Diagnosis and Treatment of Polycystic Ovary Syndrome: An Endocrine Society Clinical Practice Guideline

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Goals

- Focus on treatment of PCOS from adolescence to menopause
  - With focus on associated morbidity
- Avoid the quagmire of expert based diagnostic criteria
- Avoid overlap with previous Endocrine Society Guidelines that have addressed disorders related to PCOS
**Diagnostic Criteria for PCOS (All Expert Based)**

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<tbody>
<tr>
<td>Oligomenorrhea</td>
<td>Yes</td>
<td>Maybe</td>
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<tr>
<td>Hyperandrogenism (Biochemical and/or Clinical)</td>
<td>Yes</td>
<td>Maybe</td>
<td>Yes</td>
</tr>
<tr>
<td>Polycystic ovaries</td>
<td>No</td>
<td>Maybe</td>
<td>Maybe</td>
</tr>
</tbody>
</table>

**Executive Summary**

- We recommend maintaining the broad, inclusionary diagnostic criteria of Rotterdam (which includes the “classic NIH” and AE-PCOS criteria) while specifically identifying the phenotype.

**Caveat**

- There is phenotypic heterogeneity based on definition. Generally hyperandrogenism is associated with more severe reproductive and metabolic manifestations than polycystic ovaries.
- There is no mandatory evaluation that requires universal biochemical screening for hyperandrogenemia or polycystic ovaries on ultrasound.
Known Associated Morbidity with PCOS

- Infertility
  - Pregnancy Complications
- Obesity
- Cutaneous Manifestations
  - Hirsutism
  - Acne
  - Androgenic alopecia
- Endometrial Cancer
  - No screening
- Diabetes and Cardiovascular Risk
  - OGTT and Lipid profile

Newer Associated Morbidity with PCOS

- Sleep Disorders
  - Sleep Apnea
  - Sleep Disordered Breathing
- Abnormal Liver Function
  - Nonalcoholic Fatty Liver Disease
  - Nonalcoholic Steatohepatitis
- Mood Disorders
  - Depression
  - Anxiety

Controversies in Treatment

- Role of Hormonal Contraceptives versus “Insulin Sensitization”
  - Safety of oral contraceptive pills
  - Lifestyle
  - Metformin
- Role of Newer Treatments
  - Statins
  - GLP-1 Agonists
- Adolescents
  - Should we avoid certain treatments in adolescents?
Increased Risk of Thromboembolism in Women with PCOS on Oral Contraceptive Pills?

Bird et al, CMAJ, 2013

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cox proportional hazards models</th>
<th>Relative risk regression</th>
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<tbody>
<tr>
<td>PCOS claim</td>
<td>2.14 (1.41–3.24)</td>
<td>2.12 (1.40–3.21)</td>
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<tr>
<td>Composite PCOS definition*</td>
<td>2.24 (1.62–3.10)</td>
<td>2.23 (1.61–3.08)</td>
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<tr>
<td>PCOS symptoms and treatment</td>
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<td></td>
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<tr>
<td>Anovulation</td>
<td>1.72 (0.75–3.96)</td>
<td>1.70 (0.75–3.89)</td>
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<tr>
<td>Hirsutism</td>
<td>2.49 (1.35–4.55)</td>
<td>2.43 (1.30–4.56)</td>
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<tr>
<td>Spironolactone</td>
<td>1.89 (1.15–3.10)</td>
<td>1.86 (1.14–3.03)</td>
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</tbody>
</table>

Note: PCOS = polycystic ovary syndrome.
*Claims for PCOS, anovulation, hirsutism, spironolactone treatment, or PCOS-related procedures.

CONTRAINDICATIONS

The World Health Organization (WHO) has developed a list of absolute and relative contraindications to the use of combined OCs, based on the available evidence of risks.

