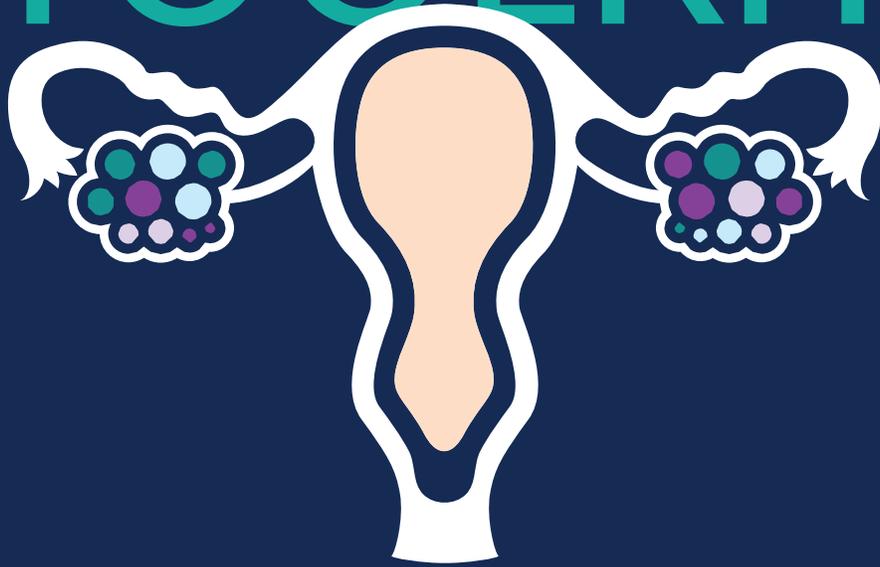


POLYCYSTIC OVARY SYNDROME
TOOLKIT





DIAGNOSTIC CRITERIA OF POLYCYSTIC OVARY SYNDROME

What are the various phenotypes of PCOS in adult women with PCOS?

The presentation of PCOS can be subdivided into four different phenotypes based on presenting features.¹

Phenotype A: HA + OvDys + PCOM

Phenotype B: HA + OvDys

Phenotype C: HA + PCOM

Phenotype D: OvDys + PCOM

AnE = Androgen Excess; OvDys = Ovulatory Dysfunction; PCOM = Polycystic Ovarian Morphology²⁻⁴

TABLE 1: Phenotypes of PCOS

DIAGNOSTIC CRITERIA	PCOS PHENOTYPES			
	AnE + OvDys	AnE + PCOM	PCOM + OvDys	AnE + PCOM + OvDys
NIH 1990	✗			
Rotterdam 2003/2006	✗	✗	✗	✗
AE-PCOS Society 2006	✗	✗		✗
NIH 2012	✗	✗	✗	✗

Exclusion of other causes of hyperandrogenemia or ovulatory dysfunction:

Other causes of androgen excess and/or ovulatory dysfunction need to be excluded prior to making a diagnosis of PCOS:

- Non-classical CAH
- Cushing syndrome
- Androgen-secreting tumors
- Drug-induced androgen excess
- Hyperprolactinemia
- Thyroid diseases⁵

Laboratory work-up to rule out other causes of androgen excess and/or ovulatory dysfunction:

- Prolactin
- Thyroid studies
- 17-OH progesterone
- Pregnancy test

Additional testing if clinically indicated by clinical presentation:

- Rule out Cushing syndrome/ adrenal androgen-secreting tumor
- Midnight salivary cortisol
- 24 hour urine collection for free cortisol
- Dexamethasone suppression test
- ACTH stimulation test to evaluate for non-classical CAH if a morning 17-hydroxyprogesterone is >200 ng/dL or clinical features suggest CAH

What is the significance of polycystic ovarian morphology in adolescence?

Consensus from the International Consortium of Pediatric Endocrinology concluded that ovarian imaging may be deferred during the diagnostic evaluation^{4,6} Pelvic ultrasound is not endorsed for the diagnosis of PCOS in women with gynecological age of less than 8 years (less than 8 years post-menarche).

Recommendations regarding Polycystic Ovarian morphology 2015 study from Witchel et. al from Hormone Research⁷

- No evidence-based reliable criteria to define PCOM have been established for adolescents.
- An ovarian volume $>12.0 \text{ cm}^3$ can be considered enlarged (compared to $>10 \text{ mL}$ in adults)
- Follicle counts should not be utilized to define PCOM in adolescents
- A multifollicular pattern (large follicles distributed throughout the ovary) is common in adolescents, does not have a relationship with hyperandrogenism, and should not be considered a pathological finding
- In healthy girls with regular menstrual cycles and without hyperandrogenism, PCOM does not indicate a diagnosis of PCOS

What criteria reflect ovulatory dysfunction?

- First year post-menarche: consecutive menstrual cycle intervals > 90 days
- After second year post-menarche: menstrual intervals persistently < 21 or > 45 days
- Lack of menses by 15 years old or 2-3 years after breast budding⁴

What are the criteria available for evaluation of Hyperandrogenism?

Biochemical hyperandrogenism:

- Elevated free testosterone⁸
- Elevated total testosterone^{2,9}
- Elevated DHEA-sulfate (suggests adrenal source of hyperandrogenism)
- **Methods for androgen measurements:**
 - Total testosterone⁷
 - Use high quality liquid chromatography-mass spectrometry or extraction/ chromatography immunoassays
 - Free testosterone — Do not use direct assay measurement. Use equilibrium dialysis or calculated based on total testosterone and SHBG^{10,11}
 - Avoid direct radioimmunoassay due to lack of sensitivity and specificity
 - Early AM blood draw preferred — diurnal variation of sex steroid secretion

Clinical Hyperandrogenism:

