Is there an external influence on sperm quality?

Fertility decline: myth or reality?

- 50% drop of semen concentration between 1940 and 1990 (from 113 to 66 million/mL) - Carlsen, 1992; Swan 2000

- Controversy: geography, season, ethnic, environmental and lifestyle factors - Auger et al., 2001; Jouannet et al., 2001; Swan, 2003; Mendiola et al., 2009
External factors

Microscopic level:
- Concentration
- Motility
- Morphology

Molecular level:
- Aneuploidy
- Oxidative stress
- DNA fragmentation

- Drugs
- Endocrine disruptors (EDs)
- Smoking
- Alcohol
- Recreational drugs
- Genital heat stress
- Psychological stress
- Cellular telephone use
- Weight and nutrition
- ...

Agents affecting the hypothalamic-pituitary-testicular axis

<table>
<thead>
<tr>
<th>Agent class</th>
<th>Example</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>GRF analogs</td>
<td>Leuprolide</td>
<td>Azoospermia, decreased spermatogenesis, hypothalamic dysfunction</td>
</tr>
<tr>
<td>Anabolic agents</td>
<td>Stanozolol</td>
<td>Azoospermia, increased testicular size, decreased sperm motility</td>
</tr>
<tr>
<td>Anti-androgens</td>
<td>Spironolactone</td>
<td>Decreased spermatogenesis, increased plasma testosterone</td>
</tr>
<tr>
<td>Serotonin inhibitors</td>
<td>Fluoxetine</td>
<td>Decreased spermatogenesis (sere in muz)</td>
</tr>
<tr>
<td>Opiates</td>
<td>Morphine</td>
<td>Azoospermia, increased pain sensitivity</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>Fluoxetine</td>
<td>Decreased libido</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>Fluoxetine</td>
<td>Decreased libido</td>
</tr>
</tbody>
</table>

Agents causing testicular or spermatic toxicity

<table>
<thead>
<tr>
<th>Agent class</th>
<th>Example</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy and radiation</td>
<td>Cyclophosphamide, Methotrexate</td>
<td>Azoospermia or oligospermia</td>
</tr>
<tr>
<td>Antihypertensives</td>
<td>Nifedipine</td>
<td>Possible decrease in fertility</td>
</tr>
<tr>
<td>Anti-inflammatories</td>
<td>Sulfasalazine</td>
<td>Decreased spermatogenesis</td>
</tr>
<tr>
<td>Environmental exposure/pesticides</td>
<td>Lead, Cadmium, Dicofol</td>
<td>Decreased spermatogenesis</td>
</tr>
</tbody>
</table>
**Disomy and diploidy frequencies in post cisplatin, etoposide and bleomycin chemotherapy (PEB-CT) patients and in controls (De Mas, 2001)**

<table>
<thead>
<tr>
<th>Disomy</th>
<th>TPSGBM</th>
<th>Mean (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>0.10</td>
<td>0.05</td>
<td>0.04</td>
</tr>
<tr>
<td>16</td>
<td>0.10</td>
<td>0.10</td>
<td>0.046</td>
</tr>
<tr>
<td>18</td>
<td>0.06</td>
<td>0.03</td>
<td>0.34</td>
</tr>
<tr>
<td>X</td>
<td>0.02</td>
<td>0.02</td>
<td>0.005</td>
</tr>
<tr>
<td>Y</td>
<td>0.01</td>
<td>0.01</td>
<td>0.008</td>
</tr>
<tr>
<td>XY</td>
<td>0.14</td>
<td>0.13</td>
<td>0.27</td>
</tr>
<tr>
<td>Diploidy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.29</td>
<td>0.24</td>
<td>0.028</td>
</tr>
</tbody>
</table>

Values are expressed as percentages.

---

**DIETHYLSTILBESTROL AND SEMEN QUALITY**

<table>
<thead>
<tr>
<th>Authors</th>
<th>Cohort</th>
<th>DES+/DES-</th>
<th>Cryptorchidism</th>
<th>Other genital abnormalities</th>
<th>Semen quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dieckmann (1987)</td>
<td>DES+/DES-</td>
<td>163/168</td>
<td>NA</td>
<td>25%/6.2% (p=0.005)</td>
<td>29%-21% (p=0.005)</td>
</tr>
<tr>
<td>Anderson (1979)</td>
<td>DES+/DES-</td>
<td>2424</td>
<td>NA</td>
<td>13%/8%</td>
<td>17%-12% (p=0.01)</td>
</tr>
<tr>
<td>Gill (1979)</td>
<td>DES+/DES-</td>
<td>120/107</td>
<td>13%</td>
<td>31%-77% (p=0.005)</td>
<td>20%-44% (p=0.030)</td>
</tr>
<tr>
<td>Shy (1984)</td>
<td>DES+/DES-</td>
<td>5129</td>
<td>NA</td>
<td>7%-5% (p=0.07)</td>
<td>21%-6% (p=0.02)</td>
</tr>
</tbody>
</table>

