Polycystic Ovary Syndrome

The polycystic ovary syndrome (PCOS) is an important cause of androgen excess, menstrual irregularity, and cardiometabolic dysfunction in women. When fully expressed, the manifestations include irregular menstrual cycles, hirsutism, obesity, insulin resistance, and anovulatory infertility.

PCOS affects a woman’s ovaries, the reproductive organs that produce estrogen and progesterone — hormones that regulate the menstrual cycle. The ovaries also produce a small amount of male hormones called androgens. And it can contribute to long-term health problems.

The ovaries release eggs to be fertilized by a man’s sperm. The release of an egg each month is called ovulation. Follicle-stimulating hormone (FSH) and luteinizing hormone (LH) control ovulation. FSH stimulates the ovary to produce a follicle — a sac that contains an egg — and then LH triggers the ovary to release a mature egg.

In PCOS, many small, fluid-filled sacs grow inside the ovaries. The word “polycystic” means “many cysts.” These sacs are actually follicles, each one containing an immature egg. The eggs never mature enough to trigger ovulation; the lack of ovulation alters levels of estrogen, progesterone, FSH, and LH. Estrogen and progesterone levels are lower than usual, while androgen levels are higher than usual.
Extra male hormones disrupt the menstrual cycle, so women with PCOS get fewer periods than usual. The exact cause of PCOS is unknown. Factors that might play a role include:

1- **Excess insulin** (hyperinsulinemia): insulin resistance, when cells can’t use insulin properly, the body’s demand for insulin increases. The pancreas makes more insulin to compensate. Extra insulin triggers the ovaries to produce more male hormones. Obesity is a major cause of insulin resistance.

2- **Genetic factor**: PCOS is genetically heterogeneous syndrome in which the genetic contributions remain incompletely described.

**Clinical Presentation**

The clinical presentation of PCOS is variable. Patients may be asymptomatic or they may have multiple gynecologic, dermatologic, or metabolic manifestations. Patients with PCOS most commonly present with signs of Hyperandrogenisim and a constellation of oligomenorrhea, amenorrhea, or infertility. Workup for PCOS is sometimes prompted by an incidental finding of multiple ovarian cysts after ultrasonography.

**Signs and symptoms:**

- Menstrual dysfunction and anovulation
- Hirsutism and acne
- Weight gain
- Male-pattern baldness
- Darkening of the skin
- Headaches
- Obesity and metabolic syndrome
- Diabetes
- Obstructive sleep apnea
Must exclude all other disorders that can result in menstrual irregularity and hyperandrogenism, including adrenal or ovarian tumors, thyroid dysfunction, congenital adrenal hyperplasia, hyperprolactinemia, acromegaly, and Cushing syndrome.

**SYMPTOMS OF PCOS**

- Irregularity in periods or absence
- Pain in the pelvic area
- Growth of the face and other body parts
- Acne
- Inexplicable weight gain
- Presence of dark patches on the back and neck
- Baldness
- Infertility

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**Diagnostic algorithm for PCOS**

A. Features of hyperandrogenism
   - **Clinical**: acne, hirsutism & androgenic alopecia
   - **Biochemical**: elevated total testosterone and/or Free androgen index

B. Menstrual & ovulatory dysfunction
   - Frequent bleeding < every 21 d
   - Infrequent bleeding > every 35 d
   - Low mid-luteal progesterone levels indicating anovulation

C. Ovarian morphology – at least one ovary possesses:
   - ≥12 follicles with diameters 2-9 mm
   - Ovarian volume may be >10 ml

- Suspect PCOS
- Exclude differential diagnoses
- Diagnose PCOS if ≥2 of A, B or C are present

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**Common conditions**
- Thyroid disease – Abnormal TSH levels
- Late-onset CAH – High early morning &/or post-ACTH stimulated 17-OHP levels
- Hyperprolactinemia – Raised prolactin levels

**Less common diseases**
- Pregnancy: High HCG
- Hypothalamic amenorrhea: Low/normal FSH & LH with low oestradiol levels
- Primary ovarian failure: low oestradiol & raised FSH & LH levels
- Androgen secreting tumors: Testosterone >5 nmol/l, elevated DHEAS levels & imaging evidence of tumor
- Cushing’s syndrome: Clinical & biochemical evidence of hypercortisolism
Polycystic ovarian syndrome treatment:-

- Guideline management

**GOALS**

PREPARE

Communicate information to the public and to women diagnosed with PCOS.

