Cardiovascular Disease Prevention in Patients with Polycystic Ovary Syndrome

Women's Health 2020:
Beyond the Annual Visit

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Financial Disclosure

Dr. Brinton has received:

- Honoraria as **consultant/advisor**: Amarin, Amgen, AstraZeneca, Esperion, Kowa, Medicure, Novartis, Regeneron and Sanofi-Aventis
- Honoraria as **speaker**: Amarin, Amgen, Esperion, Kowa, Medicure, Regeneron and Sanofi-Aventis

Dr. Brinton will discuss the following *off-label* uses:

- For PCOS: metformin, pioglitazone, spironolactone
- For NAFLD treatment (in PCOS): pioglitazone, vitamin D
- For DM2 prevention (in PCOS): pioglitazone, metformin
- For CVD prevention (in PCOS): pioglitazone, metformin

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Learning Objectives

As a result of participation in this event listeners will be enabled to:

- Discuss the major elements of the pathophysiology of polycystic ovary syndrome (PCOS)
- Evaluate those elements which contribute to the excess risk of cardiovascular disease (CVD) in PCOS
- Implement treatments to reduce CVD risk in patients with PCOS

What *is* PCOS?

- (Women of reproductive age, onset adolescence)
- ↑ **Insulin**/insulin resistance, causing
- ↑ **Androgens** (from ↑ovarian production)
- Often associated with
  - Large/numerous ovarian follicles
  - ↓ Menses & ↓fertility
  - Anxiety, depression
  - ↑ Androgenism (acne, hirsutism, male-pattern hair loss)
  - ↑ Central adipos/Met Syndr & DM2 (↓HDL ↑TG/Non-HDL)
  - ↑ ASCVD risk

After [1]Wild RA. *Steroids*. 2012;77:295-9. [2]Fauser BC et al. *Fertil Steril*. 2012;97:28-38.e25. [3]Macut D et al. *Front Horm Res*. 2013;40:51-63. [4]Lim SS et al. *Obes Rev*. 2013;14:95-109.

Criteria for Diagnosis of PCOS

- NIH (1990) – include all of the following
  - Hyperandrogenism and/or hyperandrogenaemia
  - Oligo-ovulation
  - Exclusion of related disorders
- ESHRE/ASRM (Rotterdam 2003) – two of the following
  - Oligo or anovulation
  - Clinical and/or biochemical signs of Hyperandrogenism
  - Polycystic ovaries
- Androgen Excess Society (2006) – include all of the following
  - Hirsutism and/or hyperandrogenaemia
  - Oligo – anovulation and/or polycystic ovaries
  - Exclusion of androgen excess or related disorder

Slide from Dr. Laxmi Shrikhande, Shrikhande Fertility Clinic, Nagpur, India.

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Diagnosis of PCOS

TABLE 1. Diagnostic criteria for PCOS

Criteria	NIH 1990 "classic"	Rotterdam 2003	AE-PCOS
Oligomenorrhea[a]	+	+/−	+/−
Clinical or biochemical hyperandrogenism[b]	+	+/−	+
Polycystic ovaries on ultrasound[c]	+/−	+/−	+/−

NIH, Presence of both oligomenorrhea and clinical/biochemical hyperandrogenism; Rotterdam, any two of the above criteria; AE-PCOS, presence of clinical/biochemical hyperandrogenism and one other criterion.

[a] Eight or less menses per year.

[b] Acne or hirsutism or androgenic alopecia.

[c] Ovarian volume >10 ml and/or >12 follicles less than 9 mm in size in at least one ovary.

AE-PCOS Society Statement. Wild, RA. JCEM 95; 2038 –2049, 2010.

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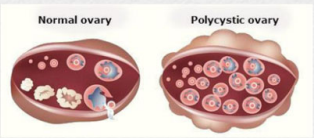
Epidemiology and Diagnosis of PCOS

- Current consensus among most professional societies requires 2 of 3 criteria:
  - Androgen excess
  - Irregular menses/anovulation
  - Polycystic ovarian morphology on ultrasound (AACE/ACE/AES propose 25 or more follicles per ovary)
- 5-20% of all women of reproductive age

Legro et al, 2013.
Slide from 2017 online presentation; Erica B. Johnstone, MD Gynecology and Reproductive Endocrinology, University of Utah

Adolescent PCOS Definition

Oligo-ovulatory androgen access
Polycystic ovarian disease (NIH)



Adolescent diagnosis:

Commonly presented by hirsutism/oligo-menorrhea

•<u>Irregular menses</u>
- At least 2 y beyond menarche
  - Oligomenorrhea- sec. amenorrhea – dysfunctional uterine bleeding
- Completed puberty & primary amenorrhea

- <u>Androgen excess</u>
  - **Clinical**: hirsutism
  - **Biochemical**: high testosterone or Free Androgen Index

Oberfield & Witchel. Horm Res Pedatr, 2017.

