PCOS Update:
Making an Accurate Diagnosis and Treatment Strategies

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Disclosures

• None

Education Objectives

1) Know the diagnostic criteria for Polycystic Ovary Syndrome and be aware of the conditions that can be mislabeled as PCOS.
2) Be familiar with the components of the syndrome and why treatment is usually a multi-faceted approach.
3) Practice up-to-date management of the reproductive and metabolic sequelae, including the appropriate use of ovulation induction agents and guidelines for weight management.
MAKING AN ACCURATE DIAGNOSIS

Polycystic Ovary Syndrome

- Endocrinopathy resulting in ovarian hyperandrogenism
- Most common symptoms:
  - Infrequent or absent menses
  - Hirsutism
  - Infertility
  - Obesity
- 7-10% of women have PCOS (NIH criteria)
- 55-91% of women with normogonadotropic anovulation

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PCOS Diagnostic Criteria

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<tbody>
<tr>
<td>Hyperandrogenism</td>
<td>Required</td>
<td>X</td>
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<tr>
<td>Oligo-/amenorrhea</td>
<td>Required</td>
<td>X</td>
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<tr>
<td>PCO morphology</td>
<td>X</td>
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- Need 2 of the following 3 criteria:
  - Hyperandrogenism: clinical or biochemical
  - Menstrual irregularities
  - PCO morphology (PCOM) ovaries (=25 follicles/ovary Vol 10cm³)
- Absence of another underlying endocrinopathy
PCOS “Imposters”

- Adolescence
- Hypothalamic Dysfunction
- Hypothyroidism
- Hyperprolactinemia
- Ovarian Failure
- Non-classical Congenital Adrenal Hyperplasia
- Androgen-Secreting Tumor
- Obesity
- Cushing Syndrome/Disease

PCOS “Imposters”

- Adolescence
  - “Immature” hypothalamic-pituitary-ovary axis may result in irregular cycles during puberty
  - Young women likely have normal ovarian reserve and fit the criteria for PCOM.
  - Require hyperandrogenemia, observe for 2-3 years
- Hypothalamic Dysfunction
  - Altered HPO axis may result in irregular cycles
  - E.g. anorexia, stress
  - Can also have PCOM, typically not hirsute
  - Medical history, gonadotropins & estradiol will be low

PCOS “Imposters”

- Hypothyroidism
  - Results in menstrual irregularities
  - Typically picked up by other symptoms and TSH
- Hyperprolactinemia
  - Results in oligo- or amenorrhea, and also galactorrhea
  - Typically picked up by symptoms and prolactin
- Ovarian Failure
  - Secondary amenorrhea
  - Can have some hirsutism, typically not terminal hair
  - Picked up by ultrasound or FSH/LH/estradiol
PCOS “Imposters”

- Non-classical Congenital Adrenal Hyperplasia
  - Results in menstrual irregularities and hyperandrogenism
  - Enzyme defect in steroid pathway (adrenal and ovary)

- Measure 17-hydroxyprogesterone to diagnose
- Important for preconception counseling
  - Autosomal Recessive condition
  - NCCAH = mildest version of CAH
  - Salt-wasting and Simple Virilizing have greater morbidity
- If affected, test partner to assess risk

Wikipedia/steroidogenesis
PCOS “Imposters”
- Androgen-secreting Tumor
  - Consider if total testosterone is > 200 ng/dL
  - Symptoms: Hirsutism, balding, voice change, body build
  - Look for tumor with pelvic ultrasound (ovaries) and CT Scan (adrenals)
  - Risk of adrenal “incidentalomas”
    - Adrenal vein sampling prior to adrenalectomy
- Cushing Syndrome/Disease
  - Cortisol excess, from ACTH-producing tumor or cortisol/steroid exposure
  - Obesity, hypertension, striae, muscle weakness, anxiety

PCOS “Imposters”
- Obesity
  - PCOS has a metabolic component
  - Many women with PCOS are overweight or obese
  - Increased weight tends to worsen phenotype
  - Obesity ≠ PCOS
    - Obesity can result in menstrual abnormalities
    - Obesity can limit ability to accurately assess ovaries
    - Rely more on hyperandrogenism to make diagnosis

Evaluation
**Making the Diagnosis**
- Testosterone Panel
- FSH/LH/estradiol
- TSH
- Prolactin
- 17-hydroxyprogesterone
- Midnight salivary cortisol
- Pelvic ultrasound

**Once Diagnosed**
- Blood pressure
- BMI
- Exam for insulin resistance
- Diabetes screening
  - HgA1c
  - 2-hr GTT (75gm)
- Fasting insulin
- Lipid panel
THE SYNDROME OF PCOS

Is PCOS the wrong name?

- The cysts in “PCOS” are an ultrasound finding, not a symptom
- Can be misleading
- NIH-called meeting 2013
  “The name PCOS is a distraction that impedes progress. It is time to assign a name that reflects the complex interactions that characterize the syndrome”
- E.g. Female Metabolic Reproductive Syndrome

The Syndrome

- Menstrual Irregularities
- Androgen Excess
  - Hirsutism
  - Acne
- Infertility
- Metabolic Sequelae
  - Diabetes
  - Cardiovascular Disease
- Depression
TREATMENT STRATEGIES

Treatment: Menstrual Regulation

- Menstrual irregularity can vary from cycles every 35 days to amenorrhea
- Combined oral contraceptives = 1st line therapy
  - 30-35 mcg ethinyl estradiol
  - Non-androgenic progestin: 3rd generation (gonanes), desogestrel/norgestimate
  - Do not need to use drospironone
- Cyclic progesterone
  - Desires fertility
  - Contraindication to estrogen therapy

