Prenatal origin of polycystic ovarian syndrome

Do we understand polycystic ovary syndrome (PCOS) any better now than we did 25 years ago?

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Medical School  University of Athens  
GREECE
Outline

• Introduction to PCOS

• Prenatal exposure to androgens
• Prenatal exposure to endocrine disruptors (EDCs)
PCOS has generated debate, passion, and confusion

A syndrome with female nature
Polycystic ovarian syndrome (PCOS)

Commonest Endocrinopathy in women of reproductive age = 6.5-6.7%

depending on ethnicity and the diagnostic criteria employed
1. Diagnostic criteria

NIH

- Chronic anovulation
- Clinical and/or biochemical hyperandrogenism

With the exclusion of other androgen excess disorders

NIH

- Chronic anovulation
- Clinical and/or biochemical hyperandrogenism
- Polycystic Ovaries

With the exclusion of other androgen excess disorders

ANDROGEN EXCESS SOCIETY: SUGGESTED CRITERIA FOR THE DIAGNOSIS OF THE POLYCYSTIC OVARY SYNDROME

1. Hirsutism and/or hyperandrogenemia
   - and
2. Oligo-anovulation and/or polycystic ovaries
   - and
3. Exclusion of other androgen excess or related disorders

ROTTERDAM

- Chronic anovulation
- Clinical and/or biochemical hyperandrogenism
- Polycystic Ovaries

With the exclusion of other androgen excess disorders
The potential role of PRENATAL EXPOSURE TO endocrine disruptors in PCOS pathogenesis

This interaction appears to start before birth and continues throughout the lifespan.

NEONATE  CHILD  ADOLESCENT  ADULT

- fetal hyperandrogenism
  -↓ birth weight
  -↑ premature adrenarche
- fetal hyperinsulinemia
  -↑ visceral adiposity

- adrenal & ovarian hyperandrogenism
  - polycystic ovarian morphology

- subfertility
  - metabolic syndrome
  - diabetes
  - dyslipidemia
  - cardiovascular risk

PRENATAL EXPOSURE TO EDC
Pathogenesis of PCOS in fetal life

**Prenatal androgenization**

- Basal insulin secretion
- Glucose-induced insulin response
- Visceral fat
- FFAs
- Sympathetic tone
- Testosterone
- Anovulation
- Chronic inflammation
- Insulin resistance
- IGT
- Dyslipidemia
- NAFLD
- Altered steroidogenic gene expression

**GENES**

**Genome-wide association studies (GWAS)**

- Rae et al., 2013
- Abbot et al., 1998-2010; Bruns et al., 2007; Nohara et al., 2013; Sun et al., 2013
- Dumesic et al., 2007
- Veiga-Lopez et al., 2008
- Hogg et al., 2011
Maternal androgenization during gestation impairs ovarian steroidogenic enzyme activity in female offspring

d 90 fetal ovary

Female fetuses collected from ewes treated with 100 mg testosterone propionate (TP) or vehicle control (C), twice weekly from d 60 to d 90 (C = 6, TP = 8)

* $P < 0.05$ and ** $P < 0.01$. 

Hogg et al., Endocrinology 2011
Prenatal androgenization impairs insulin signaling in skeletal muscles and liver of rats

Yan et al., 2013

**Skeletal muscle**

- IRS1: tubulin ratio
- IRS2: tubulin ratio
- pAKT: AKT ratio

**Liver**

- IRS1: tubulin ratio
- IRS2: tubulin ratio
- pAKT: AKT ratio

P<0.01 vs control
The potential role of BPA in the pathogenesis of PCOS

Direct hypothalamic effect

Direct metabolic effects (pancreas+adipose tissue)

Direct ovarian effect
BPA levels were significantly higher in lean (1.13±0.63 vs 0.70 ± 0.05, p<0.0007) and obese women with PCOS (0.97±0.08 vs 0.72±0.07, p<0.044), compared to normal lean and obese women, respectively.

Kandaraki et al. J Clin Endocrinol Metab. (2011)
Positive correlation between BPA with Androgens in PCOS women

Endocrine Disruptors and Polycystic Ovary Syndrome (PCOS): Elevated Serum Levels of Bisphenol A in Women with PCOS.

Kandaraki E, Chatzigeorgiou A, Livadas S, Palioura E, Economou F, Koutsilieris M, Palimeri S, Panidis D, Diamanti-Kandarakis E.

