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Clinical Practice Guideline

Recommendations from the 2023 international evidence-based guideline for the assessment and management of polycystic ovary syndrome

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Table 1. Categories of PCOS guideline recommendations.

EBR	Evidence-based recommendations: evidence sufficient to inform a recommendation made by the guideline development group.
CR	Consensus recommendations: In the absence of adequate evidence, a consensus recommendation has been made by the guideline development group, also informed by evidence from the general population.
PP	Practice points: Evidence not sought. A practice point has been made by the guideline development group where important issues arose from discussion of evidence-based or consensus recommendations.

Table 2. Quality (certainty) of evidence categories (adapted from GRADE).

High	⨁⨁⨁⨁	Very confident that the true effect lies close to that of the estimate of the effect.
Moderate	⨁⨁⨁◯	Moderate confidence in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is different.
Low	⨁⨁◯◯	Limited confidence in the effect estimate. The true effect may be substantially different from the estimate of the effect.
Very Low	⨁◯◯◯	Very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of the effect.

Table 3. The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework recommendation strength.

❖	Conditional recommendation against the option.
❖❖	Conditional recommendation for either the option or the comparison.
❖❖❖	Conditional recommendation for the option.
❖❖❖❖	Strong recommendation for the option.

No.	Type	Recommendation	Grade/quality
1		*Screening, diagnostic and risk assessment, and life stages*	
		General principles	
	PP	All diagnostic assessments are recommended for use in accordance with the diagnostic algorithm (Algorithm 1).	
1.1		**Irregular cycles and ovulatory dysfunction**	
1.1.1	CR	Irregular menstrual cycles are defined as follows: • Normal in the first year post menarche as part of the pubertal transition. • 1 to <3 years post menarche: <21 or >45 days. • 3 years post menarche to perimenopause: <21 or >35 days or <8 cycles per year. • 1 year post menarche >90 days for any 1 cycle. • Primary amenorrhoea by age 15 or >3 years post thelarche (breast development). When irregular menstrual cycles are present, a diagnosis of PCOS should be considered and assessed according to these PCOS Guidelines.	❖❖❖❖

Diagnostic algorithm in Polycystic ovary syndrome (PCOS)

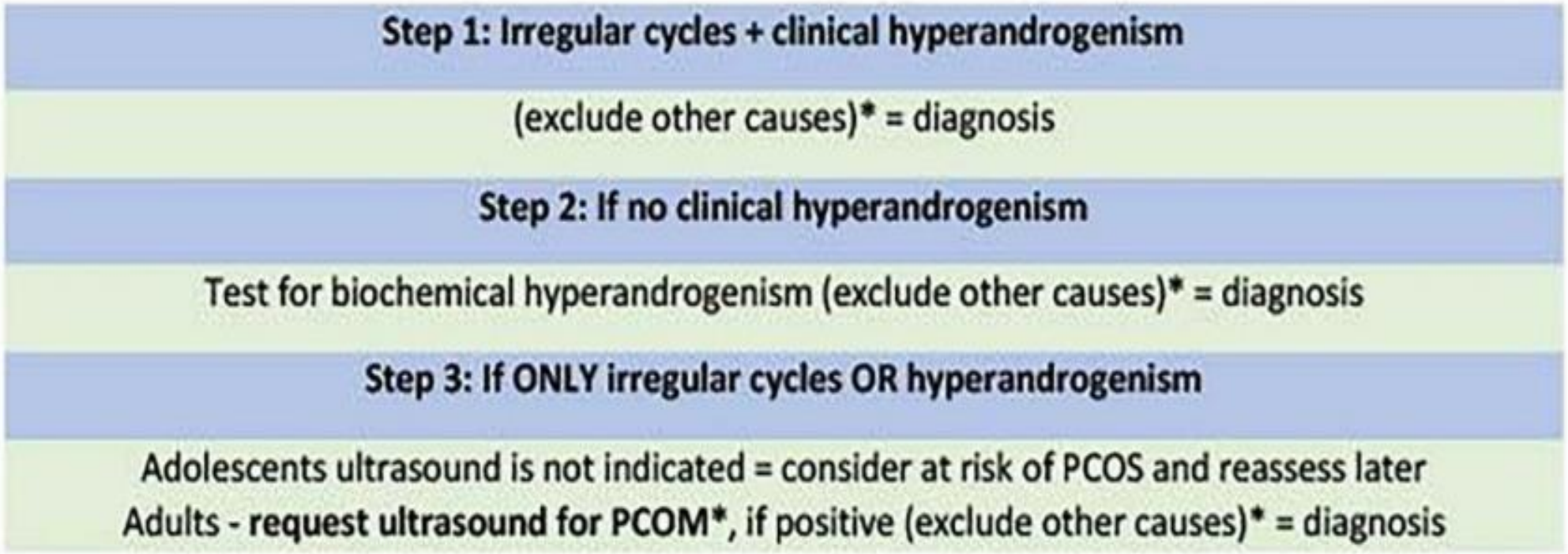


Figure 1. Algorithm 1—diagnostic algorithm for polycystic ovary syndrome (PCOS). *Exclusion of other causes = TSH, prolactin, 17-OH progesterone, FSH or others if clinically indicated (eg, Cushing's syndrome, adrenal tumours)

1.1.2	PP	The mean age of menarche may differ across populations.
1.1.3	PP	In adolescents with irregular menstrual cycles, the value and optimal timing of assessment and diagnosis of PCOS should be discussed with the patient and their parent/s or guardian/s, considering diagnostic challenges at this life stage and psychosocial and cultural factors.
1.1.4	PP	For adolescents who have features of PCOS, but do not meet diagnostic criteria, an "increased risk" could be considered and reassessment is advised at or before full reproductive maturity, 8 years post menarche. This includes those with PCOS features before combined oral contraceptive pill (COCP) commencement, those with persisting features, and those with significant weight gain in adolescence.
1.1.5	PP	Ovulatory dysfunction can still occur with regular cycles, and if anovulation needs to be confirmed, serum progesterone levels can be measured.

