Diagnosis and Management of Polycystic Ovary Syndrome

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Disclosures

Beth Lalande, MD has no financial disclosures

Objectives

1. Discuss the clinical and biochemical features of Polycystic Ovary Syndrome (PCOS).
2. Discuss the pathophysiology of PCOS.
3. Review the diagnosis of PCOS
4. Discuss the individualized management of PCOS

Polycystic Ovary Syndrome (PCOS)

- PCOS is a syndrome of ovarian dysfunction affecting 9-18% of reproductive age women worldwide. The most common endocrine abnormality of women of reproductive age
- Clinical manifestations include:
  - **chronic anovulation** (menstrual irregularity and/or PCO morphology on imaging) and
  - **hyperandrogenism** (hirsutism, acne, alopecia)
- The *syndrome* is defined by a clustering of signs and features, where no single test is diagnostic
- PCOS is associated with an increased risk of diabetes and other metabolic abnormalities which may potentially increase the risk of coronary artery disease.

Delayed Diagnosis and a Lack of Information Associated with Dissatisfaction in Women With PCOS

Cross-sectional study using online questionnaire of 1385 women in North America (53%) and Europe (42.2%) 64.8% age 18-35

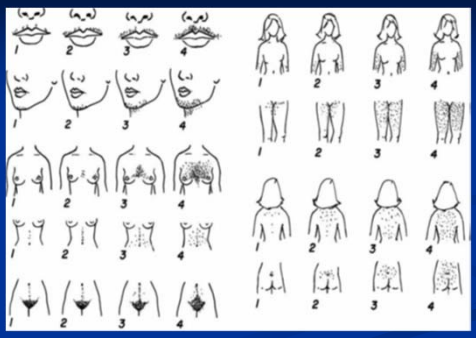
- *33.6*% reported > 2yrs before a diagnosis
- 47.1% reported seeing $\geq$ 3 health care professionals before dx
- 35.2% satisfied with diagnostic experience
- 15.6% satisfied with information received
- Most common concerns: difficulty losing weight (53.6%), irregular menstrual cycle (50.8%) and infertility (44.5%)

Gibson-Helm et al JCEM 2017;102(2):604

Clinical Manifestations of PCOS Hyperandrogenism

- Hirsutism (coarse, dark, terminal hairs in male pattern)
- Acne
- Alopecia (hair loss)--generalized, temporal, frontal

Ferriman-Gallwey Hirsutism Scoring System



JCEM 2008; 93(4):1105–1120

Clinical Manifestations of PCOS Hyperandrogenism

- Hirsutism (coarse, dark, terminal hairs in male pattern)
- Acne
- Alopecia (hair loss)--generalized, temporal, frontal
- Virilization not common--deepening of the voice, increased muscle mass, and clitoromegaly may occur but more suggestive of a virilizing (androgen secreting) tumor
- Chronic presentation, often with peripubertal onset

Differential Diagnosis of Hyperandrogenism

Etiology	Approx % of All Hyperandrogenic Patients
PCOS	85-90%
Idiopathic hirsutism	2-5%
HAIRAN syndrome	1-3%
21-OH deficient NCAH	1-10%
Ovarian Androgen Secreting Neoplasms	1/330-1/1,000
Iatrogenic/drug-related	rare
Adrenal Androgen Secreting Neoplasms	Very rare

Azziz et al JCEM 2004;89(2):347

Clinical Manifestations of PCOS Anovulation

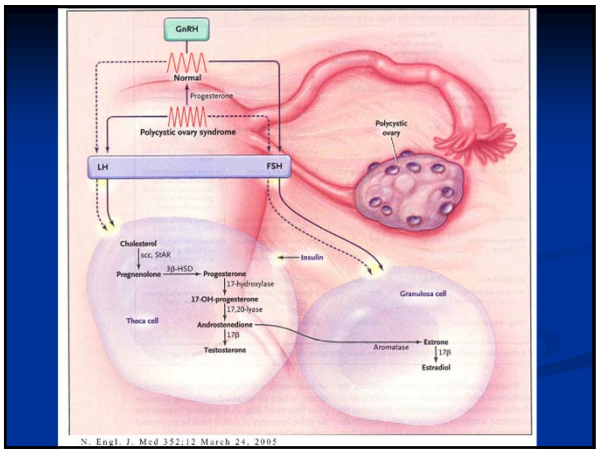
- Primary amenorrhea (lack of menarche by age 15) or secondary amenorrhea (>90 days without a period)
- Oligomenorrhea (>35 days between periods
- Polymenorrhea (bleeding at intervals of less than 25 days) **(1.5%)**
- Normal menstrual cyclicity does not necessarily signify ovulatory cycles. (20-30% of women with regular menses have oligo-anovulation)
  - Of women with regular cycles and no hirsutism, 95% are ovulatory
  - If regular cycles and hirsutism, 60% are ovulatory