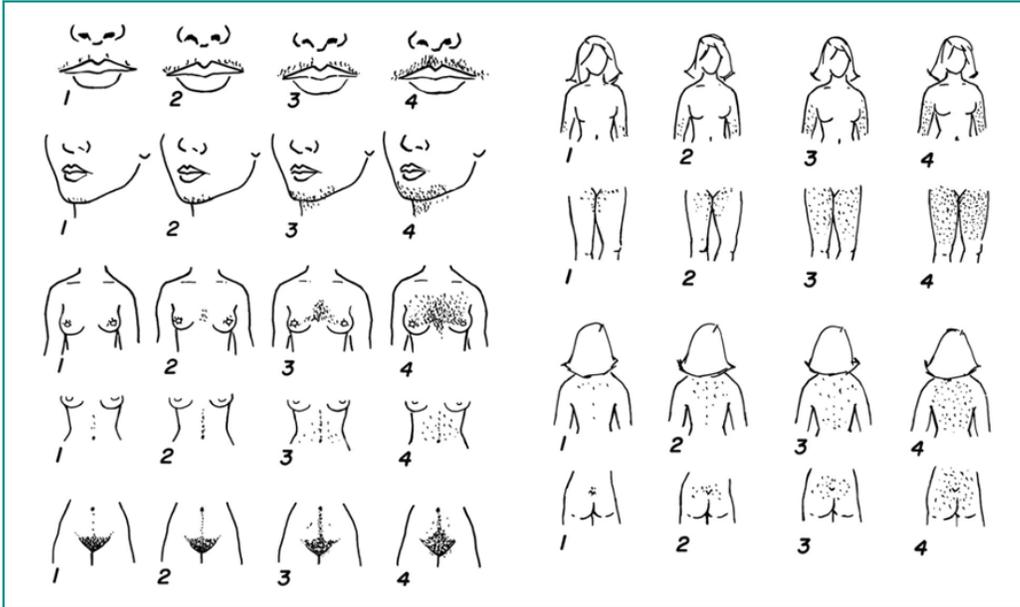
Hirsutism and acne are common clinical manifestations of clinical hyperandrogenism. Others include alopecia, hidradenitis suppurativa, and virilization.

Hirsutism:

Scales of hirsutism assessment, such as the modified Ferriman-Gallwey scale are available for quantification of hirsutism.^{5-7, 12}

- Ferriman-Gallwey score of $> 4-6$ consistent with hirsutism in adolescents
- Ethnic differences exist (normal score higher in Mediterranean populations and lower in Asian populations)
- Regardless of score, hair growth patterns that are distressing to the patient should be addressed

Ferriman-Gallwey Score



Hatch, R., et al., *Hirsutism: Implications, etiology, and management*. Am J Obstet Gynecol, 1981. **140**(7): p. 815-30.

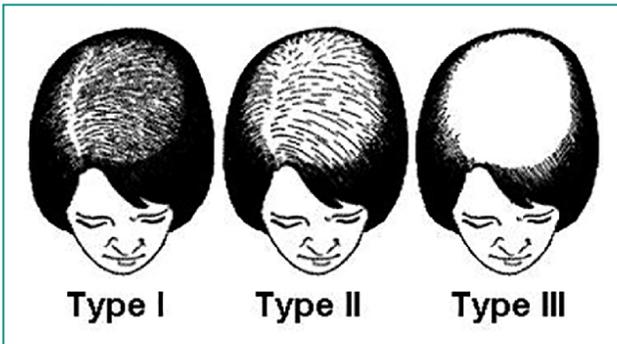
Acne:

- Moderate or severe comedonal acne (i.e., 10 or more facial lesions) in early puberty, or
- Moderate inflammatory acne through the perimenarchal years is uncommon should prompt consideration of further evaluation for hyperandrogenism¹³

Alopecia:

- Diffuse thinning of the crown with preservation of the frontal hairline¹⁴
- Classified according to the Ludwig Scale

Ludwig Scale



Hidradenitis suppurativa:

- Chronic inflammation of hair follicles
- Characterized by painful inflamed nodules in the apocrine gland-bearing areas^{15, 16}

Other signs of virilization: RARE in PCOS, consider other etiologies for androgen excess¹⁷

- Clitoromegaly (clitoral index > 33 mm: > 2.5 cm length, > 8 mm width)
- Voice deepening
- Increased muscle mass



CORE MANAGEMENT OF POLYCYSTIC OVARY SYNDROME

General Care Guidelines:

- Needs to be person-centered
- Address patient's priorities
- Should be provided in partnership with patients and their families
- **Information and education resources should be:**
 - Culturally appropriate
 - Tailored and high-quality
 - Should use a respectful and empathetic approach
 - Promote self-care and highlight peer support groups

Lifestyle counseling:

- A multidisciplinary approach with involvement of a dietitian, psychologist and endocrinologist is ideal and most effective.
- Measures such as frequent weighing to be considered in a sensitive manner since adolescent girls with PCOS have increased prevalence of disordered eating behaviors¹⁸
- Lifestyle intervention can effectively decrease BMI, testosterone levels and the free androgen index, increase SHBG concentrations, and normalize menstrual regularity comparable to the available medications and is devoid of side effects.
- A BMI SDS reduction of 0.25 or greater and exercise for 30 minutes or more daily improved cardiovascular risk factors in adolescents with PCOS and obesity¹⁹
- Bariatric surgery for weight loss may be relevant in patients with severe obesity but has not been studied systematically in adolescents with PCOS
 - In adult women, bariatric surgery decreased the incidence of PCOS symptoms from ~45% preoperatively to ~7% 12 months²⁰

Combination OCPs:

MECHANISM

- Estrogen increases hepatic production of sex hormone-binding globulin (SHBG). This reduces circulating bioavailable androgens.
- Progestins ensure endometrial decidualization and protect against proliferative endometrial pathologies. Progestins also reduce LH-driven ovarian androgen production via negative gonadotropin feedback.

