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# Polycystic ovary syndrome

Therapy for this reproductive and metabolic disorder remains focused on managing symptoms, including infertility caused by anovulation, and reducing long-term health risks such as endometrial cancer and type 2 diabetes.

**ABSTRACT: The clinical presentation of polycystic ovary syndrome is widely variable, with complaints encompassing oligomenorrhea, infertility, obesity, hirsutism, endometrial cancer, and diabetes. Community physicians caring for reproductive-age women will invariably encounter this reproductive and metabolic disorder resulting from ovarian hyperandrogenism and insulin resistance. While community physicians should be aware of the diagnostic criteria for polycystic ovary syndrome, it is more important to have a thorough understanding of symptom management and prevention of long-term complications. Historically, clomiphene citrate has been used to address infertility by inducing ovulation, with more recent evidence supporting the use of letrozole as first-line therapy for ovulation induction. These and other mainstay treatments may be needed to address anovulation, obesity, and hirsutism. Patients should also be monitored for endometrial cancer and type 2 diabetes.**

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Polycystic ovary syndrome (PCOS) is a prevalent reproductive and metabolic disorder with variable phenotypes and an underlying pathophysiology that is still not completely understood. While the earliest description of the polycystic ovary dates back to the 17th century,[1] the characterization of the present-day disorder known as PCOS was first detailed by Irving Stein and Michael Leventhal in 1935.[2] In a seminal paper, the two prominent gynecologists described a case series of seven women with enlarged ovaries associated with oligomenorrhea or amenorrhea, sterility, and clinical hyperandrogenism. Histopathologic determination of the disorder was undertaken by wedge biopsy of the ovaries. The surgical procedure that led to characterization of the disorder also serendipitously led to the first therapeutic intervention for infertile women with PCOS. Five of the seven women subsequently conceived after normalization of their menstrual cycles. One woman who did not conceive was affected by male factor infertility and the other woman was lost to follow-up.

As a result, Stein-Leventhal syndrome was the term used for more than 50 years for the heterogeneous clinical features of the disorder now known as polycystic ovary syndrome. In 1990 the first international definition of PCOS was developed, which has since been revised by various professional bodies. The lack of consensus in the definition of PCOS further highlights the uncertainty about the pathophysiology of the disorder. However, for the practising physician a thorough understanding of symptom management and prevention of long-term complications is more important than an understanding of the different diagnostic criteria for PCOS.

## Pathophysiology

The abnormal findings in PCOS are a result of ovarian hyperandrogenism[3]

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and insulin resistance.[4] Evidence suggests that the ovarian hyperandrogenism in PCOS is a result of primary ovarian dysfunction and is secondary to disordered gonadotropin activity. While not included in diagnostic criteria for PCOS, the elevated level of serum luteinizing hormone (LH) in affected patients due to inappropriate secretion has long been recognized.[5] LH is the ligand for the LH receptor on the ovarian theca cells responsible for ovarian androgen production. Genome-wide association studies conducted on hyperandrogenic subjects with PCOS revealed genome-wide significance for a locus mapping to chr 11p14.1 in the region of the follicle-stimulating hormone beta polypeptide (FSHB).[6] This single-nucleotide polymorphism was associated with LH levels that result in the elevated LH:FSH ratios often seen in PCOS, providing further support for the hypothesis that dysregulated gonadotropin secretion in PCOS leads to secondary hyperandrogenism. This gonadotropin imbalance favors an exaggerated intraovarian androgen environment under the influence of LH, and impaired folliculogenesis resulting in anovulation due to a relative FSH deficiency.

Evidence also suggests that the ovarian hyperandrogenism seen in PCOS is primary, with abnormal ovarian steroidogenesis through overexpression of the *CYP17* gene being responsible for androgen biosynthesis, as well as increased expression of the LH receptor, which would potentially render the ovarian theca cells more sensitive to LH stimulation.[7,8] The ovarian hyperandrogenism appears to play a role in the appearance of the polycystic ovary on ultrasound and the follicular arrest and anovulation that is prevalent in PCOS. The ovarian phenotype may result from either endogenous or exogenous androgens, as demonstrated in the similar ultraosonographic findings and gene expression profile studies on the ovaries of women with PCOS and the ovaries of androgen-treated female-to-male transgender individuals.[9]

Evidence for the role of insulin resistance in the pathophysiology of PCOS and ovarian hyperandrogenism is demonstrated indirectly by the findings of hyperandrogenism in female subjects with type A insulin resistance syndrome, a disorder characterized by a mutation in the insulin receptor gene.[10] Insulin contributes to the biochemical and clinical hyperandrogenism by directly enhancing theca cell ovarian androgen production in concert with LH,[4] and indirectly by lowering sex hormone-binding globulin, the carrier protein responsible for reducing circulating free testosterone levels.[11] The high prevalence of impaired glucose tolerance and type 2 diabetes in women with PCOS has led researchers to consider the role of insulin sensitizers in treating PCOS.

