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SCIENCE MOVING
PEOPLE
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Lifestyle and male reproduction

Special Interest Group Andrology

4

3 July 2011
Stockholm, Sweden

Lifestyle and male reproduction

Stockholm, Sweden
3 July 2011

Organised by
Special Interest Group Andrology

Contents

Course coordinators

Sheena Lewis (United Kingdom) and Lars Bjorndahl (Sweden)

Course description

This course will present the causal links between lifestyle choices, general male health, systemic disease and human reproductive health.
The impact on male reproductive health will be addressed as follows:
i) prenatal influences, dietary habits during childhood and puberty,
ii) adolescents and adults: obesity, diabetes and other systemic disorders, sexually transmitted infections and cancer therapies
iii) alcohol, tobacco and recreational drug use on male reproductive health

Target audience

Clinicians, paramedical staff, embryologists and andrologists with an interest in the effects of lifestyle factors on human male reproduction

Scientific programme

09.00 - 09.30	In utero influences on future male fertility: effects of environmental chemicals and life-style- **Olle Söder (Sweden)**
09.30 - 09.45	Discussion
09.45 - 10.15	Obesity and diabetes: disease and treatment effects on male fertility – **Stefan Arver (Sweden)**
10.15 - 10.30	Discussion
10.30 - 11.00	Coffee break
11.00 - 11.30	STIs – **Falk R. Ochsendorf (Germany)**
11.30 - 11.45	Discussion
11.45 - 12.15	Genetically determined susceptibility to iatrogenic therapies – **Yvonne Lundberg-Giwercman (Sweden)**
12.15 - 12.30	Discussion
12.30 - 13.30	Lunch
13.30 - 14.00	Cancer: impact of disease and therapy on male fertility – **Bernard Robaire (Canada)**
14.00 - 14.15	Discussion
14.15 - 14.45	Recreational drugs (smoking, alcohol and cannabis) – **Sheena Lewis (United Kingdom)**
14.45 - 15.00	Discussion
15.00 - 15.30	Coffee break
15.30 - 16.00	Good sperm, good brain? – **Arand Pierce (United Kingdom)**
16.00 - 16.15	Discussion
16.15 - 16.45	Exercise: Fit sperm? – **Diana Vaamonde (Spain)**
16.45 - 17.00	Discussion

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ESHRE – European Society of Human Reproduction and Embryology

What is ESHRE?

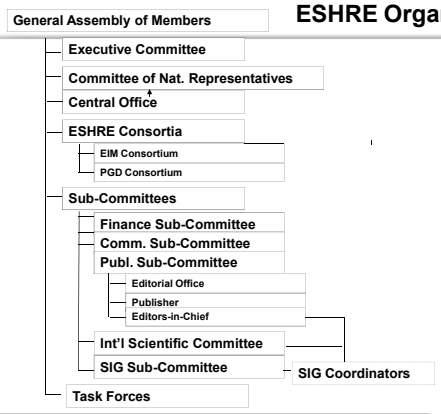
ESHRE was founded in 1985 and its **Mission Statement** is to:

- promote interest in, and understanding of, reproductive science
- facilitate research and dissemination of research findings in human reproduction and embryology to the general public, scientists, clinicians and patient associations.
- inform policy makers in Europe
- promote improvements in clinical practice through educational activities
- develop and maintain data registries
- implement methods to improve safety and quality assurance

Executive Committee 2009/2011

Chairman	• Luca Gianaroli	Italy
Chairman Elect	• Anna Veiga	Spain
Past Chairman	• Joep Geraedts	Netherlands
	• Jean François Guérin	France
	• Timur Gürgan	Turkey
	• Ursula Eichenlaub-Ritter	Germany
	• Antonis Makrigiannakis	Greece
	• Miodrag Stojkovic	Serbia
	• Anne-Maria Suikkari	Finland
	• Carlos Plancha	Portugal
	• Françoise Shenfield	United Kingdom
	• Etienne Van den Abbeel	Belgium
	• Jolieneke Schoonenberg-Pomper	Netherlands
	• Veljko Vlaisavljevic	Slovenia
	• Søren Ziebe	Denmark

ESHRE Organisation



ESHRE Journals

Human Reproduction with impact factor 3.859

Human Reproduction Update with impact factor 7.042

Molecular Human Reproduction with impact factor 3.005

Campus Activities and Data Collection

Campus / Workshops

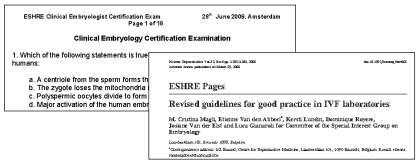
- Meetings are organised across Europe by Special Interest Groups and Task Forces
- Visit www.eshre.eu under CALENDAR

Data collection and monitoring

- European IVF Monitoring Group data collection
- PGD Consortium data collection

ESHRE Activities

- Embryology Certification
- Guidelines
- Position papers
- News magazine “Focus on Reproduction”


ESHRE Clinical Embryologist Certification Exam 20th June 2009, Amsterdam
Page 1 of 10

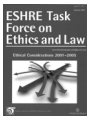
Clinical Embryology Certification Examination

1. Which of the following statements is true
humans:

a. A centriole from the sperm forms th
b. The zygote loses the mitochondria
c. Polyspermic oocytes divide to form
d. Major activation of the human embr

ESHRE Pages

Revised guidelines for good practice in IVF laboratories



ESHRE COMMUNITY

RSS feeds for news in reproductive medicine

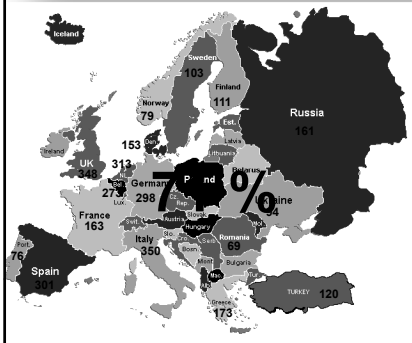
Since launch 12/2009: **1,360 Fans**

Since launch 12/2009: **190 followers** (journalists, scientific organisations, patient societies, governmental bodies)

Retweets to MHR

Find a member

ESHRE Membership (1/3)



4,017	Europe
476	Asia
372	North America
332	Middle East
221	Africa
142	Oceania
99	South America

TOTAL MEMBERSHIP*: 5 659 members

* as of July 2010

ESHRE Membership (2/3)

	1 yr	3 yrs
Ordinary Member	€ 60	€ 180
Paramedical Member*	€ 30	€ 90
Student Member**	€ 30	N.A.

