Polycystic Ovarian Syndrome – Overview of Medical Management

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New Brunswick Internal Medicine Update

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Disclosure

- I have provided previous diabetes learning programs for Novo Nordisk Canada Inc.
  - Full editorial control

- I intend to make therapeutic recommendations for medications that have not received regulatory approval.
  - "This is an on-label indication."
  - *Pharmacological treatments are mostly off-label in PCOS. However, off-label use is predominantly evidence-based and is allowed in many countries. Where it is allowed, health professionals need to inform women and discuss the evidence, possible concerns and side effects of treatment.*

Objectives

- At the end of this session, participants will be able to
  1. Discuss available medical therapies for managing symptoms in patients diagnosed with polycystic ovarian syndrome (PCOS).

Guidelines

- Today, I've drawn mainly upon:
  - 2013 Endocrine Society (PCOS)
- I've also included some material from:
  - 2018 Endocrine Society (Hirsutism)
  - 2018 American College of Obstetrics and Genecologists (PCOS)
  - 2018 International PCOS Guideline

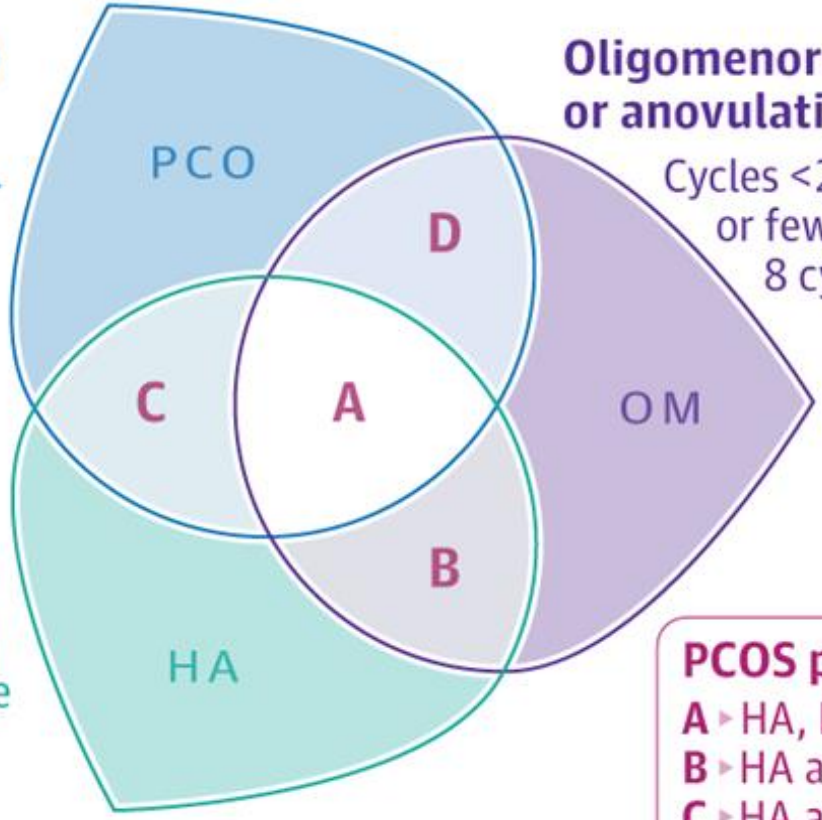
Key Point # 1 – Diagnosis

PCOS is a diagnosis of exclusion.

Polycystic ovaries (PCO)
≥20 follicles per ovary or an ovarian volume ≥10 mL in at least 1 ovary on transvaginal ultrasound

Oligomenorrhea or anovulation (OM)
Cycles <21 d or >35 d, or fewer than 8 cycles/y

Hyperandrogenism (HA)
Clinical features (hirsutism) and/or biochemical evidence (free or total testosterone levels above normal range for women)



PCOS phenotypes
- **A** ▸ HA, PCO, and OM
- **B** ▸ HA and OM
- **C** ▸ HA and PCO
- **D** ▸ PCO and OM

JAMA 2022 Update

Exclude other causes of PCOS

Hypo- or hyperthyroidism	Functional hypothalamic amenorrhea
Hyperprolactinemia	Late-onset congenital adrenal hyperplasia

- Diagnosis during adolescence should not include ultrasound and should be made ≥2 y postmenarche.
- Metabolic features, particularly insulin resistance, are common and independent of but exacerbated by obesity.

PCOS = polycystic ovarian syndrome

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PCOS Diagnosis (1)

- Rotterdam Criteria: 2 of 3
  A. Oligo- or anovulation: clinical OR biochemical
  B. Hyperandrogenism: clinical OR biochemical
  C. Ovarian size/morphology: ultrasound

AND

- Other disorders excluded
  - *1.1 We suggest that the diagnosis of polycystic ovary syndrome be made if two of the three following criteria are met: androgen excess, ovulatory dysfunction, or polycystic ovaries (Tables 1 and 2), whereas disorders that mimic the clinical features of PCOS are excluded.*

PCOS = polycystic ovarian syndrome

INTERIM UPDATE

The American College of Obstetricians and Gynecologists

WOMEN'S HEALTH CARE PHYSICIANS

2018

Box 3. Factors to Consider in the Differential Diagnosis of Polycystic Ovary Syndrome

- Androgen secreting tumor
- Exogenous androgens
- Cushing syndrome
- Nonclassical congenital adrenal hyperplasia
- Acromegaly
- Genetic defects in insulin action
- Primary hypothalamic amenorrhea
- Primary ovarian failure
- Thyroid disease
- Prolactin disorders

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PCOS Diagnosis (2)

- Other disorders excluded: TSH, prolactin, 8AM 17-OHP
  - *1.1 These include, in all women: thyroid disease, hyperprolactinemia, and nonclassic congenital adrenal hyperplasia (primarily 21-hydroxylase deficiency by serum 17-hydroxyprogesterone) (Table 3). In select women with amenorrhea and more severe phenotypes, we suggest more extensive evaluation excluding other causes (Table 4) (2QQQE).*

