Endocrine Update 2016

Metabolic Management of PCOS: Diet, Weight Loss and Medication Interventions

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Objectives

- Introduction
  - Definition
  - Pathology
  - Evaluation
- Management
  - Diet
  - Exercise
  - Medications

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Introduction

- Polycystic ovary syndrome (PCOS) is the most common endocrine disorder of reproductive-aged women (6-10% of US women affected).
- PCOS has been diagnosed by varied criteria.
- All characteristically include menstrual irregularity, hyperandrogenism (clinical or biochemical) and/or polycystic ovary morphology.
- Management of women with PCOS includes addressing reproductive function, symptoms of hyperandrogenism and metabolic consequences.

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Definition

****All require exclusion of other causes****

	NIH 1990 "Classic"	Rotterdam 2003	AES-PCOS 2006/2014
Oligomenorrehea (≤8 menses/year)	+	+/ -	+/ -
Hyperandrogenism (clinical or biochemical)	+	+/ -	+
Polycystic ovaries by ultrasound (volume >10ml and/or >12/25 follicles < 9mm in one ovary)	15% of hyperandrogenic women with "normal" cycles are anovulatory		+/ -

**Ultrasound: drawbacks
-- Subjective w/reader variability and requires an experienced ultrasonographer and radiologist.
-- Not specific: Polycystic ovaries may be present in up to 25% of normal women.

Wild et al. *J Clin Endocrinol Metab.* 2010. May;95(5):2038-49.

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Pathology

- PCOS is considered to have polygenic explanation and the full pathogenesis is not fully understood.
- Insulin resistance and hyperandrogenism are an important elements in the development of symptoms and comorbidities.
- Obesity is proposed to be an amplifier of pathology and thus worsen symptoms.

Cobin et. al. *Endocr Pract*. 2005; 11:125-134.

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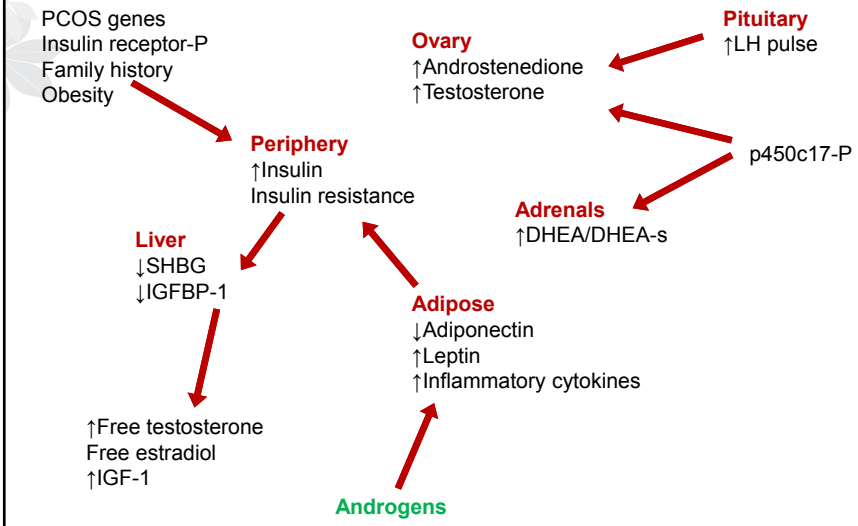

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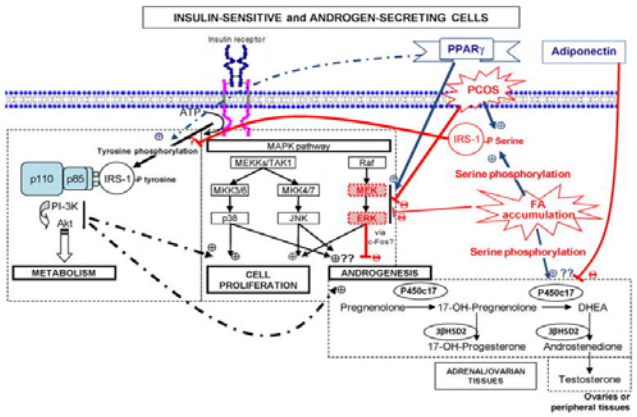

- Insulin receptor has been found to be abnormally phosphorylated resulting in inhibition of its action = insulin resistance.
- P450c17 enzyme has been found to abnormally phosphorylated resulting in increased androgen biosynthesis = hyperandrogenemia.
- Block of MEK/ERK pathways that help reduce androgenesis resulting from insulin stimulation.