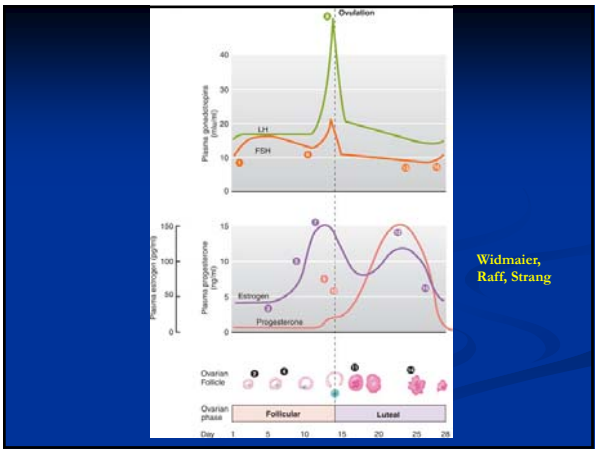
Other Clinical Manifestations of PCOS

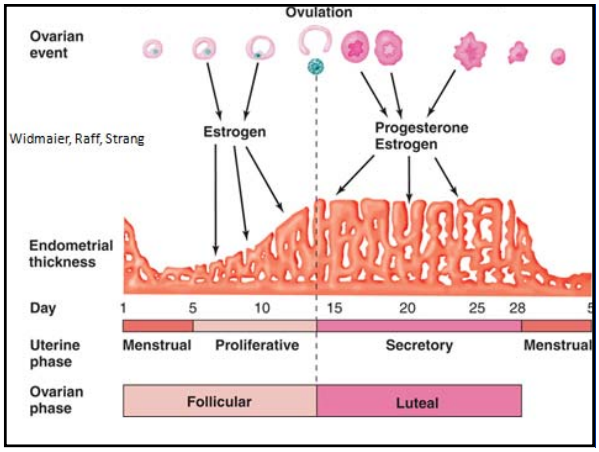
- Physical Manifestations of Insulin Resistance
  - Acanthosis nigricans
  - Skin tags
- Dyslipidemia
- NASH Nonalcoholic Steatohepatitis (fatty liver)
- Obesity
  - Approximately 50% of women with PCOS are obese
  - Obesity is often the initial complaint