Worldwide Clinical Burden of PCOS

- **Prime cause of female subfertility**
- **Association:** *hypertension, cardiovascular, diabetes-T2, insulin resistance, mood disorder, endometrial cancer*
- **Prevalence**: *2016: 112.2 million (NIH) – 186.9 million (Rotterdam) 15-49 y. age cases*
- expected ↑17% in 2016 – 2025
- No EMA/FDA approved therapy for PCOS in adolescent girls

Ibanez, L. Slide Presentation 24 Apr 2018.

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Ethnic Variation

- Consider ethnic variation in PCOS including:
  - Relatively mild phenotypes in Caucasians
  - Higher BMI in Caucasians, especially North America and Australia
  - More server hirsutism in Middle Eastern, Hispanic, and Mediterranean women
  - Increased central adiposity, insulin resistance, diabetes, metabolic risks and acanthosis in South East Asians and Indigenous Australians
  - Lower BMI and milder hirsutism in East Asians
  - Higher BMI and metabolic features in Africa

Slide from Dr. Laxmi Shrikhande, Shrikhande Fertility Clinic, Nagpur, India.

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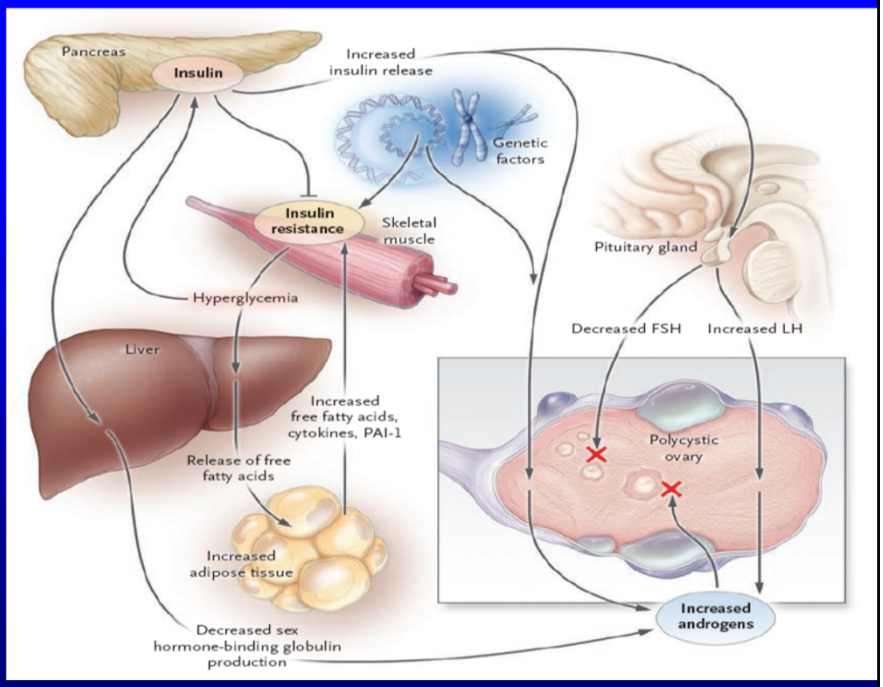
Pathophysiology of PCOS



Nestler, JE. N Engl J Med. 358;1
www.NEJM.org January 3, 2008.

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Elements of PCOS Pathophysiology

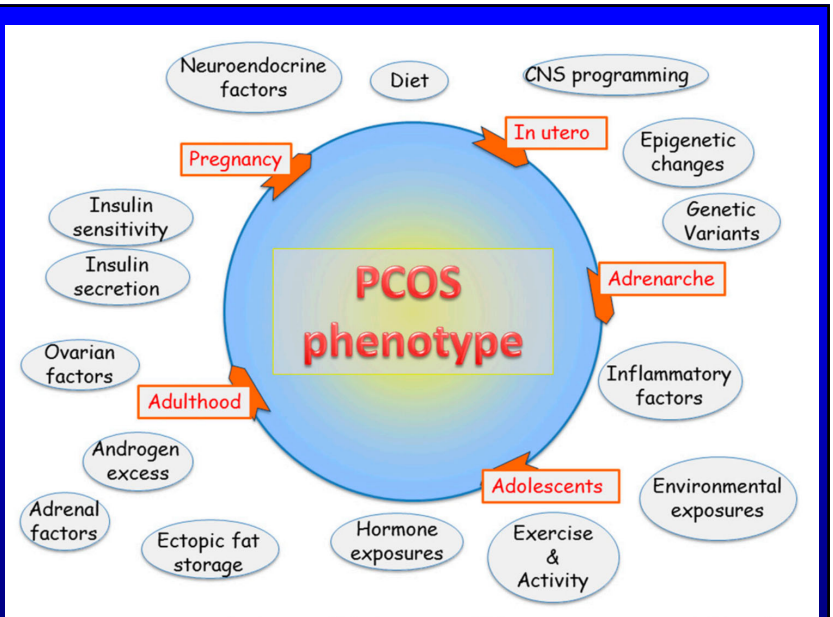

Figure 1. Factors contributing to PCOS phenotype. PCOS encompasses a woman's life cycle. Factors potentially impacting the pathophysiology of PCOS are shown in circles. Not all factors affect each individual. PCOS epitomizes a biologic network of interacting neuroendocrine, hormonal, metabolic, genetic, and environmental influences.

