Hyperandrogenism in Primary Care

Dr Wan Aizad Wan Mahmood
Consultant Endocrinologist and Diabetes
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THIS IS MODERN MEDICINE

Outlines

1. Definition
2. History
3. Clinical examinations
4. Differential diagnoses
5. Clinical algorithm
6. Biochemistry testing
7. Treatment (probably at next study day)

Guidelines

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INVITED REVIEW

WILEY

Approach to androgen excess in women: Clinical and biochemical insights

Leanne Cussen[1,2] | Tara McDonnell[1,2] | Gillian Bennett[2] | Christopher J. Thompson[1,2] | Mark Sherlock[1,2] | Michael W. O'Reilly[1,2]

Evaluation and Treatment of Hirsutism in Premenopausal Women: An Endocrine Society* Clinical Practice Guideline

Kathryn A. Martin,[1] R. Rox Anderson,[1] R. Jeffr
Rogerio A. Lobo,[4] M. Hassan Murad,[5] Michel M.

[1]Massachusetts General Hospital, Boston, Massachusetts 021
Jolla, California 92037; [3]University of Chicago, Chicago, Illinc
New York 10032; [5]Mayo Clinic Evidence-Based Practice Cent
[6]Hospices Civils de Lyon, Bron, France F-69677

*Co-Sponsoring Associations: Androgen Excess and Polycystic Ovary Syndrome Society and European Society of Endocrinology.

Recommendations From the 2023 International Evidence-based Guideline for the Assessment and Management of Polycystic Ovary Syndrome*

Helena J. Teede,[1,2] Chau Thien Tay,[1,2] Joop J. E. Laven,[2,3] Anuja Dokras,[4] Lisa J. Moran,[1,2] Terhi T. Piltonen,[5] Michael F. Costello,[2,6] Jacky Boivin,[7] Leanne M. Redman,[8] Jacqueline A. Boyle,[2,9] Robert J. Norman,[2,10] Aya Mousa,[1] and Anju E. Joham;[1,2] on behalf of the International PCOS Network†

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Definition

Clinical or biochemical evidence of elevated androgenic steroids in women

History: Key component

- Severity and duration – long-standing mild to moderate symptoms (PCOS) vs rapid virilization (non-PCOS).
- Modified Ferriman-Gallwey Index (mFG) → confounded by cosmetic measure.
- How much time spent removing hair from face, trunk and limbs – severity of hirsutism.
- Acne – highly prevalent in non-hyperandrogenic women, especially adolescence (15 to 20%)

History: Key component

- Oligomenorrhoea? – menses > 35 days apart OR < 8 periods/year)
- CV risk factors? – Obesity, smoking, dyslipidaemia, hypertension, glucose intolerances.
- Family ? – CAH, severe insulin resistant syndromes, IGT or PCOS
- Fertility plans? Current priority?
- Overt virilization? – Clitoral enlargement or deep voice