## Diagnostic criteria

Three sets of diagnostic criteria for polycystic ovary syndrome are used commonly (**Table 1**). All require the exclusion of other known disorders.

The National Institutes of Health (NIH) conference on PCOS in 1990 led to the first internationally accepted diagnostic criteria. The two criteria (clinical and/or biochemical evidence of hyperandrogenism and menstrual dysfunction) were based on expert opinion solicited through a questionnaire. In 2003 the Rotterdam criteria developed by the European Society of Human Reproduction and Embryology and the American Society for Reproductive Medicine (ESHRE/ASRM) allowed for the inclusion of polycystic-appearing ovaries on ultrasound. This was defined as 12 or more follicles measuring 2 to 9 mm in at least one ovary, or an ovarian volume greater than 10 mL in the absence of a dominant follicle. The ESHRE/ASRM diagnostic guidelines only required meeting two of three criteria (clinical and/or biochemical hyperandrogenism, oligomenorrhea and/or anovulation, and polycystic ovaries).[12] Most recently, the experts contributing to the Androgen Excess Society (AES) diagnostic guidelines required meeting two criteria (clinical and/or biochemical hyperandrogenism and either ovarian dysfunction or polycystic ovaries).[13]

**Table 1. Diagnostic criteria for polycystic ovary syndrome.**

| **National Institutes of Health criteria (1990)**<br>• Must meet both criteria | **European Society for Human Reproduction and Embryology and American Society for Reproductive Medicine Rotterdam criteria (2003)**<br>• Must meet two of three criteria | **Androgen Excess Society criteria (2006)**<br>• Must meet both criteria |
|---|---|---|
| Clinical and/or biochemical evidence of hyperandrogenism | Clinical and/or biochemical evidence of hyperandrogenism | Clinical and/or biochemical evidence of hyperandrogenism |
| Menstrual dysfunction | Oligoovulation or anovulation | Ovarian dysfunction or polycystic ovaries |
| | Polycystic ovaries | |
| Exclusion of other known disorders is required as well. | Exclusion of other known disorders is required as well. | Exclusion of other known disorders is required as well. |

The Rotterdam criteria are the most widely used for PCOS diagnosis, and like the more liberal AES criteria they allow for different phenotypes of the disorder. Prevalence estimates for PCOS obtained using the Rotterdam and AES criteria (12% to 18%) were up to twice that obtained using the NIH criteria (9%).[14] NIH-defined PCOS is the most common phenotype, and women with this phenotype are most at risk of developing reproductive and metabolic abnormalities, specifically type 2 diabetes. Women with the Rotterdam PCOS phenotype without hyperandrogenism are least at risk of reproductive and metabolic abnormalities.[15]

## Evaluation

As PCOS is ultimately a diagnosis of exclusion, other endocrinopathies that have clinical features similar to those of PCOS must be considered. If ovulatory dysfunction exists, ordering tests to rule out causes such as thyroid dysfunction and hyperprolactinemia (e.g., thyroid-stimulating hormone, prolactin assay) is imperative. Considering the possibility of other more serious causes of androgen excess, such as nonclassic congenital adrenal hyperplasia (confirmed with an elevated 17-hydroxyprogesterone level) and androgen-producing tumors (confirmed with total testosterone levels twofold above upper-normal), is also recommended. In the presence of oligomenorrhea or amenorrhea, measurement of serum FSH and estradiol may be warranted to rule out ovarian insufficiency or hypogonadotropic hypogonadism (hypogonadism of hypothalamic or pituitary origin).

