# Appendix VIII:
# Algorithms

**Algorithm 1:** **Screening, diagnostic assessment, risk assessment and life stage: Updates***

**Algorithm 2:** **Prevalence, screening, diagnostic assessment and treatment of emotional wellbeing**

**Algorithm 3:** **Lifestyle**

**Algorithm 4:** **Pharmacological treatment for non-fertility indications**

**Algorithm 5:** **Management of infertility in polycystic ovary syndrome**

## Algorithm 1: Screening, diagnostic assessment, risk assessment and life stage*

**Step 1: Irregular cycles + clinical hyperandrogenism**

(exclude other causes)* = diagnosis

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**Step 2: If no clinical hyperandrogenism**

Test for biochemical hyperandrogenism (exclude other causes)* = diagnosis

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**Step 3: If ONLY irregular cycles OR hyperandrogenism**

Adolescents ultrasound is not indicated = consider at risk of PCOS and reassess later
Adults - **request ultrasound for PCOM**, if positive (exclude other causes)* = diagnosis

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***Exclusion of other causes =s TSH, prolactin, 17-OH progesterone, FSH or if clinically indicated exclude other causes** (e.g. Cushing's syndrome, adrenal tumours etc) Hypogonadotrophic hypogonadism, usually due to low body fat or intensive exercise, should also be excluded clinically and with LH and FSH levels

### Irregular menstrual cycles

Normal in the first year post menarche = 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 one cycle
- Primary amenorrhea by age 15 or > 3 years post thelarche (breast development).

With irregular cycles, PCOS should be considered and assessed according to the guidelines,
Ovulatory dysfunction can occur with regular cycles. If anovulation suspected, check progesterone levels.

### Biochemical hyperandrogenism

Use total testosterone and free testosterone for diagnosis. If not elevated, then androstenedione and dehydroepiandrosterone sulfate could be measured, but are less specific with a limited role in PCOS diagnosis.

Highly accurate tandem mass spectrometry (LC-MS/MS) assays recommended. Direct free testosterone assays not preferred. Use lab reference ranges.

Reliable assessment of biochemical hyperandrogenism not possible on hormonal contraception.
Consider withdrawal for ≥ 3 months with alternative contraception

Biochemical hyperandrogenism role is when clinical hyperandrogenism is unclear.

Where levels are well above laboratory reference ranges, other causes should be considered.
History of symptom onset and progression is key in assessing for neoplasia, however, some androgen-secreting neoplasms may only induce mild to moderate increases in hyperandrogenism.

## Clinical hyperandrogenism

Comprehensive history and physical examination needed. Adults: acne, female pattern hair loss and hirsutism. Adolescents: severe acne and hirsutism.

Note negative psychosocial impact of clinical hyperandrogenism. Patient perception is important, regardless of apparent clinical severity.

Standardised visual scales are preferred including modified Ferriman Gallway score (mFG), a score of ≥ 4-6 = hirsutism, noting self-treatment impacts assessment.

Ludwig visual score preferred for assessing female pattern hair loss.

## Ultrasound and polycystic ovary morphology

With irregular menstrual cycles and hyperandrogenism, an ovarian ultrasound is not necessary for diagnosis.

In diagnosis, follicle number per ovary is most effective, followed by follicle number per cross-section and ovarian volume as ultrasound markers in adults.

Ultrasound should not be used for PCOS diagnosis in adolescents, due to the high incidence of multi-follicular ovaries in this life stage.

