Provincial PCOS Primary Care Clinical Pathway

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This pathway applies to adults and adolescents **> 3 years post menarche**

Suspect PCOS with a patient who has any of the following symptoms:
- Clinical or Biochemical Hyperandrogenism (hirsutism, acne, and hair loss)
- Irregular or no menstrual cycles
- Suggestive pelvic ultrasound

1. History
- Evaluate menstrual pattern (abnormal is <21 days or >35 days)
- Reproductive history and plans for pregnancy
- Hyperandrogenism
  - Hirsutism (consider ethnic variation and hair removal treatments)
  - Severe acne in youth and if acne is treatment resistant
  - Scalp hair loss
- Metabolic history:
  - Weight gain or difficulty losing weight, obesity, dyslipidemia, high blood pressure, impaired glucose tolerance and Type 2 Diabetes
- Review of prior or current medications that impact symptoms: (i.e., hormone containing contraceptive, anti-androgen and metformin)
- Family history of PCOS, hirsutism, Type 2 or gestational diabetes, Congenital Adrenal Hyperplasia

2. Assessment
Weight bias resource
- Height, weight, blood pressure
- Physical exam to assess for clinical hyperandrogenism and insulin resistance (skin tags and acanthosis nigricans)

3. Red Flags
- Severe and abrupt onset of hirsutism
- Signs of Cushing's (wide purple stretch marks, round face, central fat deposition with thin arms and legs)
- Virilization (unexpected deepening of voice or clitoromegaly)

Red flags present → **7. Urgent Advice or Referral**

No red flags

4. Investigations
Bloodwork: Timing of testing and concurrent hormone therapy is important, see expanded details.
- Prolactin
- TSH
- FSH/ LH/ Estradiol
- Lipids
- β-hCG
- Testosterone, Free, Calculated
- OGTT

If unusual or unexpected results, or difficulty in interpretation → **7. Non-Urgent Advice**

Transvaginal ultrasound:
If **only one** of the following is present, complete transvaginal ultrasound in adults (if not available/appropriate complete trans abdominal pelvic ultrasound):
- Hyperandrogenism **or**
- Irregular or no menstrual cycles

5. Confirm PCOS diagnosis if other disorders ruled out and if at least two of the following are present:
- Clinical or biochemical hyperandrogenism
- Irregular or no menstrual cycles
- Polycystic ovarian morphology

If uncertain about PCOS diagnosis → **7. Non-Urgent Advice**

8. Consider referral to appropriate provider(s)

6. PCOS Management: *Ask the patient about their perception of PCOS related symptoms, impact on quality of life, key concerns, and priorities for management*

a. For all PCOS patients offer nutrition, exercise, and lifestyle counselling:
- A balanced, healthy diet following Canada's Food Guide.
- Encourage daily physical activity.
- Encourage weight maintenance, moderate weight loss, and prevent weight gain.
- Encourage reduction or quitting of smoking and alcohol use.

b. Specific symptom management
- **Menstrual regulation (amenorrhea/oligomenorrhea)**: Consider hormonal contraceptive options, metformin, and progesterone therapy.
- **Hirsutism, acne or alopecia:** Consider hair removal options, use of combined oral contraceptive pill (COCP), antiandrogens and encourage management outlined in 6a.
- **Pre-diabetes**: Consider 6a, metformin and other insulin sensitizers.
- **Fertility**: Assess reproductive plans. Determine if referral is appropriate.
- **Weight management**: Continue and intensify 6a. Addition of anti-obesity medications can be considered.

c. Consider other associated health risks
- **Prediabetes/ Diabetes/ Hypertension/ CVD risk.**
- **Metabolic dysfunction-associated fatty liver disease (MAFLD).**
- **Endometrial hyperplasia and cancer.**
- **Psychological:** Anxiety, depression, body image, and eating disorder.
- **Obstructive Sleep Apnea.**

This primary care pathway was co-designed provincially by Primary Care Providers, Specialist Physicians (Endocrinology and Gynecology), Patient and Family Advisors, Scientists, and the Alberta Health Services (AHS) Provincial Pathways Unit. It is intended to be used in conjunction with specialty advice services, when required, to support care within the medical home.

EXPANDED DETAILS

Pathway Primer

Polycystic ovary syndrome (PCOS) is one of the most common endocrine-metabolic disorders in females. [1-4] Approximately 10-15% of females live with PCOS and this disorder impacts health and quality of life across the lifespan; from adolescence to post-menopause. [1, 2, 4-7] There is heterogeneity in the symptomatology experienced by individuals with PCOS; however, irregular menstrual cycles and hyperandrogenism are common presentations. [4, 8] PCOS is associated with a range of reproductive, cardiometabolic, and psychological features, and increased risk of pregnancy complications, including gestational diabetes and hypertension. [4, 9-24]

PCOS is diagnosed when at least two out of the following are present and other disorders (causes of menstrual irregularity and hyperandrogenemia) are excluded:

i) Menstrual irregularity or ovulatory dysfunction
ii) Clinical (hirsutism, acne) or biochemical hyperandrogenemia (most commonly, elevated testosterone)
iii) Polycystic ovary morphology (PCOM) [4]

Please Note: The revised 2023 International Guidelines for Assessing and Managing PCOS recommends serum anti-Müllerian hormone (AMH), a blood test, as an alternative marker for PCOM. The utility of AMH is limited to specific contexts, as the diagnostic thresholds for PCOS requires standardization. The laboratories involved in AMH measurements in females should use population and assay specific cut-offs. Our team is working closely with Alberta Precision Laboratory to establish specific cut-offs for AMH in PCOS. This pathway will be updated when this is established.

Other disorders that present similarly to PCOS and that need to be excluded include: [4]

- Pregnancy
- Hyperprolactinemia
- Thyroid disorder
- Congenital adrenal hyperplasia
- Androgen producing adrenal or ovarian tumor
- Cushing's syndrome
- Hypothalamic amenorrhea

This pathway aims to facilitate the diagnosis of PCOS, the management of PCOS symptoms and associated health risks, and to improve quality of life for patients living with PCOS. The guidance in this pathway is informed by the International Evidence-based Guideline for the assessment and management of Polycystic Ovary Syndrome 2023 and extensive literature review, with feedback from patient partners and providers to comply with the current resources available in Alberta.

This pathway applies only to adults and adolescents > 3 years post menarche.