mFG Score

- 9 body regions
- Terminal hair growth
- Score 0 to 4

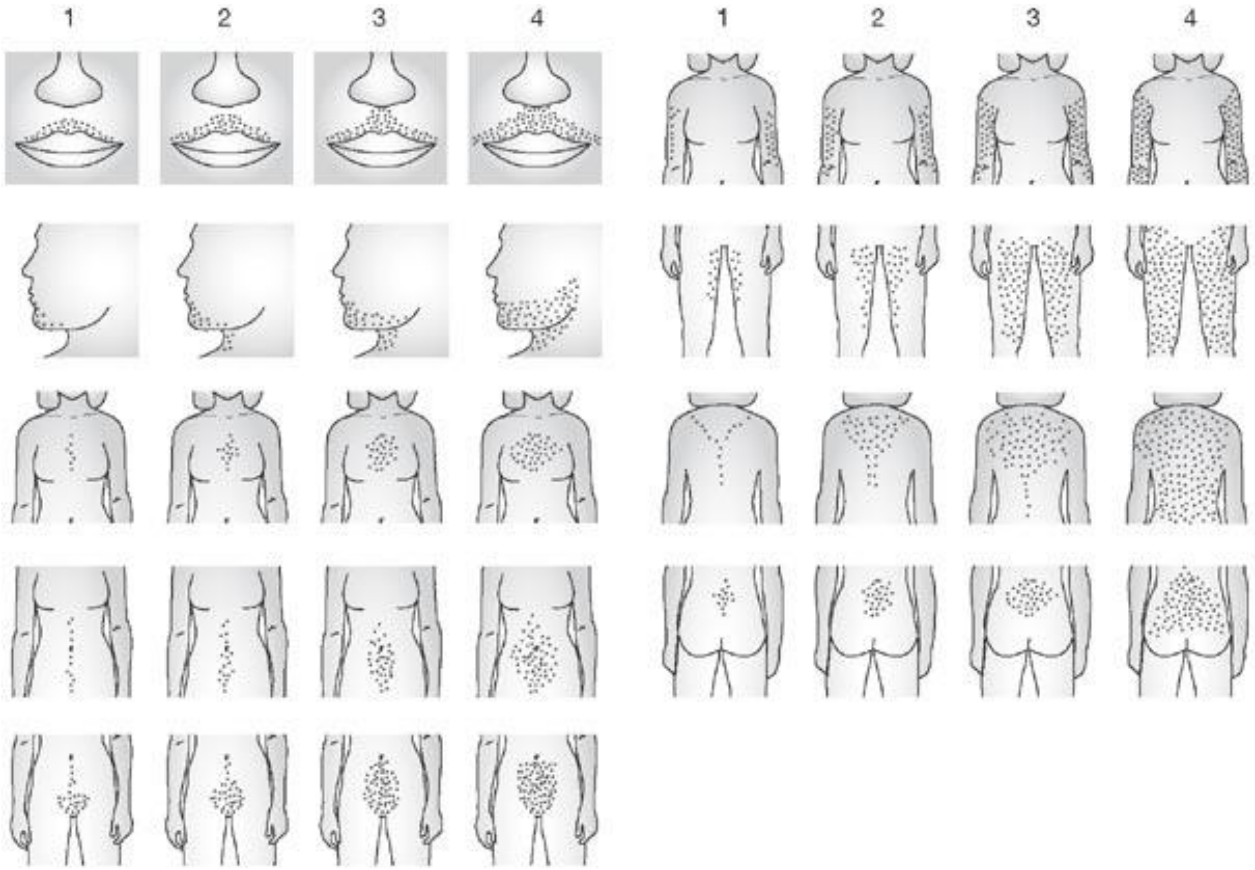
Results

≥ 8 : androgen excess

8-15: mild hirsutism

>15 : moderate or severe hirsutism

? Acne/alopecia



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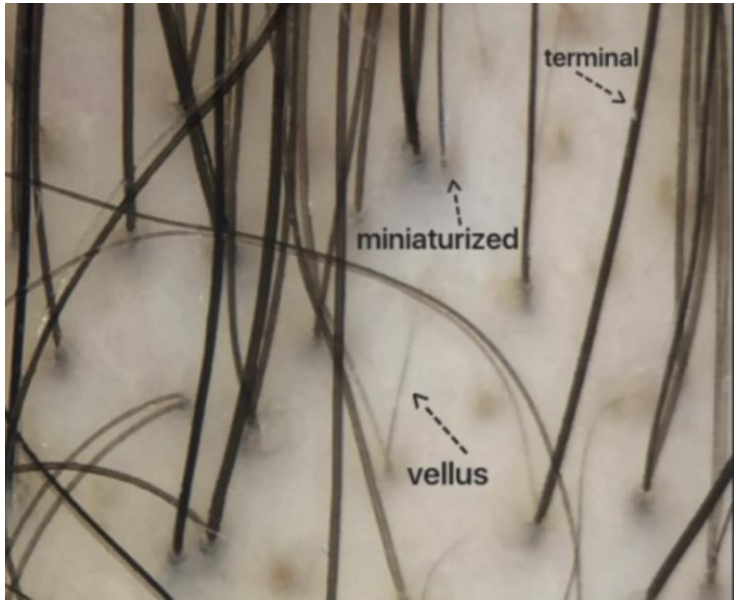
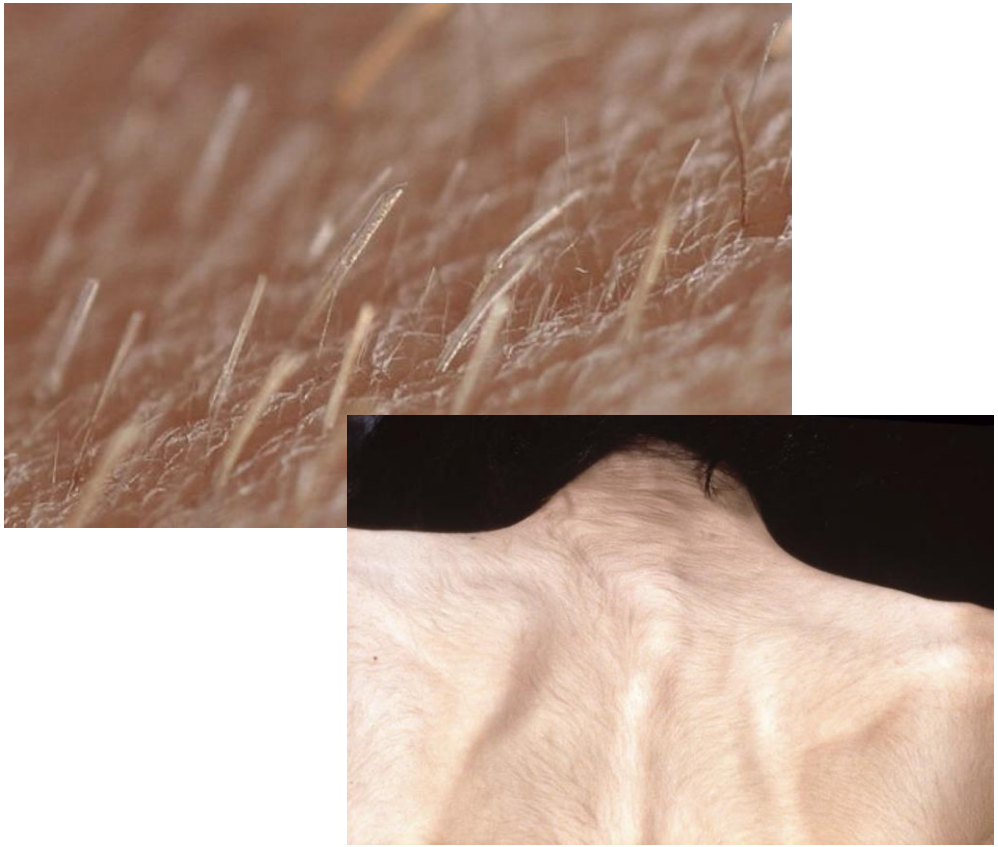
Terminal hair vs Velus hair vs Lanugo hair