Table 3. Other Diagnoses to Exclude in All Women Before Making a Diagnosis of PCOS

Disorder	Test	Abnormal Values	Reference for Further Evaluation and Treatment of Abnormal Findings; First Author, Year (Ref.)
Thyroid disease	Serum TSH	TSH > the upper limit of normal suggests hypothyroidism; TSH < the lower limit, usually < 0.1 mIU/L, suggests hyperthyroidism	Ladenson, 2000 (10)
Prolactin excess	Serum prolactin	> Upper limit of normal for the assay	Melmed, 2011 (11)
Nonclassical congenital adrenal hyperplasia	Early morning (before 8 AM) serum 17-OHP	200–400 ng/dL depending on the assay (applicable to the early follicular phase of a normal menstrual cycle as levels rise with ovulation), but a cosyntropin stimulation test (250 μg) is needed if levels fall near the lower limit and should stimulate 17-OHP > 1000 ng/dL	Speiser, 2010 (12)

17-OHP early follicular phase

PCOS = polycystic ovarian syndrome

PCOS Diagnosis (3)

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Table 4. Diagnoses to Consider Excluding in Select Women, Depending on Presentation

Other Diagnoses[a]	Suggestive Features in the Presentation	Tests to Assist in the Diagnosis	Reference for Further Evaluation and Treatment of Abnormal Findings; First Author, Year (Ref.)
Pregnancy	Amenorrhea (as opposed to oligomenorrhea), other signs and symptoms of pregnancy including breast fullness, uterine cramping, etc	Serum or urine hCG (positive)	Morse, 2011 (17)
HA including functional HA	Amenorrhea, clinical history of low body weight/BMI, excessive exercise, and a physical exam in which signs of androgen excess are lacking; multifollicular ovaries are sometimes present	Serum LH and FSH (both low to low normal), serum estradiol (low)	Wang, 2008 (18)
Primary ovarian insufficiency	Amenorrhea combined with symptoms of estrogen deficiency including hot flashes and urogenital symptoms	Serum FSH (elevated), serum estradiol (low)	Nelson, 2009 (296)
Androgen-secreting tumor	Virilization including change in voice, male pattern androgenic alopecia, and clitoromegaly; rapid onset of symptoms	Serum T and DHEAS levels (markedly elevated), ultrasound imaging of ovaries, MRI of adrenal glands (mass or tumor present)	Carmina, 2006 (16)
Cushing's syndrome	Many of the signs and symptoms of PCOS can overlap with Cushing's (ie, striae, obesity, dorsocervical fat (ie, buffalo hump, glucose intolerance); however, Cushing's is more likely to be present when a large number of signs and symptoms, especially those with high discriminatory index (eg, myopathy, plethora, violaceous striae, easy bruising) are present, and this presentation should lead to screening	24-h urinary collection for urinary free cortisol (elevated), late night salivary cortisol (elevated), overnight dexamethasone suppression test (failure to suppress morning serum cortisol level)	Nieman, 2008 (19)
Acromegaly	Oligomenorrhea and skin changes (thickening, tags, hirsutism, hyperhidrosis) may overlap with PCOS. However, headaches, peripheral vision loss, enlarged jaw (macrognathia), frontal bossing, macroglossia, increased shoe and glove size, etc, are indications for screening	Serum free IGF-1 level (elevated), MRI of pituitary (mass or tumor present)	Melmed, 2009 (20)

*OCP, metformin, spiro

OCP raises total cortisol

Abbreviations: DHEAS, dehydroepiandrosterone sulfate; HA, hypothalamic amenorrhea; hCG, human chorionic gonadotropin; MRI, magnetic resonance imaging. PCOS = polycystic ovarian syndrome; OCP = oral contraceptive pill; spiro = spironolactone

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Key Point # 1 – Summary

PCOS is a diagnosis of exclusion.

- Rotterdam 2 of 3
- TSH, prolactin, 8AM 17-OHP in all
- May need further testing

PCOS = polycystic ovarian syndrome

Key Point # 2 – Goals

Once diagnosis is made, clarify the patient's PCOS treatment goals and timeline.

PCOS = polycystic ovarian syndrome

Treatment Goals (1)

- Patient's primary goal will guide therapy
- Symptoms often guide therapy

Polycystic ovaries (PCO)
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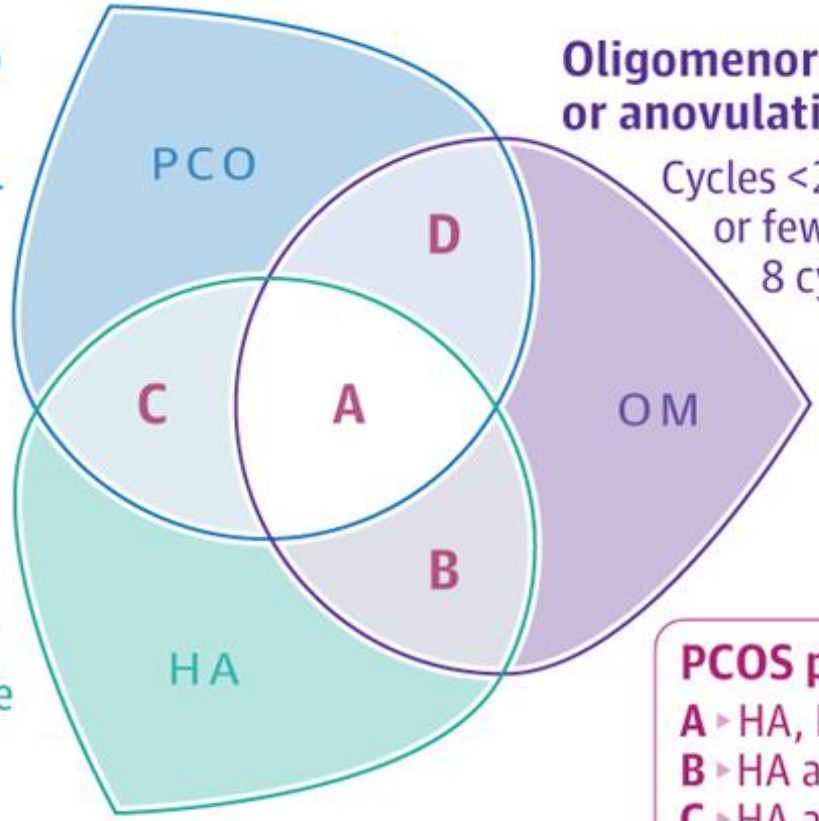

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- **C** ▸ HA and PCO
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Exclude other causes of PCOS

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- Diagnosis during adolescence should not include ultrasound and should be made ≥2 y postmenarche.
- Metabolic features, particularly insulin resistance, are common and independent of but exacerbated by obesity.