Treatment: Hirsutism

Pharmaceutical

- Combined oral contraceptive = 1st line
  - Ethinyl estradiol will bump SHBG, drop free T
  - Takes a while to see effect (months)
- Spironolactone
  - Androgen receptor antagonist
  - Also a diuretic (↑K) and aldosterone antagonist
  - 100mg once daily, increase to twice daily if needed
- Other antiandrogens: flutamide, finasteride
- Topical eflornithine
  - Limited benefit, $$$
Treatment: Hirsutism

Cosmetic Management Options
- Mechanical
- Plucking
- Shaving
- Waxing
- Creams
- Electrolysis
- Laser treatment
  - Works as follicular melanin absorbs the laser wavelength, selective thermal damage
  - Best to combine with a medical treatment

Treatment: Infertility

- Ovulation Induction
  - Oral Agents
    - Clomiphene citrate
    - Metformin
    - Letrozole
  - Gonadotropins
  - Ovarian Drilling
  - In Vitro Fertilization

Randomized Controlled Trials:
PPCOS I RCT
PPCOS II RCT

PPCOS I

Clomiphene, Metformin, or Both for Infertility in the Polycystic Ovary Syndrome

CONCLUSIONS
Clomiphene is superior to metformin in achieving live birth in infertile women with the polycystic ovary syndrome, although multiple birth is a complication.
PPCOS I Criticisms
- Obese cohort: BMI 35
- 50% NOT treatment naïve
- Infertility average 40 months (3.5 yrs)

Established clomiphene as superior to metformin for ovulation induction, even in an obese cohort.
Potential benefit of additive therapy.

PPCOS II

Letrozole versus Clomiphene for Infertility in the Polycystic Ovary Syndrome
Richard L. Legro, M.D., Robert G. Brzyski, M.D., Ph.D., Michael P. Diamond, M.D., Christina Cauthen, M.D., Ph.D., William D. Schlaff, M.D., Peter Casson, M.D., Gregory M. Chrstman, M.D., Hoi Huang, M.D., M.P.H., Qingyang Yan, Ph.D., Robert Alves, M.D., Daniel J. Hassenfeld, Ph.D., Kurt T. Bankart, M.D., G. Wayne Bales, M.D., Rebecca Usadi, M.D., Scott Lucraft, M.D., Valerie Baker, M.D., J.C. Trussell, M.D., Stephen A. Krawetz, Ph.D., Peter Snyder, M.D., Dava Ohl, M.D., Nanette Santoro, M.D., Esther Ehsan, M.D., M.P.H., and Heping Zhang, Ph.D., for the NICHD Reproductive Medicine Network

CONCLUSIONS
As compared with clomiphene, letrozole was associated with higher live-birth and ovulation rates among infertile women with the polycystic ovary syndrome. (Funded

Established letrozole as superior to clomiphene
Treatment: Infertility

- Ovulation Induction
  - Oral Agents
    - Clomiphene citrate: 50mg / 100mg / 150mg
    - Letrozole: 2.5mg / 5mg / 7.5mg
    - Cycle day 3-7
  - Metformin: goal 1500mg daily, XR formulation
  - Ultrasound monitoring/hCG trigger or Ovulation kits
  - Gonadotropins: failed ov induction/no pregnancy
  - Ovarian Drilling: alternative to gonadotropins
- In Vitro Fertilization

Chance of Live Birth best if:
- Attempting conception < 1.5 yrs
- BMI < 30
- Hirsutism score lower

OWL Study

Randomized Controlled Trial of Preconception Interventions in Infertile Women With Polycystic Ovary Syndrome
OWL Study

- Randomized trial of preconception interventions:
  1. Oral contraceptive pill (20mcg EE/NE, continuous)
  2. Lifestyle modification (goal 7% weight loss)
     - Caloric Restriction
     - Increased physical activity
     - Rx if BMI >= 30 kg/m² (sibutramine, orlistat)
  3. Combined OCPs and Lifestyle modifications

- 149 women with PCOS by Rotterdam criteria
- Mean BMI 35, 18-40 years old, no diabetes
- Intervention x 16 weeks
- 4 cycles of clomiphene/timed intercourse

OWL Study

Ovulation Rate
- OCPs 46%
- Lifestyle 60%
- Combined 67%
  (p<0.05)

Live Birth
- OCPs 12%
- Lifestyle 26%
- Combined 24%
  (p=0.13)

Treatment: Obesity/Metabolic

- Lifestyle Modification
Treatment: Obesity/Metabolic

- Lifestyle Modification
  - Caloric Restriction
  - Exercise
  - Reduces diabetes risk and other metabolic abnormalities
- Enlist help from primary care and/or weight loss center
- Recommendations
  - Food Log: My Fitness Pal, LoseIt!
  - Caloric restriction: 1200-1500 cal/day
  - Metformin if prediabetic, elevated insulin, or no success without medication. 1500-2000mg/day.

Multi-Disciplinary Approach

- Menstrual Regulation
- Hirsutism
- Infertility
- Obesity/Metabolic

Summary

- Recommend adopting the Rotterdam criteria for Polycystic Ovary Syndrome as it is the most inclusive.
- Be aware of the conditions that can be mislabeled as PCOS to ensure an accurate diagnosis.
- PCOS is a syndrome and treatment is a multi-faceted approach.
"I'm so sad it's Friday. I wish it was Monday already!"

Said No one in history, ever.