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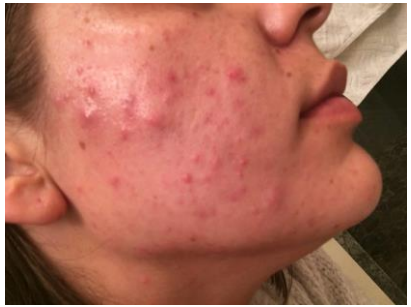
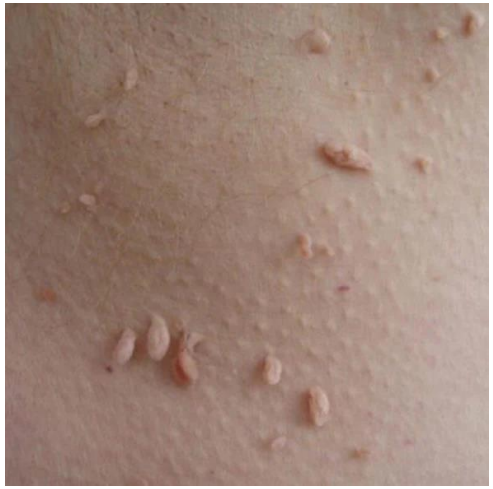
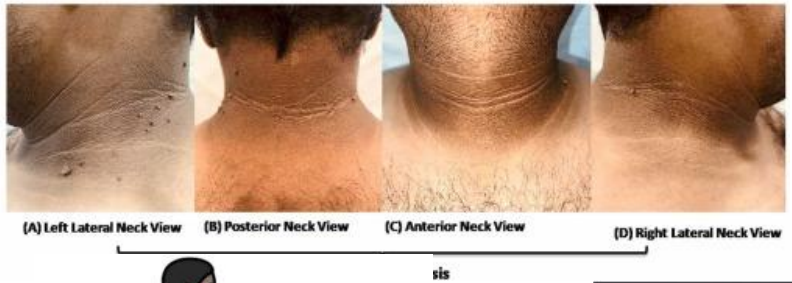
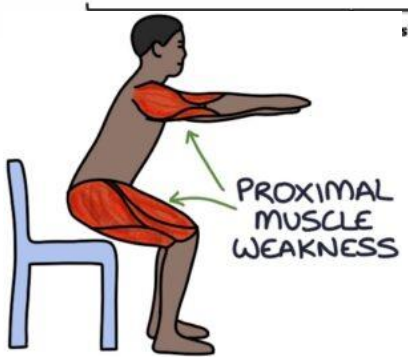
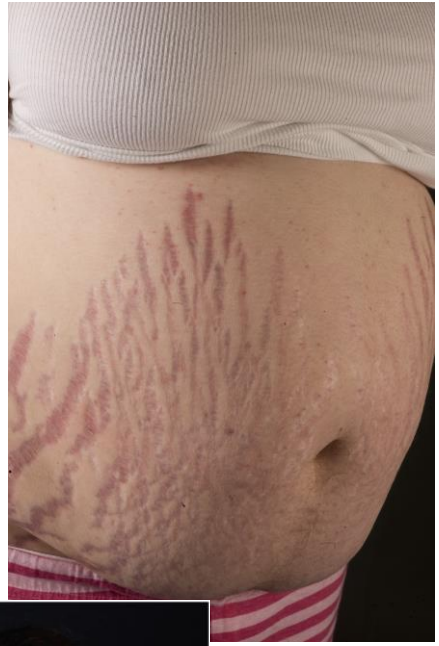
Key Examinations

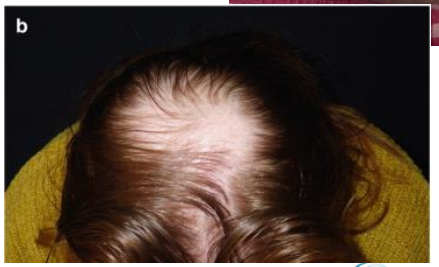












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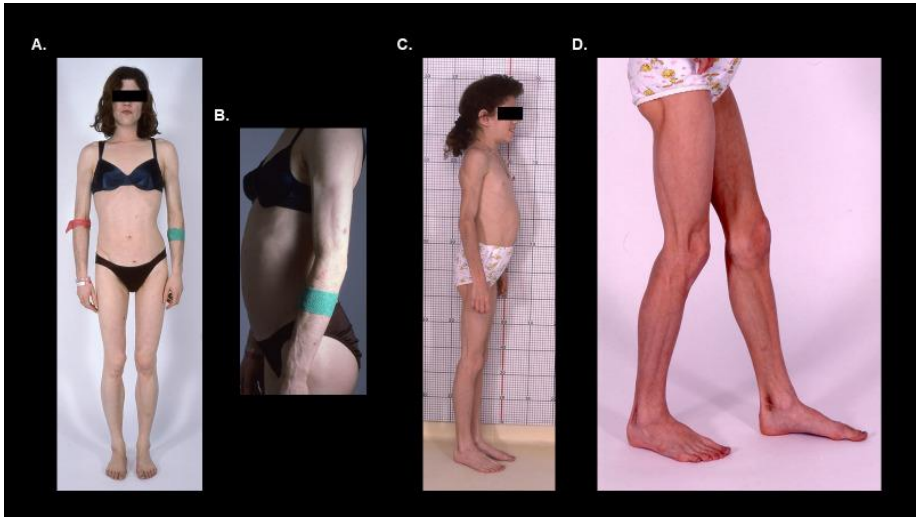
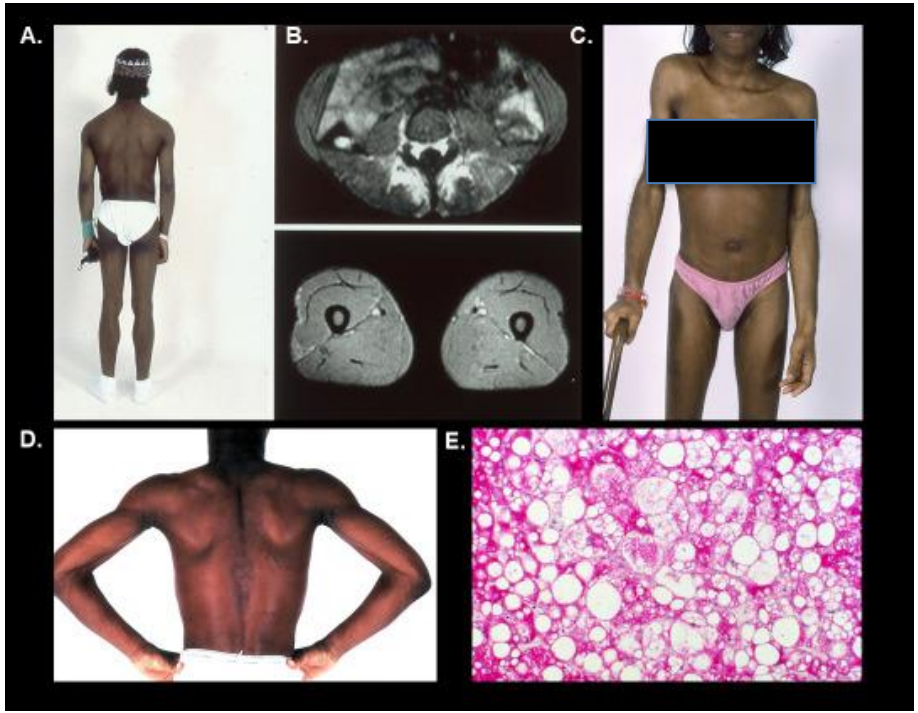
Key Examinations (Syndrome Severe Insulin Resistant, SIR)