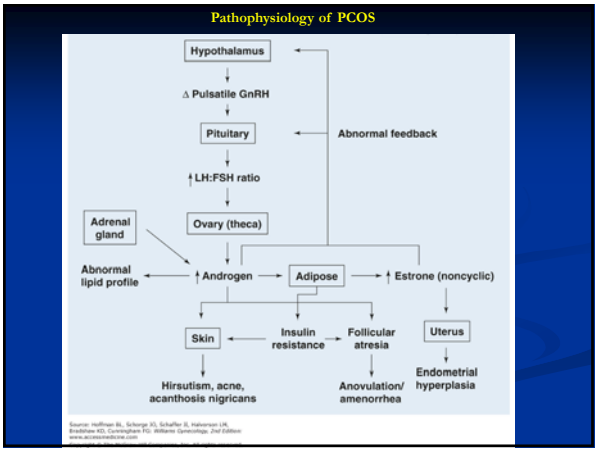
Pathophysiology of PCOS

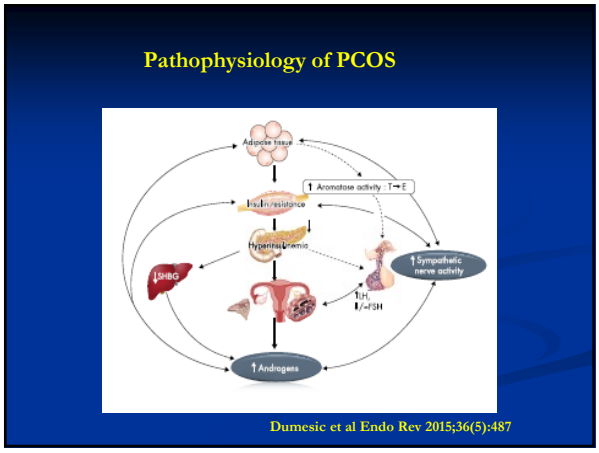
- Complex disorder and poorly understood
- Gonadotropin secretion disturbance
- Steroidogenesis disorder
- Insulin resistance

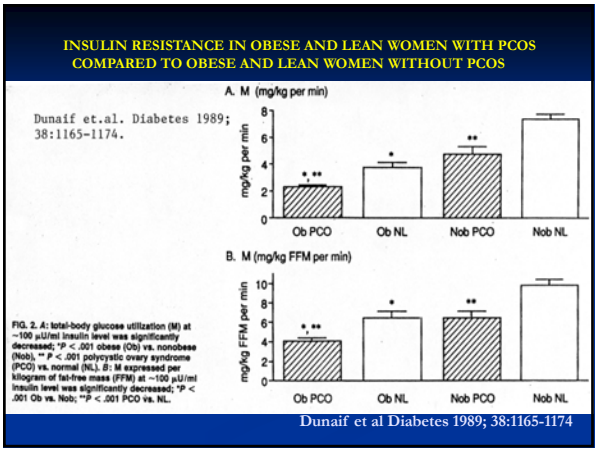

GnRH
Normal
Progesterone
Polycystic ovary syndrome
Polycystic ovary
LH
FSH
Cholesterol
scc, StAR
Pregnenolone
3β-HSD
Progesterone
17-hydroxylase
17-OH-progesterone
17,20-lyase
Androstenedione
17β
Testosterone
Insulin
Granulosa cell
Theca cell
Aromatase
Estrone
17β
Estradiol
N. Engl. J. Med 352;12 March 24, 2005


Ovulation
LH
FSH
Estrogen
Progesterone
Ovarian Follicle
Follicular
Luteal
Widmaier, Raff, Strang


Ovulation
Ovarian event
Widmaier, Raff, Strang
Estrogen
Progesterone
Estrogen
Endometrial thickness
Day
1
5
10
15
20
25
28
Uterine phase
Menstrual
Proliferative
Secretory
Menstrual
Ovarian phase
Follicular
Luteal


Pathophysiology of PCOS
Hypothalamus
Δ Pulsatile GnRH
Pituitary
Abnormal feedback
↑LH:FSH ratio
Adrenal gland
Ovary (theca)
Abnormal lipid profile
↑ Androgen
Adipose
↑ Estrone (noncyclic)
Skin
Insulin resistance
Follicular atresia
Uterus
Hirsutism, acne, acanthosis nigricans
Anovulation/ amenorrhea
Endometrial hyperplasia


Pathophysiology of PCOS
Adipose tissue
↑ Aromatase activity ↑T→E
Insulin resistance
Hyperinsulinemia
↓SHBG
↑ Sympathetic nerve activity
↑LH, ↑/→FSH
↑ Androgens
Dumesic et al Endo Rev 2015;36(5):487


INSULIN RESISTANCE IN OBESE AND LEAN WOMEN WITH PCOS COMPARED TO OBESE AND LEAN WOMEN WITHOUT PCOS
Dunaif et.al. Diabetes 1989; 38:1165-1174.
A. M (mg/kg per min)
mg/kg per min
Ob PCO
Ob NL
Nob PCO
Nob NL
B. M (mg/kg FFM per min)
mg/kg FFM per min
Ob PCO
Ob NL
Nob PCO
Nob NL
Dunaif et al Diabetes 1989; 38:1165-1174

Diagnostic Criteria for PCOS
2003 Rotterdam Consensus

at least 2 of the 3:

- Oligo- or anovulation
- Clinical and/or biochemical signs of hyperandrogenism
- Polycystic ovaries on imaging

