Understanding PCOS

Aaron H. Lim, M.D., M.B.A.
Department of Ob/Gyn, Division of Reproductive Endocrinology & Infertility
Assistant Clinical Professor, UCLA David Geffen School of Medicine
Kaiser Permanente Downey

Agenda

I. Quiz

II. History

III. Diagnosis

IV. Clinical, Biochemical, Ultrasonic, & Physical Presentations

V. Epidemiology / Prevalence

VI. Causes / Endocrinologic Pathways

VII. Health Risks

VIII. Treatment

IX. Summary / Q&A Session / References
1. What is the most common endocrinopathy in women of reproductive age?

A. Thyroid disease
B. Polycystic Ovarian Syndrome
C. Type I diabetes
D. Type II diabetes
E. Hyperprolactinemia

2. What percentage of women in the US are affected by PCOS?

A. 8%
B. 16%
C. 24%
D. 32%
E. 40%
3. All women with PCOS have polycystic-appearing ovaries.

A. True
B. False

4. What percentage of women who are normal have polycystic-appearing ovaries?

A. 10%
B. 20%
C. 30%
D. 40%
E. 50%
5. What's the annual economic healthcare cost of PCOS treatment?

A. $400,000  
B. $4 Million  
C. $4 Billion  
D. $4 Trillion

6. Match the disease responsible for the following hyperandrogenism:

- High DHEA-S  →  Cushing's Syndrome
- High Cortisol  →  Congenital Adrenal Hyperplasia
- High Testosterone  →  Polycystic Ovarian Syndrome
- High 17-OH Progesterone  →  Adrenal tumor
## Agenda

| I. Quiz |  
| II. History |  
| III. Diagnosis |  
| IV. Clinical, Biochemical, Ultrasonic, & Physical Presentations |  
| V. Epidemiology / Prevalence |  
| VI. Causes / Endocrinologic Pathways |  
| VII. Health Risks |  
| VIII. Treatment |  
| IX. Summary / Q&A Session / References |  

---

## Polycystic Ovarian Syndrome (PCOS)

### DEFINITION

- First reported by Drs. Irving Stein & Michael Leventhal in 1935 as a triad of amenorrhea, obesity, and hirsutism
- "It is a heterogenous syndrome characterized by persistent hyperandrogenic chronic anovulation frequently associated with hyperinsulinemia & insulin resistance, resulting in menstrual irregularity, infertility, and hirsutism."
- The most common endocrinopathy in reproductive-aged women
- Emerging as a common cause of menstrual disturbance in the adolescent population
PCOS

Synonyms

- Polycystic Ovarian Disease (PCOD)
- Stein-Leventhal Syndrome
- Sclerocystic Ovarian Disorder
- Functional Ovarian Hyperandrogenism
- Hyperandrogenic Chronic Anovulation (HCA)
- Ovarian Hyperandrogenic Dysfunction
- Hirsutism Anovulation Syndrome

Discovery of PCOS

Historical Chronology

- 1721 – Dr. Vallisneri gave the first histological description of the polycystic ovary
- 1844 – Dr. Chereau described sclerocystic changes in the ovary
- 1921 – Drs. Archard & Thiers described a class of bearded women with diabetes
- 1935 – Drs. Stein & Leventhal described 7 women with bilateral enlarged PCO, amenorrhea or irregular menses, infertility and masculinizing features
Discovery of PCOS

Historical Chronology

- 1948 – first paper on ovarian wedge resection (reported by Drs. Stein, Cohen, & Elson) – 75 women underwent bilateral ovarian wedge resection, 88% resulted in spontaneous menstruation & 65% of participants desiring pregnancy conceived
- 1960’s – laparotomy & bilateral ovarian wedge resection became mainstay treatment of PCOS
- Early 1970’s – endocrinology criteria used for diagnosis of PCOS
- Late 1970’s – pelvic sonogram became part of diagnosis
- 1980’s – LSC ovarian drilling became a substitute for laparotomy ovarian wedge resection

Agenda

I. Quiz

II. History

III. Diagnosis

IV. Clinical, Biochemical, Ultrasonic, & Physical Presentations

V. Epidemiology / Prevalence

VI. Causes / Endocrinologic Pathways

VII. Health Risks

VIII. Treatment

IX. Summary / Q&A Session / References
PCOS

Establishing Diagnosis

- 1990 – criteria for diagnosis of PCOS established by NIH
- 2003 – ESHRE/ASRM reached consensus definition of PCOS
- 2006 - AES (Androgen Excess Society) formed a task force to review all available data and recommend an evidence-based definition for polycystic ovary syndrome

