Diagnosis and Management of Polycystic Ovary Syndrome During Adolescence: Questions and Controversies

2017 Illinois-AACE 2017 Annual Meeting
October 14, 2017
Learning Objectives

1) Understand the challenges in making a definitive diagnosis of polycystic ovary syndrome during the adolescent years.

2) Discuss the long term reproductive and metabolic outcomes associated with polycystic ovary syndrome.

3) Discuss responses to various treatment approaches for polycystic ovary syndrome during adolescence.

4) Understand the evidence for the importance of early origins in the pathogenesis.
## Polycystic Ovary Syndrome (PCOS) – Diagnostic Criteria

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• 3 of 3:</td>
<td>• 2 of 3:</td>
<td>• 2 of 2:</td>
</tr>
<tr>
<td>✓ Chronic anovulation</td>
<td>✓ Oligo- and/or anovulation</td>
<td>✓ Clinical and/or biochemical hyperandrogenism</td>
</tr>
<tr>
<td>✓ Clinical and/or biochemical hyperandrogenism</td>
<td>✓ Clinical and/or biochemical hyperandrogenism</td>
<td>✓ Ovarian dysfunction</td>
</tr>
<tr>
<td>✓ Exclusion of other possible etiologies (CAH, androgen secreting neoplasm)</td>
<td>✓ Polycystic ovaries</td>
<td>- oligo-anovulation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- polycystic ovaries</td>
</tr>
</tbody>
</table>
PCOS Phenotypes

Diamanti-Kandarakis & Dunaif, Endocrine Reviews 2012
# Phenotypic Heterogeneity - PCOS

## Potential PCOS Phenotypes

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>NIH</th>
<th>Rotterdam AE-PCOS</th>
<th>Rotterdam AE-PCOS</th>
<th>Rotterdam AE-PCOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperandrogenism</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Hyperandrogenemia</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Oligo-anovulation</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>PCOM</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

- : Positive
- : Negative
Reproductive Phenotype

PCOS

- GnRH pulse frequency
- LH
- DHEAS
- AMH
- Testosterone
- SHBG
- Insulin
- Androgen
- Free T
- DHT

↑5αR
Metabolic Phenotype

**Insulin Resistance**

Pathophysiology of PCOS

Reproductive features:
- Altered GnRH pulse generator
- ↑ LH:FSH
- Ovarian hyperandrogenism
- Adrenal hyperandrogenism

Metabolic features:
- Insulin resistance
- Obesity
- B-cell dysfunction
- Adipose dysfunction
Hyperandrogenemia and Hyperinsulinemia

- Altered insulin action in skeletal muscle and adipose tissue
  - Increased visceral fat
  - Decreased adiponectin secretion

- Alterations in gonadotropin secretion – increase in LH:FSH
  - Co-gonadotropin to increase LH-induced androgen synthesis in theca cells
  - Decrease in SHBG

IR

T, DHEA

Insulin

HA
PCOS Diagnosis in Adolescence

The Diagnosis of Polycystic Ovary Syndrome during Adolescence

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PCOS in Adolescence
Transient Oligomenorrhea

Polycystic Morphology (PCOM) in Adolescence

• Limitations of transabdominal U/S for evaluation of PCOM
  – Compounded by obesity

• Multifollicular ovaries are normal in puberty, difficult to distinguish from PCOM

• Role of AMH as serum marker for PCOM?
PES Consensus Recommendations

1) Biochemical hyperandrogenemia using sensitive assays (LC-MS)

2) Oligo/anovulation:
   • Menstrual cycles shorter than every 20 days or longer than every 45 days at 2 years post-menarche
   • Repeated menstrual cycles longer than every 90 days within the first year of menarche
   • Lack of menses by age 15 years or 2-3 years post-thelarche

3) No role for ovarian imaging in the diagnostic work up PCOS adolescence

## Long Term Outcomes

### PCOS

<table>
<thead>
<tr>
<th>Metabolic</th>
<th>Reproductive</th>
<th>Psychological</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Type 2 diabetes</td>
<td>• Subfertility</td>
<td>• Depression/Anxiety</td>
</tr>
<tr>
<td>• Obstructive Sleep Apnea</td>
<td>• Adverse pregnancy outcomes</td>
<td></td>
</tr>
<tr>
<td>• NAFLD</td>
<td>• Endometrial cancer</td>
<td></td>
</tr>
<tr>
<td>• Cardiovascular disease (??)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Long Term Outcomes
PCOS

