Polycystic Ovarian Syndrome Guideline

Background

Polycystic Ovarian Syndrome (PCOS) is the most frequent hormonal and metabolic disease in women of reproductive age world-wide.

40% of hirsute women who have normal cycles are anovulatory.

Statistics:

-PCOS affects nearly 7-10% of the women in the U.S.

-PCOS associated with 75% of the women with amenorrhea.

- PCOS associated with 85% of women with androgen excess and hirsutism.

PCOS Complications:

• Risk of an attack and heart disease is 3-4x higher in obese patients than that of general population

• Android obesity increases risk of coronary heart disease

• Hyperandrogenism will increase visceral fat

• Fertility issues (Menstrual disorders)

• Not all PCOS patients are obese and not all obese pts have PCOS.

Abbreviations / Definitions

ACOG: American College of Obstetricians and Gynecologists

ASRM: American Society for Reproductive Medicine.

FEMM: Fertility Education Medical management

HOMA: homeostasis model assessment of insulin resistance

Hyperandrogenism: Acne, hirsutism, hair loss on scalp, infrequent or absent menstruation

PCOS: Polycystic Ovarian Syndrome

RHRI: Reproductive Health Research Institute

TVUS: Transvaginal Ultrasound

Screening and diagnostic procedures / Initial evaluation

Diagnosis

2003 Council of Rotterdam (Need 2 of 3)

1. Oligo or Anovulation
2. Clinical signs or biochemical evidence of hyperandrogenemia / hyperandrogenism.
3. Pelvic Ultrasound (US) with polycystic ovaries and exclusion of other etiologies.

(See ovarian criteria in transvaginal US below)

Other proposed PCOS criteria, See APPENDIX I

Subtypes of PCOS

Metabolic

- High BMI
- Hyperandrogenic
- Insulin Resistance (Obesity and PCOS increase Insulin Resistance).
- Abnormal lipid metabolism

Reproductive

- Hyperandrogenic
- May be lean with normal BMI
- Irregular cycles
- Insulin resistance is secondary

'In between'

- Aspects of both Metabolic and Reproductive effects

Symptoms:

OVULATORY DYSFUNCTION

- Irregular cycles (80%)
- Polycystic ovaries (See TVUS criteria)
- Mood changes
- Decreased fertility potential
- Miscarriage

History: Review of Symptoms

Obesity / inability to lose weight

Depression / irritability / tension

Sleep apnea / somnolence

Pelvic pain

Physical Assessment:

Obesity (BMI >30)

High hip to waist ratio (<0.85= normal)

Waist circumference (>35 inches = abnormal)

Acrochordons (skin tags)

Acanthosis nigricans

Gray-white breast discharge

Somnolent

Pelvic discomfort

Thinning scalp hair

Neurologic: Depression / irritability

Labs:

Total Testosterone **Thyroid stimulating hormone (TSH)**	**(optional)** **- Sex Hormone Binding Globulin (SHBG)**

Fasting Prolactin*	**-24 hr urinary free-cortisol excretion or low dose dexamethasone test**
17-hydroxyprogesterone (17-OHP)	**-Fasting Insulin**
2hr Glucose Tolerance Test (GTT)	**-FSH / LH**
Fasting Lipids	**-Vitamin D**

*NOTE: Prolactin: Should be fasting plus no breast stimulation for 24 hrs.

INSULIN RESISTANCE – See Appendix II

Imaging:

Transvaginal ultrasound (TVUS) to include assessment of ovarian morphology

-Determination of polycystic ovaries: in one or both ovaries, either 12 or more follicles measuring 2–9 mm in diameter, or increased ovarian volume (greater than 10 cm3). If there is a follicle greater than 10 mm in diameter, the scan should be repeated at a time of ovarian quiescence in order to calculate volume and area. The presence of one polycystic ovary is sufficient to provide the diagnosis.