COMMUNICATE

Prepare and assist women with the necessary information and resources needed to get tested.

OVERCOME

Assist women diagnosed with PCOS to overcome their symptoms and lessen related health risks.

SUPPORT

Provide a support network to freely and openly discuss all aspects of PCOS.

**WOMEN NOT PURSUING PREGNANCY**

1. Life style change
2. Oral contraceptive for treatment of
   - Hyperandrogenisim

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*Antiandrogens such as spironolactone must be prescribed with contraception because they can cause pseudohermaphroditism in a male fetus.*
- Menstrual dysfunction
- Providing contraceptive

- COC is associated with increased risk of VTE
- Risk factor of VTE
  - Obesity
  - Patient age
  - Family history of VTE

>> So we suggest caution for using COC for obese women and older than 40 year because of high risk of VTE.

- Alternative of COC is
  - Cyclic progestin therapy
  - Continuous progestin therapy (progestin only pills)
  - Progestin release IUD

>> They can reduce endometrial hyperplasia

- The risk of VTE is associated with ethinyl estradiol dose (less risk when EE <50 mcg)
- The lowest risk seen with COC that contain a-second generation progestin (levonorgestrel)
- VTE increase in pregnant and postpartum period
- The chronic anovulation seen in POCS is associated with increased risk of endometrial cancer and hyperplasia.
- So the first line therapy of endometrial protection is COC

- We typically start with a COC containing 20 mcg of ethinyl estradiol combined with progestin such as norethindrone or norethindrone acetate (lower risk of androgenicity and the same risk of VTE compared to levonorgestrel containing COC)
- Higher dose of ethanol estradiol (30-35) are needed to optimal suppression of ovarian androgen.
3. For women who choose not to take COC for endometrial protection alternative therapy are intermittent or continuous progestin therapy or IUD

- Medroxyprogesterone acetate (5-10 mg) for 10-14 days every one to two month.
- Patient must be aware that the progestin only therapy will not reduce the risk of acne or Hirsutism nor provide contraception.
- But continuous progestin therapy with norgestrel 0.35 mg daily provide contraception (mini pills).
- Levonorgestrel IUD provide contraception.

4. Metformin is alternative to restore menstrual cyclical as restore ovulatory menses in 30-50% of women.
   - When metformin is used we suggest monitoring that confirms ovulatory cycle and this done with luteal phase serum progestin or transvaginal ultrasound.

5. Antiandrogen
   - After 6 month if the patient not satisfied with the clinical response we add
     - Spironolactone 50-100mg twice daily
     - Other alternative antiandrogen therapy
     - Finasteride
     - Dutasteride
   - These drugs should never be used in women who are not using reliable contraception (because of the risk of preventing developing normal male genital during early pregnancy.

     - Cyproterone acetate
- Flutamide which it is non-steroidal antiandrogen (NSAA) which is used primarily to treat prostate cancer. It is also used in the treatment of androgen-dependent conditions like acne, excessive hair growth, and high androgen levels in women. But not recommended Because of hepatotoxicity

  - Hirsutism can also be treated by removal of hair by mechanical means such as shaving, waxing electrolysis, or laser treatment. In addition, eflornithine hydrochloride cream (13.9%) is a topical drug that inhibits hair growth.
  - Oral isotretinoin, a retinoid, is effective for the treatment of severe, recalcitrant nodular acne.
  - In addition to benzoyl peroxide, other nonprescription agents including salicylic acid, sulfur, alpha hydroxy acid, and tea tree oil have been used in the treatment of acne.
  - Topical minoxidil and oral finasteride are the therapeutic agents that have been most extensively studied for the treatment of androgenetic alopecia in men.