Treatment Goals (2)

- Menstrual dysfunction regulation
- Prevention of endometrial hyperplasia/carcinoma
- Contraception for those not pursuing pregnancy
- Hyperandrogenism / cutaneous manifestations
  - Acne, alopecia, hirsutism (terminal hair growth), acanthosis nigricans / skin tags (insulin resistance)
- Managing metabolic abnormalities/risk factors

- Ovulation induction for those pursuing pregnancy
  - Timeline for biological children?

Lifestyle Intervention

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- Likely beneficial for both reproductive and metabolic dysfunction
- Weight loss is 1st-line for elevated BMI
  - May require medication AND/OR bariatric surgery

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2018 **Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome**[†‡]

- *3.3 We suggest the use of exercise therapy in the management of overweight and obesity in PCOS (2QQEE).*
- *3.4 We suggest that weight loss strategies begin with calorie-restricted diets (with no evidence that one type of diet is superior) for adolescents and women with PCOS who are overweight or obese (2QQEE).*
- *2.2. For hirsute women with obesity, including those with PCOS, we also recommend lifestyle changes. (1 \|OO)*
- *Pharmacological anti-obesity agents should be considered an experimental therapy in women with PCOS for the purpose of improving fertility*
- *Bariatric surgery should be considered an experimental therapy in women with PCOS, for the purpose of having a healthy baby*

Contrave (wellbutrin/naltrexone), Saxenda (liraglutide), Wegovy (semaglutide), Orlistat (Xenical)

PCOS = polycystic ovarian syndrome

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If pregnancy desired…

- This trumps other goals
- OCP and antiandrogens are contraindicated
- See Key Point # 5

OCP = oral contraceptive pill

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If pregnancy not actively pursued…

- OCP and antiandrogens are on the table
  - See Key Points # 3 and # 4
- Patient's primary goal will direct therapy
- If patient desires future pregnancy, then re-assess goals at that point
  - See Key Point # 5

OCP = oral contraceptive pill

Endometrial Cancer Prevention (1)

- PCOS anovulation: estrogen unopposed by progesterone
  - Higher cancer risk from chronic anovulation compounded by
    - Hyperinsulinemia
    - Increased insulin-like growth factor-1 concentrations
    - Hyperandrogenemia
    - Obesity
    - Abnormal uterine bleeding
  - *2.6 Women with PCOS share many of the risk factors associated with the development of endometrial cancer including obesity, hyperinsulinism, diabetes, and abnormal uterine bleeding. However, we suggest against routine ultrasound screening for endometrial thickness in women with PCOS (2QQQE).*

PCOS = polycystic ovarian syndrome; OCP = oral contraceptive pill

Endometrial Cancer Prevention (2)

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2018 Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome†‡

- Combined OCPs contain enough progesterone to oppose estrogen/prevent this increased risk
  - *Optimal prevention for endometrial hyperplasia and endometrial cancer is not known. A pragmatic approach could include COCP or progestin therapy in those with cycles longer than 90 days.*
- If repeated anovulation > 3 months, then cyclic progesterone is usually recommended
  - Oral micronized progesterone 300mg x 14 days
  - Medroxyprogesterone 5-10mg x 10-14 days

OCP = oral contraceptive pill

Metabolic Risk Factors (1)

- PCOS is also associated with increased risk of
  - Obesity — BMI and WC
  - Insulin resistance / impaired glucose tolerance / type 2 diabetes — 75g OGTT
  - Depression — History
  - Sleep disordered breathing / obstructive sleep apnea — History / PSG
  - Nonalcoholic fatty liver disease / nonalcoholic steatohepatitis — ALT
  - Cardiovascular risk — Fasting lipids / BP

PCOS = polycystic ovarian syndrome; OGTT = oral glucose tolerance test; PSG = polysomnography

Metabolic Risk Factors (2)

- PCOS screening

Annual

  - *2.7 Increased adiposity, particularly abdominal, is associated with hyperandrogenemia and increased metabolic risk (see cardiovascular disease prevention guidelines, Ref. 2). Therefore, we recommend screening adolescents and women with PCOS for increased adiposity, by BMI calculation and measurement of waist circumference (1QQQE).*
  - *2.8 We suggest screening women and adolescents with PCOS for depression and anxiety by history and, if identified, providing appropriate referral and/or treatment (2QQEE).*
  - *2.9 We suggest screening overweight/obese adolescents and women with PCOS for symptoms suggestive of OSA and, when identified, obtaining a definitive diagnosis using polysomnography. If OSA is diagnosed, patients should be referred for institution of appropriate treatment (2QQEE).*
  - *2.10 We suggest awareness of the possibility of NAFLD and NASH but recommend against routine screening (2QQEE).*

ALT

PCOS = polycystic ovarian syndrome; OSA = obstructive sleep apnea; T2DM = type 2 diabetes

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Dysglycemia

- PCOS and insulin resistance
  - Fasting insulin levels not recommended

- PCOS and diabetes
  - Screen for impaired glucose tolerance / T2DM

Annual

  - *2.11 We recommend the use of an OGTT (consisting of a fasting and 2-hour glucose level using a 75-g oral glucose load) to screen for impaired glucose tolerance and T2DM in adolescents and adult women with PCOS because they are at high risk for such abnormalities (1QQQE). A hemoglobin A1c (HgbA1c) test may be considered if a patient is unable or unwilling to complete an OGTT (2QQEE). Rescreening is suggested every 3–5 years, or more frequently if clinical factors such as central adiposity, substantial weight gain, and/or symptoms of diabetes develop (2QQEE).*