HYPERANDROGENEMIA

- Hair growth (upper lip, around nipple area, inguinal area)
- Oily skin and hair
- Acne
- Alopecia (male pattern, frontal)
- Mood changes/ Compulsive tendencies
- Anthropomorphic changes (apple shaped, increased visceral adiposity)
- Ferriman-Gallwey Hirsutism scoring system. See Appendix III

PCOS Dx in Adolescent*

1) Irregular menses
2) Evidence of Hyperandrogenism (Biochemical and clinical)
3) Generally 2 years post menarche
4) Rule out diagnosis of other hyperandrogenisms (Congenital Adrenal Hyperplasia, Cushing's)

*(Ovaries with polycystic appearance are common in adolescents)

Rule out secondary causes

-adult-onset congenital adrenal hyperplasia (Random 17-OHP normal < 4 ng/mL or fasting < 2 ng/ml)

-hyperprolactinemia

-androgen-secreting neoplasms

Management:

Metabolic Type → Focus on Insulin Resistance

Reproductive Type → Focus on Hyperandrogenemia then Insulin Resistance

In Between→ Focus on Insulin Resistance and Hyperandrogenemia

INSULIN RESISTANCE:

From ACOG bulletin: "Improving insulin sensitivity with these agents (below), associated with a decrease in circulating androgen levels, improved ovulation rate, and improved glucose tolerance".

ACOG:

Metformin 1500-2000 mg/day (start low to avoid GI upset: 250 qd x7, 500 qd x7, 1000 qd x7, etc..)

(+ /OR)

Rosiglitazone

2-4mg/day

(or other Thiazolidinediones)

RHRI:

Metformin 1500-2500mg/day

+Rosiglitazone 2-4mg/day, if anovulatory cycle persists (or other Thiazolidinediones)

+ Vit D, if deficient

Non-Rx management:

D-Chiro-Inositol 1200 mg/day

-Reduces testosterone

-Reduces triglycerides and LDL cholesterol.

If elevated BMI:

- Nutrition referral and counseling

- Increase exercise

- Semaglutide injection (Wegovy) is FDA approved for weight loss

PCOS infertility treatment from ACOG

1.) Insulin- Sensitizing Agents (Metformin, Thiazolidinediones)

- "improving insulin sensitivity with these agents is associated with a decrease in circulating androgen levels, improved ovulation rate, and improved glucose tolerance".

- Anti-diabetic agents are not FDA approved for PCOS related menstrual dysfunction, so please document discussion.

- Metformin safest risk/benefit ratio.

2.) Aromatase Inhibitor (Letrozole)

- More effective than Clomid

- Higher birth rate and increased clinical pregnancy rate.

- Not approved by FDA (widely used), so please document discussion.

- Start 2.5/day x 5 days (start days 3,4 or 5). If no ovulation, increase to 5mg then 7.5mg

- 7.5 mg /day associated with thinning of endometrium (also seen with clomid)

Third Line Intervention: Ovarian Drilling:

- Failure after Insulin Sensitizing Agents, as well as Letrozole or Clomid therapy

-No effect metabolically

PCOS Menstrual irregularity

-Combination low-dose hormonal contraceptives are most frequently used for long-term management and are recommended as the primary treatment of menstrual disorders.

PCOS Hirsutism

None of the antiandrogen agents were developed to treat hyperandrogenism in women or are approved by the FDA for that indication. As a class, antiandrogens are teratogenic and pose a risk of feminization of the external genitalia in a male fetus (ambiguous genitalia) should the patient conceive. Therefore, they are frequently used in combination with oral contraceptives.

Mechanical hair removal (shaving, plucking, waxing, depilatory creams, electrolysis, and laser vaporization) is often the front line of treatment used by women. There is no evidence that shaving can increase hair follicle density or size of the hair shaft. Plucking can be helpful if tolerated, but care must be taken to avoid folliculitis, pigmentation, and scarring.

Other: "…clinically indistinguishable from PCOS…"
Non-classic congenital adrenal hyperplasia (NCCAH): Non-classic (late-onset) congenital CAH (NCCAH) is a less severe form of the classic type, which is usually diagnosed during neonatal screening. In late-onset CAH, there is 20-50% activity of 21-hydroxylase. The main presenting symptom is hyperandrogenism. In children, this may present as acne, precocious puberty and accelerated bone growth. When it first appears in adolescents and adults, the common presenting features are acne, oligomenorrhea and hirsutism. This can make it clinically indistinguishable from PCOS; however, PCOS is much more common.

Diagnosis of NCCAH is based on elevated levels of 17-hydroxyprogesterone (17-OHP; > 200 ng/dL), as measured in the follicular phase of the menstrual cycle.

