WHY NEW DIAGNOSTIC CRITERIA FOR DIFFERENT PCOS PHENOTYPES ARE URGENTLY NEEDED

Ricardo Azziz, M.D., M.P.H., M.B.A.
Chief Officer of Academic Health & Hospital Affairs
State University of New York (SUNY) System Administration
Research Professor, Health Policy, Management & Behavior
School of Public Health, Univ. at Albany, SUNY
Why New Diagnostic Criteria For Different PCOS Phenotypes Are Urgently Needed

• Introduction

• Phenotyping
  – Criteria vs. phenotype vs. features
  – Defining features
  – Defining ‘normal’
  – Referral bias

• Epidemiology
  – Medical bias in population selection
  – Negative diagnostic bias
  – Role of ethnicity
Introduction
POLYCYSTIC OVARY SYNDROME (PCOS): THE BASICS

• PCOS is a common, phenotypically heterogeneous, endocrine-metabolic-reproductive disorder

• PCOS is a complex genetic trait

• PCOS is characterized by the presence of: a) ovulatory/menstrual dysfunction, b) hyperandrogenism, and c) polycystic-appearing ovaries

• PCOS is associated with ↑ risk of endometrial malignancy, metabolic dysfunction (e.g. T2DM), and reproductive failure (e.g. subfertility)

• PCOS is highly prevalent, affecting between 5% and 20% of women depending on definition
STEIN-LEVENTHAL SYNDROME (1935)

- Report of 7 cases with oligo/amenorrhea and bilateral polycystic ovaries
  - Three were obese
  - Five were hirsute (one obese) and one thin acneic

- Wedge resection resulted in two pregnancies, and regular cycles in remaining
Differential Diagnosis Among 873 Consecutive Untreated Patients Evaluated for Androgen Excess

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Total #</th>
<th>% Prevalence</th>
<th>% Unbiased Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Specific disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASN</td>
<td>2</td>
<td>0.2%</td>
<td></td>
</tr>
<tr>
<td>CAH</td>
<td>6</td>
<td>0.7%</td>
<td></td>
</tr>
<tr>
<td>NCAH</td>
<td>18</td>
<td>2.1%</td>
<td>1.6%</td>
</tr>
<tr>
<td>HAIRAN</td>
<td>33</td>
<td>3.8%</td>
<td>3.1%</td>
</tr>
<tr>
<td><strong>Disorders of exclusion</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCOS</td>
<td>716</td>
<td>82.0%</td>
<td></td>
</tr>
<tr>
<td>IH</td>
<td>39</td>
<td>4.5%</td>
<td>4.7%</td>
</tr>
<tr>
<td>HA+Hirsutism</td>
<td>59</td>
<td>6.8%</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>873</td>
<td>100.0%</td>
<td></td>
</tr>
</tbody>
</table>

**THE PATHOPHYSIOLOGY OF PCOS**

- **Progesterone**
- **Insulin resistance**
  - Insulin resistance of muscle and liver
  - Adipocyte dysfunction
- **Hyperinsulinaemia**
- **Pancreas**
- **Ovary**
- **Ovulatory dysfunction**
- **Hyperandrogenism**
  - Adrenal androgens
  - ↓SHBG levels in the liver
- **Follicular arrest**
  - PCOM

**Abnormal GnRH pulsation**

**Abnormal gonadotropin levels**

**↑LH/FSH ratio**

**Hypothalamus**

**Pituitary gland**

# PREVALENCE LONG-TERM MORBIDITIES OF PATIENTS WITH PCOS

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Endometrial</th>
<th>↑, extent not certain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>↔</td>
<td></td>
</tr>
<tr>
<td>Ovarian</td>
<td>↔^a</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Metabolic</th>
<th>IGT</th>
<th>↑, in 20-30% of PCOS^b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 2 DM</td>
<td>↑, in 4-10% of PCOS (2-6 fold controls)^c</td>
<td></td>
</tr>
<tr>
<td>Metabolic SX</td>
<td>↑, in 10-50% of PCOS^c</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CVD</th>
<th>Dyslipidemia</th>
<th>↑, in 15%-50% of PCOS (1.5-2.0 fold of controls)^c</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>↑, in 10% to 40% of PCOS (1.4 to 3.5-fold of controls)</td>
<td></td>
</tr>
<tr>
<td>Cerebrovascular</td>
<td>↑ in postmenopause, in ~3% of PCOS^a</td>
<td></td>
</tr>
<tr>
<td>CHD/MI events</td>
<td>↑ in postmenopause (1.5-4.5 fold of controls^a)</td>
<td></td>
</tr>
</tbody>
</table>