- Menstruation is generally irregular during the first-year post menarche.
- Anadolescent who has features of PCOS (irregular menstrual cycle or hyperandrogenemia) but does not meet the diagnostic criteria, can be given a diagnosis of 'at risk of PCOS' and should be advised for reassessment at or before full reproductive maturity at 8 years post-menarche. [4]

Suspect PCOS with a patient who has any of the following presentations:

- Irregular or no menstrual cycles (oligomenorrhea or amenorrhea), with consideration that menstrual irregularities are common during pubertal and menopausal transition. Ovulatory dysfunction is a diagnostic feature of PCOS, and irregular menstrual cycles may reflect ovulatory dysfunction.[4]
- Hyperandrogenism: hirsutism, acne and scalp hair loss. [4]

- A pelvic ultrasound showing polycystic ovarian morphology. [4]
    - Pelvic ultrasound to assess ovarian follicular morphology is useful only in adult patients. There are normal variations in ovarian follicular morphology in adolescents aged up to 8 years post menarche, therefore, pelvic ultrasound is not recommended to use in the diagnosis of PCOS in adolescents. [4]

1. History

Menstrual pattern

- The definition of irregular menstrual cycles depends on the timing post-menarche. Irregular cycles are considered normal in the first-year post menarche as part of the pubertal transition.
- Following this, irregular menstrual cycles are defined as: [4]
    - > 1 to < 3 years post menarche: <q 21 or > q45 days
    - > 3 years post menarche to perimenopause: < 21 days or > 35 days or < 8 cycles per year
    - > 1 year post menarche with an interval of > 90 days in between cycles
- Note: In patients who present with primary amenorrhea by age 15 or >3 years post thelarche (breast development), PCOS should be considered part of the differential diagnosis as part of the primary amenorrhea assessment.

Reproductive history:

- Assess patient's history of pregnancies, pregnancy-reproductive plan, miscarriages and pregnancy complications.
    - PCOS is associated with an increased risk of pregnancy complications including gestational diabetes, gestational hypertension, and pre-eclampsia. [4, 13, 15, 21]

Hyperandrogenism (Clinical or Biochemical):

- Hyperandrogenism is a diagnostic feature of PCOS affecting 60-100% of those with the condition. It includes clinical and/or biochemical hyperandrogenism. [4]
- A comprehensive history, including medication history and a physical examination should be completed for symptoms and signs of clinical hyperandrogenism. These include hirsutism, scalp hair loss and severe acne. [4]
- The most important considerations when taking a history of hyperandrogenism are age of onset, ethnicity, duration and rate of progression of symptoms. [25] The differential diagnosis reached may be impacted based on these considerations.
    - Age of onset:
        - **Premenopausal:** More likely to have PCOS or non-classic congenital adrenal hyperplasia (NCCAH) causing hyperandrogenism.
        - **Pregnancy:** There is an increase in maternal serum androgen levels during pregnancy, therefore, gestational hyperandrogenism would be the likely reason. Ovarian tumors/Luteomas are other differentials which are associated with higher androgen concentration.
        - **Postmenopausal:** Mild hyperandrogenic symptoms can be due to relative androgen excess associated with menopausal transition or due to PCOS. Other differential will be ovarian hyperthecosis (nests of luteinized theca cells in the ovarian stroma that may form distinct nodules and these produce testosterone), and androgen producing tumors of ovaries or adrenal glands, conditions that are associated with higher androgen concentrations. [26]
    - Ethnicity:
        - **Hirsutism** is challenging to assess with variation in ethnicity and depends on current use of hair-removal products and treatments. See additional details below on strategies to account for ethnic variation in presentations of hirsutism.
    - Duration and rate of progression:
        - Abrupt onset and rapid rate of progression may indicate alternative diagnoses to PCOS. See below and Red Flags.

Hirsutism:

- Even if clinical hirsutism is not considered severe, it may still be a significant concern to the patient. [4]
- Ask about medications which may affect hair growth including testosterone, anabolic steroids, danazol, metoclopramide, minoxidil, phenytoin, as these may cause hirsutism.
- Combined oral contraceptive pills, Eflornithine and anti-androgens such as spironolactone, finasteride, flutamide, may improve hirsutism. [4]
- Standardized visual scales such as modified Ferriman Gallwey (mFG) score can be used to detect hirsutism, and account for variability in hair pattern and these are dependent on ethnicity (see below and Figure 2). In this scale, a score of 1 to 4 is given based on severity of terminal hair grown in 9 body parts.
    - Ethnicity influences the color, normal distribution, and quantity of body hair. Those individuals of Mediterranean, Middle Eastern, South Asian and Hispanic ethnicities have higher cut offs for the modified Ferriman-Gallwey Score compared to East Asians and Caucasians of Northern European ancestry. [25]
    - Abnormal total mFG scores by ethnicity are as follows:
        - ≥9 in Middle Eastern, Mediterranean, South Asian, and Hispanic women;
        - ≥8 in Blacks and European Caucasians;
        - ≥7 in Southern Chinese women;
        - ≥6 in South American women; and
        - ≥2 in Han Chinese women. [25]
    - Using the modified Ferriman-Gallwey scale can be useful for determination of baseline hair growth pattern and monitoring hirsutism following the use of interventions.