*Paramedical membership applies to support personnel working in a routine environment such as nurses and lab technicians.
**Student membership applies to undergraduate, graduate and medical students, residents and post-doctoral research trainees.

ESHRE Membership – Benefits (3/3)

1) Reduced registration fees for all ESHRE activities:

Annual Meeting	Ordinary	€ 480	(€ 720)
	Students/Paramedicals	€ 240	(€ 360)
Workshops*	All members	€150	(€ 250)

2) Reduced subscription fees to all ESHRE journals – e.g. for Human Reproduction €191 (€ 573!)

3) ESHRE monthly e-newsletter

4) News Magazine "Focus on Reproduction" (3 issues p.a.)

5) Active participation in the Society's policy-making

*workshop fees may vary

Special Interest Groups (SIGs)

The SIGs reflect the scientific interests of the Society's membership and bring together members of the Society in sub-fields of common interest

- Andrology
- Early Pregnancy
- Embryology
- Endometriosis / Endometrium
- Ethics & Law
- Safety & Quality in ART
- Psychology & Counselling
- Reproductive Genetics
- Reproductive Surgery
- Stem Cells
- Reproductive Endocrinology

Task Forces

A task force is a unit established to work on a single defined task / activity

- Fertility Preservation in Severe Diseases
- Developing Countries and Infertility
- Cross Border Reproductive Care
- Reproduction and Society
- Basic Reproductive Science
- Fertility and Viral Diseases
- Management of Infertility Units
- PGS
- EU Tissues and Cells Directive

ESHRE – Annual Meeting

- One of the most important events in reproductive science
- Steady increase in terms of attendance and of scientific recognition

Track record:

ESHRE 2010 – Rome: 9,204 participants
ESHRE 2009 – Amsterdam: 8,055 participants
ESHRE 2008 – Barcelona: 7,559 participants

Future meetings:

ESHRE 2011 – Stockholm, 3-6 July 2011
ESHRE 2012 – Istanbul, 1-4 July 2012

ESHRE 2011, Stockholm, Sweden

When: **3 - 6 July 2011**
Where: **Stockholmsmässan, Mässvägen 1, Älvsjö, Sweden**
www.stockholmsmassan.se

Chair of conference: **Kersti Lundin**

Hotel and Travel:
MCI - Stockholm Office
Phone: +46 (0)8 54651500
E-mail: eshre@mci-group.com

For updates visit www.eshre.eu

ESHRE 2011, Stockholm

Keynote Lectures

Aneuploidy in humans: what we know and we wish we knew – Terry Hassold (USA)

Historical Lecture

A brave new world with a brave old humankind; quo vadimus – E. Diczfalusy (SE)

MHR Symposium – The paternal genome

Sperm chromatin packaging – B. Robaire (CDN)

The human sperm epigenome – B. Cairns (USA)

ESHRE 2011, Stockholm: Debates

This house believes that obese women should not receive treatment until they have lost weight

- **Yes: Mark Hamilton *(UK)***
- **No: Guido de Wert *(NL) - TBC***

Paramedical invited session: Should we pay donors?

- **Yes: Herman Tournaye (BE)**
- **No: Laura Witjens (UK)**

Annual Meeting – Pre-Congress Courses

- PCC 1: The challenges of embryo transfer (Paramedical Group)
- PCC 2: The blastocyst: perpetuating life (SIG Embryology and SIG Stem Cells)
- PCC 3: From genes to gestation
  (SIG Early Pregnancy and SIG Reproductive Genetics)
- PCC 4: Lifestyle and male reproduction (SIG Andrology)
- PCC 5: Ovarian ageing (SIG Reproductive Endocrinology)
- PCC 6: The impact of the reproductive tract environment on implantation success (SIG Endometriosis/Endometrium)
- PCC 7: Adhesion prevention in reproductive surgery
  (SIG Reproductive Surgery)

Annual Meeting – Pre-congress Courses

- PCC 8: Theory and practice update in third party reproduction
  (SIG Psychology and Counselling)
- PCC 9: Ethical aspects of non-invasive prenatal diagnosis
  (SIG Ethics & Law)
- PCC 10: Patient-centered fertility services
  (SIG SQUART)
- PCC 11: Clinical management planning for fertility preservation in female cancer patients
  (TF Basic Science and TF Preservation in Severe Disease in collaboration with the US OncoFertility Consortium)
- PCC 12: Opportunities for research in female germ cell biology
  (TF Basic Science)

Annual Meeting – Pre-congress courses

- PCC 13: Assisted reproduction in couples with HIV
  (TF Fertility and Viral Diseases)
- PCC 14: Prevention of infertility – from preconception to post-menopause
  (TF Reproduction and Society)
- PCC 15: Hot topics in male and female reproduction
  (ASRM exchange course)
- PCC 16: Academic Authorship programme
  (Associate Editors ESHRE journals)
- PCC 17: Science and the media, an introduction to effective communication with the media
  (Communications SubCommittee ESHRE)

Certificate of attendance

1/ Please fill out the evaluation form during the campus

2/ After the campus you can retrieve your certificate of attendance at www.eshre.eu

3/ You need to enter the results of the evaluation form online

4/ Once the results are entered, you can print the certificate of attendance from the ESHRE website

5/ After the campus you will receive an email from ESHRE with the instructions

6/ You will have TWO WEEKS to print your certificate of attendance

Contact

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Tel: +32 (0)2 269 09 69
info@eshre.eu / www.eshre.eu

In utero influences on future male fertility: Effects of environmental chemicals and life-style

Olle Söder, MD, PhD

Professor of Pediatrics
Paediatric Endocrinologist
Paediatric Endocrinology Unit
Department of Women's and Children's Health
Karolinska Institutet
Stockholm, Sweden

Disclosure:

The speaker has received honorarium/grants for consultancy, educational assignments and research projects from the following pharmaceutical companies:

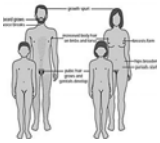
Novo Nordisk
Ferring
Ipsen

Learning Objectives:

- Basic aspects of male prenatal sexual differentiation
- Sensitive periods of male sex development
- Adverse trends in male reproductive functions
- Definition and concepts of endocrine disruptors (EDCs)
- Potential targets of EDCs affecting male reproduction
- Knowledge gaps of EDCs