^a Additional studies needed

^b Risk is higher in women with obesity or a family history of Type 2 DM

^c Less in those women with normal weight or who are less than 30 years old

THE ECONOMIC BURDEN OF PCOS IN THE U.S. IS AT LEAST 4 BILLION DOLLARS ANNUALLY:
Attributable Care Provided During The Reproductive Years

<table>
<thead>
<tr>
<th></th>
<th>Annual costs (in millions)</th>
<th>% of total costs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>For Initial Evaluation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>99</td>
<td>2.3</td>
</tr>
<tr>
<td><strong>For Treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menstrual dysfunction/AUB</td>
<td>1,350</td>
<td>30.9</td>
</tr>
<tr>
<td>Infertility</td>
<td>533</td>
<td>12.2</td>
</tr>
<tr>
<td>Type 2 DM</td>
<td>1,766</td>
<td>40.4</td>
</tr>
<tr>
<td>Hirsutism</td>
<td>622</td>
<td>14.2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>4,370</td>
<td>100</td>
</tr>
</tbody>
</table>

Azziz et al. J Clin Endocrinol Metab 90: 4650, 2005
Phenotyping

- Criteria vs. phenotype vs. features
- Defining features
- Defining ‘normal’
- Referral bias
CRITERIA OF PCOS

• **NIH 1990:** Both features, *after exclusion of other known disorders:*
  – Hyperandrogenism and/or hyperandrogenemia
  – Oligo-ovulation

• **Rotterdam 2003:** At least 2 of 3 features, *after exclusion of other known disorders:*
  – Oligo- or anovulation,
  – Clinical and/or biochemical signs of hyperandrogenism,
  – Polycystic ovaries

• **AE-PCOS Society 2006:** Both features, *after exclusion of other known disorders:*
  – Hyperandrogenism: Hirsutism and/or hyperandrogenemia
  – Ovarian dysfunction: Oligo-anovulation and/or PCOM
ROTTERDAM 2003 AND AE-PCOS 2006 ARE EXPANSIONS OF NIH 1990
## DIAGNOSTIC CRITERIA VS. PHENOTYPES OF PCOS

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>1990 US NIH criteria</th>
<th>2006 AE-PCOS criteria</th>
<th>2003 Rotterdam criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenotype A</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Phenotype B</td>
<td>Present</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Phenotype C</td>
<td>Present</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Phenotype D</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Hyperandrogenism and hirsutism**
  - Present
  - Present
  - Present
  - Absent

- **Ovulatory dysfunction**
  - Present
  - Present
  - Absent
  - Present

- **Polycystic ovarian morphology**
  - Present
  - Absent
  - Present
  - Present

_Nature Reviews | Disease Primers_

DEFINING THE FEATURES OF PCOS

• Hyperandrogenism
  – Biochemical (androgen levels), and/or
  – Clinical (e.g. hirsutism)

• Ovulatory dysfunction
  – Menstrual dysfunction, and/or
  – Ovulation detection

• Polycystic ovarian morphology (by ultrasound)
  – Volume and/or
  – AFC (follicle numbers)
ORIGIN OF CIRCULATING ANDROGENS

Ovary

- 2% → Dehydroepiandrosterone sulfate
- 5% → Dehydroepiandrosterone
- 25% → Testosterone
- 50% → $\Delta^4$-Androstenedione

Adrenal

- 50% → $\Delta^4$-Androstenedione
- 25% → Testosterone
- 95% → Dehydroepiandrosterone
- 98% → Dehydroepiandrosterone sulfate