1.2		Biochemical hyperandrogenism	
1.2.1	EBR	Healthcare professionals should use total and free testosterone to assess biochemical hyperandrogenism in the diagnosis of PCOS; free testosterone can be estimated by the calculated free androgen index.	❖❖❖❖ ⊕◯◯◯
1.2.2	EBR	If testosterone or free testosterone is not elevated, healthcare professionals could consider measuring androstenedione and dehydroepiandrosterone sulfate (DHEAS), noting their poorer specificity and greater age-associated decrease in DHEAS.	❖❖❖ ⊕◯◯◯
1.2.3	EBR	Laboratories should use validated, highly accurate tandem mass spectrometry (LC-MS/MS) assays for measuring total testosterone and if needed, for androstenedione and DHEAS. Free testosterone should be assessed by calculation, equilibrium dialysis, or ammonium sulfate precipitation.	❖❖❖❖ ⊕⊕◯◯
1.2.4	EBR	Laboratories should use LC-MS/MS assays over direct immunoassays (eg, radiometric and enzyme linked) for assessing total or free testosterone, which have limited accuracy and demonstrate poor sensitivity and precision for diagnosing hyperandrogenism in PCOS.	❖❖❖❖ ⊕⊕◯◯
1.2.5	PP	For the detection of hyperandrogenism in PCOS, the assessment of biochemical hyperandrogenism is of greatest value in patients with minimal or no clinical signs of hyperandrogenism (ie, hirsutism).	

1.2.6	PP	It is very difficult to reliably assess for biochemical hyperandrogenism in women on the combined oral contraceptive pill (COCP) as the pill increases sex hormone-binding globulin and reduces gonadotrophin-dependent androgen production. If already on the COCP and assessment of biochemical androgens is imperative, the pill should be withdrawn for a minimum of 3 months and contraception should be managed otherwise during this time.
1.2.7	PP	Repeated androgen measures for the ongoing assessment of PCOS in adults have a limited role.
1.2.8	PP	In most adolescents, androgen levels reach adult ranges at 12-15 years of age
1.2.9	PP	If androgen levels are markedly above laboratory reference ranges, causes of hyperandrogenaemia other than PCOS, including ovarian and adrenal neoplastic growths, congenital adrenal hyperplasia, Cushing's syndrome, ovarian hyperthecosis (after menopause), iatrogenic causes, and syndromes of severe insulin resistance, should be considered. However, some androgen-secreting neoplasms are associated with only mild to moderate increases in androgen levels. The clinical history of time of onset and/or rapid progression of symptoms is critical in assessing for an androgen-secreting tumour.

- Future improvements may arise from measurement of 11-oxygenated androgens and from establishing cut-off levels or thresholds based on large-scale validation in populations of different ages and ethnicities.

1.3		Clinical hyperandrogenism	
1.3.1	EBR	The presence of hirsutism alone should be considered predictive of biochemical hyperandrogenism and PCOS in adults.	❖❖❖ ⊕◯◯◯
1.3.2	EBR	Healthcare professionals could recognize that female pattern hair loss and acne in isolation (without hirsutism) are relatively weak predictors of biochemical hyperandrogenism.	❖❖❖ ⊕◯◯◯
1.3.3	CR	A comprehensive history and physical examination should be completed for symptoms and signs of clinical hyperandrogenism, including acne, female pattern hair loss and hirsutism in adults, and severe acne and hirsutism in adolescents.	❖❖❖❖
1.3.4	CR	Healthcare professionals should be aware of the potential negative psychosocial impact of clinical hyperandrogenism and should consider the reporting of unwanted excess hair growth and/or female pattern hair loss as being important, regardless of apparent clinical severity.	❖❖❖
1.3.5	CR	A modified Ferriman-Gallwey score (mFG) of 4-6 should be used to detect hirsutism, depending on ethnicity, acknowledging that self-treatment is common and can limit clinical assessment.	❖❖❖❖
1.3.6	CR	Healthcare professionals should consider that the severity of hirsutism may vary by ethnicity but the prevalence of hirsutism appears similar across ethnicities.	❖❖❖

1.3.7 PP Healthcare professionals should

- Be aware that standardized visual scales are preferred when assessing hirsutism, such as the mFG scale in combination with a photographic atlas.
- Consider the Ludwig or Olsen visual scales for assessing female pattern hair loss.
- Note that there are no universally accepted visual instruments for assessing the presence of acne.
- Recognize that women commonly treat clinical hyperandrogenism cosmetically, diminishing their apparent clinical severity.
- Appreciate that self-assessment of unwanted excess hair growth, and possibly acne and female pattern hair loss, has a high degree of validity and merits close evaluation, even if overt clinical signs of hyperandrogenism are not readily evident on examination.
- Note that only terminal hairs need to be considered in defining hirsutism, and these can reach >5 mm if untreated, vary in shape and texture, and are generally pigmented.
- Note that new-onset severe or worsening hyperandrogenism, including hirsutism, requires further investigation to rule out androgen-secreting tumours and ovarian hyperthecosis.
- Monitor clinical signs of hyperandrogenism, including hirsutism, acne, and female pattern hair loss, for improvement or treatment adjustment during therapy.

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.

No.	Type	Recommendation
		• Approach/route assessed. • Total number of 2-9 mm follicles per ovary. • Measurements in 3 dimensions (in cm) or volume of each ovary. • Other ovarian features and/or pathology including ovarian cysts, corpus lutea, dominant follicles (≥10 mm) (which should not be included in ovarian volume calculations). • Reliance on the contralateral ovary FNPO for diagnosis of PCOM, where a dominant follicle is noted. • Uterine features and/or pathology including endometrial thickness and pattern.

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.	

here in 2023, alternatively anti-Müllerian hormone (AMH) can now be used instead of ultrasound

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.

1.6		Ethnic variation	
1.6.1	EBR	Healthcare professionals should be aware of the high prevalence of PCOS in all ethnicities and across world regions, ranging from 10% to 13% globally using the Rotterdam criteria.	♦♦♦♦ ⊕⊕◯◯
1.6.2	EBR	Healthcare professionals should be aware that PCOS prevalence is broadly similar across world regions but may be higher in South East Asian and Eastern Mediterranean regions.	♦♦♦♦ ⊕⊕◯◯
1.6.3	PP	Healthcare professionals should be aware that the presentation of PCOS may vary across ethnic groups.	

