Increasing Trends in Male Reproductive Disorders, Environmental Exposures, and Implications for Human Health

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Teleconference 20 April, 2016

Nothing to declare
In all the data about Germany, it’s the one statistic that bucks the trend. Its economy is strong, its cities are regularly cited as among the best in the world to live in – but Germany is a shrinking According to the national statistics office, fewer babies were born in Germany last year than at any time in its history. A total of 663,000 children were born, 15,000 fewer than in 2010 and in stark contrast to 1964 when German births (east and west) peaked at just under 1.4 million. The rate for younger women in particular fell last year,

50% fewer children and young people!
Possible Reasons for Declining Fertility Rates

- Some social scientists and demographers:
  a. people just plan to have fewer kids and
  b. use of modern contraception and induced abortions
Total Fertility Rate (TFR), Denmark 1901–2014

45% Unintended Pregnancy Rate in USA

_Finer & Zolna, NEJM, 2016_

Pregnancy either

**Mistimed** - not wanted at the time that pregnancy occurred but at a later time

or

**Unwanted** – not wanted then or at any time in the future
Possible Reasons for Declining Fertility Rates

• Some social researchers (demographers):
  a. people intend to have fewer kids and
  b. use of modern contraception and induced abortion

• Gynecologists: Women are too old when they start trying to become pregnant
Mean ages of Danish women delivering from 1975–2014
Mean ages of Danish women delivering from 1901–2014.


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Possible Reasons for Declining Fertility Rates

• Social researchers (demographers):
  a. people intend to have fewer kids and
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• Gynecologists: Women are too old when they start trying to become pregnant

• Fecundity (ability to conceive) has declined, male or female, or both
Fewer Unintended Pregnancies and Widespread Infertility

• 40-50% of children in US and Europe are born after sex where pregnancy was not planned.
• But previously a higher number.
• Hypothesis I will discuss is: Does a general decline in male reproductive health play a role for birth rates by causing a reduction in the number of unintended pregnancies and more infertility?
Links and Trends in Male Reproductive Disorders
A Square

Testicular germ cell cancer (TGCC) ↔ Reduced fecundity and childlessness

Lower T-levels ↔ Congenital disorders of genitalia
Age-standardized incidence in DK, around 1995

From Møller, Hum Reprod 2001

Testicular Cancer

Well diagnosed and registration close to complete

Prostate Cancer
Trends in testicular germ cell cancer

Northern Europe

Modified from Znaor et al, European Urology, 2014
Trends in testicular germ cell cancer

The Americas

Modified from Znaor et al, European Urology, 2014
Trends in testicular germ cell cancer

Asia

Modified from Znaor et al, European Urology, 2014
POSSIBLE CARCINOMA-IN-SITU OF THE TESTIS

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Summary Embryonal carcinoma of the testis was detected in two infertile men in whom testicular biopsies had revealed an abnormal seminiferous epithelium with atypical germ cells. The tumours occurred within 4½ years of testicular biopsy. It is suggested that the atypical germ cells represented a carcinoma-in-situ.
Evidence for decreased fertility in men prior to development of testicular cancer

Møller & Skakkebæk, Br Med J, 1999
Links and Trends in Male Reproductive Disorders

- Testicular germ cell cancer (TGCC)
- Reduced fecundity and childlessness
- Lower T-levels
- Congenital disorders of genitalia
Sperm count of 4867 young men from the general population
Jørgensen et al, BMJ Open, 2012

Adjusted for duration of ejaculation abstinence

Similar results from Finland, Germany, USA, Japan and Australia
Should we be concerned about these publications on low sperm counts?

Some people may think:

”….after all, only one sperm is necessary for fertilization....“
Probability of pregnancy within one menstrual cycle

Increasing need for assisted reproduction

Most recent data (2015) from Danish Fertility Society shows that:

8% of the 2012 national birth cohort conceived after assisted reproduction (IVF, ICSI, IUI-H or IUI-D)

http://www.fertilitetsselskab.dk/

In addition, almost 1% of children adopted
Links and Trends in Male Reproductive Disorders
Roots in fetal development

- Testicular germ cell cancer (TGCC)
- Lower T-levels
- Reduced fecundity and childlessness
- Congenital disorders of genitalia
Gonocytes expressing OCT 4, gestational week 10
Oct-4 expression in GCNIS cells (adult, infertile male)
Testicular Dysgenesis Syndrome (TDS)

Environmental exposure
Genetic defects and polymorphisms
Lifestyle factors
Epigenetic factors

Testicular dysgenesis

Decreased Leydig cell function
Decreased INSL3 production
Decreased testosterone production

Hypospadias
Cryptorchidism

Short AGD

Disturbed Sertoli cell function

Impaired germ cell differentiation

Impaired spermatogenesis

GCNIS Testicular cancer

Reduced male fecundity influencing pregnancy rates
WHO-UNEP: Strong evidence that EDCs can have adverse effects on male reproduction at the level of the pituitary, the testicle and the gamete

- Effects in wild life
- Effects in experimental settings
- Potential effects in humans
- We are all exposed
- Possible transgenerational effects
Conclusions

- Testicular cancer is an important marker of endocrine disruption of the fetal human testis.
- Worldwide increases in testicular cancer incidence.
- Semen quality of young men now rarely meets all criteria of the WHO standard.
- Extremely low fertility rates below replacement levels have previously been seen as a result of women's choices.
- However, an increasing number of data suggest that male infertility also contributes to low birth rates.
- We and others are testing the hypothesis that environmental exposures contribute to the current epidemic of subfertility and infertility, which likely is associated with decreasing populations in many industrialized countries.
- Good news: Exposures can be reduced by better regulation of chemicals!
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