PCOS = polycystic ovarian syndrome; OGTT = oral glucose tolerance test; T2DM = type 2 diabetes

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Metformin

- Impaired glucose tolerance: prevention
- T2DM: treatment
  - This is an <u>on-label</u> indication
- 2nd-line if OCP contraindicated/not tolerated
- In vitro fertilization (prevention of complications)
  - *2.11 3.5 We suggest against the use of metformin as a firstline treatment of cutaneous manifestations, for prevention of pregnancy complications, or for the treatment of obesity (2QQEE).*
  - *3.6 We recommend metformin in women with PCOS who have T2DM or impaired glucose tolerance who fail lifestyle modification (1QQQE). For women with PCOS with menstrual irregularity who cannot take or do not tolerate HCs, we suggest metformin as second-line therapy (2QQQE).*
  - *Metformin in addition to lifestyle, could be recommended in adult women with PCOS, for the treatment of weight, hormonal and metabolic outcomes*.

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2018 **Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome**[†‡]

OCP = oral contraceptive pill; HC = hormonal contraceptives; T2DM = type 2 diabetes

Other T2DM Medications

- Thiazolidinediones / Insulin sensitizers (inositols)
  - Not recommended
- GLP-1 agonists: weight loss in obesity
  - This is an on-label indication
  - Otherwise not recommended

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2018 Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome†‡

- *3.9 We recommend against the use of insulin sensitizers, such as inositols (due to lack of benefit) or thiazolidinediones (given safety concerns), for the treatment of PCOS (1QQQE).*
- *3.9. We suggest against using insulin-lowering drugs for the sole indication of treating hirsutism. (2 \|OO)*

OCP = oral contraceptive pill; HC = hormonal contraceptives; T2DM = type 2 diabetes

Cardiovascular Risk Factors

- PCOS risk stratification
  - *2.12 We recommend that adolescents and women with PCOS be screened for the following cardiovascular disease risk factors (Table 5): family history of early cardiovascular disease, cigarette smoking, impaired glucose tolerance/T2DM, hypertension, dyslipidemia, OSA, and obesity (especially increased abdominal adiposity) (1QQEE).*

Table 5. Cardiovascular Risk Stratification in Women with PCOS

At risk—PCOS women with any of the following risk factors:
Obesity (especially increased abdominal adiposity)
Cigarette smoking
Hypertension
Dyslipidemia (increased LDL-cholesterol and/or non-HDL-cholesterol)
Subclinical vascular disease
Impaired glucose tolerance
Family history of premature cardiovascular disease (<55 y of age in male relative; <65 y of age in female relative)
At high risk–PCOS women with:
Metabolic syndrome
T2DM
Overt vascular or renal disease, cardiovascular diseases
OSA

The Androgen Excess and Polycystic Ovary Syndrome Society relied upon evidence-based studies and concluded that women with PCOS be stratified as being either at risk or at high risk for cardiovascular disease using the criteria shown (167).

PCOS = polycystic ovarian syndrome; OSA = obstructive sleep apnea; T2DM = type 2 diabetes

Key Point # 2 – Summary

Once diagnosis is made, clarify the patient's PCOS treatment goals and timeline.

- Actively pursing pregnancy?
- Other factors: menstrual, hyperandrogenism, risk

PCOS = polycystic ovarian syndrome

Key Point # 3 – OCP

If pregnancy is not desired, OCP is the next treatment step after lifestyle intervention.

OCP = oral contraceptive pill

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OCP (1)

- If not actively pursuing pregnancy→combined OCP
  - 1st-line for menstrual dysfunction/endometrial protection
  - Provides reliable contraception
    - This is an on-label indication.
  - 1st-line for hyperandrogenism

- *3.1 We recommend HCs (ie, oral contraceptives, patch, or vaginal ring) as first-line management for the menstrual abnormalities and hirsutism/acne of PCOS, which treat these two problems concurrently (1QQEE).*
- *2.1. For most women with patient-important hirsutism despite cosmetic measures, we suggest starting with pharmacological therapy (2 ⊕OOO).*
- *3.1. For the majority of women with hirsutism who are not seeking fertility, we suggest oral contraceptives as initial therapy for treating patient-important hirsutism. (2 ⊕OO)*

PCOS = polycystic ovarian syndrome; OCP = oral contraceptive pill; HC = hormonal contraceptives

OCP (2)

- OCP is not suitable in some patients
  - Contraindications (some):
    - Pregnancy
    - VTE / Stroke / MI
    - Smoking, age >35
    - Migraine with aura
    - Cirrhosis / liver cancer
    - Breast cancer

Table 2. OCs and Associated VTE Risks

Progestin Generation	Progestin Relative Androgenicity	Progestin VTE Risk Relative[a,b]	Progestin VTE Risk Absolute[b,c]	Progestin/Dose	EE Dose (mcg)
1	Medium	2.6	7	Norethindrone 0.5–1.0 mg	20, 35
2	High	2.4	6	Levonorgestrel 0.15 mg	20, 30
2–3	Low	2.5	6	Norgestimate 0.25 mg	35
3	Low	3.6	11	Gestodene 0.075 mg	20, 30
3	Low	4.3	14	Desogestrel 0.15 mg	20, 30
4	Antiandrogen	4.1	13	DSP 3 mg	20, 30
—	Antiandrogen	4.3	14	CPA 2 mg[d]	35

[a]Relative risk compared with no OC use.

[b]Vinogradova *et al.* (73); Stegeman *et al.* (57).

[c]Extra cases VTE per 10,000 women treated with OCs per year.

[d]OCs containing CPA are not available in the United States.

