Polycystic Ovary Syndrome (PCOS) Diagnosis and Management

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Endocrinology Update for Primary Care 2017
• Disclosures or financial conflicts relevant to the topic - None
Learning Objectives

• Describe the pathophysiology of PCOS
• Recognize the clinical spectrum of PCOS
• Understand the diagnostic criteria of PCOS
• Discuss the components of a complete evaluation for PCOS
• Review the management of PCOS
Ms. VV’s journey

22 yr old Caucasian female presents to your office for
- Increase in facial hair
- Acne breakouts
- Irregular periods since menarche
- Cycle frequency -20 to 80 days
- LMP -2 months back
• Increased hair in upper lips, chin, side buns, lower abdomen, back and inner thighs
• Plucking every 3 days
• No galactorrhea
• No change in voice
• No scalp hair loss
• No hot flashes
PMH

- Hypothyroidism
- Asthma

Current Medications

- Levothyroxine 100mcg daily
- Ventolin inhaler

- Non smoker, occasional alcohol in the weekends
- Junior, computer science major
- Sexually active, uses condoms
- Family history significant for thyroid disorders, diabetes and heart disease
Physical exam

- Wt -180 lbs, Ht-5ft 6”. BMI – 29.1
- BP -122/78 mm Hg
- No goiter
- No clinical stigmata for Cushing’s syndrome
- Increase coarse terminal hair in face, lower abdomen, back and inner thighs
- Acne in lower jawline
- Systemic exam was unremarkable
Labs

- TSH - 1.8 u (IU)/ml (0.4-4.5)
- Prolactin - 8 ng/ml
- Beta hCG <0.1
- Serum Total Testosterone - 0.9 ng/ml (0-0.8)
- FSH - 5 m(IU)/ml
- LH - 7 m(IU)/ml
- DHEAS – 348 mcg/dL (40-315)
What does she have?

1. Non classical congenital adrenal hyperplasia
2. Primary ovarian insufficiency
3. Androgen secreting ovarian neoplasm
4. PCOS
Polycystic Ovarian Syndrome (PCOS)

- Most common endocrinopathy in women of reproductive age
- Prevalence - 5 to 15%
- Heterogeneous presentation with variable phenotypes
Pathogenesis - PCOS
In PCOS,

- Altered Gonadotropin secretion
- Intrinsic abnormalities in ovarian steroidogenesis
- Effects of hyperinsulinemia in augmenting LH stimulation of ovarian androgen production
Pathogenesis in PCOS

Clinical presentation

• Hyperandrogenism – Acne, hirsutism, androgenic alopecia
Modified Ferriman-Gallway Scoring system
Androgenic alopecia
Clinical presentation

- Hyperandrogenism – Acne, hirsutism, androgenic alopecia
- Menstrual irregularity – Oligo/amenorrhea
- Infertility
- Signs of insulin resistance
Acanthosis Nigrans

Skin tags
Keratosis pilaris
Clinical presentation

• Hyperandrogenism – Acne, hirsutism, androgenic alopecia
• Menstrual abn – Oligo/amenorrhea
• Infertility
• Signs of insulin resistance
• Weight gain/ Obesity
Diagnostic criteria for PCOS
Rotterdam criteria

- Oligo – and/or anovulation
- Clinical and/or biochemical signs of hyperandrogenism
- Polycystic ovarian morphology (by ultrasound)

- 2 out of 3 features are required for diagnosis after exclusion of other etiologies for androgen excess
Ultrasound criteria for PCO

- Presence of 12 or more follicles in the ovary measuring 2 to 9 mm in diameter
  And/or
- Increased ovarian volume >10ml
- Only one ovary fitting this description is sufficient to define PCOM
- Transvaginal approach should be used
- Does not apply if the woman takes OCP
- If a dominant follicle (>10mm) or corpus luteum, repeat the scan in the next cycle
Ultrasound of Right and left ovaries

“String of pearls” sign
# Phenotypes in PCOS – Rotterdam criteria

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Hyperandrogenism</th>
<th>PCOM</th>
<th>Oligo-ovulation or anovulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>B</td>
<td>+</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>C</td>
<td>+</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>D</td>
<td>−</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

PCOM, polycystic ovarian morphology; PCOS, polycystic ovary syndrome.
## Conditions to exclude in the diagnosis of PCOS

<table>
<thead>
<tr>
<th>Condition</th>
<th>Hyperandrogenism</th>
<th>Ovulatory dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non classical congenital hyperplasia</td>
<td>Yes</td>
<td>Variable</td>
</tr>
<tr>
<td>Prolactinoma</td>
<td>None</td>
<td>Yes</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>None</td>
<td>May be present</td>
</tr>
<tr>
<td>Cushing’s syndrome</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Virilizing adrenal or ovarian neoplasm</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Primary ovarian insufficiency</td>
<td>None</td>
<td>Yes</td>
</tr>
<tr>
<td>Acromegaly</td>
<td>None</td>
<td>Often</td>
</tr>
</tbody>
</table>

