Polycystic Ovarian Syndrome

Background

1. Definitions

   o Polycystic ovarian syndrome (PCOS)
     ▪ Classic description
       • Amenorrhea, hirsutism, obesity, infertility, and bilaterally enlarged polycystic ovaries - representative of advanced cases
       • First presented by Stein and Leventhal in 1935

   o 1990 National Institute of Child Health and Human Disease (NICHD) proposed diagnostic criteria based on expert consensus
     ▪ All 3 criteria must be met
       • Chronic anovulation or oligo-ovulation, as evidenced by amenorrhea or oligomenorrhea
       • Clinical or biochemical evidence of hyperandrogenism or hyperandrogenemia
       • Exclusion of other causes of menstrual abnormalities and elevated androgens

   o 2003 Rotterdam Criteria (European Society for Human Reproduction and Embryology and the American Society for Reproductive Medicine) recommend that 2 of 3 criteria be present for dx
     ▪ Chronic anovulation or oligo-ovulation, as evidenced by amenorrhea or oligomenorrhea
     ▪ Clinical or biochemical evidence of hyperandrogenism or hyperandrogenemia
     ▪ Polycystic ovaries on ultrasound

   o Polycystic ovaries
     ▪ Total ovarian volume >10 cm$^3$ or presence of ≥12 follicles in one or both ovaries w/each follicle measuring 2-9 mm in diameter

   o Amenorrhea
     ▪ No menses for ≥6 months

   o Oligomenorrhea
     ▪ Menses that occurs at >35 day interval

   o Anovulation
     ▪ Cessation or suppression of ovulation

   o Oligo-ovulation
     ▪ Irregular, infrequent ovulation

   o Hyperandrogenemia
     ▪ Elevated serum levels of androgens
       • In PCOS, mild elevations of testosterone (free and total), androstenedione, and/or DHEA-S

   o Hyperandrogenism
     ▪ Clinically evident excess androgens (acne or hirsutism)

   o Infertility
     ▪ Inability to conceive after random acts of regular intercourse over one year
**Pathophysiology**

1. **Pathology**
   - Exact etiology unknown
   - Key components incl
     - Abnormal gonadotropin secretion
     - Luteinizing hormone (LH) - potentiated androgen production
     - Excess adrenal and ovarian androgens (testosterone, androstenedione)
     - Selective insulin resistance
     - Hyperinsulinemia
   - Complex trait, w/interplay from environmental factors and genetic variations
     - Growth hormone (GH) and insulin-like growth factor -1 (IGF-1) may also potentiate secretion of excess adrenal and ovarian androgens

2. **Prevalence**
   - 6-12% of women of reproductive age
   - Prevalence rates according to wt
     - Underwt 8%
     - Normal wt 10%
     - Overwt 10%
     - Obese 9%
     - Morbidly obese 12%

3. **Risk factors**
   - Obesity
   - Insulin resistance or diabetes
   - Infertility
   - Family hx of PCOS, especially 1st degree relative

4. **Morbidity**
   - Infertility 74%
   - Menstrual irregularities 70%
   - Hyperandrogenism 69%
   - Overwt and obesity >65%
   - Metabolic syndrome 43%
   - Impaired glucose tolerance 30%
   - Type II diabetes mellitus 10%
   - Recurrent spontaneous abortion
   - Gestational diabetes
   - Pregnancy- induced hypertension
   - Depression/anxiety
   - Dyslipidemias
     - Elevated total cholesterol, LDL and triglycerides
     - Decr HDL
   - Hypertension
   - CAD
   - Stroke
   - Endometrial hyperplasia and carcinoma
   - Obstructive sleep apnea
5. Clinical course
   o Normal age of menarche, followed by increasingly irregular menstrual periods, progressing to oligomenorrhea or amenorrhea, w/peripubertal onset
   o Wide spectrum of dz presentation
   o Slowly progressive obesity and signs of hyperandrogenism are characteristic
   o Chronic until menopause, but some comorbidities may persist
   o Wt loss can improve or normalize Sx and lab abnormalities