The most common clinical feature of hyperandrogenism is hirsutism: the growth of excessive hair in a male-type pattern caused by the conversion of vellus hair to terminal hair under androgen effect on the pilosebacous unit. Hirsutism is most commonly assessed using the modified Ferriman-Gallwey scale to quantify the amount of hair growth on various androgen-dependent body areas. However, race and ethnicity play a significant part in hirsutism.[16] Additionally, the Ferriman-Gallwey scoring system can be somewhat impractical in everyday clinical practice, and will be affected by a patient's recent waxing, shaving, or other depilation. Practically, hirsutism remains largely a self-reported symptom. In the absence of hirsutism, acne may be considered a clinical marker of hyperandrogenism.

A strict definition of biochemical hyperandrogenism in PCOS does not exist. A free testosterone index and a free androgen index are thought to be the most sensitive markers of biochemical hypernadrogenemia by the authors of the Rotterdam criteria.[12] However, the assay methods are variable and have significant limitations. Total testosterone is not a sensitive marker of androgen excess, but measurement may be useful if an androgen-secreting neoplasm is suspected.

Irregular or absent menstrual cycles are the most common clinical finding of PCOS and are usually identified during history taking.[13] Menstrual cycle intervals longer than 35 days are often anovulatory. If menstrual cycles are absent because of ovarian insufficiency this will be indicated by a finding of significantly elevated FSH levels. In PCOS, which is characterized by euestrogenic chronic anovulation, menstrual withdrawal bleeding can typically be induced by a 5-day to10-day course of progesterone or progestin. This provides further support for anovulation being secondary to PCOS and not being the result of ovarian insufficiency or hypogonadotropic hypogonadism. In women with less severe menstrual disturbance, serum progesterone can be measured in the mid-luteal phase (day 21 to 23) of the menstrual cycle. If ovulation has occurred, the level will be 10 nmol/L or higher.

A diagnosis of PCOS rarely requires the use of ultrasound to confirm polycystic-appearing ovaries. As symptom management is the focus in PCOS, ultrasound adds little clinical value. However, ultrasound may be warranted for investigating a pelvic mass, infertility, or pelvic pain. It is important, when possible, that the ultrasound be performed with the use of an endovaginal ultrasound probe. Furthermore, obtaining an antral follicle count in each ovary (all follicles 2 to 9 mm) is important since the ultrasound diagnostic criteria for PCOS were established by reproductive endocrinologists rather than radiologists. Finally, there is a significant overlap between the diagnoses of polycystic-appearing ovaries and normal ovaries, with 30% to 50% of women younger than 30 having 12 or more follicles per ovary.[17] This indicates that a polycystic-appearing ovary is not pathognomonic of PCOS.

## Management

In addition to infertility caused by anovulation, women with PCOS are at risk for obesity, hirsutism, endometrial cancer, and type 2 diabetes and should be managed accordingly (**Box**).

### Anovulation

While anovulation can lead to long-term health consequences such as endometrial cancer and hyperplasia, most PCOS patients will present initially with infertility. It is reasonable to begin by ruling out male factor infertility with semen analysis and to complete fallopian tube assessment if the patient has risk factors for tubal factor infertility (prior ectopic pregnancy or gynecologic surgery, ruptured appendix, history of recurrent or

severe pelvic inflammatory disease). Ovulation induction is the simplest and least expensive infertility therapy.

For years, clomiphene, a selective estrogen receptor modulator first shown to induce ovulation in 1961, has been the mainstay of ovulation induction for PCOS. More recently, letrozole, an aromatase inhibitor, has been used off-label for ovulation induction, as first described in 2001.[18] A large, multicentre RCT comparing both medications in PCOS patients with anovulatory infertility demonstrated superior live birth rates in the letrozole arm (27.5%) compared with the clomiphene arm (19.1%), with similar twin pregnancy rates (3.9% vs 6.9%).[19] While letrozole for ovulation induction in the setting of PCOS still remains off-label use, the recent discontinuation of clomiphene production in Canada, along with the superior clinical outcomes with letrozole, has made this the first-line therapy for women with PCOS and anovulatory infertility. Typically, therapy with either agent is initiated on cycle day 3 of a spontaneous or progestin-induced menstrual bleed (**Table 2**).