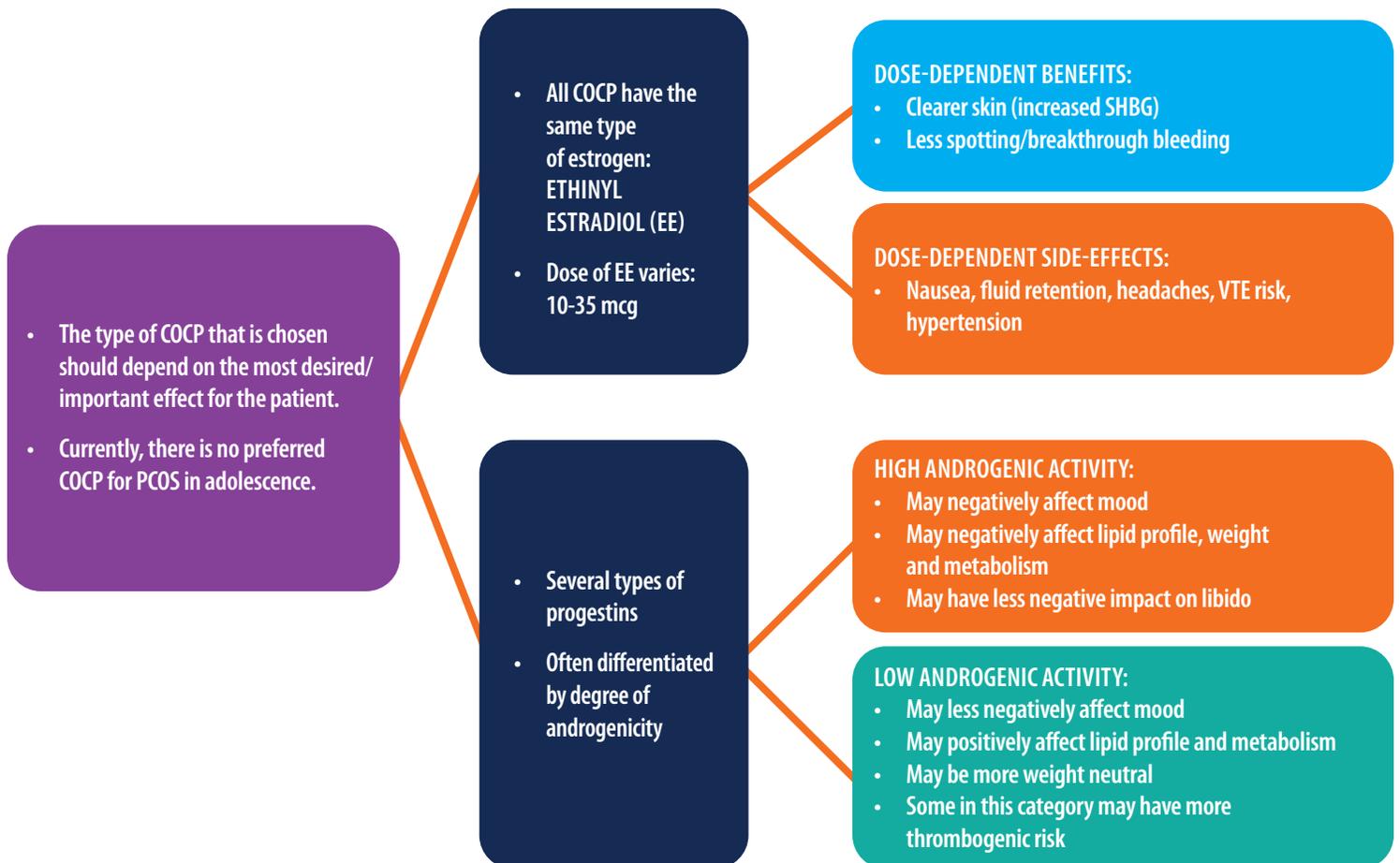
ADMINISTRATION

- COCP can be taken for three weeks a month with monthly withdrawal bleeding during placebo week.
- Alternately, most monophasic COCP can be taken continuously for three months with subsequent withdrawal bleeding. Some can be extended to 365 days a year.
- The benefit of continuous COCP administration is reduced menstrual discomfort/inconvenience and endometriosis prevention/treatment. It may also reduce premenstrual syndrome/dysphoria.

Considerations when prescribing combination OCPs²¹⁻²⁷:

THROMBOTIC RISK	DEPRESSION/ANXIETY RISK	METABOLIC/HYPERTENSION RISK
<ul style="list-style-type: none"> PCOS, independently of BMI, is a pro-thrombotic/pro-inflammatory state. Many adolescent girls with PCOS have overweight status, some have obesity. Adding metformin to the COCP treatment may reduce the adverse effect of COCP on thrombogenesis. The type of COCP (higher estrogen dose and type of progestin) may affect the thrombotic risk. 	<ul style="list-style-type: none"> PCOS is associated with anxiety and depression. Furthermore, adolescents may be at higher risk for depressive mood associated with COCP. Some COCP choices may be better for depression predisposed teens than others. 	<ul style="list-style-type: none"> Adolescents with PCOS have a higher risk of pre-diabetes and diabetes. COCP use may affect carbohydrate metabolism. COCP is contraindicated in patients with systolic BP > 140 mmHg and diastolic BP > 90 mmHg

Choosing a COCP:



Types of Progestins:

HIGH ANDROGENICITY

- Norethindrone 1.5-2.5 mg (androgenicity is dose-dependent)
- Levonorgestrel (lowest DVT risk with 20 mcg EE)
- Norgestrel (good for endometriosis)

MODERATE ANDROGENICITY

- Norethindrone 1 mg (androgenicity is dose-dependent)

LOW ANDROGENICITY

- Norethindrone 0.4-0.5 mg (androgenicity is dose-dependent)
- Norgestimate
- Drospirenone (higher thromboembolic risk*, FDA-approved for premenstrual dysphoria)
- Desogestrel (slightly higher thromboembolic risk)

*Drospirenone thrombosis risk: 10.22/10,000 women years vs 3-9/10,000 women years other progestins

LOW ANDROGENICITY PROGESTINS: Common COCP Formulations

	DROSPIRENONE 3 mg	DESOGESTREL 0.15 mg	NORGESTIMATE 0.25 mg	NORETHINDRONE 0.4 - 0.5 mg
20 mcg EE	<i>Yaz*</i> Beyaz (with folate) Jasmiel Gianvi Loryna Lo-Zumandimine Nikki Vestura	<i>Mircette*</i> Azurette Bekyree Kariva Kimidess Pimtrea Simliya Viorele Volnea		
30 mcg EE	<i>Yasmin*</i> Ocella Safyral (with folate) Tydemy (with folate) Syeda Zarah Zumandimine	<i>Desogen*</i> Apri Cyred Emoquette Enskyce Juleber Kalliga Ortho-Cept Reclipsen Solia Isibloom		
35 mcg EE			<i>Ortho-Cyclen*</i> Estarylia Femynor Mili Mono-linya Mononessa Previfem Sprintec	0.4 mg <i>Ovcon 35*</i> Belzivia Briellyn Philith Vyfemia Zenchent Femcon FE (chewable) Wymzya FE (chewable) Zenchent FE (chewable) Zeosa (chewable) 0.5 mg Cyclafem 0.5/35 Cyonanz Modicon Nortrel 0.5/35 Necon 0.5/35 Wera