Diagnostics
History
1. Menstrual irregularities
   o Start around puberty and gradually progress
   o Amenorrhea, oligomenorrhea or DUB are common
   o Some pts have regular menses, but underlying abnormal ovulation
2. Androgen excess
   o Starts around puberty and gradually progresses
   o Hirsutism and/or acne common
3. Medications
   o Exogenous androgens or progestin use
4. Lifestyle factors
   o Gradual wt gain typical
   o Often overwt or obese
5. Infertility
   o Common presenting complaint
6. Family Hx
   o Inquire about diabetes, hypertension, hyperlipidemia, cardiovascular dz, stroke, and endometrial cancer to evaluate risks
   o Family Hx of PCOS common
     ▪ Up to 40% of sisters and 20% of mothers of affected women w/PCOS will also have PCOS

Physical Exam
1. Blood pressure
   o Screen for hypertension
2. Hirsutism
   o Evaluate coarse hair growth in androgen-dependent regions
     ▪ Chin, upper lip, sideburn area, neck, periareolar region, chest, midline lower abdomen, inner thigh
3. Acne
   o Evaluate distribution and severity
4. Obesity
   o Waist to hip ratio >0.85 is abnormal and risk for co-morbid condition
     ▪ Central fat distribution pattern common
   o Body mass index (BMI)
     ▪ >30 obese
     ▪ 25-30 overwt
5. Ovarian enlargement  
   o May be felt on pelvic exam  
6. Acanthosis nigricans  
   o Associated w/insulin resistance  
7. Virilizing signs  
   o Deep voice, male-pattern baldness, masculinized body habitus (↑ muscle development), clitoromegalyurryrrura paths  
   o Virilizing signs rare w/PCOS  
      ▪ If present, consider other causes of hyperandrogenism

**Diagnostic Testing**  
1. Dx of exclusion, no single best test  
2. **Laboratory testing**  
   o Draw early morning fasting  
      ▪ If amenorrhea or oligomenorrhea → labs drawn randomly w/respect to menstrual cycle  
      ▪ In women w/regular menses → labs most accurate between days 5-9 of menstrual cycle  
   o Support dx of PCOS  
      ▪ Free testosterone and/or total testosterone mildly to moderately elevated (most sensitive indicators)  
      ▪ Androstenedione normal to mildly elevated  
      ▪ LH mildly to moderately elevated  
      ▪ FSH normal to mildly elevated  
      ▪ LH to FSH ratio > 3:1  
      ▪ Prolactin normal to mildly elevated  
   o Identification of associated conditions  
      ▪ Fasting lipid panel  
         • To identify hyperlipidemia  
      ▪ 2-hr 75 g OGTT  
         • Identify impaired glucose tolerance or diabetes  
         • Improved sensitivity compared to fasting glucose  
   o Exclude other causes  
      ▪ Amenorrhea/oligomenorrhea  
         • Urine or serum hCG (pregnancy)  
         • Prolactin (hyperprolactinemia, prolactinoma)  
         • TSH (hyper- or hypothyroidism)  
         • FSH (incr in premature ovarian failure)  
         • LH (decr in pituitary adenomas, thyroid disorders, eating disorders, and exposure to exogenous progestational agents)  
      ▪ Hyperandrogenism  
         • 17-hydroxyprogesterone  
            o Evaluate for late-onset congenital adrenal hyperplasia  
            o Random <4 ng/mL normal  
            o Morning fasting <2 ng/mL normal  
            o Basal fasting follicular phase at 8 am >4 ng/mL abnormal, consistent w/possible late-onset CAH
- **DHEA-S**
  - To evaluate for androgen-producing tumor
  - Level >700 mcg/dL abnormal, consistent w/possible androgen-producing tumor
  - Obtain in select pts w/rapidly progressive, virilizing Sx, or w/Sx of recent onset as an adult

