Polycystic Ovarian Syndrome (PCOS) - Why is this important?

- It affects between 5% and 10% of all women
- Most common cause of anovulatory infertility
- PCOS strongly associated with Insulin Resistance independent of obesity
- Insulin Resistance puts patients at risk for Type 2 DM, CAD, HTN, and Stroke.

Learning Objectives

- Review diagnostic criteria for PCOS.
- Review evidence supporting metabolic implications such as insulin resistance, dyslipidemia, and hypertension as well as their long term consequences.
- Review treatment options for irregular bleeding, ovulation induction, androgen excess, weight loss, and glucose intolerance.

PCOS Prevalence

- PCOS is the most common endocrine disorder affecting 5–10% of women of reproductive age.
- About 80% of women with history of irregular menses have underlying PCOS.
- Lack of well-defined diagnostic criteria can make identification of patients difficult.

PCOS Diagnosis

- No single confirmatory test for PCOS.
- It is a clinical diagnosis.
- Ovarian cysts are not required for diagnosis.
- Cysts are present on ultrasound in more than 90% of women with PCOS but also present in up to 25% of normal women.

PCOS Diagnostic Criteria

- Earliest definition: Stein Leventhal Syndrome = enlarged ovaries, hirsuitism and oligomenorrhea
- In 1990’s the NIH developed criteria: hyperandrogenism and oligomenorrhea.
- These 2 criteria made PCOS a diagnosis of exclusion, assuming that other causes were ruled out.
PCOS Diagnostic Criteria

Increasing improvement in US technology led to development of the “Rottingham Criteria.”
Diagnosis under this criteria is made if a pt has 2 out of 3:
Hyperandrogenism
Oligomenorrhea
Positive US per ASRM/ESHRE criteria

ASRM/ESHRE Criteria For US

12 or more follicles measuring 2–9 mm in diameter
or
Increased ovarian volume (10 cm³)
Exam assumes if there is a follicle >10 mm the scan should be repeated during a period of ovarian quiescence to calculate ovarian volume

PCOS Diagnosis

Finally: The Androgen Excess Society criteria defined PCOS as simply the presence of hyperandrogenism

PCOS Definition Summary


PCOS Diagnostic Criteria

All criteria focus on: Hyperandrogenism
Either: based on Physical Exam ex: hirsuitism or acne
Or: presence in serum of excess male hormones by lab work
Secondary causes must always be considered in patients with acute onset of symptoms.

PCOS Etiology

Exact etiology of PCOS is still unknown
Is it a Disorder of Gonadotropin Secretion?
PCOS women noted to have elevated LH to FSH levels
Increase in LH production causes increase thecal cell development and androgen production.
Low FSH decreases granulosa cell development and aromatase production with less conversion of excess androgen to estrogen giving rise to the hyperandrogenism.
PCOS Etiology

● Is it a Disorder of the ovaries and the adrenal gland hormone production?
● Both ovaries and adrenal gland in PCOS women over produce androgens leading to the cardinal physical signs
● Defect does seem to have a genetic component and in vitro studies show defect in steroidogenesis is present

PCOS Etiology

● Finally... is it a primary disorder of Insulin Resistance?
● Increased Insulin levels may stimulate gonadotropin production
● IR is linked to both adrenal and ovarian hyperadrogenism
● High Insulin levels decrease sex hormone binding hormone which in turn increases free levels of androgens

PCOS Presentation

● Initial onset in the peri-pubertal years and progressive in nature.
● Sudden onset of these symptoms suggests other differential diagnoses:
  • Cushing’s syndrome
  • Adrenal or ovarian tumor.
● Women with PCOS may have a wide range of clinical symptoms.
  • Menstrual irregularities, hirsuitism, acne, or infertility are the most common reasons for seeking medical care.