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Differential Diagnoses

- PCOS
  - Vast majority. 10% of all women. Typical onset 15 to 25 yo.
  - Caution in adolescent phase – transient irregular cycles that subsequently normalize
  - TV US if oligomenorrhea (not appropriate for younger girls with hymen intacta)
  - Mild-moderate ↑ T, A4 and/or DHEAS
  - If regular period, no PCOS morphology (US) = consider idiopathic hirsutism/androgen excess

Ultrasound PCOS Morphology

1.4		Ultrasound and polycystic ovarian morphology	
1.4.1	EBR	Follicle number per ovary (FNPO) should be considered the most effective ultrasound marker to detect polycystic ovarian morphology (PCOM) in adults.	❖❖❖❖ ⊕⊕◯◯
1.4.2	EBR	Follicle number per ovary (FNPO), follicle number per cross-section (FNPS), and ovarian volume (OV) should be considered accurate ultrasound markers for PCOM in adults.	❖❖❖❖ ⊕⊕◯◯
1.4.3	CR	PCOM criteria should be based on follicle excess (FNPO, FNPS) and/or ovarian enlargement.	❖❖❖❖
1.4.4	CR	Follicle number per ovary (FNPO) ≥ 20 in at least 1 ovary should be considered the threshold for PCOM in adults.	❖❖❖❖
1.4.5	CR	Ovarian volume (OV) ≥ 10 mL or follicle number per section (FNPS) ≥ 10 in at least 1 ovary in adults should be considered the threshold for PCOM if using older technology or image quality is insufficient to allow for an accurate assessment of follicle counts throughout the entire ovary.	❖❖❖❖
1.4.6	PP	There are no definitive criteria to define polycystic ovary morphology (PCOM) on ultrasound in adolescents; hence, it is not recommended in adolescents.	
1.4.7	PP	When an ultrasound is indicated, if acceptable to the individual, the transvaginal approach is the most accurate for the diagnosis of PCOM.	
1.4.8	PP	Transabdominal ultrasound should primarily report ovarian volume (OV) with a threshold of ≥10 mL or follicle number per section (FNPS) ≥ 10 in either ovary in adults given the difficulty of assessing follicle counts throughout the entire ovary with this approach.	
1.4.9	PP	In patients with irregular menstrual cycles and hyperandrogenism, an ovarian ultrasound is not necessary for PCOS diagnosis.	
1.4.10	PP	Thresholds for PCOM should be revised regularly with advancing ultrasound technology, and age-specific cut-off values for PCOM should be defined.	
1.4.11	PP	There is a need for training in careful and meticulous follicle counting per ovary, and clear standardized protocols are recommended for PCOM reporting on ultrasound including at a minimum the following: • Last menstrual period (or stage of cycle). • Transducer bandwidth frequency. • Approach/route assessed. • Total number of 2-9 mm follicles per ovary. • Measurements in 3 dimensions (in cm) or volume of each ovary.	

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Differential Diagnoses

- NCCAH
  - 20 to 70% of residual activity 21-hydroxylase enzyme
  - Less severe than classic CAH : less severe phenotype, adrenal androgen excess, preserved GC and MC production
  - Indistinguishable from PCOS
  - Fhx of consanguinity
  - 17 hydroxyprogesterone (17-OHP) screening. If between 5 to 12 nmol/L – need synacthen test

Differential Diagnoses

- Adrenocortical carcinoma (ACC)
  - Rare malignant tumour adrenal cortex (0.2/million/year)
  - Severe androgen excess, rapid onset, including virilization
  - DHEAS > 20 µmol/L
  - Co-secretion Cortisol (Cushingoid)

Differential Diagnoses

- Cushing's disease
  - 1-4% pre and post menopausal women with androgen excess
  - Violaceous abdominal striae, proximal weakness, bruising, osteoporosis, hypertension.
  - ↓ LH, FSH and Oestradiol
  - ↑ DHEAS and A4 (due to autonomous ACTH)
  - Misdiagnosis with PCOS in many cases
  - Overnight DST screening test

Differential Diagnoses

- Ovarian hyperthecosis (OHT)
  - Overproduction androgen from ovarian stromal cells
  - Ovarian stromal hyperplasia.
  - Majority postmenopausal, with gradual and severe androgen excess, with or without virilization.
  - ↑ testosterone with relatively normal adrenal androgen

