What Pharmacists Need to Know About Polycystic Ovary Syndrome (PCOS)

Laura Borgelt, PharmD, FCCP, BCPS
Associate Professor
University of Colorado Denver
Objectives

- Evaluate clinical manifestations, endocrine and metabolic abnormalities, and long-term risks associated with PCOS
- List diagnostic criteria for PCOS
- Compare and contrast medication used in the treatment of PCOS, including oral contraceptives, antiandrogens, insulin sensitizers, and ovulation induction agents
- Formulate a clinical plan for non-pharmacologic and pharmacologic therapy for patients with PCOS
Outline

- Clinical features
- Pathophysiology
- Long-term consequences
- Diagnostic criteria
- Treatment goals
- Non-pharmacologic therapy
- Pharmacologic therapy
- Clinical case
Introduction

- Affects 5-10% of premenopausal population
- Most common endocrinopathy in women
- Leading cause of anovulatory infertility
- First described in 1935
- Diagnosis elusive because patients present with varying symptoms
Clinical Case

KB is a 25 yr old female in clinic today for a co-consult with the medical resident and clinical pharmacists because she does not have normal periods. She has not had a normal period since she was 13 years old. She has now been trying to become pregnant for more than 15 months. She states the hair growth on her upper lip has been growing thicker the past few years, but she gets it waxed routinely. She has struggled with being obese and finds it hard to lose weight. She has walked 5 days/week for 20 minutes for the past 6 months and lost 2 pounds. She is interested in finding out what is “wrong with her” so she can become pregnant.
Clinical Case, con’t

Allergies: none
Meds: none
Family history: father with diabetes
Social history: no tobacco, occasional alcohol
Objective: Vitals WNL Height: 5’7” Weight: 205 pounds
Assessment: possible PCOS as evidenced by patient history and clinical characteristics
Plan: draw pertinent laboratory values, have patient follow-up in 1 week. Continue exercise.
Clinical Features of PCOS

- Anovulation (70-75%)
  - Usually chronic - presents as oligomenorrhea and/or amenorrhea
  - Infertility and recurrent miscarriages common

- Hyperandrogenism (70%)
  - Hirsutism, acne, alopecia

- Obesity (50%)
  - Abdominal obesity
  - Waist to hip ratio > 0.8

- Insulin resistance (75%)

Pathophysiology

- Three potential mechanisms that act alone or synergistically to create clinical presentation
- Endocrine disturbances
  - Inappropriate secretion of gonadotropins
  - Defective sex steroid synthesis or metabolism
- Metabolic disorder
  - Defect in insulin action, causing insulin resistance and hyperinsulinemia
Pathophysiology: Inappropriate Gonadotropin Secretion

- Increased LH pulse frequency and amplitude
- FSH secretion normal or decreased
- Abnormal ratio of LH:FSH is 2-3:1
- Follicle development is impaired due to premature stimulation of LH – results in anovulation or oligoovulation
- Increased LH may also stimulate ovary to increase steroidogenesis to produce excess androgen and impact sex steroid production

*Based on this information, what therapy would be helpful for hormone regulation?*
Pathophysiology: Defective Sex Steroid Synthesis and Metabolism

- Ovary and adrenal gland contribute to steroid production through similar pathway
- Increased LH, ACTH and insulin increase production of androgens
- Hyperandrogenism results
Pathophysiology: Insulin Resistance and Hyperinsulinemia

- Insulin resistance
  - Found in both lean and obese women
  - Postbinding defect in insulin-receptor signaling
  - Insulin sensitivity is selective and tissue-dependent
  - Androgen production and/or beta cell defects may exacerbate insulin resistance
  - Strong predictor of sleep apnea for PCOS patients

- Hyperinsulinemia results
  - Compensatory increase in insulin secretion secondary to peripheral insulin resistance

Fert Steril 2004;82:S181-3
PCOS: Pathophysiology Summary

Long-Term Consequences of PCOS

**DIABETES**
- 75% fulfill criteria for metabolic syndrome
- 40% have impaired glucose tolerance or type 2 diabetes by the age of 40 years
- 4 to 7-fold ↑ prevalence of type 2 diabetes

**CARDIOVASCULAR**
- 3-fold ↑ risk of lipid abnormalities
- 3-fold ↑ incidence of treated HTN
- 4 to 7-fold ↑ risk of MI

**CANCER**
- 3-fold ↑ risk of endometrial cancer

Diagnosis of PCOS (2 of 3)

- Menstrual dysfunction
  - Primarily chronic anovulation

- Clinical or biochemical signs of hyperandrogenism
  - Excluding other causes (e.g., congenital adrenal hyperplasia, prolactinoma, androgen-secreting tumors, Cushing’s syndrome)

- Polycystic ovaries (via ultrasound)
  - ≥12 follicles in at least one ovary measuring 2-9 mm in diameter and/or increased ovarian volume (>10 ml)
Radiologic Evaluation of PCOS

- Bilateral enlarged ovaries
- More than 12 follicles per ovary that are less than 10 mm (usually 2-9 mm)
- Follicles typically represent a “pearl necklace” on ultrasound
- Transvaginal ultrasound: gold standard to detect polycystic ovaries

http://www.advancedfertility.com/pco.htm
Laboratory Evaluation and Differential Diagnosis

- Exclude disorders that can mimic PCOS
- Determine if there is impaired glucose tolerance, diabetes, HTN and/or dyslipidemia
- Typical laboratory findings
  - LH/FSH ratio (>2 found in 60-70% of women)
  - ↔ to ↑ testosterone and DHEAS
  - ↓ SHBG
  - ↔ to slightly ↑ prolactin
- Others tests to consider
  - TSH, obstructive sleep apnea, endometrial biopsy

Clinical Case

KB presents to clinic today for follow-up of lab values and evaluation of probably PCOS. No changes from previous visit.