1.7		Menopause life stage	
1.7.1	CR	A diagnosis of PCOS could be considered as enduring/lifelong.	♦♦♦
1.7.2	CR	Healthcare professionals could consider that both clinical hyperandrogenism and biochemical hyperandrogenism persist in the post menopause for women with PCOS.	♦♦♦
1.7.3	CR	PCOS diagnosis could be considered post menopause if there is a past diagnosis, or a long-term history of oligo-amenorrhoea with hyperandrogenism and/or PCOM, during the earlier reproductive years (age 20-40).	♦♦♦
1.7.4	CR	Further investigations should be considered to rule out androgen-secreting tumours and ovarian hyperthecosis in postmenopausal women presenting with new-onset, severe, or worsening hyperandrogenism including hirsutism.	♦♦♦

1.8		Cardiovascular disease risk	
1.8.1	EBR	Women with PCOS should be considered at increased risk of cardiovascular disease and potentially of cardiovascular mortality, acknowledging that the overall risk of cardiovascular disease in pre-menopausal women is low.	❖❖❖ ⊕◯◯◯
1.8.2	EBR	All women with PCOS should be assessed for cardiovascular disease risk factors.	❖❖❖❖ ⊕◯◯◯
1.8.3	CR	All women with PCOS, regardless of age and BMI, should have a lipid profile (cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglyceride levels) at diagnosis. Thereafter, the frequency of measurement should be based on the presence of hyperlipidaemia and additional risk factors or global cardiovascular risk.	❖❖❖❖
1.8.4	CR	All women with PCOS should have blood pressure measured annually and when planning pregnancy or seeking fertility treatment, given the high risk of hypertensive disorders in pregnancy and the associated comorbidities.	❖❖❖❖

1.9		Impaired glucose tolerance and type 2 diabetes risk	
1.9.1	EBR	Healthcare professionals and women with PCOS should be aware that, regardless of age and BMI, women with PCOS have an increased risk of impaired fasting glucose, impaired glucose tolerance, and type 2 diabetes.	⊕⊕◯◯
1.9.2	EBR	Glycaemic status should be assessed at diagnosis in all adults and adolescents with PCOS.	⊕⊕◯◯
1.9.3	CR	Glycaemic status should be reassessed every 1-3 years, based on additional individual risk factors for diabetes.	
1.9.4	CR	Healthcare professionals, women with PCOS, and other stakeholders should prioritize preventative strategies to reduce type 2 diabetes risk.	

		Glycaemic testing	
1.9.9	EBR	Healthcare professionals and women with PCOS should recommend the 75-g oral glucose tolerance test (OGTT) as the most accurate test to assess glycaemic status in PCOS, regardless of BMI.	❖❖❖❖ ⊕◯◯◯
1.9.10	EBR	If an OGTT cannot be performed, fasting plasma glucose and/or glycated haemoglobin (HbA1c) could be considered, noting significantly reduced accuracy.	❖❖❖ ⊕◯◯◯
1.9.11	EBR	An OGTT should be considered in all women with PCOS and without pre-existing diabetes, when planning pregnancy or seeking fertility treatment, given the high risk of hyperglycaemia and the associated comorbidities in pregnancy. If not performed preconception, an OGTT could be offered at the first prenatal visit and all women with PCOS should be offered the test at 24-28 weeks gestation.	❖❖❖ ⊕◯◯◯
1.9.12	PP	Insulin resistance is a pathophysiological factor in PCOS; however, clinically available insulin assays are of limited clinical relevance and are not recommended in routine care (refer to 3.1.10).	

1.10		**Obstructive sleep apnoea**	
1.10.1	EBR	Healthcare professionals should be aware that women with PCOS have significantly higher prevalence of obstructive sleep apnoea compared with women without PCOS, independent of BMI.	❖❖❖❖ ⊕⊕⊕◯
1.10.2	EBR	Women with PCOS should be assessed for symptoms of obstructive sleep apnoea (ie, snoring in combination with waking un-refreshed from sleep, daytime sleepiness, or fatigue) and if present, screen with validated tools or refer for assessment.	❖❖❖❖ ⊕⊕⊕◯
1.10.3	PP	Simple obstructive sleep apnoea screening questionnaires (such as the Berlin questionnaire, validated in the general population) can assist in identifying obstructive sleep apnoea in women with PCOS, noting that diagnosis requires a formal sleep study.	
1.10.4	PP	Goals of treatment should target obstructive sleep apnoea-related symptom burden.	

1.11		Endometrial hyperplasia and cancer	
1.11.1	EBR	Healthcare professionals should be aware that premenopausal women with PCOS have markedly higher risk of developing endometrial hyperplasia and endometrial cancer.	⊕◯◯◯
1.11.2	PP	Women with PCOS should be informed about the increased risk of endometrial hyperplasia and endometrial cancer, acknowledging that the overall chance of developing endometrial cancer is low; therefore, routine screening is not recommended.	
1.11.3	PP	Long-standing untreated amenorrhoea, higher weight, type 2 diabetes, and persistent thickened endometrium are additional to PCOS as risk factors for endometrial hyperplasia and endometrial cancer.	
1.11.4	PP	Women with PCOS should be informed of preventative strategies including weight management, cycle regulation, and regular progestogen therapy.	
1.11.5	PP	When excessive endometrial thickness is detected, consideration of a biopsy with histological analysis and withdrawal bleed is indicated.	

1.12		Risks in first-degree relatives	
1.12.1	EBR	Healthcare professionals could consider that fathers and brothers of women with PCOS may have an increased prevalence of metabolic syndrome, type 2 diabetes, and hypertension.	♦♦♦ ⊕◯◯◯
1.12.2	PP	The cardiometabolic risk in female first-degree relatives of women with PCOS remains inconclusive.	

2.2		Depression and anxiety	
2.2.1	EBR	Healthcare professionals should be aware of the high prevalence of moderate to severe depressive symptoms and depression in adults and adolescents with PCOS and should screen for depression in all adults and adolescents with PCOS, using regionally validated screening tools.	❖❖❖❖ ⊕⊕⊕⊕
2.2.2	EBR	Healthcare professionals should be aware of the high prevalence of moderate to severe anxiety symptoms and anxiety disorders in adults and should screen for anxiety in all adults with PCOS, using regionally validated screening tools.	❖❖❖❖ ⊕⊕⊕⊕
2.2.3	CR	If moderate or severe depressive or anxiety symptoms are detected, practitioners should further assess, refer appropriately, or offer treatment.	❖❖❖❖
2.2.4	PP	Severity of symptoms and clinical diagnosis of depression or anxiety should guide management. The optimal interval for anxiety and depression screening is not known. A pragmatic approach could include screening at diagnosis with repeat screening based on clinical judgement, risk factors, comorbidities, and life events, including the perinatal period. Screening for mental health disorders comprises assessment of risk factors, symptoms, and risk of self-harm and suicidal intent.	