*Percentages indicate the relative amounts of androgens originating from sources to the left of the arrows*
ANDROGEN LEVELS IN PCOS: LIMITED SENSITIVITY OF MEASURING ONLY TOTAL T

In NIH 1990 (classic) PCOS patients, using high quality sensitive assays (for TT, FT & DHEAS) ~75% demonstrate HA

Alternatively, in NIH 1990 (classic) PCOS patients if TT alone is measured (using a high quality RIA) then only 33% of demonstrate HA

~50% of PCOS phenotype studies assessed only TT, usually using a chemiluminescent platform assay, so one can expect that in these studies detection rates for HA will be well less than 30%

SPECIFICITY AND PREDICTIVE VALUE OF CIRCULATING TT & FT, ASSESSED BY LC-MS/MS, FOR THE DIAGNOSIS OF PCOS

<table>
<thead>
<tr>
<th>Cutoff value</th>
<th>33</th>
<th>33</th>
<th>35</th>
<th>35</th>
<th>35^a</th>
<th>35</th>
<th>40</th>
<th>40^b</th>
</tr>
</thead>
<tbody>
<tr>
<td>TT ≥ (ng/dL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FT &gt; (pg/mL)</td>
<td>3.5</td>
<td>4</td>
<td>3</td>
<td>3.3</td>
<td>3.5^a</td>
<td>4</td>
<td>3.5</td>
<td>4^b</td>
</tr>
<tr>
<td>Sensitivity, %</td>
<td>73</td>
<td>66</td>
<td>74</td>
<td>73</td>
<td>71</td>
<td>65</td>
<td>70</td>
<td>64</td>
</tr>
<tr>
<td>Specificity, %</td>
<td>89</td>
<td>93</td>
<td>83</td>
<td>84</td>
<td>89</td>
<td>93</td>
<td>91</td>
<td>94</td>
</tr>
<tr>
<td>PPV, %</td>
<td>40</td>
<td>51</td>
<td>33</td>
<td>34</td>
<td>42</td>
<td>51</td>
<td>46</td>
<td>54^b</td>
</tr>
<tr>
<td>NPV, %</td>
<td>97</td>
<td>96</td>
<td>97</td>
<td>97</td>
<td>97</td>
<td>96</td>
<td>96</td>
<td>96^b</td>
</tr>
<tr>
<td>2 x PPV + NPV</td>
<td>177</td>
<td>198</td>
<td>163</td>
<td>165</td>
<td>181</td>
<td>198</td>
<td>188</td>
<td>204^b</td>
</tr>
<tr>
<td>Sensitivity, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specificity, %</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>PPV, %</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPV, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 x PPV + NPV</td>
<td></td>
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</tr>
</tbody>
</table>

^a The level(s) that have the highest combined PPV and NPV values useful for evaluation of patients in the clinical setting.

^b The level(s) that have the highest combined PPV and NPV values useful for epidemiological studies.
LIMITATIONS OF DEFINING PCOS BY ANDROGEN LEVELS

• Suppressed more rapidly by hormonal suppression than other clinical features, e.g. hirsutism
• Inaccurate and variable methods of measurement
• Normative values vary from lab to lab; and often are based on bias reference populations
• Little normative data in adolescent and older women
• May be altered by age (DHEAS) and BMI (SHBG & Free T)
• Wide variance in normal population, because....

• No tight endogenous counter-regulatory mechanism for androgens in humans
EVALUATING FOR CLINICAL HYPERANDROGENISM: THE MODIFIED F-G (mFG) SCORE
EVALUATING FOR CLINICAL HYPERANDROGENISM: THE MODIFIED F-G (mFG) SCORE

Yildiz et al, Hum Reprod Update 2010;16:51–64
Cluster analysis indicates that an mFG score of ≥3 may indicate abnormal terminal hair growth.
THE IMPACT OF REFERRAL BIAS ON THE PHENOTYPE OF PCOS

Overall, in this small analysis, referral PCOS subjects had a greater BMI as compared with local controls, which was not immediately apparent or was less severe in women with PCOS detected in unselected populations.