- **Total testosterone**
  - >150-200 ng/dL on mean of 3 measurements abnormal, consistent w/possible testosterone-producing tumor
  - Obtain in select pts w/rapidly progressive, virilizing Sx, or w/Sx of recent onset as an adult

- **Dexamethasone suppression test**
  - To evaluate for Cushing's syndrome
  - Dexamethasone 1 mg PO at 11 pm, then obtain serum cortisol level at 8 am following morning
  - Level >5 mcL/dL abnormal, consistent w/possible Cushing's syndrome
  - Obtain in select pts w/rapidly progressive, virilizing Sx, or w/Sx of recent onset as an adult

- **IGF-1**
  - Evaluate for growth hormone
  - Normal levels rule out GH excess

3. **Imaging studies**
   - Ovarian ultrasound
     - Transvaginal approach best
     - Polycystic ovaries present in 90% of women w/PCOS
       - Also present in 25% of women w/o PCOS
     - Finding of polycystic ovaries is non-diagnostic; can support dx of PCOS

4. **Procedures**
   - Endometrial biopsy
     - Evaluate for hyperplasia or malignancy 2° to prolonged unopposed estrogen stimulation
     - Perform if prolonged amenorrhea >5 months, prolonged oligomenorrhea, or DUB

**Diagnostic Criteria**

1. Women of childbearing age w/2 of following
   - Oligo- or anovulatory menstrual irregularities
   - Evidence of hyperandrogenism in absence of 2° cause
   - Enlarged ovaries w/multiple small follicular cysts on transvaginal ultrasound

**Differential Diagnosis**

1. Amenorrhea/anovulation
   - Pregnancy
   - Stress

Polycystic Ovarian Syndrome   Page 5 of 14   1.29.10
o Physical exertion
o Rapid wt changes
o Eating disorders
o Hyperprolactinemia, pituitary adenoma
o Hyperthyroidism
o Hypothyroidism
o Premature ovarian failure
o Progestational medications

2. Hyperandrogenism/hyperandrogenemia
o Adult-onset congenital adrenal hyperplasia
  ▪ 1-8% of hirsute women
o Androgen-secreting virilizing neoplasms
  ▪ Sx rapidly progressive
  ▪ Rare
o Cushing's syndrome
  ▪ Sx rapidly progressive
  ▪ Uncommon
o Acromegaly
o Medications
  ▪ Progestational agents, valproic acid

Therapeutics
Behavior Modification
1. Wt reduction through dietary changes, exercise
   o Initial intervention for all overwt or obese pts
     ▪ Diabetic-type diet favored
   o Decreases testosterone, insulin, lipids, and LH levels
   o Can improve diabetes
   o May decr hirsutism and acne
   o Can restore normal menses and fertility
     ▪ 10-15% wt reduction can result in conception in >75% of obese PCOS pts w/infertility

