Environmental influences on male reproductive development

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The best of ESHRE and ASRM
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LEARNING OBJECTIVES

- Identify environmental factors implicated in impaired semen quality, male infertility, and hypogonadism.
- Explain the importance of in utero exposure to environmental factors.
- Summarize the impact of environmental factors on the newborn, adult male, and his offspring.

At the conclusion of this presentation, participants should be able to:

DISCLOSURE

- None
“Sperm count declined 52.4% between 1973 and 2011 [38 years] among men from Western countries with no evidence of a ‘leveling off’ “.

Evidence for decreasing quality of semen during past 50 years

Elisabeth Carlsen, Alexander Gjørv, Niels Kolding, Niels E. Skakkebæk (1992)

“There has been a genuine decline in semen quality over the past 50 years”

The Question of Declining Sperm Density Revisited: An Analysis of 101 Studies Published 1934–1996


“The average decline in sperm count was virtually unchanged from Carlsen et al. (slope -0.94 vs. -0.93)”
Goal of 2017 meta-analysis

To conduct a *systematic review and meta-analysis* of:

- Recent trends in:
  - Sperm concentration (SC)
  - Total sperm count (TSC)
- Modification of these trends by *fertility status and geography*

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**Protocol**

Exclusion criteria:

- No data on humans
- Not primary data
- Fewer than 10 men
- Collection not by masturbation
- Count not by haemocytometer
- Selection criteria that could introduce bias
Men were stratified by “fertility status”

- **Unselected men**: Fertility status unknown  
  (e.g. college students, military conscripts)

- **Fertile men**: Fertility status known  
  (e.g. fathers, partners of pregnant women)

*Unselected men are most representative of the general population*

Studies stratified by geographic group

- **“Western” countries**:  
  - North America, Europe, Australia and New Zealand

- **“Other” countries**:  
  - South America, Asia and Africa

- Too few studies to subdivide further

Covariates abstracted

- Age at sample collection
- Ejaculation abstinence time
- Method of semen collection
- Methods of measuring SC and semen volume
- Number of samples per man
- Too few studies had data to control for other covariates (smoking, obesity, etc.)
Outcome variables

Time reflects (median) year of sample collection (not publication year)

Time trends measured by slope of SC or TSC per year of sample collection

• Mean SC in million/ml per year
• Mean TSC in million per year

Characteristics of included studies

<table>
<thead>
<tr>
<th>Year of data collection</th>
<th>1973-2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>Publications - N</td>
<td>185</td>
</tr>
<tr>
<td>Countries - N</td>
<td>50</td>
</tr>
<tr>
<td>Participants - N</td>
<td>42,935</td>
</tr>
<tr>
<td>Data points – N (%)</td>
<td>244 (100)</td>
</tr>
<tr>
<td>Unselected Western</td>
<td>110 (45)</td>
</tr>
<tr>
<td>Fertile Western</td>
<td>65 (27)</td>
</tr>
<tr>
<td>Unselected Other</td>
<td>30 (12)</td>
</tr>
<tr>
<td>Fertile Other</td>
<td>39 (16)</td>
</tr>
<tr>
<td>Mean (SD) SC (million/ml)</td>
<td>81 (25)</td>
</tr>
<tr>
<td>Mean (SD) TSC (million)</td>
<td>260 (89)</td>
</tr>
</tbody>
</table>

Meta-regression: Sperm concentration

52.4% decline
Comparison to previous studies

Testicular Dysgenesis Syndrome (TDS)

- Proposed by Niels Skakkebaek (2001)
- Hypothesized common in utero origin for:
  - Testicular (germ cell) cancer
  - Impaired semen quality
  - Infertility
  - Hypospadias
  - Cryptorchidism
- Causes could be environmental, genetic or both
Phthalate toxicology

- Several phthalates and their metabolites lower testosterone (best studied: DEHP, DBP, BBzP)
- Prenatal phthalate exposure shortens male anogenital distance (AGD)
- A cluster of androgen-sensitive changes termed the "phthalate syndrome" is caused by exposure to these phthalates during a narrow best studied window (the "male programming window"; days 18-21 in rats)

(Foster 2005, Grey 2006)
First published data on rodent AGD: Jackson 1912

<table>
<thead>
<tr>
<th>Average Anogenital Distance</th>
<th>(and Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, Mn.</td>
<td>Female, Mn.</td>
</tr>
<tr>
<td>2.0 (2.0–3.0)</td>
<td>1.2 (1.0–1.5)</td>
</tr>
<tr>
<td>2.3 (2.0–3.0)</td>
<td>2.7 (2.0–3.3)</td>
</tr>
<tr>
<td>3.0 (3.0–3.0)</td>
<td>4.0 (3.0–6.0)</td>
</tr>
<tr>
<td>12 (10–14)</td>
<td>13 (9–14)</td>
</tr>
</tbody>
</table>

Anogenital distance

- Male AGD about twice as long as female AGD in most mammals
- In male rodent pups, AGD is shortened by anti-androgens
- First examined as a marker of reproductive toxicity in human studies in our studies
In animals

• Adequate prenatal testosterone (in the “Male Programming Window”) is critical for mammalian male reproductive tract development
• Anti-androgenic phthalates can alter male AGD in rodents
• AGD is part of the cluster of adverse changes in the male reproductive tract is called the “phthalate syndrome”

What about humans?