Diagnostic Criteria

- 1990 NIH Criteria: all 3 required
  - Chronic anovulation; and
  - Clinical &/or biochemical signs of hyperandrogenism; and
  - Exclusion of other etiologies of hyperandrogenism (CAH, androgen-secreting tumors, Cushing’s syndrome)

- 2003 Rotterdam ESHRE (European Society of Human Reproduction)/ ASRM (American Society of Reproductive Medicine) Criteria: 2 out of 3 required
  - Oligo- or anovulation; and/or
  - Clinical &/or biochemical signs of hyperandrogenism; &/or
  - Polycystic-appearing ovaries
PCOS

**Diagnostic Criteria**

- **AES** (Androgen Excess Society) in 2006 formed a task force to review all available data and recommend an evidence-based definition for polycystic ovary syndrome.
- Result: No consensus reached
- Conclusion: “definition of this syndrome will evolve over time to incorporate new research findings.”

**What Makes the Diagnosis an Enigma?**

- No laboratory evidence required for diagnosis
- No radiologic evidence required for diagnosis
- Polycystic ovarian appearance not pathognomonic of PCOS
- Insulin resistance not included in diagnostic criteria
- A diagnosis of exclusion (needs to rule out other known causes of hyperandrogenism)
- Genetics may play a role but gene sequencing variable
- Clinical heterogeneity / varied presentation
PCOS

What Have We Learned Over The Last 10 Years?

- The parameters for defining PCOS remain vague or subjective
- There is no universally accepted definition for PCOS

Agenda

I. Quiz

II. History

III. Diagnosis

IV. Clinical, Biochemical, Ultrasonic, & Physical Presentations

V. Epidemiology / Prevalence

VI. Causes / Endocrinologic Pathways

VII. Health Risks

VIII. Treatment

IX. Summary / Q&A Session / References
Oligo / Anovulation

- Oligo-ovulation -> oligomenorrhea (infrequent menses)
- Anovulation -> amenorrhea (no menses)

Symptoms

Hyperandrogenism

- Clinical signs of hyperandrogenism:
  - Acne
  - Hirsutism
  - Acanthosis (dark discoloration around the neck &/or groin region)
  - Deepening of voice
  - Alopecia (male-pattern balding)

- Biochemical signs of hyperandrogenism:
  - Elevation of testosterone, androstenedione, DHEA-S, 17-OH progesterone, cortisol

Sources of Androgens

- Testosterone
- Androstenedione
- DHEA-S

PCOS

25% 50% 25%

25% 40% 10%

90% 60%
PCOS

Concerning Levels of Androgens

- **Testosterone**
  - < 200 mcg / ml – r/o PCOS
  - > 200 mcg / ml – order TVS to r/o ovarian tumor

- **DHEA-S**
  - < 700 mg / ml – normal
  - > 700 mg / ml – order CT scan to r/o adrenal tumor

- **17-OH Progesterone**
  - < 3 ng / ml – normal
  - 3 – 8 ng / ml – perform ACTH challenge test
  - > 8 ng / ml – r/o congenital adrenal hyperplasia

Polycystic Ovaries (PCO)

Ultrasonic Qualifying Criteria

- Contains 12 or more peripheral follicles ranging from 2 to 9 mm in diameter;

  &/or

- Increased ovarian volume (> 10 cm³)

Polycystic Ovaries (PCO)

Ultrasound

- 1078 reproductive age women screened by ultrasound*
- 17% demonstrated PCO appearance
  - 80.3% - irregular or absent cycle
  - 19.7% - normal cycle
- Conclusion: 20% of women with PCO-appearing ovaries do NOT have PCOS (i.e., PCO-appearence is NOT pathognomonic of PCOS).