- *3.2 We recommend screening for contraindications to HC use via established criteria (see Table 6 and Ref. 3) (1QQQE).*

OCP = oral contraceptive pill; HC = hormonal contraceptives; VTE = venous thromboembolism

Summary Chart of U.S. Medical Eligibility Criteria for Contraceptive Use

Centers for Disease Control and Prevention
National Center for Chronic Disease Prevention and Health Promotion

Condition	Sub-Condition	Cu-IUD		LNG-IUD		Implant		DMPA		POP		CHC	
		I	C	I	C	I	C	I	C	I	C	I	C
Hypertension	a) Adequately controlled hypertension	1*		1*		1*		2*		1*		3*	
	b) Elevated blood pressure levels (*properly taken measurements*)												
	i) Systolic 140-159 or diastolic 90-99	1*		1*		1*		2*		1*		3*	
	ii) Systolic ≥160 or diastolic ≥100†	1*		2*		2*		3*		2*		4*	
	c) Vascular disease	1*		2*		2*		3*		2*		4*	
Inflammatory bowel disease	(*Ulcerative colitis, Crohn's disease*)	1		1		1		2		2		2/3*	
Ischemic heart disease‡	Current and history of	1		2	3	2	3	3		2	3	4	
Known thrombogenic mutations†		1*		2*		2*		2*		2*		4*	
Liver tumors	a) Benign												
	i) Focal nodular hyperplasia	1		2		2		2		2		2	
	ii) Hepatocellular adenoma†	1		3		3		3		3		4	
	b) Malignant† (hepatoma)	1		3		3		3		3		4	
Malaria		1		1		1		1		1		1	
Multiple risk factors for atherosclerotic cardiovascular disease	(e.g., older age, smoking, diabetes, hypertension, low HDL, high LDL, or high triglyceride levels)	1		2		2*		3*		2*		3/4*	
Multiple sclerosis	a) With prolonged immobility	1		1		1		2		1		3	
	b) Without prolonged immobility	1		1		1		2		1		1	
Obesity	a) Body mass index (BMI) ≥30 kg/m²	1		1		1		1		1		2	
	b) Menarche to <18 years and BMI ≥ 30 kg/m²	1		1		1		2		1		2	
Ovarian cancer‡		1		1		1		1		1		1	
Parity	a) Nulliparous	2		2		1		1		1		1	
	b) Parous	1		1		1		1		1		1	
Past ectopic pregnancy		1		1		1		1		2		1	
Pelvic inflammatory disease	a) Past												
	i) With subsequent pregnancy	1	1	1	1	1		1		1		1	
	ii) Without subsequent pregnancy	2	2	2	2	1		1		1		1	
	b) Current	4	2*	4	2*	1		1		1		1	
Peripartum cardiomyopathy‡	a) Normal or mildly impaired cardiac function												
	i) <6 months	2		2		1		1		1		4	
	ii) ≥6 months	2		2		1		1		1		3	
	b) Moderately or severely impaired cardiac function	2		2		2		2		2		4	
Postabortion	a) First trimester	1*		1*		1*		1*		1*		1*	
	b) Second trimester	2*		2*		1*		1*		1*		1*	
	c) Immediate postseptic abortion	4		4		1*		1*		1*		1*	
Postpartum (*nonbreastfeeding women*)	a) <21 days					1		1		1		4	
	b) 21 days to 42 days												
	i) With other risk factors for VTE					1		1		1		3*	
	ii) Without other risk factors for VTE					1		1		1		2	
	c) >42 days					1		1		1		1	
Postpartum (*in breastfeeding or nonbreastfeeding women, including cesarean delivery*)	a) <10 minutes after delivery of the placenta												
	i) Breastfeeding	1*		2*									
	ii) Nonbreastfeeding	1*		1*									
	b) 10 minutes after delivery of the placenta to <4 weeks	2*		2*									

Condition	Sub-Condition	Cu-IUD		LNG-IUD		Implant		DMPA		POP		CHC	
		I	C	I	C	I	C	I	C	I	C	I	C
Pregnancy		4*		4*		NA*		NA*		NA*		NA*	
Rheumatoid arthritis	a) On immunosuppressive therapy	2	1	2	1	1		2/3*		1		2	
	b) Not on immunosuppressive therapy	1		1		1		2		1		2	
Schistosomiasis	a) Uncomplicated	1		1		1		1		1		1	
	b) Fibrosis of the liver†	1		1		1		1		1		1	
Sexually transmitted diseases (STDs)	a) Current purulent cervicitis or chlamydial infection or gonococcal infection	4	2*	4	2*	1		1		1		1	
	b) Vaginitis (*including trichomonas vaginalis and bacterial vaginosis*)	2	2	2	2	1		1		1		1	
	c) Other factors relating to STDs	2*	2	2*	2	1		1		1		1	
Smoking	a) Age <35	1		1		1		1		1		2	
	b) Age ≥35, <15 cigarettes/day	1		1		1		1		1		3	
	c) Age ≥35, ≥15 cigarettes/day	1		1		1		1		1		4	
Solid organ transplantation†	a) Complicated	3	2	3	2	2		2		2		4	
	b) Uncomplicated	2		2		2		2		2		2*	
Stroke‡	History of cerebrovascular accident	1		2		2	3	3		2	3	4	
Superficial venous disorders	a) Varicose veins	1		1		1		1		1		1	
	b) Superficial venous thrombosis (acute or history)	1		1		1		1		1		3*	
Systemic lupus erythematosus†	a) Positive (or unknown) antiphospholipid antibodies	1*	1*	3*		3*		3*	3*	3*		4*	
	b) Severe thrombocytopenia	3*	2*	2*		2*		3*	2*	2*		2*	
	c) Immunosuppressive therapy	2*	1*	2*		2*		2*	2*	2*		2*	
	d) None of the above	1*	1*	2*		2*		2*	2*	2*		2*	
Thyroid disorders	Simple goiter/ hyperthyroid/hypothyroid	1		1		1		1		1		1	
Tuberculosis† (*see also Drug Interactions*)	a) Nonpelvic	1	1	1	1	1*		1*		1*		1*	
	b) Pelvic	4	3	4	3	1*		1*		1*		1*	
Unexplained vaginal bleeding	(suspicious for serious condition) before evaluation	4*	2*	4*	2*	3*		3*		2*		2*	
Uterine fibroids		2		2		1		1		1		1	
Valvular heart disease	a) Uncomplicated	1		1		1		1		1		2	
	b) Complicated‡	1		1		1		1		1		4	
Vaginal bleeding patterns	a) Irregular pattern without heavy bleeding	1		1	1	2		2		2		1	
	b) Heavy or prolonged bleeding	2*		1*	2*	2*		2*		2*		1*	
Viral hepatitis	a) Acute or flare	1		1		1		1		1		3/4*	2
	b) Carrier/Chronic	1		1		1		1		1		1	1
Drug Interactions													
Antiretrovirals used for prevention (PrEP) or treatment of HIV	Fosamprenavir (FPV) All other ARVs are 1 or 2 for all methods.	1/2*	1*	1/2*	1*	2*		2*		2*		3*	
Anticonvulsant therapy	a) Certain anticonvulsants (phenytoin, carbamazepine, barbiturates, primidone, topiramate, oxcarbazepine)	1		1		2*		1*		3*		3*	
	b) Lamotrigine	1		1		1		1		1		3*	
Antimicrobial therapy	a) Broad spectrum antibiotics	1		1		1		1		1		1	
	b) Antifungals	1		1		1		1		1		1	
	c) Antiparasitics	1		1		1		1		1		1	
	d) Rifampin or rifabutin therapy	1		1		2*		1*		3*		3*	
SSRIs		1		1		1		1		1		1	
St. John's wort		1		1		2		1		2		2	