Transvaginal ultrasound approach is preferred in diagnosis of PCOS, if sexually active or if acceptable to the individual

Using ultrasound transducers with a frequency bandwidth including 8 MHz, the PCOM threshold is a follicle number per ovary of ≥ 20 and/or an ovarian volume ≥ 10 ml on either ovary, avoiding corpora lutea, cysts or dominant follicles

Serum AMH could be used for defining PCOM in adults as an alternative to pelvic ultrasound. Either serum AMH OR ultrasound may be used but not both to avoid overdiagnosis*

## Anti-mullerian hormone (AMH) *

Serum AMH could be used for defining PCOM in adults as an alternative to pelvic ultrasound. Either serum AMH OR ultrasound may be used but not both to avoid overdiagnosis*

## Ethnic variation and prevalence

PCOS prevalence appears similar across ethnicities and is 10-13% globally by International guideline/Rotterdam criteria*

## Menopause life stage

A diagnosis of PCOS is considered enduring. Postmenopausal women presenting with new-onset, severe or worsening hyperandrogenism including hirsutism, require further investigation to rule out androgen-secreting tumours and ovarian hyperthecosis.

## Cardiovascular disease risk*

Women with PCOS have an increased risk of cardiovascular disease and potentially of cardiovascular mortality, but overall risk premenopause is low.*

All with PCOS should be assessed for individual cardiovascular risk factors and global CVD risk.

All women with PCOS, regardless of age and BMI, should have a fasting lipid profile (total cholesterol, low density lipoprotein cholesterol, high density lipoprotein cholesterol and triglyceride level at diagnosis). Thereafter, measurement should be guided by the results and the global CVD risk.

All women with PCOS should have blood pressure measured annually and when planning pregnancy or fertility treatment.

## Impaired glucose tolerance and type 2 diabetes

Regardless of age and BMI, impaired glucose tolerance and type 2 diabetes are increased in PCOS, with risk independent of, yet exacerbated by BMI Glycaemic status should be assessed at baseline in all with PCOS and thereafter, every one to three years, based on presence of other diabetes risk factors (including a BMI > 25 kg/m² or in Asians > 23 kg/m², history of abnormal glucose tolerance or family history of diabetes, hypertension or high-risk ethnicity.

In high risk women an oral glucose tolerance test (OGTT is the most accurate test for dysglycaemia with fasting glucose or HbA1c second-line due to lower accuracyOGTT should be offered in all with PCOS when planning pregnancy or seeking fertility treatment, given increased hyperglycaemia and comorbidities in pregnancy.

If not performed preconception, an OGTT should be offered at the first prenatal visit, and all women with PCOS should be offered the test at 24-28 weeks gestation.

## Obstructive sleep apnea

Women with PCOS have a significantly higher prevalence of obstructive sleep apnea.*

If symptoms of PCOS are present, then screen with validated tools or refer for assessment and goals of treatment should target related symptom burden.

## Endometrial cancer

Health professionals and women with PCOS should be aware of a two to six fold increased risk of endometrial cancer in premenopausal women with PCOS; however absolute risk remains low.

Health professionals should have a low threshold for investigation of endometrial cancer in PCOS, with transvaginal ultrasound and/or endometrial biopsy recommended with persistent thickened endometrium and/or risk factors including prolonged amenorrhea, abnormal vaginal bleeding or excess weight. Routine ultrasound screening of endometrial thickness in PCOS is not recommended.

Long-standing untreated amenorrhea, higher weight and persistent thickened endometrium are additional to PCOS, are risk factors for endometrial hyperplasia and endometrial cancer. Optimal prevention for endometrial hyperplasia and endometrial cancer is not known. A pragmatic approach could include COCP or progestin therapy in those with cycles longer than 90 days.

## Risk of PCOS and cardiometabolic risk in first-degree relatives*

Fathers and brothers of women with PCOS may have an increased prevalence of metabolic syndrome, type 2 diabetes, and hypertension, with inadequate data in female relatives.*