Baptiste Cg. *J Steroid Biochem Mol Biol.* 2010 Oct;122(1-3):42-52.

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PCOS genes
Insulin receptor-P
Family history
Obesity

Ovary
↑Androstenedione
↑Testosterone

Pituitary
↑LH pulse

p450c17-P

Periphery
↑Insulin
Insulin resistance

Adrenals
↑DHEA/DHEA-s

Liver
↓SHBG
↓IGFBP-1

Adipose
↓Adiponectin
↑Leptin
↑Inflammatory cytokines

↑Free testosterone
Free estradiol
↑IGF-1

Androgens

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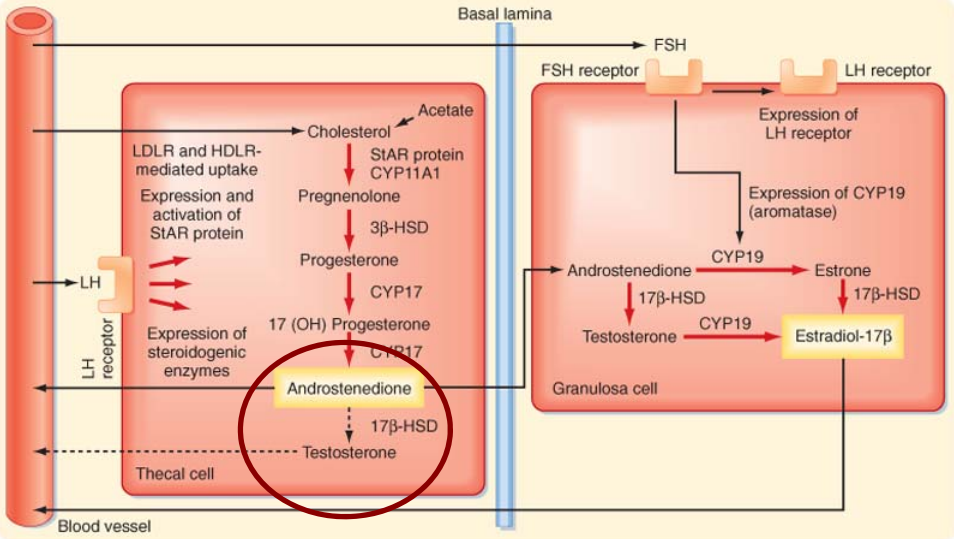

Koeppen & Stanton: Berne and Levy Physiology, 6th Edition.
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PCOS genes
Insulin receptor-P
Family history
Obesity

Ovary
↑Androstenedione
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Pituitary
↑LH pulse

p450c17-P

Periphery
↑Insulin
Insulin resistance

Adrenals
↑DHEA/DHEA-s

Liver
↓SHBG
↓IGFBP-1

Adipose
↓Adiponectin
↑Leptin
↑Inflammatory cytokines

↑Free testosterone
Free estradiol
↑IGF-1

Androgens

Elevated androgens

Insulin resistance

Obesity

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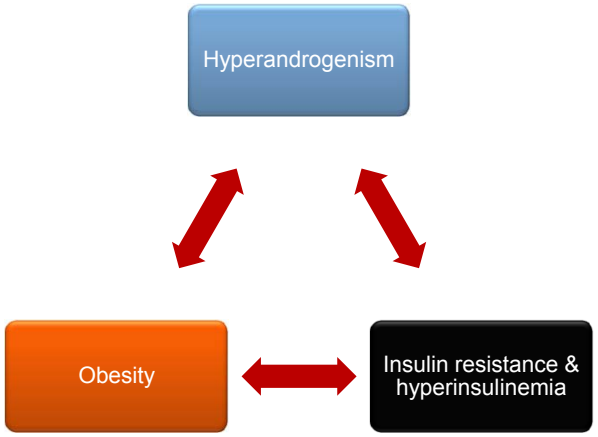
Proposed PCOS-Obesity Cycle



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Evaluation

History	Physical	Laboratory
Pubertal age/sexual development	Vitals (BP, BMI, waist circumference)	Pregnancy test
Menstrual history (menarche, menstrual pattern)	Cutaneous manifestations (acne, hirsutism, acanthosis, skin tags)	Gonadotropins (high LH or LH:FSH ratio >2-2.5)*
Reproductive history	General exam	Prolactin, Thyroid (TSH) Androgens (Testosterone**, DHEA-s) Adrenal steroids (excess cortisol, 17-OHP) AMH (>4.5nl/mL)***
Obesity (onset, progression)	May require pelvic exam (GYN)	Glycemic evaluation: fasting glucose, Hemoglobin A1c, c-peptide/insulin level, 2 hr glucose tolerance
Androgen related symptoms (acne, hirsutism, virilization)		Lipids (low HDL, high trigs, high LDL)
Family history		Hepatic function (fatty liver)
		Renal function (for treatment)

*Only present in 1/3 of PCOS women
**Assay quality is important. Ensure using female reference range.
*** Assay issues.