Reproductive Life Cycle

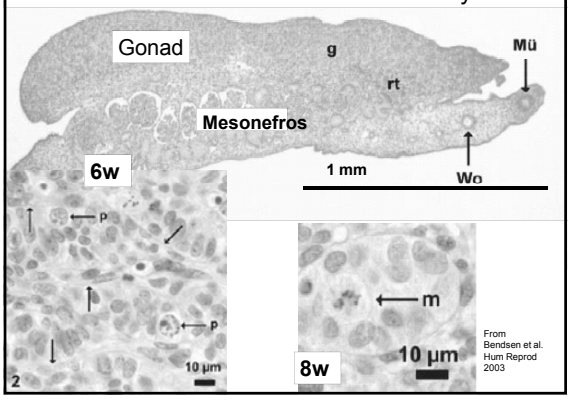
- Conception
- Sex determination
- Sex differentiation
- Birth
- Growth
- Puberty
- Adolescence
- Fertility
- Ageing
- Death



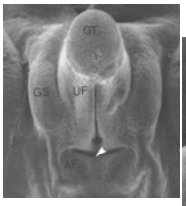
Chronology of early steps in human sex differentiation

Event (start)	*Age (dpc)*	*CRL(mm)*
• Genetic sex (fertilisation)	0	
• PGC differentiation and migration	28	4
• Formation of gonadal ridge	32	5
• PGCs reach gonadal ridge	37	10
• Sex determination ♂ testis	43	15
♀ ovary	49	20
• Leydig cells appear	55	30
• Androgen, INSL3; estrogen	63	40
• Testicular descent (1st phase)	64	

Testis determination in human embryo



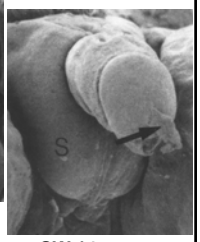
External genitalia



GW 7

GW 11

Girl



GW 14

Boy

Differentiation of external genitalia

Homologous structures:

Glans penis = Clitoris

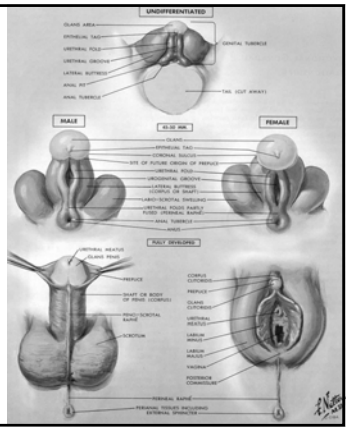
Corpus penis = Labiae min.

Scrotum = Labiae maj.

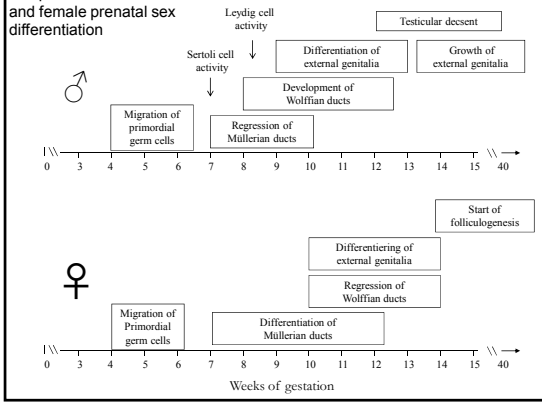
Due to androgen action
T/DHT + AR (5α-R!)

T to ♀ = virilisation

Too little T to ♂ = Incomplete masculinization

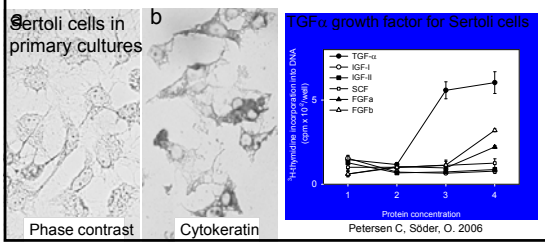


Temporal events in male and female prenatal sex differentiation



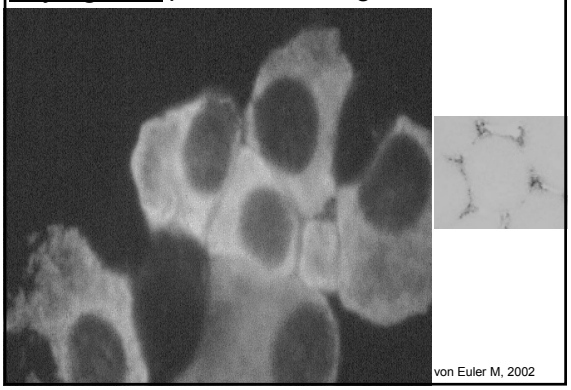
Sertoli cells critical for testis development

Adult Sertoli cell number determines testicular size and volume of spermatogenesis (sperm output)



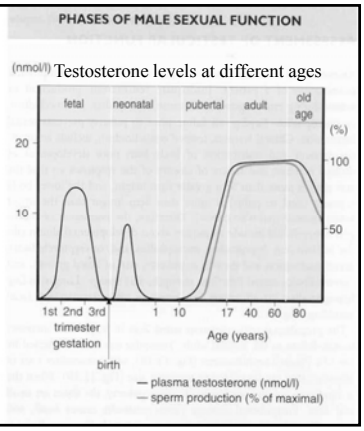
Petersen C, Söder, O. 2006

Leydig cells produce androgen



von Euler M, 2002

Leydig cells are active in fetal life, neonatally and from puberty throughout adult life



Hormonal status of the human fetus

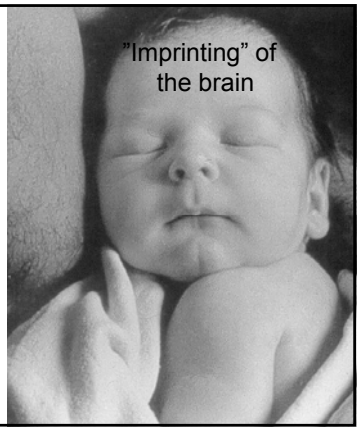
♂ Androgen⇑
Estrogen~ (= ♀)

♀ Estrogen~
Androgen⇓ (active protection)

Gender dimorphic differentiation of the brain important part of human sex differentiation:

- Prenatal
  - genetic
  - hormonal
- Postnatal
  - neonatal?
  - pubertal

Affects:
- psychosexual identity
- behavior



Pre- and postnatal development of the

BRAIN

Gender specific brain differentiation

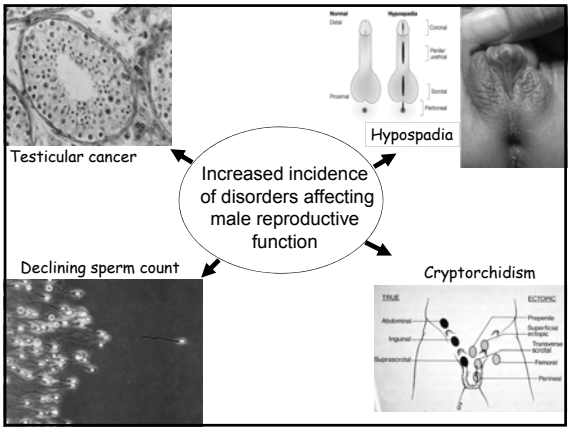
Gender-typic behaviour

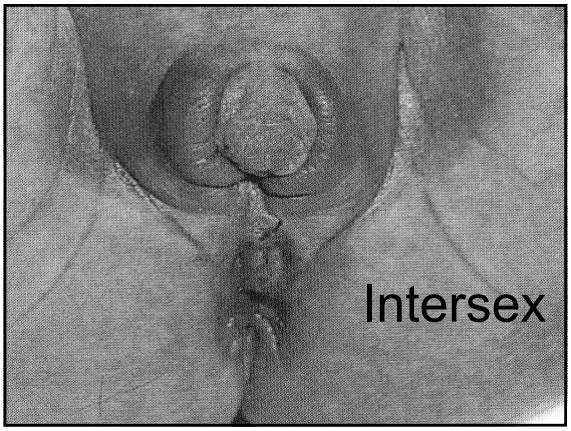
Gender identity disorder?

Meyer-Bahlburg HF et al., 2004

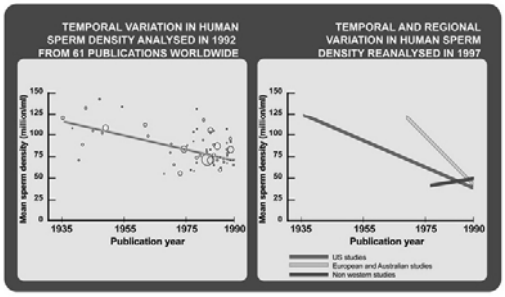
Androgen-sensitive events in male prenatal sex differentiation

- Development of male external genitalia
- Testicular descent
- Development of male internal (Wolffian) structures
- Priming of male-type metabolism
- Differentiation of the CNS

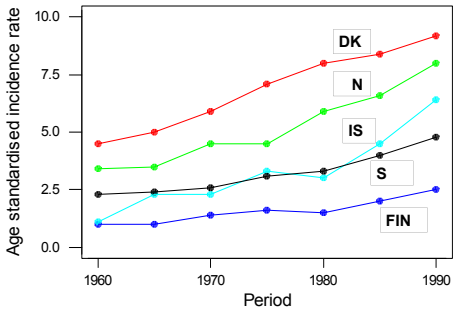




Decline in human sperm count



Increasing incidence of testicular cancer



Source: Nordic cancer registrys

Undescended Testicles (Cryptorchidism)

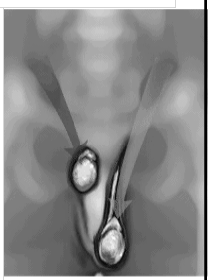
lost common malformation in boys

Androgen-dependent 2nd phase of lescent mostly affected. Anti-androgens?

Poor data in old incidence studies

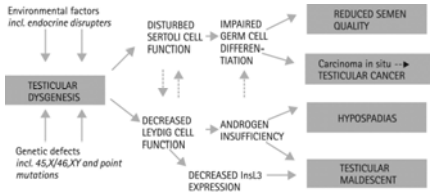
Danish-Finnish study shows great regional variability mirroring incidence of testicular cancer:

4x > birth incidence Denmark vs. Finland
4x increase in Denmark since 1950s



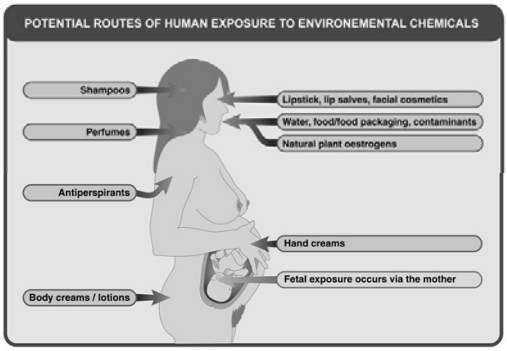
(Boisen et al, 2004)

Suggested common pathogenesis of disorders of male reproductive functions



Early events!

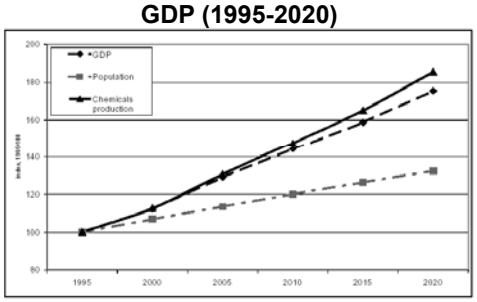
(Bay K et al., 2006)



Global perspective on synthetic chemicals

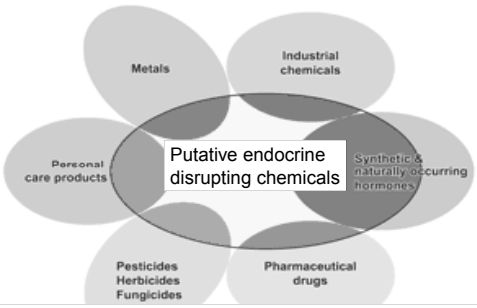
- >100,000 man-made chemicals
- 400 million tonnes yearly production
- 85% no safety information
- 300 synthetic chemicals in human blood (incl. in blood of EU Commissioners -WWF)
- Higher levels of “modern” chemicals in children in “three generations study” (WWF Detox)
- >200 chemicals in cord blood (www.ewg.org/reports/bodyburden2)

Estimated increase of chemicals production, world population, and GDP (1995-2020)



OECD 2001

Endocrine disrupting chemicals (EDCs)



EDCs are chemicals common in the environment such as pharmaceuticals and over-the-counter drugs, natural hormones, personal care products like soaps and cosmetics, industrial by-products, plastics and pesticides.

Endocrine disrupters

(*endocrine disruptor, endocrine modulators, endocrine toxicants, hormonally active chemicals, hormone mimics*)

Kavlock et al., 1996: "an exogenous agent that interferes with the production, release, transport, metabolism, binding, action or elimination of natural hormones in the body responsible for the maintenance of homeostasis and the regulation of developmental processes"

WHO, 2002: "an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations"

Putative EDCs have structures akin to hormones, and include:

- Several **pesticides** and their breakdown products that are now banned, such as DDT
- **PCB**s, a persistent group of chemicals still found in electrical equipment that pollutes lake and stream sediments in many industrial regions
- **Dioxins**, a group of toxic chemical byproducts from paper production and incineration
- Compounds used in plastics such as **phthalates** and **bisphenol A**.