OCP (4)

- Other factors to consider
  - PROS
  - CONS
- Individual assessment

Table 6. Considerations for Use of Combined HCs, Including Pill, Patch, and Vaginal Ring, in Women with PCOS Based on Relevant Conditions

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Criteria	Further Classification	Conditions 1	2	3	4
		A condition for which there is no restriction for the use of the contraceptive method	A condition for which the advantages of using the method generally outweigh the theoretical or proven risks	A condition for which the theoretical or proven risks usually outweigh the advantages of using the method	A condition that represents an unacceptable health risk if the contraceptive method is used
Age	Menarche to <40 y	X			
	>40 y		X		
Smoking	Age ≥35 y		X		
	Age ≥35 y and smokes <15 cigarettes/d			X	
	Age ≥35 y and smokes ≥15 cigarettes/d				X
Obesity	BMI <30 kg/m^2		X		
	BMI ≥30 kg/m^2		X		
Hypertension	History of gestational hypertension	X			
	Adequately controlled hypertension			X	
	Elevated blood pressure levels (properly taken measurements): systolic, 140–159 mm Hg; or diastolic, 90–99 mm Hg			X	
	Elevated blood pressure levels (properly taken measurements): systolic, ≥160 mm Hg; or diastolic, ≥100 mm Hg				X
Dyslipidemia	Known hyperlipidemias		X	X	
Depression	Depressive disorders	X			
Unexplained vaginal bleeding (suspicious for serious condition)	Before evaluation[a]		X		
Diabetes	History of gestational diabetes		X		
	Nonvascular diabetes, insulin or non-insulin dependent		X		
	Vascular disease including neuropathy, retinopathy, nephropathy[b]			X	X
	Diabetes duration >20 y[b]			X	X

The boxes indicate the recommendation for the condition. The four possible recommendations are a spectrum ranging from condition 1, which favors the use of the pill, to condition 4, which discourages the use of the pill. [Adapted from: US Medical Eligibility Criteria for Contraceptive Use. *MMWR Recomm Rep*. 2010;59:1–86 (3), with permission. © Centers for Disease Control and Prevention.]

[a] If pregnancy or an underlying pathological condition (such as pelvic malignancy) is suspected, it must be evaluated and the category adjusted after evaluation.

[b] The category should be assessed according to the severity of the condition.

OCP = oral contraceptive pill

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OCP (5)

- No OCP is best / preferred
  - *3.2 For women with PCOS, we do not suggest one HC formulation over another (2QQEE).*
  - *3.3. For most women, we do not suggest one oral contraceptive over another as initial therapy, as all oral contraceptives appear to be equally effective for hirsutism, and the risk of side effects is low. (2 \|OO)*
- Some are reportedly more androgenic
  - Least androgenic: Lolo, Tricira Lo, Tricyclen Lo
- Some contain antiandrogens
  - e.g. Diane 35 (cyproterone)

PCOS = polycystic ovarian syndrome; OCP = oral contraceptive pill; HC = hormonal contraceptive

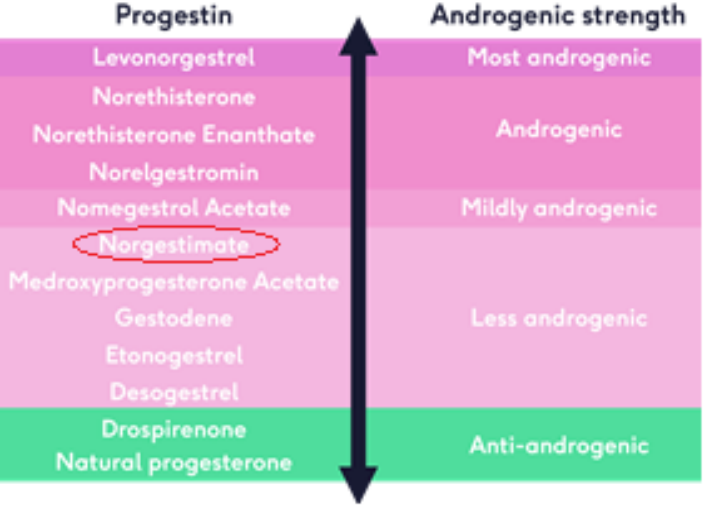
Table 1

Activity of Progestin Agents

Generation	Progestin	Estrogenic	Progestational	Androgenic
First	Norethindrone	++	++	++
	Ethynodiol diacetate	++	+++	+
	Norgestrel	–	+++	+++
	Norethindrone acetate	++	++	++
Second	Levonorgestrel	–	++++	++++
Third	Norgestimate	–	++	++
	Desogestrel	+/–	++++	++
Fourth	Drospirenone	–	+/–	–

+/– indicates low to no activity.
– indicates no activity.
Source: References 3, 8, 18.