## Algorithm 2: Prevalence, screening, diagnostic assessment and treatment of emotional wellbeing

| Psychological domains | Screening protocol/tools | Intervention |
|---|---|---|
| **Quality of life (QoL)** | Lower QoL scores in PCOS. | Capture and consider women's perceptions of their symptoms, impact on their QoL, key concerns and priorities for management.<br><br>Target treatment to areas of greatest concern to those with PCOS. |
| **Anxiety and depressive symptoms** | High prevalence of moderate to severe anxiety and depressive symptoms in adults; and depressive symptoms in adolescents.<br><br>Routine screening for all at diagnosis and subsequently based on clinical judgement, considering risk factors, comorbidities and life events.<br><br>Suggested screening based on regional guidelines and use regionally validated tools<br>• Factors including obesity, infertility, hirsutism need consideration along with use of hormonal medications in PCOS, which may independently exacerbate depressive and anxiety symptoms and other aspects of emotional wellbeing. | **If initial screening is positive:**<br><br>Assess risk factors and symptoms using age, culturally and regionally appropriate tools and/or refer to an appropriate professional for further assessment.<br><br>If treatment is warranted, psychological therapy and/or pharmacological treatment should be offered to women with PCOS, informed by regional clinical practice guidelines.<br><br>**Psychological therapy:**<br><br>Women diagnosed with a mental health disorder should be offered psychological therapy as first-line management, guided by regional guidelines and the preference of the woman with PCOS.<br><br>**Pharmacological treatment:**<br><br>Avoid inappropriate treatment with antidepressants or anxiolytics and consider impact on weight. Where mental health disorders are clearly documented and persistent, or if suicidal symptoms are present, treatment of depression or anxiety should be informed by clinical regional practice guidelines. |

| Psychological domains | Screening protocol/tools | Intervention |
|---|---|---|
| **Psychosexual dysfunction** | Multiple factors that may contribute to psychosexual dysfunction in PCOS (such as higher weight, hirsutism, mood disorders, infertility and PCOS medications).<br><br>Psychosexual dysfunction requires not only low psychosexual function, but also related distress. | If psychosexual dysfunction is suspected, further assessment, referral or treatment should follow as appropriate. |
| **Body image** | Negative body image has been described in PCOS and can be screened based on regional guidelines or by a stepped approach. | Consider the impact of PCOS features such as hirsutism, acne, and weight gain in assessing and addressing body image in PCOS. |
| **Eating disorders and disordered eating** | Eating disorders and disordered eating need to be considered, regardless of weight, especially in the context of weight management and lifestyle interventions. | If concerns are identified:<br>• Assess risk factors and symptoms using age, culturally and regionally appropriate tools.<br>• Refer to an appropriate health professional for further mental health assessment. If this is not the patient's usual healthcare provider, inform. |
| **Information needs and patient care** | Information, education and resources are a high priority for women with PCOS. | Information, education and resources should be provided in a respectful and empathic manner. Health professionals should employ shared decision making and support patient agency. |

## Algorithm 3: Lifestyle

| Weight stigma |
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| Healthcare professionals should recognise that many women with PCOS experience weight stigma in healthcare and other settings and that this has negative biopsychosocial impacts. |
| **Factors affecting weight gain in PCOS** |
| Whilst the specific mechanisms are unclear, it is recognised that many women with PCOS will have underlying mechanisms that drive greater longitudinal weight gain |
| **Obesity and weight assessment** |
| Women with PCOS have higher weight gain and obesity which can impact health and emotional wellbeing. In addressing this, consider related stigma, negative body image and/or low self-esteem by use of a respectful and considerate approach, considering personal sensitivities, marginalization and potential weight-related stigma. |
| Prevention of weight gain and encouraging evidence-based and socio-culturally appropriate healthy lifestyle is important in PCOS from adolescence. |
| **Effectiveness of lifestyle interventions** |
| Healthy lifestyle behaviours (healthy eating and regular physical activity) should be recommended in all women with PCOS, to achieve and/or maintain healthy weight and to optimise general and metabolic health, and quality of life across the life course. Ethnic groups at high cardiometabolic risk require more consideration. |
| Lifestyle management goals and priorities should be co-developed in partnership with women with PCOS, and value women's individualised preferences. |
| Awareness of weight stigma is important when discussing lifestyle management with women with PCOS. All patient interactions should be patient-centred and value women's individualised healthy lifestyle preferences and cultural, socioeconomic and ethnic differences. |
| Adolescent and ethnic-specific body mass index and waist circumference categories should be considered when optimising lifestyle and weight. |
| **Behavioural strategies** |
| Lifestyle interventions could include behavioural strategies such as goal-setting, self-monitoring, problem solving, assertiveness training, reinforcing changes and relapse prevention, to optimise weight management, healthy lifestyle and emotional wellbeing in women with PCOS. |