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Management

- PCOS imparts a significant health care-related economic burden
- Diagnostic evaluation ~ 2%
- Screening for the disorder appears be a cost-effective strategy → earlier diagnosis, intervention → prevention of serious sequelae

	Annual cost in millions of US dollars (% of total)
Initial evaluation	99 (2.3)
Treatment	4271 (97.7)
▪ Menstrual dysfunction/AUB ▪ Infertility ▪ DM type 2 ▪ Hirsutism	1350 (30.9) 533 (12.2) 1766 (40.4) 622 (14.2)
Total cost	4370 (100)

Azziz et al. *J Clin Endocrinol Metab*. 2005; 90:4650–4658.

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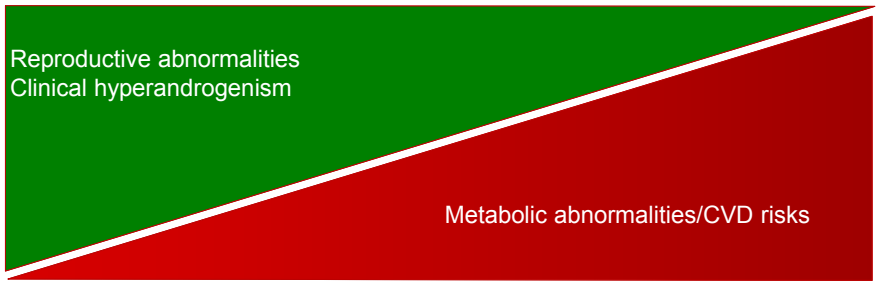
Management

Age related changes in the PCOS phenotype



Adolescence ***Adult fertile age*** ***Menopause/Postmenopause***

Slide adapted from R. Khawaja ppt slide

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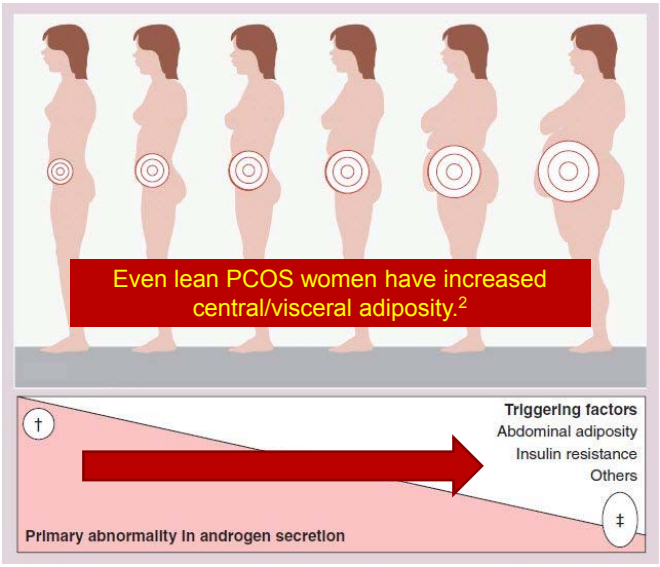
Obesity amplifies symptoms of androgen excess[1]



1. Alpanes M et al. *Expert Rev. Endocrinol. Metab*. 7(1), 91-102. 2012.
2. Pasquali R et al.*Horm Res* 39:179-187. 1993.

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PCOS Management

- Weight loss improves hormone imbalance through improved insulin levels/sensitivity.
  - Decreased P450c17 enzyme activity, reduced leptin.
  - Reduced androgens, increased SHBG, improved ovulation/fertility → unique finding in PCOS women.
- Insulin lowering drugs reduced androgen concentration and improve SHBG levels.
  - Results were positive even without changes in weight.
  - Some data to suggest that obese PCOS women have favorable weight loss.
- Antiandrogens improve IR/HI in all PCOS women.
- OCPs reduce androgen activity and may improve weight/insulin sensitivity in some.

Gambineri et al. *Int J Obes Relat Metab Disord.* 2002 Jul;26(7):883-96.