Ehrmann NEJM 352:12 2005
Evaluation

- TSH
- Prolactin
- 17 hydroxyprogesterone (early morning)
- Serum total testosterone and free testosterone
- Beta- hCG
Additional tests

- Transvaginal USS
- 75 gm 2hr – Oral glucose tolerance test
- Dehydroepiandrosterone sulfate (DHEAS)
- LH/FSH
- Antimullerian hormone (AMH)
- Sex hormone binding globulin (SHBG)
Clinical Components of PCOS

Oligo-anovulation
Hyperandrogenism
Glucose intolerance
Endometrial hyperplasia
Dyslipidemia
Infertility
Depression and anxiety disorder
NAFLD
Sleep apnea

Management of PCOS

PCOS: changing women’s health paradigm

Metabolic disease

Reproductive disorders

(young age)
- menstrual disorders
- hirsutism
- contraception
- sexual health
- infertility

(older age)
- pregnancy complications
- quality of life
- type 2 diabetes
- cardiovascular disease
- cancer risk?
Hyperandrogenism

• Oral contraceptives
Oral contraceptives

• Estrogen – progestin combination
• Progestin component suppresses LH and thus ovarian androgens
• Estrogen enhances hepatic production of SHBG, hence reduces free testosterone
• Progestin in the pill can compete with 5α reductase at the level of androgen receptor
## Level of androgenic activity of progesterone in OCP

<table>
<thead>
<tr>
<th>Level</th>
<th>Progesterone component</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Norgestrel</td>
</tr>
<tr>
<td></td>
<td>Levonorgestrel</td>
</tr>
<tr>
<td>Moderate</td>
<td>Norethindrone</td>
</tr>
<tr>
<td></td>
<td>Norethindrone acetate</td>
</tr>
<tr>
<td>Low</td>
<td>Norgestimate</td>
</tr>
<tr>
<td></td>
<td>Desogestrel</td>
</tr>
<tr>
<td></td>
<td>Drospirenone</td>
</tr>
<tr>
<td></td>
<td>Dienogest</td>
</tr>
</tbody>
</table>

- **1st generation**: Norethindrone
- **2nd generation**: Norgestrel, Levonorgestrel
- **3rd generation**: Norgestimate, Desogestrel, Drospirenone, Dienogest
Hyperandrogenism

- Oral contraceptives
- Antiandrogens – Spironolactone, cyproterone acetate, Flutamide
Antiandrogens

Spironolactone

- Antimineralocorticoid – moderate antiandrogenic activity at doses of 100-200mg daily
- Teratogenic – feminization of male fetus
- Should be always combined with effective contraception
- Flutamide androgen receptor antagonist – limited use as hepatotoxic
Hyperandrogenism

- Oral contraceptives
- Antiandrogens – Spironolactone, cyproterone acetate, Flutamide
- Finasteride – 5α reductase inhibitor
- Topical therapies – Vaniqa, laser, electrolysis
Topical therapies

Vaniqa – Eflornithine hydrochloride

- Inhibitor of enzyme ornithine decarboxylase in human skin
- Approved for facial hirsutism

Laser, electrolysis may be beneficial for limited period
Menstrual irregularity

- Combined OCP
- Cyclic progesterone – oral medoxyprogesterone for endometrial protection from hyperplasia
- Endometrial biopsy if amenorrhea > 1 year
- 2.7 fold increased risk for endometrial cancer
- Ovulations have been reported in up to 32% of cycles
Back to Ms. VV

- Started on OCP
- She was educated about the long term metabolic complications of PCOS
- Screened for diabetes and dyslipidemia
- Referred to nutritionist
- Encouraged to exercise
- Other options of antiandrogen therapies and topical therapies reviewed
Ms. VV – Part 2

- 31yrs, married
- Works as software developer
- **Planning pregnancy**

- Topical therapies for increased facial hair
- Stopped OCP six months back
- Only 1 menstrual cycle since stopping OCP
• BMI – 32
• Normotensive
• HBA1c -5.6
• No recent hospitalization
• She walks for 30 mins twice a week
What would you be next line of management to induce ovulation?

1. Metformin
2. Ovulating agents – Clomiphene or Letrozole
3. Myoinositol
4. GnRH therapy
5. Laparoscopic ovarian drilling
Infertility

• A recent study showed preconception weight reduction (7%) prior to ovulation induction leads to improved ovulation

Clomiphene citrate
• SERM – binds to estrogen receptors in the hypothalamus and inhibits negative feedback of endogenous estrogen
• Compensatory increase in GnRH and FSH drives follicular development and ovulation

Letrozole
• Aromatase inhibitor – prevent estrogen biosynthesis from androgens and through hypothalamic/pituitary feedback increase FSH secretion and follicular development

Legro RS et al JCEM Nov 2015
Clomiphene, Metformin, or Both for Infertility in the Polycystic Ovary Syndrome