| Dietary intervention |
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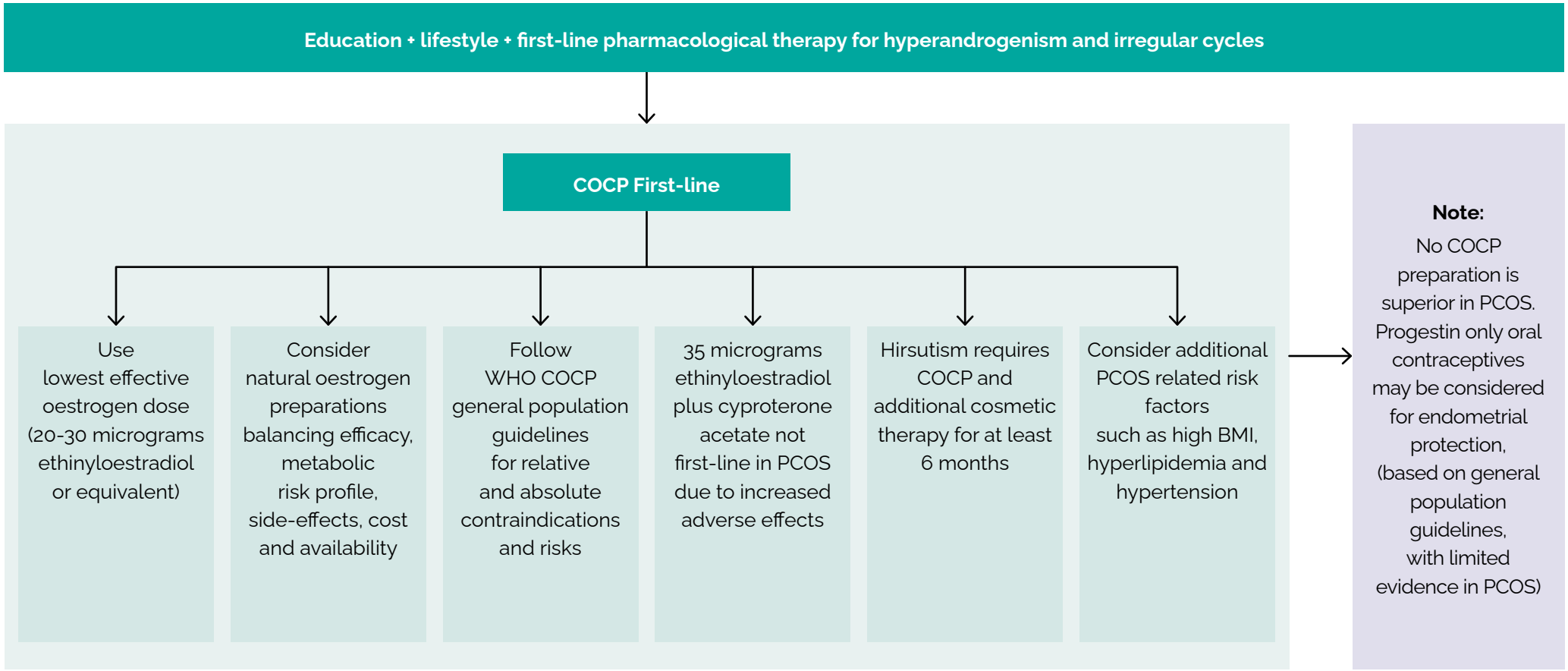
| General healthy eating principles should be followed for all women with PCOS across the life course, with no evidence to support any one type of diet composition over another for anthropometric, metabolic, hormonal, reproductive or psychological outcomes. . |
| Barriers and facilitators to optimise engagement and adherence to dietary change should be discussed, including psychological factors, physical limitations, socioeconomic and sociocultural factors, as well as personal motivators for change. |
| Referral to suitably trained allied healthcare professionals needs to be considered when women with PCOS need support with optimising their diet. |
| **Exercise intervention** |
| There is a lack of evidence supporting any one type and intensity of exercise being better than another for anthropometric, metabolic, hormonal, reproductive or psychological outcomes. |
| Health professionals should encourage and advise the following for prevention of weight gain and maintenance of health:<br>• in adults from 18-64 years, a minimum of 150 to 300 min/week moderate-intensity physical activity or 75 to 150 min/week vigorous-intensity or equivalent combination of both over the week<br>• in adolescents, > 60 minutes moderate to vigorous-intensity physical activity/day including those that strengthen muscle and bone at least 3 times weekly.<br>• activity best performed in bouts of > 10 minutes duration, aiming to achieve at least 30 minutes daily on most days. |