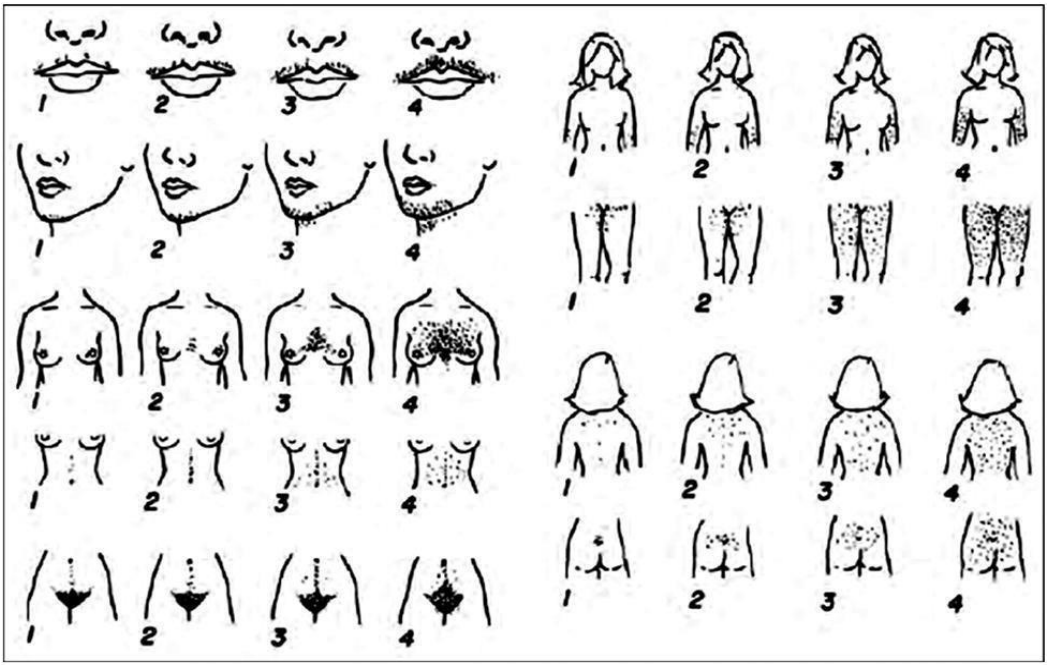

Figure 1. Modified Ferriman-Gallwey Score (mFG).[25]

Hair loss (alopecia):

- Consider using Ludwig visual scales (Figure 2) for assessing scalp pattern hair loss.
- Using these scales can be useful for determination of baseline hair loss and monitoring hair loss following the use of interventions.

Grade	*Description*	*Clinical aspect*
Grade I:	Perceptible thinning of the hair on the crown, limited in the front by a line situated 1–3 cm behind the frontal hair line.	
Grade II:	Pronounced rarefaction of the hair on the crown within the area seen in Grade I.	
Grade III:	Full baldness (total denudation) within the area seen in Grades I and II.	

Figure 2. Ludwig Scale

Acne:

- Acne is a common skin condition, which is one of the common dermatological manifestations of PCOS. A higher prevalence of severe or treatment resistant form of acne may be observed in those with PCOS due to higher circulating androgens. [27]

Metabolic history:

- Difficulty managing body weight, weight gain, obesity, dyslipidemia, metabolic syndrome, Type 2 diabetes, hypertension, and sleep disordered breathing are all associated with PCOS. [4]

Review prior or current medications that impact PCOS symptoms including menstrual irregularities.
These may include:

- Hormone containing contraceptive
- Anti-androgens
- Metformin

Family history:

- PCOS, Hirsutism, Type 2 diabetes, gestational diabetes, gestational hypertension, and Congenital Adrenal Hyperplasia.

2. Assessment

- Complete height and weight, and blood pressure measurements.
    - Healthcare professionals should be aware of their weight biases and the impact this may have on their approach to requesting anthropometric measurements in those with PCOS. Providers can refer to the Practitioner_Guide_Personal_Use-edited.pdf (obesitycanada.ca).
    - Blood pressure is important to measure as an early sign of cardiovascular risk associated with PCOS. [11, 18, 24]
- Complete a physical exam to assess clinical hyperandrogenism (see above) and insulin resistance (skin tags and acanthosis nigricans).

Figure 3. Image of acanthosis nigricans on patient's neck.

3. Red Flags

Screen all patients presenting with PCOS symptoms for the following red flags:

Abrupt and or progressive onset of severe hirsutism and virilization (unexpected deepening of voice and/or clitoromegaly). New, abrupt, and rapid onset is considered increased hair growth over weeks to months (for example, rapid hair growth in 12 months compared to gradual onset of hair growth over 48 months).

- This may indicate an androgen-producing tumor or ovarian hyperthecosis and requires further investigation. Consider testing testosterone and if results are high, request urgent advice or a referral to an Endocrinologist.
- Concerning scenarios include:
    - Onset and progression of hirsutism/virilization over less than twelve months
    - Initial presentation during pregnancy or menopause
    - Very high testosterone/androgen levels

Signs of Cushing's syndrome

- Along with rapid weight gain, if patient has the following physical findings [28]:
    - Wide purple stretch marks on the abdomen, trunk, breast, and other body parts
    - Round face with facial plethora
    - Central fat deposition with thin arms and legs and dorsocervical fat deposition
- If clinical suspicion is high, consider urgent advice or referral to an Endocrinologist or General Internist before ordering confirmatory testing.

Clinical pearl: High random or morning cortisol, in the absence of Cushing's signs **does not rule in** Cushing's.

- Random and morning cortisol can be high when using estrogen/oral contraceptives. [29]
- Morning cortisol can also be high if there is presence of sleep disordered breathing/obstructive sleep apnea. [30]
- If your patient is on estrogen/contraceptives, and serum cortisol is high, further tests are needed:
    - Order a 24-hour urine cortisol.
        - If normal and no signs of Cushing's, you can rule out Cushing's.
        - If high 24-hour urine cortisol, request an urgent referral or advice from an Endocrinologist or a General Internist.

4. Investigations

The diagnosis of PCOS requires the combination of suggestive features and exclusion of differential diagnoses (i.e., exclusion of other conditions causing menstrual irregularities and hyperandrogenemia). [4]

Individuals with severe hirsutism require a more extensive evaluation for serious causes of androgen excess (androgen-secreting ovarian and adrenal tumors and ovarian hyperthecosis) as outlined in section 3, see Red Flags).

For FSH/LH/estradiol: Phase of the menstrual cycle affects these lab results. Hormonal contraceptives need to be discontinued for at least 3 months before testing for these hormones and testosterone/androgen levels. [4] If discontinuation of hormonal contraception is not possible, patient can be considered "at risk of PCOS".

Pregnancy test/Beta-HCG:

- Pregnancy causes cessation of menstruation. Unexpected and unintended pregnancy is common.

Thyroid Stimulating Hormone (TSH):

- Thyroid hormone disorders are often associated with menstrual irregularity. Thyroid hormone abnormalities can also be associated with tiredness, difficulties with weight management, and other nonspecific symptoms.
- For more information on thyroid hormone testing see Choosing Wisely Canada: Endocrinology Metabolism.

Prolactin:

- High prolactin is associated with oligomenorrhea and amenorrhea.
- It is normal to have high prolactin in physiological situations such as pregnancy and lactation.
- The most common pathological cause of hyperprolactinemia is prolactinoma, a benign tumor of the pituitary gland.
- Many common medications may increase prolactin levels by affecting dopamine release: for example, antidepressants, GI motility modifiers, opiates, and estrogen.