Epidemiology

- Medical bias in population selection
- Negative diagnostic bias
- Role of ethnicity
DETERMINING THE PREVALENCE OF PCOS

• **Type 1:** Population-based

• **Type 2:** Defined population undergoing assessments for non-medical reasons

• **Type 3:** Defined population undergoing assessment for unrelated medical assessment
<table>
<thead>
<tr>
<th>Reference</th>
<th>Location</th>
<th>Population</th>
<th>% PCOS in population</th>
<th>Mean BMI of population (kg/M²)</th>
<th>% Obesity in country*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knochenhauer et al, 1998</td>
<td>Birmingham, AL, USA</td>
<td>Pre-employment physical at one university</td>
<td>4.7</td>
<td>24.9</td>
<td>32.2%</td>
</tr>
<tr>
<td>Diamanti-Kandarakis et al, 1999</td>
<td>Lesbos, Greece</td>
<td>Free medical evaluation offered to local population</td>
<td>6.8</td>
<td>26.7</td>
<td>21.9%</td>
</tr>
<tr>
<td>Michelmore et al, 1999</td>
<td>Oxford, UK</td>
<td>Recruited from 2 universities and 2 general practices, for ‘a study of women’s health issues’</td>
<td>8.0</td>
<td>23.0</td>
<td>23.0%</td>
</tr>
<tr>
<td>Asuncion et al, 2000</td>
<td>Madrid, Spain</td>
<td>Caucasian female blood donors</td>
<td>6.5</td>
<td>23.8</td>
<td>13.1%</td>
</tr>
</tbody>
</table>
# Prevalence of PCOS by Differing Criteria in Unselected Adult Women Worldwide

<table>
<thead>
<tr>
<th>Reference</th>
<th>Location</th>
<th>Population</th>
<th>% PCOS in population by NIH 1990</th>
<th>% PCOS in population by AE-PCOS 2006</th>
<th>% PCOS in population by Rotterdam 2003</th>
<th>Mean BMI of population (kg/M²)</th>
<th>% Obesity in country*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knochenhauer et al, 1998</td>
<td>Birmingham, AL, USA</td>
<td>269</td>
<td>4.0%</td>
<td></td>
<td></td>
<td>26.9</td>
<td>33.8%</td>
</tr>
<tr>
<td>Diamanti-Kandarakis et al, 1999</td>
<td>Lesbos, Greece</td>
<td>192</td>
<td>6.8%</td>
<td></td>
<td></td>
<td>26.7</td>
<td>18.1%</td>
</tr>
<tr>
<td>Michelmore et al, 1999</td>
<td>Oxford, UK</td>
<td>224</td>
<td>8.0%</td>
<td></td>
<td></td>
<td>23.0</td>
<td>23.0%</td>
</tr>
<tr>
<td>Asuncion et al, 2000</td>
<td>Madrid, Spain</td>
<td>154</td>
<td>6.5%</td>
<td></td>
<td></td>
<td>23.8</td>
<td>16.0%</td>
</tr>
<tr>
<td>Lowe et al, 2005</td>
<td>Melbourne, Australia</td>
<td>100</td>
<td></td>
<td>5.5%</td>
<td></td>
<td>--</td>
<td>24.6%</td>
</tr>
<tr>
<td>Yildiz et al, 2008</td>
<td>Birmingham, AL, USA</td>
<td>675</td>
<td>9.4%</td>
<td></td>
<td></td>
<td>35.7</td>
<td>33.8%</td>
</tr>
<tr>
<td>Chen et al, 2008</td>
<td>Guangzhou, China</td>
<td>915</td>
<td>2.2%</td>
<td></td>
<td></td>
<td>20.9</td>
<td>--</td>
</tr>
<tr>
<td>Kumarapeli et al, 2008</td>
<td>Gampaha, Sri Lanka</td>
<td>2,915</td>
<td></td>
<td>6.3%</td>
<td></td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>March et al, 2009</td>
<td>Adelaide, Australia</td>
<td>728</td>
<td>8.7%</td>
<td>12.0%</td>
<td>17.8%</td>
<td>24.6%</td>
<td></td>
</tr>
<tr>
<td>Moran et al, 2010</td>
<td>Mexico City, Mexico</td>
<td>150</td>
<td>6.0%</td>
<td>6.6%</td>
<td>27.5</td>
<td>30.0%</td>
<td></td>
</tr>
<tr>
<td>Tehrani et al, 2011</td>
<td>Tehran, Iran</td>
<td>1,002</td>
<td>8.5%</td>
<td></td>
<td></td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>Tehrani et al, 2011</td>
<td>Ghazin, Kermanshah, Golestan &amp; Hormozgan, Iran</td>
<td>1,126</td>
<td>7.1%</td>
<td>11.7%</td>
<td>14.6%</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>Mehrabian et al, 2011</td>
<td>Isfahan, Iran</td>
<td>820</td>
<td>7.0%</td>
<td>8.2%</td>
<td>15.2%</td>
<td>25.7</td>
<td>--</td>
</tr>
<tr>
<td>Yildiz et al, 2012</td>
<td>Ankara, Turkey</td>
<td>392</td>
<td>6.1%</td>
<td>15.3%</td>
<td>19.9%</td>
<td>24.2</td>
<td>15.2%</td>
</tr>
</tbody>
</table>