Progestin	Androgenic effect
Levonorgestrel	High
Norgestrel	High
Norethindrone	Medium
Norethindrone acetate	Medium
Ethynodiol diacetate	Low
Norgestimate	None
Desogestrel	None
Drosperinone	Antiandrogenic



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Hormones	Product Names	Gonadotrophic Axis Inhibition	Influence on SHBG Level	Intrinsic Androgenic Effect	Antiandrogenic Effect: Block of Androgen Receptor	Antiandrogenic Effect: Inhibition of 5-α-Reductase on Skin
Estrogen						
Ethinyl estradiol	In all combined oral contraceptive	✓	Elevate	None	No	No
Progestins						
Estranes						
Norethindrone	Brevicon, Modicon, Necon, Nelova, Norinyl, Ortho-novum, Ovcon, Jenest, Tri-Norinyl	✓	Reduce (counter estrogen SHBG elevation effect)	Low	No	In vitro +++
Norethindrone acetate	Microgestin Fe, Loestrin, Microgestin, Estrostep Lolo	✓	Reduce (counter estrogen SHBG elevation effect)	Low	No	No data
Ethynodiol diacetate	Demulen, Zovia	✓	Reduce (counter estrogen SHBG elevation effect)	Low	No	No data
Norethynodrel		✓	Reduce (counter estrogen SHBG elevation effect)		No	In vitro ++
Gonanes						
Norgestrel	Lo/Ovral, Low-Ogestrel	✓	Reduce (counter estrogen SHBG elevation effect)	High	No	No data
Levonorgestrel	Alesse, Aviane, Levlite, Levlen, Levora, Logynon ED, Nordette, Tri-Levlen, Triphasil, Trivora, Loette, Microgynon, Monofeme, Nordiol, Seguilar ED, Trifeme, Triphasil, Triquilar	✓	Reduce (counter estrogen SHBG elevation effect)	High	No	In vitro ++
New gonanes						
Desogestrel	Desogen, Ortho-Cept, Mircette, Cyclessa, Marvelon 28	✓	Reduce (counter estrogen SHBG elevation effect)	Medium-low	No	No data
Noregestimate	Ortho-Cyclen, Ortho Tri-Cyclen Tricira Lo TriCyclen Lo	✓	Reduce (counter estrogen SHBG elevation effect)	Very low	No	In vitro +++
Gestodene	Minulet, Tri-Minulet, Trioden, Femoden, Harmonet, Gynera, Minesse	✓	Reduce (counter estrogen SHBG elevation effect)	High	No	In vitro +
Antiandrogenic progestins						
Cyproterone acetate	Brenda-35, Diane-35	✓	No influence	None	+++	+ (In vitro +)
Chlormadinone acetate	Belara, Luteran	✓	No influence	None	+	+
Dienogest	Climodien, Valette	Action is mainly peripheral	No influence	None	++	+
α-Spironolactone						
Drospirenone*	Yasmin	✓	No influence	None	++	No effect

✓=present; SHBG=sex hormone binding globulin; +=low effect; ++=medium effect; +++=high effect; *antimineralocorticoid intrinsic effect: inhibits aldosterone receptor

Source: SKINmed © 2005 Le Jacq Communications, Inc.

OCP (7)

- Review with patients that changes take time
  - Minimum 6 months for cutaneous manifestations
  - Sometimes more than 12 months

- 3.7. For all pharmacologic therapies for hirsutism, we suggest a trial of at least 6 months before making changes in dose, switching to a new medication, or adding medication. (2|OOO)

Key Point # 3 – Summary

If pregnancy is not desired, OCP is the next treatment step after lifestyle intervention.

- Consider patient factors
  - Exclude contraindications
- Any OCP can be used

OCP = oral contraceptive pill

Key Point # 4 – Hyperandrogenism

For a patient using reliable contraception whose hyperandrogenism symptoms are suboptimal after 6 months of OCP, spironolactone is the next step.

OCP = oral contraceptive pill

Antiandrogens (1)

- If not actively pursuing pregnancy
  - OCP can lower androgen levels
    - Yaz/Diane 35: this is an on-label indication for acne
  - Antiandrogens usually 2nd-line

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Table 3. Antiandrogens Used for the Treatment of Hirsutism

Antiandrogens	Dosing
CPA[a]	50–100 mg/d on menstrual cycle days 5–15, with EE 20–35 mg on days 5–25
Spironolactone	100–200 mg/d [given in divided doses (twice daily)]
Finasteride	2.5–5 mg/d
Flutamide[b]	250–500 mg/d (high dose) 62.5 to ≤250 mg/d (low dose)

[a]Not available in the United States; also prescribed as an OC (2 mg CPA + 35 mcg EE).

[b]Flutamide not recommended because of hepatotoxicity.

- *Women with severe hirsutism or contraindications to HC may require other therapies such as antiandrogens (spironolactone, flutamide, finasteride, etc) or mechanical hair removal (laser, electrolysis, etc).*
- *3.5. If patient-important hirsutism remains despite 6 months of monotherapy with an oral contraceptive, we suggest adding an antiandrogen. (2 \|OO)*
- *3.6. We do not suggest one antiandrogen over another (2 \|OO). However, we recommend against the use of flutamide because of its potential hepatotoxicity. (1 \|OO)*

PCOS = polycystic ovarian syndrome; OCP = oral contraceptive pill; HC = hormonal contraceptives

Antiandrogens (2)