FSH, LH, and estradiol:

- These investigations together help differentiate PCOS from ovarian insufficiency and functional/hypothalamic amenorrhea.
- Ideally, these hormones should be checked in the follicular phase (day 2-4 of menstruation) when levels for LH/FSH/estradiol are expected to be lowest.
- In cases of amenorrhea, LH/FSH/estradiol can be done anytime during the menstrual cycle to rule out primary ovarian insufficiency and functional amenorrhea.
- Result interpretation:
    - FSH is high and estradiol is low in ovarian insufficiency (e.g., in menopause).
    - FSH, LH and estradiol are low in functional/hypothalamic amenorrhea; a disorder of chronic anovulation, which is often associated with calorie restrictive diets, substance use and psychological stress.
- Note: LH/FSH ratio was historically used for diagnosis of PCOS, but it is not accurate and should not be used to diagnose PCOS.

Biochemical hyperandrogenism:

- Hyperandrogenism is a diagnostic feature of PCOS. [4] The assessment of biochemical hyperandrogenism is of value in patients with minimal or no clinical signs of hyperandrogenism (e.g. hirsutism). [4]
- It is recommended that testosterone is checked to assess biochemical hyperandrogenism for the diagnosis of PCOS. In Alberta this test can be ordered as **Testosterone, Free, Calculated**. The result report includes a Free Testosterone, which is calculated using Total Testosterone, Albumin, and Sex Hormone Binding Globulin. The report also lists all components and their values.

- Total testosterone alone identifies 20-30% of those with PCOS with biochemical hyperandrogenism, and calculated unbound or free testosterone can identify 50-60% of those with biochemical hyperandrogenism. [4]
    - If total testosterone or free testosterone is not elevated, could consider measuring androstenedione and dehydroepiandrosterone sulfate (DHEAS), however these have low specificity to reflect hyperandrogenism. [4]
    - Repeated androgen testing in the ongoing assessment of PCOS is not needed once a diagnosis of PCOS is established. Instead, monitoring clinical features of hyperandrogenism (i.e., improvement in hirsutism, acne, scalp hair loss) has greater merit in determining success of treatments.[4]

Other relevant biochemistry:

In those with amenorrhea, hyperandrogenemia and features of hypercortisolism, See Red Flags.

17-OH-Progesterone (17-OHP):

- Ideally follicular phase 17-OHP needs to be measured to rule out non-classic congenital hyperplasia (NCCAH). NCCAH is an autosomal recessive condition. Those with NCCAH present with similar symptoms to those with PCOS, therefore, it is clinically difficult to differentiate the two disorders with absolute certainty. [31, 32]
- The prevalence of NCCAH is approximately 50 times less than that of PCOS and only affects between 1-10% of females with hyperandrogenemia, depending on ethnicity. [31]
- Ethnicity may be important for diagnosis of NACCAH. NCCAH is uncommon in African-American females and is more common in female patients of Eastern European Jewish origin (prevalence 1:27), Hispanic (prevalence 1:40), Slavic (prevalence 1:50) or Italian origin (prevalence 1:300). [31]
    - **The test for 17-OHP is not automated, and there is a limitation in testing capacity in Alberta. Therefore, this test is not recommended for every patient with a clinical suspicion of PCOS in Alberta at present. This recommendation may change in the future**.
    - It is important to test individuals:
        - Of Eastern European Jewish descent, Hispanic, Slavic, or Italian descent.
        - Individuals who are suspected of PCOS with healthy-weight BMI (18.5-24.9).
        - In individuals with PCOS planning for pregnancy immediately but 17-OHP has never been checked, given the risk that offspring could be affected with a more severe classic 21-hydroxylase deficiency if the partner is also a carrier of the recessive gene mutation.
    - If the screening test is positive for high follicular phase 17-OHP (6-30 nmol/L), an ACTH stimulation test is then completed to confirm a diagnosis of NCCAH. [33]
    - Complete a referral to an Endocrinologist if the follicular phase 17 OHP is completed and is high.

Testing for metabolic risk factors:

- If PCOS is suspected, cardiometabolic risk factors should also be assessed as patients with PCOS are at higher risk of cardiovascular disease and diabetes. [4, 11, 12, 18, 23, 24, 34-38]
    - This includes glycemic testing, a lipid panel, blood pressure and body weight.

Glycemic testing:

- Regardless of age and BMI, women with PCOS have an increased risk of diabetes. [23, 24, 39] Glycemic status should be assessed in all individuals at risk of PCOS. [4]
- A 75g oral glucose tolerance test (OGTT) is the most accurate test to assess glycemic status in PCOS or suspected PCOS to rule out impaired fasting glucose (IFG) and impaired glucose tolerance (IGT). [39]
- If an OGTT cannot be performed, fasting plasma glucose and/or glycated hemoglobin (HbA1c) could be considered, which are not as accurate. [4, 39]
- Glycemic status should then be reassessed every one to three years, based on additional individual risk factors for diabetes. [4, 39]
    - Note: Insulin resistance is a pathophysiological feature of PCOS, however checking fasting insulin is of limited clinical relevance and therefore not recommended for routine care. Clinical examination for signs of insulin resistance (acanthosis nigricans, obesity) and the OGTT can be used to assess risk of pre-diabetes and diabetes. [4, 34, 39]

Other metabolic tests:

- All patients with PCOS, regardless of age and BMI, should have a lipid profile assessment at diagnosis. [4] Low HDL-cholesterol, and high triglycerides, total cholesterol and apo-lipoprotein B are common lipid abnormalities in those with PCOS. [18, 24, 40-43]
- If a patient presents with additional metabolic risk factors (e.g., high BMI, metabolic syndrome) consider screening for Metabolic Dysfunction-Associated Fatty Liver Disease (MAFLD; formerly NAFLD) as those with PCOS are at increased risk for MAFLD. [24, 44-46] See the Non-Alcoholic Fatty Liver Disease (NAFLD) Primary Care Pathway (albertahealthservices.ca).