And

- Absence of secondary causes (CAH, androgen-secreting tumors, Cushing's syndrome)

Diagnosis of PCOS

- Diagnosis of PCOS is suspected by history and clinical suspicion
- Biochemical evaluation is for excluding less common causes of hirsutism and menstrual irregularities (CAH, thyroid disease, hyperprolactinemia, androgen secreting tumors and hypercortisolism) and detecting hyperandrogenemia in the absence of clinical hyperandrogenism (HA)
- Tests for insulin resistance are not required to make a diagnosis of PCOS
- Pelvic ultrasound is not required for diagnosis

Diagnosis of PCOS in Adolescents

- Diagnosis of PCOS in adolescent girls based on clinical and /or biochemical hyperandrogenism (after exclusion of other pathologies) in the presence of persistent oligomenorrhea
- Anovulatory symptoms and PCO morphology are not sufficient to make a dx in adolescents, as they may be evident in normal stages in reproductive maturation.

Biochemical Evaluation of PCOS
Suggested Labs for Diagnostic Evaluation

- Prolactin
- TSH
- 17-hydroxyprogesterone

  Measurement of androgens is not required unless needed for documentation of hyperandrogenemia in the absence of clinical hyperandrogenism or if clinical concern of an androgen secreting tumor
- Total testosterone +/- free testosterone
- DHEA-S
- possible screening for Cushing's syndrome/hypercortisolism with LNSC or 1 mg DST

Biochemical Evaluation of PCOS

- Gonadotropin dynamics are altered in PCOS, but measurement of LH and FSH (LH:FSH ratios) not part of diagnostic criteria
- **Mid luteal phase progesterone** may be needed to determine ovulatory function in a patient who appears to be eumenorrheic.

Labs are frequently normal with a PCOS diagnosis. Labs are primarily obtained to exclude other etiologies of HA and menstrual irregularity, not to "rule-in" PCOS

Ultrasound Criteria for PCOS
2003 Rotterdam Consensus and Endocrine Soc CPG 2013

- Presence of or more follicles in each ovary measuring 2-9 mm in diameter, and/or increased ovarian volume (>10 ml) in the absence of a dominant follicle
- Does not apply to women taking OCPs
- Only one ovary fitting this definition is sufficient for diagnosis of PCO
- If there is evidence of a dominant follicle (>10 ml) or a corpus luteum, repeat scan next cycle

Utility of Ultrasound in PCOS Diagnosis

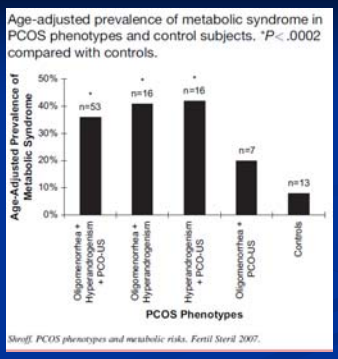
- not required for diagnosis
- most patients with PCOS (>80%) have polycystic ovaries
- 20-25% of women of reproductive age meet U/S criteria of polycystic ovaries
- >70% of women with polycystic ovaries have no clinical abnormality

PCOS Subtypes Allowed by Rotterdam Criteria

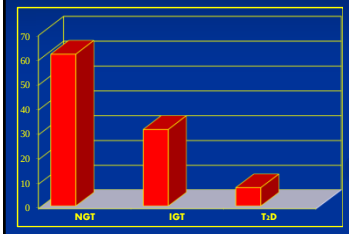
	HA Hyperandrogenism	OA Oligo/anovulation	PCOM PCO morphology	Estimated Proportion of Referred PCOS Pop %,95% CI	Estimated Proportion of Un-selected PCOS Pop %, 95%CI
Classic PCOS "A"	+	+	+	50 (46-54)	19 (13-27)
Classic PCOS "B"	+	+	-	13 (11-17)	25 (15-37)
Ovulatory PCOS "C"	+	-	+	14 (12-16)	34 (25-46)
Non HA PCOS "D"	-	+	+	17 (13-22)	19 (14-25)

Lizneva et al. Fert Ster 2016;08:1121

PCOS Phenotypes and Metabolic Risk



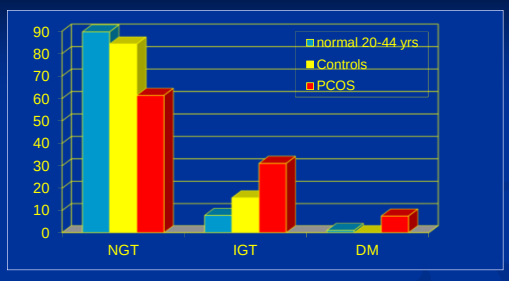
Prevalence of IGT & Type 2 DM in PCOS



- 254 women with PCOS
- age 14-44 yrs.