Pharmacologic
1. Individualize Tx
   o Evaluate pts desire for fertility or contraception
   o Tailor Tx accounting for reproductive issues, Sx control, and long-term health risk reduction
2. Regulation of menses, prevention of endometrial hyperplasia, and reduction of risk for endometrial cancer
   o Low-dose estrogen (ethinyl estradiol) and low-androgenic activity progestin combination OCPs
     ▪ Progestins w/lower androgenicity formulations recommended
     ▪ Norgestimate, norethindrone, desogestrel, or drospirenone
     ▪ Drospirenone acts as an anti-androgen, similar to spironolactone
     ▪ Avoid norgestrel, levonorgestrel (higher androgenicity formulations)
   o Cyclic progestin
     ▪ Allows maintenance of fertility
- May cause or worsen wt gain, acne, and hirsutism
- Natural progesterone (prometrium) 200 mg PO BID, or 400 mg PO qD x10-14 days/month\textsuperscript{11}
- Medroxyprogesterone 5-10 mg PO qD x10-14 days/month\textsuperscript{5}
- Norethindrone 5-20 mg PO qD x10-14 days/month
  - **Continuous progestin**
    - Depot medroxyprogesterone 150 mg IM q3 months
    - Progestin OCPs
    - May cause or worsen wt gain, acne, and hirsutism
  - **Estrogen combination OCPs**
    - More effective than metformin
  - **Metformin 500 mg PO BID-TID, or 850 mg PO BID\textsuperscript{11}**
    - Cycles normalize in 4-6 mos
  - **Thiazolidinediones**
    - Pioglitazone 30 mg PO qD, rosiglitazone 4 mg PO qD
    - May help regulate menses\textsuperscript{21}
    - No change in BMI\textsuperscript{21,22}
    - Minimize use
      - Concern for adverse CV effects
      - Minimal evidence to support use

3. **Treatment of infertility**
   - **Clomiphene**
     - 50-100 mg PO qD x5 days starting on menstrual cycle day 5\textsuperscript{5}
     - Ovulation in 50-75\% of women\textsuperscript{5,11}
     - Pregnancy rates 18-40\%\textsuperscript{5,11}
     - Live birth rates 22.5\%\textsuperscript{24}
     - Multiple gestation in 3-6\%\textsuperscript{11,24}
     - More effective than metformin
     - Exposure >12 months may incr risk of ovarian cancer\textsuperscript{11}
   - **Letrozole**
     - 5 mg PO qD for 5 days, starting on menstrual cycle day 3
     - Ovulation in 67\%\textsuperscript{25}
     - Pregnancy rates 15\%\textsuperscript{25}
     - Risk of multiple gestation
     - Exposure >12 mos may incr risk of ovarian cancer
   - **Metformin**
     - 500 mg PO BID-TID, or 850 mg PO BID\textsuperscript{5,11}
     - Restores menstrual cycles and ovulation in 45-95\% of pts in 4-6 mos
     - Higher doses more effective
     - Live birth rates 7\%\textsuperscript{24}
     - Used alone or w/clomiphene
       - Insignificant incr in live birth rates w/this combination\textsuperscript{24}
     - Appears safe in early pregnancy\textsuperscript{11,13}
     - May reduce miscarriage risk
     - No incr risk of multiple gestation\textsuperscript{24}
   - **Thiazolidinediones**
     - Pioglitazone 30 mg PO qD\textsuperscript{21} rosiglitazone 4 mg PO qD 22
• Improves frequency of ovulation\textsuperscript{23}
  • Rosiglitazone may incr ovulation rate to 33%
• Minimal evidence on pregnancy rates, live birth rates, effects and safety in early pregnancy
• Minimize use
  • Concern for adverse CV effects
  • Minimal evidence to support use
  
  o Gonadotropins (leuprolide)
    • For failure of above methods
    • Requires injection
    • Costly
    • Multiple gestation occurs in up to 30%
    • Refer to specialist

4. Tx of hirsutism
  
  o Low-dose estrogen combination OCPs\textsuperscript{5,11}
    • Lower androgenicity formulations recommended\textsuperscript{11}
      • Norgestimate, norethindrone, desogestrel, or drospirenone
      • Avoid norgestrel, levonorgestrel as these are higher androgenicity formulations
  
  o Antiandrogens
    • Spironolactone 25-100 mg PO BID\textsuperscript{5}
      • If used in combination w/OCPs containing drospirenone (a spironolactone agonist), use lower dose of spironolactone and monitor for hyperkalemia\textsuperscript{13}
      • More effective than metformin
    • Flutamide 250 mg PO qD to BID\textsuperscript{5}
    • Cyproterone 25-50 mg PO qD x 10 days/month\textsuperscript{5}
    • Finasteride 1 mg PO qD\textsuperscript{13}
    • *All antiandrogens are teratogenic
      • May cause feminization of external male genitalia in developing male fetus
      • Concomitant use of contraception recommended
      • Avoid use of antiandrogens if treating for infertility
  