Pelvic ultrasound:

- An ovarian ultrasound is not necessary to confirm a diagnosis of PCOS in patients with irregular menstrual cycles and hyperandrogenism (i.e., already meeting the minimum two criteria for diagnosis of PCOS). However, in adults with only one diagnostic feature of PCOS (menstrual irregularity or hyperandrogenemia), use ultrasound to evaluate polycystic ovary morphology (PCOM). [4]
- Since laboratory assay is not standardized, AMH is not recommended as an alternate to pelvic ultrasound at this time in Alberta. In addition to age, AMH is influenced by many factors including body mass index, day of menstrual cycle. PCOM or AMH is not validated to be used in adolescents. The Guideline recommends either serum AMH or pelvic ultrasound to be used to define PCOM; however, both tests should not be performed to limit overdiagnosis. [4]
- There are no definitive criteria to define PCOM by ultrasound in adolescents, therefore, this evaluation is not recommended for this developmental age group. [4]
- Follicle number per ovary (FNPO), follicle number per cross section (FNPS) and ovarian volume are considered accurate ultrasound markers of polyfollicular morphology in adults and this is used to define PCOM using transvaginal ultrasound. [4] Note: FNPO and FNPS may not be included in radiology report for PCOM.
    - A FNPO of >20, or ovarian volume of >10 ml or FNPS >10 in at least one ovary is considered the threshold for PCOM. [4]
- Transvaginal ultrasound is preferred over abdominal ultrasound to accurately assess ovarian morphology and follicle numbers. [4] Patient preference should still be considered as some patients may have a strong preference of one form of ultrasound over another. For example, young patients who are not sexually active or those who have experienced past trauma may not be comfortable with a transvaginal ultrasound.
- Transabdominal ultrasound may suffice if the patient declines a transvaginal approach but may produce less accurate results. [4]
    - If using transabdominal ultrasound, an ovarian volume of >10ml or FNPS >10 in either ovary in adults may be considered the threshold for PCOM. [4]

5. Confirm PCOS Diagnosis

Confirm PCOS diagnosis if other disorders are ruled out and if at least two of the following are present: [4]

- Clinical or biochemical hyperandrogenism
- Irregular menstrual cycles (oligomenorrhea or amenorrhea)
- Polycystic ovary morphology on pelvic ultrasound

If there is an unusual presentation, atypical symptoms, or difficulty in interpreting the results, request advice from a relevant specialist.

6. PCOS Management

6A. Nutrition, exercise, and lifestyle counseling

Healthy lifestyle behaviors encompassing healthy eating and regular physical activity are recommended in all of those with PCOS to optimize health, quality of life, body composition, cardiometabolic risk and weight management (maintaining weight, preventing weight gain and/or weight loss). [4]

Lifestyle

- A healthy lifestyle supports cardiometabolic health, optimizes blood glucose, lipid profile and weight management. [4]
- There are benefits to a healthy lifestyle in those with PCOS even in the absence of weight loss. [4]
- Encourage reduction or quitting of smoking and alcohol use.

Nutrition and diet

- There is no specific diet that is recommended in PCOS. A healthy diet following Health Canada guidelines, Eat Well Live Well is recommended.
- Ideally the diet should be co-designed between a Registered Dietitian and the patient to meet food preferences, allowing for a flexible, individual, and sustainable approach to achieve nutritional goals and avoid restrictive and nutritionally unbalanced diets as per population guidelines. [4]
    - Alberta Health Link Dietitian Service
    - Referring patients for nutrition services.

Exercise

- Some physical activity is better than none, and all forms of exercise can have health benefits. Advise sustainable physical activity based on individual ability, preferences and goals. Referral to an exercise specialist (which may be available through your primary care network, depending on local resources) for assistance with exercise program design may be helpful.
- Recommendations for the prevention of weight gain and maintenance of general health for adults (18-64 years) include:
    - Aiming for a minimum of 150 to 300 minutes of moderate-intensity activities or 75 to 150 minutes of vigorous-intensity aerobic activity per week or an equivalent combination of both types of activity throughout the week, plus muscle strengthening activities (e.g., resistance training/flexibility) on two non-consecutive days per week. [4]
- Recommendations for adolescents include:
    - Aiming for at least 60 minutes of moderate- to vigorous-intensity physical activity per day, including muscle strengthening activities, at least three times per week. [4]

6B. Specific Symptom Management

Shared decision making between the patient (and parent/s or guardian/s if the patient is an adolescent) and the healthcare provider will facilitate individualized plans to address specific symptoms of PCOS.

Understanding an individual's preferences and values to treat symptoms and treatment outcomes should be considered when prescribing medications.

Management of menstrual irregularities

- Any form of combined hormonal contraceptives can be used to regularize the menstrual cycle based on individual preference.
- Combined oral contraceptive pills (COCPs) are commonly prescribed for adults and adolescents with PCOS to ameliorate the hormonal disturbances and normalize menstrual irregularities. When prescribing hormonal contraception or COCP in adults and adolescents with PCOS general population guidelines should be considered. [4]
- Where COCP is contraindicated, not accepted, or not tolerated, metformin may be considered for irregular menstrual cycles. [4]
- Metformin alone can be considered in adolescents 'at risk' of or with PCOS for menstrual cycle regulation, however, there is limited evidence. [4]
- When estrogen is contraindicated or not preferred by the patient, progestin only contraception such as progestin only pills, IUD, Intramuscular injection, subdermal implant can be used. Continuous use of progesterone prevents buildup of endometrium and may therefore cause amenorrhea.
- If prolonged amenorrhea (>90 days), rule out pregnancy, and consider performing a progesterone withdrawal test:
    - A progesterone withdrawal test can help evaluate a patient's outflow tract and endometrium build up.
    - To complete the test use Medroxyprogesterone acetate 10 mg orally once daily for 7 to 10 days, or micronized progesterone 200 to 400 mg daily for 7 to 10 days. [47]
    - A withdrawal bleed usually occurs two to seven days after the challenge test.
    - A negative progesterone withdrawal test usually signifies an outflow tract abnormality or inadequate estrogenization. [7, 47]
    - If no withdrawal bleed, recommend pelvic ultrasound to assess for endometrial thickness and seek advice or referral to gynecology.

Clinical pearl: Metformin is associated with gastrointestinal side-effects that are dose dependent and self-limiting. Metformin use may be associated with low vitamin B12 levels, particularly for those at risk of deficiency (diabetes, vegan diet, pernicious anemia). Starting at a low dose, with 500 mg increments 1-2 weekly and extended-release preparations may minimize side-effects and improve adherence. Suggested daily maximum dose of metformin is up to 2 g/day.

Management of hirsutism, acne, or alopecia

Hormonal therapies, anti-androgens, and hair-removal treatments are the mainstays of treatment for clinical signs of androgen excess. Some therapies may be beneficial for treatment of multiple signs of hyperandrogenism.