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PCOS Management

- **Obesity**
  - At least 50% of PCOS women are obese.
  - Obesity is thought to exacerbate PCOS.
  - History of weight gain typically precedes the symptoms of PCOS.
  - There are links between androgen excess, insulin resistance and adipose.

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Lifestyle Modifications

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Weight loss

- Modest weight loss:
- Improved insulin resistance
- Reduced hyperandrogenism
- Reduced ovarian volume and follicular number.
- Reduced miscarriage rates.
- Improved psychological parameters (self-esteem, anxiety, depression scores)

Moran LJ. Et al. *Semin Reprod Med.* 2008;26(1):85-92

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Nutrition

- Nutritionist consultation
  - Reading nutrition labels
  - Portion management
  - Meal planning/dietary requirements
- Diet modifications for a balanced diet

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Dietary intervention studies in PCOS

- Heterogeneous studies for dietary intervention with various forms of calorie restriction, some with meal replacements with range of weight loss results (0 to 15% of body weight) demonstrate:
  - Reduction in androgen levels and/or improvement in SHBG.
  - Improved menstrual regularity/ovulation and pregnancy rates.
  - Reduction in hirsutism.
  - Reduction in insulin levels and insulin resistance parameters.
  - Improved lipid profiles.

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Nutrition

- Behavioral modification to establish lifelong nutritional changes

Suggestions:
Aim at reduction of psychosocial stressors
Identify and correct abnormal eating behaviors (e.g., binge eating) Develop alternative coping strategies for stress, depression, and low self-esteem
Stress the need to develop lifelong healthy eating patterns Discourage undertaking drastic calorie reduction diets Support the patients' optimism regarding weight loss Recommend daily tracking of food intake and physical activity as well as weekly self-weighing
Set goals for weight loss and body weight Modify the patient's environment to reduce stimuli leading to food intake and to enhance behaviors that will support weight management
Increase awareness of perceptions of patient's self and weight

Panidis et al. *Endocrine*. 2013 (44) 583-90.

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Lifestyle Modifications: Exercise

- Promotes reduction in visceral fat and increased muscle metabolism.
- 90 overweight/obese PCOS patients, randomized study → 40 mins supervised exercise for 3 days/week x 3 months[1]
  - Reduction in BMI, WC, Insulin level/IR vs no exercise.
  - No change in androgen levels.

Vigorito C. *J Clin Endocrinol Metab* 92: 1379–1384, 2007

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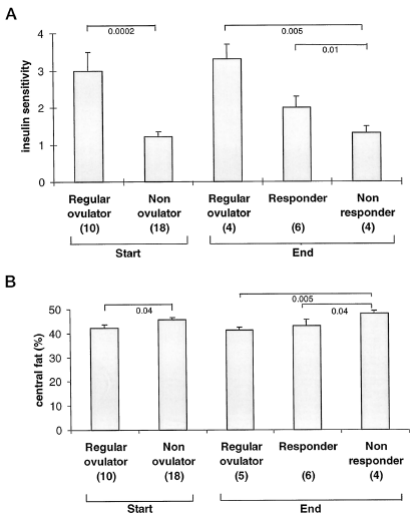
Exercise

- Improvement in menstrual abnormality & ovulation
  - 6-month lifestyle program intervention including diet/ exercise restored normal menstrual cycles in 60% of anovulatory women with PCOS
  - Improved insulin sensitivity in responders vs non-responders even without a significant change in BMI



Huber-Buchholz MM. et al. *J Clin EndocrinolMetab* 84: 1470–1474, 1999.

Exercise

- **Combination aerobic and resistance training:**
- improved insulin resistance greater than aerobic exercise alone
- reduction in visceral fat and increase in lean mass
- improvement in SHBG
- improved basal metabolic rate

Moran LJ. Et al. *Semin Reprod Med.* 2008;26(1):85-92

Exercise intervention studies in PCOS

- Heterogeneous, some randomized with controls, range of weight loss (but often still showed reduction in fat mass or measurements other than weight) demonstrated:
- Improved ovulation, menses, pregnancy rates.
- Improved SHBG levels, +/- changes in androgens
- Improved insulin levels & lipid profiles, lower inflammatory markers.

Moran LJ. et al. *Fertil Steril* 2009;92:1966–82.

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Exercise

Suggestions
Moderate intensity aerobic activity for 30 mins x 5 days/week (brisk walking)
Vigorous intensity aerobic activity for 20 mins x 3 days/week (jogging)
Resistance training on 2 nonconsecutive days/week

Panidis et al. *Endocrine*. 2013 (44) 583-90.