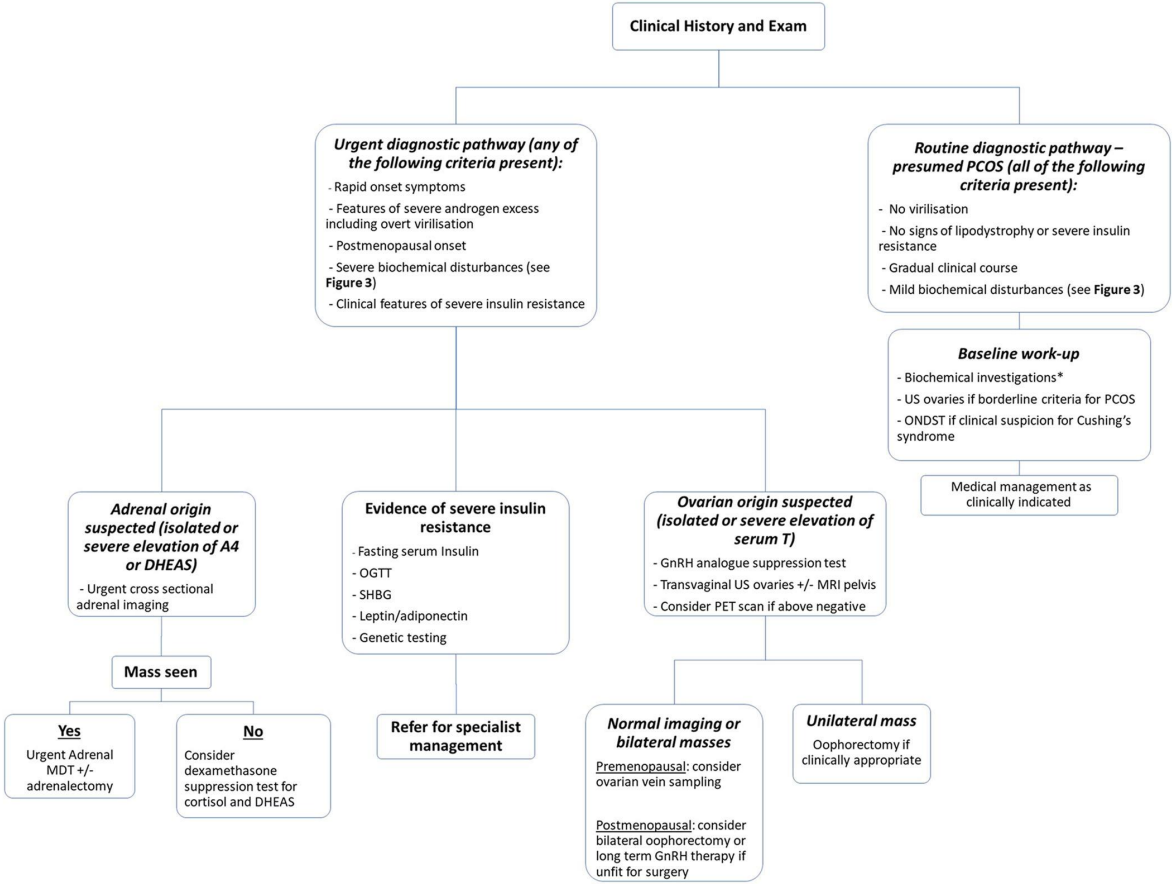
Differential Diagnoses

- Virilizing ovarian tumours
  - Severe androgen excess, with virilizing in 50%, rapid onset.
  - 5% of all ovarian tumours.
  - Can be indistinguishable to ovarian hyperthecosis
  - Serum T between 6 to 20 nmol/L

Differential Diagnoses

- Syndromes of Severe Insulin Resistance (SIR)
  - Monogenic disorders
  - Severe hyperinsulinaemia drives ovarian androgen with pituitary LH
  - Acanthosis nigricans, strong fhx T2D, normal BMI
  - Fasting insulin > 150 pmol/L and peak insulin > 1500 pmol/L (OGTT)
  - ↑ T > 10 nmol/L

Overall Clinical Approach



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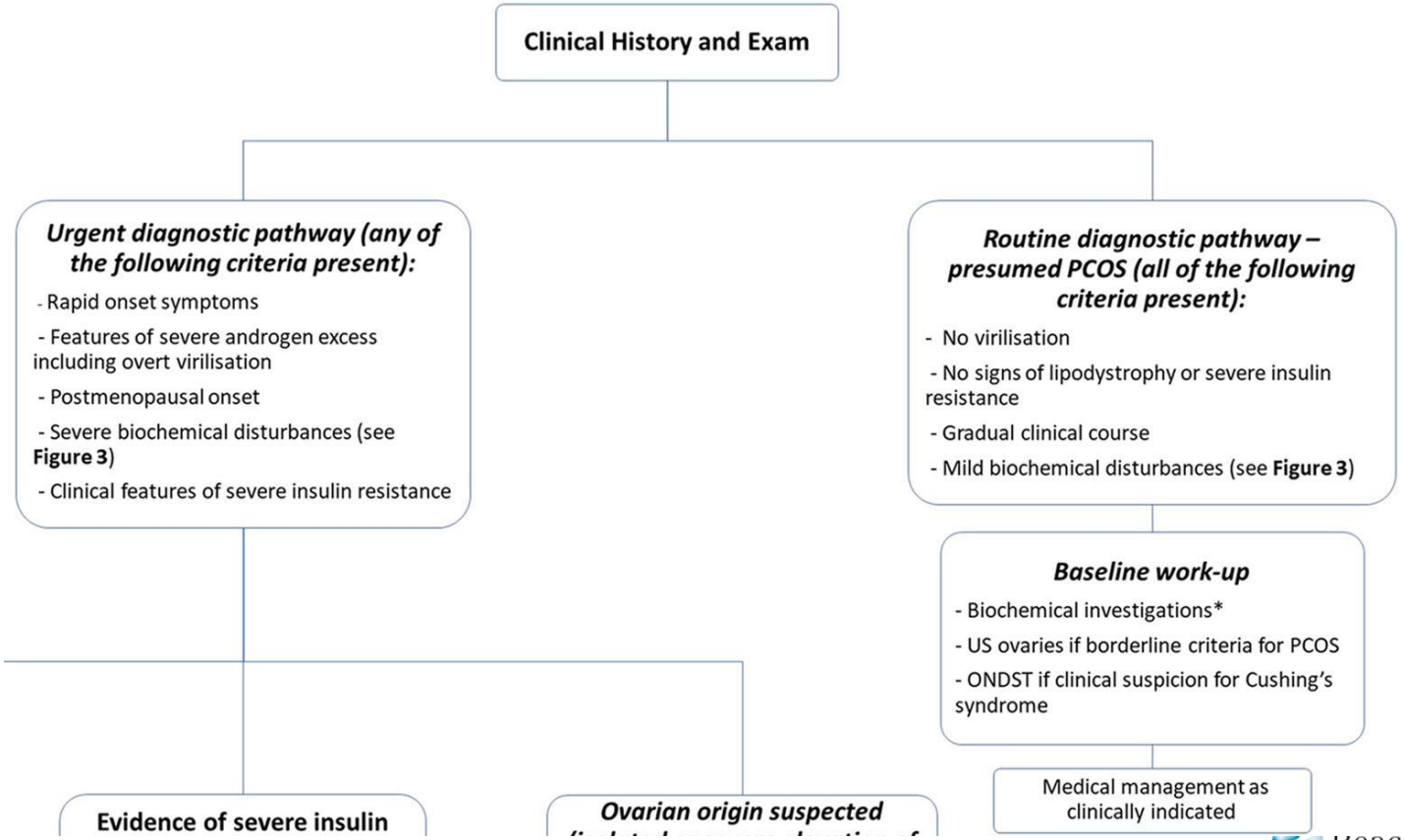
Clinical Approach Primary Care