Hirsutism management:

- Combined hormonal contraception/COCP is the first line for treatment of hirsutism. Antiandrogenic properties of combined contraception are related to both components of the pill: estrogen and progestin.
- COCP could be used in adults with PCOS, and in adolescents 'at risk' or with PCOS for management of hirsutism. [4]
- 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 six months of hormonal contraception and/or cosmetic therapy. [4]

- In those with contraindications to COCP or when COCP's are poorly tolerated, anti-androgens can be considered for use for hirsutism, provided effective contraception is used. [4]
- Spironolactone at 25-100 mg/day appears to be effective, well tolerated and to have lower risk of adverse effects . [4]
    - Note: Spironolactone can cause hyperkalemia, particularly in the setting of renal insufficiency or in combination with other medication such as ACE inhibitors. [48]
- Removal of excess body hair may involve cosmetic methods such as bleaching, waxing, shaving, electrolysis, laser hair removal, or topical depilatories. Some individuals may develop cutaneous allergic reactions to topical depilatories.
- A topical cream medication, eflornithine hydrochloride; 13.9%, can be applied twice a day to unwanted areas of hair growth to prevent new hair from growing. It is usually not covered by insurance and must be used every day, or the hair will re-grow.

Clinical pearl: When anti-androgens are used and if pregnancy is possible, individuals must be educated and counseled, including adults and adolescents with PCOS, parent(s) or guardians, regarding the risk of incomplete development of external genitalia of male fetuses (undervirilisation). To prevent this risk, those who can get pregnant should be counseled to use effective contraception while taking anti-androgens. [4]

Acne management:

- Acne is common in the general population and in individuals with PCOS. [27] Topical treatments with retinoids, benzoyl peroxide and topical antibiotics are commonly used.
- Use of COCPs for treating acne in PCOS patients can be added to topical acne therapy or used as monotherapy. [27]
- Dermatology consultation may be necessary to manage difficult to treat acne. [4, 27]

Alopecia management:

- Unlike acne and hirsutism, medical management of hair loss is much more difficult. In addition to proper nutrition, adequate sleep, scalp hygiene, treatments used for management of hirsutism and acne (COCP and anti-androgens), and minoxidil might be beneficial.
- Dermatology referral may be necessary.

PCOS and fertility

All individuals with PCOS should have an assessment of their reproductive plan and be provided education on optimization of reproductive health when appropriate. Those with PCOS can be reassured that pregnancy can often be successfully achieved naturally or at times with assistance. Patients may need referral to a fertility specialist or other specialist as appropriate.

PCOS and pregnancy planning:

Those with PCOS are at risk of infertility due to anovulation. PCOS related comorbidities such as obesity, metabolic disturbances and hyperandrogenemia can pre-dispose those with PCOS to a higher risk of adverse pregnancy outcomes, including gestational diabetes, hypertensive disorders, preterm birth, and miscarriage. [4, 13, 15, 21]

- Those with PCOS are at risk of infertility due to anovulation. PCOS related comorbidities such as obesity, metabolic disturbances and hyperandrogenemia can pre-dispose those with PCOS to a higher risk of adverse pregnancy outcomes, including gestational diabetes, hypertensive disorders, preterm birth, and miscarriage. [4, 13, 15, 21]
- Whenever possible, preconception health optimization should be considered including optimizing body weight, blood pressure, diet and nutritional status, exercise, sleep, mental and emotional health, and smoking cessation and reducing alcohol. [4]
- Diet and lifestyle counseling should also be offered to those who are pregnant with PCOS, given the risk of higher pre-pregnancy weight, excess gestational weight gain and pregnancy complications. [4]

- Blood pressure measurement should be performed when planning pregnancy or seeking fertility treatment, given the high risk of hypertensive disorders in pregnancy and the associated comorbidities in those with PCOS. [4]
- A 75 g 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 hyperglycemia and the associated comorbidities in pregnancy. If not performed preconception, an 75 g OGTT could be offered at the first prenatal visit and all women with PCOS should be offered the test at 24-28 weeks gestation. [4]
- Prenatal vitamin supplementation with folic acid should be started for routine preconception care.

PCOS and assisted reproduction:

- Patients with PCOS may need assistance in getting pregnant. They may need ovulation induction and/or assisted reproductive procedures such as IUI, IVF, ovarian drilling.
    - Letrozole is the first-line pharmacological treatment for ovulation induction in those with PCOS, with no other infertility factors.
- Metformin could be used alone, in those with PCOS with anovulatory infertility and no other infertility factors, to improve clinical pregnancy and live birth rates. However, advise patients that there are more effective ovulation agents and consider referral to a fertility specialist as appropriate.

Clinical pearl: Infertility is a multifactorial condition. In addition to anovulation, there could be other factors such as tubal pathology, male factor (low sperm count) and others. Standard infertility workup should still be completed in patients with PCOS who are having difficulty conceiving.

Weight management

- For some people with PCOS, weight management, including weight maintenance and weight loss, can improve clinical symptoms including menstrual irregularity, anovulation, clinical hyperandrogenism and cardiometabolic risk factors. [4] Please see the recommendations in both sections 6A and 6C.

Anti-obesity medications:

- Liraglutide, semaglutide (glucagon-like peptide-1 (GLP-1) receptor agonists), tirzepatide (a dual GLP-GIP (gastric inhibitory polypeptide) receptor agonist) or orlistat could be considered, in addition to active lifestyle intervention, for the management of higher body weight in adults with PCOS. [4]
- It is important to ensure effective contraception when pregnancy is possible, for those who take GLP-1 receptor agonists. There is limited evidence for long-term use and safe use during pregnancy for GLP-1 receptor agonists. [4]
- GLP-1 analogs should be stopped at least 2 months before pregnancy. [4]

Clinical pearl: Gradual dose escalation for GLP-1 receptor agonists is recommended to reduce gastrointestinal adverse effects. Counting the clicks in a semaglutide pen in between dose increments can help deliver a smaller amount, which is still effective yet better tolerated. For example, 18 clicks for 0.25 mg, 36 for 0.5 mg and 72 for 1 mg of semaglutide. For more information see semaglutide click-counting.