Witchel, SF. J Endo Soc. August 2019
Vol. 3, Iss. 8.

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Pathophysiology

- Ovarian disorder
- Ectopic (hepato-visceral) fat storage & insulin resistance/hyperinsulinemia
- Neuroendocrine alterations: kisspeptin & GABA signaling, GnRH & gonadotropin secretion
- Genetic polymorphisms: *DENND1A*, *FSHB*, *LHCG-R*
- Epigenetics: methylation, miRNAs
- Altered sympathetic nerve activity
- **Multiple interconnected factors**

Horm Res Paediatr 2017

[Tena-Sempere, Witchel, Auchus, García-Rudaz, López-Bermejo & Ong]

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Increased Endogenous-Testosterone Predicts Diabetes Incidence in Women

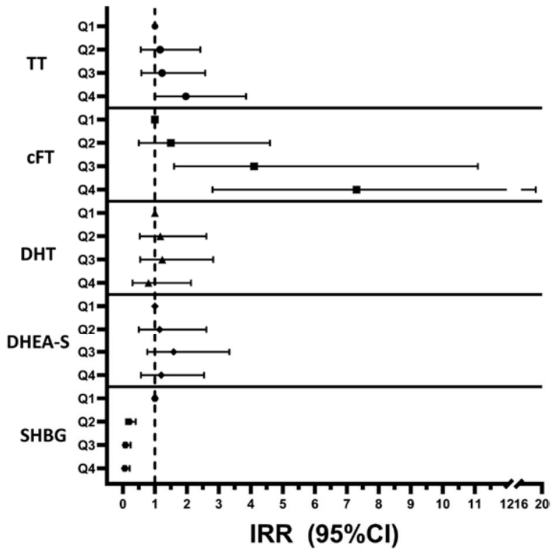

Figure 2. Risk of type 2 diabetes according to quartiles of endogenous androgens, with lowest quartile (Q1) as reference, presented as incidence rate ratios (IRRs) from multivariate Poisson regression models. 95%CI, 95% confidence interval; cFT, calculated free testosterone; DHEA-S, dehydroepiandrosterone-sulfate; DHT, dihydrotestosterone; SHBG, sexual hormone-binding globulin; TT, total testosterone.

Rasmussen, JJ. J Endocr Soc. 2020 May

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Genetics of PCOS

- Heritability ~70% (twin studies)[1]
- 16 genetic loci explain only a small % of heritability[1]
  - Metabolic traits (e.g. GATA4/NEIL2 locus)[1]
    - Fasting insulin, lipid levels,
  - HPO Axis[1]
    - LHCGR, FSHR, and FSHB gene loci (non-coding regions)
  - Epigenetic modifications[1] (methylation and miRNAs) affecting adipose tissue and muscle[1]
- Genetic variability in 5-alpha-reductase gene may set up variability in response to testosterone[2]

1. Witchel, SF. J Endo Soc. August 2019 Vol. 3, Iss. 8.
2. Torchen, LC. JCEM 101; 2069 –2075, 2016.

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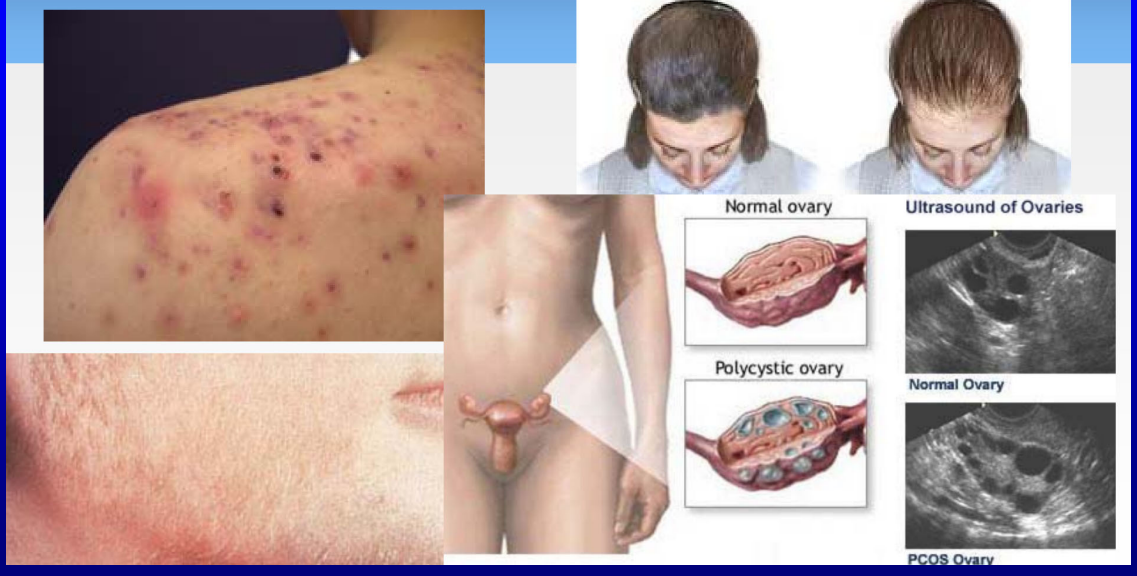
PCOS signs