Biochemistry

- Baseline reproductive profiles – FSH, LH, Oestradiol, 17-OHP, T, SHBG, DHEAS, A4, Prolactin, TFT.
- Early morning, day 2 to 5 of menstrual cycle (if possible)
- If on OCP, need 3/12 washout prior to androgen testing
- Consider : HbA1c, lipid profiles
- Total testosterone
  - Need SHBG to calculate FAI. Please send SHBG.
  - Reflective ovarian androgen.
  - < 5nmol/L = no need adnexal or adrenal imaging

Biochemistry

- Androstenedione (A4)
  - Produced by both ovary and adrenals
  - >15 nmol/L = CAH or ACC
  - > 10 nmol/L + postmenopausal = ACC
- DHEAS
  - Adrenal androgen
  - Severe elevation in premenopausal women likely PCOS. If postmenopausal, think of ACC.
  - > 20 µmol/L + premenopausal = image adrenal
  - > 5 µmol/L + postmenopausal = image adrenal

Summary

- Highlights key history – severity, onset, virilization
- mFG score, purple striae, rapid weight gain, acne, alopecia
- PCOS (majority) but consider others – NCCAH, Cushings, ACC, Ovarian tumour or hyperthecosis, Severe SIR syndrome
- Urgent vs routine pathway
- Basic biochem – FSH, LH, Oestradiol, 17-OHP, T, SHBG, DHEAS, A4, Prolactin, TFT. Early morning, day 2 to 5 of menstrual cycle (if possible)

Thank you

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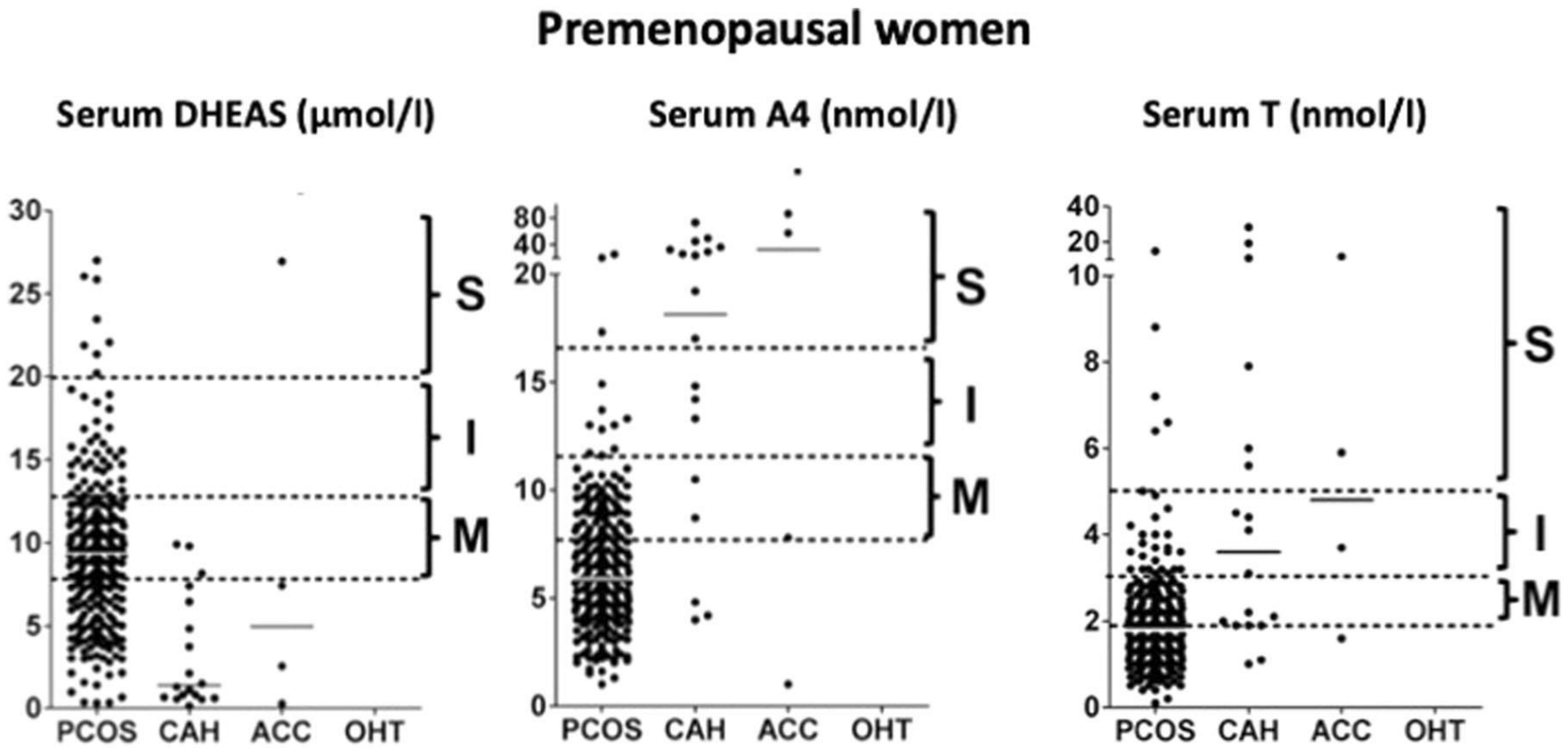
Extra Slides