PCOS Presentation

● Symptom/Prevalence:
  • Infertility 75%
  • Hyperandrogenism 70% hirsuitism, acne male patterned hair loss
  • Amenorrhea/ Oligomenorrhea 50%
  • Obesity 60–80%
  • Abnormal uterine bleeding 30%
  • Normal menstruation 20%
  • Insulin Resistance 75%

PCOS Presentation

● Symptoms and signs
  • Acanthosis Nigrans
  • Insulin Resistance up to 70%
  • Impaired Glucose Tolerance  up to 40%
  • Type 2 DM 10%

PCOS Presentation

● Acanthosis nigricans is a skin condition that causes dark, thickened and velvety skin in body folds and creases.
● It typically affects the armpits, groin and neck
Differential Diagnosis of PCOS

The differential diagnosis includes other causes of hyperandrogenism:

- Thyroid Dysfunction
- Prolactin excess
- Non classical congenital adrenal hyperplasia
- Cushing syndrome
- Androgen-secreting adrenal or ovarian tumors
- Exogenous androgen use
- Primary Ovarian Failure

Non-virilizing signs/sxs include:

- Hirsutism: course hair growth in androgen-dependent body areas such as sideburn area, chin, upper lip, periareolar area, chest, lower abdominal midline and thigh.
- Acne generally moderate to severe
- Oily skin
- Abnormal menstrual cycles
- Infertility/first trimester miscarriage

Non-virilizing signs/sxs include:

- Clitoromegaly
- Deepening of the voice
- Male pattern balding
- Masculinization of body habitus
- Increased libido

*much less commonly seen than non-virilizing symptoms and if severe indicate other causes of hyperandrogenism

Virilizing signs/sxs include:

- Obesity; waist circumference > 88 cm/ 35 inches
- BMI >30
- Acanthosis Nigrans
- HTN
- History of weight gain, CAD, OSA

PCOS History and Physical

- Signs of Insulin Resistance
- History of weight gain, CAD, OSA

PCOS Endocrine Abnormalities on Laboratory Tests

- Elevated Testosterone levels
- Elevated adrenal production of DHEAS
- Elevated LH:FSH ratio > 2:1
- Insulin resistance with hyperinsulinemia
Screening Tests for PCOS

- ACOG recommends that all women with a suspected diagnosis of PCOS should be screened with
  - 17-hydroxyprogesterone level to R/O late onset CAH (Level C).
- PCOS and late onset CAH are distinguished from each other only by laboratory testing.

Suggested Laboratory Evaluation of PCOS

- Prolactin level: to r/o prolactinoma USUALLY prolactinoma would be associated with galactorrhea and prolactin level of >100 mg/l; mild persistent elevation can be seen in 3 – 7% PCOS
- Testosterone level / total: values may be normal in PCOS; OCP use lowers value and generally pt needs to be off x 3 months for true value. Values in PCOS = or < 150 ng/dl; >200 ng/dl warrants r/o adrenal or ovarian tumor
- Bioavailable/Free testosterone or SHBG + Total testosterone can be drawn as a more accurate reflection of active testosterone levels.
**Suggested Labs**

- **Fasting lipid profile**: HDL < 50 mg/dl and Triglyceride >150 = abnormal
- **Fasting glucose**: >126 mg/dl = DM
  <100 mg/dl nml
  110-125 impaired fasting
- **OGTT 75 gm load**:
  Nml 2 hr glucose = 140mg/dl
  Impaired glucose tolerance 2 hr 140-199
  DM 2 hr .=200

**Congenital Adrenal Hyperplasia (CAH)**

- Late-onset presents in early adulthood.
- Autosomal Recessive.
- Presents with oligomenorrhea and/or hirsutism.
- 90% due to 21-hydroxylase deficiency.
- Patients with 21-hydroxylase deficiency do not form cortisol in normal amounts.
- Diagnostic test is elevated fasting unstimulated 17-hydroxyprogesterone.
  always > 2 ng/mL (200 ng/ dl) .
  - Results affected by OCP use
  - All abnormal tests should be confirmed with ACTH stimulation test. Consider endocrine referral :) .