**Personal communication by author
PCOS PREVALENCE (95% CI) RATES ACCORDING TO UNSELECTED POPULATION STUDIES: META-ANALYSIS

Bozdag et al, Hum Reprod. 2016;31:2841-2855
NEGATIVE DIAGNOSTIC BIAS IN EPIDEMIOLOGIC STUDIES OF PCOS

- The minimal diagnosis of PCOS generally requires:
  - H&P (incl. mFG scoring)
  - TVU/S
  - Blood testing to exclude other disorders
  - F/u of blood tests to exclude other disorders (e.g. ACTH stimulation test to R/O adrenal hyperplasia)

- The minimal diagnosis of controls generally requires:
  - H&P (incl. mFG scoring)

- This results in negative detection bias for PCOS, and underestimation of PCOS prevalence
  - Greater number of PCOS subjects do not complete their evaluation, compared to controls
NEGATIVE DIAGNOSTIC BIAS IN EPIDEMIOLOGIC STUDIES OF PCOS

• One approach that address the negative detection bias is to assign a ‘diagnostic weight’ to those subjects not completing their evaluation

• Subdivide subjects into subphenotypes of ‘possible PCOS’ based solely on H&P
  – Hirsutism + oligo-amenorrhea
  – Oligo-amenorrhea only
  – Hirsutism only

• In each subphenotypic group determine:
  – # Proven PCOS, i.e. completed evaluation and known to have PCOS
  – # Proven not-PCOS, i.e. completed evaluation and known not to have PCOS
  – # Possible PCOS, i.e. not completing their evaluation

• Assign a ‘diagnostic weight (DW)’ to those remaining subjects with ‘Possible PCOS’
  – DW for each subphenotype = # Proven PCOS / Total # of subjects completing evaluation
  – Additional number of ‘proven’ PCOS = # Possible PCOS x DW
NEGATIVE DIAGNOSTIC BIAS IN EPIDEMIOLOGIC STUDIES OF PCOS

• Impact of addressing incomplete phenotyping using ‘diagnostic weighing’
  
  – 4.0% of 270 subjects undergoing a pre-employment physical at UAB between 1995–1996, and completing their evaluation, had PCOS (Knochenhauer et al, 1998)
  
  – 6.5% of 400 subjects undergoing a pre-employment physical at UAB between 1998–1999, including weighing those with incompletely evaluated ‘possible PCOS’, had PCOS (Azziz et al, 2004)

The prevalence of PCOS in 400 unselected black and white women of the S.E. U.S. is shown in the bar chart. The prevalence is 8.0% for black women (n=223), 4.8% for white women (n=166), and 6.6% for all women (n=400). This data is from Azziz et al. J Clin Endocrinol Metab 89:2745, 2004.
THANK YOU