As insulin resistance is a common feature of PCOS, the use of insulin sensitizing agents, particularly metformin, for treatment of anovulatory infertility is physiologically reasonable. Early studies demonstrated ovulation rates of up to 90% in women treated with metformin and clomiphene,[20] and ovulation rates of 75% in women who remained anovulatory on clomiphene single-agent therapy.[21] However, the Pregnancy in Polycystic Ovary Syndrome (PPCOS I) trial[22] comparing metformin, clomiphene, and metformin plus clomiphene found metformin alone was inferior to clomiphene alone and to metformin plus clomiphene. Metformin plus clomiphene outperformed clomiphene alone in ovulation rate, but with pregnancy and live birth rates that were similar. Thus, there appears to be no role for metformin as a single agent for ovulation induction in PCOS, and a limited role for metformin as adjuvant treatment for ovulation induction.

### Obesity

Obesity is prevalent in 50% to 80% of women with PCOS.[15] Both the PPCOS I trial[22] and the PPCOS II trial[23] comparing letrozole and clomiphene demonstrated live birth rates approximately twofold higher for women with a BMI less than 30 kg/m$^2$ than for women with a BMI greater than 35 kg/m$^2$ (PPCOS I) and 39 kg/m$^2$ (PPCOS II). While both studies definitively demonstrated that a high BMI has an adverse effect on response to ovulation induction with oral agents, evidence of a positive effect for weight loss in women with infertility secondary to anovulation was lacking until recently. Now a trial of obese women with anovulatory infertility who were randomly assigned to either a lifestyle intervention (exercise and diet for 6 months) or no lifestyle intervention has found a significant improvement in live birth rates for women in the lifestyle intervention group (number needed to treat with lifestyle intervention to result in 1 additional spontaneous live birth without fertility therapy = 6).[24] Subjects in the lifestyle intervention group lost 4.4 kg on average during the 6-month pre-fertility treatment intervention.[25] Diet and exercise as first-line therapy for

**Box. Diagnosing and managing polycystic ovary disease syndrome**

- A diagnosis of polycystic ovary disease syndrome (PCOS) must exclude other causes and include two of the following:
  - Oligomenorrhea or amenorrhea.
  - Clinical or biochemical hyperandrogenism.
  - Polycystic ovaries (> 12 follicles 2–9 mm or volume > 10 mL).
- In addition to infertility caused by anovulation, women with PCOS are at risk for obesity, hirsutism, endometrial cancer, and type 2 diabetes.
- Off-label use of letrozole for ovulation induction (2.5 mg, 5.0 mg, and 7.5 mg daily, from cycle days 3–7 or 5–9) has been found to be safe and effective.
- Clomiphene citrate, the drug commonly used in the past for ovulation induction, may be difficult to obtain because the only manufacturer in Canada has stopped production.
- Oral contraceptive use remains the first-line therapy for hirsutism and has demonstrated a reduction in risk of endometrial cancer.
- Metformin use and lifestyle interventions have been found to reduce risks associated with type 2 diabetes.

**Table 2. Recommendations for inducing ovulation with letrozole or clomiphene.**

| | Letrozole | Clomiphene |
|---|---|---|
| **Initial regimen** | 2.5 mg daily on cycle day 3–7 (5 days) | 50 mg daily on cycle day 3–7 (5 days) |
| **Indication for increase** | Absence of ovulation | Absence of ovulation |
| **How much to increase** | 2.5 mg daily increment | 50 mg daily increment |
| **Maximum daily dose** | 7.5 mg daily | 150 mg daily |
| **Treatment duration** | 6 ovulatory cycles | 6 ovulatory cycles |
| **Confirmation of ovulation** | Serum progesterone > 10 nmol/L at cycle day 21–23 | Serum progesterone > 10 nmol/L at cycle day 21–23 |

anovulatory infertility in obese women with PCOS is supported by both common sense and well-designed clinical research.

### Hirsutism

Hirsutism is the result of elevated circulating free testosterone acting on the pilosebaceous unit to convert vellus hair to terminal hair. Removal of unwanted hairs by electrolysis or mechanical depilation will be a temporary solution if the underlying endocrine disorder is not treated. The androgen effect responsible for hirsutism can potentially be reduced by decreasing androgen production, increasing androgen-binding capacity to reduce circulating levels, or reducing androgen action at the androgen receptor. However, individuals with hirsutism must be counseled to be patient, as response to endocrine therapy takes at least 3 to 6 months in concordance with the hair growth cycle.