ABSOLUTE CONTRAINDICATIONS (with PCOS risk factors highlighted)

- Smoker over the age of 35 (≥ 15 cigarettes per day)
- Hypertension (systolic ≥ 160mm Hg or diastolic ≥ 100mm Hg)
- Current or past history of venous thromboembolism (VTE)
- Migraine headache with focal neurological symptoms
- Diabetes with retinopathy/nephropathy/neuropathy
RELATIVE CONTRAINDICATIONS

- Smoker over the age of 35 (< 15 cigarettes per day)
- Adequately controlled hypertension
- Hypertension (systolic 140–159mm Hg, diastolic 90–99mm Hg)
- Migraine headache over the age of 35
- Users of medications that may interfere with combined OC metabolism

Consider carefully before prescribing to PCOS

Population Effects: OCP and Diabetes

- No effect of OCP on glucose metabolism in NHANES III
- Minimal effect on Diabetes Development in Nurse’s Health Study II
  - 2 cases per 100,000 woman years among current users
  - NO effect on past users
  - Chasan-Taber et al, Diabetes Care 1997

Meta-Analysis: PCOS, OCP and Metabolic Consequences

- OCP use significantly associated with an increase in high-density lipoprotein cholesterol (HDL-C) (P = 0.004) and triglycerides (P = 0.004).
- Significant heterogeneity was found in glucose and homeostatic model assessments-IR.
- CONCLUSIONS Use of OC was not associated with clinically significant adverse metabolic consequences

Is there one pill that is more effective than another in treating PCOS?

No clear data, but a lot of marketing.
Should women with PCOS be given extended cycle pills?

Perhaps- but this is based on extrapolating from other data
Conclusions- Hormonal Contraception (HC)

- HC is unlikely to significantly increase diabetes risk, but does lower ovarian and endometrial cancer risk
- HC is more effective than metformin in treating menstrual irregularity and hirsutism
- Women with PCOS have more contraindications to the use of HCs than other women
  - Screen women carefully before prescribing

Adverse effects of the common treatments for polycystic ovary syndrome: A systematic review and meta-analysis.

Domecq JP\textsuperscript{1,2}, Prutsky G\textsuperscript{1,2}, Mullan R\textsuperscript{1,3}, Sundaresh V\textsuperscript{1}, Wang A\textsuperscript{1}, Erwin P\textsuperscript{1}, Welt C\textsuperscript{4}, Ehrmann D\textsuperscript{5}, Montori V\textsuperscript{1,2,6}, Murad MH\textsuperscript{1,7}

Conclusions: Drugs commonly used to treat PCOS appear to be associated with low risk of severe adverse effects. Patients and clinicians must carefully extrapolate and consider safety data from other populations in the context of PCOS.
Limited Role for Metformin

- **3.5** We suggest against the use of metformin as a first-line treatment of cutaneous manifestations, prevention of pregnancy complications, or for the treatment of obesity. (2/**☆☆☆☆☆☆☆**)

- **3.6** We recommend metformin in women with PCOS who have T2DM or IGT who fail lifestyle modification. (1/☆☆☆☆☆☆☆☆☆☆☆☆☆☆☆☆☆☆☆) For women with PCOS with menstrual irregularity who cannot take or do not tolerate Hormonal Contraceptives, we suggest metformin as second-line therapy. (2/☆☆☆☆☆☆☆☆☆☆☆☆☆☆☆☆☆☆☆)

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**Pregnancy Rate by BMI Group in Infertile Women with PCOS**

* Significant compared to baseline

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**Fecundity per Ovulation in PPCOS**
• AUTHORS' CONCLUSIONS: No RCTs were located that assessed the effects of preconception advice on the chance of a live birth or other fertility outcomes in people who perceived that they may be infertile and were investigating the possibility of medical treatment to address subfertility.
Lifestyle modification programs in polycystic ovary syndrome: Systematic review and meta-analysis.


Conclusions: The available evidence suggests that Lifestyle Modification decreases insulin resistance in overweight or obese women with PCOS. Metformin has similar effects. Translation of these short-term effects to patient-important outcomes – beyond diabetes prevention, remains uncertain.