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Diet and Exercise

- 6 month intervention with weekly sessions that included exercise and information on nutrition compared to the “drop out” group.

	Completed (n = 67)	‘Drop-out’ (n = 20)
Change in body mass index (kg/m^2)	−3.7 ± 1.6	−0.4 ± 1.4[a]
Resumed spontaneous ovulation (%)	90	0.0[b]
Pregnancy (%)		
Spontaneous	27	0.0[b]
Treatment	53	0.0[b]
Miscarriages (%)	18	0.0
Total women pregnant (%)[c]	77.6	0.0[b]
Total women with live birth (%)	67	0.0[b]

[a] $P < 0.001$.
[b] $P < 0.001$.
[c] Nine (13%) avoiding treatment.

Clark AM. *Hum Reprod.* 1998 Jun;13(6):1502-5.

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Lifestyle modifications

- Dietary intervention alone: 4 weeks to 15 months in duration, small sample sizes, no true RCT. Improvements in weight loss (5-15%), biochemical hyperandrogenism, menstrual cyclicity, ovulation, fasting insulin and glucose and glucose tolerance.
- Exercise: Improved reproductive and meatbolic features.
- Lifestyle programs (diet/behavioral and/or exercise): improved hyperandrogenism and menstrual function, modest weight loss & weight loss seems to improve pregnancy and miscarriage rate.
- Dietary macronutrient modification: High protein moderate carbohydrate vs HC-MP have similar effects on weight as well as reporoductive and metabolic features. VLC diets reduce weight, insuilin and androgens but no compared to conventional diets.
- Antiobesity pharmacologic agents: sibutramine decreased weight, improved metabolic and reproductive parameters. Less data on other drugs.
- Bariatric surgery: future option for research.

Moran LJ. et al. *Fertil Steril* 2009;92:1966–82.

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Lifestyle modifications

- Lifestyle modification should focus on combining behavioral, dietary and exercise management.
- Calorie reduction diets (500-1000 kcal/day with <30% total calories from fat, <10% from saturated fat, increased consumption of fiber, fruits and vegetables) for a goal of 5-10%weight loss over a 6-12 month period.
- Support from a structured program is likely more beneficial than the dietary composition itself with focus on individualization, follow up and support.
- Exercise is important for successful results with a goal of 30 mins per day.

Moran LJ. et al. *Fertil Steril* 2009;92:1966–82.

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Medications

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Hormonal therapy

- Oral Contraceptives
  - Recommended if menstrual cycle > 3 months to avoid endometrial hyperplasia and cancer [2015 Guidelines].
  - Suppression of ovarian androgen production and increasing SHBG
- Results: regulation of menstrual cycles, improve androgenic symptoms.
  - Effective in improving hirsutism (60-100% of patients).

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Hormonal therapy

- Oral contraceptives recommended due to more data
  - pass through liver → greater SHBG increase but some data now suggest that some patches can increase SHBG too
- Combination therapy with estrogen and progestin compounds.
- Limited data investigating the efficacy of different formulations, but there currently is no consensus on preferred agents.

Rocca ML. et al. *Expert Opin Pharmacother.* 2015 Jun;16(9):1369-93

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Hormonal therapy

- Estrogen
  - Lower doses (20mcg) limit the estrogen related side effects, have some effect on acne but less data for hirsutism. [maybe useful if age > 40]
  - Ethinylestradiol (EE2) 20-35mcg used to suppress HPG axis
  - Etradiol valerate (E2V) has shorter half-life (may have less lipid, glucose effects, decreased VTE/CV risk) – more data needed.

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Hormonal therapy

- Progestin
- Newer progestins have less androgenic effect (vs levonorgestrol) but increased risk of VTE.
- Avoid high androgenic progestin (levonorgestrel)
- Consider thrombogenic impact
- Drospirenone is an AR antagonist and has anti-mineralocorticoid property
  - Doses are small so limit in anti-androgenic effect compared to other OCPs
  - VTE risk higher (vs levonorgestrol)

Rocca ML. et al. *Expert Opin Pharmacother.* 2015 Jun;16(9):1369-93

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Hormonal therapy: Progestins

Generation	Progestin	Estrogenic	Androgenic
1st	Norethindrone Ethynodiol diacetate Norgestrel Norethindrone	++ ++ -- ++	++ + +++ ++
2nd	Levonorgestrel	--	++++
3rd	Norgestimate Desogestrel	-- +/--	++ ++
4th	Drospironone	--	--

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Hormonal therapy – Risk > Benefit (2013)

- Age ≥ 35 year in smoker
- Hypertension (esp if uncontrolled)
- Diabetes with vascular disease
- Dyslipidemia ?