6. Gonadotropin releasing hormone agonists:
   - Leuprolide
   - Goserline
   - Gonadorelin
   - Triptolin

**WOMEN PURSuing PREGNANCY**

1. Weight loss — for anovulatory women with PCOS who are overweight or obese, we suggest weight loss prior to initiating ovulation induction therapy. The approach to obesity management is the same as that for patients without PCOS, starting with lifestyle changes (diet and exercise) followed by pharmacotherapy (if not pursuing pregnancy).
➢ Even modest weight loss of 5 to 10 percent has been associated with an improvement in metabolic status.

2. Ovulation induction medications

● For oligoovulatory women with PCOS undergoing ovulation induction, we now suggest letrozole as first-line therapy over clomiphene citrate, regardless of the patient’s BMI. Before starting letrozole, the clinician must discuss that this use of the drug is not approved by the US Food and Drug Administration (FDA) for this purpose and that there is an available alternative (clomiphene citrate).

● Clomiphene citrate had been the first-line drug for this population for many years, with metformin used as an alternative. However, both clomiphene and metformin appear to be less effective for live birth rates than letrozole.

● Metformin – Metformin is a drug whose major effect is to reduce hepatic glucose output and thereby lower serum insulin concentrations. Metformin has been used to promote ovulation either alone or in combination with clomiphene, but clomiphene or letrozole monotherapy appears to be superior to metformin monotherapy on live birth rates. Its role in treating infertility is limited.

● Gonadotropin therapy – Another method to induce ovulation is administration of exogenous gonadotropins.
Other medications

Thiazolidinedione therapy has been investigated for induction of ovulation, but we do not suggest its use because of concern about its cardiovascular safety.

Although women with PCOS are not likely gonadotropin-releasing hormone (GnRH) deficient, pulsatile GnRH is moderately effective for ovulation induction. It is currently available in Europe, but not in the United States. In one study of 41 patients undergoing 114 ovulation induction cycles, 56 percent of women ovulated, and 40 percent of ovulatory patients achieved pregnancy [54]. Ovulatory cycles were associated with lower BMI and fasting insulin, and higher baseline serum follicle-stimulating hormone (FSH) concentrations. Thus, pulsatile GnRH may be a reasonable option, particularly for lean women with PCOS.

• Acupuncture — Infertility centers often offer acupuncture as an adjunctive therapy to women with PCOS undergoing ovulation induction or in vitro fertilization. However, available evidence suggests that it does not improve live birth rates when used alone or combined with clomiphene citrate.

• Laparoscopic surgery — In the past, wedge resection of the ovaries was a standard treatment for infertility in women with PCOS. However, this approach has been abandoned, both because of the efficacy of clomiphene and because of the high incidence of pelvic adhesions seen with wedge resection. A substitute for wedge resection, laparoscopic ovarian laser electrocautery, may be effective in some women with PCOS. However, given the other pharmacologic options for ovulation induction, surgery is not often indicated. The use of laparoscopic surgery for ovulation induction in PCOS is discussed in detail elsewhere.
• In vitro fertilization — if weight loss, ovulation induction with medications, and/or laparoscopic ovarian laser electrocautery are unsuccessful, the next step is in vitro fertilization. Without co-interventions, women with PCOS are at increased risk for

PCOS related acne:
1-Topical benzyl peroxide +topical antibiotic (clindamycin/erythromycin)
2-Retinoid (isotretinoin, tretinoin)
3-Hormonal contraception
4-Antiandrogen (spirolactone).

Dyslipidemia — the approach to treatment of dyslipidemia in women with PCOS is the same as for other patients with dyslipidemia. Exercise and weight loss are the first line approach, followed by pharmacotherapy, if needed.

Statins — Statins are effective for dyslipidemia in women with polycystic ovary syndrome (PCOS), but do not appear to have other clinically important metabolic or endocrine effects.

Obstructive sleep apnea — Sleep apnea, a common disorder in women with PCOS, is an important determinant of insulin resistance, glucose intolerance, and type 2 diabetes, treatment with continuous positive airway pressure (CPAP) improved insulin sensitivity and reduced diastolic blood pressure.