Treatment Issues

• Hormonal contraceptives first line for menstrual disorder/hirsutism
• Clomiphene citrate first line for infertility
  – Newer Data Emerging about Letrozole
• Lifestyle first line for CVD risk factor improvement

Adolescents-Less Data, More Speculation

• Focus on hyperandrogenism as the diagnostic criterion (i.e. hirsutism or hyperandrogenemia)
  – Oligo-ovulation and polycystic ovaries are a normal part of reproductive maturation
  – Begin Hormonal Contraceptives for stigmata at Tanner Stage 4 if amenorrheic with exclusion of other causes
• Is there an expanded role for metformin/lifestyle in this population?
PCOS Guidelines Summary

• A Particularly Challenging Guideline
  – Complex, Controversial Diagnosis Lifetime Implications
    (Severity?)

• Difficult to Please all Constituencies
  – We followed Endocrine Society policies
  – We responded to all feedback we received from
    Endocrine Society Committees and Membership

What could the Clinical Chemist do for the Clinician Managing PCOS?

Guideline Based
• Diagnostic Panel
  – T and SHBG
  – 17-OHP, PRL, TSH
• Fasting Metabolic Panel
  – Lipid profile
  – 75g 2h OGTT with 0 and 2h Glucose

Research Based
• Fertility Panel
  – AMH, FSH, Anti-Chlamydial Antibody
Disclosures

- Grant/Research Support: Sysmex America, Siemens Healthcare Diagnostics
- Salary/Consultant Fees: None
- Board/Committee/Advisory Board Membership: NACB, ABCC
- Stocks/Bonds: None
- Honorarium/Expenses: Sysmex America, Siemens Healthcare Diagnostics
- Intellectual Property/Royalty Income: None

Definitions of PCOS

NIH-1990 Criteria
1. Hyperandrogenism and/or hyperandrogenemia,
2. Menstrual dysfunction,
3. Exclusion of other known disorders

Rotterdam 2003 Criteria (2 of 3)-ESHRE/ASRM*
1. Oligo and/or anovulation, or
2. Clinical and/or biochemical signs of hyperandrogenism, or
3. Polycystic ovaries (PCO) and
4. Exclusion of related disorders

Androgen Excess-PCOS Society 2006 Criteria
1. Clinical and/or biochemical hyperandrogenism with either oligo/anovulation and/or PCO, excluding related disorders

*Supported by:
- 2012 NIH Evidence-based Methodology Workshop on PCOS
- 2013 Endocrine Society Practice Guideline (JCEM 98: 4565-4592)
Phenotypes of PCOS

<table>
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<tr>
<th>Potential Phenotypes</th>
<th>A</th>
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<td>Hyperandrogenemia</td>
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<tr>
<td>Oligomenorrhea</td>
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<td>+</td>
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<tr>
<td>Polycystic ovaries</td>
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Diagnosis of PCOS in Adults

• Detailed clinical history – establish onset of symptoms
• Confirmation of PCOS features, including:
  • Androgen Excess (hyperandrogenemia and/or hyperandrogenism)
  • Ovulatory dysfunction
  • Polycystic ovarian morphology
• Exclusion of related disorders in all patients:
  • Thyroid dysfunction
  • Hyperprolactinemia
  • Non-Classic CAH
• Exclusion of other related disorders in specific patients:
  • Pregnancy
  • Hypothalamic Amenorrhea
  • Primary Ovarian Insufficiency
  • Acromegaly
  • Cushing’s Syndrome
  • Androgen Secreting Neoplasms

Diagnosis of PCOS in Adolescents

Diagnostic Criteria
• Clinical and/or biochemical hyperandrogenism
• Persistent Oligomenorrhea (2 or more years)
• Rule out related syndromes

Evidence
• Polycystic ovaries and oligomenorrhea are common particularly in the first year of menarche
• Signs of Hyperandrogenism differ in adolescence - Acne is common and non-specific and hirsutism is less severe
• Hyperandrogenemia – Normal ranges for androgens in puberty are not well defined
• Polycystic Ovaries – Rotterdam criteria are for adults – AMH may be an alternative
Confirmation of Androgen Excess

