The Thrifty Gene Hypothesis: How has the PCOS Phenotype Survived Evolution

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Disclosure

- Past President of the Dutch Society for Reproductive Medicine (DSRM)

- Past Chairman of the Task force Reproductive Endocrinology of the Royal Dutch College of Obstetrics and Gynaecology (RDCOG)

- Received unrestricted research grants from Ferring®, Merck Serono®, MSD®, Organon®, Serono® and Shering-Plough®

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- Member of advisory boards of Danone, Euroscreen, Astra Zenica and Roche

- Past Member of the Editorial Board of Human Reproduction

- Member of the Editorial Board of Human Reproduction Update and Journal of the Endocrine Society
Learning Objectives

- Provide some insights into the prevalence of PCOS worldwide
- Share some of the recent genetic data concerning PCOS with you
- Introduce you to the concept that PCOS is an Ancient disorder
- Introduce the Thrifty Gene Hypothesis
- Provide some evidence which contradicts the Thrifty gene Hypothesis
- Introduce a new concept of male and female genetic drift and evolutionary conflict
- Take Home Messages
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EPIDEMIOLOGY OF PCOS
## Epidemiology of PCOS

(Goodarzi et al, Fertil Steril 2011)

### Prevalence of PCOS amongst different Ethnicities

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**Is PCOS an Ancient Disorder?**
(Azziz, Fertil Steril 2016)

**THE MIGRATION OF ANATOMICALLY MODERN HUMANS**

Evidence from fossils, ancient artefacts and genetic analyses combine to tell a compelling story.

Two routes jump out as prime candidates for the human exodus out of Africa. A northern route would have taken our ancestors from their base in eastern sub-Saharan Africa across the Sahara desert, then through Sinai and into the Levant. An alternative southern route may have charted a path from Ethiopia or Ethiopia in the Horn of Africa across the Red Sea to Madagascar and into Yemen and around the Arabian peninsula. The plausibility of these two routes as gateways out of Africa has been studied as part of the UK’s Natural Environment Research Council’s programme “Environmental Factors in the Chronology of Human Evolution & Dispersal” (EFCHED).

During the last ice age, from about 80,000 to 11,000 years ago, sea levels dropped as the ice sheets grew, exposing large swaths of land now submerged under water and connecting regions now separated by the sea. By reconstructing ancient shorelines, the EFCHED team found that the Bab el-Mandeb Strait, now around 30 kilometers wide and one of the world’s busiest shipping lanes, was then a narrow, shallow channel.

Early humans may have taken this southern route out of Africa. The northern route appears easier, especially given the team’s finding that the Red Sea was dry during the last ice age. But crossing the Saharan desert is no small matter. EFCHED scientist Simon Armitage of the Royal Holloway University of London has found clues as to how this might have been possible. During the past 150,000 years, North Africa has experienced abrupt switches between dry, and conditions and a humid climate. During the longer wetter periods huge lakes existed in both Chad and Libya, which would have provided a “humid corridor” across the Sahara.

Armitage has discovered that these lakes were present around 10,000 years ago, when there is abundant evidence for human occupation of the Saharan, as well as around 115,000 years ago, when our ancestors first moved southwest into India. It is unknown whether another humid corridor appeared between about 65,000 and 50,000 years ago, the most likely time frame for the human exodus. Meanwhile, accumulating evidence is pointing to the southern route as the most likely jumping-off point.
Overall incidence ranging from 5 – 15% is fairly constant in different populations and ethnic subgroups

PCOS is an “old paleolytic disease” associated with:

- Menstrual cycle disturbances
- Anovulation and Subfertility
- Hirsutism, Acne and Alopecia
- Obesity
- Insulin resistance and impaired glucose metabolism
- Metabolic syndrome
- Type II DM and Cardiovascular disease
- Endometrial cancer
- Depression and Anxiety,
- Low self esteem
- Disturbed sexuality and sexual satisfaction

An Evolutionary and Reproductive paradox?

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**Epidemiology of PCOS**

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THRIFTY GENE HYPOTHESIS
**Thrifty Phenotype / Genotype**  
(Chakravarthy and Booth, J Appl Physiol 2004)

- **Physical activity**
- **Food procurement**
  - Feast-famine cycling
  - Physical activity-rest cycling
  - Reduction of skeletal muscle glycogen and triglyceride stores

**Cycling of Metabolic Processes**
- Fuel depots
- Metabolic proteins
- Blood insulin
- Insulin sensitivity

**Gene & Genotype Selection**

- "Thrifty" genes & genotype selected
  - Conserve muscle glycogen
  - Replenish muscle glycogen

**Improved survival**
Thrifty Phenotype / Genotype
(Chakravarthy and Booth, J Appl Physiol 2004)

Relative physical inactivity

FEAST
(Intake glucose and fat)

Successful Physical Activity
(Hunt or Gather)

THRIFTY STORAGE
(Replenish skeletal muscle glucose and TG; more efficient storage of excess glucose and TG in adipose tissue)

Contracting skeletal muscle increases GLUT4 & AMPK

FAMINE & ACTIVITY
(Essentially Simultaneous)
(Decrease glycogen and TG stores)

(More thrifty storage = more likely to survive through next famine/activity phase until next feast.)
**Thrifty Phenotype / Genotype**
(Chakravarthy and Booth, J Appl Physiol 2004)