**Suggested Laboratory to Evaluate PCOS**

- **DHEA-S**: Levels may be slightly elevated in PCOS.

- **LH/FSH** can be drawn to calculate ratio but test is neither sensitive or specific. Levels affected by OCP

- **Pregnancy Test**

- **TSH**

**Lab Tests for SUDDEN onset of Hyperandrogenism**

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total testosterone level</strong></td>
<td>Slightly elevated in PCOS</td>
</tr>
<tr>
<td>Total testosterone &gt; 200 ng/dL</td>
<td>suspicious for adrenal or ovarian tumor</td>
</tr>
<tr>
<td>therefore additional evaluation with pelvic US, CT or MRI indicated</td>
<td></td>
</tr>
</tbody>
</table>

| **Serum DHEAS level**         | Slightly elevated in PCOS                   |
| DHEAS level > 8 ng/ml         | suspicious for adrenal tumor                |
| therefore additional evaluation should include adrenal gland imaging with CT or MRI |

| **24 hour urine cortisol or overnight dexamethasone** | Urine free cortisol >20 ug/d is suggestive of Cushing’s Syndrome |

**Prevalence of Conditions**

- **Adrenal tumors**: 2 per million
- **Cushing’s Syndrome**: 2 per million
- **Androgen secreting ovarian tumors**: < 1 per million

**Intermediate and Long-Term Consequences Associated with PCOS**

- Infertility
- Recurrent spontaneous abortion
- Depression/anxiety
- Dyslipidemias
- Total cholesterol (elevated)
- LDL cholesterol (elevated)
- HDL cholesterol (decreased)
- Triglycerides (elevated)
- Hypertension
- Type 2 diabetes mellitus
- Coronary atherosclerosis
- Cerebrovascular accidents
- Endometrial carcinoma

**NOTE**: Listed in order from most common to least common.
Clinical Syndromes associated with Insulin Resistance

- Type 2 diabetes
- Cardiovascular disease
- Essential hypertension
- Polycystic ovary syndrome
- Non-alcoholic fatty liver disease (NASH)
- Certain forms of cancer - breast, colon, liver, prostate
- Sleep apnea

PCOS Consequences

- Insulin Resistance - up to 75%
  - Evaluate for HTN, OSA, NASH, Metabolic Syndrome, etc.
- Endometrial Hyperplasia
  - Chronic anovulation, obesity and hyperinsulinaemia are associated with endometrial hyperplasia and endometrial cancer.
  - This is likely due to prolonged exposure to unopposed estrogen.
  - Endometrial cancer risk is 3 times that of general population.

PCOS Consequences

- Dyslipidemias
  - 70% of women with PCOS will have abnormal lipid panels.
  - Elevated triglycerides and LDL and low HDL are the most common abnormalities.
  - All women with PCOS should be screened with fasting lipid panel (Level A).
- Obesity
  - 60–80% of women with PCOS are obese.
  - It is predominantly of the android type with increased hip to waist ratio (>0.8).

PCOS Complications

- Impaired Glucose Tolerance / Type 2 Diabetes
  - Up to 40% of women with PCOS have impaired glucose tolerance (IGT).
  - Risk of IGT and Type 2 Diabetes Mellitus (DM) is increased in both obese and non-obese women with PCOS.
  - Retrospective studies have shown 2 to 5 fold increase of type 2 diabetes in women with PCOS.