- Hyperandrogenemia
  - Supranormal concentrations of circulating androgens
    - Testosterone (T) – total bioavailable or free
    - Adrenal Androgens (rare) - DHEA, and/or DHEA-S
  - Total Testosterone assays have limitations
    - Not standardized across platforms
      - Centers for Disease Control – Testosterone standardization program – to date – 8 LC/MS/MS methods and 1 immunoassay
    - Subject to significant biological variability – diurnal, menstrual cycle/OCP therapy, age, race/ethnicity

Free Testosterone Assays

- Testosterone circulates free (2 – 3%) and associated with binding proteins (albumin and Sex Hormone Binding Globulin (SHBG))
- Free Testosterone correlates with clinical presentation of PCOS and is elevated in 60 – 70% of women with clinical hyperandrogenism
- Serum Free Testosterone + SHBG concentrations together are highly predictive of PCOS
- Calculation Methods are the most common and are dependent on robust assays for TT and SHBG with appropriate reference intervals

**Recommended Methods**
1. Equilibrium dialysis
2. Direct Testosterone measurement by GC-MS or LC/MS/MS following extraction
3. Calculation of free Androgen Index from TT and SHBG
4. Mathematical Modeling = i.e. \[ \%FT = 6.11 - 2.38 \log_{10} \text{SHBG} \times 10^9 \]

The Free Androgen Index and SHBG in PCOS

- Free Androgen Index (FAI) (Total Testosterone/SHBG) X100
- Correlates with free Testosterone in women (not men)
- SHBG concentrations are decreased in some women with PCOS, but may be related to obesity and not PCOS
- FAI decreases shown with lifestyle modification in PCOS women
**Total Testosterone Immunoassays**

- Total Testosterone: Immunoassays not recommended for evaluation of women and children

**Recommendations for Testosterone Normal Ranges in Women**

- Established in normal women
- Exclude those with: menstrual/ovulatory dysfunction, hyperandrogenism, and other PCOS related symptoms
- Use age, race, and BMI specific ranges
- Collect samples at same time during the day and menstrual cycle

**DHEA and DHEA-S**

- Made in the Adrenals
- DHEA-S – primary form
- Combined they are the most abundant steroid
- DHEA-S preferred test abundance and long half life
- ~25-35% of PCOS pts w/ increased DHEA-S
- DHEA-S may be due to sulfotransferase activity, not steroid synthesis
Antimüllerian Hormone and PCOS

- Healthy women: synthesized by the ovarian granulosa cells, circulating concentrations decline with age, marker of ovarian reserve
- AE/PCOS: Significantly increased, concentrations correlate with disease severity, ovarian dysfunction and fertility, and hyperandrogenism
- May be used to differentiate among various AE disorders

Identification of Ovulatory Dysfunction

<table>
<thead>
<tr>
<th>Follicular phase</th>
<th>Luteal phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days of menstrual cycle</td>
<td>Progesterone</td>
</tr>
<tr>
<td>0 4 5 12 16 20 24 28</td>
<td>Progesterone</td>
</tr>
</tbody>
</table>

**Annulation**

- Bleeding:
  - <21 days apart
  - >35 days apart
- Low luteal phase P4

**Mid-luteal phase** (day 20 – 24) progesterone >10 ng/mL - normal ovulation.

J. Clin Pathol 2003; 56:261-7

Confirmation of Polycystic Ovaries

**Limitations**

- Not standardized
- Not specific for PCOS
- High resolution transvaginal ultrasound technology not always available or appropriate
- Subjective

(Rotterdam Criteria):

- >12 follicles measuring 2 – 9 mm (99% Specificity and 75% sensitivity)
- Increased Ovarian Volume > 10 cm³
- No Dominant follicle in either Ovary

- No Oral Contraceptives

**Limitations**

- Not standardized
- Not specific for PCOS
- High resolution transvaginal ultrasound technology not always available or appropriate
- Subjective
Gonadotropin Abnormalities

- Increased secretion of LH – GnRH/LH pulse frequency with normal to decreased FSH
- Ratio LH/FSH > 2 – 3 suggestive of PCOS
- LH pulsatility affected by BMI
- LH/FSH ratio – not diagnostic in obese women