J Clin Endocrinol Metab. 2011 Mar;96(3):..
Neonatal Exposure to Bisphenol A and Reproductive and Endocrine Alterations Resembling the Polycystic Ovarian Syndrome in Adult Rats

Fernandez et al. 2010

GnRH interpulse intervals

BPA

500 μg/50 μL (high) or 50 μg/50 μL or 5 μg/50 μL (low)
Prenatal Exposure to Endocrine Disruptors and the Ovary

Diamanti-Kandarakis E, Gore AC. Endocrine Disruptors and Puberty, Humana Press, 2012

Ovarian organization/morphology

- ↓ Ovarian size/weight (Genistein, MXC)
- Ovarian cysts (DES)
- Multioocyte follicles (BPA)

Folliculogenesis

- (-) primordial follicle (DES)
- (-) late preantral stages (MXC, BPA)
- (-) corpora lutea formation (anovulation) (BPA, Genistein)

Steroidogenesis

- Impaired steroidogenesis (BPA, DES)

Ovarian cellular/molecular phenomena (gene induction/expression)

- (-) ER $\beta$ expression (DDE)
- Aneuploidy (BPA)

Oocyte chromosomal abnormalities

- (+) AMH production (MXC)

Intraovarian local factors production

- (+) AMH production (MXC)
PRENATAL EXPOSURE TO BISPHENOL A and PCOS

Effects in the OVARY-studies with RODENTS

ENDOCRINE DISRUPTOR

EFFECT

Bisphenol A

Disruption of expression of Ovarian Steroidogenesis

BISPHENOL A

- pregnant Suffolk ewes
- sc administration
- from days 30 to 90 of gestation
- 0,5 mg/Kg

↑ in the expression of 3β1HSD and 3β2HSD (age-dependent)

↑ in the expression of Cyp19 and 5-Reductase at fetal day 65

Veiga-Lopez et al. Endocrinology, May 2013
BPA exposure throughout **gestation and lactation**
(normal diet vs high-fat diet)

EFFECT

**Normal diet (50 μg/kg *d* BPA)**
- ↑ body weight
- ↑ serum insulin
- impaired glucose tolerance in adult offspring

**High-fat diet (50 μg/kg *d* BPA)**
SEVERE METABOLIC SYNDROME
- Obesity
- dyslipidemia
- hyperleptinemia,
- Hyperglycemia
- Hyperinsulinemia
- glucose intolerance

Wei et al, Endocrinology, 2011
Soy but not bisphenol A (BPA) induces hallmarks of polycystic ovary syndrome (PCOS) and related metabolic co-morbidities in rats

Heather B. Patisaul, Natalie Mabrey, Heather B. Adewale, Alana W. Sullivan

Reproductive Toxicology 49 (2014) 209–218

Soy (soy diet; n = 8)

PCOS-related hallmarks

REPRODUCTIVE

CYSTIC FOLLICLES

P < 0.001

METABOLIC

↑ BASELINE GLUCOSE LEVELS

<table>
<thead>
<tr>
<th>Exposure Group</th>
<th>Baseline</th>
<th>10 min</th>
<th>30 min</th>
<th>60 (min)</th>
<th>120 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soy-Free</td>
<td>64.60 ± 2.38</td>
<td>281.20 ± 8.15</td>
<td>203.60 ± 17.09</td>
<td>135.20 ± 10.48</td>
<td>97.00 ± 3.77</td>
</tr>
<tr>
<td>BPA</td>
<td>75.50 ± 3.39</td>
<td>250.40 ± 23.55</td>
<td>197.90 ± 13.13</td>
<td>137.00 ± 10.90</td>
<td>103.81 ± 4.21</td>
</tr>
<tr>
<td>Soy</td>
<td>85.10 ± 3.53</td>
<td>285.64 ± 22.63</td>
<td>228.46 ± 18.47</td>
<td>151.27 ± 10.32</td>
<td>106.64 ± 4.16</td>
</tr>
<tr>
<td>BPA + Soy</td>
<td>81.10 ± 2.64</td>
<td>292.80 ± 22.91</td>
<td>241.10 ± 17.84</td>
<td>170.00 ± 9.13</td>
<td>116.23 ± 6.02</td>
</tr>
<tr>
<td>EE</td>
<td>86.70 ± 5.55</td>
<td>314.30 ± 13.67</td>
<td>244.10 ± 10.79</td>
<td>163.40 ± 6.26</td>
<td>113.00 ± 3.86</td>
</tr>
</tbody>
</table>
Soy but not bisphenol A (BPA) induces hallmarks of polycystic ovary syndrome (PCOS) and related metabolic co-morbidities in rats