## Algorithm 4: Pharmacological treatment for non-fertility indications

**Off-label prescribing:** COCPs, metformin and other pharmacological treatments are generally off-label in PCOS, as pharmaceutical companies have not applied for approval in PCOS. However, off-label use is predominantly evidence-based and is allowed in many countries. Where it is allowed, health professionals should inform women and discuss the evidence, possible concerns and side-effects of treatment.

In those with a clear PCOS diagnosis or in adolescents at risk of PCOS (with symptoms)



## Second-line Pharmacological Therapies

### COCP + Lifestyle + Metformin

The combination of COCP and metformin appears to offer little additional benefit over COCP or metformin alone, in adults with PCOS with a BMI ≤ 30 kg/m².COCP – first-line for management of hirsutism and irregular menstrual cycles

Metformin – metabolic

Most beneficial in high metabolic risk groups including those with diabetes risk factors, impaired glucose tolerance or high-risk ethnic groups.

### COCP + Anti-Androgens

Anti-androgens could be considered to treat hirsutism in women with PCOS, if there is a suboptimal response after a minimum of six months of COCP and/or cosmetic therapy.

Whenever pregnancy is possible, women must be used strongly counselled regarding the use of concurrent effective contraception to prevent male fetal virilisation.

Combination therapy can be tried in androgenic alopecia.

### Metformin + Lifestyle

With lifestyle, in adults should be considered for weight, hormonal and metabolic outcomes and could be considered in adolescents.

Most useful with BMI ≥ 25 kg/m² and in high risk ethnic groups. Side-effects, including GI effects, are dose related and self-limiting. Consider starting low dose, with 500 mg increments 1-2 weekly. Suggested maximum daily dose: 2.5 g in adults, 2 g in adolescents.

Metformin appears safe long-term. Ongoing monitoring required and has been associated with low vitamin B12.

