UPDATES IN PCOS RESEARCH: FACTS & PERSPECTIVES

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NEED TO UNDERSTAND INCREASING MORE COMPLEX BIOLOGICAL SYSTEMS
MULTI- AND INTERDISCIPLINARY RESEARCH WILL BE REQUIRED TO SOLVE THE “PUZZLE” OF COMPLEX DISEASES AND CONDITIONS

- Genes
- Behavior
- Diet/Nutrition
- Infectious agents
- Environment
- Society
- ???
UPDATES IN PCOS: FACTS & PERSPECTIVES

DETERMINANTS OF POLYCYSTIC OVARY SYNDROME

- Evolutionary
- Epidemiologic
- Genetic
EVOLUTIONARY DETERMINANTS OF PCOS

PCOS: AN EVOLUTIONARY PUZZLE

• Reduced fertility and fecundity

• However, it has persisted hundreds of thousands of years with a significant prevalence (5-15% of female population)
PCOS: ADAPTIVE EVOLUTION

Metabolic Advantages = “Thrifty Gene Hypothesis”

- Past: food shortage → “thrifty” phenotype conserved energy
- Multigenerational facultative adjustment to food scarcity

- No negative selection in populations with a long history of successful agriculture
- Prevalence of PCOS is too low to reflect the past positive selection

Immune Advantages = “Hygiene Hypothesis”

- Past: pathogen-rich ancestral environments → disease protection offered by ↑ inflammatory state
- Contemporary small societies with ↑ pathogens → no capacity for facultative adjustment of inflammation

Reproductive Longevity Advantages

- PCOS ~ associated with enhanced reproductive longevity
- PCOS locus near RAD50 - DNA double-strand break repair
- ↑ AMH in PCOS - larger ovarian primordial follicle pool

- Studies do not confirm later age at menopause

References:
Musculoskeletal Advantages

- Greater muscle mass, bone density, possible aggressiveness → favored survival in the past

- Difficult to understand how increased androgenization at the cost of reduced fertility enhanced overall ‘fitness’
However, **LITTLE** evidence for a strong positive selection of PCOS-susceptibility alleles (e.g. prevalence would be higher)
PCOS: NON-ADAPTIVE EVOLUTION

Persistence theory

• PCOS was **Asymptomatic**
• or
• PCOS traits were in **Balance** in the population:
  • one group has a ‘fitness’ advantage / another has a ‘fitness’ disadvantage
  • e.g. “good for men / bad for women”, where several genetic loci associated with the disorder differently modulate the reproductive parameters of men vs. those of women

• Little data is yet available
Source population
UPDATES IN PCOS: EPIDEMIOLOGIC PERSPECTIVE

PCOS in source population

TO STUDY
- Disease Frequency
- Measures of Association (Risks)
- Causality
UPDATES IN PCOS: EPIDEMIOLOGIC PERSPECTIVE

PCOS in source population

PCOS seeking medical care
UPDATES IN PCOS: EPIDEMIOLOGIC PERSPECTIVE

PCOS in source population

PCOS seeking medical care

TO STUDY
• Diagnostic modalities
• Treatment options
EPIDEMIOLOGIC DETERMINANTS OF PCOS

PCOS in source population

Disease Frequency

PCOS seeking medical care

Association with
- Metabolic
- Reproductive
- Mood
- Cardiovascular
Are PCOS patients seeking medical care representative of the disorder?
Epidemiologic Determinants of PCOS

Referral Bias (?)

3 original study – general and clinical PCOS
• same region / same center / same tools

USA (NIH PCOS) Ezeh et al.
• ↑ prevalence of the more severe PCOS phenotypes
• greater BMI
• more severe hirsutism
• more pronounced hyperandrogenemia

China (Rott 2003 PCOS) Ma et al.
• ↑ prevalence of PCOS phenotype A and
• ↑ rate of menstrual dysfunction

Spain (Functional HA) Luque-Ramírez et al.
• ↑ more hirsute,
• ↑ % clinical and biochemical HA,
• ↑ % obesity
• ↑ % prevalence of PCOS
**Epidemiologic Determinants of PCOS**

**Refferal Bias (?)**

**Design**
- Systematic review and meta-analysis.
  - 41 study
  - N=13796 Patient(s)
  - Extended 2003 Rotterdam criteria
  - PUBMED, EMBASE, Cochrane Library
  - 2003–2016
  - Observational studies

**Main Outcome Measure(s)**
- PCOS phenotypes
  - in general
  - clinical population
REFFERAL BIAS (?)

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- Systematic review and meta-analysis.
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Main Outcome Measure(s)
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EPIEMIOLOGIC DETERMINANTS OF PCOS

RELATION OF HYPERANDROGENISM TO METABOLIC COMPLICATIONS IN PCOS

Vs non-hyperandrogenic PCOS phenotypes and controls³

Hyperandrogenic PCOS phenotypes have:

- A six- to eightfold increased risk of MS vs control group¹
- ↑ IR than non-hyperandrogenic PCOS in some studies²
- ↑ risk of hepatic steatosis

Non-hyperandrogenic PCOS phenotypes have

- No significant difference in the prevalence of MS vs. controls¹
- Similar mean TG and HDL levels vs. controls¹
- Conflicting data on prevalence of IR

## REFFERAL BIAS

### PREVALENCE OF PCOS PHENOTYPES (%, 95% CI)

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>General</th>
<th>Clinical</th>
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<tbody>
<tr>
<td>Phenotype A</td>
<td>19% (13%–27%)</td>
<td>50% (46%–54%)</td>
</tr>
<tr>
<td>Phenotype B</td>
<td>25% (15%–37%)</td>
<td>13% (11%–17%)</td>
</tr>
<tr>
<td>Phenotype C</td>
<td>34% (25%–46%)</td>
<td>14% (12%–16%)</td>
</tr>
<tr>
<td>Phenotype D</td>
<td>19% (14%–25%)</td>
<td>17% (13%–22%)</td>
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<table>
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<th>P</th>
<th>P</th>
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<td></td>
<td>&lt;0.001</td>
<td>0.026</td>
<td>&lt;0.001</td>
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Epidemiologic Determinants of PCOS

PCOS in source population ≠ PCOS seeking medical care

19%  25%  34%  19%

50%  13%  14%  17%

Epidemiologic Determinants of PCOS

Refferal Bias: BMI

General Population: 3 studies

- Control: 0.18 kg/m²
- PCOS: 0.53 kg/m²

95% CI, 0.15 - 0.51 kg/m², P<0.001

Clinical Population: 2 studies

- Control: 0.18 kg/m²
- PCOS: 0.53 kg/m²

95% CI, 0.15 - 0.51 kg/m², P=0.30

Does the current data confirm the “Persistence Hypothesis’ (i.e. PCOS was essentially asymptomatic in prehistory)?
Settings

- Scientific Center of Family Health Protection and Human Reproduction
- Two regions:
  - Irkutsk
  - Ulan-Ude
- 4 cites
- Collected at baseline
- 2015 - 2017 years
ES-PEP: Eastern Siberia PCOS Epidemiology and Phenotype Study

- 5162 women are undergoing screening, ages 18-85 yrs.
- Cross-sectional / longitudinal design / 10 years follow-up
- Well defined exposures and outcomes for White and Asian
  - PCOS / H/ HA/ PCOM
  - Validated liquid chromatography-tandem mass spectrometry for T

<table>
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<tr>
<th>SITE</th>
<th>N, total</th>
<th>N, &lt; 45 years old</th>
<th>N, ≥45 years old</th>
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<td>1063</td>
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<tr>
<td>Water Distribution Company, Ulan-Ude</td>
<td>353</td>
<td>165</td>
<td>188</td>
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<tr>
<td>Buryat State University, Ulan-Ude</td>
<td>936</td>
<td>568</td>
<td>395</td>
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<tr>
<td>Total</td>
<td>8162</td>
<td>4543</td>
<td>3646</td>
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</table>
ONGOING STUDIES: ES-PEP STUDY

Race

Caucasian (Russian) vs Asian (Buryat ~ northern subgroup / Mongols)
Design: Cross-Sectional Community - Based Study

Study aim: To determine the prevalence of PCOS and the PCOS subphenotypes in unselected women in Nsawam, Ghana

Population: 36,687 in 2014 with a population growth rate of 1.4% per annum
- 3,052 houses
- 8,832 households
## GENETIC DETERMINANTS OF PCOS: GWAS

<table>
<thead>
<tr>
<th>LOCUS</th>
<th>NEAREST GENE</th>
<th>SNP</th>
<th>P</th>
<th>DISCOVERY</th>
<th>REPLICATION</th>
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<tr>
<td>3 2p21</td>
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<td>11 12q14.3</td>
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<tr>
<td>12 12q13.2</td>
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<td>16 20q13.2</td>
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</table>

The potential for gene discovery to improve diagnosis and treatment of PCOS is promising, though there is much to be done in the field before the current findings can be translated to the clinic.
SUMMARY

• Persistence theory

• Need longitudinal data for PCOS in general population to understand
  • Causation
  • Risks

• Further explore genetic/epigenetic factors

ACKNOWLEDGMENTS

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Ricardo Azziz ¹,²
Yen Hao Chen¹

RUSSIA
Larisa Suturina³

Adanu RM⁴
Igor Stravinsky, 1951: “The Rake's Progress”

Tom Rakewell deserts Anne Trulove by marrying Baba the Turk, the famous bearded lady.