Legro RS et al. *Clin Endocrinol Metab* 98: 4565–4592, 2013.

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Anti-androgen therapy

- Anti-androgens:
  - Block androgen effect via regulating target gene expression (pilosebacious unit, hair follicle).
- Result: Reduction in acne, alopecia and hirsutism.
- Options:
  - Competitive antagonism: **spironolactone**, cyproterone acetate*, flutamide*
  - 5αR inhibition (prevents T → DHT): finasteride 5mg/day, dutasteride

** Not available in the US.*

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Anti-androgen therapy

- Spironolactone
  - Aldosterone antagonist
  - Mildly competes with DHT for androgen receptor
  - Moderate local blocking of 5αR activity
    - T → DHT conversion blocked in skin and hair follicle
  - Competes with androgens for SHBG binding
  - May reduce GnRH → LH (↓ androgen steroidogenesis)
- Dosing: 100-200mg/day divided into 2 doses
  - Monitor for hyperkalemia
  - Avoid dehydration in hotter weather
  - Potential teratogen (male fetus)

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Anti-androgen therapy

Analysis 1.2. Comparison 1 100mg spironolactone versus placebo for hirsutism, Outcome 2 Ferriman-Galwey score.

Review: Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne

Comparison: 1 100mg spironolactone versus placebo for hirsutism

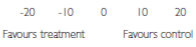
Outcome: 2 Ferriman-Galwey score

Study or subgroup	Spironolactone N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Moghetti 2000	10	10 (3.5)	10	17.2 (5)		100.0 %	-7.20 [-10.98, -3.42]
Total (95% CI)	**10**		**10**			**100.0 %**	**-7.20 [-10.98, -3.42]**

Heterogeneity: not applicable

Test for overall effect: Z = 3.73 (P = 0.00019)

Test for subgroup differences: Not applicable



Brown J et al. *Cochrane Database Syst Rev.* 2009 Apr 15;(2): CD000194

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Anti-androgen therapy

Analysis 1.1. Comparison 1 100mg spironolactone versus placebo for hirsutism, Outcome 1 Subjective improvement in hair growth.

Review: Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne

Comparison: 1 100mg spironolactone versus placebo for hirsutism

Outcome: 1 Subjective improvement in hair growth

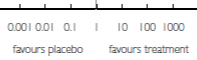
Study or subgroup	100mg oral SPL n/N	placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
McLellan 1989	8/11	3/11		63.1 %	5.67 [1.11, 29.04]
Moghetti 2000	4/10	0/10		36.9 %	10.75 [1.27, 91.00]
Total (95% CI)	**21**	**21**		**100.0 %**	**7.18 [1.96, 26.28]**

Total events: 12 (100mg oral SPL), 3 (placebo)

Heterogeneity: Chi² = 0.22, df = 1 (P = 0.64); I² =0.0%

Test for overall effect: Z = 2.98 (P = 0.0029)

Test for subgroup differences: Not applicable



Brown J et al. *Cochrane Database Syst Rev.* 2009 Apr 15;(2): CD000194

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Insulin sensitizer

- Metformin[1]
  - IGT or DM2 who fail TLC
  - Menstrual irregularity and contraindication/intolerance to OCPs.
- Improved lipid parameters, reduced testosterone, improved LH/FSH ratio, improved glycemic regulation[2]
- Decreased weight and BMI[3]
- Decreased miscarriage, gestational DM, pre-eclampsia, pre-term delivery[4]

1. Legro RS et al. *Clin Endocrinol Metab* 98: 4565–4592, 2013.
2. Al-Nozha O et al. *Pathophysiology* 2013:S0928.
3. Ziaee O et al. *Acta Med Indoes* 2012;44:16-22.
4. Zheng J et al. *J Endocrinol Invest* 2013: April.

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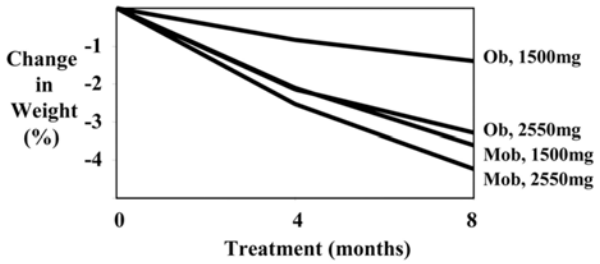
Metformin

- Dose response effect on weight loss in obese PCOS women



- Doubling of menses.
- Decline in leptin.
- Lower TC, LDL-c.
- Some improvement in IR in higher dose.

