolactin (slightly increased in PCOS, much increased in hyperprolactinaemia)
  - TSH (thyroid dysfunction can also induce androgen excess)

When refer?

To endocrinologist:

- Rapid progressive hirsutism < 6 months or late onset
- Signs of virilisation (cliteromegaly, low voice)
- Testosterone > 5 nmol/L
- Increased 17 OH progesterone

To gynaecologist:

- Irregular cycle
- Known to have PCOS
- Suspecting PCOS (history and lab)

Making diagnosis of PCOS important as these women are at risk for metabolic syndrome, infertility, diabetes and the sequelae need to be prevented where possible

If there is pregnancy wish: only suggest cosmetic measures

References

1. van Zuuren EJ, Fedorowicz Z, Carter B, Pandis N. Interventions for hirsutism (excluding laser and light-based therapy alone). Cochrane Database Syst Rev. 2015 Apr 28;4:CD010334
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5. Martin KA, Chang J, Ehrmann DA, Ibanez L, Lobo RA, Rosenfield RL, et al. Evaluation and treatment of hirsutism in premenopausal women: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metabol 2008;93(4):1105-20

1. + > 200 other references, to be found in ref 1

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