If the basal level of 17-OHP is above 200 ng/dL, it is advisable to run a follow-up ACTH-stimulation test to confirm the diagnosis; a patient with NCCAH will respond to the ACTH with an exaggerated rise in 17-OHP, confirming the diagnosis of NCCAH.

Summary

PCOS affects women metabolically, as well as their reproductive system.

PCOS may initiate a referral for infertility or abnormal uterine bleeding (AUB)

-however, complications from PCOS affect women long term, not just in their reproductive goals

-these include metabolically, cardiovascular system, and psychologically for their whole lives.

Assessment starts with history, physical exam, biochemical assessment, and subtyping.

Management depends on patient goals.

-Treatment has shown benefits with insulin sensitizing agents, as insulin resistance complicates PCOS.

-Diet and lifestyle changes should be made in conjunction with prescriptive methods.

-Collaboration with the primary care team is important, especially for management of lipid levels as preventative measure for cardiovascular complications.

Follow up / Next steps

- Follow- up Labs and weight, 3-4 months after initiation of treatment.
- Many patients will report resumption of cycles or weight loss.
- Some patients will need longer schedule for tapering up on medications due to side effects (GI upset, nausea, vomiting with Metformin)

Approved MCH CCBG 12/8/23 njm
Written 11/18/23 mcm

APPENDIX I

1990 National Institute of Health (need both)

"The 1990 National Institutes of Health (the NIH criteria), which allow for a clinical diagnosis without the use of an imaging study. In addition, the NIH criteria require the presence of irregular menses, while the other criteria do not".

1. chronic anovulation
2. Clinical signs or biochemical evidence of hyperandrogenemia/hyperandrogenism.

2009 Androgen Excess Society (need all)

1. Clinical signs or biochemical evidence of hyperandrogenemia/hyperandrogenism.
2. Ovulatory dysfunction
3. Exclusion other etiologies

Rotterdam and NIH Criteria

Proposed diagnostic criteria for polycystic ovary syndrome

NIH consensus criteria 1990[1] (all required)	Rotterdam criteria 2003*[2] (two out of three required)	AES definition 2008[3] (all required)
Menstrual irregularity due to oligo- or anovulation	Oligo- or anovulation	Clinical and/or biochemical signs of hyperandrogenism
Clinical and/or biochemical signs of hyperandrogenism	Clinical and/or biochemical signs of hyperandrogenism	Ovarian dysfunction – oligo/anovulation and/or polycystic ovaries on ultrasound
Exclusion of other disorders: NCCAH, androgen-secreting tumors	Polycystic ovaries (by ultrasound)	Exclusion of other androgen excess or ovulatory disorders

NIH: National Institutes of Health; AES: Androgen Excess Society; NCCAH: nonclassic congenital adrenal hyperplasia; PCOS: polycystic ovary syndrome.

* Rotterdam criteria also require exclusion of other conditions that mimic PCOS. Criteria were developed at a 2003 consensus meeting held in Rotterdam (European Society of Human Reproduction and Embryology [ESHRE]/American Society of Reproductive Medicine [ASRM] consensus workshop group).

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1. *Zawadski JK, Dunaif A. Diagnostic criteria for polycystic ovary syndrome: Towards a rational approach. In: Polycystic Ovary Syndrome (Current Issues in Endocrinology and Metabolism), Dunaif A, Givens JR, Haseltine FP, Merriam GE (Eds), Blackwell Scientific Inc, Boston 1992. p.377.*
2. *Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Hum Reprod 2004; 19:41.*
3. *Azziz R, Carmina E, Dewailly D, et al. The Androgen Excess and PCOS Society criteria for the polycystic ovary syndrome: The complete task force report. Fertil Steril 2009; 91:456.*

FEMM / RHRI

PHENOTYPE A	PHENOTYPE B	PHENOTYPE C	PHENOTYPE D
HyperAndrogenism	HyperAndrogenism	HyperAndrogenism	HypoAndrogenism
Ovulation Dysfunction	Ovulation Dysfunction	Ovulation Dysfunction	Ovulation Dysfunction
Polycystic Ovarian Morphology	Polycystic Ovarian Morphology	Polycystic Ovarian Morphology	Polycystic Ovarian Morphology

APPENDIX II

INSULIN RESISTANCE:

Basal: Insulin: > 10 uIU/mL

Values at 30, 60, 90 min 100 uIU/mL

Value at 120 min > 60 uIU/mL

Insulin resistance based on HOMA Score

HOMA-IR SCORE: homeostasis model assessment of insulin resistance

HOMA- Insulin Resistance

The HOMA-IR is being used extensively for estimates of beta cell function and insulin resistance, both in clinical practice and studies, with the caveat that it cannot be used on patients on insulin.