PCOS

Physical Findings

- Male-pattern balding
- Hair thinning
- Facial hair
PCOS

Physical Findings

Agenda

I. Quiz

II. History

III. Diagnosis

IV. Clinical, Biochemical, Ultrasonic, & Physical Presentations

V. Epidemiology / Prevalence

VI. Causes / Endocrinologic Pathways

VII. Health Risks

VIII. Treatment

IX. Summary / Q&A Session / References
PCOS

Epidemiology

- Affects 5%-10% of all reproductive-aged women
- Leading cause of infertility
  - Accounts for about 50% of women presenting for fertility treatment
  - PCOS is responsible for up to 75% of all cases of anovulatory infertility.
- PCOS accounts for 95% of cases of hyperandrogenism
- PCOS is responsible for over 20% of all cases of amenorrhea

Prevalence In The United States

- Caucasians - 5%
- African-American - 8%
- Hispanic - 13%
PCOS

Causes

- Elevation of Insulin?
- High LH?
- Genetics*?
  - Rate of PCOS in mothers of affected subjects – 24%
  - Rate of PCOS in sisters – 32%
  - In-utero androgen exposure?
- Weight?
- Lifestyle?

PCOS

Genetic Aspect

- Complex genetic trait disorder
- CYP11A – possible PCOS gene?
- Mode of inheritance is unclear
- Familial basis is common (mother, sisters, aunts, female cousins)
- Male homologue to PCOS in women: balding prior to age 30


Correlations

- 50-70%: hyperinsulinemia
- 38-87%: obesity
- 31%: glucose intolerance
- 7.5%: type 2 DM
PCOS

One Potential Pathway – Insulin Resistance

- Insulin Resistance
- Hypoinsulinemia (Elevated Levels of Insulin in the Blood)
  - Decreased Sex Hormone Binding Globulin (SHBG) Production by the Liver
  - Increased Ovarian Production of Androgens (Male Hormones)
  - Decreased Abnormal GnRH (Pulsatile Stimulation)
- Disordered Release of LHFSH (Phallic Hormones that Stimulate the Ovary)
- Hyperandrogenism (Elevated Blood Levels of Male Hormones)
- Oligo-anovulation (Absent or Irregular Ovulation)
- PCOS

Potential Pathway

- Abnl GnRH pulsatile stimulation
- Luteinising hormone
- Insulin, insulin-like growth factor
- Thecal cells
- Extraovarian androgen
- Dysregulation of androgen secretion
- Ovarian steroidogenesis block
- Intraovarian androgen
- Hyperandrogenaemia (Testosterone)
- Follicular atresia

Pathophysiology of PCOS

Agenda

I. Quiz

II. History

III. Diagnosis

IV. Clinical, Biochemical, Ultrasonic, & Physical Presentations

V. Epidemiology / Prevalence

VI. Causes / Endocrinologic Pathways

VII. Health Risks / HealthCare Cost

VIII. Treatment

IX. Summary / Q&A Session / References
Women With PCOS

RISKS

- 10% have type 2 Diabetes
- 30% have impaired glucose intolerance
- 70% are obese
- 63% of all endometrial cancer in premenopausal women

PCOS

HealthCare Cost

$4.4 Billion: Total Annual Expenditure

Diabetes Care, $1,800
DUB Therapy, $1,350
Hirsutism Treatment, $622
Initial Evaluation, $93
Fertility Treatment, $533

Agenda

I. Quiz

II. History

III. Diagnosis

IV. Clinical, Biochemical, Ultrasonic, & Physical Presentations

V. Epidemiology / Prevalence

VI. Causes / Endocrinologic Pathways

VII. Health Risks

VIII. Treatment

IX. Summary / Q&A Session / References

PCOS

Treatment Goals

- Amelioration of hyperandrogenic symptoms (hirsutism, acne, scalp hair loss)
- Management of underlying metabolic abnormalities and reduction of risk factors for type 2 diabetes and cardiovascular disease
- Prevention of endometrial hyperplasia and carcinoma, which may occur as a result of chronic oligo or anovulation
- Ovulation induction for those pursuing pregnancy
Treatment

Prevention of Diabetes & CV Disease

Lifestyle Changes

- 100 participants (all BMIs > 30 Kg/m2)
- Caloric restrictions to 1200-1400 Kcal daily plus physical activity
- Result after 20 months:
  - 15.4% - persistent
  - 47.7% - partial improvement
  - 36.9% - complete disappearance of PCOS


---

104 postmenopausal women who had clinical features of PCOS had a higher chance of having:

- Diabetes
- Obesity
- Metabolic syndrome (3 of 5 risk factors):
  - FBS ≥ 100
  - BP > 135/85
  - HDL < 50
  - TG > 150
  - Waist size ≥ 35 inches
- Coronary artery disease (CAD)

TREATMENT

Focus on Decreasing the Circulating Insulin

- Avoid carbohydrates by themselves and instead combine them with proteins and fats
- Space carbohydrates out during the day. This will cause less of a rise in blood sugar and hence less of a sharp rise in insulin as opposed to eating all carbohydrates in a single meal.
- Consume carbohydrates that have a low glycemic index as opposed to those that have a high glycemic index.
- Whenever possible avoid carbohydrates that tend to increase appetite such as pasta.