PCOS and supplements

- Individuals with PCOS often use various supplements to improve PCOS symptoms. It is important to ask patients about their current use of supplements and how these are being used to manage PCOS symptoms.
- The use of nutritional supplements and complementary therapies may at times be useful in individuals in addition to a healthy balanced diet and lifestyle habits; however, there is insufficient quality evidence to support individual supplements or therapies to improve PCOS symptoms. Shared decision making with patients and monitoring of use of supplements when clinically relevant is recommended. [4, 49, 50]
- Patients may have a dietary inadequacy, or a specific nutrient deficiency related to PCOS and referral to a Registered Dietitian can be recommended for a complete diet-nutritional assessment. [49]

The following supplements may be relevant to PCOS management:

- **Inositol:**
  - Inositol (in any form) supplementation could be considered based on individual preferences and values, noting limited harm and potential for improvement in metabolic measures, however there is limited evidence for clinical benefits including hormone regulation, ovulation, insulin metabolism, hirsutism or management of body weight. [4, 49]
- **Vitamin D:**
  - Vitamin D is derived primarily from exposure to sunlight and from dietary sources such as fortified dairy, oily fish, and dairy products. Vitamin D deficiency is common in northern climate. Therefore, routine testing to check for low vitamin D level is not necessary.
  - Vitamin D is important for calcium metabolism and maintaining bone health, metabolic and endocrine functions. [51]
  - Low Vitamin D may be associated with insulin resistance, and levels may be lower in obese compared with non-obese people. [51]
  - If sun exposure and dietary intake is inadequate, then supplementation is recommended following population guidelines.
- **Omega 3 fatty acids:**
  - Long chain omega-3 fatty acids found in fatty fish and fish oil supplements, may have beneficial effects on blood triglycerides and total cholesterol in those with PCOS. [41, 52] Long chain omega-3 fatty acids can improve blood pressure, lipid profile and inflammation, and have potential to impact primary and secondary prevention of cardiovascular disease and reduce overall metabolic risk. [41, 52-54]
- **Folic acid and other B-group vitamins (B1-Thiamin, B6-pyridoxine, B12-methylcobalamin):**
  - All females, including those with PCOS, in the reproductive age group (12–45 years of age) who have preserved fertility should be advised to take folic acid supplementation to prevent neural tube defects during medical wellness visits (e.g., birth control renewal, Pap testing, yearly gynecological examination) regardless of whether a pregnancy is planned. As pregnancies can be unplanned, this recommendation applies to all women who may become pregnant. [55]
  - B-group vitamin deficiency in PCOS has been reported and is associated with long-term and/or high dose use of metformin. [55-57] Ensuring those with PCOS follow a healthy balanced diet; meeting the dietary recommendations for B vitamins is important for general health, energy metabolism and homocysteine metabolism (low homocysteine is a risk factor for cardiovascular disease). [55-58]
- **Probiotics-prebiotics:**
  - Meta-analyses have shown that probiotic supplementation may have a beneficial effect on BMI, fasting plasma glucose, and lipids in PCOS. There remains limited data on optimal probiotic strains, prebiotic types, length of use, and doses. [59] The most common fermented foods such as yogurt, miso, and kimchi, naturally contain probiotics.

6C. Consider other associated health risks

Those living with PCOS are at increased risk of several associated health conditions, therefore thorough screening and evaluation for these risks is essential in the management of PCOS. [4, 24]

Pre-diabetes and diabetes:

Regardless of age and BMI, those with PCOS have an increased risk of impaired fasting glucose, impaired glucose tolerance and type 2 diabetes. [4, 12, 23, 24, 34]

- Follow guidelines in 6A and Diabetes Canada prevention guidelines for management of glucose abnormalities. [34]
- Metformin alone can be considered in adults with PCOS to manage weight, insulin resistance, glucose, and lipid profile, and evidence shows this can have the greatest benefit in those with a BMI ≥ 25 kg/m^2. [4]

Cardiovascular disease risk:

- **Blood pressure should be checked at least annually.**
- Individuals with PCOS often have risk factors associated with cardiovascular disease including increased blood pressure, blood lipids and obesity, and should be considered at increased risk of cardiovascular disease and potential for increased cardiovascular morbidity and mortality. [4, 11, 12, 18, 24, 35-38]
- Test for and treat any lipid abnormalities appropriately.
    - If blood lipids are high, follow general population guidelines for management:
        - Dyslipidemia and CVD prevention (Canadian Cardiovascular Society Guidelines)
        - Prevention and Management of Cardiovascular Disease Risk in Primary Care (Toward Optimized Practice)

Metabolic dysfunction-associated fatty liver disease (MAFLD):

- The prevalence of MAFLD is significantly higher and more severe in individuals with PCOS. [24, 44-46]
- Diet and lifestyle modification should be the basis of management, see 6A.
- In addition to healthy dietary patterns and physical activity, a reduction of alcohol consumption is recommended.
- Insulin sensitizers and glucagon-like peptide-1 agonists may help manage and treat MAFLD. [44-46, 60]
- Bariatric surgery may also show improvement of MAFLD in obese women with PCOS. [46]

Endometrial hyperplasia and cancer:

- Premenopausal women with PCOS have a higher risk of developing endometrial hyperplasia and endometrial cancer. [4, 9, 14, 17] Inform the patient about this risk. At least 4 cycles per year is recommended to prevent endometrial hyperplasia. [4, 9, 14, 17, 61]
    - Long-standing untreated amenorrhea, increased body weight, type 2 diabetes, family history of endometrial hyperplasia and a persistent thickening of endometrium (>16mm), are additional risk factors with PCOS for endometrial hyperplasia and endometrial cancer. [4, 9, 14, 17, 61]
    - Endometrial hyperplasia and cancer can be diagnosed by endometrial biopsy. Indications for an endometrial biopsy include: [62]
        - All patients over 40 years of age with abnormal uterine bleeding.
        - Younger patients with abnormal uterine bleeding and risk factors (stated above).
        - Failed medical management of abnormal uterine bleeding, or persistent uterine bleeding.
- Preventative strategies for endometrial hyperplasia include weight management and menstrual cycle regulation. [4]
    - Combined hormonal contraceptives are often used as the first line agents which can prevent endometrial buildup by ensuring a predictable bleeding cycle.
    - Regular progesterone therapy prevents endometrial hyperplasia. Progesterone containing contraception such as progestin only pills [4], and levonorgestrel-releasing intrauterine device (IUD) can be used to prevent endometrial hyperplasia and menstrual irregularity. An IUD could be used for contraception in women with contraindications or intolerance to COCP.