Study for Future Families II (SFF II):

• Built on our pregnancy cohort study, the Study for Future Families (SFF I)
• SFF II designed to assess infant genital development in relation to prenatal phthalate exposure

Participants in SFF?

• Women seen for routine prenatal care 2000-2002 in:
  • Columbia MO
  • Minneapolis MN
  • Los Angeles CA
  • New York NY (later dropped)
  • Iowa City IA (added in 2003)
• Their partners
Study design:
- Multi-center, pregnancy cohort study
- Archived for later analysis:
  - Serum
  - Urine
  - Seminal fluid
- Measured biomarkers of:
  - Exposure
  - Outcomes
  - Confounders
Infant Exams

- Anthropometry
- Male genital exam
  - Anogenital distance (AGD) (ano-scrotal, ano-penile)
  - Testicular descent
  - Penile length and width
  - Scrotal size and condition
- AGD also measured in females

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Results: DEHP metabolite concentration associated with shortened male AGD

<table>
<thead>
<tr>
<th>Monomer Metabolite</th>
<th>25th</th>
<th>50th</th>
<th>75th</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEHHP</td>
<td>6.0</td>
<td>11.4</td>
<td>20.1</td>
</tr>
</tbody>
</table>

Likelihood of short AGD

- 4.6x
- 13x
Higher DEHP exposure was also associated with other genital endpoints:

- Decreased testicular descent
- Reduced penile width
- Reduced AGD
- Reduced scrotal size


Conclusions from SFF II:

- AGD is a reliable and repeatable measure in human infants
- AGD is a marker of prenatal androgen exposure
- Results of SFF II support a phthalate syndrome in humans

(Swan et al. 2005, 2008)

The Infant Development and the Environment Study (TIDES):

- Women recruited by 13 weeks gestation in 4 US cities (2010-2012)
- Urine and questionnaires collected in each trimester
- Serum collected in first trimester
- AGD measured at birth and one year
- 758 infants with first trimester phthalates and AGD
Covariates for multivariable regression

- Age at exam
- Gestational age
- Weight-for-length Z-score (WHO standard)
- Maternal age
- Clinical center
- Time of day urine collected
- Specific gravity

Results: First trimester DEHP and boys' AGD and penile width (PW)

Boys' AGD and PW in relation to MEHP, MEHHP, MEOHP and ΣDEHP:

P-values (0.05-0.008)

Swan et al 2015

Does short male AGD matter?

- Boys with genital defects (hypospadias and cryptorchidism) have shorter AGD (Hsieh 2008 and 2012, Jain 2013, Thankamony 2014)
- In rodents, short AGD predicts low sperm count and problems with fertility
- Is AGD related to semen parameters and fertility in humans?
Rochester Young Men’s Study (RYMS)

Volunteers, 18-21 years of age recruited in Rochester NY, 2009-2010
Blood, urine and semen sample collected
Questionnaire (demographics, life style, etc.)
Physical exam:
  Height and weight
  Testicular volume
  AGD_{AS} (ano-scrotal) (N=126)
  AGD_{AP} and AGD_{AS} (N=181)

Mendiola et al., 2011, Environ Health Perspect.

Eisenberg et al. 2011
Conclusions

• Sperm concentration has declined significantly in Western men
• TDS hypothesis suggests short AGD and low sperm count share a common fetal origin
• Prenatal exposure to anti-androgenic phthalates shortens male AGD
• AGD in infancy reflects the hormonal environment in early pregnancy
• In adult men, shorter AGD is associated with reduced sperm count and infertility

Thanks to:

• **Sperm meta-analysis**: Hagai Levine, Niels Jorgenson, Anderson Andrade, Jaime Mendiola, Rachel Pinotti, Irina Mendis, Dan Weksler-Derri
• **TDS hypothesis**: Niels Skakkebaek
• **The Phthalate Syndrome**: Paul Foster, Earl Gray
• **Study for Future Families (SFF)**: Bruce Redmon, Erma Drobnis, Christina Wang, Amy Sparks
• **The Infant Development and the Environment Study (TIDES)**: Sheela Sathyanarayana, Ruby Nguyen, Emily Barrett, Nicole Bush
• **Rochester Young Men’s Study (RYMS)**: Jaime Mendiola

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• Study participants in SFF, TIDES and RYMS
• Study staff of SFF, TIDES and RYMS

And thank you for listening! Questions???