• Association with Type 2 diabetes well-established
• Early IGT: 30% prevalence of IGT in PCOS reported in both adult and adolescent cohorts
• Hyperglycemia mainly post-prandial in early dysglycemia: A1C & fasting blood glucose not sensitive

• Danish National Register, cohort >70,000*
  – Hazard Ratio T2D: 4.0 (3.7-4.3, p<0.0001)
  – Age of onset for T2D was younger in PCOS compared with population (31 v. 35 years)

## Long Term Outcomes

**PCOS - CVD**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>PCOS Events</th>
<th>Total</th>
<th>Control Events</th>
<th>Total</th>
<th>Weight</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lunde 2007</td>
<td>2</td>
<td>131</td>
<td>12</td>
<td>723</td>
<td>17.6%</td>
<td>0.92 [0.20, 4.15]</td>
<td>2007</td>
</tr>
<tr>
<td>Schmidt 2011</td>
<td>6</td>
<td>32</td>
<td>8</td>
<td>95</td>
<td>15.9%</td>
<td>2.51 [0.80, 7.89]</td>
<td>2011</td>
</tr>
<tr>
<td>Itlikhar 2012</td>
<td>5</td>
<td>309</td>
<td>6</td>
<td>343</td>
<td>27.1%</td>
<td>0.92 [0.28, 3.06]</td>
<td>2012</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>815</strong></td>
<td><strong>2379</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>1.94 [1.19, 3.17]</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>28</td>
<td></td>
<td>50</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 4.11, df = 4 (P = 0.39); I² = 3%
Test for overall effect: Z = 2.65 (P = 0.008)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>PCOS Events</th>
<th>Total</th>
<th>Control Events</th>
<th>Total</th>
<th>Weight</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cibula 2000</td>
<td>6</td>
<td>28</td>
<td>38</td>
<td>752</td>
<td>18.1%</td>
<td>5.12 [1.96, 13.38]</td>
<td>2000</td>
</tr>
<tr>
<td>Wild 2000</td>
<td>15</td>
<td>319</td>
<td>42</td>
<td>1060</td>
<td>25.0%</td>
<td>1.20 [0.65, 2.19]</td>
<td>2000</td>
</tr>
<tr>
<td>Lunde 2007</td>
<td>2</td>
<td>131</td>
<td>12</td>
<td>723</td>
<td>10.9%</td>
<td>0.92 [0.20, 4.15]</td>
<td>2007</td>
</tr>
<tr>
<td>Cheang 2008</td>
<td>5</td>
<td>24</td>
<td>11</td>
<td>158</td>
<td>15.0%</td>
<td>3.52 [1.10, 11.22]</td>
<td>2008</td>
</tr>
<tr>
<td>Schmidt 2011</td>
<td>2</td>
<td>32</td>
<td>5</td>
<td>95</td>
<td>9.3%</td>
<td>1.20 [0.22, 6.51]</td>
<td>2011</td>
</tr>
<tr>
<td>Itlikhar 2012</td>
<td>13</td>
<td>309</td>
<td>15</td>
<td>343</td>
<td>21.8%</td>
<td>0.96 [0.45, 2.05]</td>
<td>2012</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>843</strong></td>
<td><strong>3131</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>1.70 [0.92, 3.11]</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>43</td>
<td></td>
<td>123</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.29; Chi² = 10.90, df = 5 (P = 0.05); I² = 54%
Test for overall effect: Z = 1.71 (P = 0.09)

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Long Term Outcomes

**PCOS – Endometrial Carcinoma**

- Increased risk largely related to chronic anovulation and unopposed estrogen
- Obesity a significant contributing risk factor

## Treatment of PCOS – Reproductive Features

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progestin suppresses LH levels - ↓ ovarian HA</td>
<td>Restore regular menstrual cycles</td>
</tr>
<tr>
<td>Estrogen increases SHBG - ↓ bioavailable androgen</td>
<td>Improve biochemical HA</td>
</tr>
<tr>
<td>+/- improvement in hirsutism and acne</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Androgen receptor blockade</td>
<td>Improvement in hirsutism and acne</td>
</tr>
<tr>
<td>Inhibition of 17-hydroxylase and 17,20-desmolase</td>
<td></td>
</tr>
</tbody>
</table>
## Treatment of PCOS – Metabolic Features