HOMA-IR = (Fasting insulin in mIU/L x Fasting glucose in mg/dL) / 405

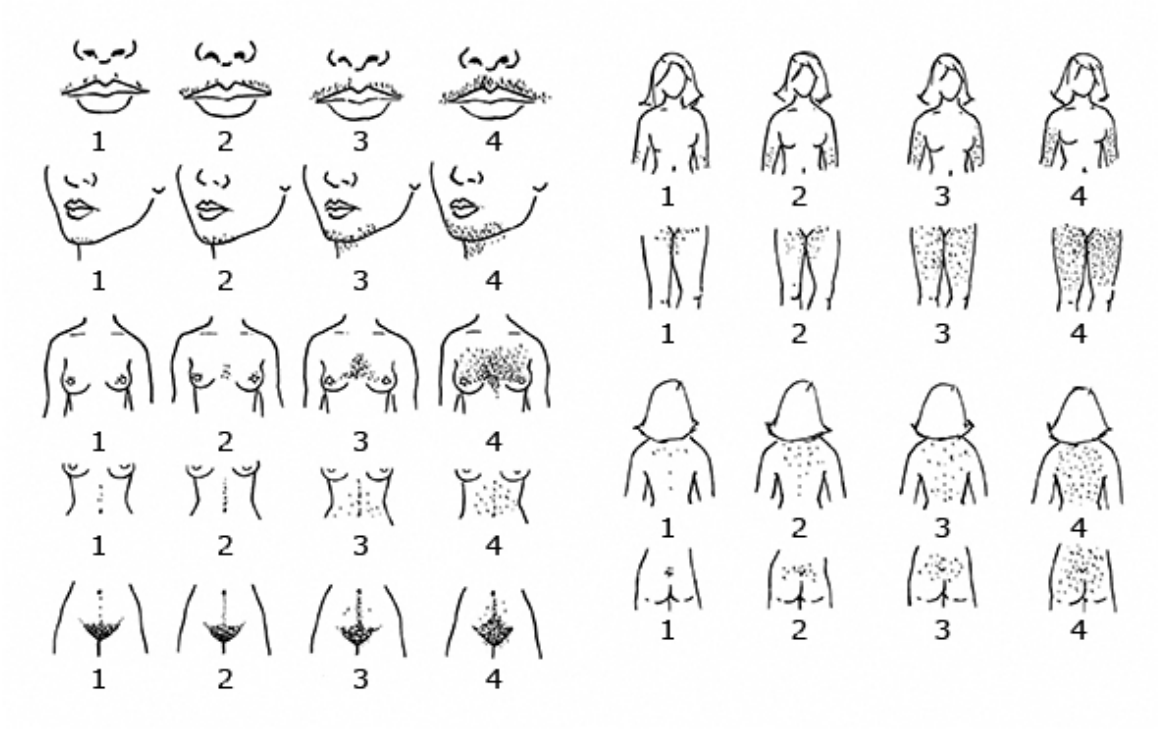
Normal reference levels for HOMA-IR range between 0.7 and 2.0.

Several studies use the 2.0 value as cut-off for increased insulin resistance.

APPENDIX III

Ferriman-Gallwey Hirsutism Scoring System

Grading of severity of hirsutism in patients



Ferriman-Gallwey hirsutism scoring system. Each of the 9 body areas that is most sensitive to androgen is assigned a score from 0 (no hair) to 4 (frankly virile), and these are summed to provide a hormonal hirsutism score. "Focal" hirsutism (score 1 to 7) is a common normal variant, whereas generalized hirsutism (score of 8 or more) is abnormal in the general United States population. The normal score is lower in East Asian and American Asian populations and higher in Mediterranean populations.

Referenced [Grading of hirsutism - UpToDate]

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