Richard S. Legro, M.D., Huiman X. Barnhart, Ph.D., William D. Schlaff, M.D., Bruce R. Carr, M.D., Michael P. Diamond, M.D., Sandra A. Carson, M.D., Michael P. Steinkampf, M.D., Christos Coutifaris, M.D., Ph.D., Peter G. McGovern, M.D., Nicholas A. Cataldo, M.D., Gabriella G. Gosman, M.D., John E. Nestler, M.D., Linda C. Giudice, M.D., Ph.D., Phyllis C. Leppert, M.D., Ph.D., and Evan R. Myers, M.D., M.P.H., for the Cooperative Multicenter Reproductive Medicine Network*
Ovulation and pregnancy rates in PPOS-I

Live birth rate
- 22.5% in clomiphene citrate
- 7.2% in Metformin
- 26.8% in combination group

p=0.31
p<0.001

Legro et al
Cur Op Dec 2012
• 750 infertile women with PCOS randomized to Letrozole or Clomiphene

Live birth rate - Letrozole (27.5%) vs clomiphene citrate (19.1%), p = 0.007

Ovulation rate - Letrozole (61.7%) vs clomiphene citrate (48.3%), p < 0.001
LETRAZOLE VS. CLOMIPHENE FOR INFERTILITY IN PCOS

A  All Patients

- N=750
- P=0.01

B  BMI, ≤30.3

- N=250
- P=0.39

C  BMI, >30.3 to ≤39.4

- N=249
- P=0.03

D  BMI, >39.4

- N=251
- P=0.09

Days from Randomization to Live Birth
Live Birth (%)
Role of metformin in Ovulation induction

• Adjuvant ovulation induction therapy
• Benefit is greatest in the obese PCOS subgroup

• Use of metformin as pretreatment for 3 months prior to beginning clomiphene citrate induction found significant weight loss and improved live births in metformin arm in obese PCOS women

J Clin Endocrinol Metab, May 2012, 97(5):1492–1500
Other options

- **Gonadotrophins** – low dose FSH
- **IVF** - Third line of therapy
- **Inositol therapy**
  - Phase II studies did not show any benefit
- **Laparoscopic ovarian drilling**
  - Refractory to clomiphene and unwilling for gonadotrophins
  - Concerns about long term effects on ovarian function
What would you be next line of management to induce ovulation?

1. Metformin
2. **Ovulating agents** – Clomiphene or **Letrozole**
3. Myoinositol
4. GnRH therapy
5. Laparoscopic ovarian drilling
Ms.VV : Part 3

- 34 yrs
- Healthy 2yr old girl
- Pregnancy was complicated by gestational diabetes
- Continues to have irregular periods
- Increased hirsutism
- Unable to lose weight postpartum
-Feels low, stressed and tired all the time
• BMI – 34
• BP – 138/82 mm Hg
• 75 gm OGTT
  – Fasting glucose -101
  – 2hr glucose -166
What would you do next?

1. Refer her to the nutritionist
2. Start Metformin
3. Screen her for depression
4. Screen her for sleep apnea
5. All of the above
Metabolic risks

- Screening for IGT and T2 DM should be performed with a 75gm OGTT
- HbA1c – annually
- IR is more prevalent and severe in classic phenotype
- 23-35% prevalence of impaired glucose tolerance
- 4 to 10% increased risk of Type 2 diabetes
Insulin resistance and glucose intolerance

• Weight reduction – lifestyle interventions
• Metformin
• Thiazolidinediones - avoid

• Screen for hypertension, lipid abnormalities and sleep apnea
PCOS and Obstructive sleep apnea

- 5-10 times more frequent in women with PCOS
- Insulin resistance and glucose intolerance were highly correlated with the presence and severity of OSA independent of BMI
- Screen for symptoms of OSA and refer to sleep clinic

Ehrmann DA Steroids 2012
PCOS and Depression

- Meta-analysis have shown increased depression scores independent of BMI
- Women with PCOS especially those with concurrent anxiety symptoms have a higher prevalence of eating disorders

Dokras A et al Fertil Steril Jan 2017
What would you do next?

1. Refer her to the nutritionist
2. Start Metformin
3. Screen for depression
4. Screen for sleep apnea
5. All of the above
Take home points

• PCOS is a heterogeneous condition with variable phenotypic presentation

• Rotterdam criteria includes 2 of 3 features - clinical or biochemical hyperandrogenism, menstrual irregularities, PCOM in the absence of other conditions causing androgen excess

• PCOS women have aberrations in gonadotrophin secretion with hyperinsulinemia amplifying ovarian androgen biosynthesis
Take home points

• Management of PCOS should be tailored according to patient’s needs

• Screen for CVD risk factors – glucose intolerance, hypertension, lipid abnormalities and sleep apnea

• Life style interventions and multidisciplinary approach indicated
Thank you

Clinical Services - University of Washington Medical Center

• PCOS clinic
• Diabetes clinic
• Osteoporosis clinic
• General Endocrine clinic

• E mail: tsubbu@uw.edu