Insulin Resistance & Metabolic Syndrome

- IR: 50 – 75% Women with PCOS, MS: ~33% PCOS cases
- Clinical symptoms: hypertension, central obesity, acanthosis nigricans
- Methods to establish Insulin Resistance in PCOS are controversial.
  1. Euglycemic clamp: "Gold Standard". IV glucose and insulin over 2hrs. Maintain normal fasting blood glucose concentrations. The more glucose needed, the more likely the patient is insulin resistant. Caveats: expensive, invasive, labor intensive.
  2. OGTT – Recommended by ACOG for assessment of DMII and IGT

<table>
<thead>
<tr>
<th>Glucose (mg/dL)</th>
<th>Interpretation</th>
<th>Insulin (mcU/L)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting &lt; 126</td>
<td>111 – 126 mg/dL, impaired fasting</td>
<td>&lt; 25*</td>
<td>*Assay dependent</td>
</tr>
<tr>
<td>2hr &lt; 140</td>
<td>141 – 200 mg/dL, impaired tolerance</td>
<td>&lt; 50*</td>
<td>80 mcU/L = IR</td>
</tr>
</tbody>
</table>

Fasting Methods for Insulin Resistance

- Glucose/Insulin ratio (G/I): G/I < 4.5 – IR in PCOS
- Fasting Insulin – No real cut-off for insulin resistance
  - Lack of assay standardization
  - No clear association between clinical dz or response to therapy
- Guidelines:
  1. "There is no role for routine testing for insulin in most patients with diabetes..." including PCOS patients
  2. "There is no role for measurement of insulin in assessment of cardiometabolic risk" including in PCOS patients.”
  3. "Optional tests to consider: Fasting insulin levels in younger women, those with severe stigmata of IR and hyperandrogenism, or those undergoing ovulation induction"

NACB Guidelines and Recommendations for Laboratory Analysis in the Diagnosis and Management of Diabetes Mellitus . 2011
ACOG Practice Bulletin #108, October 2009. PCOS
PCOS – A Diagnosis of Exclusion

Disorders to exclude in all women with a PCOS picture:

- **Thyroid dysfunction** –
  - Considered in Anovulatory AE/PCOS
  - Accounts for < 1% of patients with androgen excess
  - Serum TSH > normal – hypothyroid, < normal – hyperthyroid

- **Hyperprolactinemia** –
  - Considered in Anovulatory AE/PCOS
  - Present in up to 30% of patients with amenorrhea
  - Accounts for < 1% of patients with androgen excess
  - Associated with excess production of adrenal androgens < 1% of patients with androgen excess
  - Serum Prolactin > normal

Non-Classic Congenital Adrenal Hyperplasia

- **CAH** - Impaired cortisol biosynthesis
  - **Classic**: early presentation- picked up on newborn screen
  - **Non-classic**: premature puberty, AE, menstrual abnormalities

Routine screening for NCCAH
- Basal 17-hydroxyprogesterone (17-OHP)
  - Collected early morning, during follicular phase
- Cosyntropin (ACTH) stimulation with complete adrenal steroid profile:
  - Borderline cases
  - Differentiate 21-hydroxylase deficiency from other mutations

Diagnoses to Rule out in Women with Amenorrhea

- Pregnancy – considered in premenopausal women with amenorrhea and other symptoms
  - Serum human chorionic gonadotropin (hCG) above normal
- Hypothalamic amenorrhea – considered in women with Amenorrhea and low body weight, excessive exercise, etc...
  - Serum FSH and LH and low normal or low and serum estradiol is low
- Primary Ovarian Insufficiency – considered in women with Amenorrhea and signs of estrogen deficiency
  - Serum FSH is elevated with low serum estradiol
PCOS– Other Diagnoses to Rule out

Cushing’s Syndrome
- Overlap with clinical and biochemical signs of PCOS
  > 80% menstrual irregularities,
  > 60% hirsutism, and > 40% with
  Acne, some with PCO, hGAM,
- Patients with multiple, suspicious clinical signs should be screened
  - 24 hr urinary free cortisol – Elevated,
  - Midnight salivary cortisol – Elevated, or
  - Overnight Dexamethasone suppression test – Not suppressed
- Cushing’s syndrome is rare in hyperandrogenic women (<1%)


