How to make environment safe to protect reproductive health

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Disclosures

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Fertility rates decline globally
Testosterone levels have declined
Sperm counts have declined
Virtanen, Jorgensen, Toppari
Semen quality in the 21st century
Nature Reviews Urology 2017
Young men from the Finnish general population

Sperm concentrations according to year of birth

Adjusted for duration of ejaculation abstinence

Jørgensen et al 2011, IJA
Semen quality in Finland

According to Bonde et al. 1998 Lancet

Jørgensen et al. 2011 Int J Androl
Trends in testicular germ cell cancer

Northern Europe

Modified from Znaor et al, European Urology, 2014
Testicular cancer. Trends in age-standardized (World) incidence rate per 100,000.
Skakkebaek et al. Physiol Rev 2016
Fetal origin of adult testicular problems: The Testicular Dysgenesis Syndrome (TDS) Hypothesis

- Environmental exposure
- Genetic defects and polymorphisms
- Lifestyle factors
- Epigenetic factors

Testicular dysgenesis
- Decreased Leydig cell function
  - Decreased INSL3 production
  - Hypospadias
  - Cryptorchidism
- Androgen insufficiency
  - Short AGD
- Impaired Sertoli cell function
  - Impaired germ cell differentiation
  - Decreased testosterone production
  - Impaired spermatogenesis
  - GCNIS Testicular cancer

Reduced male fecundity influencing pregnancy rates

Skakkebaek et al. Physiol Rev 2016
Katharina Main

4957 families
2562 boys
Danish-Finnish Birth Cohort Study

• All newborn boys of volunteer mothers (born 1997 - 1999)
  • Questionnaire during pregnancy
  • Clinical examinations
    • All boys: At birth and at 3 months of age
    • Cases and controls: Also at 18 months of age
• Biological samples
  • Blood sample at 10 - 15 gestational weeks
  • Placenta
  • Breast milk (4-8 weeks after birth)
  • Blood sample at 3 months of age
Testicular germ cell cancer: Association with other reproductive disorders

Prevalence of genital malformations in boys

Sperm concentrations in DK and FIN

Boisen et al. Lancet 2004; JCEM 2005

Jørgensen et al. Hum Reprod 2001; 2002
Sertoli cell number determines the sperm output

Johnson et al. 1984 Biol Reprod
Exposure to anti-androgens

- Hypospadias
- Cryptorchidism
- Nipple retention
- Shortened anogenital distance
- Dysgenetic testicular structure
- Impaired spermatogenesis
Anti-androgens

• Effects are additive
• Compounds at levels way below their NOAEL show effects
• E.g., vinclozolin, prochloraz, p,p’DDE, and DBP together can cause hypospadias in 100 % of pups when 0% of pups show hypospadias after single chemical exposure
Phthalates and Cumulative Risk, NRC 2008

Fetal Androgen Insufficiency

- Other Stressors
- Decreased Testosterone
- Decreased Dihydrotestosterone
- Block Androgen Receptor
- Mutated Receptor

Decreased Androgen Receptor activity at target tissue

Interference with Androgen Mediated development

Production of androgen mediated Reproductive tract malformations

Sperm Quality

Cryptorchidism

\( \Delta \)AGD

Nipple Retention

Hypospadias

LC tumors

Other retro tract Malformations
Distinct Chemical Signatures of Danish and Finnish Breast Milk: dioxins

Krysiak-Baltyn et al., Int. J. Androl. 2010
Validation of national chemical fingerprints of pollution

J.P. Antignac et al. Country-specific chemical signatures of persistent organic pollutants (POPs) in breast milk of French, Danish and Finnish women Environmental Pollution, Volume 218, 2016, 728–738
What to do?

• Get rid of persistent organic pollutants – Stockholm convention
• Identify anti-androgenic chemicals and regulate
  • QSAR
  • in vitro
  • in vivo (vinclozolin would not be identified without in vivo experiments)
  • Consider always mixture effects
• Protect development – young men and women, children
• Do not wait proof of human effects
• Avoid unknown risk if possible (would you drink unknown liquid from an unlabeled bottle?)
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Dioxin exposure pre- AND post-natally affects sperm numbers

Mocarelli et al EHP
119:713-718 2011
PCBs & Dioxins

Koskenniemi et al. Env Health 2015

Study Group
- Case N=30
- Control N=29

Ln (Total - TEq)

Age when breastfeeding was discontinued (months)

Prenatal  Breast milk  Diet
Breast milk (log) sum of BDE 47, 153, 99, 100, 26, and 66 (ng/g fat)

Polybrominated flame retardants

Main et al.,
EHP 2007