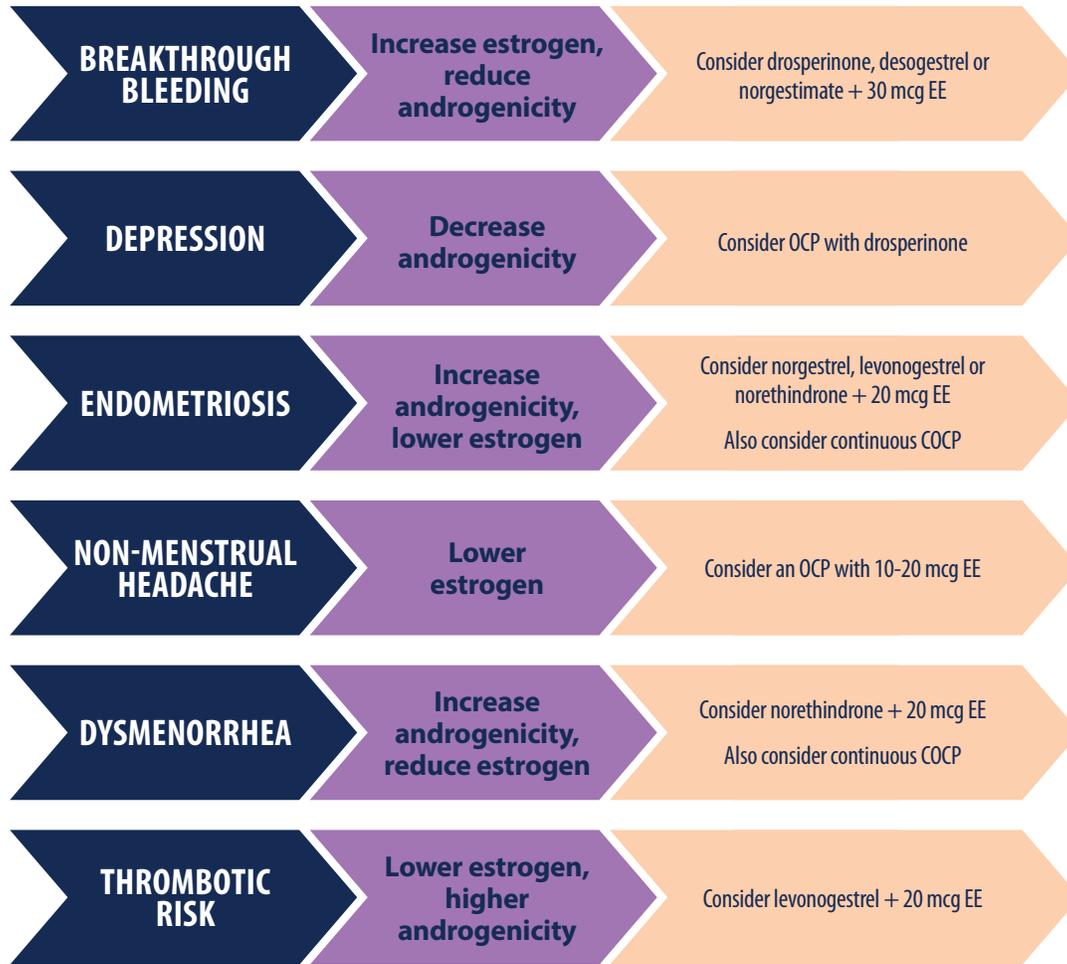
*Indicates original trade name

HIGH & MODERATE ANDROGENICITY PROGESTINS: Common COCP Formulations

	NORGESTREL 0.3 mg	LEVONORGESTREL 0.1-0.15 mg	NORETHINDRONE 1.5 mg	NORETHINDRONE 1.0 mg
10 mcg EE				<i>Lo-Loestrin Fe*</i>
20 mcg EE		0.1 mg <i>Alesse/Delyla*</i> Larissia Aubra Lutera Aviane Orsythia Balcofra Sronyx Falmina Vienva <i>Lo-Seasonique*</i> (84 days + 7 days 10 mcg EE) Amethyst (365 days – 0.9/20)		1 mg (most have Fe option available) <i>Loestrin</i> Blisovi Gildess Junel Larin Microgestin Melodetta 24 Fe chewable Taytulla (with ferrous fumarate) Gemmilly (with ferrous fumarate)
30 mcg EE	<i>Lo/Ovral*</i> Cryselle Ellnest Low-ogestrel	0.15 mg <i>Nordette*</i> Kurvelo Levora Altavera Marlissa Ayuna Portia Chateal <i>Seasonale*</i> (84 days) <i>Seasonique*</i> (84 days + 7 days 10 mcg EE)	1.5 mg (most have Fe option available) <i>Loestrin 1.5/30*</i> Aurovela 1.5/30 Blisovi 1.5/30 Gildess 1.5/30 Hailey 1.5/30 Junel 1.5/30 Larin 1.5/30 Microgestin 1.5/30	

*Indicates original trade name

Troubleshooting Adverse Effects with COCPs



Alternative Forms of Hormone Therapy if Contraindications to Estrogen

ESTROGEN CONTRAINDIICATION

- No hormonal therapy lifestyle
- Cyclic oral medroxyprogesterone acetate
- Continuous oral norethindrone acetate*
- 12-week IM medroxyprogesterone acetate**
- Levonogestrel IUD***
- Etonogestrel implant***

DIFFICULTY TAKING PILLS

- No hormonal therapy lifestyle
- 12-week IM medroxyprogesterone acetate**
- Levonogestrel IUD***
- Etonogestrel implant***
- Combined contraceptive patch**#
- Combined contraceptive ring**#

#Improves cosmesis

*moderate contraceptive; **good contraceptive; ***excellent contraceptive

Metformin

Indications: Diagnosis of PCOS with higher consideration for use in those with family history of T2DM, central obesity or clinical evidence of insulin resistance

Dose: Regular formulation 1,000 mg BID; Extended release 2,000 mg daily

Precautions: Possible side effects include gastrointestinal side effects (nausea, diarrhea), decreased vitamin B12 levels and lactic acidosis (primarily in patients with renal impairment). Discontinue prior to procedures with anesthesia or IV contrast.