Nonalcoholic steatohepatitis — the prevalence of nonalcoholic steatohepatitis (NASH) appears to be increased in women with PCOS both weight loss and metformin use appear to improve metabolic and hepatic function in these women.
<table>
<thead>
<tr>
<th>Drug/device</th>
<th>TYPICAL DOSAGE</th>
<th>DESCRIPTION</th>
<th>Side effect</th>
<th>Comments</th>
</tr>
</thead>
</table>
| Metformin   | 1,500 to 2,250 mg daily | insulin-sensitizing agent | Gastrointestinal upset, lactic acidosis, increase in homocysteine levels | *Insulin resistance (first-line therapy)  
*Menstrual irregularities (second-line therapy added to hormonal contraceptive)  
*Hirsutism (third-line therapy added to hormonal contraceptives and spironolactone) |
| Spironolactone | 50 mg daily to 100 to 200 mg daily | Antiandrogenic antimineralocorticoid | Hyperkalemia, nausea, breast tenderness | *Hirsutism (second-line therapy added after 6 months of oral contraceptive therapy if not improved)  
*Acne (second-line therapy) |
| Clomiphene | 50 to 100 mg daily | Ovulation induction agent, selective estrogen receptor modulator | Multiple pregnancy or ovarian hyper stimulation, thromboembolism, visual disturbance | Infertility (first-line therapy)  
Pregnancy category x |
| Eflornithine | 13.9% cream applied to affected area twice daily | inhibits hair growth | Mild skin irritation | Inhibits hair  
Mild hirsutism (second-line therapy growth) |
<p>| Finasteride | 5 mg daily | 5-alpha-reductase inhibitor | Hypersensitivity reaction, decreased libido | Hirsutism (weak recommendation because of inconsistent study results). |</p>
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<th>Side Effects</th>
<th>Pregnancy Category</th>
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<tbody>
<tr>
<td>Flutamide</td>
<td>250 mg once or twice daily</td>
<td>Nonsteroidal antiandrogen, Liver toxicity, thrombocytopenia, leukopenia, hot flashes</td>
<td>x</td>
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<tr>
<td>Hormonal contraceptives</td>
<td></td>
<td>Nausea, headache, spotting, thrombophlebitis, deep venous thrombosis</td>
<td>Menstrual irregularities, hirsutism, acne (first-line therapy)</td>
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<tr>
<td>Letrozole</td>
<td>2.5 to 7.5 mg daily for 5 day</td>
<td>Nonsteroidal competitive inhibitor of aromatase; inhibits conversion of adrenal androgens</td>
<td>Osteoporosis, thromboembolism, MI, hot flashes, arthralgia</td>
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<tr>
<td>Levonorgestrel-releasing intrauterine system</td>
<td>5 years</td>
<td>Intrauterine device</td>
<td>Amenorrhea</td>
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<tr>
<th>Symptoms</th>
<th>Treatment</th>
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<tr>
<td>Obesity, weight gain</td>
<td>Weight loss options include:</td>
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<tr>
<td></td>
<td>• changes to diet</td>
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<tr>
<td></td>
<td>• exercise</td>
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<tr>
<td></td>
<td>• medications*</td>
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<tr>
<td>Hirsutism (hairiness)</td>
<td>• medications*</td>
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<tr>
<td></td>
<td>• cosmetic treatments, i.e. waxing, bleaching, laser, electrolysis</td>
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<tr>
<td></td>
<td>• weight loss</td>
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<tr>
<td>Acne</td>
<td>• topical creams</td>
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<tr>
<td></td>
<td>• medications*, i.e. oral contraceptive pill, anti-androgens, retinoids</td>
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<tr>
<td>Insulin resistance</td>
<td>• weight loss</td>
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<td></td>
<td>• medications*</td>
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<tr>
<td>Infertility caused by</td>
<td>• weight loss</td>
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<tr>
<td>irregular periods and oвуlation</td>
<td>• medications*, oral contraceptive pill</td>
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Reference:
