BMJ Best Practice

Polycystic ovary syndrome

Straight to the point of care

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Summary

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy in women of reproductive age.

A leading cause of infertility and pregnancy complications.

Associated with insulin resistance, metabolic syndrome, metabolic dysfunction-associated steatotic liver disease (formerly nonalcoholic fatty liver disease), and increased risk of developing type 2 diabetes.

Main treatment goals are to reduce hyperandrogenism or to induce fertility.

Letrozole and clomiphene are considered first-line pharmacologic treatments for infertility in PCOS. Increasing evidence suggests that letrozole may be superior to clomiphene.

Definition

PCOS includes symptoms of hyperandrogenism, presence of hyperandrogenemia, oligo/anovulation, and polycystic ovarian morphology on ultrasound.[1] [2] [3] [4]

Epidemiology

PCOS affects about 6% of women of reproductive age in the US and Europe using the 1990 National Institutes of Health criteria, 10% to 15% of women using the Androgen Excess and PCOS Society criteria, and 10% to 20% of women using the 2003 Rotterdam criteria.[7] [8] Similar rates are reported in China (10%) and Mexico (6%), suggesting the prevalence does not vary across ethnicities or different regions of the world.[9] [10] [11]

There do seem to be differences in the phenotype of PCOS within and between countries.[8] [12] For example, studies report greater impairments in glucoregulatory status in Hispanic compared with white women in the US, and lower rates of ovulatory PCOS in the US compared with Europe.[8] [13] The reported frequency of hirsutism is lower in East Asia and higher among indigenous Australians.[7] [11]

There have been no prospective studies that document incidence rates for PCOS.

PCOS accounts for 80% to 90% of cases of hyperandrogenism in women. In one large series of women presenting with androgen excess or ovulatory dysfunction, approximately 80% had PCOS, 3% had the hyperandrogenism-insulin resistance-acanthosis nigricans syndrome, 1.5% had 21-hydroxylase-deficient nonclassic adrenal hyperplasia, 0.6% had 21-hydroxylase-deficient classic adrenal hyperplasia, and 0.2% had androgen-secreting tumors.[14]

Men in families with PCOS may have manifestations including excessive hairiness, premature male-pattern baldness, elevated levels of dehydroepiandrosterone sulfate, abnormal hormonal responses to dynamic testing, and aberrations in insulin sensitivity and secretion.[15] [16]

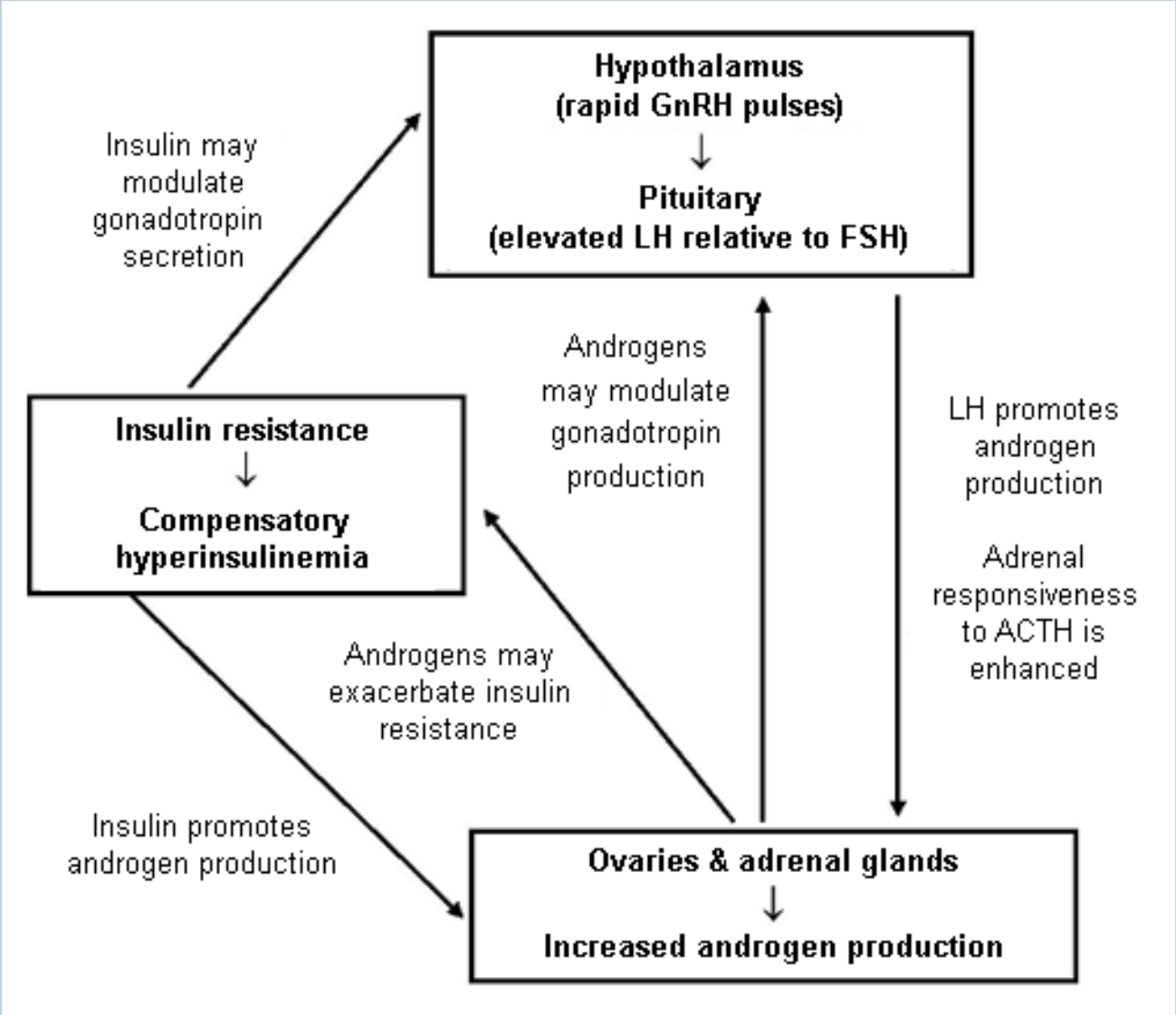
Etiology

The etiology of polycystic ovary syndrome (PCOS) is unknown. It is a syndrome wherein multiple systems are affected and the site of the primary defect is unclear. Various lines of evidence have supported primary defects in the hypothalamic-pituitary axis, postulating increased amplitude and frequency of pulses of luteinizing hormone (LH), or defects involving the ovaries through an intrinsic problem leading to androgen overproduction. Some theories postulate defects in insulin sensitivity with insulin resistance leading to compensatory hyperinsulinemia.

PCOS appears to be inherited as a common complex disorder. Multiple genes, each with mild or moderate effects on overall disease risk, are likely to be involved.[17] One twin study calculated the heritability of PCOS at 70%, suggesting that most PCOS risk depends on genetic factors.[18] The actual PCOS susceptibility genes have yet to be definitively identified. A large genome-wide association study conducted in Chinese individuals robustly identified genetic variants in or near 3 genes (DENND1A, THADA, LHCGR) as risk factors for PCOS.[19] Variation in DENND1A was subsequently associated with PCOS in several European-origin cohorts.[20] [21] [22] [23] A subsequent genome-wide association study in Chinese individuals increased the number of susceptibility loci to 11.[24] Three genome-wide association studies in predominantly European-origin cohorts increased the total number of PCOS susceptibility variants to 25.[25] [26] [27] Most loci discovered in one ethnic group appear to affect PCOS risk in other ethnic groups, suggesting an ancient origin of PCOS.[28] Susceptibility loci include genes for the LH receptor, the follicle-stimulating hormone receptor, and the follicle-stimulating hormone beta subunit, suggesting a key role for disordered gonadotropin function in PCOS. Epigenetic changes (DNA alterations independent of the primary nucleotide sequence; e.g., DNA methylation) may also play a role in PCOS susceptibility, as evidenced by differential X-chromosome inactivation in PCOS.[29] [30]

Pathophysiology

The pathophysiology of PCOS is not well understood, mainly due to lack of knowledge of the location of the primary defect. There are several candidates: ovary, adrenal, hypothalamus, pituitary, or insulin-sensitive tissues. It is possible that there are subsets of women with PCOS wherein each of these proposed mechanisms serves as the primary defect.



Simplified diagram of the main pathogenic factors in PCOS. ACTH, adrenocorticotropic hormone; FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone

From the collection of Dr M.O. Goodarzi; used with permission

Investigations have elucidated some of the interactions between these systems. Insulin resistance leads to compensatory insulin hypersecretion by the pancreas in order to maintain normoglycemia. The resulting hyperinsulinemia promotes ovarian androgen output and may also promote adrenal androgen output. High insulin levels also suppress hepatic production of sex hormone-binding globulin, which exacerbates hyperandrogenemia by increasing the proportion of free circulating androgens.[12] Another factor that promotes ovarian androgen output is the fact that women with PCOS are exposed long term to high levels of LH. This LH excess seems to be a result of an increased frequency of gonadotropin-releasing hormone

pulses from the hypothalamus.[12] [31] The abnormal hormonal milieu may also contribute to incomplete follicular development that results in polycystic ovarian morphology.[12]

Classification

Proposed classification[5] [6]

There is no formal classification system for PCOS. The following has been proposed:

- Mild PCOS (accounts for 16% of affected women): characterized by irregular periods, polycystic ovaries on ultrasound, mildly elevated androgen concentrations, normal insulin concentrations, unknown long-term risks
- Ovulatory PCOS (accounts for 16% of affected women): characterized by normal periods, polycystic ovaries on ultrasound, elevated androgen concentrations, increased insulin concentrations, unknown long-term risks
- Hyperandrogenism and chronic anovulation (accounts for 7% of affected women): characterized by irregular periods, normal ovaries on ultrasound, elevated androgen concentrations, increased insulin concentrations, potential long-term risks
- Severe PCOS (accounts for 61% of affected women): characterized by irregular periods, polycystic ovaries on ultrasound, elevated androgen concentrations, increased insulin concentrations, potential long-term risks.

Case history

Case history #1

An 18-year-old woman presents with a chief complaint of hirsutism. She needs to wax her upper lip and chin twice a week. This has been a problem for 4 years. She also has excess hairs on her upper back and lower abdomen. Her periods are irregular, occurring every 2-3 months. Embarrassment about the facial hirsutism has affected her social life, and she is finding she feels depressed much of the time.

Case history #2

A 32-year-old woman presents with a chief complaint of difficulty becoming pregnant. She was prescribed oral contraceptives at the age of 17 years because of irregular periods (4-6 periods per year). She continued with oral contraception until 30 years of age, at which point she and her husband decided they wanted to have a baby. Since ceasing oral contraception, she has gained 15 pounds and has only 3 to 5 periods per year. She has actively been trying to conceive, with no results.

Other presentations

The most common presentations are hirsutism and infertility. Women typically present with oligo- or anovulation, manifesting as infrequent, irregular menstrual periods. Polycystic ovary syndrome (PCOS) may also more rarely present with irregular and heavy menstrual bleeding. Some women present with regular menses and hirsutism, and on further investigation are found to have anovulatory cycles. There are no pathognomic features that suggest PCOS. It is largely a diagnosis of exclusion.

Approach

There are no pathognomonic features that suggest polycystic ovary syndrome (PCOS), and it is largely a diagnosis of exclusion.

History

Common features include hirsutism (affecting 60%), acne (20%), and scalp hair loss (5%); irregular and infrequent periods (often <8 per year); weight gain; and infertility.[3]

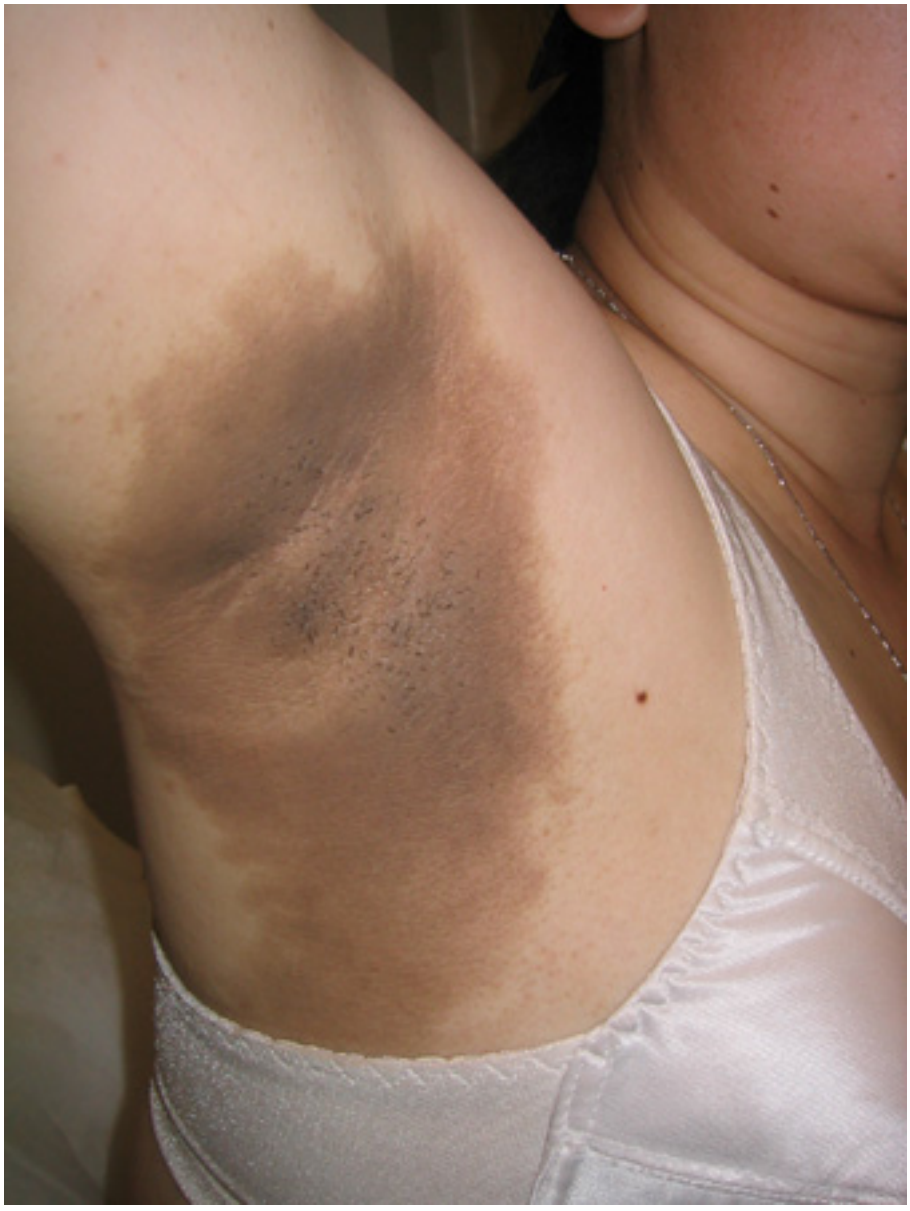
Symptoms typically begin at the time of puberty and, in younger women, may be difficult to distinguish from the irregular menses that often occur in the first year after menarche.[50] [51] Up to 85% of menses are anovulatory during the first year after menarche, and up to 60% in the third year; increased body mass index is a predictor of persistent anovulation. If oral contraceptives were begun at a young age, symptoms may be masked until therapy is stopped, which may delay the presentation and diagnosis.

While criteria for PCOS during adolescence are controversial, guidelines recommend that both oligo-ovulation and hyperandrogenism must be present to diagnose PCOS in a teenager:[52] [53] [54]

- Infrequent/reduced menstrual bleeding or amenorrhea should be present for at least 2 years after menarche (or primary amenorrhea at age 15 years or >3 years after breast development).[53] [55] Oligo- or anovulation may manifest irregular as menstrual bleeding, defined as >90 days for any one cycle 1 year post menarche; <21 or >45 days for those 1 to <3 years post menarche; <21 days to >35 days or <8 cycles per year for those ≥3 years post menarche to perimenopause.[53]
- Biochemical hyperandrogenemia should be present.[52] [56]

Physical exam

- Hirsutism is the most characteristic physical exam finding. Acne and/or alopecia may be present. The degree of hyperandrogenism is typically mild to moderate. Frank virilization is rare.
    - Hirsutism can be quantified using the modified Ferriman-Gallwey score, with levels ≥4-6 indicating hirsutism.[53] It is important to ask about excess hair growth, because women often use methods of mechanical or local hair removal. Thus, the physical exam may not disclose hirsutism.
    - Acne may be masked by acne therapy. Severe acne persisting beyond adolescence may be more indicative of PCOS.
    - Typically, scalp hair loss in PCOS is at the vertex and crown, with relatively intact frontal hairline. Hair on the sides of the head may be preserved.
- Body mass index and waist circumference should be assessed in all women with PCOS.[57] Depending on culture and ancestry, 30% to 80% of women with PCOS are overweight or obese, with central obesity (waist-to-hip ratio >0.85 or waist circumference >88 cm).
- Women may have elevated blood pressure as a part of the hypertension sometimes associated with this syndrome.
- Acanthosis nigricans, usually subtle, may be seen more in obese women with PCOS.



Acanthosis nigricans involving the axilla of an obese white woman

From the collection of Melvin Chiu, MD, UCLA; used with permission

- Sweating or oily skin may occur.

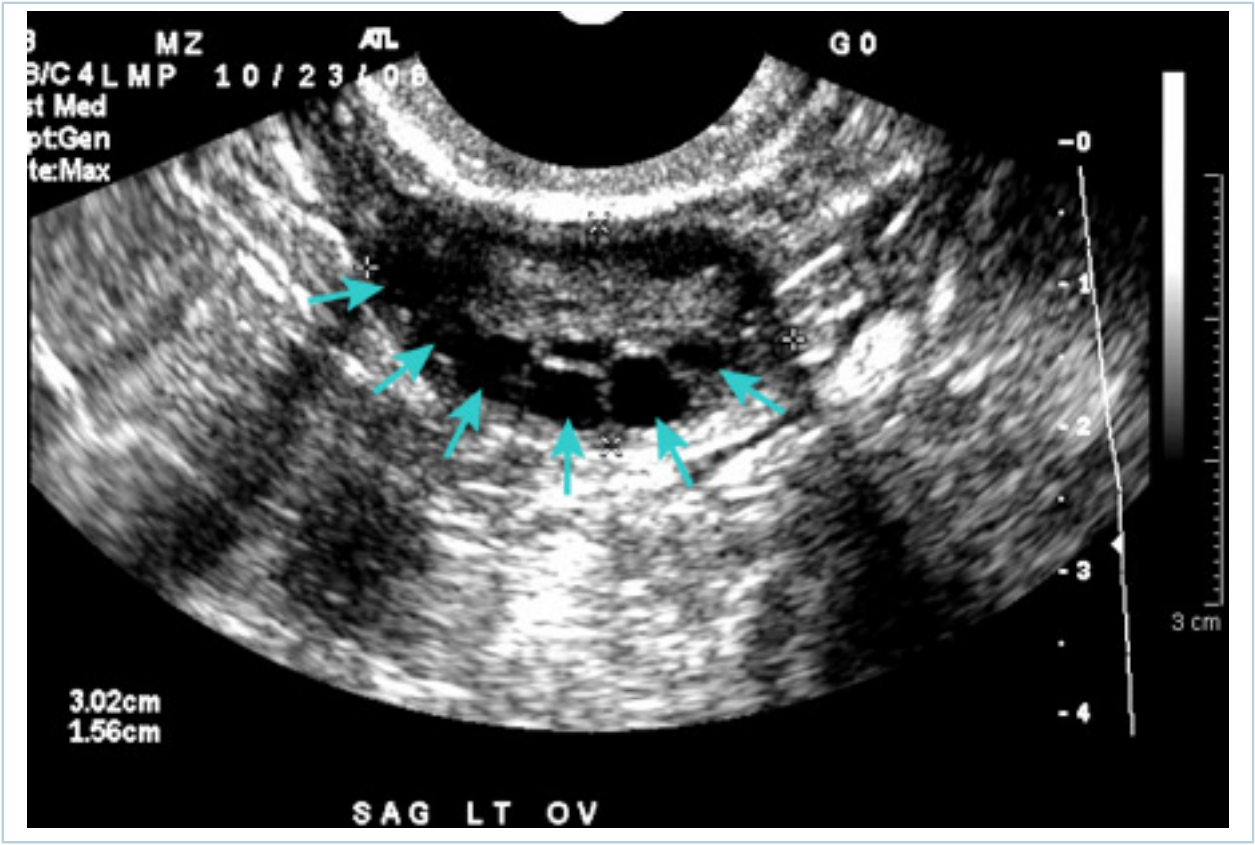
Investigations

Hirsutism present

- The diagnosis of PCOS can be made when infrequent/reduced menstrual bleeding also exists.
- If infrequent/reduced menstrual bleeding is not present in a hirsute woman, evaluate for presence or absence of ovulation (by luteal-phase progesterone measurement or basal body temperature monitoring). Anovulatory cycling may occur, particularly in hirsute women. If such measures are consistent with anovulation, PCOS may be diagnosed in hirsute women.
- If the hirsute woman has ovulatory cycles, the next step is to perform a transvaginal ultrasound to examine the ovaries. If polycystic ovarian morphology is documented, then PCOS can be diagnosed. In adults, pelvic ultrasound may be replaced by serum anti-Mullerian hormone (AMH) levels.[53]

- Polycystic ovaries are present in 75% of women with PCOS, but are also seen in up to 25% of normal women and women with other endocrinopathies such as congenital adrenal hyperplasia, hyperprolactinemia, or hypothalamic amenorrhea.[3]
- Ultrasound should be done in the early follicular phase (day 3-5) after a spontaneous or progestin-withdrawal-induced menstruation, or randomly in women with infrequent/reduced menstrual bleeding. If evidence of a dominant follicle (>10 mm) or a corpus luteum is seen, the ultrasound should be repeated at the next cycle.[2]
- Polycystic ovarian morphology is a risk factor for ovarian hyperstimulation syndrome in women undergoing ovulation induction (with clomiphene or gonadotropins). Therefore, an ultrasound before ovulation induction may be useful.
- If endometrial thickening is found, an endometrial biopsy is indicated to determine whether endometrial hyperplasia or cancer is present. Routine ultrasound screening for endometrial thickness is not recommended.[53]
- It should be noted that ovarian volume and follicular number decrease with age, so standard criteria may not be applicable to women >40 years of age.[58] Also, multifollicular ovaries may be observed during puberty, subsiding once the normal menstrual pattern is established.[52]
- In one meta-analysis, the pooled sensitivity of AMH for diagnosis of PCOS was 0.78 (95% CI: 0.74 to 0.81) and pooled specificity was 0.87 (95% CI: 0.84 to 0.90).[59] However, there was substantial heterogeneity between studies and optimal cut-off values have not been defined.[59]

- Consider adolescents with only hyperandrogenism (and no irregular cycles) “at risk” of PCOS and reassess later.[53] Ultrasound and AMH levels are not recommended for diagnosis of PCOS in adolescents due to poor specificity in this age group.[53]



Polycystic ovarian ultrasound

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Hirsutism absent

- If hirsutism is not present, serum androgens should be measured to evaluate for hyperandrogenism. The most commonly measured androgens are total and free testosterone and dehydroepiandrosterone sulfate (DHEAS). Biochemical hyperandrogenism is best assessed by calculated free testosterone, free androgen index, calculated bioavailable testosterone, or by high quality testosterone assays such as liquid chromatography tandem mass spectrometry or extraction/chromatography affinity immunoassays.[53] If any of these are elevated, the diagnostic sequence is the same as when hirsutism is present.
    - Levels >2 standard deviations above the mean qualifies as a positive test. Testosterone levels are difficult to measure in women; even assays using liquid chromatography mass spectrometry exhibit poor precision at the low levels characteristically found in women.[60] Additionally, many laboratory reference ranges for androgens in women did not carefully exclude women with PCOS.[61] [62]
    - Hyperandrogenemia is present in 60% to 80% of women with PCOS: 70% have elevated free testosterone, 40% have elevated total testosterone, 25% have elevated dehydroepiandrosterone sulfate.[3] In obese women, sex hormone-binding globulin levels are low, resulting in elevated free testosterone and often normal total testosterone.
    - Androgen level tests should be performed in the follicular phase (in cycling women), in the morning, and at least 3 months after cessation of any hormonal therapies. An exception to these hormonal therapies is a cyclic progestin.[63]

- If hirsutism is not present, all androgen levels are normal, and there is a history of infrequent/reduced menstrual bleeding, an ovarian ultrasound or serum AMH measurement should be performed in adults.[53] Combined with such a history, polycystic ovarian morphology allows a diagnosis of PCOS to be made (Rotterdam criteria only).[2]
- Consider adolescents with only irregular cycles (and no hyperandrogenism) "at risk" of PCOS and reassess later.[53] Ultrasound and AMH levels are not recommended for diagnosis of PCOS in adolescents due to poor specificity.[53]
- Levels of androstenedione or DHEAS may be checked if other androgens are normal, but these have lower specificity and DHEAS has greater age-associated decrease.[53] Androstenedione measurement may increase the number of women identified as hyperandrogenemic by 10%.[3] The American College of Obstetricians and Gynecologists PCOS guideline suggests evaluating DHEAS is of little value except in cases of rapid virilization.[64]
- Checking dehydroepiandrosterone is of little value.

Tests in all women

- Thyroid-stimulating hormone, prolactin, and 17-hydroxyprogesterone should be measured in all women to exclude disorders that may resemble PCOS (thyroid dysfunction, hyperprolactinemia, and 21-hydroxylase-deficient adrenal hyperplasia, respectively).[53] [64] However, low-level prolactin elevations (20-30 ng/mL) are common in PCOS without associated galactorrhea or pituitary adenoma on imaging.
- In uncertain cases, elevated luteinizing hormone (LH)/follicle-stimulating hormone (FSH) ratio may support a diagnosis of PCOS.
    - LH pulses are abnormally elevated (frequency and amplitude), leading to increased serum LH levels and LH/FSH ratio >3 in only two-thirds of women with PCOS. LH/FSH ratio is elevated more often in lean women. This ratio is helpful only if positive, and is not diagnostic.
    - Checking LH and FSH is also useful to rule out hypothalamic amenorrhea (levels low) or perimenopause/ovarian failure (levels high).
- Given the high frequency of insulin resistance and metabolic syndrome in PCOS, an oral glucose tolerance test and fasting lipid panel should be performed in all women at diagnosis to evaluate metabolic risk factors.[53] [64]
    - Diabetes is defined as fasting glucose ≥126 mg/dL, or 2-hour glucose ≥200 mg/dL.
    - Prevalence of abnormal glucose tolerance (impaired fasting glucose, impaired glucose tolerance, or diabetes) is as high as 40% in women with PCOS.[5] In one meta-analysis, the odds of prevalent impaired glucose tolerance was 3.3, and of prevalent diabetes 2.9, in women with PCOS.[65]
    - All women should be screened for impaired glucose tolerance with an oral glucose tolerance test. Those with normal glucose tolerance should be rescreened at least every 2 years. Those with impaired glucose tolerance should be screened annually for type 2 diabetes.[66]
    - Assessment of insulin resistance/hyperinsulinemia is problematic, given variability in insulin assays and the need for population-specific normative ranges. However, insulin levels may be measured to give insight into whether insulin resistance is present. Fasting insulin >10 to 15 microunits/mL may suggest insulin resistance.
    - During the oral glucose tolerance test, a peak insulin of 100-150 microunits/mL may indicate mild insulin resistance, 150-300 microunits/mL moderate insulin resistance, and >300 microunits/mL severe insulin resistance.[67]

- Fasting plasma glucose or hemoglobin A1c are less accurate than oral glucose tolerance testing, but may be considered as second-line alternatives if an oral glucose tolerance test cannot be performed.[53] [68]

History and exam

Key diagnostic factors

female of reproductive age (common)

- Symptoms typically start at the time of puberty. However, if oral contraceptives were begun at a young age, symptoms may be masked until therapy is stopped, which may delay the presentation and diagnosis.

irregular menstruation (common)

- Irregular menses is a common manifestation of oligo- or anovulation, occurring in 75% of women with polycystic ovary syndrome (PCOS). Guidelines from the International PCOS Network define irregular menstrual cycles as follows: <21 or >45 days for those 1 to <3 years post menarche; <21 or >35 days or <8 cycles per year for those ≥3 years post menarche to perimenopause; >90 days for any one cycle for those 1 year post menarche; primary amenorrhea by age 15 years or >3 years after breast development.[53] Irregular menstruation is normal in the first year post menarche.
- Women with regular periods may also have anovulatory cycles. Up to 40% of hirsute regularly menstruating women have anovulatory cycles when further investigated.[3]
- As women with PCOS age (i.e., >30 years), cycle length may shorten and some women may experience regular cycles.[69]

infertility (common)

- Often a presenting complaint.

hirsutism (common)

- Present in 60% of women with polycystic ovary syndrome.[3]
- Hirsutism is the presence of terminal hairs (thick, pigmented) in androgen-dependent areas (upper lip, chin, chest, back, upper arm, shoulders, linea alba, periumbilical region, thigh, buttocks). Hirsutism can be quantified using the modified Ferriman-Gallwey score, with levels ≥4-6 indicating hirsutism.[53]
- It is not to be confused with hypertrichosis (diffuse vellus hairs).
- Some ethnic groups, particularly East Asians, are less prone to express hirsutism.[7] [70]
- It is important to ask about excess hair growth, because women often use methods of mechanical or local hair removal. Thus, the physical exam may not disclose hirsutism.

Other diagnostic factors

acne (common)

- May be masked by acne therapy. Acne is present in 15% to 25% of women with polycystic ovary syndrome (PCOS).[3]
- Severe acne persisting beyond adolescence may be more indicative of PCOS.
- Acne is a nonspecific feature; many women with acne will not have PCOS.

overweight or obesity (common)

- Depending on culture and ancestry, 30% to 80% of women with polycystic ovary syndrome (PCOS) are overweight or obese, with central obesity (waist-to-hip ratio >0.85 or waist circumference >88 cm).
- Body mass index and waist circumference should be assessed in all women with PCOS.[57]

hypertension (common)

- Nonspecific, but commonly seen.
- Blood pressure should be measured in all women with polycystic ovary syndrome.[57]

scalp hair loss (uncommon)

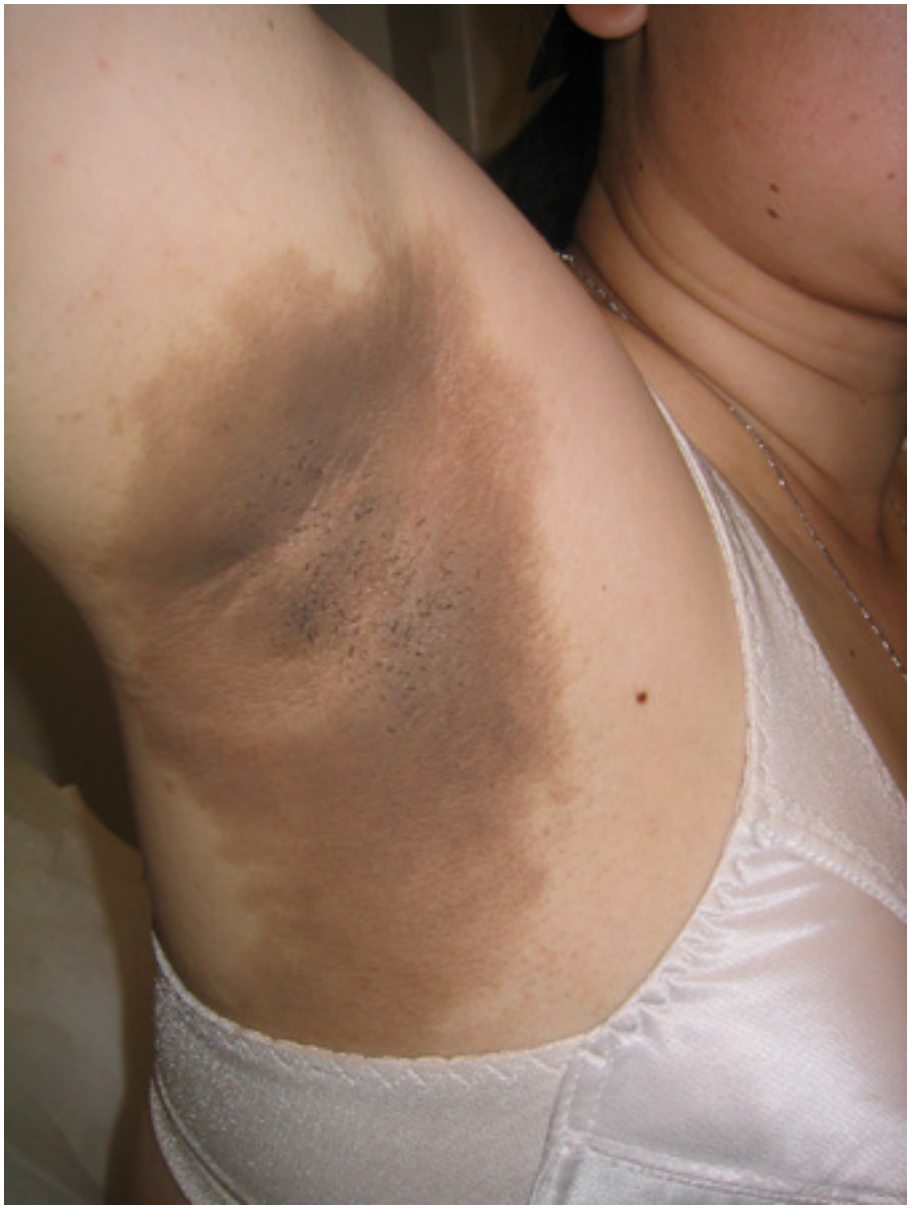
- The exact prevalence of alopecia in polycystic ovary syndrome (PCOS) is unknown, but may be as low as 5%.[3]
- It is not a very specific symptom, because many other disorders can cause alopecia.
- Typically, scalp hair loss in PCOS is at the vertex and crown, with relatively intact frontal hairline. Hair on the sides of the head may be preserved.

oily skin or excessive sweating (uncommon)

- Hyperhidrosis and/or seborrhea may be a manifestation of hyperandrogenism.
- The exact prevalence of such symptoms in polycystic ovary syndrome is not known.

acanthosis nigricans (uncommon)

- Usually subtle. Seen more often in obese women with polycystic ovary syndrome. This is a reflection of hyperinsulinemia.



Acanthosis nigricans involving the axilla of an obese white woman

From the collection of Melvin Chiu, MD, UCLA; used with permission

- Acanthosis nigricans is dermal hyperplasia visible as brown or gray, velvety, occasionally verrucous, hyperpigmented areas over the nape of the neck, also the vulva, axillae, groin, umbilicus, submammary areas, elbows, and knuckles. Skin tags are often found in the neck area also.
- Obese African-American and Hispanic women tend to have clinical acanthosis nigricans.
- Other causes include diabetes, excess corticosteroids or growth hormone (endogenous or exogenous), nicotinic acid, or gastric adenocarcinoma.

Risk factors

Strong

family history of PCOS

- First-degree female relatives of women with PCOS have a 20% to 40% prevalence of PCOS, significantly increased compared with the general population (prevalence 6% to 13%).[7] [32] [33]
- PCOS appears to be inherited as a common, complex genetic condition.[34]

premature adrenarche

- Premature adrenarche (early onset of pubic/axillary hair and apocrine sweat gland development) is followed by development of PCOS in up to 50% of cases.[35]

obesity

- Multiple causality analyses using genetic data have consistently found that obesity causes PCOS.[25] [36][37] Childhood/adolescent adiposity may have a greater impact on PCOS risk than adulthood adiposity.[38] On the other hand, having PCOS does not appear to increase the risk of obesity.[37]

Weak

low birth weight

- Might predispose to development of hyperandrogenism later in life by predisposing to premature adrenarche and hyperinsulinemia.[39] [40] [41] One national registry-based cohort study found that being born small for gestational age as a risk factor for future PCOS was mediated by maternal obesity and smoking.[42]

fetal androgen exposure

- Daughters of women with congenital adrenal virilizing disorders may develop features of hyperandrogenism.[43]
- The fact that PCOS did not occur more frequently in females with a male co-twin than in females with a female co-twin argues against fetal androgen exposure as a major factor in the development of PCOS.[44] Studies of umbilical cord blood of infants born to women with PCOS have yielded conflicting results, such as no elevation in androgen levels, or testosterone levels similar to male cord blood.[45] [46]

environmental endocrine disruptors

- Higher levels of bisphenol A have been observed in PCOS women compared with matched controls.[47] Elevated bisphenol A in PCOS has been linked to insulin resistance and hyperandrogenism.[48] [49] It remains to be established whether such environmental factors are causative in PCOS.

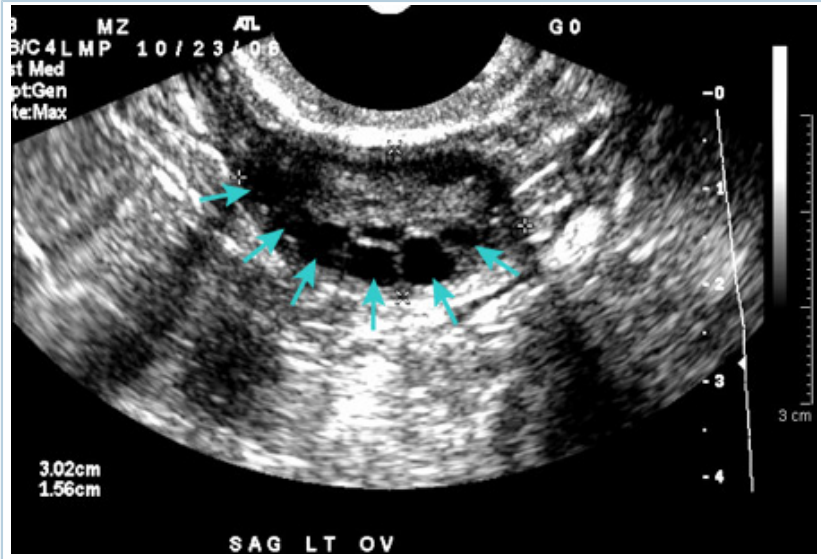
Tests

1st test to order

Test	Result
serum 17-hydroxyprogesterone • Performed to exclude 21-hydroxylase-deficient nonclassic (adult-onset) adrenal hyperplasia (NCAH). • If the value is between 200 and 800 ng/dL, a level obtained 60 minutes after adrenocorticotropic hormone stimulation is indicated to rule out the disorder.[71] Stimulated values >1000 ng/dL (usually >1500 ng/dL) occur when the woman has NCAH.	**above 800 ng/dL indicates adrenal hyperplasia**
serum prolactin • This test is performed to exclude hyperprolactinemia, which may present with oligo- or anovulation. • However, low-level prolactin elevations (20-30 ng/mL) are common in polycystic ovary syndrome without associated galactorrhea or pituitary adenoma on imaging.	**elevation may suggest prolactinoma**
serum thyroid-stimulating hormone • Active thyroid dysfunction may present with oligo- or anovulation, or irregular and heavy menstrual bleeding.	**abnormal in thyroid disease**
oral glucose tolerance test • Fasting glucose measurement, followed by glucose measurement 2 hours after administration of 75 g of glucose given orally. • Prevalence of abnormal glucose tolerance (impaired fasting glucose, impaired glucose tolerance, or diabetes) is as high as 40% in polycystic ovary syndrome (PCOS).[5] In one meta-analysis, the odds of prevalent impaired glucose tolerance was 3.3, and of prevalent diabetes 2.9, in PCOS.[65] • All women should be screened for impaired glucose tolerance with an oral glucose tolerance test. Those with normal glucose tolerance should be rescreened at least every 2 years. Those with impaired glucose tolerance should be screened annually for type 2 diabetes.[66] • Assessment of insulin resistance/hyperinsulinemia is problematic, given variability in insulin assays and the need for population-specific normative ranges. However, insulin levels may be measured to give insight into whether insulin resistance is present. • Fasting insulin >10 to 15 microunits/mL may suggest insulin resistance. • During the oral glucose tolerance test, a peak insulin of 100-150 microunits/mL may indicate mild insulin resistance, 150-300 microunits/mL moderate insulin resistance, and >300 microunits/mL severe insulin resistance.[67]	**fasting glucose level between 100 and 125 mg/dL is impaired fasting glucose; impaired glucose tolerance is 2-hour glucose of 140-199 mg/dL; diabetes is defined as fasting glucose ≥126 mg/dL, or 2-hour glucose ≥200 mg/dL**
fasting lipid panel • Dyslipidemia is often observed in polycystic ovary syndrome (PCOS).[72] [73] [74] Assessment of fasting lipids has been advocated for all women with PCOS.[57] • Treatment may be instituted if cardiovascular risk is increased, based on overall evaluation of risk factors.	**elevated total cholesterol, LDL-cholesterol, triglycerides; low HDL-cholesterol**

Other tests to consider

Test	Result
serum total and free testosterone • Elevation >2 standard deviations above the mean qualifies as a positive test. Many laboratory reference ranges for androgens in women did not carefully exclude women with polycystic ovary syndrome (PCOS).[61] [62] Testosterone levels are difficult to measure in women; even assays using liquid chromatography mass spectrometry exhibit poor precision at the low levels characteristically found in women.[60] • Hyperandrogenemia is present in 60% to 80% of women with PCOS: 70% have elevated free testosterone, 40% have elevated total testosterone, 25% have elevated dehydroepiandrosterone sulfate.[3] • In obese women, sex hormone-binding globulin levels are low, resulting in elevated free testosterone and often normal total testosterone. Androgen level tests should be performed in the follicular phase (in cycling women), in the morning, and at least 3 months after cessation of any hormonal therapies. An exception to these hormonal therapies is a cyclic progestin.[63]	**elevated**
serum dehydroepiandrosterone sulfate (DHEAS) • May be done if other serum androgens are normal. Elevation >2 standard deviations above the mean qualifies as a positive test. Many laboratory reference ranges for androgens in women did not carefully exclude women with polycystic ovary syndrome (PCOS).[61] • Hyperandrogenemia is present in 60% to 80% of women with PCOS: 70% have elevated free testosterone, 40% have elevated total testosterone, 25% have elevated DHEAS.[3] • DHEAS levels are the only elevated androgen in 10% of women with PCOS. • The American College of Obstetricians and Gynecologists PCOS guideline suggests evaluating DHEAS is of little value except in cases of rapid virilization.[64]	**elevated**
serum androstenedione • May be done if other serum androgens are normal. Measurement may increase the number of women identified as hyperandrogenemic by 10%.[3]	**elevated**
pelvic ultrasound • Polycystic ovaries are present in 75% of women with polycystic ovary syndrome (PCOS), but are also seen in up to 25% of normal women and women with other endocrinopathies such as congenital adrenal hyperplasia, hyperprolactinemia, or hypothalamic amenorrhea.[3]	**≥20 follicles in each ovary measuring 2-9 mm in diameter, and/or increased ovarian volume (≥10 mL) in either or both ovaries (using endovaginal ultrasound at 8 MHz); endometrial lining >5 to 7 mm in thickness indicates endometrial thickening. If using older ultrasound technology or transabdominal ultrasound, focus on ovarian volume ≥10 mL in either ovary as a positive test**

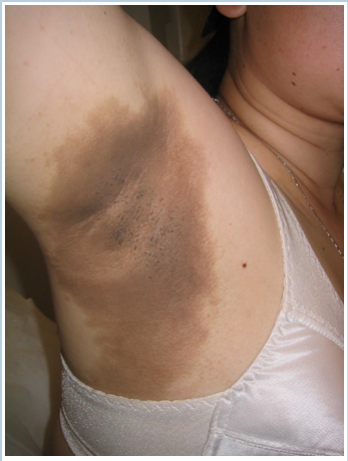
Test	Result
 *Polycystic ovarian ultrasound* *From the collection of Dr M. O. Goodarzi; used with permission* • Transvaginal ultrasound, where appropriate, gives higher-resolution images of the ovaries than transabdominal ultrasound. Ovarian volume may be estimated as 0.5 x length x width x thickness.[2] • Ultrasound should be done in the early follicular phase (day 3-5) after a spontaneous or progestin-withdrawal-induced menstruation, or randomly in women with infrequent/reduced menstrual bleeding. If evidence of a dominant follicle (>10 mm) or a corpus luteum is seen, the ultrasound should be repeated at the next cycle.[2] • Polycystic ovarian morphology is a risk factor for ovarian hyperstimulation syndrome in women undergoing ovulation induction (with clomiphene or gonadotropins). Therefore, an ultrasound before ovulation induction may be useful. • If endometrial thickening is found, an endometrial biopsy is indicated to determine whether endometrial hyperplasia or cancer is present. Routine ultrasound screening for endometrial thickness is not recommended.[53] • It should be noted that ovarian volume and follicular number decrease with age, so standard criteria may not be applicable to women >40 years of age.[58] Also, multifollicular ovaries may be observed during puberty, subsiding once the normal menstrual pattern is established.[52] • The International PCOS Network guideline recommends against ultrasound for diagnosis of PCOS in adolescents due to poor specificity.[53]	
serum anti-Mullerian hormone • May be considered as an alternative to pelvic ultrasound in adults. Not recommended for diagnosis of polycystic ovary syndrome (PCOS) in adolescents due to poor specificity in this age group.[53] • One meta-analysis reported a pooled sensitivity of 0.78 (95% CI: 0.74 to 0.81) and a specificity of 0.87 (95% CI: 0.84 to 0.90) for diagnosing PCOS.[59] However, there was substantial heterogeneity between studies and optimal cut-off values have not been defined.[59]	**elevated**

Test	Result
basal body temperature monitoring • Up to 20% of women suspected of having polycystic ovary syndrome report regular menses.[3] In such cases, investigation to document anovulation may be indicated.	**biphasic pattern indicates ovulation has occurred; flat pattern indicates anovulation**
luteal phase progesterone measurement • Performed on day 20-24 of the menstrual cycle. • Up to 20% of women suspected of having polycystic ovary syndrome report regular menses.[3] In such cases, investigation to document anovulation may be indicated.	**>2-8 ng/mL indicates ovulation has occurred**
serum LH and follicle-stimulating hormone (FSH) • LH pulses are abnormally elevated (frequency and amplitude), leading to increased serum LH levels and LH/FSH ratio >3 in only two-thirds of women with polycystic ovary syndrome (PCOS). • LH/FSH ratio is elevated more often in lean women. This ratio is helpful only if positive, and is not diagnostic. • Checking LH and FSH is also useful to rule out hypothalamic amenorrhea (levels low) or perimenopause/ovarian failure (levels high).	**LH/FSH ratio >3 suggests PCOS**
hemoglobin A1c or fasting plasma glucose • Given the high frequency of insulin resistance and metabolic syndrome in PCOS, testing should be performed in all women at diagnosis to evaluate metabolic risk factors.[53] [64] • Fasting plasma glucose or hemoglobin A1c are less accurate than oral glucose tolerance testing, but may be considered as second-line alternatives if an oral glucose tolerance test cannot be performed.[53] [68]	**fasting glucose level between 100 and 125 mg/dL is impaired fasting glucose; hemoglobin A1c of 5.7% to 6.4% (39-47 mmol/mol) is consistent with prediabetes; diabetes is defined as fasting glucose ≥126 mg/dL, or hemoglobin A1c ≥6.5% (≥48 mmol/mol)**

Differentials

Condition	Differentiating signs / symptoms	Differentiating tests
21-hydroxylase deficiency	• Partial deficiency of the 21-hydroxylase enzyme within the cortisol biosynthetic pathway results in accumulation of androgenic precursors. • Clinical presentation may be indistinguishable from that of PCOS. • Certain ethnic groups are at risk: Yupik Eskimos, Ashkenazi Jews, and Hispanic, Italian, and Yugoslav women. • Very rare in African-Americans.	• A morning, follicular-phase 17-hydroxyprogesterone level <200 ng/dL rules out the disorder. A value >800 ng/dL rules it in. Intermediate values prompt cosyntropin (adrenocorticotropic hormone) stimulation testing. • Women with nonclassic congenital adrenal hyperplasia always have a stimulated (60 minutes) 17-hydroxyprogesterone value >1000 ng/dL (usually >1500 and <10,000 ng/dL).
Thyroid dysfunction	• Thyroid dysfunction may lead to menstrual irregularities. However, unlike in most cases of PCOS, hyperandrogenism is absent. • Clinical features of hypothyroidism (e.g., lethargy, cold intolerance) or hyperthyroidism (e.g., weight loss, nervousness, heat intolerance) may be present.	• Thyroid-stimulating hormone level greater (primary hypothyroidism) or less than (hyperthyroidism) the normal range.
Hyperprolactinemia	• Hyperprolactinemia may lead to infrequent or absent menses. • Mild hyperandrogenic features may be observed. • Galactorrhea is usually present. • There may be headache or visual field deficit.	• Prolactin level greater than the upper limit of the normal range. However, some women with PCOS have prolactin levels that are slightly elevated.[2]
Cushing syndrome	• Circulating cortisol and androgen levels are elevated, resulting in obesity, hirsutism, acne, and menstrual irregularity. • Usually with moon facies, central fat deposition, hypertension, muscle wasting, abdominal striae, and osteoporosis.	• Screen for Cushing syndrome with 24-hour urinary free cortisol (normal <90 microgram/24 hours for radioimmunoassay or <50 microgram/24 hours for high-performance liquid chromatography) or low-dose dexamethasone suppression test (e.g., overnight: 1 mg at 11 p.m.

Condition	Differentiating signs / symptoms	Differentiating tests
	• Adrenal carcinomas in particular are inefficient at synthesizing cortisol and can release large amounts of androgenic precursors, leading to severe hirsutism and virilization.	or midnight), with 8 a.m. plasma cortisol the next morning. Normally a.m. cortisol is suppressed to <5 micrograms/dL (<1.8 micrograms/dL with modern cortisol assays sensitive to detect 1 microgram/dL). An alternative screening test is late p.m. salivary cortisol.
Androgen-secreting neoplasms	• These are steroid-producing tumors of the adrenal or ovary. • Autonomous androgen production often produces rapid-onset (within months) progressive virilization (frontal balding, severe hirsutism, increased muscle bulk, deepened voice, clitoromegaly).	• Baseline total testosterone >200 ng/dL (or free testosterone >2 ng/dL) warrants ultrasound of the ovaries (but may miss small hilus cell tumor). • Dehydroepiandrosterone sulfate >7000 ng/mL should prompt CT of the adrenals.[75] • Some androgen-producing tumors may be associated with serum testosterone <200 ng/dL. • Most women with testosterone >200 ng/dL have PCOS or hyperandrogenism-insulin resistance acanthosis nigricans syndrome. The rapidity of onset of virilization (<2 years) or onset late in life is a better predictor of neoplasm than androgen levels.[76]
Syndromes of severe insulin resistance	• Degrees of insulin resistance, hyperinsulinemia, and hyperandrogenism tend to be more severe than in PCOS. • Also known as hyperandrogenic insulin-resistant acanthosis nigricans syndrome.	• Diagnosis is based on fasting insulin >80 microunits/mL and/or peak insulin >300 microunits/mL during a 3-hour 75 g oral glucose tolerance test, provided that beta cells are functional (reflected in normal glucose levels).

Condition	Differentiating signs / symptoms	Differentiating tests
	 *Acanthosis nigricans involving the axilla of an obese white woman* *From the collection of Melvin Chiu, MD, UCLA; used with permission* • Lipodystrophy may be present.	
Androgenic/anabolic drugs	• History of use or abuse of testosterone, anabolic steroids, danazol, dehydroepiandosterone, androstenedione, 19-norprogestins, norgestrel, levonorgestrel, or norethindrone. • Severity of hyperandrogenism varies depending on dose and duration of drug use.	• Depending on agent used, blood evaluation for androgen levels may or may not be diagnostically useful.
Hypogonadotropic hypogonadism	• Presents with oligoanovulation, but hyperandrogenism is absent.	• Low serum follicle-stimulating hormone and estradiol.
Premature ovarian failure	• Presents with anovulation, but hyperandrogenism is absent.	• High serum follicle-stimulating hormone and low serum estradiol.
Apparent cortisone reductase deficiency	• Functional decrease in 11-beta-hydroxysteroid dehydrogenase type 1, leading to decreased conversion of inactive cortisone to cortisol. • As a result of enhanced peripheral clearance of cortisol, there is less feedback suppression of adrenocorticotropic	• Ratio of tetrahydrocortisols to tetrahydrocortisone is very low (0.04-0.08, normally 0.5-2.0). • Both adrenals often enlarged. • Urinary free cortisol may appear elevated.[77]

Condition	Differentiating signs / symptoms	Differentiating tests
	hormone, resulting in adrenal androgen excess. • Clinically may be indistinguishable from PCOS.[77]	

Criteria

1990 National Institutes of Health criteria[1]

All of the following must be present:

- Hyperandrogenism and/or hyperandrogenemia
- Oligo- or anovulation
- Exclusion of other disorders.

2003 Rotterdam criteria[2]

Two of the following three must be present, and other disorders must be excluded:

- Hyperandrogenism and/or hyperandrogenemia
- Oligo- or anovulation
- Polycystic ovaries on ultrasound.

2006 Androgen Excess Society criteria[3]

All of the following must be present:

- Hyperandrogenism (hirsutism) and/or hyperandrogenemia
- Ovarian dysfunction: oligoanovulation and/or polycystic ovarian morphology
- Exclusion of other disorders.

Approach

Depending on the needs or goals of the woman, therapy is typically focused on either improvement of fertility or treatment of the symptoms of hyperandrogenism (e.g., hirsutism). Long-term measures should also be taken to restore regular menses and prevent endometrial hyperplasia.

Lifestyle management including a healthy diet and regular physical activity is recommended for all women with polycystic ovary syndrome (PCOS) to optimize general health, quality of life, metabolic health, fertility outcomes, and health during pregnancy.[53] [64] [81][82]

With infertility where fertility is desired

The first-line and safest measure to restore ovulation is weight loss (in overweight or obese women). Weight loss alone (even as little as 5% to 7%) may restore ovulation in up to 80% of overweight or obese women (possibly by reducing hyperinsulinemia and thus hyperandrogenism).[64] [83][84] [85] [86] Weight loss is also beneficial from a cardiovascular standpoint, and may improve subsequent pregnancy outcomes.[87] Studies suggest dietary interventions, exercise, and/or behavioral coaching are effective for weight loss in PCOS, but no particular exercise or dietary composition (beyond caloric restriction) can be recommended over another.[64] [81] [88]

If weight loss is unsuccessful, pharmacologic ovulation induction therapy is recommended. The International PCOS Network and American College of Obstetricians and Gynecologists guidelines recommend letrozole as the first-line option.[53] [64] Increasing data suggest that letrozole improves ovulation, pregnancy, and live birth rates compared with clomiphene.[89] [90] [91] However, the use of letrozole may be off-label in some countries, and some guidelines recommend clomiphene as the preferred option.[92]

Alternative first-line options include clomiphene plus metformin (preferred to clomiphene alone), clomiphene alone, or metformin alone (less effective but low cost and no monitoring).[53] Gonadotropins are primarily recommended as a second-line option if other pharmacologic treatments are ineffective, but the 2023 International PCOS Network guideline recommends that they may be considered first line as an alternative to clomiphene with or without metformin, acknowledging the increased cost, expertise, and monitoring requirements, and the potential for multiple pregnancy associated with gonadotropin treatment.[53]

Guidelines recommend optimizing preconception health and lifestyle for all women with PCOS, but weight loss is not recommended as first-line fertility treatment for normal-weight women with PCOS.[53] In these women, letrozole or clomiphene should be first-line.

Letrozole

Aromatase inhibitors such as letrozole reduce the conversion of androgens to estrogens. This reduction in estrogen synthesis reduces estrogen negative feedback on the hypothalamus/pituitary, allowing follicle-stimulating hormone to increase and stimulate follicle growth and ovulation.[93] The Pregnancy in Polycystic Ovary Syndrome II trial (PPCOS II, sample size 750) found that letrozole was superior to clomiphene in the live birth rate.[94] Meta-analyses of randomized controlled trials have found letrozole to be superior to clomiphene for pregnancy, live birth, and ovulation and similar to laparoscopic ovarian drilling for live birth.[89] [90] [91] Rates of miscarriage, ovarian hyperstimulation syndrome, and multiple pregnancies are similar between letrozole and clomiphene.[90]

It is hoped that aromatase inhibitors may be effective in women who are resistant to clomiphene; however, too few studies comparing letrozole with placebo in such women have been performed to definitively answer this question.[95] By contrast, meta-analysis of randomized controlled trials in clomiphene-resistant women with PCOS found that letrozole and laparoscopic ovarian drilling were similarly effective in terms of ovulation, pregnancy, and live birth.[96] A randomized controlled trial in clomiphene-resistant PCOS found that letrozole and the combination of clomiphene plus metformin produced similar rates of ovulation and pregnancy.[97] One meta-analysis of individual participant data from six randomized controlled trials found that letrozole was superior to clomiphene regarding time to pregnancy, rate of pregnancy, and live birth rate, with no interaction between treatment and BMI on the primary outcome of live birth, suggesting letrozole is superior regardless of BMI.[89]

Metformin

Metformin can restore ovulation/menses to the point where conception is possible. However, 6-9 months may be needed for the full effect. Some data suggest that metformin may be less effective in women with body mass index (BMI) greater than 27-32 kg/m².[98] [99] [100] Patient characteristics that may predict metformin response have not been firmly identified. Some experts believe all women with PCOS may benefit, while others would give metformin only to women who are overweight/obese or who appear to have insulin resistance. One meta-analysis found that the rate of clinical pregnancy was slightly higher with metformin treatment compared with placebo (47.7% vs. 42.9%) for nonobese women with PCOS, but concluded more data is needed before metformin is recommended for nonobese women.[101] Metformin appears to increase ovulation and pregnancy rates, but it has not conclusively been found to improve live birth rates.[100]

Meta-analyses suggest that continuing metformin throughout pregnancy may decrease rates of early pregnancy loss and premature birth, with no effect on gestational diabetes, preeclampsia, or fetal abnormalities.[102] [103] [104] However, in a series of randomized trials, children born to women with PCOS who were treated with metformin (from late first trimester to delivery) had increased BMI compared with children born to women with PCOS in the placebo group.[105]

Clomiphene

Clomiphene is a nonsteroidal antiestrogen that inhibits estrogen negative feedback on the hypothalamus/pituitary, which in turn leads to an increase in follicle-stimulating hormone secretion that may allow follicular maturation and ovulation.

Clomiphene is a very commonly used fertility treatment and effective in achieving pregnancy.[106] Up to 25% of patients will have clomiphene resistance due to ovarian unresponsiveness. There is a 5% to 10% risk of multiple pregnancy. In a clinical trial comparing clomiphene, metformin (and clomiphene plus metformin), multiple birth occurred in 6% of the clomiphene group and 0% of the metformin group (and in 3.1% in the clomiphene plus metformin group).[107]

A meta-analysis found that compared with early follicular phase administration of clomiphene, administration during the late luteal phase resulted in a higher total number of follicles, yet rates of ovulation and pregnancy were similar.[108]

Dexamethasone may be added to clomiphene if adrenal androgen excess is present.

Clomiphene plus metformin

If three treatment cycles of clomiphene have failed, it is reasonable to add metformin. Some studies, but not all, suggest that adding metformin to clomiphene may be efficacious if clomiphene alone is unsuccessful. It is also reasonable to start with clomiphene plus metformin rather than either agent alone for treatment of anovulatory infertility.[53]

A Cochrane review concluded that clomiphene plus metformin results in a 60% higher pregnancy rate compared with clomiphene alone, but data for live birth rates are inconclusive.[100] Another meta-analysis comparing clomiphene plus metformin to clomiphene alone found the combination yielded a 28% higher clinical pregnancy rate but no differences in live birth rate.[109] However, in two randomized trials, clomiphene was similar in pregnancy or live birth rate to clomiphene plus metformin.[107] [110] In one of these trials, metformin did not affect the dose of clomiphene needed to achieve ovulation.[111] In the other trial, subgroup analysis found metformin efficacious for pregnancy in older (age >28 years) women or those with increased central obesity.[112]

While adding metformin to clomiphene seems to improve ovulation rates, the impact on live birth rate has been questioned. Other meta-analyses found clomiphene plus metformin to increase pregnancy and live birth versus clomiphene alone in clomiphene-resistant women.[113] [114]

Second-line treatment

If these measures fail, injectable treatments such as gonadotropins should be given. Gonadotropins (human menopausal gonadotropins [hMG]: luteinizing hormone [LH] plus follicle-stimulating hormone [FSH]) directly act on the ovary, stimulating follicular recruitment and maturation. In women with PCOS who have anovulatory infertility and clomiphene resistance, the International PCOS Network recommends that gonadotropins are preferable to clomiphene plus metformin, gonadotropins alone are preferred to gonadotropins plus clomiphene, and either gonadotropins or laparoscopic ovarian surgery can be offered.[53]

Treatment with gonadotropins is associated with a high risk of multiple pregnancies (twins in 20% to 30%, triplets in 1% to 2%) and ovarian hyperstimulation syndrome (OHSS), especially if many follicles reach intermediate size or if serum estradiol is too high. Mild OHSS (abdominal distention, nausea, vomiting, diarrhea) is common. Severe OHSS may cause extreme cystic ovarian enlargement (pain, hemorrhagic cysts, torsion), vascular hyperpermeability (ascites, hydrothorax, hypoproteinemia, electrolyte disturbance, hemoconcentration, oliguria, pulmonary edema), and, in the most severe cases, thrombosis (sometimes at unusual sites, e.g., subclavian or internal jugular vein) or thromboembolism.

Close follow-up and careful dosing are required to avoid OHSS.

In PCOS, lower doses of hMG are used because of the increased risk of OHSS compared with women without PCOS. FSH alone and hMG have similar rates of OHSS, pregnancy, and live birth.[115] Polycystic ovarian morphology is a risk factor for OHSS. Therefore, ultrasound evaluation of the ovaries may assist in selecting the initial dose of gonadotropins.

The step-up and step-down approaches with FSH were compared in clomiphene-resistant women with PCOS. The pregnancy rates did not differ, but the step-up approach had higher rates of ovulation and lower rates of OHSS.[116] Another trial found a sequential step-up and step-down protocol to have higher pregnancy and lower miscarriage rates then either step-up or step-down protocols.[117]

Gonadotropins are usually given as sole therapy; however, adding metformin might reduce the risk of ovarian hyperstimulation syndrome.[118] [119] Preliminary evidence suggests that taking metformin

during ovulation induction with gonadotropin, followed by timed intercourse or intrauterine insemination, might increase rates of pregnancy and live birth.[119] [120] [121]

Third-line treatment

In the most difficult cases, in vitro fertilization (IVF) or laparoscopic ovarian drilling is performed.

Laparoscopic ovarian drilling (the use of electrocautery or laser to reduce the amount of functional ovarian tissue to reduce androgen production, also reduces inhibin production, allowing FSH to rise and stimulate ovarian aromatase) can restore ovulation and result in pregnancy rates of 25% to 65%. While there is no risk of hyperstimulation or multiple births with ovarian drilling, there is a risk of postoperative adhesion formation (much less than previous ovarian wedge resection techniques) and ovarian atrophy.[122]

One meta-analysis comparing laparoscopic ovarian drilling with medical induction of ovulation (including gonadotropins, clomiphene, letrozole, metformin, and others alone and in combination) in women with anovulatory PCOS who had clomiphene resistance found a lower live birth rate with laparoscopic ovarian drilling; when the analysis was restricted to trials with a low risk of bias, the live birth rates were similar.[123] Furthermore, in women with anovulatory PCOS who had clomiphene resistance, laparoscopic ovarian drilling versus medical induction of ovulation was associated with similar rates of pregnancy and miscarriage but lower rates of multiple pregnancy and ovarian hyperstimulation syndrome.[123]

There is no conclusive evidence that laparoscopic ovarian drilling leads to diminished ovarian reserve or premature ovarian failure.[124] Unilateral and bilateral ovarian drilling may have similar efficacy in clinical pregnancy and live birth rates.[125] Ovarian drilling may be most effective in clomiphene-resistant women, with BMI <30 kg/m², and preoperative LH above 10 IU/L.[126] [127]

In typical IVF protocols, gonadotropins are given to promote multifollicular growth so that multiple mature oocytes can be aspirated. Despite more frequent cycle cancellation (failure to retrieve oocytes) and higher rates of miscarriage than in controls, women with PCOS have more oocytes obtained per retrieval and similar pregnancy and live birth rates per cycle.[128] [129] One meta-analysis found that while not impacting pregnancy or birth rates, metformin administration during IVF and intracytoplasmic sperm injection (ICSI) cycles may reduce the risk of ovarian hyperstimulation syndrome and miscarriage, and improve implantation rates.[130] [131] The effect of metformin in reducing the risk of ovarian hyperstimulation during IVF or ICSI cycles with metformin has been confirmed in another meta-analysis; however, this meta-analysis did not find that metformin reduced the incidence of spontaneous abortion.[132]

Not desiring current fertility: hyperandrogenic features alone

Weight loss should be encouraged, but is less efficacious for androgenic symptoms than for therapy of infertility or infrequent/reduced menstrual bleeding. All pharmacologic therapies for hirsutism should be trialed at least 6 months before making changes in dose, switching to a new medication, or adding medication.[12] [78]

Oral contraceptive pills (OCP)

In most women with hyperandrogenic symptoms, an oral contraceptive pill (OCP: cyclic estrogen plus a progestin) is an appropriate choice of initial treatment. OCPs are more effective for acne than for hirsutism.

The Endocrine Society hirsutism clinical practice guidelines and the International PCOS Network guidelines do not recommend one particular OCP over another.[53][78] OCP therapy modestly inhibits gonadotropin secretion, and thus gonadotropin-sensitive ovarian androgen production, and increases hepatic production of sex hormone-binding globulin (SHBG), which further decreases free testosterone. If free testosterone and SHBG are not normalized after 3 months, the possibility of an androgen-secreting neoplasm should be considered.

Levonorgestrel is the most androgenic progestin and OCPs that contain a progestin with androgenic activity (e.g., levonorgestrel, norethindrone) have often been avoided in practice due to concerns they would be less effective for symptoms like hirsutism. This was not observed in meta-analysis.[133] However, levonorgestrel can have an adverse effect on metabolic biomarkers and therefore it tends to be avoided in women with PCOS.[78] Newer, less-androgenic progestins include desogestrel or norgestimate. Drospirenone is a spironolactone analog with antiandrogenic and antimineralocorticoid properties. Pills with these newer, lower-androgenicity progestins may, however, confer a higher risk of venous thromboembolism than older pills, although one large prospective study found no such risk.[134] [135] [136] [137] Given this possible risk of venous thromboembolism with newer pills, some practitioners still prefer to use levonorgestrel- or norethindrone-containing pills.

OCPs should not be used before epiphyseal closure. Contraceptive pills should be avoided or used with caution in women with risk factors (e.g., smoking [especially if age is ≥35 years], history of thromboembolism, or migraine with aura). Other reasons for caution include poorly controlled hypertension, diabetes of long duration (>20 years), and diabetes with vascular complications.[138]

Antiandrogens

The Endocrine Society advises against antiandrogen monotherapy as initial therapy for hirsutism because of its teratogenic potential (unless women are on adequate contraception).[78] For women who are not sexually active, have undergone permanent sterilization, or are on long-acting reversible contraception, initial therapy with OCP or antiandrogens as monotherapy are both options.[78] If monotherapy is to be used, the decision is tailored to the woman's needs, with a particular focus on adverse effects.

Women with severe hirsutism or contraindications to hormonal contraception may need to be considered for treatment with antiandrogens.[31] [78] Antiandrogens are androgen receptor blockers (e.g., spironolactone, cyproterone) or 5-alpha-reductase inhibitors (e.g., finasteride). Cyproterone is not available in the US. Antiandrogens (especially finasteride) should be avoided in pregnancy due to potential for ambiguous genitalia in male fetus. Flutamide is not recommended because of potential hepatotoxicity. Antiandrogens should be used for at least 6 months before judging efficacy.[78] The maximal effect on hirsutism may take 9-12 months (compared with the effect on acne, which usually responds within 2 months). Acne is more responsive to therapy while alopecia is less responsive. Contraceptive measures are advisable given theoretical teratogenicity.

In many cases, a combination of antiandrogen and oral contraceptive may be needed, particularly for hirsutism or severe acne. The combination has the added benefit of preventing pregnancy, while increasing efficacy by targeting two different processes: androgen production and androgen action. The Endocrine Society recommends monotherapy first line for hirsutism, and if symptoms remain after 6 months to add in an antiandrogen.[78]

Metformin

The Endocrine Society advises against using insulin-lowering drugs for the sole indication of treating hirsutism.[78] Meta-analyses suggest that metformin is associated with decreased testosterone and androstenedione levels and increased SHBG levels, with limited evidence of improvement in hirsutism.[133] [139][140] One Cochrane review also found that metformin may be less effective in improving hirsutism compared with the OCP in women with PCOS who are overweight.[141] Another meta-analysis of 51 studies concluded that metformin (alone or as adjuvant therapy) may improve acne scores.[142]

Adding metformin might improve results compared with monotherapy or dual therapy.[133] [141] Thus, for the specific goal of treating hyperandrogenism, it is best suited as add-on therapy to OCPs, anti-androgens, or OCPs plus anti-androgens. In one meta-analysis, metformin plus spironolactone was more effective for reducing BMI and serum androgen levels than metformin alone, but there was no significant effect on hirsutism score or gonadotropin levels.[143] The 2023 International PCOS Network guideline suggests that the combination of OCPs and metformin may be most beneficial in high risk metabolic groups, including women with BMI >30 kg/m², risk factors for diabetes, impaired glucose tolerance, or high-risk ethnic groups.[53]

To avoid gastrointestinal adverse effects, metformin should be taken with food and the dose titrated slowly over 4-6 weeks. Extended-release metformin has a slightly lower incidence of gastrointestinal adverse effects. Limited evidence suggests that metformin may promote weight loss, particularly at higher doses (>1500 mg/day) and with longer duration of therapy (>8 weeks).[144]

Long-acting gonadotropin-releasing hormone (GnRH) analogs

In very severe or refractory ovarian hyperandrogenism, GnRH analogs (e.g., leuprolide) plus estrogen yield profound suppression of gonadotropins and suppress ovarian steroid synthesis.[78] GnRH agonists are best combined with estrogen (OCPs) to increase sex hormone-binding globulin and protect bones from resultant hypoestrogenemia (women on GnRH without estrogen replacement may lose 4% to 8% trabecular bone after 6 months) and avoid severe vasomotor symptoms. With the estrogen replacement, a progestin must also be given to protect the endometrium.[78]

Mechanical hair removal or topical therapy

At any stage of therapy for hirsutism, mechanical or local hair removal is a useful adjunct to remove hairs that do not respond to medical therapy.[78]

To destroy terminal hair follicles, electrolysis (or laser, which works best with light skin and dark hair) is useful after ≥6 months of hormonal therapy has halted the appearance of new terminal hairs.

Topical eflornithine slows growth of facial hair in 20% to 40% of women by 8 weeks.[145] It should be discontinued if no results are noted by 4-6 months.

For androgenetic alopecia, topical minoxidil treatment may be effective but must be used for several months.[146]

With both topical eflornithine and minoxidil, benefit subsides if the agent is discontinued.

Not desiring current fertility: infrequent/reduced menstrual bleeding alone

Anovulatory women with PCOS have chronic estrogenization without progesterone exposure, leading to risk of abnormal uterine bleeding, endometrial hyperplasia, and cancer.

Therefore, treatments that induce ovulation (e.g., weight loss or metformin) or provide progesterone exposure (OCPs or a cyclic progestin) should be given to these women.

Weight loss is the preferred treatment for overweight or obese women. The OCP or metformin is used if ineffective, or if weight is normal. If an OCP is not tolerated or desired by the patient, or if there are contraindications to an OCP, cyclic progestin should be given.[12] A cyclic progestin is also used in refractory cases.

Among the older OCPs, ethynodiol/ethinyl estradiol is considered low androgenic and may be useful if a larger dose of estrogen is needed. This higher-estrogen-dose pill may be able to induce menses in women with persistent amenorrhea. Persistent amenorrhea may indicate endometrial atrophy resulting from hyperandrogenism (thin endometrial width on ultrasound). The risk-benefit ratio must be carefully considered when using higher-dose pills.

The International PCOS Network guidelines do not recommend a particular OCP over another.[53]

Not desiring current fertility: hyperandrogenic features plus infrequent/reduced menstrual bleeding

These women are treated with a combined approach:

- Preferred treatment is weight loss (if overweight) plus OCPs
- Oral contraceptive plus an antiandrogen is used if this proves ineffective
- Long-acting GnRH analog plus estrogen is used for refractory cases
- Metformin may be used adjunctively for weight loss plus oral contraceptives, or for oral contraceptives plus antiandrogen
- For any stage of treatment, topical or mechanical hair removal may be added.

Treatment algorithm overview

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Acute (summary)		
with infertility and desiring fertility		
	1st	weight loss
	1st	letrozole
	1st	clomiphene
	adjunct	metformin
	adjunct	dexamethasone
	1st	metformin
	2nd	gonadotropins
	adjunct	metformin
	3rd	in vitro fertilization
	adjunct	metformin
	3rd	laparoscopic ovarian drilling

Ongoing (summary)

not desiring current fertility

with hyperandrogenic features alone	1st	oral contraceptive pill
	adjunct	metformin
	adjunct	mechanical hair removal or topical therapy
	2nd	antiandrogen
	adjunct	metformin
	adjunct	mechanical hair removal or topical therapy
	2nd	antiandrogen plus oral contraceptive pill
	adjunct	metformin
	adjunct	mechanical hair removal or topical therapy
	3rd	long-acting GnRH analog plus oral contraceptive pill
	adjunct	mechanical hair removal or topical therapy
with infrequent/reduced menstrual bleeding alone	1st	weight loss
	2nd	oral contraceptive pill
	2nd	metformin
	3rd	cyclic progestin
with hyperandrogenic features plus infrequent/ reduced menstrual bleeding	1st	weight loss
	plus	oral contraceptive pill
	adjunct	metformin
	adjunct	mechanical hair removal or topical therapy
	2nd	antiandrogen plus oral contraceptive pill
	adjunct	metformin
	adjunct	mechanical hair removal or topical therapy
	3rd	long-acting GnRH analog plus oral contraceptive pill

Ongoing			(summary)
		adjunct	mechanical hair removal or topical therapy

Treatment algorithm

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Acute

with infertility and desiring fertility

1st **weight loss**

» The first-line and safest measure to restore ovulation is weight loss (in overweight or obese women). Weight loss alone (even as little as 5% to 7%) may restore ovulation in up to 80% of overweight or obese women (possibly by reducing hyperinsulinemia and thus hyperandrogenism).[64] [83][84] [85] Weight loss is also beneficial from a cardiovascular standpoint, and may improve subsequent pregnancy outcomes.[87] Studies suggest dietary interventions, exercise, and/or behavioral coaching are effective for weight loss in polycystic ovary syndrome (PCOS), but no particular exercise or dietary composition (beyond caloric restriction) can be recommended over another.[64] [81][88]

» If weight loss is unsuccessful, pharmacologic ovulation induction therapy is recommended.

» Guidelines recommend optimizing preconception health and lifestyle for all women with PCOS, but weight loss is not recommended as first-line fertility treatment for normal-weight women with PCOS.[53] In these women, letrozole or clomiphene should be first-line.

1st **letrozole**

Primary options

» letrozole: 2.5 mg orally once daily for 5 consecutive days initially, increase by 2.5 mg/day increments in subsequent cycles until ovulation is achieved, maximum 7.5 mg/day

» The International PCOS Network and American College of Obstetricians and Gynecologists guidelines recommend letrozole as the first-line option for medical treatment of infertility in women with PCOS.[53] [64] Increasing data suggest that letrozole improves ovulation, pregnancy, and live birth rates compared with clomiphene.[89] [91] However, the use of letrozole may be off-label in some countries, and some guidelines recommend clomiphene as the preferred option.[92]

Acute

» The Pregnancy in Polycystic Ovary Syndrome II trial (PPCOS II, sample size 750) found that letrozole was superior to clomiphene in the live birth rate.[94] Meta-analyses of randomized controlled trials have found letrozole to be superior to clomiphene and similar to laparoscopic ovarian drilling for pregnancy and live birth.[90] [91]Rates of miscarriage, ovarian hyperstimulation syndrome, and multiple pregnancies appear to be similar between letrozole and clomiphene.[90]

1st **clomiphene**

Primary options

» clomiphene: 50 mg orally once daily for 5 consecutive days initially, increase by 50 mg/day increments in subsequent cycles until ovulation achieved, maximum 150 mg/day

» Clomiphene is a nonsteroidal antiestrogen that inhibits estrogen negative feedback on the hypothalamus/pituitary, which in turn leads to an increase in follicle-stimulating hormone secretion that may allow follicular maturation and ovulation.

» A very commonly used fertility treatment and effective in achieving pregnancy.[106] Increasing data suggest that letrozole improves ovulation, pregnancy, and live birth rates compared with clomiphene.[89] [91] The International PCOS Network and American College of Obstetricians and Gynecologists guidelines recommend letrozole as the first-line option for pharmacologic treatment of infertility in women with PCOS.[53] [64] However, use of letrozole may be off-label in some countries, and some guidelines recommend clomiphene as the preferred option.[92]

» Up to 25% of patients will have clomiphene resistance due to ovarian unresponsiveness. There is a 5% to 10% risk of multiple pregnancy. In a clinical trial comparing clomiphene, metformin (and clomiphene plus metformin), multiple birth occurred in 6% of the clomiphene group and 0% of the metformin group (and in 3.1% in the clomiphene plus metformin group).[107]

» A meta-analysis found that compared with early follicular phase administration of clomiphene, administration during the late luteal phase resulted in a higher total number of follicles, yet rates of ovulation and pregnancy were similar.[108]

Acute

adjunct **metformin**

Treatment recommended for SOME patients in selected patient group

Primary options

» metformin: 500 mg orally (immediate-release) three times daily, or 850-1000 mg orally (immediate-release) twice daily; 1500-2000 mg orally (extended-release) once daily

» If three treatment cycles of clomiphene have failed, it is reasonable to add metformin. Some studies, but not all, suggest that adding metformin to clomiphene may be efficacious if clomiphene alone is unsuccessful. It is also reasonable to start with clomiphene plus metformin rather than either agent alone as treatment of anovulatory infertility.[53] The 2023 International PCOS Network guideline suggests clomiphene plus metformin is preferred to clomiphene alone.[53]

» A Cochrane review concluded that clomiphene plus metformin results in a 60% higher pregnancy rate compared with clomiphene alone, but data for live birth rates are inconclusive.[100] Another meta-analysis comparing clomiphene plus metformin to clomiphene alone found the combination yielded a 28% higher clinical pregnancy rate but no differences in live birth rate.[109] However, in two randomized trials, clomiphene was similar in pregnancy or live birth rate to clomiphene plus metformin.[107] [110] In one of these trials, metformin did not affect the dose of clomiphene needed to achieve ovulation.[111] In the other trial, subgroup analysis found metformin efficacious for pregnancy in older (age >28 years) women or those with increased central obesity.[112]

» While adding metformin to clomiphene seems to improve ovulation rates, the impact on live birth rate has been questioned. Other meta-analyses found clomiphene plus metformin to increase pregnancy and live birth versus clomiphene alone in clomiphene-resistant women.[113] [114]

» To avoid gastrointestinal adverse effects, metformin should be taken with food and the dose titrated slowly over 4-6 weeks. Extended-release metformin has a slightly lower incidence of gastrointestinal adverse effects.

Acute

adjunct **dexamethasone**

Treatment recommended for SOME patients in selected patient group

Primary options

» dexamethasone: 0.25 to 0.5 mg orally once daily for 3-6 months

» If clomiphene fails to result in pregnancy, adding dexamethasone may be considered if the patient has evidence of adrenal androgen excess.

» Suppression of adrenal androgen production with glucocorticoids may improve ovulatory function.

» Adding dexamethasone to clomiphene improves the pregnancy rate compared with clomiphene alone.[106]

1st **metformin**

Primary options

» metformin: 500 mg orally (immediate-release) three times daily, or 850-1000 mg orally (immediate-release) twice daily; 1500-2000 mg orally (extended-release) once daily

» Guidelines suggest that metformin alone is less effective than other ovulation induction agents, but it is associated with lower rates of multiple pregnancy, lower cost, and no monitoring requirements and may be considered as an alternative first-line option.[53] Metformin can restore ovulation/menses to the point where conception is possible. However, 6-9 months may be needed for the full effect.

» Some data suggest that metformin may be less effective in women with a body mass index greater than 27-32 kg/m².[98] [99] [100] Patient characteristics that may predict metformin response have not been firmly identified. Some experts believe all women with PCOS may benefit, while others would give metformin only to women who are overweight/obese or who appear to have insulin resistance. One meta-analysis found that the rate of clinical pregnancy was slightly higher with metformin treatment compared with placebo (47.7% vs. 42.9%) for nonobese women with PCOS, but concluded more data is needed before metformin is recommended for nonobese women.[101]

Acute

» Metformin appears to increase ovulation and pregnancy rates, but it has not conclusively been found to improve live birth rates.[100]

» Meta-analyses suggest that continuing metformin throughout pregnancy may decrease rates of early pregnancy loss and premature birth, with no effect on gestational diabetes, preeclampsia, or fetal abnormalities.[102] [103] [104] However, in a series of randomized trials, children born to women with polycystic ovary syndrome (PCOS) who were treated with metformin (from late first trimester to delivery) had increased body mass index compared with children born to women with PCOS in the placebo group.[105]

» To avoid gastrointestinal adverse effects, metformin should be taken with food and the dose titrated slowly over 4-6 weeks. Extended-release metformin has a slightly lower incidence of gastrointestinal adverse effects. Metformin does not have adverse effects on the kidneys or liver in women with PCOS.[147]

2nd **gonadotropins**

Primary options

» follitropin alfa: consult specialist for guidance on dose

OR

» follitropin beta: consult specialist for guidance on dose

Secondary options

» menotropins: consult specialist for guidance on dose

» Gonadotropins (human menopausal gonadotropins [hMG]: luteinizing hormone plus follicle-stimulating hormone [FSH]) directly act on the ovary, stimulating follicular recruitment and maturation.

» Gonadotropins are primarily recommended as a second-line option if other pharmacologic treatments are ineffective, but the 2023 International PCOS Network guideline recommends that they may be considered first-line as an alternative to clomiphene with or without metformin, acknowledging the increased cost, expertise, and monitoring requirements, and the potential for multiple pregnancy associated with gonadotropin treatment.[53]

Acute

» In women with PCOS who have anovulatory infertility and clomiphene resistance, the International PCOS Network recommends that gonadotropins are preferable to clomiphene plus metformin, gonadotropins alone are preferred to gonadotropins plus clomiphene, and either gonadotropins or laparoscopic ovarian surgery can be offered.[53]

» Treatment with gonadotropins is associated with a high risk of multiple pregnancies (twins in 20% to 30%, triplets in 1% to 2%) and ovarian hyperstimulation syndrome (OHSS), especially if many follicles reach intermediate size or if serum estradiol is too high. Mild OHSS (abdominal distention, nausea, vomiting, diarrhea) is common. Severe OHSS may cause extreme cystic ovarian enlargement (pain, hemorrhagic cysts, torsion), vascular hyperpermeability (ascites, hydrothorax, hypoproteinemia, electrolyte disturbance, hemoconcentration, oliguria, pulmonary edema), and, in the most severe cases, thrombosis (sometimes at unusual sites, e.g., subclavian or internal jugular vein) or thromboembolism.

» Close follow-up and careful dosing are required to avoid OHSS.

» In PCOS, lower doses of hMG are used because of the increased risk of OHSS compared with women without PCOS. FSH alone and hMG have similar rates of OHSS, pregnancy, and live birth.[115] Polycystic ovarian morphology is a risk factor for OHSS. Therefore, ultrasound evaluation of the ovaries may assist in selecting the initial dose of gonadotropins.

» The step-up and step-down approaches with FSH were compared in clomiphene-resistant women with PCOS. The pregnancy rates did not differ, but the step-up approach had higher rates of ovulation and lower rates of OHSS.[116] Another trial found a sequential step-up and step-down protocol to have higher pregnancy and lower miscarriage rates then either step-up or step-down protocols.[117]

adjunct **metformin**

Treatment recommended for SOME patients in selected patient group

Primary options

» metformin: 500 mg orally (immediate-release) three times daily, or 850-1000 mg orally (immediate-release) twice daily;

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1500-2000 mg orally (extended-release) once daily

» Gonadotropins are usually given as sole therapy; however, adding metformin might reduce the risk of ovarian hyperstimulation syndrome.[118] [119] Preliminary evidence suggests that taking metformin during ovulation induction with gonadotropin, followed by timed intercourse or intrauterine insemination, might increase rates of pregnancy and live birth.[119] [120] [121]

3rd **in vitro fertilization**

» In typical protocols, gonadotropins are given to promote multifollicular growth so that multiple mature oocytes can be aspirated. Despite more frequent cycle cancellation (failure to retrieve oocytes) and higher rates of miscarriage than in controls, women with polycystic ovary syndrome have more oocytes obtained per retrieval and similar pregnancy and live birth rates per cycle.[128] [129]

» There is a significant risk of ovarian hyperstimulation syndrome, which can be avoided by close monitoring, use of lower doses of gonadotropins, and early cycle cancellation.[115]

adjunct **metformin**

Treatment recommended for SOME patients in selected patient group

Primary options

» metformin: 500 mg orally (immediate-release) three times daily, or 850-1000 mg orally (immediate-release) twice daily; 1500-2000 mg orally (extended-release) once daily

» While having no effect on live birth rates, giving metformin during assisted reproduction may increase clinical pregnancy rates and reduce ovarian hyperstimulation syndrome.[148] Meta-analyses found that while not impacting pregnancy or live birth rates, metformin administration during in vitro fertilization and intracytoplasmic sperm injection cycles may reduce the risk of ovarian hyperstimulation syndrome, and improve implantation rates.[130] [131] [132]

3rd **laparoscopic ovarian drilling**

» Laparoscopic ovarian drilling (the use of electrocautery or laser to reduce the amount of

Acute

functional ovarian tissue to reduce androgen production, also reduces inhibin production, allowing follicle-stimulating hormone to rise and stimulate ovarian aromatase) can restore ovulation and result in pregnancy rates of 25% to 65%.

» No risk of hyperstimulation or multiple births, but risk of postoperative adhesion formation (much less than previous ovarian wedge resection techniques) and ovarian atrophy.[122]

» One meta-analysis comparing laparoscopic ovarian drilling with medical induction of ovulation (including gonadotropins, clomiphene, letrozole, metformin, and others alone and in combination) in women with anovulatory polycystic ovary syndrome (PCOS) who had clomiphene resistance found a lower live birth rate with laparoscopic ovarian drilling; when the analysis was restricted to trials with a low risk of bias, the live birth rates were similar.[123] Furthermore, in women with anovulatory PCOS who had clomiphene resistance, laparoscopic ovarian drilling versus medical induction of ovulation was associated with similar rates of pregnancy and miscarriage but lower rates of multiple pregnancy and ovarian hyperstimulation syndrome.[123]

» There is no conclusive evidence that laparoscopic ovarian drilling leads to diminished ovarian reserve or premature ovarian failure.[124]

» Unilateral and bilateral ovarian drilling may have similar efficacy in clinical pregnancy and live birth rates.[125]

» Lean (body mass index [BMI] <25 kg/m²) women may have better ovulatory and pregnancy responses to ovarian ablation than obese women.[126]

» Ovarian drilling may be most effective in clomiphene-resistant women, with BMI <30 kg/m², and preoperative luteinizing hormone above 10 IU/L.[127]

Ongoing

not desiring current fertility

with hyperandrogenic features alone

1st **oral contraceptive pill**

» Weight loss should be encouraged, but is less efficacious for androgenic symptoms than for therapy of infertility or infrequent/reduced menstrual bleeding.

» In most women with hyperandrogenic symptoms, an oral contraceptive pill (OCP: cyclic estrogen plus a progestin) is an appropriate choice of initial treatment. All pharmacologic therapies for hirsutism should be trialed at least 6 months before making changes in dose, switching to a new medication, or adding medication.[12] [78]

» The Endocrine Society hirsutism clinical practice guidelines and the International PCOS Network guidelines do not recommend one particular OCP over another.[53][78] OCPs are more effective for acne than for hirsutism.

» OCP therapy modestly inhibits gonadotropin secretion, and thus gonadotropin-sensitive ovarian androgen production, and increases hepatic production of sex hormone-binding globulin (SHBG), which further decreases free testosterone. If free testosterone and SHBG are not normalized after 3 months, the possibility of an androgen-secreting neoplasm should be considered.

» Levonorgestrel is the most androgenic progestin and OCPs that contain a progestin with androgenic activity (e.g., levonorgestrel, norethindrone) have often been avoided in practice due to concerns they would be less effective for symptoms like hirsutism. This was not observed in meta-analysis.[133] However, levonorgestrel can have an adverse effect on metabolic biomarkers and therefore it tends to be avoided in women with PCOS.[78] Newer, less-androgenic progestins include desogestrel or norgestimate.

» Drospirenone is a spironolactone analog with antiandrogenic and antimineralocorticoid properties. Pills with these newer, lower-androgenicity progestins may, however, confer a higher risk of venous thromboembolism than older pills, although one large prospective study found no such risk.[134] [135] [136] [137] Given this possible risk of venous thromboembolism with newer pills, some practitioners still prefer to

Ongoing

use levonorgestrel- or norethindrone-containing pills.

» OCPs should not be used before epiphyseal closure. Caution is advised if cardiovascular risk factors are present.[149] Contraceptive pills should be avoided or used with caution in women with risk factors (e.g., smoking [especially if age is ≥35 years], history of thromboembolism, or migraine with aura). Other reasons for caution include poorly controlled hypertension, diabetes of long duration (>20 years), and diabetes with vascular complications.[138]

» Various OCPs are available; consult your local drug formulary for more information.

adjunct **metformin**

Treatment recommended for SOME patients in selected patient group

Primary options

» metformin: 500 mg orally (immediate-release) three times daily, or 850-1000 mg orally (immediate-release) twice daily; 1500-2000 mg orally (extended-release) once daily

» The choice of agents to use is individualized, taking into account the clinical picture and preferences regarding adverse effects.

» For the specific goal of treating hyperandrogenism, metformin is best suited as add-on therapy to oral contraceptive pills (OCPs), antiandrogens, or OCPs plus antiandrogens. The Endocrine Society advises against using insulin-lowering drugs for the sole indication of treating hirsutism.[78] Metformin is associated with decreased testosterone and androstenedione levels and increased sex hormone-binding globulin levels, with limited evidence of improvement in hirsutism.[133] [139] [140] [141] However, adding metformin might improve results compared with monotherapy or dual therapy.[133] [141]

» Limited evidence suggests that metformin may promote weight loss, particularly at higher doses (>1500 mg/day) and with longer duration of therapy (>8 weeks).[144] A meta-analysis of 51 studies concluded that metformin (alone or as adjuvant therapy) may improve acne scores.[142]

Ongoing

» The 2023 International PCOS guideline suggests that the combination of OCPs and metformin may be most beneficial in high risk metabolic groups, including women with BMI >30 kg/m², risk factors for diabetes, impaired glucose tolerance, or high-risk ethnic groups.[53]

» To avoid gastrointestinal adverse effects, metformin should be taken with food and the dose titrated slowly over 4-6 weeks. Extended-release metformin has a slightly lower incidence of gastrointestinal adverse effects.

adjunct **mechanical hair removal or topical therapy**

Treatment recommended for SOME patients in selected patient group

Primary options

» eflornithine topical: (13.9%) apply sparingly to the affected area(s) twice daily

OR

» minoxidil topical: (2% to 5%) apply 1 mL to scalp twice daily

» Medical therapy for hirsutism is more effective in impeding or slowing further growth than in regressing hair growth. (Terminal hairs generally do not revert to vellus.)

» Adjunctive mechanical removal is recommended (does not worsen hirsutism). Endocrine therapy leads to thinner (less visible) hair shafts, and longer telogen (resting) phase (fewer hairs at any time). To destroy terminal hair follicles, electrolysis (or laser, which works best with light skin and dark hair) is useful after ≥6 months of hormonal therapy has halted the appearance of new terminal hairs.

» Topical eflornithine slows growth of facial hair in 20% to 40% of women by 8 weeks.[145] It should be discontinued if no results are noted by 4-6 months.

» For androgenic alopecia, topical minoxidil treatment may be effective but must be used for several months.[146]

» With both topical eflornithine and minoxidil, benefit subsides if the agent is discontinued.

2nd **antiandrogen**

Primary options

» spironolactone: 50-100 mg orally twice daily

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Secondary options

» finasteride: 5 mg orally once daily

» Weight loss should be encouraged, but is less efficacious for androgenic symptoms than for therapy of infertility or infrequent/reduced menstrual bleeding.

» The Endocrine Society advises against antiandrogen monotherapy as initial therapy for hirsutism because of its teratogenic potential (unless women are on adequate contraception).[78] For women who are not sexually active, have undergone permanent sterilization, or are on long-acting reversible contraception, initial therapy with oral contraceptive pill or antiandrogens as monotherapy are both options.[78] If monotherapy is to be used, the decision is tailored to the woman's needs, with a particular focus on adverse effects.

» Women with severe hirsutism or contraindications to hormonal contraception may need to be considered for treatment with antiandrogens.[31] [78]

» Antiandrogens are androgen receptor blockers (e.g., spironolactone, cyproterone) or 5-alpha-reductase inhibitors (e.g., finasteride). Cyproterone is not available in the US.

» Antiandrogens (especially finasteride) should be avoided in pregnancy due to potential for ambiguous genitalia in male fetus. Antiandrogens should be used for at least 6 months before judging efficacy.[78] The maximal effect on hirsutism may take 9-12 months (compared with the effect on acne, which usually responds within 2 months). Acne is more responsive to therapy while alopecia is less responsive.

» Contraceptive measures are advisable given theoretical teratogenicity.

adjunct **metformin**

Treatment recommended for SOME patients in selected patient group

Primary options

» metformin: 500 mg orally (immediate-release) three times daily, or 850-1000 mg orally (immediate-release) twice daily; 1500-2000 mg orally (extended-release) once daily

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» The choice of agents to use is individualized, taking into account the clinical picture and preferences regarding adverse effects.

» For the specific goal of treating hyperandrogenism, metformin is best suited as add-on therapy to oral contraceptive pills (OCPs), antiandrogens, or OCPs plus antiandrogens. The Endocrine Society advises against using insulin-lowering drugs for the sole indication of treating hirsutism.[78] Metformin is associated with decreased testosterone and androstenedione levels and increased sex hormone-binding globulin levels, with limited evidence of improvement in hirsutism.[133] [139] [140] [141] However, adding metformin might improve results compared with monotherapy or dual therapy.[133] [141]

» Limited evidence suggests that metformin may promote weight loss, particularly at higher doses (>1500 mg/day) and with longer duration of therapy (>8 weeks).[144] A meta-analysis of 51 studies concluded that metformin (alone or as adjuvant therapy) may improve acne scores.[142]

» To avoid gastrointestinal adverse effects, metformin should be taken with food and the dose titrated slowly over 4-6 weeks. Extended-release metformin has a slightly lower incidence of gastrointestinal adverse effects.

adjunct **mechanical hair removal or topical therapy**

Treatment recommended for SOME patients in selected patient group

Primary options

» eflornithine topical: (13.9%) apply sparingly to the affected area(s) twice daily

OR

» minoxidil topical: (2% to 5%) apply 1 mL to scalp twice daily

» Medical therapy for hirsutism is more effective in impeding or slowing further growth than in regressing hair growth. (Terminal hairs generally do not revert to vellus.)

» Adjunctive mechanical removal is recommended (does not worsen hirsutism). Endocrine therapy leads to thinner (less visible) hair shafts, and longer telogen (resting) phase (fewer hairs at any time). To destroy terminal hair follicles, electrolysis (or laser, which works

Ongoing

best with light skin and dark hair) is useful after ≥6 months of hormonal therapy has halted the appearance of new terminal hairs.

» Topical eflornithine slows growth of facial hair in 20% to 40% of women by 8 weeks.[145] It should be discontinued if no results are noted by 4-6 months.

» For androgenetic alopecia, topical minoxidil treatment may be effective but must be used for several months.[146]

» With both topical eflornithine and minoxidil, benefit subsides if the agent is discontinued.

2nd **antiandrogen plus oral contraceptive pill**

Primary options

» spironolactone: 50-100 mg orally twice daily

Secondary options

» finasteride: 5 mg orally once daily

» The choice of agents to use is individualized, taking into account the clinical picture and preferences regarding adverse effects.

» In many cases, a combination of antiandrogen and oral contraceptive may be needed, particularly for hirsutism or severe acne. The combination has the added benefit of preventing pregnancy, while increasing efficacy by targeting two different processes: androgen production and androgen action.

» The Endocrine Society recommends monotherapy first line for hirsutism, and if symptoms remain after 6 months to add in an antiandrogen.[78] All pharmacologic therapies for hirsutism should be trialed at least 6 months before making changes in dose, switching to a new medication, or adding medication.[12] [78]

» Antiandrogens are androgen receptor blockers (e.g., spironolactone, cyproterone) or 5-alpha-reductase inhibitors (e.g., finasteride). Cyproterone is not available in the US.

» Contraceptive measures are advisable with antiandrogens given theoretical teratogenicity. Antiandrogens (especially finasteride) should be avoided in pregnancy due to potential for ambiguous genitalia in male fetus.

» Various OCPs are available; consult your local drug formulary for more information.

Ongoing

adjunct **metformin**

Treatment recommended for SOME patients in selected patient group

Primary options

» metformin: 500 mg orally (immediate-release) three times daily, or 850-1000 mg orally (immediate-release) twice daily; 1500-2000 mg orally (extended-release) once daily

» The choice of agents to use is individualized, taking into account the clinical picture and preferences regarding adverse effects.

» For the specific goal of treating hyperandrogenism, metformin is best suited as add-on therapy to oral contraceptive pills (OCPs), antiandrogens, or OCPs plus antiandrogens. The Endocrine Society advises against using insulin-lowering drugs for the sole indication of treating hirsutism.[78] Metformin is associated with decreased testosterone and androstenedione levels and increased sex hormone-binding globulin levels, with limited evidence of improvement in hirsutism.[133] [139] [140] [141] However, adding metformin might improve results compared with monotherapy or dual therapy.[133] [141]

» Limited evidence suggests that metformin may promote weight loss, particularly at higher doses (>1500 mg/day) and with longer duration of therapy (>8 weeks).[144] A meta-analysis of 51 studies concluded that metformin (alone or as adjuvant therapy) may improve acne scores.[142]

» To avoid gastrointestinal adverse effects, metformin should be taken with food and the dose titrated slowly over 4-6 weeks. Extended-release metformin has a slightly lower incidence of gastrointestinal adverse effects.

adjunct **mechanical hair removal or topical therapy**

Treatment recommended for SOME patients in selected patient group

Primary options

» eflornithine topical: (13.9%) apply sparingly to the affected area(s) twice daily

OR

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» minoxidil topical: (2% to 5%) apply 1 mL to scalp twice daily

» Medical therapy for hirsutism is more effective in impeding or slowing further growth than in regressing hair growth. (Terminal hairs generally do not revert to vellus.)

» Adjunctive mechanical removal is recommended (does not worsen hirsutism). Endocrine therapy leads to thinner (less visible) hair shafts, and longer telogen (resting) phase (fewer hairs at any time). To destroy terminal hair follicles, electrolysis (or laser, which works best with light skin and dark hair) is useful after ≥6 months of hormonal therapy has halted the appearance of new terminal hairs.

» Topical eflornithine slows growth of facial hair in 20% to 40% of women by 8 weeks.[145] It should be discontinued if no results are noted by 4-6 months.

» For androgenetic alopecia, topical minoxidil treatment may be effective but must be used for several months.[146]

» With both topical eflornithine and minoxidil, benefit subsides if the agent is discontinued.

3rd **long-acting GnRH analog plus oral contraceptive pill**

Primary options

» leuprolide: 3.75 mg intramuscularly once monthly; 11.25 mg intramuscularly every 3 months

» Weight loss should be encouraged, but is less efficacious for androgenic symptoms than for therapy of infertility or infrequent/reduced menstrual bleeding.

» Long-acting gonadotropin-releasing hormone (GnRH) analogs (e.g., leuprolide) yield profound suppression of gonadotropins and suppress ovarian steroid synthesis.

» Only to be used in severe or refractory ovarian hyperandrogenism.[78] GnRH agonists are best combined with estrogen (oral contraceptive pills) to increase sex hormone-binding globulin and protect bones from resultant hypoestrogenemia (women on GnRH without estrogen replacement may lose 4% to 8% trabecular bone after 6 months) and avoid severe vasomotor symptoms.

Ongoing

» With the estrogen replacement, a progestin must also be given to protect the endometrium.[78]

» Various OCPs are available; consult your local drug formulary for more information.

adjunct **mechanical hair removal or topical therapy**

Treatment recommended for SOME patients in selected patient group

Primary options

» eflornithine topical: (13.9%) apply sparingly to the affected area(s) twice daily

OR

» minoxidil topical: (2% to 5%) apply 1 mL to scalp twice daily

» Medical therapy for hirsutism is more effective in impeding or slowing further growth than in regressing hair growth. (Terminal hairs generally do not revert to vellus.)

» Adjunctive mechanical removal is recommended (does not worsen hirsutism). Endocrine therapy leads to thinner (less visible) hair shafts, and longer telogen (resting) phase (fewer hairs at any time). To destroy terminal hair follicles, electrolysis (or laser, which works best with light skin and dark hair) is useful after ≥6 months of hormonal therapy has halted the appearance of new terminal hairs.

» Topical eflornithine slows growth of facial hair in 20% to 40% of women by 8 weeks.[145] It should be discontinued if no results are noted by 4-6 months.

» For androgenetic alopecia, topical minoxidil treatment may be effective but must be used for several months.[146]

» With both topical eflornithine and minoxidil, benefit subsides if the agent is discontinued.

with infrequent/reduced menstrual bleeding alone **1st** **weight loss**

» Anovulatory women with polycystic ovary syndrome (PCOS) have chronic estrogenization without progesterone exposure, leading to risk of abnormal uterine bleeding, endometrial hyperplasia, and cancer. Therefore, treatments that induce ovulation or provide progesterone exposure should be given.

Ongoing

» Weight loss is the preferred treatment for overweight or obese women. The oral contraceptive pill or metformin is used if ineffective, or if weight is normal.

» Weight loss alone (even as little as 5% to 7%) may restore ovulation in up to 80% of overweight or obese women (possibly by reducing hyperinsulinemia and thus hyperandrogenism).[64] [83][84] [85] Studies suggest dietary interventions, exercise, and/or behavioral coaching are effective for weight loss in PCOS, but no particular exercise or dietary composition (beyond caloric restriction) can be recommended over another.[64] [81] [88]

2nd **oral contraceptive pill**

» The progestin withdrawal results in menses and negates risk of endometrial hyperplasia.

» Among the older oral contraceptive pills (OCPs), ethynodiol/ethinyl estradiol is considered low androgenic and may be useful if a larger dose of estrogen is needed. This higher-estrogen-dose pill may be able to induce menses in women with persistent amenorrhea. Persistent amenorrhea may indicate endometrial atrophy resulting from hyperandrogenism (thin endometrial width on ultrasound). The risk-benefit ratio must be carefully considered when using higher-dose pills.

» OCPs should not be used before epiphyseal closure. Avoid or use with caution in women with risk factors (e.g., smoking [especially if age is ≥35 years], history of thromboembolism, or migraine with aura). Other reasons for caution include poorly controlled hypertension, diabetes of long duration (>20 years), and diabetes with vascular complications.[138]

» Pills with newer, lower-androgenicity progestins (e.g., desogestrel, norgestimate) may confer a higher risk of venous thromboembolism than older pills, although one large prospective study found no such risk.[134] [135] [136] [137] Given this possible risk of venous thromboembolism with newer pills, some practitioners still prefer to use levonorgestrel- or norethindrone-containing pills.

» The International PCOS Network guidelines do not recommend a particular OCP over another.[53]

» Various OCPs are available; consult your local drug formulary for more information.

Ongoing

2nd **metformin**

Primary options

» metformin: 500 mg orally (immediate-release) three times daily, or 850-1000 mg orally (immediate-release) twice daily; 1500-2000 mg orally (extended-release) once daily

» May be used to improve menstrual irregularity.

» To avoid gastrointestinal adverse effects, metformin should be taken with food and the dose titrated slowly over 4-6 weeks. Extended-release metformin has a slightly lower incidence of gastrointestinal adverse effects.

» Limited evidence suggests that metformin may promote weight loss, particularly at higher doses (>1500 mg/day) and with longer duration of therapy (>8 weeks).[144]

3rd **cyclic progestin**

Primary options

» progesterone micronized: 200-400 mg orally once daily for 10 days each month

OR

» medroxyprogesterone: 5-10 mg orally once daily for 10 days each month

Secondary options

» norethindrone: 2.5 to 10 mg orally once daily for 10 days each month

» Should be given if the oral contraceptive pill (OCP) is not tolerated or desired by the patient, or if there are contraindications to an OCP.[31] A cyclic progestin is also used in refractory cases.

with hyperandrogenic features plus infrequent/ reduced menstrual bleeding

1st **weight loss**

» Women with hyperandrogenic features plus infrequent/reduced menstrual bleeding are treated with a combined approach. Preferred treatment is weight loss (if overweight) plus the oral contraceptive pill.

» Weight loss alone (even as little as 5% to 7%) may restore ovulation in up to 80% of overweight or obese women (possibly by reducing hyperinsulinemia and thus hyperandrogenism).[64] [83][84] [85] Studies suggest dietary interventions, exercise, and/

Ongoing

or behavioral coaching are effective for weight loss in polycystic ovary syndrome, but no particular exercise or dietary composition (beyond caloric restriction) can be recommended over another.[64] [81][88]

plus **oral contraceptive pill**

Treatment recommended for ALL patients in selected patient group

» Oral contraceptive pill (OCP: cyclic estrogen plus a progestin) therapy modestly inhibits gonadotropin secretion, and thus gonadotropin-sensitive ovarian androgen production, and increases hepatic production of sex hormone-binding globulin (SHBG), which further decreases free testosterone. If free testosterone and SHBG are not normalized after 3 months, the possibility of an androgen-secreting neoplasm should be considered.

» OCPs with progestins with androgenic activity (e.g., levonorgestrel, norethindrone) should be avoided. Newer, less-androgenic progestins include desogestrel and norgestimate.

» Drospirenone is a spironolactone analog with antiandrogenic and antimineralocorticoid properties. Pills with these newer, lower-androgenicity progestins may, however, confer a higher risk of venous thromboembolism than older pills, although one large prospective study found no such risk.[134] [135] [136] [137] Given this possible risk of venous thromboembolism with newer pills, some practitioners still prefer to use levonorgestrel- or norethindrone-containing pills. The International PCOS Network guidelines do not recommend a particular OCP over another.[53]

» OCPs should not be used before epiphyseal closure. Caution is advised if cardiovascular risk factors are present.[149] OCPs should be avoided or used with caution in women with risk factors (e.g., smoking [especially if age is ≥35 years], history of thromboembolism, or migraine with aura). Other reasons for caution include poorly controlled hypertension, diabetes of long duration (>20 years), and diabetes with vascular complications.[138]

» Various OCPs are available; consult your local drug formulary for more information.

adjunct **metformin**

Treatment recommended for SOME patients in selected patient group

Ongoing

Primary options

» metformin: 500 mg orally (immediate-release) three times daily, or 850-1000 mg orally (immediate-release) twice daily; 1500-2000 mg orally (extended-release) once daily

» The choice of agents to use is individualized, taking into account the clinical picture and preferences regarding adverse effects.

» For the specific goal of treating hyperandrogenism, metformin is best suited as add-on therapy to oral contraceptive pills (OCPs), antiandrogens, or OCPs plus antiandrogens. The Endocrine Society advises against using insulin-lowering drugs for the sole indication of treating hirsutism.[78] Metformin is associated with decreased testosterone and androstenedione levels and increased sex hormone-binding globulin levels, with limited evidence of improvement in hirsutism.[133] [139] [140] [141] However, adding metformin might improve results compared with monotherapy or dual therapy.[133] [141]

» Limited evidence suggests that metformin may promote weight loss, particularly at higher doses (>1500 mg/day) and with longer duration of therapy (>8 weeks).[144] A meta-analysis of 51 studies concluded that metformin (alone or as adjuvant therapy) may improve acne scores.[142]

» To avoid gastrointestinal adverse effects, metformin should be taken with food and the dose titrated slowly over 4-6 weeks. Extended-release metformin has a slightly lower incidence of gastrointestinal adverse effects.

adjunct **mechanical hair removal or topical therapy**

Treatment recommended for SOME patients in selected patient group

Primary options

» eflornithine topical: (13.9%) apply sparingly to the affected area(s) twice daily

OR

» minoxidil topical: (2% to 5%) apply 1 mL to scalp twice daily

» Medical therapy for hirsutism is more effective in impeding or slowing further growth than in

Ongoing

regressing hair growth. (Terminal hairs generally do not revert to vellus.)

» Adjunctive mechanical removal is recommended (does not worsen hirsutism). Endocrine therapy leads to thinner (less visible) hair shafts, and longer telogen (resting) phase (fewer hairs at any time). To destroy terminal hair follicles, electrolysis (or laser, which works best with light skin and dark hair) is useful after ≥6 months of hormonal therapy has halted the appearance of new terminal hairs.

» Topical eflornithine slows growth of facial hair in 20% to 40% of women by 8 weeks, and facial hair returns if eflornithine is discontinued.[145] It should be discontinued if no results are noted by 4-6 months.

» For androgenetic alopecia, topical minoxidil treatment may be effective but must be used for several months.[146]

» With both topical eflornithine and minoxidil, benefit subsides if the agent is discontinued.

2nd **antiandrogen plus oral contraceptive pill**

Primary options

» spironolactone: 50-100 mg orally twice daily

Secondary options

» finasteride: 5 mg orally once daily

» Weight loss should be encouraged in overweight women.

» The choice of agents to use is individualized, taking into account the clinical picture and preferences regarding adverse effects.

» Oral contraceptive pills are more effective for acne than for hirsutism. A combination with antiandrogens is usually necessary for hirsutism or severe acne. The combination has the added benefit of preventing pregnancy, while increasing efficacy by targeting two different processes: androgen production and androgen action.

» Antiandrogens are androgen receptor blockers (e.g., spironolactone, cyproterone) or 5-alpha-reductase inhibitors (e.g., finasteride). Cyproterone is not available in the US.

» Contraceptive measures are advisable with antiandrogens given theoretical teratogenicity. Finasteride is particularly dangerous to a male fetus.

Ongoing

» Various oral contraceptive pills are available; consult your local drug formulary for more information.

adjunct **metformin**

Treatment recommended for SOME patients in selected patient group

Primary options

» metformin: 500 mg orally (immediate-release) three times daily, or 850-1000 mg orally (immediate-release) twice daily; 1500-2000 mg orally (extended-release) once daily

» The choice of agents to use is individualized, taking into account the clinical picture and preferences regarding adverse effects.

» For the specific goal of treating hyperandrogenism, metformin is best suited as add-on therapy to oral contraceptive pills (OCPs), antiandrogens, or OCPs plus antiandrogens. The Endocrine Society advises against using insulin-lowering drugs for the sole indication of treating hirsutism.[78] Metformin is associated with decreased testosterone and androstenedione levels and increased sex hormone-binding globulin levels, with limited evidence of improvement in hirsutism.[133] [139] [140] [141] However, adding metformin might improve results compared with monotherapy or dual therapy.[133] [141]

» Limited evidence suggests that metformin may promote weight loss, particularly at higher doses (>1500 mg/day) and with longer duration of therapy (>8 weeks).[144] A meta-analysis of 51 studies concluded that metformin (alone or as adjuvant therapy) may improve acne scores.[142]

» To avoid gastrointestinal adverse effects, metformin should be taken with food and the dose titrated slowly over 4-6 weeks. Extended-release metformin has a slightly lower incidence of gastrointestinal adverse effects.

adjunct **mechanical hair removal or topical therapy**

Treatment recommended for SOME patients in selected patient group

Primary options

» eflornithine topical: (13.9%) apply sparingly to the affected area(s) twice daily

OR

Ongoing

» minoxidil topical: (2% to 5%) apply 1 mL to scalp twice daily

» Medical therapy for hirsutism is more effective in impeding or slowing further growth than in regressing hair growth. (Terminal hairs generally do not revert to vellus.)