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Decreased hepatic glucose output</td>
<td>• Reduction in central obesity +/- weight loss?</td>
</tr>
<tr>
<td>• Some effects on insulin sensitivity</td>
<td>• More modest improvement in HA, anovulation</td>
</tr>
<tr>
<td></td>
<td>• Modest risk reduction in T2DM</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Improvement in insulin resistance</td>
<td>• Greater impact risk reduction T2DM</td>
</tr>
<tr>
<td></td>
<td>• Can normalize HA in subset of morbidly obese PCOS</td>
</tr>
</tbody>
</table>
Treatment of PCOS - Choice of OCP

- EE dose: 20 mcg, 30 mcg, 35 mcg, 50 mcg
- Monophasic vs. triphasic
- Continuous vs. Intermittent therapy
- Progestin

<table>
<thead>
<tr>
<th>Progestin</th>
<th>Androgenic Activity</th>
<th>Thrombosis OR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norethindrone</td>
<td>++</td>
<td>3.9 (1.4-10.6)</td>
</tr>
<tr>
<td>Levonorgestrel</td>
<td>++++</td>
<td>3.6 (2.9-4.6)</td>
</tr>
<tr>
<td>Norgestimate</td>
<td>+</td>
<td>5.9 (1.7-21.0)</td>
</tr>
<tr>
<td>Desogestrel</td>
<td>++</td>
<td>7.3 (5.3-10.0)</td>
</tr>
<tr>
<td>Drospirenone</td>
<td>-</td>
<td>6.3 (2.9-13.7)</td>
</tr>
</tbody>
</table>

Treatment of PCOS – Impact of Weight Loss

- In bariatric surgery populations, weight loss can result in resolution of metabolic and reproductive features of PCOS

- Weight loss resulting from hypocaloric diet + metformin has resulted in improvement in insulin sensitivity, androgen concentrations, hirsutism scores, menstrual cyclicity

- Pre-conception weight loss improves ovulation rates in women undergoing ovulation induction
# Treatment of PCOS in Adolescence

<table>
<thead>
<tr>
<th></th>
<th>Metformin N=6</th>
<th>Placebo N=10</th>
<th>OCP N=10</th>
<th>Lifestyle N=8</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
<td>Post</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td>35.0</td>
<td>35.7</td>
<td>34.9</td>
<td>35.5</td>
</tr>
<tr>
<td><strong>Total T</strong></td>
<td>47.8</td>
<td>49.7</td>
<td>64.4</td>
<td>71.6</td>
</tr>
<tr>
<td><strong>FAI</strong></td>
<td>10.8</td>
<td>10.9</td>
<td>15.6</td>
<td>16.8</td>
</tr>
<tr>
<td><strong>FG score</strong></td>
<td>8.3</td>
<td>8.2</td>
<td>11.6</td>
<td>11.6</td>
</tr>
<tr>
<td><strong>Fasting insulin</strong></td>
<td>20.8</td>
<td>19.8</td>
<td>26.4</td>
<td>29.1</td>
</tr>
</tbody>
</table>

*p<0.05

**p<0.01

Hoeger K et al *JCEM* 2008 93(11): 4299-4306.
Early Origins

PCOS

Premature Pubarche

Birth size (LGA/SGA)

Genetic Risk

Peripubertal Obesity

Intrauterine factors
Premature Pubarche & PCOS

- Ibanez et al: 16 of 35 girls with PP followed for > 2.5 years after menarche developed oligomenorrhea, hirsutism, ovarian hyperandrogenism

Ibanez L et al. JCEM 1993 76:1599-1603.
Premature Pubarche & PCOS

- Post-pubertal ovarian hyperandrogenism correlated with prepubertal androgen levels

Figure: Rosenfield RL JCEM 2007 92:787-796
Data: Ibanez L et al. JCEM 1993 76:1599-1603
PCOS: Preventative Interventions?

Ibanez et al. JCEM 89(9) 2004
Early Origins

PCOS

- Premature Pubarche
- Birth size (LGA/SGA)
- Peripubertal Obesity
- Intrauterine factors
- Genetic Risk
Birth Weight and PCOS

Birth Weight and PCOS

Incidences risk ratios (IRR) (95% confidence interval [CI]) of polycystic ovary syndrome (PCOS) in relation to birth weight.

Early Origins

PCOS

Premature Pubarche

- Birth size (LGA/SGA)
- Peripubertal Obesity
- Intrauterine factors
- Genetic Risk
Intrauterine Factors

Prenatal androgen exposure in primates results in phenocopies of PCOS in the offspring.