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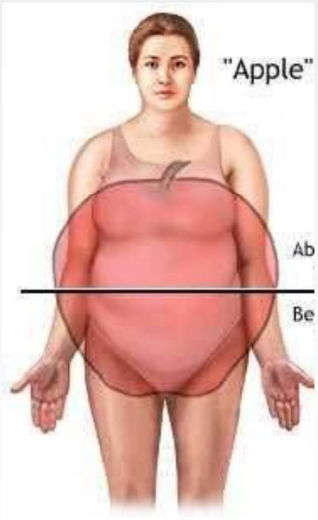
Associated comorbidities

- Obesity (60-80%)
- Type 2 diabetes (7-10%)
- Chronic hypertension
- Metabolic syndrome
- Obstructive sleep apnea



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Diagnoses to *Exclude* in Possible PCOS

- *Hyper*thyroidism or *hypo*thyroidism
- Non-classical Congenital Adrenal Hyperplasia
- ↑ Prolactinemia
- Pregnancy
- Uncommon/Rare causes
  - Androgen-secreting tumor
  - Cushing's syndrome
  - Acromegaly
  - Hypothalamic amenorrhea
  - Primary ovarian insufficiency

Legro, RS. Endoc Soc Statement. J Clin Endocrinol Metab 2013;98(12):4565–4592.

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Evaluation: Hyperandrogenism

- 17-hydroxyprogesterone to rule out non-classic congenital adrenal hyperplasia
  - >200 ng/dl requires ACTH stimulation test
- Free testosterone by equilibrium dialysis is the most sensitive androgen (i.e., highest proportion of women will be positive)

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Evaluation: Obesity and Metabolic Syndrome

- All women with PCOS should be screened for metabolic syndrome (3 of 5, per AHA guidelines):
  - BMI >30 kg/m2
  - Waist circumference >35 inches
  - Blood pressure > 130/85
  - Fasting lipids (HDL <50 mg/dl, triglycerides >150 mg/dl)
  - 2 hour, 75 gram oral glucose tolerance test (fasting glucose >100 mg/dl)

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Evaluation: Depression

- Major depressive disorder is more common in women with PCOS (OR 3.8)
- All women with PCOS should be screened for depression and anxiety
  - Hamilton Depression Rating Scale, Beck Depression Inventory

Mansson, 2008

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Evaluation: Obstructive sleep apnea

- Women with PCOS are:
  - 30 times as likely to have sleep disordered breathing
  - 9 times as likely to have daytime sleepiness, after adjustment for BMI
- Women with symptoms of snoring and/or daytime sleepiness should undergo polysomnography

Vzontgas, 2001

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PCOS as a CVD Risk Factor

- Need PCOS history along with other female-specific CVD risk Hx:
  - PCOS, pregnancy related (pre-eclampsia, gestational DM), early menopause
- CVD risk reduction likely best done by addressing component abnormalities: lipids, hypertension, hyperglycemia, insulin resistance

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LDL-C and Non-HDL Goals in PCOS

TABLE 2. PCOS risk categories and lipid target values[a]

	Risk	LDL target values, mg/dl (mmol/liter)[b]	Non-HDL target values, mg/dl (mmol/liter)[b]
PCOS	At optimal risk	≤130 (3.37)	≤160 (4.14)
PCOS with obesity, hypertension, dyslipidemia, cigarette smoking, IGT, subclinical vascular disease	At risk	≤130 (3.37)	≤160 (4.14)
PCOS with MBS	High risk	≤100 (2.59)	≤130 (3.37)
PCOS with MBS and other risk factors,[c] or with T2DM, or in presence of overt vascular and/or renal disease		≤70 (1.81)	≤100 (2.59)

[a] Values are based on at least 12-h fasting lipid determinations. Predictive utility for CVD events based on nonfasting lipoprotein lipid values has not yet been clearly validated.

[b] To convert mg/dl to mmol/liter, divide by 39.

[c] Odds of CVD increase with number of MBS components and with other risk factors, including smoking, poor diet, physical inactivity, obesity, family history of premature CVD (<55 yr of age in male relative, <65 yr of age in female relative) and subclinical vascular disease.

AE-PCOS Society Statement Wild RA JCEM 2010. 95;2038–2049.