O: Significant lab findings:

LH:FSH ratio 3.5 (high), TSH 3.5 IU/ml (normal), free testosterone 70 ng/dl (high normal) and FPG 116 mg/dl

A: PCOS as evidence by menstrual dysfunction and hirsutism. Lab values support diagnosis. Impaired glucose tolerance based on FPG (100-125 mg/dl).

P: Continue non-pharmacologic regimen, with more aggressive diet and exercise. Options for hair removal discussed and referred to clinical pharmacy for pharmacotherapy recommendations.
Treatment Goals

- Maintain normal endometrium
- Block actions of androgen on target tissues
- Reduce insulin resistance and hyperinsulinemia (when present)
- Correct anovulation and improve fertility (if desired)
- Weight reduction (if applicable)
- Prevent long-term complications
- Treatment based on symptoms and goals
- Short-term and long-term goals should be set
Non-pharmacologic Therapy

- **Weight reduction**
  - Decreasing body weight 5-10% significantly reduces hyperandrogenism, insulin resistance and anovulation
  - Incidence of eating disorders higher in PCOS

- **Psychotherapy**

- **Hair removal**
  - Shaving
  - Chemical bleaching and waxing
  - Laser removal
Pharmacologic Options

- Combined oral contraceptives
- Antiandrogens
- Ovulation-induction agents
  - Clomiphene citrate
  - Gonadotropins
- Insulin-sensitizing agents
  - Metformin
  - Thiazolidinediones (TZDs)
- Combination therapy
Pharmacologic Therapy

- **Combined Oral Contraceptives**
  - Formulation should contain low dose estrogen ($\leq 35$ mcg EE) and low- to non-androgenic progestin
  - Beneficial for anovulation and hyperandrogenism (acne, hirsutism)
  - Beneficial for reduction in endometrial cancer
  - No to minimal impact on metabolic profile in PCOS (glucose, lipids, body fat distribution)
  - Ideal for patients seeking contraception
Pharmacologic Therapy

Agents for hirsutism

- Antiandrogens: spironolactone
  - Reduces hair growth by 40-88% when used in large doses (100-200 mg daily)
  - May take 6-9 months for improvement
  - Combination with COC improves hirsutism in up to 75% of women, treats hormonal/metabolic manifestations of PCOS, and avoids potential teratogenic effects

- Eflornithine hydrochloride cream 13.9% (Vaniqa™)
  - 2 times/day for 4-8 weeks has slowed hair growth and improved appearance in 58% of women
Clinical Case

Would you consider an antiandrogen in KB for hirsutism?
Ovulation Induction Agents

- Clomiphene citrate
- Gonadotropins
- Insulin sensitizers
Clomiphene Citrate

- One of two initial agents for ovulation induction in patients with PCOS (other - metformin)
- Antiestrogenic effect on hypothalmus
  - Increases GnRH to cause increased FSH and LH
  - Increased FSH develops follicles and increases estradiol concentrations to produce positive feedback on hypothalamic-pituitary system (which increases LH and LH surge occurs)
- Ovulation successful in 50-80% of women with PCOS
- Conception occurs in 35-50% after several ovulatory cycles
- 25-40% of women “clomiphene-resistant”
- Metformin may be added if inadequate response
Clomiphene Citrate

Dosing

- Initial dose: 50 mg/day for 5 days started on day 5 after spontaneous or progestin-induced menses
- Determine if ovulation occurred
- If not, increase dose to 100 mg/day
- Continue dose that causes ovulation
- May repeat cycle as early as 30 days after previous cycle as long as pregnancy ruled out
- Attempt 3 cycles before considering another regimen
- Long-term (>6 cycles) use not recommended due to concern for ovarian cancer
Clomiphene citrate

- Ovarian hyperstimulation syndrome rare
- Multiple gestation ranges from 5-10% with higher order multiple gestation ~1%
- Side effects: vasomotor symptoms, sleep disturbances, bloating, nausea, vomiting, breast discomfort, ovarian enlargement, visual changes
- Although pregnancy category X, little evidence of spontaneous abortion or birth defects
Gonadotropins

- Promote ovarian follicular growth
- Administered for 9-14 days after menses, followed by 10,000 units hCG, which triggers ovulation
- Various products
  - Human menopausal gonadotropin (contains both LH and FSH)
  - Urofollitropin (highly purified FSH)
  - Recombinant human FSH
Insulin-sensitizing Agents