All patients given same general recommendations about benefits of lifestyle modification through diet and exercise.
No specific intervention or framework was provided.
Limitation: No placebo (researchers stated prior study showed weight loss in a smaller placebo compared trial)

Harborne LR. *J Clin Endocrinol Metab* 90: 4593–4598, 2005.

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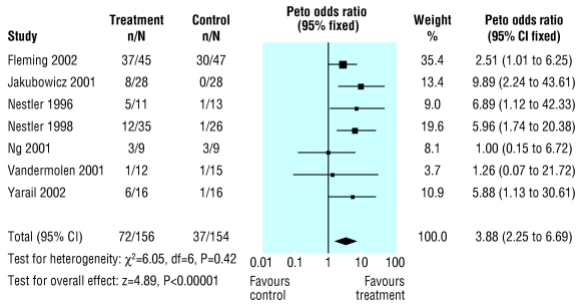
Metformin

- Positive effect of compared with placebo on ovulation

Comparison: Metformin versus placebo or no treatment (clinical outcomes)
Outcome: Ovulation rate



Ovulation response --
→ Metformin vs Placebo: 46% vs 24% (NNT 4.4)

→ Metformin+CC vs CC: 76% vs 42% (NNT 3)

This review did not show significant weight change

Lord JM. *BMJ.* 2003 Oct 25;327(7421):951-3.

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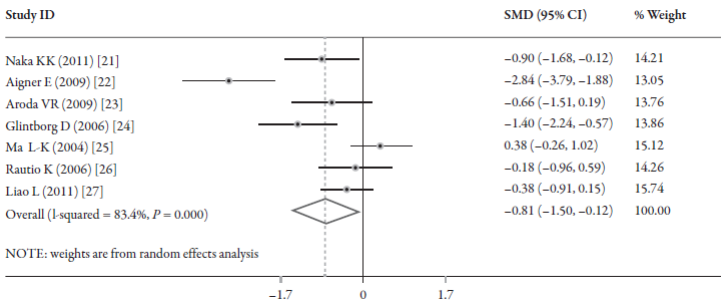
Insulin sensitizer

- Thiazolidinedione (TZD) vs placebo on hyperinsulinemia



- Similar results for fasting glucose
- No significant benefit for hirsutism, androgen levels

Du Q. et al. *Adv Ther.* 2012 Sep;29(9):763-74

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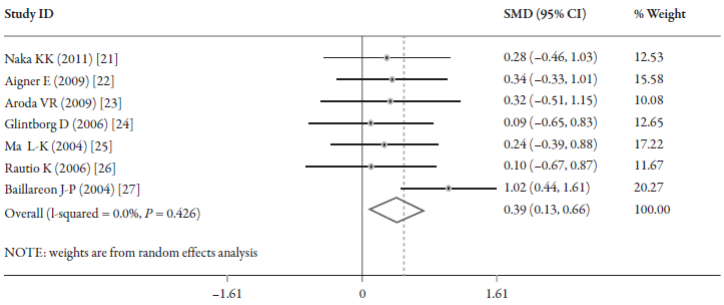
Thiazolidinedione

- TZDs vs placebo - body weight was increased



Du Q. et al. *Adv Ther.* 2012 Sep;29(9):763-74

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Treatment options and effects in PCOS

Treatment	Menstrual regularity	Androgen level	Insulin sensitivity	Hirsutism improved
TLC	↑	↓	↑	No
Hormonal contraceptives	↑	↓	---	Yes
Insulin sensitizers	↑	↓	↑	No
Androgen blockers	↑	↓	No	Yes

Hecht BN. Et al. *Arch Dis Child*. 2015 Nov;100(11):1076-83.

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Treatment	Mechanism of action	Side effects	Notes
Hormonal contraceptives	Inhibits HPG axis → ↓ovarian androgens ↓free T (↑SHBG)	VTE (Factor V Leiden def) Changes in lipids	Avoid high androgenic & thrombognic progestin ~30 mcg EE2 preferred Drospirenone or cyproterone acetate preferred progestins **smokers
Metformin	↑insulin sensitivity	GI, potential risk of lactic acidosis	1500-2500mg/day
TZDs	↑insulin sensitivity	↑ body weight	
Spironolactone	AR antagonist	hyperK, polyuria, teratogen, ↓BP	100-200mg/day
Finasteride	↓5a reductase	teratogen	5-7.5mg/day
Flutamide	AR antagonist	liver, breast pain, teratogen	250-500mg/day
Topical creams	↓hirsutism	skin irritation	long term effect?