» Adjunctive mechanical removal is recommended (does not worsen hirsutism). Endocrine therapy leads to thinner (less visible) hair shafts, and longer telogen (resting) phase (fewer hairs at any time). To destroy terminal hair follicles, electrolysis (or laser, which works best with light skin and dark hair) is useful after ≥6 months of hormonal therapy has halted the appearance of new terminal hairs.

» Topical eflornithine slows growth of facial hair in 20% to 40% of women by 8 weeks, and facial hair returns if eflornithine is discontinued.[145] It should be discontinued if no results are noted by 4-6 months.

» For androgenetic alopecia, topical minoxidil treatment may be effective but must be used for several months.[146]

» With both topical eflornithine and minoxidil, benefit subsides if the agent is discontinued.

3rd **long-acting GnRH analog plus oral contraceptive pill**

Primary options

» leuprolide: 3.75 mg intramuscularly once monthly; 11.25 mg intramuscularly every 3 months

» Weight loss should be encouraged in overweight women.

» Long-acting gonadotropin-releasing hormone (GnRH) analogs (e.g., leuprolide) yield profound suppression of gonadotropins and suppress ovarian steroid synthesis.

» Only to be used in severe or refractory ovarian hyperandrogenism.[78] GnRH agonists are best combined with estrogen (oral contraceptive pills) to increase sex hormone-binding globulin and protect bones from resultant hypoestrogenemia (women on GnRH without estrogen replacement may lose 4% to 8% trabecular bone after 6 months) and avoid severe vasomotor symptoms.

Ongoing

» With the estrogen replacement, a progestin must also be given to protect the endometrium.[78]

» Various oral contraceptive pills are available; consult your local drug formulary for more information.

adjunct **mechanical hair removal or topical therapy**

Treatment recommended for SOME patients in selected patient group

Primary options

» eflornithine topical: (13.9%) apply sparingly to the affected area(s) twice daily

OR

» minoxidil topical: (2% to 5%) apply 1 mL to scalp twice daily

» Medical therapy for hirsutism is more effective in impeding or slowing further growth than in regressing hair growth. (Terminal hairs generally do not revert to vellus.)

» Adjunctive mechanical removal is recommended (does not worsen hirsutism). Endocrine therapy leads to thinner (less visible) hair shafts, and longer telogen (resting) phase (fewer hairs at any time). To destroy terminal hair follicles, electrolysis (or laser, which works best with light skin and dark hair) is useful after ≥6 months of hormonal therapy has halted the appearance of new terminal hairs.

» Topical eflornithine slows growth of facial hair in 20% to 40% of women by 8 weeks, and facial hair returns if eflornithine is discontinued.[145] It should be discontinued if no results are noted by 4-6 months.

» For androgenetic alopecia, topical minoxidil treatment may be effective but must be used for several months.[146]

» With both topical eflornithine and minoxidil, benefit subsides if the agent is discontinued.

Emerging

Alpha-glucosidase inhibitors

Small studies have found that acarbose may reduce androgen levels, improve hirsutism, and ameliorate menstrual irregularity in women with polycystic ovary syndrome (PCOS), as well as improving markers of cardiovascular risk.[150] Its use is limited by gastrointestinal adverse effects.

Statins

Statins given in conjunction with oral contraceptive pills, have been shown to further reduce circulating androgen levels, improve the lipid profile, reduce hirsutism, and improve markers of inflammation in PCOS.[151] Studies have also suggested statins may be beneficial in conjunction with metformin.[152] While one Cochrane review found that atorvastatin reduced androgen levels (including total testosterone, free androgen index, androstenedione, and dehydroepiandrosterone) in women with PCOS, another Cochrane review concluded that it is uncertain whether statins improve hirsutism, acne, testosterone, or menstrual regularity due to limited evidence.[153] [154] At least one study found that statins may reduce insulin sensitivity in PCOS, and a meta-analysis concluded atorvastatin therapy may reduce insulin resistance in PCOS.[155] [156] In general, statins have been associated with a risk of new-onset diabetes, and women appear particularly susceptible.[157] While they are still experimental, further trials may establish a role for statins in PCOS. Although statin use is not recommended solely to treat hyperandrogenism in PCOS, treatment is acceptable in women who meet current cardiovascular risk-based criteria.[31][158]

Weight loss medications

Weight loss agents such orlistat and rimonabant have been given to women with PCOS in a few clinical trials. These agents appear to facilitate weight loss and result in beneficial metabolic and hormonal effects.[159] [160] One meta-analysis found that orlistat significantly reduced BMI in women with PCOS compared with placebo, but the evidence was very-low certainty.[161] Another meta-analysis reported improved weight, hormonal, lipid, insulin, and fertility outcomes with orlistat plus oral contraceptive pills compared with oral contraceptive pills alone.[162]

Bariatric surgery

A few small trials have followed obese women with PCOS after bariatric surgery. Most women had restoration of regular menstrual cycles, accompanied by reduction in hyperandrogenic signs and symptoms, and some women were able to become pregnant.[159] [163] One meta-analysis of six studies found that sleeve gastrectomy in women with PCOS resulted in reduced menstrual irregularity, lower testosterone levels, and increased sex hormone-binding globulin, along with improvement in BMI and glycemic and lipid parameters.[164] A meta-analysis found that the prevalence of PCOS dropped from 46% to 7% after bariatric surgery, with improvements in menstrual irregularity and hirsutism.[165] Some data suggest that bariatric surgery may be more effective for pregnancy outcomes than metformin in women with PCOS and BMI >40 kg/m^2.[166]

Pulsatile gonadotropin-releasing hormone (GnRH)

Pulsatile GnRH can be given through automated intravenous or subcutaneous infusion pump to induce ovulation. This treatment has minimal risk and about a 50% ovulation rate. The main advantage is no risk of multiple gestation or ovarian hyperstimulation. However, effectiveness in live birth rate has not been adequately established.[167] Thus, this choice may be best for women at risk for ovarian hyperstimulation syndrome (OHSS) or who have experienced severe OHSS.

Gonadotropins in vitro

A highly experimental measure to avoid ovarian hyperstimulation syndrome during in vitro fertilization is to retrieve immature oocytes and treat these with gonadotropins in vitro to mature them before fertilization and implantation.[168] Very limited randomized trial evidence suggests that in vitro maturation may

increase clinical pregnancy rate.[169] In the absence of sufficient randomized trials, a meta-analysis of current evidence suggested higher rates of clinical pregnancy and implantation with this technique but was inconclusive on whether the live birth rate was increased.[170]

Elective freezing of embryos

A multicenter trial randomized 1508 infertile women with PCOS who were undergoing their first cycle of in vitro fertilization to receive either one or two fresh embryos or one or two embryos that had been previously frozen; the latter group experienced higher rates of live birth, lower pregnancy loss, and lower frequency of ovarian hyperstimulation syndrome; however, they had higher rates of preeclampsia.[171] In this trial, singleton pregnancies arising from frozen embryos were more likely to be large for gestational age while twin pregnancies had a higher risk of preeclampsia.[172] More studies are needed to establish the role of frozen embryo transfer in the management of infertile women with PCOS.

Acupuncture

A handful of studies have promoted acupuncture as a fertility treatment in PCOS; however, given inconclusive evidence of reproductive benefit in the limited number of randomized controlled trials (RCTs) that have been conducted to date, and the possibility of harm, this treatment must be considered experimental.[173] Meta-analysis of the few available RCTs in women undergoing assisted reproductive technology suggested improvement in pregnancy rates but no benefit on live birth rate with manual or electroacupuncture, although the included studies were deemed insufficiently robust to draw firm conclusions.[174] [175] Subsequent to this meta-analysis, a multicenter trial randomized 1000 women with PCOS to active or sham acupuncture, with or without clomiphene (250 in each group); while clomiphene increased live births, active acupuncture did not.[176]

Thiazolidinediones

Insulin-sensitizing thiazolidinediones (e.g., rosiglitazone, pioglitazone) have been studied in PCOS, but in far fewer studies than metformin. They are not commonly used in PCOS because they can lead to weight gain. In the US, from 2010 to 2013, rosiglitazone use was restricted due to a possible increased risk of myocardial infarction. Long-term pioglitazone use has been linked to a possible risk of bladder cancer. Animal studies suggest that thiazolidinediones may be associated with fetal growth restriction.[177] Thiazolidinediones appear to have similar effects to metformin regarding ovulation and pregnancy in PCOS.[178] One meta-analysis reported that thiazolidinediones alone and metformin plus a thiazolidinedione are more effective for improving lipid metabolism than metformin alone.[179]

Glucagon-like peptide-1 (GLP-1) receptor agonists

Meta-analyses have found that exenatide and liraglutide can improve weight and glucose levels in women with PCOS.[180] [181] The most significant adverse effect was nausea.[182] One meta-analysis found that liraglutide plus metformin was more effective than metformin alone in terms of weight loss, waist circumference, fasting glucose, and fasting insulin, but the incidence of adverse reactions was high.[180] In a few studies, these agents modestly improved androgen levels and improved menstrual frequency, and some data suggests increased pregnancy and ovulation rates compared with metformin.[181] [182] [183] One small study found that treatment with semaglutide resulted in weight loss and normalization of menstrual cycles in the majority of treated women with PCOS.[184] More studies are needed of newer GLP-1 receptor agonists in PCOS.

Primary prevention

There have been no clinical trials of primary prevention measures in polycystic ovary syndrome (PCOS). It is thought that lifestyle intervention (healthy diet, frequent exercise) and/or metformin therapy may prevent PCOS, but without appropriate clinical trials, the potential efficacy of these interventions for primary prevention is unclear.

Secondary prevention

- Weight loss and metformin may prevent diabetes and atherosclerosis. This is based on extrapolation from clinical trials in non-PCOS populations (prediabetic and diabetic).[57] [189] [190]
- Lifestyle modification - including increased physical activity and healthy diet resulting in weight loss and improved body composition (e.g., reduced percent body fat, reduced waist-hip ratio) - is also likely to prevent diabetes and reduce cardiovascular risk in women with polycystic ovary syndrome (PCOS), although this has not been studied as a long-term preventive measure in PCOS.[189] [248]
- Women with PCOS should discuss with their mother and sisters that they have increased risk of PCOS compared with the general population. Screening of younger sisters may lead to early identification of PCOS.

Patient discussions

- Increased physical activity and a healthy diet are indicated in women with PCOS.[188]
- Consultation with a nutritionist is often useful in assisting the woman in healthy food choices.
- Caloric restriction is the most important dietary factor in weight loss. The macronutrient composition of the diet has not been shown to make a difference as long as calories are restricted.
- Women should be advised on the chronic nature of PCOS and that symptoms often recur if therapy is prematurely discontinued.
- Direct women to evidence-based resources on PCOS, self-management, and a healthy lifestyle.[53] [247] A variety of organizations offer online patient information and resources:

[Resources for Women with PCOS] (https://mchri.org.au/guidelines-resources/community/pcos-resources)

[World Health Organization: polycystic ovary syndrome] (https://www.who.int/news-room/fact-sheets/detail/polycystic-ovary-syndrome)

[Centers for Disease Control and Prevention: PCOS (polycystic ovary syndrome) and diabetes] (https://www.cdc.gov/diabetes/basics/pcos.html)

[Androgen Excess and PCOS Society] (http://www.ae-society.org)

[The Hormone Health Network: information on PCOS] (https://www.hormone.org/-/media/hormone/files/patient-guides/hhn_pcos_infographic_view.pdf)

See also, Patient leaflets

Monitoring

Monitoring

- Women should be evaluated every 3 months for treatment response and development of any adverse effects. Once stable, monitoring is every 6 months.
- Combination therapy may be required to achieve results in ameliorating hyperandrogenism.
- Long growth cycle of hair follicles mandates that treatments directed against hirsutism not be abandoned prematurely. Medical therapy against hirsutism should be given for at least 6 months before deciding on efficacy.[12][78]
- Women undergoing hormonal infertility treatment (letrozole, clomiphene, gonadotropins, assisted reproductive technologies) will require frequent follow-up.
- As a fertility treatment, metformin is given long term.

FOLLOW UP

Complications

Complications	Timeframe	Likelihood
infertility	**short term**	**high**
Infertility is a major complication of polycystic ovary syndrome (PCOS), affecting most women. Women with PCOS may have a pregnancy rate significantly less than the rate of successful ovulation induction.[31] [107]		
pregnancy complications	**short term**	**high**
It has been suggested that women with polycystic ovary syndrome (PCOS) have a high incidence of spontaneous pregnancy loss. However, whether early pregnancy loss is increased is controversial because studies have been inadequate. Overweight or obese BMI and fertility treatment use have been associated with pregnancy loss, but the association between pregnancy loss and PCOS status on its own remains unclear.[12] Once pregnancy is established, morbidity increases, particularly if the woman is obese. Hyperglycemia may cause congenital anomalies. Meta-analyses have found increased rates of gestational diabetes, pregnancy-induced hypertension, preeclampsia, cesarean delivery, miscarriage, hypoglycemia, preterm delivery, newborn admission to the neonatal intensive care unit, neonatal asphyxia, and perinatal mortality in PCOS.[194] [195] [196] [197] The increased risks of miscarriage, gestational diabetes, pregnancy-induced hypertension, and cesarean section in PCOS seem to be independent of obesity.[197] Guidelines recommend offering an oral glucose tolerance test to all women with PCOS when planning pregnancy or fertility treatment. If not performed preconception, offer testing at the first prenatal visit and again at 24-28 weeks gestation.[53]		
type 2 diabetes	**long term**	**high**
Women with polycystic ovary syndrome (PCOS) have 3 times the normal risk for type 2 diabetes. About 20% to 40% of obese women with PCOS have glucose intolerance or type 2 diabetes by the end of their fourth decade.[203] In one meta-analysis, the odds ratio of prevalent impaired glucose tolerance was 3.3 and that of prevalent diabetes was 2.9 in PCOS.[65] One meta-analysis examining nonobese women with PCOS found their odds of type 2 diabetes was 1.5 compared with nonobese controls.[204] A subsequent meta-analysis found that women with PCOS and obesity had a risk ratio for developing type 2 diabetes of 3.24 compared with women without PCOS; nonobese women with PCOS had a risk ratio of 1.62, but the increased risk was not statistically significant compared with women without PCOS.[205] Conversely, 20% to 50% of reproductive-age women with type 2 diabetes have PCOS, and up to 1 in 5 girls with type 2 diabetes may have PCOS.[206] [207] [208]		
cardiovascular disease (CVD)	**long term**	**high**
Women with polycystic ovary syndrome (PCOS) have an increased risk of cardiovascular disease in later life.[188] The cardiometabolic profile is adversely altered in PCOS and numerous CVD risk factors (e.g., body mass index [BMI], dyslipidemia, hypertension, insulin resistance, metabolic syndrome, deficiencies in insulin secretion) are increased.[209] Markers of early or subclinical atherosclerosis are also often increased in PCOS, as well as inflammatory and thrombotic markers.[57] [222] [223] For example, women with PCOS have higher coronary artery calcium scores on electron-beam computed tomography scan and greater carotid intima-media thickness, even after adjusting or matching for BMI.[224] [225][226] Black women may have an increased cardiometabolic risk compared with white		

Complications	Timeframe	Likelihood

women.[227] However, there is no definitive evidence that PCOS is associated with an increase in CVD events (e.g., myocardial infarction [MI]).

A study of postmenopausal women (mean age 71 years), which retrospectively assigned PCOS diagnosis, found an increased CVD rate in the nondiabetic, non-oophorectomized subgroup.[228] In contrast, one retrospective cohort study (mean duration of follow-up 24 years, mean age at last follow-up 47 years) found no increase in dyslipidemia, hypertension, or cardiovascular events in women with PCOS.[229] Similarly, there was no increase in either CHD or MI in 346 PCOS women and 8950 controls of mean age 39 years.[230] These results suggest that while PCOS might increase the risk of CVD in older women, it does not increase premature CVD. Consistent with this, a 20-year retrospective study (>12,000 patient-years follow-up) found that CVD risk in PCOS increased with age: >25% of those ages 65 years and older had angina or MI.[231]

Meta-analyses suggest that women with PCOS have a 1.3-fold greater risk of developing composite CVD, ischemic heart disease, and stroke compared with women without PCOS.[232] [233] [234] A large meta-analysis of 9 cohort studies found PCOS was associated with an increased risk of stroke but not all-cause mortality; among 5 studies wherein risk estimates were adjusted for body mass index, the risk of stroke was slightly attenuated but lost statistical significance.[234] One meta-analysis of 16 studies examined a broad composite outcome consisting of coronary artery disease, CVD, MI, angina, heart failure, and ischemic heart disease; PCOS was associated with this composite outcome in premenopausal but not postmenopausal women in the 12 population-based studies included. Numbers of cases in each component of the composite outcome were too low for reliable conclusions.[235]

Guidelines recommend assessing all women with PCOS for individual cardiovascular risk factors and global CVD risk.[53] [64] Specific CVD risk factors include family history of early CVD (<55 years in a male relative and <65 years in a female relative); cigarette smoking; impaired glucose tolerance or type 2 diabetes; hypertension; dyslipidemia; obstructive sleep apnea; and obesity (especially central obesity).

metabolic dysfunction-associated steatotic liver disease (MASLD)	**long term**	**high**

MASLD (formerly known as nonalcoholic fatty liver disease [NAFLD]) may be present in 40% to 55% of women with polycystic ovary syndrome (PCOS).[236] [237] [238] In those with PCOS, higher androgen levels correlate with an increased risk of MASLD.[239] [240] The risk of MASLD in PCOS appears to be independent of obesity.[240] [241] Ten percent of women with MASLD may develop liver injury and inflammation (metabolic dysfunction-associated steatohepatitis [MASH], formerly known as nonalcoholic steatohepatitis). Of those with MASH, 20% to 30% may progress further to cirrhosis. The increased prevalence of MASLD in PCOS is independent of weight, and women with PCOS may be at higher risk of progressing to MASH and cirrhosis.[242]

Interventions for MASLD include weight loss and insulin-sensitizing agents, antioxidants, and lipid-lowering agents.[243]

endometrial hyperplasia or cancer	**long term**	**low**

Untreated anovulatory women with polycystic ovary syndrome (PCOS) have chronic estrogen exposure with no progesterone exposure, leading to risk of abnormal uterine bleeding, endometrial hyperplasia, and cancer.[244] [245] One meta-analysis found a 3-fold increased risk of endometrial cancer in PCOS (9% lifetime risk in PCOS versus 3% in unaffected women).[246]

metabolic syndrome	**variable**	**high**

One meta-analysis of 46 studies found that the prevalence of the metabolic syndrome in polycystic ovary syndrome (PCOS) women is 30%.[198] Other large meta-analyses have suggested an overall two- to three-fold increased odds of prevalent metabolic syndrome in PCOS. Adolescents with PCOS have more than 3 times increased odds of metabolic syndrome compared with controls.[199] One meta-analysis found that when stratified by weight category, the increased odds remained significant only in