Treatment - Acne and Hirsuitism

- All combination OCPs effective
- OCPs decrease androgen levels by suppressing LH and stimulating sex hormone binding globulin (SHBG).
- OCPs with low androgenic progestins (norgestimate, desogestrel) may be most effective for acne and hirsuitism (Level B)

Treatment of Hirsuitism

- Mechanical
  - Shaving or depilation
  - Electrolysis (Level A)
  - Laser epilation (Level A)
  - 30–50% reduction at 6 mos after multiple txs
- Combination Oral Contraceptive Pills
  - OCPs with low androgenic progestins most effective
Hirsuitism Treatment

- **Metformin**
  - Reduces hirsuitism after 12 mos tx (Level A)

- **Androgen Receptor Blockers**
  - A full clinical effect may take 6 months or more
  - Spironolactone 25–100mg bid (Level A)
  - Flutamide 250 mg daily x 12 mos (Level A)
  - Cyproterone acetate–ethinylestradiol 50–100mg daily (Level A) (not avail in US)
  - Finasteride 1 mg a day (Level C)

- **Topical**
  - Ornithine Decarboxylase Inhibitor (Vaniqa)
  - 13.9% cream BID (Level C)

- **Combination therapy**
  - OCP + antiandrogen may be most effective (Level C)

Oligomenorrhea/Amenorrhea Treatment

- Weight loss
- OCPs
- Metformin
- Cyclic progesterone
- All treatment options above prevent development of endometrial hyperplasia

Treatment of Oligomenorrhea and Prevention of Endometrial Hyperplasia

**Weight Loss**
- Decreases serum testosterone, insulin, and LH levels
- Cyclic menstruation has been reported with weight loss as little as 5% of initial weight

**Oral Contraceptive Pill**
- Regulates menstrual cycles
  - Associated with a > 50% reduction in endometrial cancer risk in general population, but magnitude of risk reduction in women with PCOS not yet known
  - Use 30–35 mcg of ethinyl estradiol and progestin with little androgenic activity

OCP Benefits for PCOS

- Regular withdrawal bleeding
- Reduction in the risk of endometrial hyperplasia or cancer
- Reduction in LH secretion and consequent reduction of ovarian androgens
- Increased sex hormone binding globulin production and consequent free testosterone reduction
- Improvement in acne and hirsuitism

Cyclic Progesterone

- Type of progestin, dose, and frequency to prevent endometrial cancer in women with PCOS is not known.
- Oral provera 10mg daily for ten days either monthly or every three months recommended.
Treatment of Oligomenorrhea and Prevention of Endometrial Hyperplasia

**Metformin**
- 500mg PO BID–TID
- Restores menstrual cyclicity in 68–95% of patients treated for as short of a time as 4–6 months

Prevention of Endometrial Cancer

- PCOS women who do not want to use medications on a regular basis, ACOG recommends transvaginal US every 6–12 mos
- Women with endometrial thickness of > 10mm should undergo an artificially induced bleed.
- If the endometrium is still thickened on follow-up US, endometrial biopsy is recommended.

PCOS Presentation

- Which of the following is considered first line therapy for infertility associated with PCOS?
  - [ ] Weight loss
  - [ ] Clomiphene citrate
  - [ ] Metformin
  - [ ] All of the above

Treatment of Infertility in PCOS

- All of the above.
- Weight loss should be the mainstay of treatment for all women with PCOS (Level A).
- Clomid, metformin and thiazolidinediones (TZDs) can all improve ovulation and pregnancy rates in PCOS women (Level A).
- In a Cochrane review, metformin was found to be an effective **first line agent to treat anovulation** in PCOS women.
  - *There was a significant reduction in fasting insulin levels, BP, and LDL (Level A).*

Treatment of Infertility in PCOS

**First Line Therapy is Weight loss**
- Changes in body weight have been associated with improved ovulation and pregnancy rates.
- Weight loss as little as 5% of initial weight has shown benefit.

Clomiphene Citrate (Clomid)

- Initiates ovulation by anti-estrogenic effect on hypothalamus, results in increased GnRH release: increased FSH drives the development of ovarian follicles.
- Up to 80% of women with PCOS will ovulate in response to clomiphene and 50% of these women will conceive.
Treatment of Infertility in PCOS

**Metformin**
- Randomized trials using metformin have shown improved ovulatory frequency in women with PCOS (Level A).
- Metformin in doses of 500 mg BID/TID restored menstrual cyclicity in 68–95% of patients treated for four to six months.
- Metformin with clomiphene increases ovulation and pregnancy rates compared to clomiphene alone (Level A).