2.3		Psychosexual function	
2.3.1	CR	Healthcare professionals could consider the multiple factors that can influence psychosexual function in PCOS including higher weight, hirsutism, mood disorders, infertility, and PCOS medications.	♦♦♦
2.3.2	CR	Permission to discuss psychosexual function should be sought noting that the diagnosis of psychosexual dysfunction requires both low psychosexual function combined with related distress.	♦♦♦♦

2.5		**Eating disorders**	
2.5.1	EBR	Eating disorders and disordered eating should be considered in PCOS, regardless of weight, especially in the context of weight management and lifestyle interventions (see sections 2.4 and 3.6).	♦♦♦ ⊕⊕◯◯
2.5.2	PP	If disordered eating or eating disorders are suspected, appropriately qualified practitioners should further assess via a full diagnostic interview. If an eating disorder or disordered eating is detected, appropriate management and support should be offered.	

2.8		Antidepressant and anxiolytic treatment	
2.8.1	CR	Psychological therapy could be considered first-line management, and antidepressant medications are considered in adults where mental health disorders are clearly documented and persistent, or if suicidal symptoms are present, based on general population guidelines.	❖❖❖
2.8.2	PP	Lifestyle intervention and other therapies (eg, COCP, metformin, and laser hair removal) that target PCOS features should be considered, given their potential to improve psychological symptoms. Where pharmacological treatment for anxiety and depression is offered in PCOS, healthcare professionals should apply caution: • To avoid inappropriate treatment with antidepressants or anxiolytics. • To limit use of agents that exacerbate PCOS symptoms, including weight gain. Healthcare professionals should be aware that not managing anxiety and depression may impact adherence to PCOS treatment/management.	

3		*Lifestyle management*	
3.1		Effectiveness of lifestyle interventions	
3.1.1	EBR	Lifestyle intervention (exercise alone or multicomponent diet combined with exercise and behavioural strategies) should be recommended for all women with PCOS, for improving metabolic health including central adiposity and lipid profile.	❖❖❖❖ ⊕◯◯◯
3.1.2	CR	Healthy lifestyle behaviours encompassing healthy eating and/or physical activity should be recommended in all women with PCOS to optimize general health, quality of life, body composition, and weight management (maintaining weight, preventing weight gain, and/or modest weight loss).	❖❖❖❖
3.1.3	PP	Healthcare professionals should be aware that lifestyle management is a core focus in PCOS management.	
3.1.4	PP	Lifestyle management goals and priorities should be co-developed in partnership with women with PCOS and value women's individualized preferences.	
3.1.5	PP	There are benefits to a healthy lifestyle even in the absence of weight loss.	

3.1.7	PP	Healthcare professionals should be aware of weight stigma when discussing lifestyle management with women with PCOS (see 3.6).
3.1.8	PP	Healthy lifestyle and optimal weight management, in the context of structured, intensive, and ongoing clinical support, appears equally effective in PCOS as in the general population.
3.1.9	PP	In those who are not overweight, in the adolescent and at key life points, the focus should be on healthy lifestyle and the prevention of excess weight gain.
3.1.10	PP	Insulin resistance is a pathophysiological factor in PCOS; however, clinically available insulin assays are of limited clinical relevance and should not be used in routine care (refer to 1.9.12).

3.3		Dietary intervention	
3.3.1	EBR	Healthcare professionals and women should consider that there is no evidence to support any 1 type of diet composition over another for anthropometric, metabolic, hormonal, reproductive, or psychological outcomes.	❖❖❖ ⊕◯◯◯
3.3.2	CR	Any diet composition consistent with population guidelines for healthy eating will have health benefits and, within this, healthcare professionals should advise sustainable healthy eating tailored to individual preferences and goals.	❖❖❖❖
3.3.3	PP	Tailoring of dietary changes to food preferences, allowing for a flexible, individual, and co-developed approach to achieving nutritional goals, and avoiding unduly restrictive and nutritionally unbalanced diets are important, as per general population guidelines.	
3.3.4	PP	Barriers and facilitators to optimize engagement and adherence to dietary change should be discussed, including psychological factors, physical limitations, socioeconomic and sociocultural factors, and personal motivators for change. The value of broader family engagement should be considered. Referral to suitably trained allied healthcare professionals needs to be considered when women with PCOS need support with optimizing their diet.	

3.4		Exercise intervention	
3.4.1	EBR	Healthcare professionals and women could consider that there is a lack of evidence supporting any 1 type and intensity of exercise being better than another for anthropometric, metabolic, hormonal, reproductive, or psychological outcomes.	⧫⧫⧫ ⊕◯◯◯
3.4.2	CR	Any physical activity consistent with population guidelines will have health benefits and, within this, healthcare professionals should advise sustainable physical activity based on individual preferences and goals.	⧫⧫⧫⧫

3.4.3 CR Healthcare professionals should encourage and advise the following in concordance with general population physical activity guidelines: ❖❖❖❖

- All adults should undertake physical activity as doing some physical activity is better than none.
- Adults should limit the amount of time spent being sedentary (eg, sitting and screen time) as replacing sedentary time with physical activity of any intensity (including light intensity) provides health benefits.
- For the prevention of weight gain and maintenance of health, adults (18-64 years) should aim for a minimum of 150-300 minutes of moderate-intensity activities or 75-150 minutes of vigorous-intensity aerobic activity per week or an equivalent combination of both spread throughout the week, plus muscle strengthening activities (eg, resistance/flexibility) on 2 non-consecutive days per week.
- For promotion of greater health benefits including modest weight loss and prevention of weight regain, adults (18-64 years) should aim for a minimum of 250 min/week of moderate-intensity activities or 150 min/week of vigorous intensities or an equivalent combination of both, plus muscle strengthening activities (eg, resistance/flexibility) ideally on 2 non-consecutive days per week.
- Adolescents should aim for at least 60 minutes of moderate- to vigorous-intensity physical activity per day, including activities that strengthen muscle and bone at least 3 times per week.

3.4.4	PP	Physical activity is any bodily movement produced by skeletal muscles that requires energy expenditure. It includes leisure-time physical activity, transportation (eg, walking or cycling), occupational activities (ie, work), household chores, playing games, sports or planned exercise, or activities in the context of daily, family, and community activities.
3.4.5	PP	Aerobic activity is best performed in bouts of at least a 10 minute duration, aiming to achieve at least 30 minutes daily on most days.

3.6		Weight stigma	
3.6.1	EBR	Many women with PCOS experience weight stigma in healthcare and other settings and the negative biopsychosocial impacts of this should be recognized.	⊕⊕◯◯
3.6.2	CR	Healthcare professionals should be aware of their weight biases and the impact this has on their professional practice and on women with PCOS.	
3.6.3	CR	Health policy makers, managers, and educators should promote awareness of weight stigma and invest in weight stigma education and minimization strategies.	