FOLLOW UP

Complications	Timeframe	Likelihood
the overweight or obese women with PCOS.[200] When measured directly, insulin sensitivity has been found to be 30% lower in women with PCOS compared with controls.[201] PCOS is a risk factor for insulin resistance independent of obesity, but insulin resistance is worse in magnitude if obesity is present.[202]		
dyslipidemia	**variable**	**high**
Serum lipids should be checked every 3-5 years after 35 years of age in women with polycystic ovary syndrome (PCOS) for early detection of dyslipidemia. Women with PCOS commonly have increased low-density lipoprotein cholesterol and triglyceride levels and decreased high-density lipoprotein cholesterol levels.[209]		
hypertension	**variable**	**high**
Polycystic ovary syndrome increases the risk of incident hypertension, with the risk greater in premenopausal women compared with postmenopausal women.[210] Measure blood pressure annually and when planning pregnancy or fertility treatment.[53]		
psychological complications	**variable**	**high**
Overall quality of life of women with polycystic ovary syndrome (PCOS), particularly those with hirsutism, has been found to be decreased, with increased rates (15% to 60%) of stress, reactive depression, social isolation, and minor psychological abnormalities.[211] [212] PCOS negatively impacts quality of life in adolescent girls, mediated in large part by body weight concerns.[213] Assessment for mood disorders should be undertaken in all women with PCOS.[57] [214] These include depression, anxiety and panic disorders, and eating disorders.[53] A meta-analysis found increased risk of depressive symptoms (3.8-fold) and anxiety symptoms (5.6-fold) in women with PCOS, which remained significant in body mass index-matched analyses.[215] Increased rates of anxiety and depression are also reported among adolescent girls with PCOS.[216] Women with PCOS have more significant body image concerns than women without PCOS, and one meta-analysis found that the odds of carrying a diagnosis of an eating disorder (e.g., binge-eating disorder, bulimia nervosa) were 3.9-fold higher in women with PCOS compared with controls.[217] [218]		
obstructive sleep apnea	**variable**	**high**
About 20% to 45% of women with polycystic ovary syndrome (PCOS) have sleep apnea or sleep-disordered breathing. Thus, all women with PCOS should be screened for these conditions.[219] [220] [221] If symptoms suggestive of sleep apnea are present, refer for assessment.[53]		

Prognosis

Polycystic ovary syndrome (PCOS) is a chronic condition. There is no cure. Thus, management options are targeted at alleviating the signs and symptoms to reduce morbidity. Another goal of treatment is to prevent the development of complications such as type 2 diabetes and cardiovascular disease in later life.[188] There have been no clinical trials demonstrating the efficacy of any agent in terms of preventing complications. Many experts believe that weight loss and metformin may prevent diabetes and atherosclerosis.[189] [190]

In PCOS, therapy is generally continued throughout the reproductive years. If treatments are stopped during that time, symptoms generally recur. As women with PCOS get older or reach menopause, hyperandrogenic manifestations may improve as ovarian function declines, allowing withdrawal of therapies directed against

hyperandrogenism.[191] [192] However, in some women with PCOS who enter menopause, clinical and biochemical hyperandrogenism may persist.[31] [193]

Diagnostic guidelines

International

Evaluation and treatment of hirsutism in premenopausal women (https://www.endocrine.org/clinical-practice-guidelines) [78]

Published by: The Endocrine Society **Last published:** 2018

Clinical review: guide to the best practices in the evaluation and treatment of polycystic ovary syndrome - part 1 (https://pubmed.ncbi.nlm.nih.gov/26509855) [79]

Published by: American Association of Clinical Endocrinologists; American College of Endocrinology; Androgen Excess and PCOS Society Disease State **Last published:** 2015

Clinical review: guide to the best practices in the evaluation and treatment of polycystic ovary syndrome - part 2 (https://pubmed.ncbi.nlm.nih.gov/26642102) [80]

Published by: American Association of Clinical Endocrinologists; American College of Endocrinology; Androgen Excess and PCOS Society Disease State **Last published:** 2015

International evidence-based guideline for the assessment and management of polycystic ovary syndrome (https://www.monash.edu/medicine/sphpm/mchri/pcos/guideline) [53]

Published by: Monash University on behalf of the NHMRC Centre for Research Excellence in Women's Health in Reproductive Life, in partnership with the American Society for Reproductive Medicine, Endocrine Society, European Society of Endocrinology, and European Society of Human Reproduction and Embryology, and in collaboration with professional societies and consumer advocacy groups internationally **Last published:** 2023

Assessment of cardiovascular risk and prevention of cardiovascular disease in women with the polycystic ovary syndrome (https://ae-society.org/publications) [57]

Published by: Androgen Excess and Polycystic Ovary Syndrome Society **Last published:** 2010

Treatment guidelines

International

Evaluation and treatment of hirsutism in premenopausal women (https://www.endocrine.org/clinical-practice-guidelines) [78]

Published by: The Endocrine Society **Last published:** 2018

Practice bulletin: polycystic ovary syndrome (https://www.acog.org/clinical/clinical-guidance/practice-bulletin) [185]

Published by: American College of Obstetricians and Gynecologists **Last published:** 2018 (reaffirmed 2022)

Ovulation induction in polycystic ovary syndrome (https://pubmed.ncbi.nlm.nih.gov/29921434) [92]

Published by: Society of Obstetricians and Gynaecologists of Canada **Last published:** 2018

Clinical review: guide to the best practices in the evaluation and treatment of polycystic ovary syndrome - part 1 (https://pubmed.ncbi.nlm.nih.gov/26509855) [79]

Published by: American Association of Clinical Endocrinologists; American College of Endocrinology; Androgen Excess and PCOS Society Disease State **Last published:** 2015

Clinical review: guide to the best practices in the evaluation and treatment of polycystic ovary syndrome - part 2 (https://pubmed.ncbi.nlm.nih.gov/26642102) [80]

Published by: American Association of Clinical Endocrinologists; American College of Endocrinology; Androgen Excess and PCOS Society Disease State **Last published:** 2015

International evidence-based guideline for the assessment and management of polycystic ovary syndrome (https://www.monash.edu/medicine/sphpm/mchri/pcos/guideline) [53]

Published by: Monash University on behalf of the NHMRC Centre for Research Excellence in Women's Health in Reproductive Life, in partnership with the American Society for Reproductive Medicine, Endocrine Society, European Society of Endocrinology, and European Society of Human Reproduction and Embryology, and in collaboration with professional societies and consumer advocacy groups internationally **Last published:** 2023

Treatment of obesity in polycystic ovary syndrome (https://www.fertstert.org/article/S0015-0282(08)03909-5/fulltext) [186]

Published by: Androgen Excess and Polycystic Ovary Syndrome Society **Last published:** 2009

International

The polycystic ovary syndrome (https://www.ese-hormones.org/research/special-interest-groups/recommendations-for-diagnosis-and-management-of-the-polycystic-ovary-syndrome) [187]

Published by: European Society of Endocrinology **Last published:** 2014

Online resources

1. Resources for Women with PCOS (https://mchri.org.au/guidelines-resources/community/pcos-resources) *(external link)*

2. World Health Organization: polycystic ovary syndrome (https://www.who.int/news-room/fact-sheets/detail/polycystic-ovary-syndrome) *(external link)*

3. Centers for Disease Control and Prevention: PCOS (polycystic ovary syndrome) and diabetes (https://www.cdc.gov/diabetes/basics/pcos.html) *(external link)*

4. Androgen Excess and PCOS Society (http://www.ae-society.org) *(external link)*

5. The Hormone Health Network: information on PCOS (https://www.hormone.org/-/media/hormone/files/patient-guides/hhn_pcos_infographic_view.pdf) *(external link)*

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- Teede HJ, Tay CT, Laven JJE, et al. Recommendations from the 2023 international evidence-based guideline for the assessment and management of polycystic ovary syndrome. J Clin Endocrinol Metab. 2023 Sep 18;108(10):2447-69. Full text (https://academic.oup.com/jcem/article/108/10/2447/7242360) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/37580314?tool=bestpractice.bmj.com)
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Images

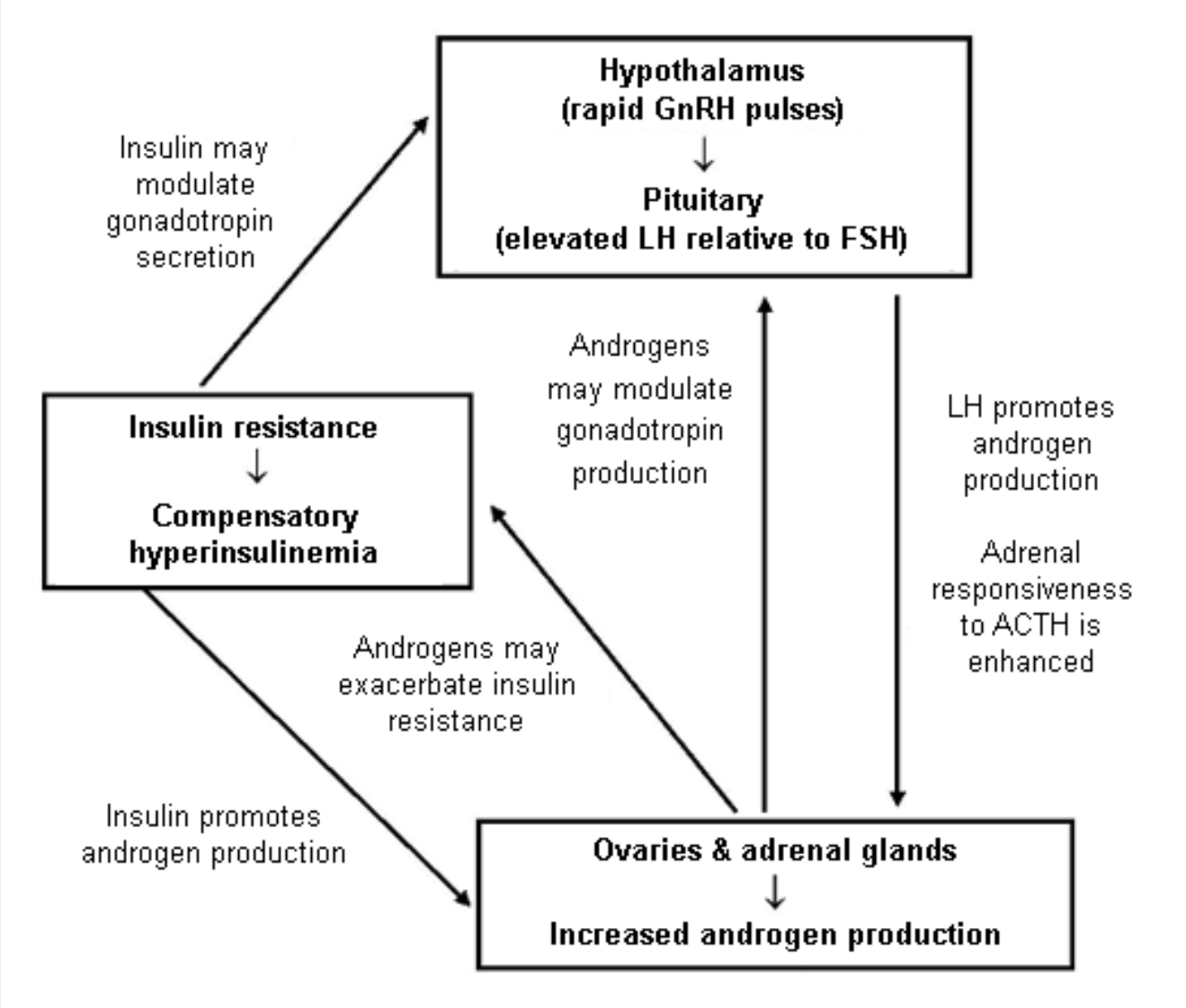

Figure 1: Simplified diagram of the main pathogenic factors in PCOS. ACTH, adrenocorticotropic hormone; FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone

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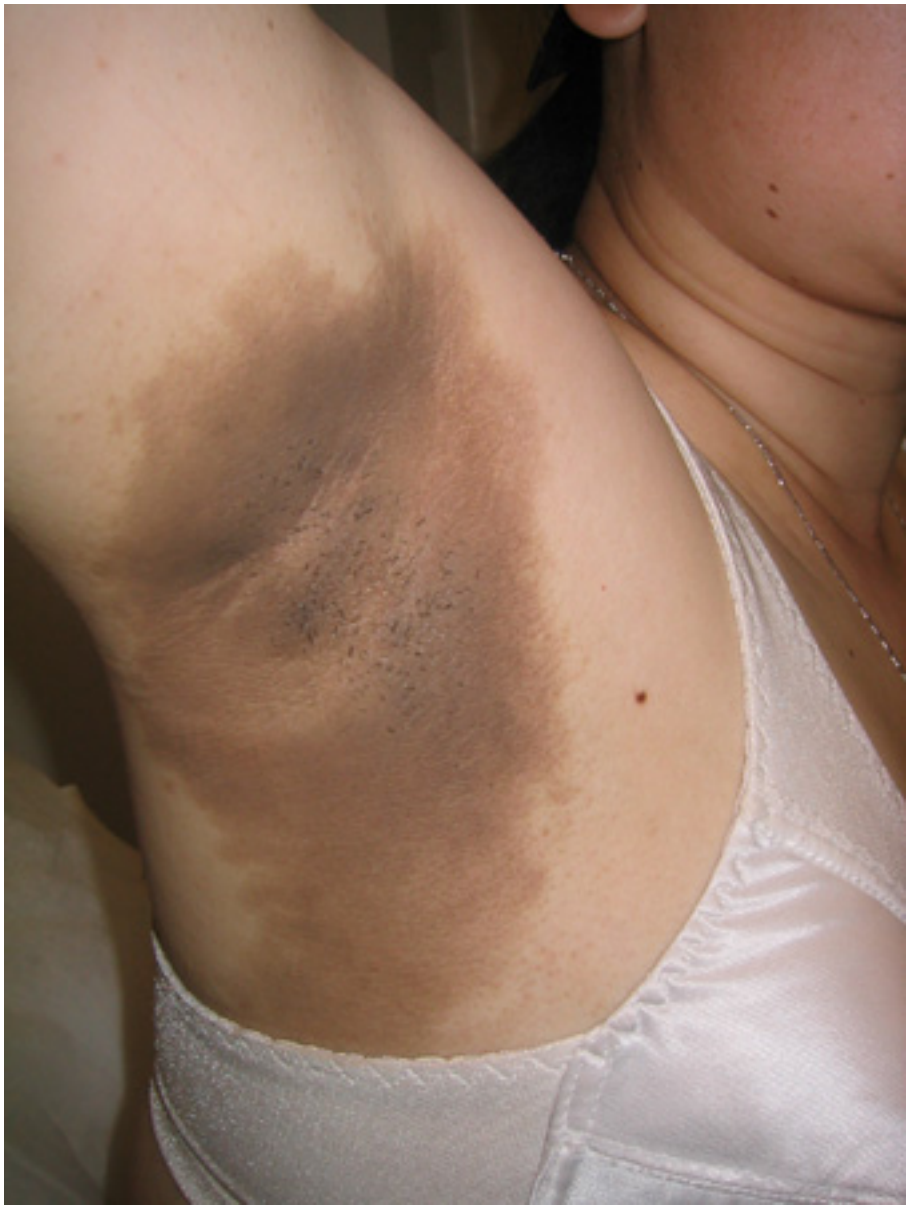

Figure 2: Acanthosis nigricans involving the axilla of an obese white woman

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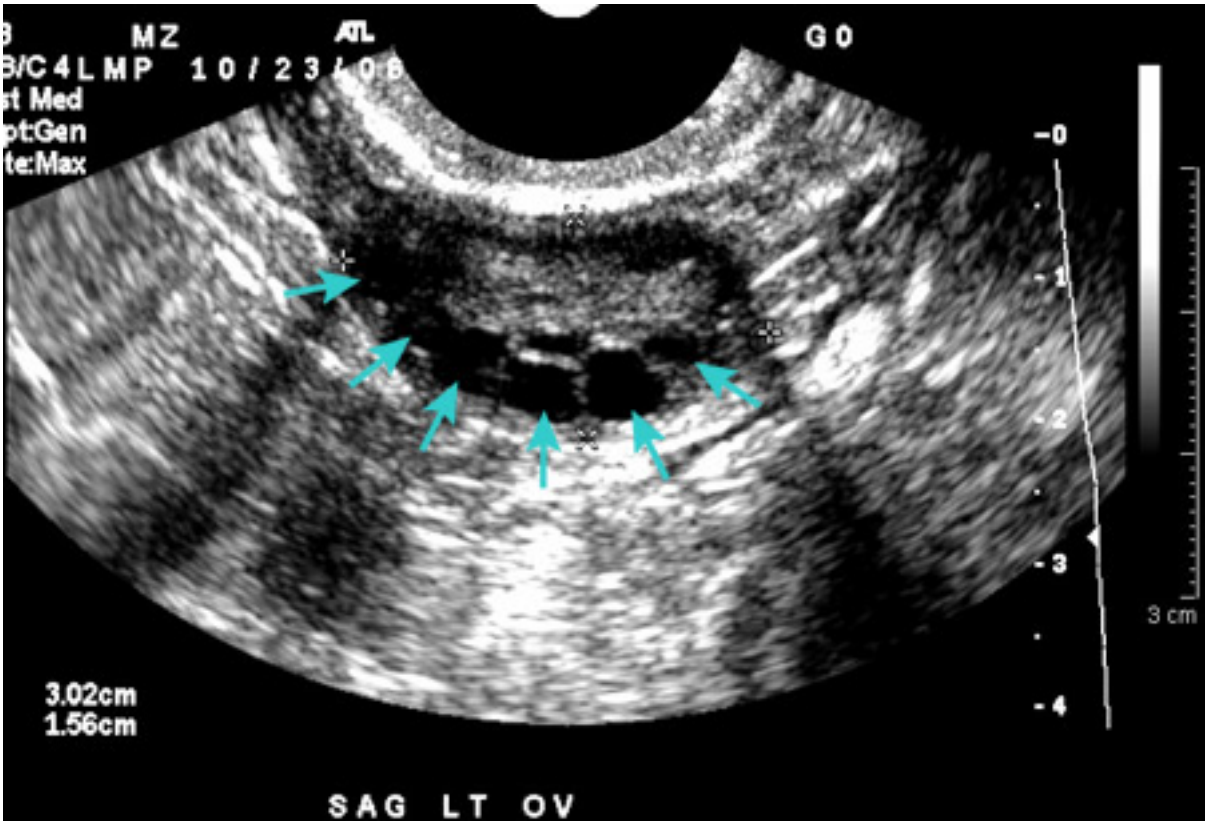

Figure 3: Polycystic ovarian ultrasound

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Figure 1 – BMJ Best Practice Numeral Style

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numerals < 1: 0.25

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