Severity Androgen Excess Premenopausal



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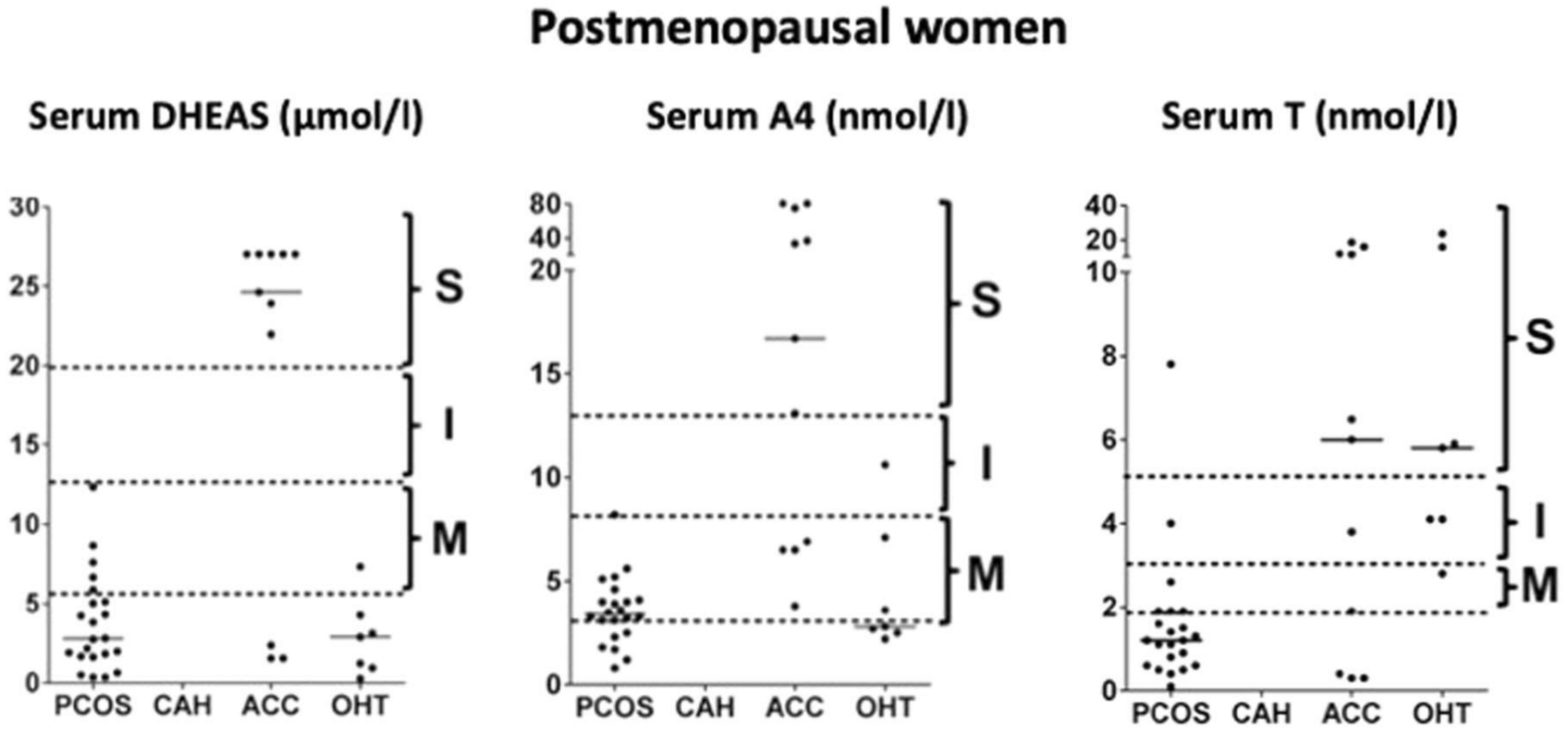
Severity Androgen Excess Postmenopausal



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AMH to characterize PCOS Morphology

1.5		**Anti-Müllerian hormone in the diagnosis of PCOS**	
1.5.1	EBR	Serum anti-Müllerian hormone (AMH) could be used for defining PCOM in adults.	❖❖❖ ⊕⊕⊕◯
1.5.2	EBR	Serum AMH should only be used in accordance with the diagnostic algorithm, noting that in patients with irregular menstrual cycles and hyperandrogenism, an AMH level is not necessary for PCOS diagnosis.	❖❖❖❖ ⊕⊕⊕◯
1.5.3	EBR	We recommend that serum AMH should not be used as a single test for the diagnosis of PCOS.	❖❖❖❖ ⊕⊕⊕◯
1.5.4	EBR	Serum AMH should not yet be used in adolescents.	❖❖❖❖ ⊕⊕⊕◯
1.5.5	PP	Either serum AMH or ultrasound may be used to define PCOM; however, both tests should not be performed to limit over-diagnosis.	
1.5.6	PP	Laboratories and healthcare professionals need to be aware of factors that influence AMH in the general population including the following: • Age: Serum AMH generally peaks between the ages of 20-25 years in the general population. • Body mass index (BMI): Serum AMH is lower in those with higher BMI in the general population. • Hormonal contraception and ovarian surgery: Serum AMH may be suppressed by current or recent COCP use. • Menstrual cycle day: Serum AMH may vary across the menstrual cycle.	
1.5.7	PP	Laboratories involved in AMH measurements in females should use population- and assay-specific cut-offs.	