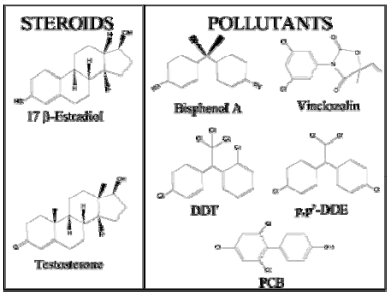
EDCs *CONT´D*

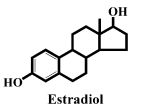
- Several naturally occurring substances such as **phytoestrogens** (e.g., soy isoflavones – genestein) and **anti oxidants** (e.g., resveratrol)
- **Fungicides** used in fruit (e.g., vinclozolin)
- Brominated **flame retardants**

…and many more

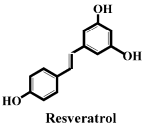
Important chemicals of ”modern life”. Often small lipophilic molecules that pass cell membranes and are easily absorbed not only via food and water, but also through the skin or by inhalation

Many EDCs structurally similar to steroid hormones





Estradiol



Resveratrol

Supornsilchai V et al. 2005

Classification of Endocrine Disruptors

Hormone-modulating effects of EDCs:

1. estrogenic activity, e.g., phytoestrogens
2. anti-androgenic activity, e.g., pesticides
3. anti-estrogenic activity
4. androgenic activity
5. thyroid hormonal effects

Evidence base for endocrine disrupting actions

1. Chemicals found in environment

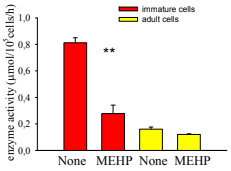
2. Exposure data (wild life, humans, human fetuses)

3. Epidemiology of disorders (genital malformations, sperm counts, etc.)

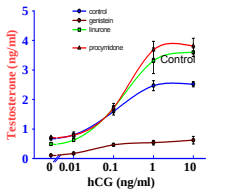
4. "Disease" related to exposure
   a. Wild life (fish, reptiles, birds, whales, turtles, etc.)
   b. Experimental animals ("proof of concept")
   c. Humans disorders

Proof-of-principle studies in exp. animals
(primary cultures)

Phthalates suppress 5α-reductase in immature but not adult Leydig cells *in vitro*

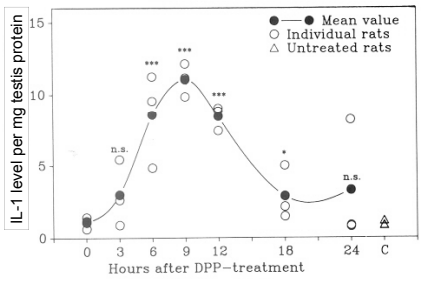


Effect of EDCs on hCG-induced steroidogenesis by Leydig cells *ex vivo*



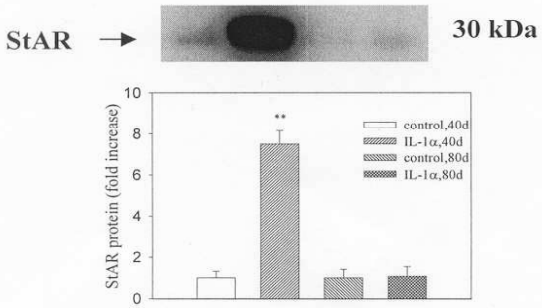
See, Svechnikov et al. 2010

Cytokine level in rat testis after single oral dose of di-penthyl-phthalate



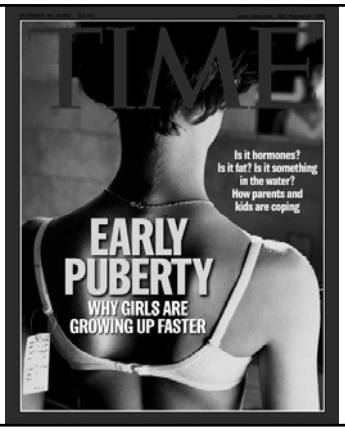
Granholm et al. 1992

IL-1α induces StAR expression in immature but not adult Leydig cells



See, Svechnikov et al., 2010

Late changes in timing of onset of puberty



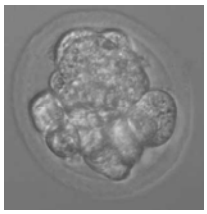
Proposed causes of changes of pubertal timing

1. Nutritional (obesity/anorexia; cf., secular trend)
2. Psychosocial ("exposure to a sexualized society")
3. Environmental (EDCs)
4. Combinations of above
5. Wrong diagnosis ("breast" in obesity)

Exposure to EDCs and timing of puberty in human beings

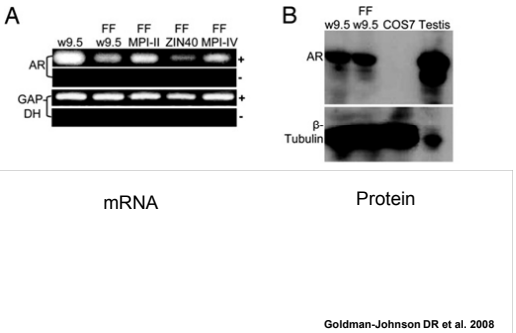
Reported effect	*Sex*	*EDC*	*Exposure*	*Ref.*
Earlier onset				
Menarche, pubarche	F	**PBB**s	Prenatal	Blanck et al. -00
Thelarche	F	**Phthalate**s	Childhood	Colon et al. -00
Menarche	F	**DDE**	Prenatal	Vasiliu et al. -04
CPP	F	**DDE**	Pre-/postnatal?	Krstevska-K et al. -01
Later onset				
Breast stage	F	**Dioxin**	Childhood	Den Hond et al. -02
Pub. stage, test. vol.	M	**PCB**s	Childhood	Den Hond et al. -02
Genital stage	M	**PCBs, PCDF**s	Prenatal	Guo et al. -04
Pub. stage, menarche	F	**Lead**	Childhood	Wu et al., Selevan et al. -03
No association				
Pub. stage	F,M	**PCB**s	Prenatal, lactat.	Gladen et al. -00
Menarche, pub. stage	F,M	**DDE**	Prenatal, lactat.	Gladen et al. -00
Pub. stage, test. vol.	M	**PCB**s	Prenatal	Mol et al. -02
Menarche, pub. stage	F	**Dioxin, PCB**s	Childhood	Den Hond et al. -02
Menarche	F	**PCB**s	Prenatal	Vasiliu et al. -04
Menarche	F	**Dioxin**	Prepubertal	Warner et al. -04

Stem cells novel target for EDC actions?