- Ovarian/adrenal hyperandrogenism
- Oligomenorrhea
- Polyfollicular ovaries
- ↑ LH
- Abdominal obesity
- Insulin resistance
- Impaired glucose tolerance
- Dyslipidemia

Abbott & Dumesic
Early Origins of PCOS

- Premature Pubarche
- Birth size (LGA/SGA)
- Peripubertal Obesity
- Genetic Risk
- Intrauterine factors
Peripubertal Obesity & PCOS

Early Origins

PCOS

Premature Pubarche

- Birth size (LGA/SGA)
- Peripubertal Obesity
- Intrauterine factors
- Genetic Risk
Elevated T Levels
\(~40\%\) Sisters Affected - Bimodal

Genetic Studies in PCOS

GWAS

PCOS First-Degree Relatives (FDRs)
Previous Findings: PCOS FDRs

Infancy

- ↑ leptin (cord blood)
- ↓ androstenedione & estradiol (cord blood)

Childhood (Prepubertal)

- ↑ Post-stimulated insulin
- ↑ AMH
- ↓ androstenedione & estradiol (cord blood)

Early Puberty

- ↑ DHEAS
- ↑ BMI
- ↑ AMH
FDRs At-Risk DI

Sensitivity Index (min⁻¹/[mU/mL])

AIRg (µ IU/ml)

Control Girls

Increased Risk T2D

FDRs

FDRs with dysglycemia
β-Cell Dysfunction FDRs

Sensitivity Index

$p = 0.11$

(min⁻¹/mU/ml)

FDR
$n = 11$

Control
$n = 9$
Steroid Hormone Metabolites

**Increased 5α-Reductase Activity & Increased Glucocorticoid Metabolites – PCOS Women**

Cholesterol → 5-PD → Preg → 5-PT

17-OHPreg → 17-OHP → 11-Deoxycortisol → Cortisol

DHEA → 16OH-DHEA → PT → 17HP → DHEA → Δ4A → Testosterone

Androsterone, Etiocholanolone → DHT, 18OH-Corticosterone → Aldosterone

Corticosterone, THA, 5αTHA, THB, 5αTHB → Cortisone
Increased 5α-Reductase Activity

PCOS Daughters

* $p = 0.04$
Are there distinctions in the hyperandrogenemia observed in PCOS daughters and obese girls?
Differing Genetic Risk PCOS
PCOS-d v. OB-g

~ 40% PCOS daughters

7-10% Obese girls
Similar Increase in Free T

PCOS daughters & Obese girls

<table>
<thead>
<tr>
<th></th>
<th>Free T (ng/dl)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-g</td>
<td></td>
<td>18</td>
</tr>
<tr>
<td>PCOS-d</td>
<td></td>
<td>37</td>
</tr>
<tr>
<td>OB-g</td>
<td></td>
<td>23</td>
</tr>
</tbody>
</table>

Values: 0.0002 (L-g vs. PCOS-d), 0.02 (L-g vs. OB-g)
Decreased AMH

Obese girls

- L-g (n=18)
- PCOS-d (n=38)
- OB-g (n=23)

AMH ng/mL

- L-g: 2.0 ng/mL
- PCOS-d: 5.0 ng/mL
- OB-g: 0.6 ng/mL

P-values:
- L-g vs. PCOS-d: 0.06
- L-g vs. OB-g: 0.09
- PCOS-d vs. OB-g: <0.001
Timeline for Reproductive Function & Findings in PCOS FDRs

- **Ovarian sex steroid production**
  - Fetal life
  - Mini Puberty
  - Childhood
  - Puberty
  - Reproduction

- **Adrenal androgen production**
  - Fetal life
  - Mini Puberty
  - Childhood
  - Adrenarche

**PCOS FDRs**
- Decreased Δ^4^A
- Increased DHEAS
- Increased T
- Increased AMH

**PCOS FDRs Findings**
- Increase 5αR activity

**Timeline**
- Birth
- 1 y
- 6-8y
- 10-16y
- 52y
Conclusions

• PCOS is a common endocrine disorder affecting 7-10% of reproductive aged women

• Significant reproductive and metabolic consequences: subfertility and increased diabetes risk, impact on CVD risk unclear

• Treatment with combination OCPs first line for improvement if symptoms associated with hyperandrogenemia, mitigation of endometrial CA risk

• PCOS likely has developmental and/or genetic origins:
  – High heritability
  – Milder features of the disorder seen in FDRs
  – Phenocopies in androgen-exposed animal models
Acknowledgements

- Andrea Dunaif, MD

- Genetics mentors:
  - Margrit Urbanek, PhD
  - M Geoffrey Hayes, PhD

- Funding:
  - R01 DK073411 (Dunaif)
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  - K23 HD090274 (Torchen)