The oral contraceptive pill (OCP) remains the first-line therapy for hirsutism because of its effect on androgen production.[26] First, the estrogen component of the OCP increases sex hormone-binding globulin levels, resulting in greater androgen-binding capacity, and reducing circulating free testosterone levels. Second, the progestin component suppresses pituitary LH production, reducing the stimulation of ovarian theca cell androgen synthesis under LH stimulation. Certain OCP progestins such as drosperinone and cyproterone acetate function as androgen receptor antagonists, and have a theoretical advantage over other progestins. OCP use offers the additional benefit of reducing acne, if present, and provides protection against endometrial cancer and menstrual cycle irregularity.

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Women with hirsutism who do not respond adequately to OCP treatment may benefit from other anti-androgen therapies such as spironolactone or finasteride. Spironolactone is a mineralocorticoid antagonist that also functions as a weak androgen receptor antagonist. As well, spironolactone reduces the activity of 5-alpha reductase (the enzyme responsible for converting testosterone to the more potent dihydrotestosterone), and reduces testosterone biosynthesis. Daily doses of spironolactone (100 mg) for at least 6 months have been shown to reduce hirsutism.[27] Finasteride, a 5-alpha reductase inhibitor, has a theoretical role in management of hirsutism, but clinical trial results have been inconsistent.[28] When OCP use alone is ineffective, it is prudent to use anti-androgen therapies in conjunction with OCP due to the potential teratogenic effects of these agents in the case of inadvertent pregnancy.

### Endometrial cancer

Endometrial cancer prevalence is documented to be significantly higher (by 2.7-fold) in women with PCOS.[29] However, it is difficult to determine whether PCOS is an independent risk factor for endometrial cancer because many of the common presenting features of PCOS (obesity, infertility, diabetes, unopposed estrogen/irregular menstrual cycles) are independent risk factors for endometrial cancer. Regardless, heightened awareness and monitoring for endometrial cancer in women with PCOS is warranted, and risk-reduction strategies should be undertaken. While weight loss and exercise are recommended for managing PCOS in obese women, evidence for these as effective therapy for protection against endometrial cancer is lacking.

Oral contraceptive use has consistently been found to reduce risk of endometrial cancer. OCP use appears to provide a risk reduction of approximately 50%, and the protective effect seems to last up to 20 years after stopping OCP use.[30] Additionally, relative reduction of endometrial cancer risk seems to be approximately two-fold lower in women who have used the OCP for 12 years compared with women using it for 4 years.[31]

Some women with PCOS and irregular menstrual cycles and anovulation resulting in unopposed estrogen may not tolerate OCP therapy, or OCP use may be contraindicated. Cyclic progesterone therapy (e.g., 200 mg Prometrium PO daily for 10 to

14 days per month, 5 to 10 mg medroxyprogesterone PO daily for 10 to 14 days per month) may be a reasonable option for inducing cyclic menses and providing progestational effect against unopposed estrogen. Alternatively, a progestin-releasing intrauterine contraceptive device may provide similar, noncontraceptive benefit.[32] While all of these therapies represent off-label use, they are generally accepted as appropriate therapy in the circumstances.

### Type 2 diabetes

When controlling for other risk factors, PCOS remains an independent risk factor for developing impaired glucose tolerance (RR 2.5) and type 2 diabetes (RR 4.0).[33] Although management of diabetes is beyond the scope of this article, it is possible to recommend exercise and weight loss to reduce the risk of progression from impaired glucose tolerance to diabetes.[34] Metformin use may also be considered, given that it is known to have a modest effect despite being less effective than lifestyle intervention in reducing diabetes risk. Patients with PCOS should be monitored for diabetes if they have a BMI greater than 30 kg/m$^2$ (or greater than 25 kg/m$^2$ for Asian patients) or have a family history of diabetes, acanthosis nigricans, or hyperandrogenism with anovulation.[29]

## Summary

Polycystic ovary syndrome remains a prevalent reproductive and metabolic disorder with variable phenotypes and an underlying pathophysiology that is not completely understood. Making a diagnosis of PCOS is beneficial but not essential. Therapy remains focused on managing symptoms (infertility caused by anovulation, obesity, hirsutism) and reducing long-term health risks (endometrial cancer, type 2 diabetes). BCMJ

**Competing interests**

Dr Havelock has received honoraria and speaking fees from EMD Serono and Merck, companies engaged in producing fertility treatments and technology. He has also received a research grant from Ferring Pharmaceuticals, a company engaged in developing and marketing products for reproductive health.

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