Heather B. Patisaul a,b,*, Natalie Mabrey a, Heather B. Adewale a, Alana W. Sullivan a

Understanding how dietary and environmental exposures interact to influence reproductive health and development is of seminal importance, particularly given that soy consumption is growing in popularity among Western populations and BPA exposure is ubiquitous
Exogenous AGES:
Environmental sources of AGES and inflammation

Figure 1. Chemical structures of some representative AGES found in foods and
EMERGING ENVIRONMENTAL TRIGGERS OF PCOS
Advanced Glycated End products (AGEs)/Glycotoxins

Reactive derivatives of nonenzymatic glucose–protein reactions that form irreversibly

Diamanti-Kandarakis et al 2014

Uribarri et al 2007; Brownlee et al. 1984
Polycystic ovary syndrome offspring display increased oxidative stress markers comparable to gestational diabetes offspring

151 mother/neonate pairs

FIGURE 1

FIGURE 2

G. Boutzios, S Livadas, C. Piperi, N. Vitoratos, C. Adamopoulous, D. Hassiakos and E. Diamanti-Kandarakis,

Fertility and Sterility 2013

The pathophysiological mechanisms behind the increased risk of adverse pregnancy outcomes among women with polycystic ovary syndrome are not fully known.
Advanced glycation end-products accumulation compromises embryonic development and achievement of pregnancy by assisted reproductive technology

Significant negative correlations of FF AGEs: $R = -0.32$, $P < 0.0001$ with follicular growth with number of oocytes retrieved

Jinno et al: Hum Reprod.2011

N= 157 ART-patients (71 PCOS, 86 non-PCOS)
Dietary glycotoxins affect scavenger receptor expression and the hormonal profile of female rats

Antonios Chatzigeorgiou¹², Eleni Kandaraki³, Christina Piperi³, Sarantis Livadas⁴, Athanasios G Papavassiliou³, Michael Koutsilieris¹, Apostolos Papalois⁵ and Evanthia Diamanti-Kandarakis⁴

![Graph A: LA and HA (SR-A, RAGE, Actin)]

![Graph B: L-AGE and H-AGE (RAGE, SR-A cellular expression)]
High Androgens effect on rat Ovarian antioxidant system

PCOS Rat model

Decreased anti-oxidant defence

Mitochondrial dysfunctions

ROS

RAGE

AGE

NH₂-protein + RCS

Decreased anti-glycation defence

Altered glucose metabolism

Tissue accumulation: OVARY

Molecular Medicine 2012
Control, AGEs staining

PCOS: AGEs staining showing stronger localization in Granulosa

Histochemistry and Cell Biology; JANUARY 2007
Evanthia Diamanti-Kandarakis et al.
a novel treatment strategy for ovarian dysfunction by decreasing dietary AGEs or AGEs effects should be considered. 

**Jinno et al: Hum Reprod.2011**
PCOS throughout life & environmental influence

In utero
Exposure to
Androgens
BPA
High AGEs/Soy?

Predisposing
In utero
Environment

Early catch-up
or Continued
Weight gain

Premature
adrenarche

Hyperandrogenic
hyperinsulinemic
anovulation

Lifelong exposure to
Overnutrition
High AGE /Soy diets?
Environmental pollutant BPA?

Fetus Birth Infant Child Adolescent Adult

Abbott et al 1997-2011
Fernandez et al 2010

dezegher & Ibanez 2006
El.Kandaraki et al 2011
CONCLUSIONS

• Intrauterine environment may influence the developmental programming of PCOS in the female fetus.

• Fetal androgen excess and fetal exposure to endocrine disruptors, mainly BPA, involved in the developmental programming of PCOS.

• Evolving dietary components in excess (Soy, AGEs) may prove to be among the preventable factors affecting programming PCOS.

Since results which support the hypothesis that hormonally active diets may contribute to risk when consumed throughout gestation and post-natal life.
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