- **Thrifty Storage**
  - (High storage of excess glucose and TG in adipose tissue; little goes to skeletal muscle)
  - Unlimited food supply with no exercise
    - Skeletal muscle glycogen & TG stores are NOT decreased
    - Skeletal muscle GLUT4 and AMPK levels are NOT increased

- **Famine & Activity**
  - (Essentially Simultaneous)
  - (Decrease glycogen and TG stores)
  - Exercise breaks STALL and restores metabolic cycling

- **Thrifty Storage**
  - (Replenish glucose and TG to skeletal muscle; store excess glucose and TG in adipose tissue)

- **FEAST**
  - (Intake glucose and fat)
  - Unlimited food supply

- **Famine/Physical Activity**
  - (Decreased glycogen and TG stores)

- **STALL**
  - No Cycling of Metabolic Processes—fuel gets shunted into an even greater and unhealthy storage, precipitating the METABOLIC SYNDROME
  - Constantly low skeletal muscle β-oxidation enzymes
  - Relatively constant high blood insulin and insulin resistance

- Exercise reduces skeletal muscle glucose & TG and increases muscle GLUT4 & AMPK
- Cycle no longer stalls because glucose and TG are taken up and metabolized by skeletal muscle
Fertility First Hypothesis
(Corbett et al., Am J Human Biology, 2009)
Thrifty Phenotype / Genotype
(Azziz et al., Fertil Steril 2011)

- Thrifty Phenotype might have survived although it has some impact on fertility because:
  - Earlier resumption of ovulation after famine
  - Better spacing of offspring since women with PCOS do have ovulations although less than women without PCOS
  - Better survival of offspring due to better food supply to smaller families
  - Due to increased intervals between birth older sisters could serve as allo-mothers
  - With aging, PCOS women may have attained significant nurturing skills, given their wisdom and strength to survive a physically demanding environment
  - Lower maternal morbidity and mortality rates due to a decreased exposure to pregnancy
  - Increased bone and muscle strength
  - Increased insulin resistance leading to a more adaptive phenotype during food scarcity
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OTHER POSSIBLE EXPLANATIONS
What is wrong about the thrifty genes?
(Speakman, Ann Rev Nutrition, 2013)

- Food scarcity is not the same as famine
- Famines leading to large scale mortality within populations are relatively seldom and happen once in about 150 years

- Suppose the fat storage gene that is most efficient is prevalent in about 3% of the population whereas the least effective one is present in about 1.5% of cases.
- To spread the thrifty gene throughout the population we would need about 600 famine cycles e.g. 90,000 years
- 90,000 years is about 1/500 of the period since Australopithecus
- Any mutation that produced a thrifty allele within the first 99.8% of hominin history with this effect on mortality would therefore have gone to fixation !!!
Fecundity in women with PCOS
(Kalra et al., Fertil Steril, 2013; Day et al., Nature Communications 2015)
Reproductive Success of women with PCOS
(Holte et al., Fertil Steril, 2011)

Fecundity in women with PCOS

Number of children in women with PCOS
Birth Spacing Mortality and Morbidity in Offspring
(Population Reference Bureau 2009)

**FIGURE 3. INFANT MORTALITY BY BIRTH INTERVAL**

- **Deaths per 1,000 infants under 1**
  - Cambodia: 162
  - Mali: 158
  - Ghana: 131
  - Benin: 121
  - Uganda: 120
  - Bangladesh: 101
  - Haiti: 97
  - Nepal: 96

- **IBS (months)**: Less than 2-year space between births vs. 3-year space between births

**Length of Birth Interval**

- **IBS (months)**:
  - Berlin
  - Burkina Faso
  - Cameroon
  - Cent. Africa
  - Cote d'Ivoire
  - Ghana
  - Mali
  - Niger
  - Nigeria
  - Senegal
  - Comoros
  - Kenya
  - Madagascar
  - Malawi
  - Namibia
  - Rwanda
  - Tanzania
  - Uganda
  - Zambia
  - Zimbabwe

**Maternal death rate per 10,000 women**

- **Duration of birth interval (in months)**
  - 0–14: 9.5
  - 15–20: 4.4
  - 21–26: 4.2
  - 27–32: 3.7
  - 33–68: 4.9
  - ≥69: 5.5
Health issues in offspring of women with PCOS
(Doherty et al., Obstetrics & Gynecology 2015)
PCOS: A Sexual Conflict?
(Casarini et al., RBM Online 2016)
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TAKE HOME MESSAGES
Conclusions

- PCOS is a frequent reproductive disorder with an incidence between 5 and 15% depending on the definition used.

- PCOS must have emerged during the Palaeolithic period given the relatively small differences between the prevalence as well as between the genetic markers amongst different ethnic groups.

- The thrifty gene hypothesis states that in ancient times some nutritional and metabolic characteristics associated with PCOS might have been advantageous whereas the same features in the current time became disadvantageous.

- In contrast with the thrifty gene hypothesis PCOS is not associated with:
  - Increased or decreased fecundity
  - Decreased or increased fertility
  - Increased birth spacing
  - Better health in offspring
  - Decreased Foetal or Maternal morbidity

- It seems that PCOS is merely the results of nonadaptive mechanisms, such as genetic drift and sexually antagonistic selection, which have permitted the trait to persist in humans over millennia without any benefits accruing to women who possess it.
Acknowledgements

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