Legro, R et al. JCEM 1999;84:165

Glucose Tolerance in PCOS



Legro, R et al. JCEM 1999;84:165

Risk of Diabetes in Women with PCOS

- Diagnosis of PCOS confers a 5-10 X increased risk of developing T2DM
- Prevalence of glucose intolerance in U.S. women with PCOS 30-35% and 3-10% had T2DM
- Non obese women with PCOS had 10-15% of IGT and 1-2% prevalence of T2DM
- Limited studies have shown glycohemoglobin is not sensitive to detect IGT

Legro, R et al. JCEM 1999;84:165
Ehrman, D et al. Diabetes Care 1999;22:141

Risk of Diabetes in Women with PCOS

Development and Risk Factors of Type 2 Diabetes in a Nationwide Population of Women With Polycystic Ovary Syndrome

Katrine Hass Rubin, Dorte Glintborg ✉, Mads Nybo, Bo Abrahamsen, Marianne Andersen

The Journal of Clinical Endocrinology & Metabolism, Volume 102, Issue 10, 1 October 2017, Pages 3848–3857, https://doi.org/10.1210/jc.2017-01354

Prospective study in Denmark
Odds ratio of 4 for the development of T2DM and GDM in women with PCOS
Risk adversely affected by higher BMI, lipids, insulin and glucose levels upon PCOS dx

Recommendations for Diabetes Screening in Women with PCOS

Endocrine Society Clinical Practice Guidelines
JCEM 2013;98(12):4565

- OGTT (consisting of a fasting and a 2-hr glucose level using a 75-g oral glucose load) to screen for IGT and T2DM in adolescents and adult women with PCOS
- HbA1c may be considered if a patient is unable or unwilling to complete OGTT
- Rescreening suggested every 3-5 yrs, or more frequently if clinical factors such as central adiposity, weight gain, symptoms of hyperglycemia

BMI With Age in PCOS

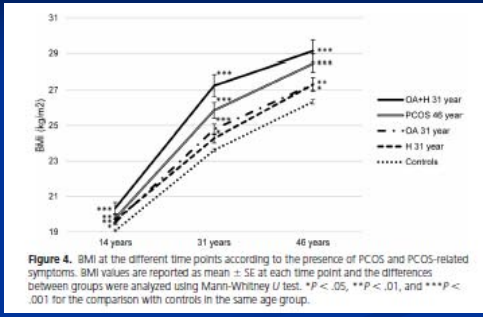


Figure 4. BMI at the different time points according to the presence of PCOS and PCOS-related symptoms. BMI values are reported as mean ± SE at each time point and the differences between groups were analyzed using Mann-Whitney *U* test. **P* < .05, ***P* < .01, and ****P* < .001 for the comparison with controls in the same age group.

Ollila et al JCEM 2016 101 739

BMI With Age in PCOS

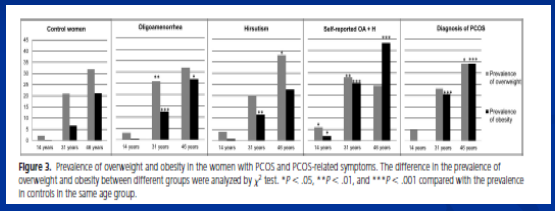


Figure 3. Prevalence of overweight and obesity in the women with PCOS and PCOS-related symptoms. The difference in the prevalence of overweight and obesity between different groups were analyzed by χ^2 test. **P* < .05, ***P* < .01, and ****P* < .001 compared with the prevalence in controls in the same age group.