- The overall chance of developing endometrial cancer is low, therefore routine screening in the absence of menstrual abnormalities is not recommended. [4]
- If a patient has heavy or frequent menstrual abnormalities, see the Provincial Adult Abnormal Uterine Bleeding Primary Care Clinical Pathway for advice on workup and management of any associated

Psychological/mental health:

Mental health concerns related to the physical sequelae of PCOS are common. [10, 20, 22, 24, 63]

- Diet and lifestyle intervention and other therapies (e.g. hormonal contraception, metformin, manual hair removal) that target PCOS features have potential to improve psychological symptoms. [4, 63] See 6A.

Depression and anxiety:

- PCOS is associated with a high prevalence of moderate to severe depressive symptoms and anxiety. [4, 22, 63, 64] Screening for depression in all adults and adolescents with PCOS is recommended using validated screening tools. [4]
    - **For Depression: Use the Patient Health Questionnaire - PHQ-9:**
        - PHQ-9 is a patient-reported tool that asks a patient to answer 9 questions on depression. See Patient Health Questionnaire (PHQ-2 & PHQ-9).
    - **For Generalized Anxiety Disorder: Use the GAD-7:**
        - GAD-7 is a patient-reported tool that asks the patient to answer 7 questions on anxiety. See Self-Test for Anxiety (GAD-7).

Manage as per guidelines for the general population and refer appropriately. [4, 63, 64]

Body image:

- Those with PCOS are at increased risk for experiencing poor body image and body dissatisfaction, and this can be associated with excess body weight, depression, anxiety, self-esteem, eating disorders and overall reduced quality of life. [4, 63, 64]
- Awareness of poor body image in those with PCOS can help identify a management plan that includes 6A and referral to a psychologist or psychiatrist for assessment and on-going management. [4, 63, 64]

Eating disorders:

- Eating disorders and disordered eating should be considered in PCOS, regardless of body weight, particularly in the context of weight management and lifestyle interventions. [4, 10, 22, 63]
- If disordered eating or eating disorders are suspected, refer to a psychologist or psychiatrist for assessment and management.
- Eating disorder support network of Alberta and referral form.
    - Addressing a Possible Eating Disorder (Point-of-Care Reference) Common Practice
    - Questions for Eating Disorder Care (Point-of-Care Reference)

Obstructive sleep apnea:

- Patients with PCOS have a higher prevalence of obstructive sleep apnea, independent of their BMI. [4, 65]
- Assess for symptoms (i.e., snoring in combination with waking unrefreshed from sleep, daytime sleepiness, or fatigue) and if present, screen with validated tools or refer for assessment. A diagnosis of sleep apnea requires a formal sleep study. [4]
- Please refer to the Uncomplicated Obstructive Sleep Apnea pathway for further information.

7. Advice Options

In addition to where specified in the clinical pathway algorithm, you can request non-urgent advice at any point when uncertain about medications, next steps in treatment, imaging, or resources available. Available specialists for Gynecology and Endocrinology may be zone dependent.

Zone	Program	Online Request	Phone Number
Urgent Telephone			
All Zones	RAAPID	N/A	**North:** 1-800-282-9911 or 780-735-0811 **South:** 1-800-661-1700 or 403-944-4486
Non-Urgent Electronic			
All Zones	Netcare eReferral		N/A
Non-Urgent Telephone			
Calgary	Specialist Link	Online Request	403-910-2551
Edmonton, North	ConnectMD	Online Request	1-844-633-2263

8. Referral Process

Referral pathways are guidelines to help referring providers know what information, labs and diagnostic imaging are required with their referral to a specialty. These pathways are co-designed with Primary and Specialty Care, AHS Operations, and patients to ensure the right amount of information is included throughout the referral process to triage the patient as quickly as possible.

To ensure referring providers have referral information at their fingertips, referral pathways may link to clinical pathways when available. AHS manages referral pathways and extensive work is ongoing as part of the Alberta Surgical Initiative. If you have questions or want to know more about the referral pathway development process, please email access.ereferral@ahs.ca.

- **Urgent Referral –** Call surgeon on call via RAAPID or call 911 ***(if applicable).***
- For all referrals to Gynecology please ensure to follow the Provincial Gynecology, Adult Referral Pathway.
- For referrals to Endocrinology:
    - Search Endocrinology on the Alberta Referral Directory.
    - For Calgary Zone follow:
        - Endocrinology_AccessPathway_Jan2019 (specialistlink.ca)
    - For Edmonton Zone:
        - Division of Endocrinology and Metabolism: 3B Kaye Edmonton Clinic: e-referral in Connect Care. Fax: 780-492-6444
        - Garneau Endocrinology: Physician referral form GE_Referral_Form.pdf
        - C-endo (a division of C-health): c-health.ca/wp-content/uploads/2023/07/ACTIVE-C-endo-Edmonton-ABPM-Referral-Form-2023.pdf
        - Zia Medical: ziamedical.ca/endocrinology
- For referrals to Feritility Specialists:
    - There are covered and non-covered services available and are zone dependent.
    - Please refer to the Alberta Referral Directory to search for information in your zone.

BACKGROUND

About this pathway

- This pathway was developed in collaboration with Endocrinologists, Gynecologists, Primary Care Physicians, Patient and Family Advisors, and the Alberta Health Services Provincial Pathways Unit (AHS PPU).
- Condition-specific clinical pathways are intended to offer evidence-based guidance to support primary care providers in caring for patients with a range of clinical conditions.

Authors and conflict of interest declaration

- The authors represent a multi-disciplinary Co-Design Project Team. Additional review and expertise provided by the multiple Provincial Working-Group members. Membership available on request by emailing AlbertaPathways@ahs.ca.

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Pathway review process, timelines

- Primary care pathways undergo scheduled review every two to three years, or earlier if there is a clinically significant change in knowledge or practice. The next scheduled review is **January 2028**. However, we welcome feedback at any time. Please send us your feedback here.

Copyright information

PROVIDER RESOURCES

Resources	Link
International Evidence-based Guideline for the assessment and management of polycystic ovary syndrome 2023	Evidence-Based-Guidelines-2023.pdf (monash.edu)

PATIENT RESOURCES

Resources	Link
Patient Pathway on MyHealthAlberta > A webpage and two PDF formats are available to allow for easy printing, download, or scanning a QR code with the patient's smart phone for more information at their convenience.	Your Journey with PCOS: myhealth.alberta.ca/HealthTopics/pcos-pathway/Documents/pcos-pathway-summary.pdf

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