Monitoring: 1) Risk of lactic acidosis increased with impaired renal function, check renal function yearly; 2) Risk of Vitamin B12 deficiency, measure yearly.

- Metformin is an insulin sensitizer used alone or in combination with oral contraceptives and/or antiandrogens in women and adolescents with PCOS.
- Metformin is not FDA approved as a treatment for PCOS although it is widely used off-label, is cost effective, and has a good safety profile for long-term use. Insulin resistance has been documented in clamp studies in 75% of lean women and 95% of women with overweight and PCOS, which supports the use of metformin in this population.²⁸
- Metformin, in addition to lifestyle improvements, should be considered in treatment of adolescents with PCOS.
- Metformin may offer greater benefit in high metabolic risk groups including those with risk factors of diabetes, impaired glucose tolerance or a member of a high-risk ethnic groups.²⁸
- Off-label use when relevant should be discussed with patients as well as the possibility of adverse effects such as gastrointestinal side effects and low vitamin B12 levels.
- Considering starting at a low dose of 500 mg daily and increasing by 500 mg every 1-2 weeks as tolerated with a maximum dose of 2,000 mg daily. Consider the use of extended release metformin due to the benefit of once daily dosing improving adherence and the potential decrease in gastrointestinal side effects.²⁸
- Evidence is limited in adolescents due to few quality studies and overall mixed results on the benefit of metformin on metabolic end points and hyperandrogenism.
- A meta-analysis that included 20 randomized controlled trials (19 in women, 1 in adolescents²⁹) of metformin vs placebo showed that metformin improves weight, BMI, waist to hip ratio, testosterone, SHBG, and triglycerides in women with PCOS.
- In a randomized placebo-controlled trial of metformin in adolescents with overweight and obesity with PCOS, metformin resulted in clinically significant improvement in menstrual regularity, reduced serum testosterone levels, and increased HDL cholesterol levels. There was no significant reduction in BMI in either group.³⁰
- A multicenter, randomized, double-blind placebo-controlled trial in adolescents with obesity showed a decrease in BMI when metformin was added to a lifestyle intervention program after 48 weeks.³⁰
- A randomized controlled trial of women with PCOS who were treated with metformin had decreases in BMI, total testosterone and free androgen index and an increase in SHBG, at 6 months of treatment.³¹

Spirolactone

Indications: Treatment of hirsutism, acne, and/or alopecia due to hyperandrogenism

Dose: 100 to 200 mg daily divided BID

Precautions: Use in combination with contraception due to teratogenicity

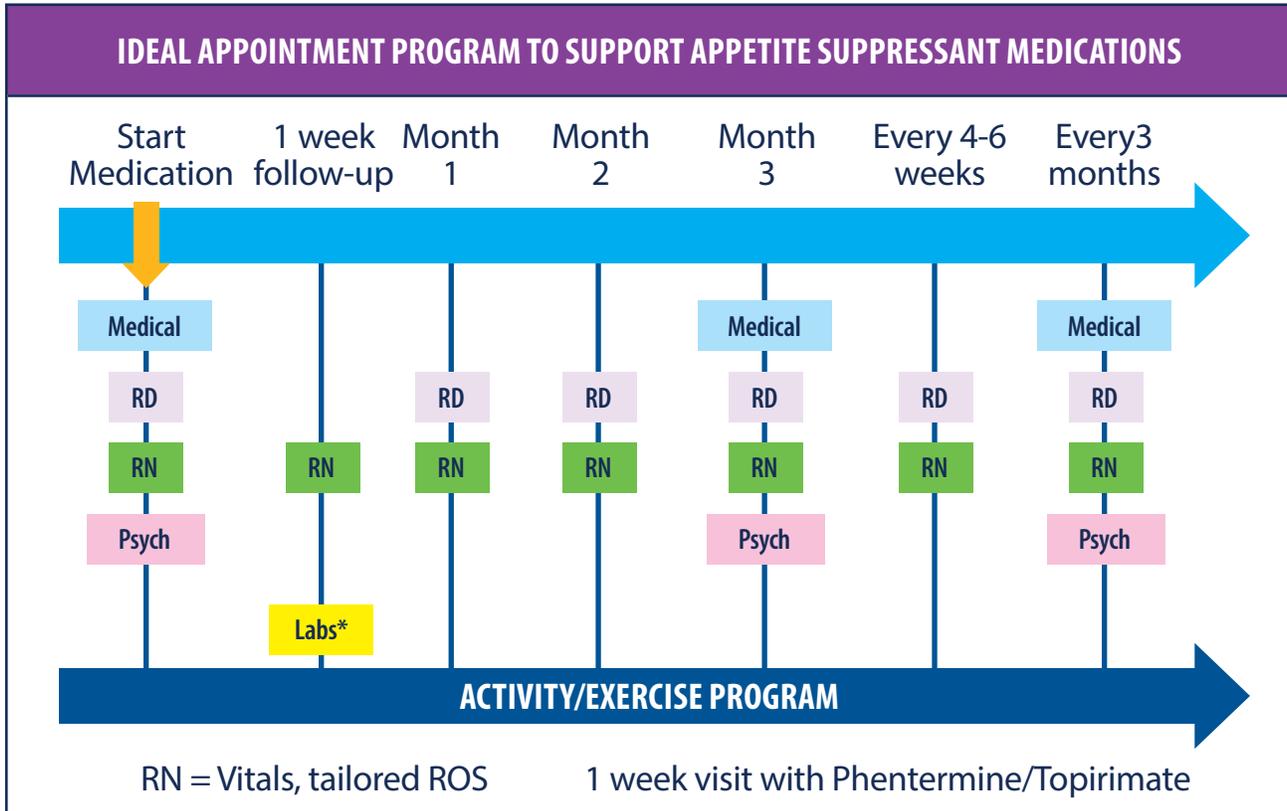
Monitoring: 1) Risk of hyperkalemia, check serum potassium 1-2 months after therapy initiation;
2) Risk for low blood pressure (orthostasis; need for appropriate hydration)