- Metformin
- Rosiglitazone
- Pioglitazone
Metformin

- Appropriate dose for PCOS
- Moving towards first-line therapy for improvement of menstrual cycles
  - Increases menstrual cyclicity
  - Improves spontaneous ovulation
  - Promotes fertility
- Normal menstrual cycles in 78-96% of women treated for 4-6 months
- Decreases testosterone, LH, LH:FSH ratio and increases SHBG
- Few studies done on other clinical symptoms, but have shown reduced hirsutism, body weight, BMI
Metformin vs Clomiphene Citrate

- 626 infertile women with PCOS
- Randomized to clomiphene, metformin or combination up to 6 months

![Bar chart showing live birth rate and conception rate for Metformin, Clomiphene, and Combination treatments.](New Engl J Med 2007;356:551-66)
115 Asian women with newly diagnosed PCOS

Treatment
- Metformin 500 mg TID
- Clomiphene incremental dosing
- Combination

Primary outcomes
- Ovulation
- Pregnancy
- Live birth

Fertil Steril 2009;91:514-21
Efficacy Predictors for Response to Metformin or Clomiphene

- **Metformin**
  - Insulin resistance
  - Low BMI

- **Clomiphene**
  - Less hyperandrogenic
  - Low BMI
Thiazolidinediones

- Reduce insulin resistance
  - Improve sensitivity to insulin in muscle and adipose tissue
  - Inhibit hepatic gluconeogenesis

- Direct effect on ovary
  - Decrease testosterone and estradiol production

- Are they better, worse or similar when compared with metformin?

J Clin Endocrinol Metab 2005;90:1360-1365
J Clin Endocrinol Metab 2005;90:6099-6105
Human Reproduction 2003;18:1210-1218
Metformin or Rosiglitazone or Both?

- 100 women nonobese PCOS women with normal insulin sensitivity

- Treatment regimens BID x 6 mo:
  - Metformin 850 mg
  - Rosiglitazone 4 mg
  - Combination of both
  - Placebo

- Primary outcome:
  - Frequency of ovulation

\*p<0.05 for comparison with placebo
\†p<0.05 for comparison with rosiglitazone

Fertil Steril 2004;82:893-902
Ovulation Rates Over 6 Months

- Metformin Group (n=28)
- Rosiglitazone Group (n=22)
- Combination Group (n=20)
- Placebo Group (n=30)

Ovulation rates (%)

No. of months: 1, 2, 3, 4, 5, 6

Fertil Steril 2004;82:893-902
Metformin vs. Rosiglitazone in Clomiphene-Citrate Resistance

- Randomized controlled trial of 25 women with clomiphene-resistant PCOS
- Rosiglitazone 4 mg twice daily or metformin 500 mg three times daily for 3 treatment cycles with clomiphene
- Main outcomes: ovulation and pregnancy rates

<table>
<thead>
<tr>
<th></th>
<th>Rosiglitazone + CC</th>
<th>Metformin + CC</th>
<th>p-value</th>
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<tbody>
<tr>
<td>Ovulation Rate</td>
<td>18/28 (64%)</td>
<td>12/33 (36%)</td>
<td>p=0.035</td>
</tr>
<tr>
<td>Pregnancy Rate</td>
<td>6/12 (50%)</td>
<td>5/13 (39%)</td>
<td>p=0.58</td>
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Fertil Steril 2006;85:428-435
Pioglitazone: Pregnancy Rates

- **Objective**
  - Efficacy of pioglitazone on fecundity in infertile pts with PCOS resistant to clomiphene, metformin, or dexamethasone

- **Results**
  - 7 out of 9 became pregnant after an average of 11.3 weeks of pioglitazone
  - 3 miscarriages occurred
Clinical Case

KB has been referred to the clinical pharmacist for a therapy recommendation. She has been compliant with her diet and exercise regimens, but unable to lose weight. She desires to become pregnant in the near future.

O: BP 134/88  HR 74  Temp 98.7F  Ht: 5’7”  Wt: 204#

A: PCOS. Desire to meet patient and treatment goals. Options include ovulation-induction agents and insulin sensitizing agents.

P: What do you think?
PCOS: Treatment Algorithm

1. Conception desired? [Y/N]
   - Y
     - Obese? [Y/N]
       - Y: Lifestyle
         - Y: Expectant management
         - N: Metformin + Clomiphene
     - N: Clomiphene
2. N
   - Sexually active? [Y/N]
     - Y: COC
     - N
       - Ovulation? [Y/N]
         - Y: Expectant management
         - N: Metformin + Clomiphene
3. 2nd line options:
   - TZDs, spironolactone, fertility agents
PCOS: Conclusions

- PCOS is a heterogeneous disorder with various clinical, endocrine, and metabolic features
- Two of the following three needed for diagnosis: menstrual dysfunction, hyperandrogenism, polycystic ovaries
- Treatment regimens based on individual patient needs
- Clomiphene and metformin are considered first line therapies for infertility
- Combination therapy may be needed
QUESTIONS?

laura.borgelt@ucdenver.edu