Hecht BN. Et al. *Arch Dis Child*. 2015 Nov;100(11):1076-83.
Rocca ML. et al. *Expert Opin Pharmacother.* 2015 Jun;16(9):1369-93

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Fertility management

- Fertility treatments
  - Control/induce ovulation cycles
  - Assist with insemination → IVF
- Management:
  - First line → TLC
  - 2nd line → ovulation induction
    - Clomiphene citrate (+/- metformin)
  - Gonadotropines and aromatase inhibitors (letrozole and anastrozole) for ovulation induction

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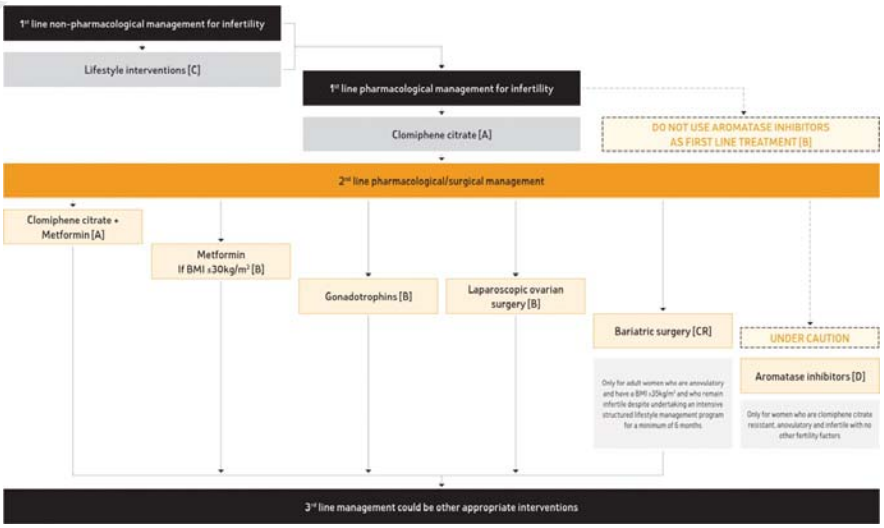
Management of infertility in women with PCOS.



Marie L. Misso et al. Hum. Reprod. Update 2012;18:301-312

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PCOS Medications - Summary

- Dermatologic symptoms
  - 1st line: OCPs
  - 2nd line: anti-androgen (OCPs alone not great at managing alopecia/hirsuitism) → spironolactone
  - 3rd line: Finasteride 5mg/day with OCP.
  - Not recommended (unless other indication): metformin
- Metabolic management (IGT, DM2): metformin.
- Fertility: Clomiphene

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Co-morbidites

- Metabolic syndrome
  - ~40% of PCOS women in US; 2-fold higher than general US population
  - Incidence is 4-5 X higher in PCOS adolescents than controls
- Ovulatory dysfunction and infertility
  - May still have successful pregnancy (fecundity may be delayed)
  - Increased incidence of spontaneous miscarriage
- Obstructive sleep apnea
  - Majority of PCOS women have poor sleep quality; related to insulin resistance
- Depression and other quality of life measures
  - Approximately 50% of PCOS women have elevated depression scores
- Liver disease: NAFLD, NASH.
- Endometrial cancer
  - Related to endometrial hyperplasia.

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Co-morbidites

- Diabetes
  - Impaired glucose tolerance
  - Hyperinsulinemia (insulin resistance, β cell dysfunction)
  - PCOS women are 4-5 X more likely to have diabetes than normal women
  - Both lean and obese women are at risk
- Cardiovascular disease
  - Exact prevalence in PCOS women unknown
  - Related to risk factors: MBS, HTN, lipids, etc.
- Nonalcoholic fatty liver disease (NASH)

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PCOS Management

- Not a cure but ***management*** of symptoms.
- Lifestyle modification: nutrition, diet, exercise, weight loss through calorie restricted diet.
- Medical management (medications, bariatric surgery?), including reduction of other CV risks and comorbidities and screening for mental health issues.

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Resources:

- AACE/ACE and AES-PCOS Society November 2015 Guidelines.
- Endocrine Society PCOS 2013 guidelines.
- Treatment of obesity in PCOS position state of Androgen Excess and PCOS Society 2008.

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