- Spirolactone is an aldosterone antagonist with anti-androgenic properties. It is most commonly used as a potassium-sparing diuretic.
- Usually used in a dose of 100 to 200 mg daily in 2 divided doses. It can be used as a single therapy³² but side effects like spotting and the risk for teratogenicity (undervirilization of the male fetus) make it an undesirable single agent. Thus, it is most commonly used in combination with COCP.
- In combination with COCP, it has been shown to decrease hirsutism. It does not affect hairs that are already present but new hairs grow in slower and thinner. The improvement becomes evident after 6-9 months of treatment. The combination of spiroolactone and COCP improved hirsutism better than metformin, spiroolactone or COCP alone.³³
- Other side effects include breast tenderness, polyuria, polydipsia, hyperkalemia, postural hypotension presenting as dizziness, lethargy, nausea, intermenstrual bleeding, and headache.

Appetite Suppressants

Use of appetite suppression can be a component of a comprehensive lifestyle treatment plan. Typically, this includes a visit with a medical provider at baseline, 3 and 6 months, and a visit with a dietitian monthly. Nurse check-in is to check for side-effects and vitals monitoring. Other monitoring is specific to the medication.

Recommendations are to do a 6-month trial, and if patient is successful in weight loss or are least cessation of weight gain, continue. If results are not achieved within 6 months, stop therapy.



MEDICATION	DOSE	COMMON SIDE EFFECTS	SAFETY MONITORING	PREGNANCY	COST
Phentermine ³⁴	8-15 mg every morning	Hypertension Anxiety Nausea	Blood pressure and basic metabolic panel 1 week after initiation of therapy	Not recommended	Not covered by insurance. Can use GooddayRx or other similar discount programs, approx. \$10-30/month
Topiramate ³⁴	75-150 mg at night, start at 25 mg and escalated dose once a week	Depression Fatigue Memory problems Nausea		Not recommended Decreases efficacy of estrogen contraceptives	Often covered by insurance
Liraglutide ³⁵	Up to 3 mg SQ a day. Titrate up to full dose	Nausea Hypoglycemic symptoms	ALT, AST, BUN, Cr at baseline	Not recommended	Patient assistance program from Novo Nordisk for those with private insurance

Phentermine and Topiramate are often used together to balance out the side effects. This combination is similar to the brand name medication Qsymia. When used together, 8 mg of phentermine and 75 mg of topiramate are adequate to achieve results.



EVALUATION AND MANAGEMENT OF COMMON PCOS COMORBIDITIES

Metabolic Screening:

- **Every appointment (at least every 6 months):**
 - Measure blood pressure
 - Measure Weight/Calculate BMI
- **Annually:**
 - Fasting lipids
 - Hepatic function panel
 - Hemoglobin A1C (or more frequently if nearing DM threshold)*

*Oral glucose tolerance test (OGTT) is recommended in high-risk women with PCOS (BMI > 25 kg/m²), history of impaired fasting glucose, history of impaired OGTT, family history of diabetes mellitus type 2, hypertension or high-risk ethnicity²⁸. Should be repeated every 1-3 years depending on the presence of other diabetes risk factors.

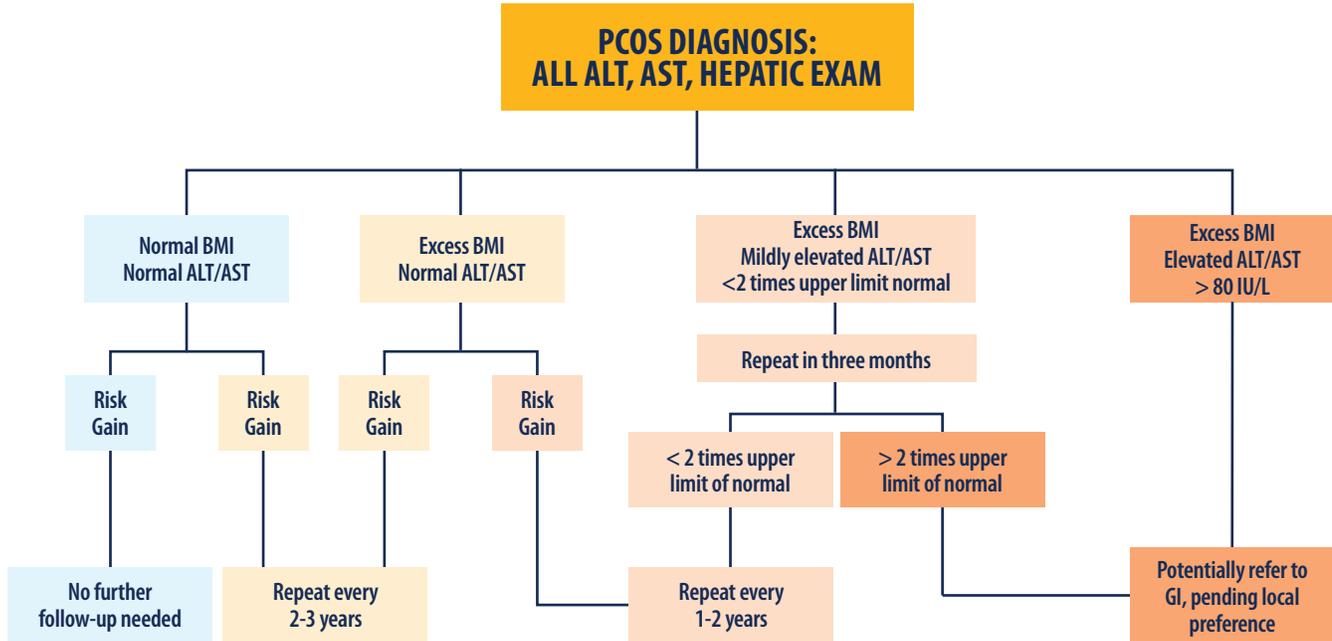
Dyslipidemia:

- Adolescents with PCOS have increased risk for dyslipidemia characterized by elevated total cholesterol, LDL-cholesterol) and triglycerides and low HDL-cholesterol levels¹⁸
- Metformin and statins are the predominant drugs used to treat dyslipidemia in PCOS
- **Mechanism:**
 - Metformin — improvement in hypertriglyceridemia due to improvement in insulin sensitivity
 - Statins — inhibit HMG-coenzyme A reductase, the rate limiting step in cholesterol synthesis, and thus directly reduce circulating cholesterol
- A meta-analysis comparing combined statin and metformin with metformin alone showed reduction in total cholesterol, triglycerides and no significant adverse impact on measures of insulin sensitivity.³⁶

Prediabetes:

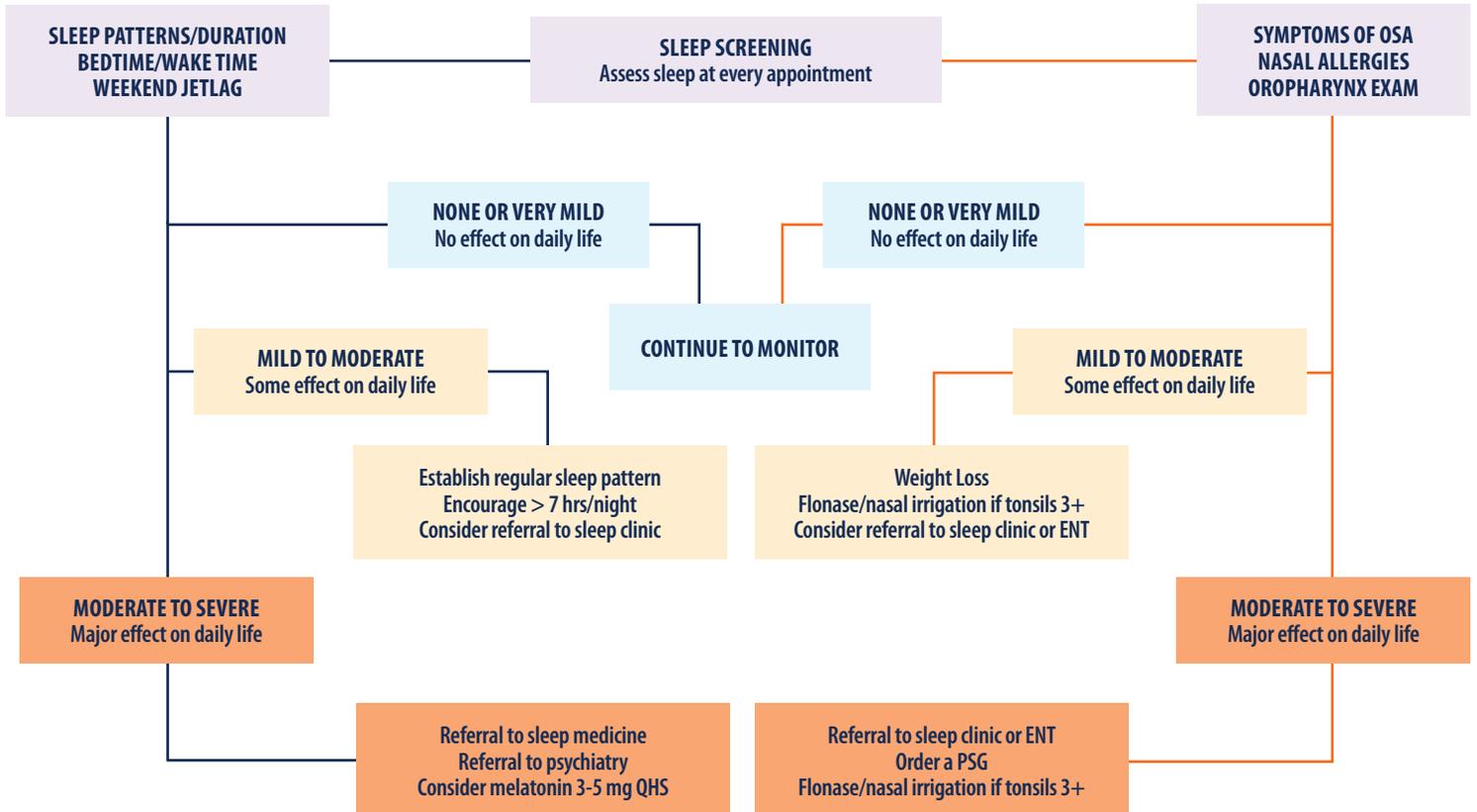
- **American Diabetes Association definition:**
 - Impaired fasting glucose, which is a fasting plasma glucose of 100 to 125 mg/dL (5.6–6.9 mmol/L), or
 - Impaired glucose tolerance, which is a 2-hour plasma glucose after 75 g of oral glucose intake of 140 to 199 mg/dL (7.8–11.0 mmol/L), or
 - Glycated hemoglobin (HbA1c) of 5.7% to 6.4% (39–46 mmol/mol).
- Diagnostic tools: fasting plasma glucose test, oral glucose tolerance test, and glycosylated hemoglobin (HbA1C) levels.
- Recent ADA guidance indicated that HbA1C can be used for screening for diabetes in adolescent patients³⁷
- **Prediabetes in an adolescent with or 'at risk' of PCOS: There is increased long-term risk of diabetes in patients with PCOS. Approximately 5-10% patients with prediabetes are estimated to convert to diabetes annually. Adolescents with PCOS have about a two-fold prevalence of glucose intolerance compared to an adolescent with obesity and without PCOS**
 - 2% of women with PCOS progress from normoglycemia to T2D every year
 - 15-20% convert from normal to impaired glucose tolerance (decreased to 2% on metformin)³⁸
 - 16% progress from impaired glucose tolerance to T2D³⁹
- Metformin can be combined with lifestyle intervention to treat prediabetes in an adolescent with PCOS and prediabetes.