Androgen Secreting Neoplasms (ASN)
- Adrenal or Ovarian
- Overlap with clinical and biochemical signs of PCOS
- Clinical hx- rapid onset of severe symptoms
- Rare (<0.3%) of hyperandrogenic patients
- Marked increase in Testosterone and DHEAS

Patients with rapid onset, severe AE should be screened
- Serum total Testosterone > 1.5 ng/mL not sensitive for ASN
- Ultrasound of Ovaries, MRI of Adrenals

Acromegaly
- Excessive growth hormone after skeletal maturity (closure of long bones)
- 90% are pituitary adenoma secreting GH
- Several overlapping signs with PCOS – including oligomenorrhea, skin changes and hirsutism.
- Work up should be considered in women with signs of a pituitary tumor and/or growth hormone excess (headaches, visual field disturbances, macroglossia, increased size of hands or feet, etc…)
- Laboratory Work up
  - Screening – Elevated Insulin like growth factor – 1 (IGF-1)
  - Confirmation - Oral Glucose Tolerance testing (OGTT)
  - Glucose induced GH suppression test
  - Visualization of pituitary mass on MRI
Long Term Management of PCOS

- **Type II Diabetes** – PCOS women have a 5 – 10x increased risk
  - All patients should be screened for Impaired Glucose Tolerance (IGT) with 2 hr OGTT
  - Hemoglobin A1c may be less sensitive for diagnosis of IGT
  - Normal – re-screen every 3 - 5 years (arbitrary due to lack of evidence)

**CVD Risk Assessment**

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Odds ratio</th>
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<tbody>
<tr>
<td>BMI</td>
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<tr>
<td>Age</td>
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</tr>
<tr>
<td>Hypertension</td>
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</tr>
<tr>
<td>Diabetes</td>
<td>3.0</td>
</tr>
<tr>
<td>ATHEROSCLEROSIS INDEX</td>
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</tr>
<tr>
<td>Fasting glucose</td>
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</tr>
<tr>
<td>2 hour glucose</td>
<td>1.5</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>1.1</td>
</tr>
<tr>
<td>HDL cholesterol</td>
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Consensus Statement by the AES on Assessment of CV Risk (JCEM 2010)

Current Recommendations for PCOS Diagnostic Criteria and Work up

**Diagnostic Criteria**
- Rotterdam 2003 – NIH, Endocrine Society (ES), and European Society of Endocrinology (ESE)
- Androgen Excess-PCOS Society 2006 Criteria – Androgen Excess/PCOS Society (AES)

**Identification of hyperandrogenism**
- Improve and harmonize methods – NIH, AES
- Implement ethnic/age-specific reference intervals – NIH, European Society of Human Reproduction and Embryology/American Society of Reproductive Medicating (ESHRE/ASRM)
- Hirsutism is a good marker of hyperandrogenism – ESHRE/ASRM, AES
- Free or Bioavailable Testosterone Calculations = First line testing – PCOS Australian Alliance (PCOS-AA)

PCOS Biomarkers – What’s new?

The –Omis approach
- **Metabolomics** – Abnormalities in several pathways including: protein, lipid, carbohydrate, TCA cycle metabolites – may by PCOS phenotype specific
- **Proteomics** – profiling has identified novel markers involved in metabolic pathways as well as inflammatory, cytoskeletal, oxidative stress, and more...
- **Genomics** – microRNA, Genome Wide Association Studies

The bottom line – We need to understand the underlying physiology in order to identify good markers of disease.
Conclusions

• Polycystic Ovary Syndrome causes significant morbidity worldwide.
• Proper diagnosis and management of PCOS reduces associated symptoms and may prevent comorbidities.
• Improvement and standardization of diagnostic criteria for PCOS is required: sensitive and standardized testosterone assays, less subjective clinical and ultrasonographic evaluations.
• Long-term outcome and genetic studies are necessary to better understand and manage PCOS.
• Collaboration among caregivers (primary care, endocrinologists, OB-GYNs, radiologists, and laboratorians) may improve diagnostic efficiency, accuracy, and management of a PCOS patient.

References