Goldman-Johnson DR et al. 2008

Androgen Receptor
expressed in murine embryonic stem cells



mRNA

Protein

Goldman-Johnson DR et al. 2008

Knowledge gaps

Still poor data (incl. low power) on:

- environmental contamination of chemicals
- human exposure
- fetal exposure
- reporting of congenital malformations

- neurocognitive disorders
- gender identity
- fertility, sperm counts

- effects of low doses/complex mixtures rather than single substances

Preventive strategies

Proactive attitude

Fill the knowledge gaps

Precautionary principle

Cited Papers and Recommended Reading

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Bendsen E, Byskov AG, Laursen SB, Larsen HP, Andersen CY, Westergaard LG. Number of germ cells and somatic cells in human fetal testes during the first weeks after sex differentiation. Hum Reprod. 2003 Jan;18(1):13-8.

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Letter. Assessing chemical risk: societies offer expertise. Science 331: 1136, 2011

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Obesity and Diabetes: disease and effects on male fertility

Stefan Arver MD, PhD
Assoc Professor, Director
Centre for Andrology and Sexual Medicine
Karolinska University Hospital and Karolinska Institutet
Stockholm, Sweden

Theme of the Lecture

- Male reproductive function depends on
  Spermatogenesis producing “fertile spermatozooa”
  Ejaculation of “healthy gamets”
  Erectile function sufficient for intercourse
  Sexual drive and sufficient frequency of gamet delivery
- Fertile female partner with similar interest

Diabetes and Obesity

- Hypothalamic-Pituitary-Gonadal axis
- Spermatogenesis
- Ejaculatory Function
- Sexual function
- Psycho-social impact of Obesity and Diabetes
- Co-morbidities and pharmacological
- Susceptibility to environmental factors

Solution?

IVF – ICSI

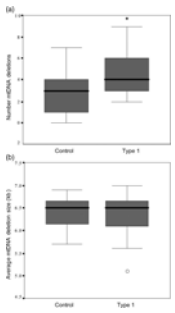
Insulin dependant diabetes mellitus: implications for male reproductive function

	Group			
	Control (n = 29)	**Diabetic (n = 27)**	*P*-value	WHO[a] normal
Age (years)[b]	32.7 ± 0.7	34.0 ± 2.0	0.52	
^{3}HbA1c (%)[b]	5.3 ± 0.1	8.2 ± 0.2	<0.0001	
Semen volume (ml)[b]	**3.3 ± 0.2**	**2.6 ± 0.3**	**<0.05**	2–4
Sperm concentration (10^6ml^{-1})[c]	51 [28–100]	64 [30–151]	0.22	>20
Total sperm output (10^6)[c]	173 [89–338]	198 [99–450]	0.84	—
Motility (%)[b]	47.3 ± 2.8	46.0 ± 4.2	0.79	>50
Normal morphology (%)[b]	11.7 ± 0.8	11.1 ± 0.6	0.56	>14

[a]World Health Organization normal reference values (WHO, 1999).
[b]Values expressed as mean ± SEM.
[c]Values expressed as median [inter-quartile range].

Agbaje I et al. Hum. Reprod. 2007;22:1871-1877

A boxplot comparing mtDNA deletions in sperm from control (n = 29) and diabetic men (n = 27, Type 1 diabetes mellitus) (a) mtDNA deletion number.



Agbaje I et al. Hum. Reprod. 2007;22:1871-1877

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Human Reproduction

Table 2. Assisted reproductive outcomes by treatment.Values are *n* (%).[a]

Treatment	*Patients*	*Cycles*	*Eggs harvested*	*Eggs fertilized*	*Normally fertilized eggs*	*Embryo transfers*	*Clinical pregnancies /cycle*	*Overall clinical pregnancies /cycle BRFC (2007)*[a]
IVF	6	12	66	45 (68)	35 (78)	12	*0*	119/438 (27.2)
ICSI	13	20	198	123 (62)	110 (89)	18	*1 (5)*	91/316 (28.8)
FET	5	7	–	–	–	7	*2 (29)*	30/141 (21.3)
Total	18[b]	39	264	168	145	37	*3*	240/895 (26.8)

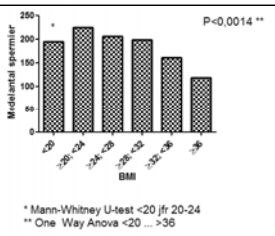
J Mulholland C Mallidis I Agbaje and N McClure Reproductive BioMedicine Online
Volume 22, Issue 2, February 2011, Pages 215-219

Genes with most significantly altered expression found in DM men compared with non-DM fertile men. *Oxidative Stress and DNA repair*

Gene	Known functions	Fold change	P
PIP5K	Intracellular signalling	4345	,002
Septin 4	Sperm structure/movement	1139	,002
Eukaryot. transl. initiation factor 4 1	mRNA translation	526	,004
Interleukin 1 receptor, type II	Cytokine response prevention	218	,004
Murine sarc. viral oncog. homolog	Human proto-oncogene	105	,005
Homeodomain interact. prot kinase 1	Transcriptional regulation	35	,009
Chromosome 19 open read fr 19	Sperm outer dense fibers	7	,001
Adenylosuccinate lyase	Purine synthesis	6	,002
Islet cell autoantigen 1, 69kDa	Autoantigen, type 1 DM	6	,0004
SPATA 20	Member of thioredoxin family	5	,002
POLD2	DNA replication and repair	4	,0003
Stromal cell-derived factor 2-like 1	Stress inducible protein	-3	,001
Voltage-dependent anion channel 3	Mitochondrial membrane channel	-3	,004
Cytokine-inducible protein CIP29	Cell proliferation	-5	,010
F-box protein 34	Cell cycle regulation	-10	,005
Zinc finger protein 541	Transcription regulation	-13	,0001
ODC AZ 1	Polyamine biosynthesis	-14	,0004
BBX	Transcription regulation	-23	,004
CutA divalent cation tolerance homol	Signal transduction	-27	,0001
Testis nuclear RNA-binding protein	Inhibits MAP kinase activation	-40	,001
B4GALT2	Biosynthesis, cell membrane component	-1122	,008