TREATMENT

Focus on Decreasing the Circulating Insulin

- Regular exercise - brings down insulin levels and helps with weight loss
- Exercise on a regular basis (5x per week – 20 min each)
- Aerobic exercise burns calories, aids in weight control, lowers blood pressure, raises HDL cholesterol (good cholesterol) and may decrease insulin resistance.
- Resistance training builds lean muscle mass and increase insulin sensitivity
Hyperandrogenic Symptoms

Hirsuitism

- Combination BCP (↑SHBG -> ↓ Free Testosterone)
- Spironolactone (50-100 mg po daily or bid)
- Vaniqa (Efornithine) – topical cream to inhibit hair growth
- Laser / photoepilation (intense pulsed light)
- Temporary measures:
  - Epilation (plucking)
  - Waxing
  - Depilation (dissolves hair)
  - Shaving
  - Bleaching


Acne

- Hormonal agents
  - Combination BCP
  - Spironolactone (50-100 mg po daily)
- Topical retinoids
  - Tretinoin (Retin-A)
  - adapalene
- Topical antimicrobials
  - Benzoyl peroxide (i.e., Proactiv)
  - Clindamycin
  - Erythromycin
- Oral antibiotics
  - Tetracycline, doxycycline, minocycline
  - Erythromycin
- Oral Isotretinoin (teratogenic; category X)
**Treatment**

**Prevention of Endometrial Hyperplasia / Cancer**

- If patient is NOT interested in pregnancy:
  - Combination BCP
  - Transdermal patch (OrthoEvra)
  - Contraceptive vaginal ring (Nurvaring)
  - Progestin pill – also known as mini-pill (Nora-BE)
  - Progestin-containing IUD (Mirena)
  - Subdermal implant (Nexplanon)
  - Progestin injection (DepoProvera)

- If patient is interested in pregnancy:
  - Cyclic progesterin (Medroxyprogesterone / Prometrium)
  - Metformin

---

**PCOS**

**Metformin & Ovulation**

61 PCOS Women with BMI > 28

- 26 received Placebo alone
  - 1/26 ovulated (4%)
- 35 received Metformin 1500 mg/d
  - 14/35 ovulated (40%)

\[ P < 0.005 \]

*Nestler, et al. NEJM. 1998*
Treatment

#1 Cause of Infertility - PCOS

Ovulation Induction Medications

- **Clomiphene** - an antiestrogen that stimulates the pituitary gland to increase the release of gonadotropins which in turn stimulates the ovaries
- **Metformin** - reduces circulating insulin and androgen levels and restores normal ovulation in some women with PCOS
- **Letrozole** - interferes with the production of estrogen. This in turn stimulates the pituitary gland to increase the release of gonadotropins
- **Gonadotropin** – directly stimulates the ovaries to increase follicular recruitment & maturation


---

PCOS

Ovulation Induction: Metformin + Clomiphene (50 mg)

46 PCOS Women

- 25 received placebo
- 21 received metformin 1500 mg/d

- 2 ovulated (8%)
- 19 ovulated (90%)

P< 0.0001

*Nestler, et al. NEJM. 1998
SUMMARY

PCOS

- The most common endocrinopathy in reproductive-aged women
- The number one cause of infertility
- Cause of PCOS is multifactorial
- Definition remains vague despite advances in medicine
- Lifestyle changes can lead to improvement &/or disappearance of PCOS
- Treatment of PCOS is directed at the symptom presentation
- Early recognition can diminish future risks of:
  - Cardiovascular diseases
  - Diabetes
  - Hypertension
  - Endometrial hyperplasia or cancer
QUESTIONS?

DISCUSSION?

REFERENCES

REFERENCES

- Moran LJ, Hutchison SK, Norman RJ, Teede HJ. Lifestyle changes in women with polycystic ovary syndrome. Cochrane Database System Review. 2011.
- Nestler JE, Jakubowicz DJ, de Vargas AF, et al. Insulin stimulates testosterone biosynthesis by human thecal cells from women with polycystic ovary syndrome by activating its own receptor and using inositolglycan mediators as the signal transduction system. Journal of Clinical Endocrinology & Metabolism. 1999; 83: 2001-2005

The Meaning of Life ……

"Live as if you were to die tomorrow. Learn as if you were to live forever."