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PCOS Is a "Pleiotropic" Risk Factor for Premature CVD

- Comorbidities often present and possibly causal
  - Oligomenorrhea, anovulatory cycles
  - Hyperandrogenism: hirsutism, male-pattern baldness, acne
  - **Obstructive Sleep Apnea**
  - **Fatty liver (NAFLD)**
  - **Central & visceral obesity,**
  - **Vitamin D deficiency**
  - **Metabolic syndrome, insulin resistance,** acanthosis nigricans
  - **Primary HTG**
  - **Type 2 Diabetes**
- Mild case may mimic *normal* adolescence
- Keep on the "differential diagnosis list" in many settings
- Diagnosis is simple but sometimes difficult
- It has somewhat specific treatments

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↑CVD Risk in Polycystic Ovary Syndrome: In Women <50 y/o

(Danish Cohort)

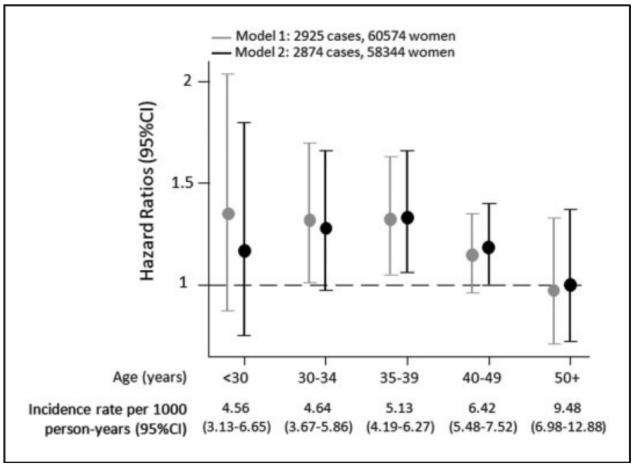

Figure 1. Incidence rates, hazard ratios and 95% confidence intervals (CIs) for the risk of incident cardiovascular disease by polycystic ovary syndrome status in the full cohort, and stratified by age group, Denmark, 1994–2015. Model 1: Age adjusted; Model 2: Age, year of first assisted reproductive technology treatment, baseline parity, gestational diabetes, relationship status, level of education.

Oliver-Williams, C. et al. Eur J Prev Cardiol epub 2020

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PCOS Treatments (CVD-Preventive Highlighted)

- **Diet (↓calories, ↓sat'd fat, ↓sugar, ↑fiber)**
- **Exercise**
- **Weight loss—benefit often with just ~5% wt decrease**
- **Insulin sensitizing/DM2 prevention:**
  - **Metformin*, pioglitazone*,** (↑fertility), others?**
- **Lipid treatment—statins, fibrates, omega-3, niacin?**
- **BP Rx—ACEi, ARB, (*not* thiazide or Beta-block due to ↑DM2)**
- **Obesity Rx—diet, lifestyle, meds? bariatric surgery?**
- Anti-androgens: estrogen, cyproterone, spironol., GNRH analog
- Oral contraceptives (w/ low-androg progest, e.g. norethindrone or drospirenone, esp.good for menstrual irreg & hirsutism)
- Other hormonal Rx: clomiphene (stimulates ovulation)
- Ovarian drilling

After AE-PCOS Society Statement Wild RA JCEM 95; 2038 –2049, 2010.

*Restoration of fertility may necessitate contraception. **Not preferred due to "safety"?—largely *spurious* concern.

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Potential benefits of exercise

- Exercise interventions associated with a 50-60% rate of resumption of ovulation (Harrison et al, 2011)
- Palomba et al (2008) reported a 35% pregnancy rate over the course of a 24 week intervention with exercise for 30 minutes, 3 times per week.
- Mario et al (2016) noted decreased serum androgens, FAI, BMI, and waist circumference in active versus sedentary women with PCOS

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"First-Line" PCOS Medications (Diet & Lifestyle *Always First*)

- Oral Contraceptives
  - Especially good for acne & hirsutism
  - Must select progestin w/ low androgenicity, e.g. norethindrone or drospirenone, but
  - Requires contraception cessation w/ pregnancy
  - May cause thrombosis (DVT, VTE, PE), esp bad w/ prior Hx or in smokers
- Clomiphene
  - Especially for anovulation (direct stimulation of ovulation)
  - Restores fertility (esp. in morbid obesity), but
  - May cause endometrial thinning
  - May cause multiple-fetus pregnancy
- Metformin
  - Especially effective in metabolic syndrome/pre-diabetes
  - Good in BMI <35 down to normal-weight pts
  - Good insulin sensitization & restoration of fertility
  - Potential for CVD risk reduction

Legro, RS Endoc Soc Statement. J Clin Endocrinol Metab 2013; 98 (12) 4565– 4592. Johnson, NP. Metformin for PCOS. Ann Translational Med. 2014 Jun; 2(6);56. Lucidi, RS, PCOS Medications, Medscape, Sep 19, 2019;