4		*Management of non-fertility features*
4.1		Pharmacology treatment principles in PCOS
	PP	Shared decision-making between the patient (and parent/s or guardian/s, if the patient is a child) and the healthcare professional is required.
	PP	An individual's characteristics, preferences, and values must be elicited and considered when recommending any intervention alone or in combination.
	PP	Understanding how individual adults and adolescents value treatment outcomes is essential when prescribing medications.
	PP	Medical therapy is generally not approved for use specifically in PCOS, and recommended use is therefore evidence based, but off-label. Healthcare professionals need to inform adults, adolescents, and their parents/s or guardian/s and discuss the evidence, possible concerns, and side effects. Regulatory agencies should consider approval of evidence-based medications for use 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.	❖❖❖ ⊕◯◯◯

4.3		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.

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.	

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.	❖❖❖
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.	

No.	Type	Recommendation
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.

4.6		Anti-androgen pharmacological agents	
4.6.1	EBR	In combination with effective contraception, anti-androgens could be considered to treat hirsutism in women with PCOS, if there is a suboptimal response after a minimum of 6 months of COCP and/or cosmetic therapy.	❖❖❖ ⊕◯◯◯
4.6.2	CR	Given the negative psychological impact of female pattern hair loss, anti-androgens in combination with COCP could be trialled, acknowledging the lack of evidence in the PCOS population.	❖❖❖
4.6.3	PP	Whenever pregnancy is possible, healthcare professionals must educate and counsel women and adolescents, parents/s or guardian/s, regarding the risks of incomplete development of external genital structures of male foetuses (undervirilization) when anti-androgens are used. To prevent this, women who can get pregnant should be strongly counselled to use effective contraception (eg, intrauterine device or COCPs).	
4.6.4	PP	Anti-androgens could be considered to treat hirsutism, in the presence of another effective form of contraception, for women with contraindications for COCP therapy or when COCPs are poorly tolerated.	

4.6.5 PP When prescribing anti-androgens, based on general population recommendations, healthcare professionals should consider that

- Spironolactone at 25-100 mg/day appears to have lower risks of adverse effects.
- Cyproterone acetate at doses ≥ 10 mg is not advised due to an increased risk including for meningioma.
- Finasteride has an increased risk of liver toxicity.
- Flutamide and bicalutamide have an increased risk of severe liver toxicity.
- The relatively limited evidence on anti-androgens in PCOS needs to be appreciated with small numbers of studies and limited numbers of participants.

4.7		Inositol	
4.7.1	EBR	Inositol (in any form) could be considered in women with PCOS based on individual preferences and values, noting limited harm, potential for improvement in metabolic measures, yet with limited clinical benefits including in ovulation, hirsutism, or weight.	❖❖❖ ⊕◯◯◯
4.7.2	EBR	Metformin should be considered over inositol for hirsutism and central adiposity, noting that metformin has more gastrointestinal side effects than inositol.	❖❖❖ ⊕◯◯◯
4.7.3	PP	Women taking inositol and other complementary therapies are encouraged to advise their healthcare professional.	
4.7.4	PP	Specific types, doses, or combinations of inositol cannot currently be recommended in adults and adolescents with PCOS, due to a lack of quality evidence.	
4.7.5	PP	Shared decision-making should include discussion that regulatory status and quality control of inositol in any form (like other nutrient supplements) can differ from those for pharmacological products and doses and qualities may vary.	
4.7.6	PP	Policy makers and healthcare professionals have a responsibility to ensure women have access to unconflicted, evidence-based information to inform shared decision-making, whilst also acknowledging and respecting individual values and preferences, including for complementary therapies.	

4.8		**Mechanical laser and light therapies for hair reduction**	
4.8.1	EBR	Mechanical laser and light therapies should be considered for reducing facial hirsutism and for related depression, anxiety, and quality of life in women with PCOS.	❖❖❖ ⊕◯◯◯
4.8.2	EBR	A greater number of laser treatment sessions may be required in women with PCOS, compared with women with idiopathic hirsutism, to achieve hair reduction.	❖❖❖ ⊕◯◯◯
4.8.3	CR	Adverse effects appear limited in the hands of experienced and suitably qualified providers, and women should be encouraged to seek hair reduction therapies from such providers.	❖❖❖❖
4.8.4	PP	Where laser hair removal is prescribed, the following need to be considered: • Wavelength and delivery of laser treatment vary by skin and hair colour. • Laser is relatively ineffective in women with blond, grey, or white hair. • The addition of combined oral contraceptive pills (COCP), with or without anti-androgens, to laser treatment may provide greater hair reduction and maintenance compared to laser alone. • Low- and high-fluence lasers appear to have similar efficacy in reducing facial hair, while low-fluence laser has reduced associated pain.	

4.8.5	PP	Mechanical hair removal with Intense Pulse Light (IPL) could be considered, albeit benefits may be less pronounced compared to laser treatment. There is no evidence to support the efficacy of home-based IPL kits.
4.8.6	PP	Policy makers should consider funding this evidence-based effective therapy for women with PCOS to alleviate distressing symptoms of hirsutism and related negative impact on quality of life, body image, and psychological health.

No.	Type	Recommendation	Grade/quality
4.9		**Bariatric/metabolic surgery**	
4.9.1	CR	Bariatric/metabolic surgery could be considered to improve weight loss, hypertension, diabetes (prevention and treatment), hirsutism, irregular menstrual cycles, ovulation, and pregnancy rates in women with PCOS.	❖❖❖
4.9.2	CR	Bariatric/metabolic surgery in women with PCOS should be informed by general population guidelines.	❖❖❖❖
4.9.3	CR	PCOS is a metabolic condition and could be considered an indication at a lower BMI threshold for bariatric/ metabolic surgery similarly to other metabolic conditions including diabetes.	❖❖❖
4.9.4	CR	Women should be strongly counselled on the likelihood of rapid return of fertility and the need to commit to effective contraception, ideally prior to surgery. Even when pregnancy is desired, contraception should be continued until a stable weight is achieved, usually after 1 year, to avoid significantly increased risk of growth restriction, prematurity, small for gestational age, pregnancy complications, and prolonged hospitalization of the infant.	❖❖❖❖