Ollila et al JCEM 2016;101:739

Similarities of PCOS and Metabolic Syndrome Related to Insulin Resistance

- Central obesity
- Hyperinsulinemia
- Low SHBG
- Abnormal lipids (elevated TG, low HDL)
- Higher prevalence of IGT and diabetes.
- Increased risk of non alcoholic steatohepatitis (fatty liver)
- Increased risk of obstructive sleep apnea

INDIVIDUALIZED Management of PCOS

Treat presenting complaint
Think about long-term consequences

- **Treatment of symptoms of anovulation**

-regulate menses
-induce ovulation
-endometrial cancer risk reduction

- **Treatment of symptoms of hyperandrogenism**
- **Treatment of obesity and metabolic disorders**

-Obesity management
-Diabetes screening and prevention
-Lipid management and cardiovascular disease risk reduction
-Sleep apnea screening

- **Screening and treatment for anxiety/depression**

Treatment of Menstrual Irregularity in PCOS

- If overweight or obese: calorie-restricted diet, exercise, weight loss
- Hormonal contraceptives
- Cyclic or continuous oral progesterone
- Progestin-eluting IUDs

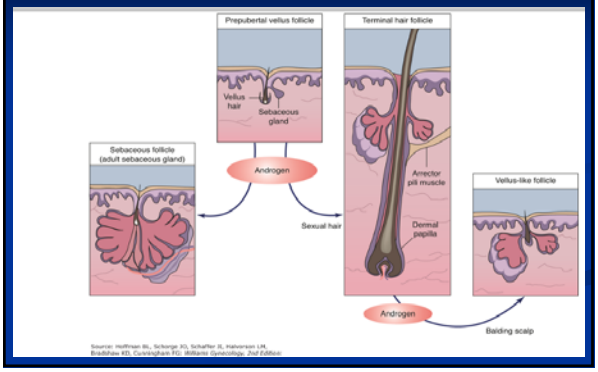
Treatment of Hyperandrogenism in PCOS: OCPs

- Suppress ovarian androgen secretion by suppression of gonadotropins
- Increase SHBG
- Decrease free testosterone and free androgen index
- Improve hirsutism
- Regulate menses and provide adequate progestin for endometrial protection

Treatment of Hyperandrogenism in PCOS: spironolactone

- Competitive inhibitor of androgen receptor
- Improves hirsutism, acne and alopecia
- Does not inhibit androgen secretion
- Requires reliable contraception
- 3-4 months before clinical response is evident

Pilosebaceous Unit



Treatment of Obesity in PCOS

Obesity exacerbates hyperandrogenism, ovulatory dysfunction and metabolic risk in PCOS

- Lifestyle therapy including a calorie restricted diet and regular exercise
- Medications FDA approved for obesity treatment
- Bariatric surgery (BMI >40 and >35 with comorbidities)

Weight loss has beneficial effects on reproductive and metabolic dysfunction

PCOS Diet

- 12 week study of high protein 30% and low carb 40% vs. low protein 15% and high carb 55%
- Equally effective for weight loss, menstrual cyclicity, insulin resistance, dyslipidemia, and abdominal fat
- Extremely low carb diet efficacy?

Moran LJ et al. JCEM 2003;88:812

Obstructive Sleep Apnea

- Women with PCOS develop OSA at equal or higher rates than men (thought to be a function of hyperandrogenism and obesity.
- After controlling for BMI, women with PCOS were 30 times more likely to have OSA and at lower risk when taking OCPs
  Vgontzas JCEM 2001;86:517
- Women with PCOS had higher apnea-hypopnea index compared with weight matched controls (22.5 ±6 vs 6.7 ± 1.7 P≤.01) *Shahar et al. Am J Respir Crit Care Med 2003*

Screen women with PCOS for symptoms suggestive of OSA and obtain polysomnography to secure a diagnosis

Metformin Therapy in PCOS

- Metformin has historically been used for treatment of PCOS since 1996
- Early trials suggested benefit for weight reduction, decrease in serum androgens, restoration of menstrual cyclicity in PCOS women with oligomenorrhea, and ovulation induction – metformin often used "off -label"

Metformin Therapy in PCOS

- Metformin is advised for women with PCOS who have T2DM or IGT who fail lifestyle modification
  Endocrine Society Clinical Practice Guideline JCEM 2013;98(12)4565
- Target dose 1500-2000 mg/day
- Retrospective data suggests metformin may delay conversion to IGT and diabetes
  Sharma ST et al Endocr Pract 2007;13:373