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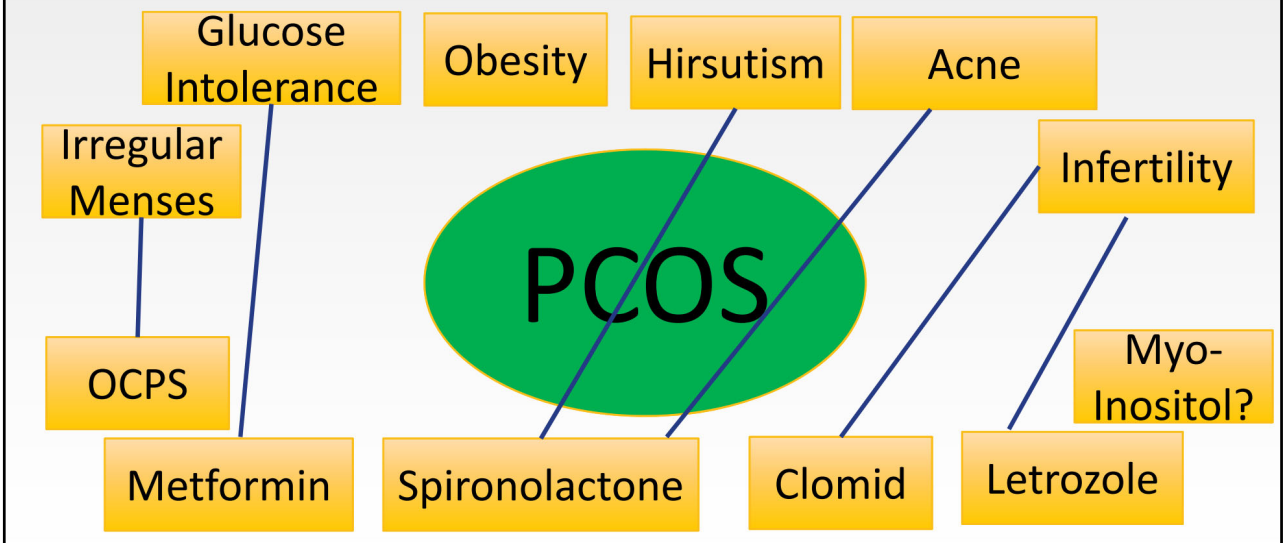
Managing PCOS



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Treating Hirsutism

Local

- Physical (focal) hair removal (laser, electrolysis, plucking)
- Topical creams

Systemic

- Oral contraceptives
- Oral antiandrogens (*must* use contraception)
  - Spironolactone 50 mg bid
  - Finasteride 5-7.5 mg/d

Witchel, SF. J Endo Soc. August 2019 Vol. 3, Iss. 8; and 2017 online presentation; Erica B. Johnstone, MD Gynecology and Reproductive Endocrinology, University of Utah

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Treating Acne

Local

- Antibiotic creams
- Astringent/drying creams (e.g. benzoyl peroxide)
- Topical retinoids

Systemic

- Oral contraceptives
- Oral retinoids (must also have contraception)

Witchel, SF. J Endo Soc. August 2019 Vol. 3, Iss. 8.

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Vitamin D Deficiency vs. NAFLD & Obesity in PCOS

- Patients with NAFLD are usually obese and at high risk for vitamin D deficiency
- Endocrine Society guidelines: screen for vitamin D deficiency if BMI ≥30 mg/m^2, treat if vitamin D <20 ng/mL[1]
- Vitamin D receptor highly expressed in hepatic stellate cells, where it is *antifibrogenic* in preclinical studies
- Vitamin D supplem ↓ALT in women with PCOS (RCT x 3 mos N = 40)[3]

1. Holick. J Clin Endocrinol Metab. 2011;96:1911. 2. Ebrahimpour-Koujan. Trials. 2019;20:153. 3. Javed. Nutrients. 2019;11(1).

Combination Rx for Adolescent PCOS?

Fixed-dose combination of 3 "old" medications*:

- Metformin (850 mg ER): traditional 1st-line, ↑ insulin sensit.
- Pioglitazone (7.5 mg, v. low dose): ↑↑ insulin sensitivity
- Spironolactone (50 mg): weak diuretic & anti-androgen

Prior data show that metformin and pioglitazone are very effective for PCOS, but little work done on spironolactone alone, or any other combination Rx

**Each reduces hepatic fat: Garg, A. Curr Opin Endocrin Diab Obes, 2012; Sivalingham, Hum Reprod Update, 2015; Diaz, Pediatric Diabetes, 2015; Cusi, Ann Int Med, 2016*

Rx of PCOS: Metformin, Pioglitazone & Spironolactone vs. Oral Contraceptives

TABLE 1 Auxological, endocrine-metabolic, body composition, and abdominal fat partitioning assessments in girls with PCOS (n = 51)