4.10		**Pregnancy outcomes**	
4.10.1	EBR	Women with PCOS have higher risk pregnancies, and healthcare professionals should ensure that PCOS status is identified during antenatal care, and appropriate monitoring and support are provided.	❖❖❖❖ ⊕◯◯◯
4.10.2	EBR	Healthcare professionals should recognize that pregnant women with PCOS have an increased risk of the following: • Higher gestational weight gain. • Miscarriage. • Gestational diabetes. • Hypertension in pregnancy and preeclampsia. • Intrauterine growth restriction, small for gestational age babies, and low birth weight. • Preterm delivery. • Caesarean section.	❖❖❖❖ ⊕◯◯◯

4.10.3	EBR	Assisted reproductive technology in women with PCOS should be considered as not conferring additional risk of miscarriage, preterm birth, impaired foetal growth, and caesarean section, over that observed in women without PCOS.	♦♦♦ ⊕◯◯◯
4.10.4	EBR	Women with PCOS should be considered as not having an increased risk of large for gestational age babies, macrosomia, and instrumental delivery.	♦♦♦ ⊕◯◯◯

4.11		Metformin in pregnancy	
4.11.1	EBR	Healthcare professionals should be aware that metformin in pregnant women with PCOS has not been shown to prevent the following: • Gestational diabetes. • Late miscarriage (12 weeks + 1 day to 21 weeks + 6 days gestational age). • Hypertension in pregnancy. • Preeclampsia. • Macrosomia or birthweight ≥ 4000 g.	❖❖❖❖ ⊕⊕◯◯
4.11.2	EBR	Metformin could be considered in some circumstances (eg, risk for preterm birth) to reduce preterm delivery and limit excess gestational weight gain, in pregnant women with PCOS.	❖❖❖ ⊕⊕⊕◯
4.11.3	PP	Women should be counselled that the consequences of metformin exposure on long-term offspring health remain unclear and there is a suggestion of increased childhood weight, although causality is not certain.	
4.11.4	PP	Side effects of metformin are mostly mild, transient gastrointestinal symptoms and are not worse in pregnancy.	

5		*Assessment and treatment of infertility*
		General principles
	PP	All fertility treatment in PCOS should be guided by the fertility treatment algorithm (Algorithm 2).
	PP	Those with PCOS should be reassured that pregnancy can often be successfully achieved either naturally or with assistance.
	PP	Prenatal vitamin supplementation should be commenced with ovulation induction therapy aligned to routine preconception care.

No.	Type	Recommendation	Grade/quality
	PP	The use of ovulation induction agents, including letrozole, metformin, and clomiphene citrate, is off-label in many countries. Where off-label use of ovulation induction agents is allowed, healthcare professionals need to inform women and discuss the evidence, possible concerns, and side effects.	
	PP	There should be ongoing monitoring of patients for adverse effects and infants for congenital anomalies, in all studies conducted with ovulation induction agents, and these should be reported in any published papers.	

5.1		**Preconception risk factors**	
5.1.1	EBR	Women with PCOS should be counselled on the adverse impact of excess weight on clinical pregnancy, miscarriage, and live birth rates, following infertility treatment.	⊕◯◯◯
5.1.2	CR	Consistent with routine preconception care, in women with PCOS planning pregnancy, weight, blood pressure, smoking, alcohol, diet and nutritional status, folate supplementation (higher dose in those with BMI > 30 kg/m^2), exercise, sleep, and mental, emotional, and sexual health should be considered and optimized to improve reproductive and pregnancy outcomes and overall health.	❖❖❖❖

5.2		Tubal patency testing	
5.2.1	CR	In women with PCOS and infertility due to anovulation alone with normal semen analysis, the risks, benefits, costs and timing, and techniques of tubal patency testing in relation to the cost and complexity of the treatment should be considered on an individual basis, depending on personal history and population prevalence, prior to starting ovulation induction with timed intercourse or intrauterine insemination.	♦♦♦

5.3		Letrozole	
5.3.1	EBR	Letrozole should be the first-line pharmacological treatment for ovulation induction in infertile anovulatory women with PCOS, with no other infertility factors.	⊕⊕⊕⊕
5.3.2	PP	The use of letrozole is still off-label in many countries. Where it is not allowed, clinicians could use other ovulation induction agents.	
5.3.3	PP	Letrozole should not be given where there is any possibility of a pre-existing pregnancy, though there is no evidence for increased teratogenicity compared to other ovulation induction agents.	

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.	⊕⊕◯◯

5.4.2		*Clomiphene citrate versus metformin*	
5.4.2.1	EBR	Clomiphene citrate could be used in preference to metformin in women with PCOS with anovulatory infertility and no other infertility factors, to improve ovulation, clinical pregnancy, and live birth rates.	⧫⧫⧫ ⊕⊕◯◯
5.4.2.2	PP	The risk of multiple pregnancies is increased with clomiphene citrate use (alone or in combination with metformin), and therefore, clomiphene cycles may require ultrasound monitoring.	

5.4.3		*Clomiphene citrate and metformin versus clomiphene citrate alone*	
5.4.3.1	EBR	Clomiphene citrate combined with metformin could be used rather than clomiphene citrate alone in women with PCOS with anovulatory infertility and no other infertility factors to improve ovulation and clinical pregnancy rates.	⧫⧫⧫ ⊕⊕◯◯
5.4.4		*Clomiphene citrate and metformin versus metformin alone*	
5.4.4.1	EBR	Clomiphene citrate combined with metformin could be used rather than metformin alone in women with PCOS with anovulatory infertility and no other infertility factors to improve live birth rates.	⧫⧫⧫ ⊕⊕◯◯
5.4.4.2	PP	Monitoring of combined cycles will need to be equivalent to clomiphene citrate alone.	

No.	Type	Recommendation	Grade/quality
5.4.5		*Clomiphene citrate versus Letrozole*	
5.4.5.1	EBR	Letrozole should be used rather than clomiphene citrate in women with PCOS with anovulatory infertility and no other infertility factors to improve ovulation, clinical pregnancy, and live birth rates.	⊕⊕◯◯
5.4.5.2	PP	Current evidence demonstrates no difference in foetal abnormality rates between letrozole or clomiphene citrate ovulation induction or natural conception.	