Nonalcoholic Steatohepatitis: Fatty Liver Disease

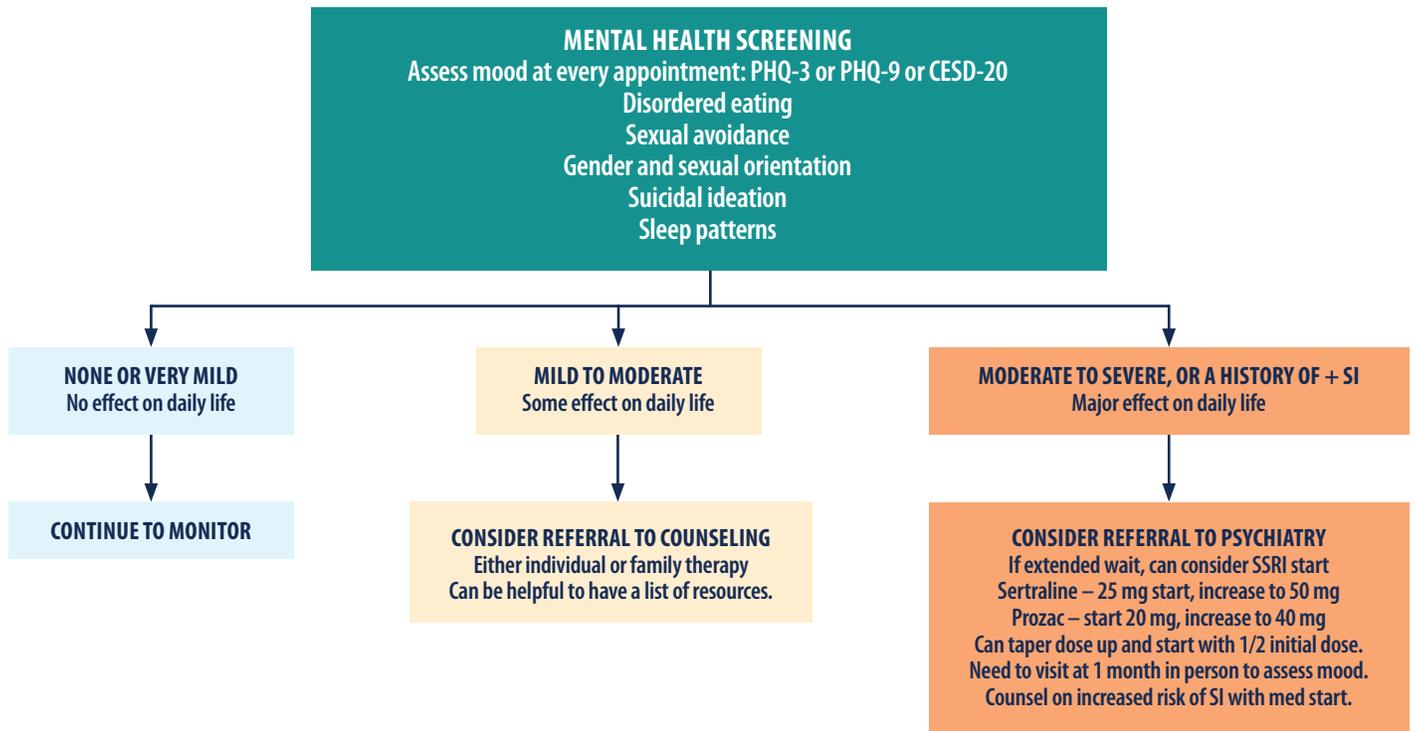


Risk factors include: significantly rising BMI, changing glycemia, new obstructive sleep apnea

Sleep Disorders



Mood Disorders



Acne

COMEDOMES	MILD	MODERATE PUSTULAR	NODULOCYSTIC
OTC benzoyl peroxide wash	OTC benzoyl peroxide wash	OTC salicylic acid wash + BP	OTC benzoyl peroxide wash
OR	OR	OR	
OTC salicylic acid wash	OTC salicylic acid wash	Clindamycin topical + BP	Clindamycin topical
	OR	AND	Topical retinoid 0.5%
	Topical retinoid OTC Adapalene 0.1%	Topical retinoid Rx Adapalene 0.5%	3-month minocycline*
Topical retinoid OTC Adapalene 0.1%	Clindamycin topical	3-month minocycline*	Oral retinoid*
Clindamycin topical	3-month minocycline*		
3-month minocycline*			

*Typically managed by dermatology

Other Common Dermatologic Comorbidities

HIRSUTISM	ANDROGENIC ALOPECIA	HIDRADENITIS SUPPERATA	ACANTHOSIS NIGRICANS
Estrogen therapy	Estrogen therapy	Estrogen therapy	Lifestyle changes
Spironolactone	Spironolactone	Spironolactone	Metformin
Topical eflornithine	Minoxidil foam for men	Chlorhexidine gluconate 2x a week prevention Daily with active lesion	12% ammonium lactate topical
		3-month minocycline*	

*Typically managed by dermatology

Dysfunctional Uterine Bleeding Management Algorithm

***POTENTIAL CONTRAINDICATIONS TO ESTROGEN INCLUDE:

- Migraine with aura
- Hypercoagulable state
- Personal history of VTE
- Liver tumor or dysfunction

- Significant active bleeding (soaking through 1-2 pads/tampons per hour)
 - Severe anemia (Hgb < 7 g/dL)
 - Symptomatic anemia (Hgb < 9 g/dL)

REFER TO ED

MILD/MODERATE BLEEDING

Hgb NORMAL

MILD ANEMIA
(Hgb 9 dg/dL – lower limit of normal)

MODERATE ANEMIA
(Hgb 7-8.9 dg/dL)

CONTRAINDICATION TO ESTROGEN?*

NO

YES

NORGESTREL + 30 mcg EE
35 mcg, taper: QID x 3 days,
TID x3 days, BID x 2 days, then daily
DO NOT advance taper if still actively bleeding

MEDROXYPROGESTERONE
10 mg, taper: QID x 3 days,
TID x3 days, BID x 3 days, then daily
DO NOT advance taper if still actively bleeding

Ferritin < 15 ng/mL

- Order multiple packs and write pharmacy instructions "needed for menstrual suppression"
- Ferrous sulfate 130 mg elemental iron daily; start once taper reaches BID timing
- Consider prescribing Zofran ODT for nausea

MVI with iron daily

Ferrous sulfate 130 mg elemental iron daily

Offer hormonal control if eligible***
Scheduled ibuprofen 600 mg for first three days of taper
Follow-up in clinic within 1 week

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