**Human semen quality and EDCs**

<table>
<thead>
<tr>
<th>Effects</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>SC</td>
<td>Dalinge et al., 2002</td>
</tr>
<tr>
<td>SQ</td>
<td>Hauser et al., 2002</td>
</tr>
<tr>
<td>SM (CASA)</td>
<td>Richthoff et al., 2003</td>
</tr>
<tr>
<td>Pedicel (CB153)</td>
<td>Han et al., 2003</td>
</tr>
<tr>
<td>Pedicel (p,p' DDE)</td>
<td>Rijnberg et al., 2004</td>
</tr>
<tr>
<td>Pedicel (CB153 et p,p' DDE)</td>
<td>Abd et al., 2000</td>
</tr>
<tr>
<td>Phthalates</td>
<td>Swan et al., 2003</td>
</tr>
<tr>
<td>Phthalates</td>
<td>Dally et al., 2003</td>
</tr>
</tbody>
</table>
Environmental exposure to phthalates and DNA damage in human sperm using the neutral comet assay

- Population without identified sources of exposure to phthalates
- 168 men recruited: semen + urine sample
- 8 phthalate metabolites measured in urine by using HPLC and mass spectrometry
- COMET ASSAY

Table 3: Adjusted regression coefficients for a change in comet assay parameters associated with an 10% increase in phthalate excretion levels (p=0.015)

<table>
<thead>
<tr>
<th>Phthalate</th>
<th>Comet effect</th>
<th>Coefficients for comet assay parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>DEP</td>
<td>-1.31 (0.05 to 0.47)</td>
<td></td>
</tr>
<tr>
<td>DBP</td>
<td>7.00 (0.17 to 0.63)</td>
<td></td>
</tr>
<tr>
<td>DiBP</td>
<td>3.05 (0.25 to 0.05)</td>
<td></td>
</tr>
<tr>
<td>DiNP</td>
<td>9.04 (1.05 to 0.95)</td>
<td></td>
</tr>
<tr>
<td>MEP</td>
<td>2.00 (0.15 to 0.55)</td>
<td></td>
</tr>
<tr>
<td>MEHP</td>
<td>1.20 (1.25 to 0.93)</td>
<td></td>
</tr>
<tr>
<td>MEHBP</td>
<td>-0.12 (0.99 to 0.79)</td>
<td></td>
</tr>
<tr>
<td>MHP</td>
<td>0.00 (0.40 to 0.60)</td>
<td></td>
</tr>
</tbody>
</table>

The first human data to demonstrate that urinary MonoEthyl Phthalate, at environmental levels, is associated with increased DNA damage in sperm

Duty et al., 2003

Microscopic level:
- Sperm concentration
- Sperm motility
- Sperm morphology

Molecular level:
- Sperm aneuploidy
- Seminal oxidative stress
- Sperm plasma membrane phospholipids asymmetry
- Sperm DNA fragmentation

Smoking

Maternal smoking:
- Adverse and irreversible effect on semen quality in male descendants
- Higher risk of birth defects and childhood cancer
**Alcohol**

- In vivo, sperm alteration, not related to nutritional or hepatic status
  - Morphology, motility, concentration ...
  - Maturation arrest, SCOS
  - Progressive alcohol-induced sperm alterations resulting in spermatogenic arrest reversible after alcohol withdrawal
- In vitro, reduction of sperm motility and morphology, with a dose-related response
- Increased risk for XY sperm aneuploidy
- Possible synergistic effect of alcohol and smoking

**Recreational drug use**

- **Cocaine**
  - In vivo: association of cocaine use and sperm concentration, motility and morphology
  - In vitro: a decrease in straight line velocity and linearity

- **Cannabis**
  - In vitro: reduced sperm progressive motility and acrosome reaction
  - In vivo: potent inhibitor of mitochondrial O2 consumption in human sperm

**Genital heat stress**

- Heat exposure reduces sperm quality
- Sedentary postures increases scrotal temperature:
  - Car drivers
  - Heated floor
  - Wet heat (Jacuzzi or hot baths)
  - Laptop computer users

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  - Wet heat (Jacuzzi or hot baths)
  - Laptop computer users
Psychological stress

- General population:
  Small effect. (Hjollund et al., 2004)