Metformin and Caloric Restriction

- Metformin 850 mg bid plus 1200-1400 kcal/d diet was superior to low-calorie diet alone in facilitating weight loss in obese women with and without PCOS
  Pasquali R et al JCEM 2000;85:2767
- 2009 meta-analysis of treatment with metformin in women with PCOS showed a significant decrease in BMI vs placebo
  Moran LJ et al Fertil Steril 2009;92:1966
- Metformin-induced weight loss appears to preferentially involve adipose tissue
  Stumvoll M et al NEJM 1995;333:550

Metformin and Ovulatory Function

- Metformin will restore ovulatory function in approximately 50 % of women with PCOS
- Second line therapy but not proven to be endometrial protective
- Met 500 mg tid vs placebo x 6 months
  50% had ovulatory cycles
  Moghetti P et al JCEM 2000;85:139
- Meta-analysis of 13 trials, women treated with metformin had a 4x higher chance of ovulating vs placebo
  Tang T et al. Cochrane Database Syst Rev 2012 CD003053

Metformin and IVF Pretreatment

- Metformin before or during IVF cycles does not appear to improve clinical pregnancy or live-birth rates
- Metformin administration before or during IVF cycles does appear to reduce the risk of ovarian hyperstimulation syndrome
  Tso et al Cochrane Review 2009
  Palomba BJOG 2013
  Palomba Fert Ster 2011

Metformin Therapy in PCOS

From the international evidence-based guideline for the assessment and management of PCOS:

"Metformin in addition to lifestyle, could be recommended in adult women with PCOS, for the treatment of weight, hormonal and metabolic outcomes.

Metformin in addition to lifestyle, should be considered in adult women with PCOS with BMI ≥ 25 kg/m2 for management of weight and metabolic outcomes."

Teede H et al Human Repro 2018;33 1602-1618

Metformin Therapy in PCOS

- NOT advised for treatment of hirsutism, prevention of pregnancy complications, or for the treatment of obesity
- Second line therapy for menstrual irregularity in women who cannot take or are intolerant of hormonal contraceptives

Endocrine Society Clinical Practice Guideline
JCEM 2013;98(12)4565

Metformin Therapy in PCOS


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

Teede H et al Human Repro 2018;33 1602-1618

Treatment of Infertility in PCOS

- Weight loss if overweight
- Clomiphene citrate and aromatase inhibitors recommended as first-line therapy for anovulatory infertility
- 2012 meta-analysis of 38 MET trials 3495 women, MET did not improve live-birth rate, alone or with clomiphene citrate
  Tang T et al Cochrane Rev 2012
- Metformin may be used as adjuvant therapy for infertility to prevent ovarian hyperstimulation syndrome in women with PCOS undergoing IVF

Endocrine Society Clinical Practice Guideline
JCEM 2013;98(12)4565

Psychosocial Issues

Screen for symptoms of depression and anxiety

- Prevalence of depression and anxiety is higher in women with PCOS than in the general population
- Approximately 20% incidence of depression
- 7 fold increased risk of suicide

Dokras Steroids 2012;77:338

Mansson et al Psychoneuroendocrinology 2008;33:1132
Elsenbruch et al JCEM 2003;88:5801

Summary

- PCOS is more than a cosmetic or infertility problem--Many of the women with PCOS have underlying insulin resistance and the same features seen in the metabolic syndrome, including central obesity, increased risk of diabetes, dyslipidemia, OSA, NASH
- Insulin resistance has a key pathogenic role in PCOS (both intrinsic and obesity-related)
- Clinical manifestations include chronic ovulatory dysfunction and hyperandrongenism—hirsutism, acne, and alopecia
- Predominantly a clinical diagnosis. Biochemical evaluation is to exclude other causes of menstrual irregularity and hyperandrogenism, and *not* to "rule in" PCOS. Normal lab evaluation is typical in PCOS patients.
- Several different possible phenotypes that correlate with metabolic risk
- PCOS requires individualized management with consideration of long term consequences – need for screening and management of obesity and metabolic risk factors