— Mahatma Gandhi
Weight Loss

- 13 women signed up for a six-month weight loss program:
  - Treatment group lost an avg of 13.9 lbs
  - Decreased fasting blood insulin & testosterone levels
  - Increased SHBG concentrations
  - 92% resumed ovulation (12 of 13)
  - 85% became pregnant (11 of 13)

Medical Therapy

- Clomid is an antiestrogen that stimulates the pituitary gland to increase the release of gonadotropins which in turn stimulates the ovaries. Approximately one-third to one half of patients who take Clomid will conceive. Conception generally will occur within 3-4 treatment cycles and at doses of 50mg/day or 100mg/day for 5 days. Clomid at these doses has minimal side effects but does increase the incidence of multiple pregnancy to 3%-5%.
- Gonadotropins are given as daily injections, usually for 7-10 days, and safe administration requires frequent monitoring to avoid hyperstimulation. The drugs themselves are costly as is the frequent monitoring with blood test and pelvic ultrasound studies that is required. In addition there is a 20% - 30% incidence of multiple pregnancy when these drugs are used.
- Letrazole is a drug developed for the treatment of breast cancer and interferes with the production of estrogen. This in turn stimulates the pituitary gland to increase the release of gonadotropins in a manner similar to Clomid which in turn stimulates the ovaries. The use of letrazole for Ovulation Induction is off label. In addition there are some controversial studies suggesting that letrazole may increase the incidence of birth defects. For this reason many reproductive endocrinologists are reluctant to prescribe letrazole.
TREATMENT

Medical Therapy

Thiazolidinediones have been shown to reduce hyperandrogenism and restore ovulation in some PCOS patients. Rather than gastrointestinal side effects, liver toxicity is the main concern with these agents. Liver tests should be performed frequently for the first year and periodically thereafter. These medications should not be started in women with any evidence of liver disease. Present data clearly confirms that the use of insulin sensitizing agents for ovulation induction in PCOS patients who want to conceive is appropriate. Because these medications correct the underlying metabolic abnormalities associated with PCOS, it is more than likely that their long term use may delay the emergence or reduce the likelihood of developing Type 2 diabetes, elevated cholesterol, high blood pressure and cardiovascular disease. Since data are lacking, long-term use of insulin sensitizing agents for this purpose cannot be recommended at present however all indications from early studies are very encouraging.

Surgical Therapy

Laparoscopic Ovarian Drilling: Laparoscopic ovarian drilling is the modern version of bilateral ovarian wedge resection first described by Stein and Leventhal in 1935. Although still major surgery it is less invasive and if done by a physician skilled in operative Laparoscopy is less likely to result in significant pelvic adhesions. However it still carries with it the inherent risks associated with any surgical procedure and for this reason is generally not considered to be appropriate as the first treatment of choice. The premise of the surgery, just as is the case for BOWR, is that destruction of ovarian tissue leads to a decrease in androgen production by the ovaries which in turn leads to a decrease in LH released by the pituitary gland which in turn restores normal ovarian function. At best, results of ovarian drilling are the same as the same achieved with medical treatment, and therefore our feeling is that the procedure should be reserved for special situations.
## TREATMENT

### Surgical Therapy

Directed at symptoms of PCOS:
At the present time insulin sensitizing agents are often used as first line of therapy for PCOS patients interested in achieving pregnancy. These agents do need to be prescribed in conjunction with the implementation of a carbohydrate restricted diet as well as weight loss for those PCOS patients who are obese, along with increased exercise.

The best studied insulin sensitizing agent available in the United States for women with PCOS is metformin (Glucophage®), a biguanide that has been available for forty years. Metformin reduces circulating insulin and androgen levels and restores normal ovulation in some women with PCOS. Even if metformin alone does not restore regular ovulation, it often improves a woman's response to fertility drugs. Gastrointestinal irritation, especially diarrhea, nausea/vomiting and flatulence and abdominal discomfort are common side effects. These symptoms usually improve after a few weeks particularly if patients start with a small dose of medication and gradually increase to the full dose. Lactic acidosis is a rare but serious adverse effect of metformin. Metformin is not recommended for patients with kidney, lung, liver, or heart disease.

---

**February 25, 2014 | © 2011 Kaiser Foundation Health Plan, Inc. For internal use only.**