- Infertile couples:
  Weak association between psychological factors and impaired semen quality. (Zorn et al., 2008)

Kobe earthquake and reduced sperm motility

- Before and After the Kobe earthquake, reduced sperm motility was observed. (Fukuda et al., 1996)

- Magnitude of >6 on the Richter scale

Cellular telephone use

- Escalating concerns about the adverse effects of cell phones on human health and male reproductive system

- Negative effects on sperm parameters of prolonged use of cell phones: sperm count, motility, viability, and morphology. (Fejes et al., 2005, Bishnoi et al., 2007, Agerwal et al., 2012)

- Impact of radiofrequency electromagnetic waves on semen quality?
Weight and nutritional habits

France:
- 67% M 35-74 years overweight with 20.6%>30
- 54% M 35-44 years overweight or obese
- 3% (1965) to 16% (2000) children overweight or obese

Monitoring national du risque artériel, MONA LISA 2005-2007

Nutritional imprinting

From Pascale Chavatte-Palmer, INRA

DEVELOPMENTAL ORIGIN OF ADULT DISEASE

From Pascale Chavatte-Palmer, INRA, 2009
Low maternal nutrition during pregnancy reduces the number of Sertoli cells in the newborn lamb

Martin et al. 2002

- the number of Sertoli cells: 43.0 +/- 2.5 for HighME v. LowME 34.5 +/- 2.0 x 10^8; P=0.018) per testis

MATERNAL OBESITY

Danish study of 1984-87: 347/5109 sons in 2006

MATERNAL DIET

Maternal vitamin B12 deficiency affects spermatogenesis at the embryonic and immature stages in rat

- Germinal cells of the embryo
- Sperm: OAT
- Reversibility?

35.5% of 172 M and 23.3% 223 F
>43.3% of couples
39% of M with OAT
BMI IN ADOLESCENCE

583 teenagers from 1980 (12, 15, 18 years) to 2001 (33, 36 et 39 years)

6091 young americans recorded from 17-24 years in 1981 to 2004 (47 years)

BMI AND FERTILITY

Retrospective epidemiological studies
- USA: 1329 couples, 1/4 infertile
  - dose-response curve BMI and infertility OR = 1.12
  - Cut-off BMI>32
  - Sallmen et al. 2006

- Denmark: 47835 couples with living birth
  - dose-response curve BMI et hypofertility, overweight OR=1.15, obesity OR=1.49
  - Ramlau-Hansen et al. 2007

- Norway: 26303 couples with pregnancy
  - dose-response curve BMI et hypofertility, overweight OR=1.19, obesity OR=1.36
  - Nguyen et al. 2007

BMI AND SPERM QUALITY

A controversial issue !!

<table>
<thead>
<tr>
<th>Reference</th>
<th>Population</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jensen et al. 2004</td>
<td>Healthy males (military service)</td>
<td>BMI&gt;25: [sperm]</td>
</tr>
<tr>
<td>Fejes et al. 2005</td>
<td>Male from infertile couples</td>
<td>81 [sperm] and mobility correlated to weight, TT, TH</td>
</tr>
<tr>
<td>Magnusdottir et al. 2005</td>
<td>Male from infertile couples</td>
<td>72 3x more obese male in case of infertility factor</td>
</tr>
<tr>
<td>Koloszar et al. 2005</td>
<td>Male from infertile couples</td>
<td>With sperm N 274 [sperm] if BMI&gt;30</td>
</tr>
<tr>
<td>Kort et al. 2006</td>
<td>Male from infertile couples</td>
<td>520 mobility and DNA fragmentation with BMI</td>
</tr>
<tr>
<td>Hammoud et al. 2008</td>
<td>Male from infertile couples</td>
<td>526 More OAT related to obesity</td>
</tr>
<tr>
<td>Chavarro et al., 2009</td>
<td>Male from infertile couples</td>
<td>483 [sperm] if BMI&gt;35 et DNA fragmentation</td>
</tr>
<tr>
<td>Pauli et al. 2008</td>
<td>Fertiles + infertiles</td>
<td>87 No impact</td>
</tr>
<tr>
<td>Aggerholm et al. 2008</td>
<td>Fertiles + infertiles</td>
<td>2139 No impact</td>
</tr>
<tr>
<td>Li et al. 2009</td>
<td>Healthy males</td>
<td>1346 No impact</td>
</tr>
</tbody>
</table>
BMI AND SPERM QUALITY

META-ANALYSIS

MECHANISMS

- Secondary subclinical hypogonadotropic hypogonadism
- Insulin (abdominal fat levels) and leptin
- Direct testicular impact
- Toxics and EDs in the fatty tissue
- Scrotal temperature
- Polygenic obesity
  - Heredity of the alimentary behavior
  - "obesogenic" environment
  - FTO, PTER, BCHR, MANF, NPC1
**VITAMIN**