	OC[b] (n = 27)			SPIOMET (n = 24)		
	Start[a]	1 y	Δ 0-1 y	Start[a]	1 y	Δ 0-1 y
Auxology						
Age	15.7 ± 0.3	16.7 ± 0.3***		15.8 ± 0.3	16.8 ± 0.3***	
Birth weight Z-score	−0.5 ± 0.2			−0.6 ± 0.2		
BMI, kg/m^2	24 ± 1	25 ± 1**	0.8 ± 0.3	25 ± 1	25 ± 1	−0.04 ± 0.41
BMI Z-score	0.8 ± 0.2	1.1 ± 0.3*	0.2 ± 0.1	1.1 ± 0.2	1.0 ± 0.2	−0.1 ± 0.1
Δ Z-score birth weight–BMI	1.3 ± 0.3			1.7 ± 0.3		
Endocrinology and metabolism						
Testosterone, nmol/L[c]	1.2 ± 0.1	0.7 ± 0.1***	−0.5 ± 0.1	1.3 ± 0.1	0.8 ± 0.1***	−0.4 ± 0.1
SHBG, nmol/L[c]	32 ± 3	58 ± 5***	26 ± 5	31 ± 2	29 ± 2	−2 ± 2******
FAI[c]	4.4 ± 0.4	2.0 ± 0.6**	−2.4 ± 0.7	5.0 ± 0.6	3.2 ± 0.3***	−1.8 ± 0.5
Fasting insulin, pmol/L[d]	86 ± 10	103 ± 12*	17 ± 8	71 ± 9	48 ± 5**	−23 ± 8*****
HOMA-IR[d]	2.6 ± 0.3	3.1 ± 0.4	0.5 ± 0.3	2.1 ± 0.3	1.3 ± 0.1**	−0.8 ± 0.3*****
HDL-cholesterol, nmol/L[c]	1.3 ± 0.0	1.3 ± 0.1	0.0 ± 0.0	1.3 ± 0.1	1.4 ± 0.0*	0.1 ± 0.0****
LDL-cholesterol, nmol/L[c]	2.3 ± 0.1	2.6 ± 0.1**	0.3 ± 0.1	2.3 ± 0.1	2.3 ± 0.1	0.0 ± 0.1****
Triglycerides, nmol/L[c]	0.6 ± 0.0	0.7 ± 0.0*	0.1 ± 0.0	0.7 ± 0.1	0.7 ± 0.0	0.0 ± 0.1
HMW adiponectin, mg/L[d]	7 ± 1	9 ± 2	2 ± 1	5 ± 1	12 ± 2***	7 ± 2****
usCRP, mg/L[d]	1.1 ± 0.2	2.9 ± 0.5***	1.8 ± 0.4	1.7 ± 0.3	0.8 ± 0.2**	−0.9 ± 0.3******

Malpique, R. Pediatric Obesity. 2019;14;e12500.

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Rx of PCOS: Metformin, Pioglitazone & Spironolactone vs. Oral Contraceptives *(continued)*

TABLE 1 Auxological, endocrine-metabolic, body composition, and abdominal fat partitioning assessments in girls with PCOS (n = 51)

	OC[b] (n = 27)			SPIOMET (n = 24)		
	Start[a]	1 y	Δ 0-1 y	Start[a]	1 y	Δ 0-1 y
Abdominal fat (MRI)[f]						
Subcutaneous fat, cm^2	173 ± 20	196 ± 22*	23 ± 10	193 ± 25	196 ± 22	3 ± 14
Visceral fat, cm^2	40 ± 4	43 ± 4	3 ± 3	44 ± 3	35 ± 2*	−9 ± 4****
Hepatic fat, %	17 ± 1	20 ± 1	3 ± 2	18 ± 1	10 ± 1***	−9 ± 1******
Central fat (hepato-visceral fat)	58 ± 4	63 ± 5	5 ± 4	61 ± 4	44 ± 2***	−17 ± 4******

Abbreviations: BMI, body mass index; DXA, dual X-ray absorptiometry; FAI, free androgen index; HDL, high-density lipoprotein; HMW, high-molecular weight; HOMA-IR, homeostasis model assessment insulin resistance; LDL, low-density lipoprotein; MRI, magnetic resonance imaging; OC, oral contraceptive; PCOS, polycystic ovary syndrome; SHBG, sex hormone–binding globulin; SPIOMET, spironolactone, pioglitazone, and metformin; usCRP, ultra-sensitive C-reactive protein.

*$P \leq 0.05$ for within-subgroup changes (Δ) from start.