  o Metformin
    • 500 mg PO BID-TID or 850 mg PO BID\textsuperscript{5,11}
    • Produces modest improvement
    • Similar efficacy to OCPs
  
  o Thiazolidinediones
    • Pioglitazone 30 mg PO qD\textsuperscript{21} rosiglitazone 4 mg PO qD\textsuperscript{22}
    • May be effective for hirsutism, shown to decr hyperandrogenism\textsuperscript{21,22,23}
    • Minimize use
      • Concern for adverse CV effects
      • Minimal evidence to support use
  
  o Topical eflornithine hydrochloride cream BID\textsuperscript{13}
  
  o Topical depilatories
    • OTC formulations
5. Tx of acne
   o Low-dose estrogen OCPs\textsuperscript{5,11}
     - Lower androgenicity formulations recommended\textsuperscript{11}
       - Norgestimate, norethindrone, desogestrel, or drospirenone
       - Avoid norgestrel, levonorgestrel (higher androgenicity formulations)
     - Similar efficacy to metformin
   o Metformin
     - 500 mg PO BID-TID, or 850 mg PO BID\textsuperscript{5,11}
   o Thiazolidinediones
     - Pioglitazone 30 mg PO qD\textsuperscript{21} rosiglitazone 4 mg PO qD\textsuperscript{22}
     - May reduce acne, shown to decr hyperandrogenism\textsuperscript{21,22,23}
     - Minimize use
       - Concern for adverse CV effects
       - Minimal evidence to support use
   o Antiandrogens
     - Spironolactone
       - 25-100 mg PO BID
       - If used w/OCPs containing drospirenone (spironolactone agonist), use lower dose of spironolactone and monitor for hyperkalemia\textsuperscript{13}
       - Teratogenic - avoid if treating for infertility
   o Traditional acne preparations
     - Topical
       - Antibiotics, benzoyl peroxide, retinoids
     - Oral
       - Antibiotics, retinoids
     - Avoid teratogenic medications if treating for infertility

6. Reduction of hyperglycemia, hyperinsulinemia
   o Metformin
     - 500 mg PO BID-TID, or 850 mg PO BID\textsuperscript{5}
     - Recheck lab parameters 3-4 mos after beginning Tx
   o Thiazolidinediones
     - Pioglitazone 30 mg PO qD\textsuperscript{21} rosiglitazone 4 mg PO qD\textsuperscript{22}
     - 2nd-line agents to metformin\textsuperscript{23}
     - Minimize use
       - Concern for adverse CV effects
       - Minimal evidence to support use

7. Reduction of hyperlipidemia
   o Statins, fibrates, niacin, omega-3 fatty acids

Surgical
1. Tx of infertility
   o Ovarian drilling, ovarian wedge resection, ovarian cautery/laser vaporization\textsuperscript{5}
     - Evidence limited regarding effectiveness\textsuperscript{5}
     - Potential surgical complications\textsuperscript{5} may not address underlying metabolic abnormalities\textsuperscript{13}
**Adjunct Mechanical Treatment**

1. **Tx of hirsutism**
   - Plucking, shaving, waxing, electrolysis, laser vaporization\(^{13}\)

**Follow-up**

1. Routine blood pressure, lipid, and diabetes screening\(^5\)
2. Diabetes
   - Consider metformin or thiazolidinedione, benefit in PCOS
3. Screen for depression and anxiety\(^{11,13}\)
   - Common in adolescents, related to self-esteem/appearance
   - In adults infertility may also contribute
4. Encourage wt loss for overwt or obese pts
5. Individualize Tx based on
   - Desire for fertility or contraception
   - Tx of Sx
   - Reduction of long-term risks
6. Tx likely to change over course of pts reproductive yrs