- Vitamin C: 20% of adults (H)
- Vitamin A: 30-45% adults
- Vitamin E: 40-65%

**MINERAL**

- Copper and Zinc: 25-50%
- Calcium: 8% of M
- Magnesium: 18% of M

**Deficiencies (biological tags)**

- Vitamin B1: 22% of adults
- Vitamin B2: 22% of M
- Vitamin B6: 15% of M
- Vitamin C: 12% of M
- Vitamin D: 12% of M
- Copper: 15% of M
- Selenium: 30% of adults

**Polyunsaturated fatty acid PFA**

- 6/3 ratio in sperm related to food
- PFA on sperm membrane
- Providing necessary fluidity during fertilization
- Generating oxidative stress

**FOLATE (B9)**

- Folate and human reproduction
- Importance of folic acid and antioxidants in protecting against birth defects
- Impact of folate and folic acid status on human reproduction
- Role of folic acid in one-carbon metabolism and DNA synthesis
- Ethical considerations in using folic acid supplementation during pregnancy

*Wathes and Aitken 2007*
VITAMINS

- Sperm count, motility, morphology
- Fertilization
- Sperm count, DNA, motility, morphology
- Spermatogenesis, spermiation, steroidogenesis
- Excess: from oligozoospermy to complete meiosis arrest
- Deficiency: early arrest BUT reversible, AR

Livera et al., 2002; Zervos et al., 2005; Ghyselinck et al., 2006

SELENIUM (Se)

- Positive correlation between [Se] and [sperm] and motility
- Deficiency in Se: weight reduction of testis and morphological alteration of sperm cells, not compensated by E vitamin or any other antioxidants!

Zinc (Zn)

- Essential for the spermatogenesis: DNA synthesis, AR, antioxidant
- High seminal concentration ++++, lower for infertile M

DIETARY PATTERN AND SEMEN QUALITY
- BMI 23.2
- BMI 23.5
- Inverse relation between soy food intake and sperm concentration
- Overweight and obese
- High sperm concentration
- Vit C (400 mg/j)
- Vit E (400 mg/j)
- Vit A (18 mg/j)
- Zn (500 μmol/j)
- Se (1 μmol/j)
- Antioxidant Supplementation Increases the Risk of Skin Cancers in Women but Not in Men
  - S. Hercberg et al., 2007, The Journal of Nutrition
DIET…

- No effect on free or total testosterone T (Laenen et al. 1994)
- Increase of free and total T, without effect on E2 (Muhammad et al. 2004)
- Increase of free and total T, without effect on sexual life (Kaukua et al. 2003)
- Improvement of the sexual function (Esposito et al. 2009)

---

Effect of Diet on Testicular Function and Quality of Life in Obese Men

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pre-Bariatric Surgery</th>
<th>Post-Bariatric Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy</td>
<td>1171 kcal</td>
<td>1468 kcal</td>
</tr>
<tr>
<td>Body Weight</td>
<td>129.4 kg</td>
<td>117.8 kg</td>
</tr>
<tr>
<td>Fat Mass</td>
<td>41.4 kg</td>
<td>33.1 kg</td>
</tr>
<tr>
<td>Systolic Blood Pressure</td>
<td>142 mmHg</td>
<td>124 mmHg</td>
</tr>
<tr>
<td>Diastolic Blood Pressure</td>
<td>84 mmHg</td>
<td>73 mmHg</td>
</tr>
<tr>
<td>Serum Testosterone</td>
<td>4.3 ng/dl</td>
<td>6.2 ng/dl</td>
</tr>
<tr>
<td>Serum Estradiol</td>
<td>22 pg/dl</td>
<td>35 pg/dl</td>
</tr>
<tr>
<td>Serum DHEA</td>
<td>550 ng/dl</td>
<td>700 ng/dl</td>
</tr>
<tr>
<td>Serum CRP</td>
<td>9 mg/L</td>
<td>5 mg/L</td>
</tr>
<tr>
<td>Quality of Life (QoL)</td>
<td>3.4</td>
<td>2.8</td>
</tr>
<tr>
<td>Physical Activity Score</td>
<td>2.6</td>
<td>3.2</td>
</tr>
<tr>
<td>Mental Health Index</td>
<td>6.3</td>
<td>5.8</td>
</tr>
</tbody>
</table>

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Clinical Review

Role of Nutrition in Preventing Cancer

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FOODS THAT FIGHT INFERTILITY?