Combined OCP in PCOS

4.2		Combined oral contraceptive pills	
4.2.1	EBR	Combined oral contraceptive pills (COCP) could be recommended in reproductive age adults with PCOS for management of hirsutism and/or irregular menstrual cycles.	❖❖❖ ⊕◯◯◯
4.2.2	EBR	The COCP could be considered in adolescents at risk or with a clear diagnosis of PCOS for management of hirsutism and/or irregular menstrual cycles.	❖❖❖ ⊕◯◯◯
4.2.3	EBR	Healthcare professionals could consider that there is no clinical advantage of using high-dose ethinylestradiol (≥30 μg) versus low-dose ethinylestradiol (<30 μg) when treating hirsutism in adults with PCOS.	❖❖❖ ⊕◯◯◯
4.2.4	EBR	General population guidelines should be considered when prescribing COCP in adults and adolescents with PCOS as specific types or doses of progestins, oestrogens, or combinations of COCP cannot currently be recommended.	❖❖❖ ⊕◯◯◯
4.2.5	EBR	The 35 μg ethinyl oestradiol plus cyproterone acetate preparations should be considered as second-line therapy over other COCPs, balancing benefits and adverse effects, including venous thromboembolic risks.	❖❖❖ ⊕◯◯◯
4.2.6	EBR	Progestin only oral contraceptives may be considered for endometrial protection, based on general population guidelines, acknowledging that evidence in women with PCOS is limited.	❖❖❖ ⊕◯◯◯
4.2.7	PP	When prescribing COCPs in adults and adolescents with PCOS and adolescents at risk of PCOS • It is important to address main presenting symptoms and consider other treatments such as cosmetic therapies. • Shared decision-making (including accurate information and reassurance on the efficacy and safety of COCP) is recommended and likely to improve adherence. • Natural oestrogen preparations and the lowest effective oestrogen doses (such as 20-30 μg of ethinyl oestradiol or equivalent) need consideration, balancing efficacy, metabolic risk profile, side effects, cost, and availability. • The relatively limited evidence on COCPs specifically in PCOS needs to be appreciated with practice informed by general population guidelines. • The relative and absolute contraindications and side effects of COCPs need to be considered and be the subject of individualized discussion. • PCOS-specific features, such as higher weight and cardiovascular risk factors, need to be considered.	

Metformin in PCOS

4.3		**Metformin**	
4.3.1	EBR	Metformin alone should be considered in adults with PCOS and a BMI ≥ 25 kg/m^2 for anthropometric and metabolic outcomes including insulin resistance, glucose, and lipid profiles.	❖❖❖ ⊕◯◯◯
4.3.2	EBR	Metformin alone could be considered in adolescents at risk of or with PCOS for cycle regulation, acknowledging limited evidence.	❖❖❖ ⊕◯◯◯
4.3.3	CR	Metformin alone may be considered in adults with PCOS and BMI < 25 kg/m^2, acknowledging limited evidence.	❖❖❖
4.3.4	PP	Where metformin is prescribed, the following need to be considered: • Shared decision-making needs to consider feasibility and effectiveness of active lifestyle intervention. Women should be informed that metformin and active lifestyle intervention have similar efficacy. • Mild adverse effects, including gastrointestinal side-effects, are generally dose dependent and self-limiting. • Starting at a low dose, with 500 mg increments 1-2 weekly and extended-release preparations, may minimize side effects and improve adherence. • Suggested maximum daily dose is 2.5 g in adults and 2 g in adolescents. • Use appears safe long term, based on use in other populations; however, indications for ongoing requirement need to be considered. • Use may be associated with low vitamin B12 levels, especially in those with risk factors for low vitamin B12 (eg, diabetes, post bariatric/metabolic surgery, pernicious anaemia, and vegan diet), where monitoring should be considered.	

5.4		**Clomiphene citrate and metformin**	
5.4.1		*Metformin versus placebo*	
5.4.1.1	EBR	Metformin could be used alone, in women with PCOS with anovulatory infertility and no other infertility factors, to improve clinical pregnancy and live birth rates, whilst informing women that there are more effective ovulation agents.	❖❖❖ ⊕⊕◯◯

Metformin and Combined OCP in PCOS

4.4		**Metformin and combined oral contraceptive pills**	
4.4.1	EBR	COCP could be used over metformin for management of hirsutism in irregular menstrual cycles in PCOS.	❖❖❖ ⊕◯◯◯
4.4.2	EBR	Metformin could be used over COCP for metabolic indications in PCOS.	❖❖❖ ⊕◯◯◯
4.4.3	EBR	The combination of COCP and metformin could be considered to offer little additional clinical benefit over COCP or metformin alone, in adults with PCOS with a BMI $\leq$ 30 kg/m^2.	❖❖❖ ⊕◯◯◯
4.4.4.	PP	In combination with the COCP, metformin may be most beneficial in high metabolic risk groups including those with a BMI > 30 kg/m^2, diabetes risk factors, impaired glucose tolerance, or high-risk ethnic groups.	
4.4.5	PP	Where COCP is contraindicated, not accepted, or not tolerated, metformin may be considered for irregular menstrual cycles. For hirsutism, other interventions may be needed.	

Anti-Obesity in PCOS

4.5		Anti-obesity pharmacological agents	
4.5.1	CR	Anti-obesity medications, including liraglutide, semaglutide, and both glucagon-like peptide-1 (GLP-1) receptor agonists and orlistat, could be considered, in addition to active lifestyle intervention, for the management of higher weight in adults with PCOS as per general population guidelines.	❖❖❖

No.	Type	Recommendation	Grade/quality
4.5.2	PP	Healthcare professionals should ensure concurrent effective contraception when pregnancy is possible for women who take GLP-1 receptor agonists, as pregnancy safety data are lacking.	
4.5.3	PP	Gradual dose escalation for GLP-1 receptor agonists is recommended to reduce gastrointestinal adverse effects.	
4.5.4	PP	Shared decision-making, when discussing GLP-1 receptor agonist use with women with PCOS, needs to consider side effects and the potential need for long-term use in weight management, given the high risk for weight regain after discontinuation and the lack of long-term safety data.	