- There are some exceptions
  - *3.2. For most women with hirsutism, we suggest against antiandrogen monotherapy as initial therapy (because of the teratogenic potential of these medications) unless these women use adequate contraception (2 |OOO). However, for women who are not sexually active, have undergone permanent sterilization, or who are using long-acting reversible contraception, we suggest using either oral contraceptives or antiandrogens as initial therapy (2 |OOO). The choice between these options depends on patient preferences regarding efficacy, side effects, and cost.*
  - *3.8. In patients with severe hirsutism causing emotional distress and/or in those women who have used oral contraceptives in the past and have not experienced sufficient improvement, we suggest initiating combination therapy with an oral contraceptive and antiandrogen (2 |OO). However, we suggest against combination therapy as a standard first-line approach. (2 |OO)*
  - *In combination with the OCP, antiandrogens should only be considered in PCOS to treat hirsutism…or androgen-related alopecia.*

PCOS = polycystic ovarian syndrome; OCP = oral contraceptive pill

Spironolactone

- Several mechanisms: binds to androgen receptor, inhibits androgen production, inhibits 5-α-reductase
- Dosing: 25mg BID, titrated to 100mg BID
- Contraindications: pregnancy, hyperkalemia,
- Side effects: hyperkalemia, diuresis, orthostasis, menorrhagia, feminization of male fetus
- Monitoring: as per use in hypertension
  - BP, fluid status, electrolytes, creatinine

Cyproterone

- Mechanism: binds to androgen receptor, inhibits 5-α-reductase
- Dosing: 50-100mg on menstrual days 5-15, 20-35mg on days 5-25 (combined estrogen)
- Contraindications: pregnancy, liver disease, VTE, severe depression
- Side effects: worsened depression, menorrhagia, hepatotoxicity, feminization of male fetus
- Monitoring: depression, LFTs, CBC, glucose (T2DM)

LFTs = liver function; VTE = venous thromboembolism

Finasteride

- Mechanism: inhibits 5-α-reductase
- Dosing: 2.5mg, titrated to 5mg
- Contraindications: pregnancy
- Side effects: decreased libido, GI upset, headaches, decreased libido, feminization of male fetus
- Monitoring: none

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Other therapies

- Flutamide: not recommended (hepatotoxicity)
- Vaniqa (topical eflornithine): this is on-label for facial hair
  - Not recommended
- Statins: only if meet usual indications
- OSA therapy: can improve metabolic risk factors
  - E.g. blood pressure, insulin resistance
- Gondaotropin-Releasing Hormone (GnRH): 3rd or 4th-line (OBGYN)

- *3.10 We suggest against the use of statins for treatment of hyperandrogenism and anovulation in PCOS until additional studies demonstrate a favorable risk-benefit ratio (2QQEE). However, we suggest statins in women with PCOS who meet current indications for statin therapy (2QQEE).*
- *3.10. We suggest against using gonadotropin-releasing hormone agonists except in women with severe forms of hyperandrogenemia (such as ovarian hyperthecosis) who have a suboptimal response to oral contraceptives and antiandrogens. (2 ⊕OOO)*
- *3.11. We suggest against the use of topical antiandrogen therapy for hirsutism. (2 ⊕OOO)*

PCOS = polycystic ovarian syndrome; OSA = obstructive sleep apnea

Key Point # 4 – Summary

For a patient using reliable contraception whose hyperandrogenism symptoms are suboptimal after 6 months of OCP, spironolactone is the next step.

- Same monitoring as if used for hypertension
- Other therapies available

OCP = oral contraceptive pill

Key Point # 5 – Fertility

For patients actively pursuing pregnancy, referral to OBGYN or fertility centre is recommended after 12 months without success.

Infertility has many causes

- Other causes of infertility should be excluded
  - Similar to initial workup of PCOS
    - BhCG, FSH, LH, estradiol, TSH, etc.

- *2.2 Women with PCOS are at increased risk of anovulation and infertility; in the absence of anovulation, the risk of infertility is uncertain. We recommend screening ovulatory status using menstrual history in all women with PCOS seeking fertility. Some women with PCOS and a eumenorrheic menstrual history may still experience anovulation and a midluteal serum progesterone may be helpful as an additional screening test (1QQEE).*
- *2.3 We recommend excluding other causes of infertility, beyond anovulation, in couples where a woman has PCOS (1QQEE).*

PCOS = polycystic ovarian syndrome

Induction Overview

- Aromatase inhibition (letrozole): 1st-line
  - *Letrozole should be considered first line pharmacological treatment for ovulation induction in women with PCOS with anovulatory infertility and no other infertility factors to improve ovulation, pregnancy and live birth rates.*
- Clomiphene: 1st-line (no longer available in Canada)
- Gonadotropins: 2nd-line (on-label for amenorrhea/infertility)
- Metformin (prevent ovarian hyperstimulation syndrome)
  - *3.7 We recommend clomiphene citrate (or comparable estrogen modulators such as letrozole) as the first-line treatment of anovulatory infertility in women with PCOS (1QQQE).*
  - *3.8 We suggest the use of metformin as an adjuvant therapy for infertility to prevent ovarina hyperstimulation syndrome in women with PCOS undergoing in vitro fertilization (2QQEE).*
  - *Metformin could be used alone in women with PCOS, with anovulatory infertility and no other infertility factors, to improve ovulation, pregnancy and live birth rates, although women should be informed that there are more effective ovulation induction agents.*

PCOS = polycystic ovarian syndrome

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INTERIM UPDATE
The American College of Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS
2018

human reproduction ESHRE PAGES
2018 Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome†‡

Key Point # 5 – Summary

For patients actively pursuing pregnancy, referral to OBGYN or fertility centre is recommended after 12 months without success.

- May accept sooner if advancing age
- Exclude causes of infertility

Treatment Summary

	Hyper-androgenism	Endometrial hyperplasia	Anovulation	Metabolic syndrome	Contra-ception
↓weight	☑	☑	☑	☑	☒
Metformin	?	☒	☑	☑	
OCP	☑ (acne)*	☑	☑	☑	☑
Anti-androgens					
- Spironolactone	☑			?BP	
- Cyproterone		☒	☒		☒
- Finasteride				☒	
- Vaniqa	☑ (facial)				

*Ethinyl estradiol and drospirenone (Yaz), Ethinyl estradiol and cyproterone (Diane 35)

OCP = oral contraceptive pill

Questions?

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