Second Line Therapy
- **Gonadotropins**
  - Use of low-dose (Level B)
- **Ovarian drilling**
  - Does not improve cumulative ongoing pregnancy rates compared with gonadotropins but is associated with fewer multiple pregnancies (Level A)
  - Miscarriage rates same for gonadotropins and ovarian drilling (Level A)

Rule Out Type 2 Diabetes in PCOS
- The American Diabetes Association recommends screening women with PCOS (high-risk individual) with either a fasting plasma glucose (FPG) or an oral glucose tolerance test (OGTT) by age 30.
- The oral glucose tolerance test (OGTT) is a more sensitive test for diagnosing diabetes in women with PCOS (Level A).
- A prospective study of 254 women with PCOS demonstrated that only 3.2% were diagnosed with diabetes based on a FPG as compared to 7.5% using an OGTT.

**Insulin Resistance Treatment**
- Lifestyle modification
- Weight loss
- Increased physical activity, exercise
- Insulin sensitizer medication (Metformin, TZD).
- Consider other IR syndromes
  - HTN, CVD, Sleep Apnea, NASH, etc.

Summary of PCOS Management

<table>
<thead>
<tr>
<th>Women who desire contraception</th>
<th>Combination OCPs</th>
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<tr>
<td>Treatment</td>
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**Summary of PCOS Management**

<table>
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<th>Women who desire pregnancy/ovulation induction</th>
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**Treatment**

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**Summary of Evidence – Based Recommendations**

**Level A**

(Good and consistent scientific evidence)

- All women with PCOS should be screened for glucose intolerance with a 2 hr glucose tolerance test with a 75 gram challenge.
- All women with PCOS should be screened for dyslipidemia with a fasting lipid panel.
- Insulin-sensitizing drugs are effective in improving clinical and biochemical features of PCOS.
- Laser treatment is effective for facial hirsuitism caused by PCOS.
- Spironolactone in combination with OCPs are effective in reducing hirsuitism and/or acne.

**Level B**

(Limited or inconsistent scientific evidence)

- OCPs containing desogestrel or norgestrel significantly improve acne and hirsuitism.
- Improvements in insulin sensitivity, by weight loss or by the use of insulin-sensitizing agents, may favorably improve many risk factors for diabetes and cardiovascular disease in women with PCOS.
- When using gonadotropins to induce ovulation, low-dose therapy is recommended because it offers a high rate of monofollicular development and significantly lower risk of ovarian hyperstimulation in women with PCOS.
- The benefit and role of surgical therapy (ovarian drilling) in ovulation induction in women with PCOS is now proven and causes fewer multiple gestations.

**Level C**

(Primarily on consensus/ expert opinion)

- Although vaniqua cream has been effective in treating facial hirsuitism in women, additional benefits or risks for women with PCOS are unknown.
- All women with a suspected diagnosis of PCOS should be screened for hypothyroidism.
- Combining medical interventions may be the most effective way to treat hirsuitism. Combined therapy with an ovarian suppression agent and an antiandrogen appears effective in treating hirsuitism in women with PCOS. The best pill or antiandrogen is unknown.
- The optimal progestin, duration, and frequency of treatment to prevent endometrial cancer in women with PCOS is unknown.
- The effects of insulin-sensitizing agents on early pregnancy are unknown: metformin appears safe, but any additional effect at reducing pregnancy loss is uncertain.
- The best or initial treatment for hirsuitism, ovulation induction, or prevention of long-term metabolic sequelae for women with PCOS is unknown. All of these conditions may benefit from lifestyle modification as initial treatment.
References

- American Academy of Family Physicians: www.aafp.org
- Polycystic Ovarian Syndrome: www.pcosupport.org
- American Infertility Association: www.americaninfertility.org