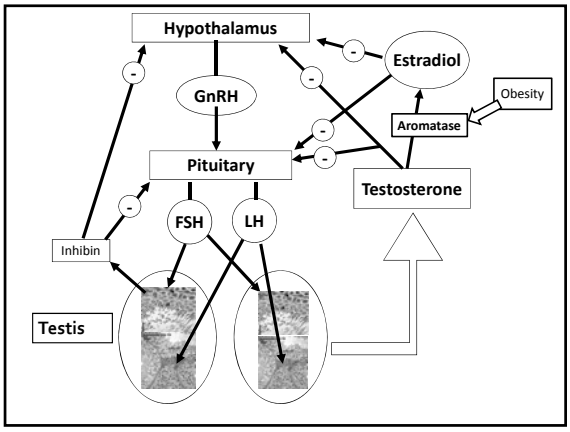
C. Mallidis et al Fertility and Sterility Volume 92, Issue 6, December 2009, Pages 2085-2087

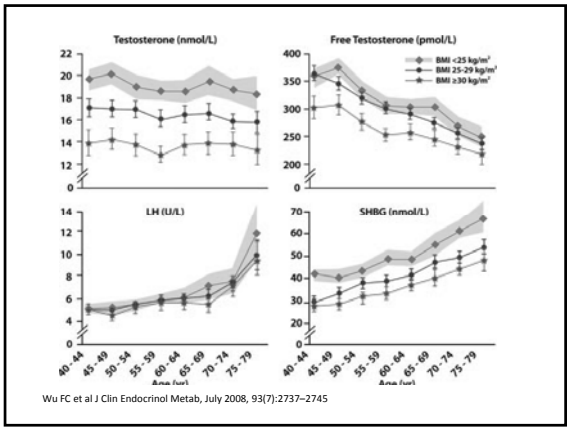
Increased BMI decreased sperm count
N= 3281



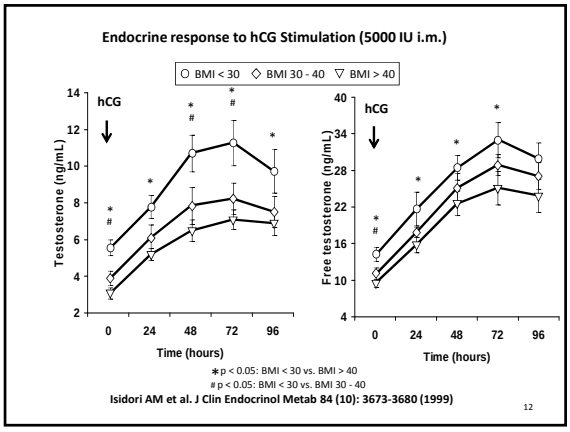
* Mann-Whitney U-test <20 jfr 20-24
** One Way Anova <20 ... >36

Arver, Björndahl, , Ekström , Kvist, Lehtihet, Tu to be pulished 2011

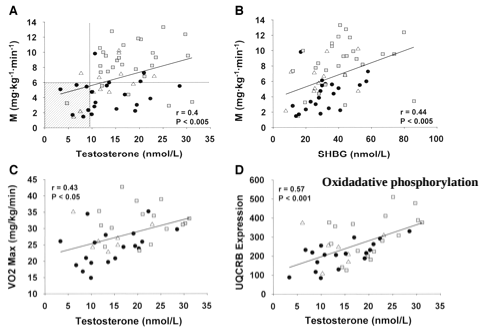




Wu FC et al J Clin Endocrinol Metab, July 2008, 93(7):2737–2745



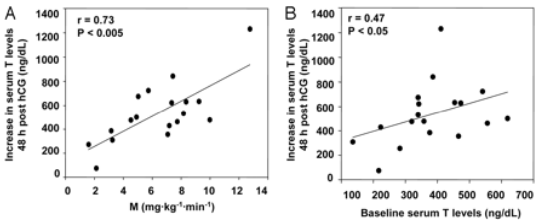
Relationship Between Testosterone Levels, Insulin Sensitivity, and Mitochondrial Function in Men



Pitteloud et al Diabetes Care, 28:1636, 2005

13

Increasing Insulin Resistance Is Associated with a Decrease in Leydig Cell Testosterone Secretion in Men



Pitteloud et al. JCEM 90(5):2636, 2005

14

Mechanism of Erection i.e. smooth muscle relaxation

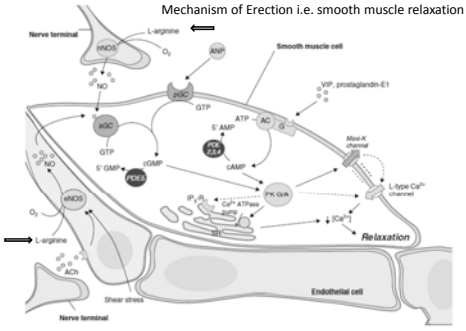
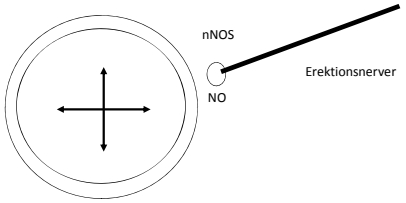


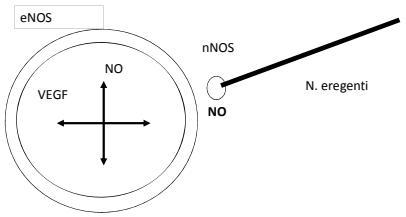
Figure 1. Molecular mechanisms of penile smooth muscle relaxation. Pathways involved in the relaxation of the cavernous smooth muscle cells are explained in detail in section 3.1 on the physiology of penile erection. Targets for emerging stimulatory acting drugs are depicted in italic and blue. Targets for emerging inhibitory acting drugs are depicted in italic and red.

Albersen et al 2010 Expert Opin. 15(3)

Initial dilatation Neurogenic



Continued dilatation Shear Stress, VEGF + NO



Musicki et al PNAS 33:1171, 1005

Diabetes & vascular & erectile function

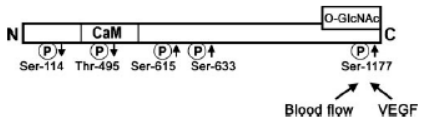
Diabetic endothelial dysfunction was originally described in human corpus cavernosum from men with ED

Saenz de Tejada et al N Engl J Med 320, 1025, 1989

Acute & chronic hyperglycemia increases oxidative stress and reactive oxygen species with further progress of endothelial dysfunction.