**Special Populations**

1. Adolescence
   - May present w/moderate/severe acne or hirsutism, obesity, irregular menses, or other signs of hyperandrogenism
   - PCOS is a frequent cause of hyperandrogenism
   - Suspect hyperandrogenism if acne occurs early or is difficult to treat
   - Concerning menstrual irregularities incl
     - Primary amenorrhea (no menses by age 15)
     - Oligomenorrhea or 2\(^{°}\) amenorrhea
     - DUB (menses < every 21 days, menstrual flow lasting >8 days, or heavy bleeding)
     - Lack of menstrual Sx
   - Consider ovarian U/S
   - Exclude other causes of hyperandrogenism and menstrual irregularities
   - Perform Dx lab evaluation
   - Screen for comorbid conditions of impaired glucose tolerance, diabetes, and hyperlipidemia
   - Adolescents w/PCOS should be treated
     - Lifestyle intervention w/dietary modification and exercise is 1st line in overwt or obese pts
     - OCPs or progestins can help w/regulation of menses
     - Metformin appears safe, effective, and well-tolerated in adolescents
       - Can help reduce central adiposity, decr circulating androgens, incr HDL and regulate menses
     - Spironolactone can be used to Tx acne and hirsutism if unsatisfactory response to OCPs
2. Infertility
   - Avoid teratogenic medications
3. Pregnancy
   - Avoid teratogenic medications
   - Metformin may decr rate of 1st trimester spontaneous abortion
   - If pregnancy occurs, pts at risk for spontaneous abortion, gestational diabetes mellitus, or pregnancy-induced hypertension

Pearls
1. PCOS
   - Oligo-ovulation/ anovulation w/biochemical hyperandrogenemia and/or clinical hyperandrogenism
2. Metabolic abnormalities
   - Insulin resistance
3. Untreated PCOS
   - Long-term health risks
     - Diabetes, cardiovascular dz, endometrial cancer
   - Immediate issues
     - Menstrual irregularities, hyperandrogenism, and infertility
4. Wt loss and exercise are initial interventions that can effectively address metabolic abnormalities of PCOS and improve fertility
5. Individualize Tx and adjust over course of their reproductive yrs, from adolescence through menopause

Patient Education

Evidence-Based Inquiry
1. Do insulin-sensitizing drugs increase ovulation rates for women with PCOS?
2. How effective and safe is metformin as a treatment for hirsutism in women with polycystic ovary syndrome?
3. What is the most effective treatment for polycystic ovary syndrome for patients who cannot tolerate metformin?

SORT Recommendations*
Based on good and consistent scientific evidence (Level A)
1. Exercise and dietary changes reduce diabetes risk similar to or better than medication
2. Insulin sensitizing agents decrease circulating androgen levels, improve ovulation rate, and improves glucose tolerance
3. Clomiphene citrate is 1st-line treatment for ovulation induction
4. Eflornithine plus laser treatment is superior to laser treatment alone for hirsutism

Based on limited and inconsistent scientific evidence (Level B)
1. Screen for impaired glucose tolerance and diabetes with a fasting glucose and 2-hour glucose challenge
2. Screen for cardiovascular risk factors (lipids, BMI)
3. Weight loss can
1.2.9.10

- Improve pregnancy rates, glucose levels, and lipids
- Decrease hirsutism

Based on consensus and expert opinion (Level C)

1. Combination low dose oral contraceptive pills are recommended as the primary treatment for menstrual disorders
2. Women at high risk for adult onset congenital adrenal hyperplasia should have a 17-hydroxyprogesterone value checked
3. When gonadotropins are used, a low-dose regimen is recommended
4. No best treatment for hirsutism


References


Author: Kirsten Stoesser, MD, & Joseph Stanford, MD, Utah Valley FMR

Editor: Linda French, MD, Toledo Hospital FMR