**$P \leq 0.01$ for within-subgroup changes (Δ) from start.

***$P \leq 0.001$ for within-subgroup changes (Δ) from start.

****$P \leq 0.05$ for between-subgroup changes (Δ) 0-1 year.

*****$P \leq 0.01$ for between-subgroup changes (Δ) 0-1 year.

******$P \leq 0.001$ for between-subgroup changes (Δ) 0-1 year.

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Metformin, Pioglitazone & Spironolactone Reduce Hepatic Fat vs. OC in Adolescent PCOS

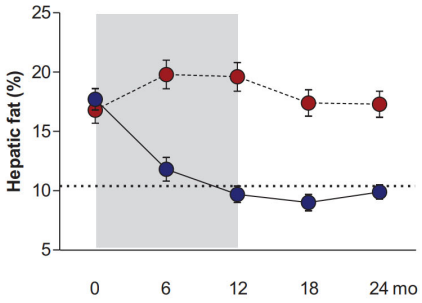

Figure 2. Hepatic fat content (by magnetic resonance imaging) in nonobese adolescent girls with PCOS who were randomized to receive either an oral contraceptive (OC; N = 31; red circles) for 12 months, or a low-dose combination of spironolactone-pioglitazone-metformin (SPIOMET; N = 31; blue circles) for 12 months; subsequently, both subgroups were untreated for 12 months. Body weight did not change in either subgroup. The dotted line indicates the average level in healthy control girls of similar age. Results are expressed as mean ± SEM. $P < 0.0001$ for on-treatment change between subgroups.

Ibanez, L. J Endoc Society, Volume 4, Issue 5, May 2020

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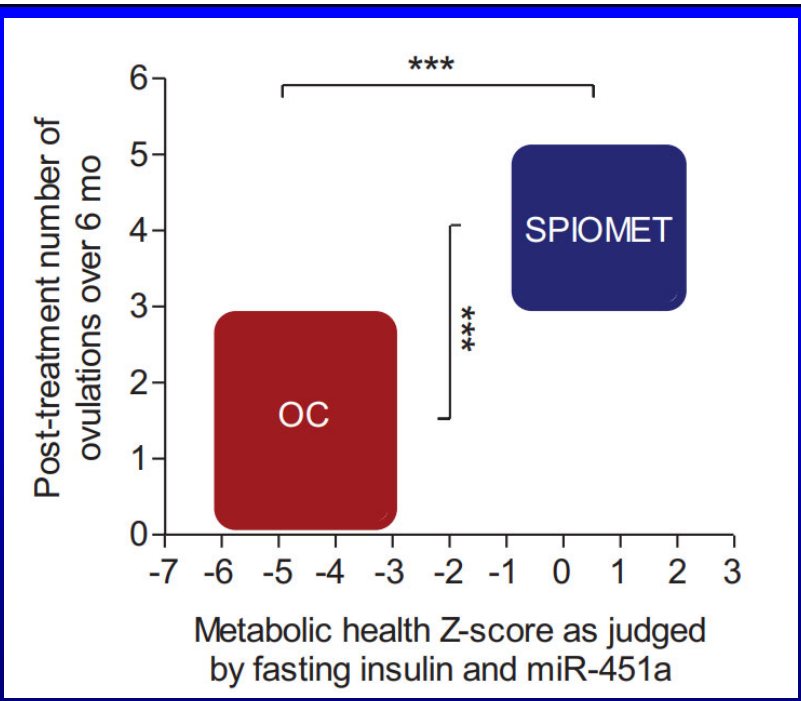
Metformin, Pioglitazone & Spironolactone May Increase Menses Better Than OC (Adolescent PCOS)



Ibanez, L. J Endoc Society, Volume 4, Issue 5, May 2020

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Combination Rx for Adolescent PCOS?

Data are preliminary so main point is *conceptual*
Fixed-dose combination of 3 "old" medications:

- Metformin (850 mg ER): traditional 1st-line, ↑ insulin sensit.
- Pioglitazone (7.5 mg, v. low dose): ↑↑ insulin sensitivity
- Spironolactone (50 mg): weak diuretic & anti-androgen*

(Some evidence for ↓CVD with all 3: pio>metf>spironolactone)
Suggestion: might consider use of these 3 medications separately, allowing individual dose-titration (cost/month ~$4+$11+$9 = ~$24 w/o any pill cutting)

**Spironolactone also blocks two adverse consequences of pioglitazone:*
1. *Osteoporosis in women*
2. *Salt & water retention*

Summary: PCOS & CVD

- PCOS is fairly common (~2-15% of women in reproductive years) but Dx often *missed*
- PCOS usu. requires ***multiple*** treatment approaches—specific to patient's co-morbidities
- ↑ CVD risk, but CVD can be *prevented:*
  - Diet and lifestyle ***always first*** (vit D?)
  - Rx dyslipidemia—statins, fibrates, om-3?—good data
  - Rx HBP—generally *avoid* thiazides & beta-blockers
  - Prevent diabetes in MetSynd/pre-diabetes (pioglit & metf)
  - Rx diabetes (esp w/ pioglitazone & metformin)
  - Detect early ASCVD (>40 y/o: CAC or poss. carotid US)

After AE-PCOS Society Statement Wild RA JCEM 95; 2038 –2049, 2010.