5.5		Gonadotrophins	
5.5.1	EBR	Gonadotrophins alone could be considered rather than clomiphene citrate in therapy naïve women with PCOS with anovulatory infertility and no other infertility factors to improve ovulation, clinical pregnancy, and live birth rates (refer to PP 5.5.6).	❖❖❖ ⊕⊕◯◯
5.5.2	EBR	Gonadotrophins alone could be used over gonadotrophins combined with clomiphene citrate in women with PCOS who are anovulatory and infertile with clomiphene citrate resistance or failure and no other infertility factors.	❖❖❖ ⊕⊕◯◯
5.5.3	EBR	Gonadotrophins could be considered rather than the combination of clomiphene citrate and metformin in women with PCOS who are anovulatory and infertile, with clomiphene citrate resistance and no other infertility factors.	❖❖❖ ⊕◯◯◯
5.5.4	EBR	Either gonadotrophins or laparoscopic ovarian surgery could be used in women with PCOS who are anovulatory and infertile, with clomiphene citrate resistance and no other infertility factors, following counselling on higher live birth rate and higher multiple pregnancy rates with gonadotrophins.	❖❖ ⊕⊕◯◯

5.5.6 PP Where gonadotrophins are to be prescribed, the following should be considered:

- Cost of the intervention for ovulation induction.
- Expertise required for the use of the intervention for ovulation induction.
- The degree of intensive ultrasound monitoring that is required.
- A low-dose step-up gonadotrophin protocol should be used to optimize the chance of monofollicular development.
- Implications of potential multiple pregnancy.

5.6		Laparoscopic ovarian surgery	
5.6.1	EBR	Laparoscopic ovarian surgery could be second-line therapy for women with PCOS who are anovulatory and infertile, with clomiphene citrate resistance and no other infertility factors.	⊕⊕◯◯
5.6.2	PP	When using laparoscopic ovarian surgery, the following should be considered: • Comparative cost of the intervention for ovulation induction. • Expertise required for the safe use of the intervention for ovulation induction. • Both intraoperative and postoperative risks, which are higher in women who are above healthy weight.	

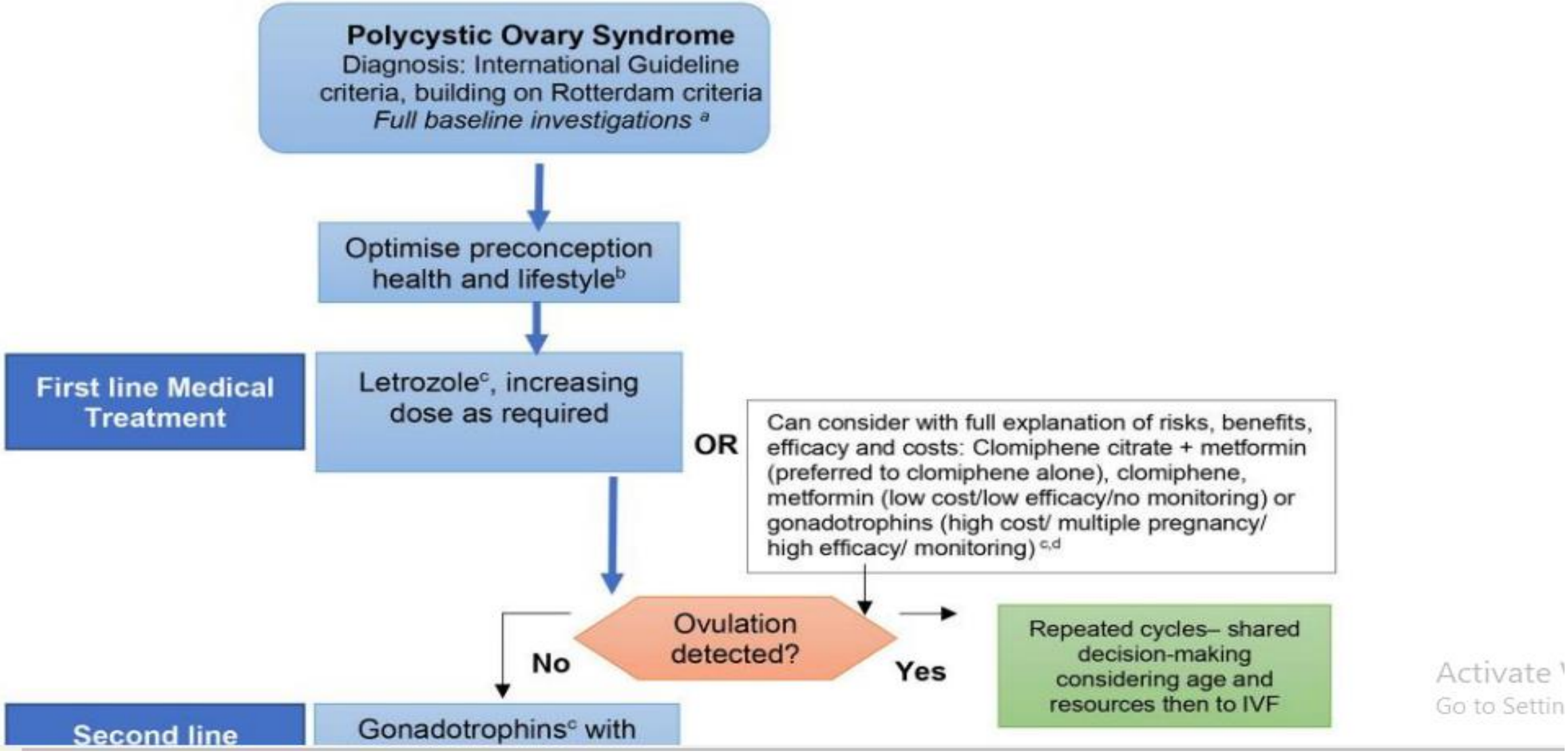
5.7		***In vitro* fertilization and *in vitro* maturation**	
5.7.0.1	CR	In the absence of an absolute indication for *in vitro* fertilization (IVF)/intracytoplasmic sperm injection (ICSI), IVF could be offered in women with PCOS and anovulatory infertility, if first- or second-line ovulation induction therapies have failed.	❖❖❖
5.7.0.2	PP	In women with anovulatory PCOS, the use of IVF is effective and when elective single-embryo transfer is used, multiple pregnancies can be minimized.	
5.7.0.3	PP	Women with PCOS undergoing IVF/ICSI treatment should be counselled prior to starting treatment about the increased risk of ovarian hyperstimulation syndrome and options to reduce the risk should be offered.	