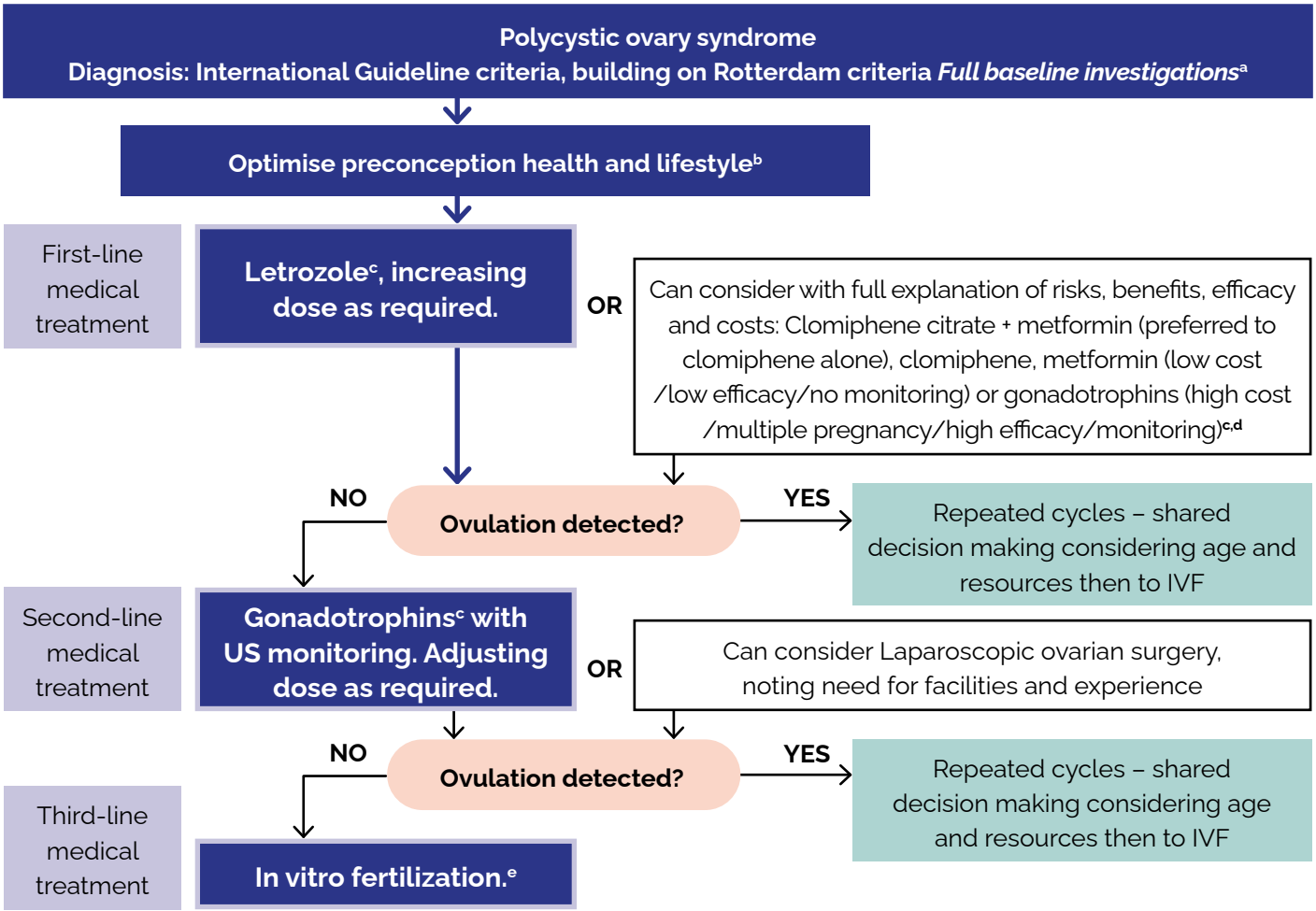
Anti-obesity medications could be considered, in addition to active lifestyle intervention, for the management of higher weight in adult women with PCOS, considering cost, contraindications, side-effects, availability and regulatory status and avoiding pregnancy when on therapy.

Inositol (in any form) may be considered in women with PCOS based on individual preferences and values, given limited harm, potential for reduced biochemical hyperandrogenism and metabolic measures, with limited clinical benefits for ovulation, hirsutism or weight.

Mechanical laser and light therapies should be considered for reducing facial hirsutism. Wavelength and delivery of laser treatment should be recommended taking into account skin colour. Laser is relatively ineffective in women with blond, grey or white hair. The addition of COCP, with or without anti-androgens, to laser treatment may provide greater hair reduction and maintenance compared to laser alone.

## Algorithm 5: Management of infertility in polycystic ovary syndrome

**Central Blue Pathway follows best practice evidence and is preferred**




**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 optimise 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 in vitro maturation if available.

*Teede HJ, et al on behalf of the International PCOS Network. Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome 2023. Fertility and Sterility, 2023; J Clinical Endocrinology and Metabolism 2023, Human Reproduction 2023, European J Endocrinology 2023.*