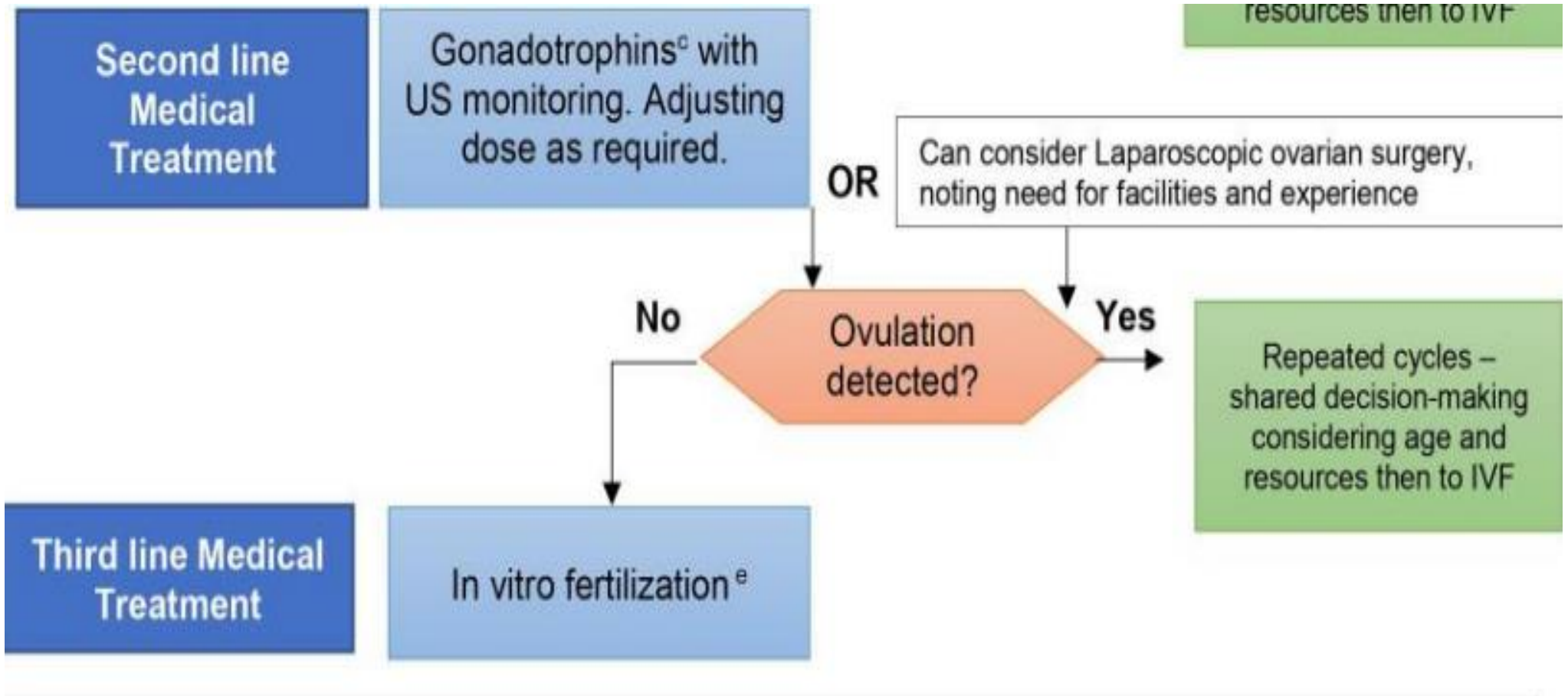
5.7.5		*Adjunct metformin*	
5.7.5.1	EBR	Adjunct metformin therapy could be used before and/or during FSH ovarian stimulation in women with PCOS undergoing IVF/ICSI treatment with GnRH agonist long protocol, to reduce the risk of developing ovarian hyperstimulation syndrome and miscarriage.	⊕⊕⊕ ⊕⊕◯◯

5.7.6		In vitro *maturation*
5.7.6.1	EBR	The use of in vitro maturation (IVM) and ICSI could be considered in women with PCOS as an alternative to a stimulated IVF/ICSI cycle, where an embryo is frozen and replaced in a subsequent embryo transfer cycle, acknowledging there is no risk of ovarian hyperstimulation syndrome, but a lower cumulative live birth rate.

5.8		**Inositol**	
5.8.1	EBR	Inositol in any form alone, or in combination with other therapies, should be considered experimental therapy in women with PCOS with infertility, with benefits and risks currently too uncertain to recommend the use of these agents as fertility therapies.	❖❖❖ ⊕◯◯◯
5.8.2	PP	There is limited evidence with uncertain results, on the effect of inositol on ovulation, clinical pregnancy, and live birth rates.	
5.8.3	PP	Side effects and safety are not known for inositol.	
5.8.4	PP	Women need to be aware that these agents can have limited regulation with variable dose, quality, consistency, and combination with other agents.	
5.8.5	PP	Women's personal goals and preferences should be considered when discussing complimentary therapies.	
5.9		**Anti-obesity pharmacological agents**	
5.9.1	CR	We recommend using anti-obesity agents in PCOS for reproductive outcomes only in research settings to establish the efficacy and safety.	

Infertility algorithm for Polycystic ovary syndrome (PCOS)
Central blue pathway follows best practice and is preferred




Second line Medical Treatment
Gonadotrophins[c] with US monitoring. Adjusting dose as required.
OR
Can consider Laparoscopic ovarian surgery, noting need for facilities and experience
No
Ovulation detected?
Yes
Repeated cycles – shared decision-making considering age and resources then to IVF
Third line Medical Treatment
In vitro fertilization[e]

a. Baseline investigations (see narrative):
   i. Diagnosis of PCOS - Endocrine profile and pelvic ultrasound scan
   ii. Assessment of BMI, BP & glycemic status (OGTT / HbA1c)
   iii. Routine preconception assessments (Rubella immunity, infection screen etc..), advice and supplementation.
   iv. Additional investigations: semen analysis and consider tubal patency assessment
b. Healthy lifestyle encompassing healthy eating and regular physical activity should be recommended in all those with PCOS to limit adverse impacts on fertility and fertility treatment outcomes and to optimize health during pregnancy
c. Off label prescribing: Letrozole, metformin and other pharmacological treatments are generally off label in PCOS, as pharmaceutical companies have not applied for approval in this condition. However, recommended off label use is evidence-based and allowed in many countries. Where it is allowed, health professionals should inform women and discuss the evidence, possible concerns and side effects of treatment.
d. Compared to letrozole, metformin has lower efficacy, cost and multiple pregnancy rate and gonadotrophins have higher efficacy, cost and multiple pregnancy rate. Both may be an alternative first line choice for informed women.
e. In vitro fertilization (IVF) - Third line unless other infertility factors (e.g. male, tubal). PCOS specific protocols to minimise risk of ovarian hyperstimulation syndrome, consider invitro maturation if available.