Triggle et al J Smooth Muscle Res 39, 249, 2003

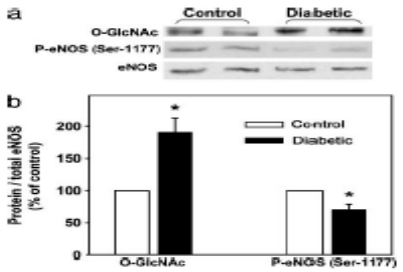
Phosphorylation of eNOS Reglulates NOS aktivity



Glukosylation at site Ser-1177 the site for Phosphorylation

Musicki et al PNAS 33:1171, 1005

Glycosylation inhibits phosphorylation



Musicki et al PNAS 33:1171, 1005

Summary

- Obesity and Diabetes type 2 are closely linked
- Supressed Gonadal function is common in obesity independent of age
- Diabetes cause increased oxidative stress and glycosylation of key proteins
- Endothelial dysfunction and neuropathy cause erectile and ejaculatory dysfunction (Dunsimur WD and Holmes SA Diabetes Medicine 1996:13;700-708)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Disclosures

- No relationship or other activities to disclose in relation to this presentation
- No potential conflict of interest

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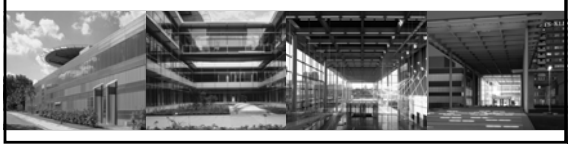
STI‘s

Prof. Dr. med. Falk R. Ochsendorf
Vice-Director Klinik f. Dermatologie, Venerologie u. Allergologie

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Learning objectives

- After the lecture the participant is able to
  - describe the different prevalences worldwide
  - Explain the difficulties to define the real impact of STI‘s
  - substantiate why STI‘s are relevant for infertility
  - list 3 pathogens relevant for male infertility
  - describe how to care for HIV-infected couples

STI and male infertility

- Are STI's relevant ?
- Which are relevant ?
- Which sequelae ?
  What to do ?

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STI prevalence (2001)

	Population aged 25 – 40 y (*10^6)	Prevalence (10^5)	Prevalence/ 1000	Annual Incidence
Western Europe	203	4	20	17
Sub Saharan Africa	269	32	119	69
South and South East Asia	955	48	50	151

After: Lunenfeld & van Steirteghem 2004

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Relevance of STI's for infertility

- Primary infertility
  - Developing countries < 2 % - 4 % – 8 %
- Secondary infertility
  - Egypt, Bolivia, Peru 15 – 20%
  - Bangladesh, Haiti 20 – 25 %
  - Kambodscha, India, Indonesia > 25 %
  - 14/23 Sub-Saharan states > 25 %
  - Zimbabwe > 62 %

→ Causes:
  - STI, poor hygiene post partum

After: Lunenfeld & van Steirteghem 2004

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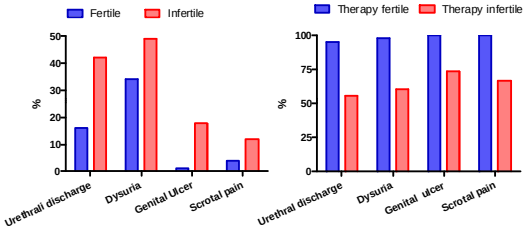
STI and infertility in Nigeria



Case control study; 150 fertile, 150 infertile men

Okonofua et al. 2005

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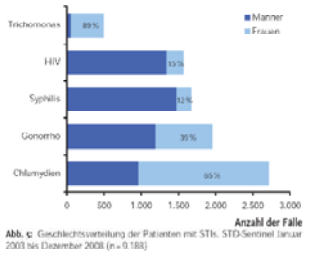
STI‘s in Germany



RKI 3/2010

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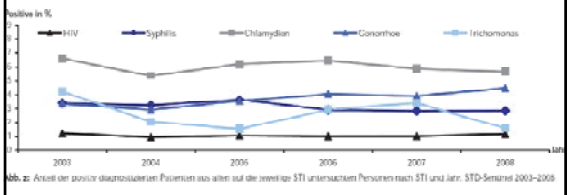
STI ‘s in Germany



RKI 3/2010

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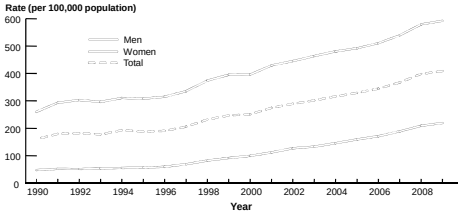
Chlamydia-Rates by Sex,United States,1990-2009



NOTE: As of January 2000, all 50 states and the District of Columbia had regulations that required chlamydia cases to be reported.

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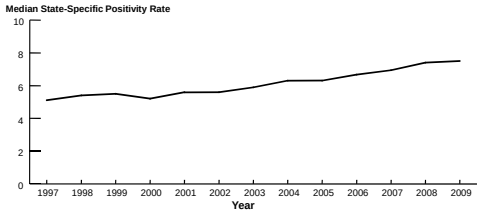
Chlamydia—Median State-specific Positivity Rates Among Women Aged 15–24 Years Tested in Family Planning Clinics, Infertility Prevention Project, United States, 1997–2009



NOTE: As of 1997, all 10 U.S. Department of Health and Human Services (HHS) regions, which represent all 50 states, the District of Columbia, and outlying areas, reported chlamydia positivity data.

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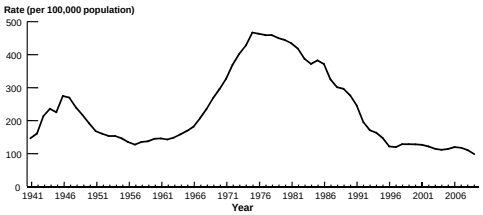
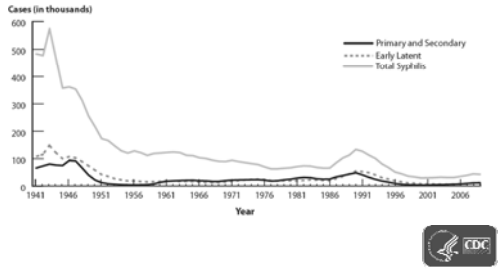
Gonorrhea—Rates, United States, 1941–2009



Syphilis—Reported Cases by Stage of Infection, United States, 1941–2009



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Mechanismus	Female → male	Male → female
Spreading of disease	Male disease	Female disease Female infertility Infection of oocyte, embryo, stillbirth, fetal abnormality
Changes of - Spermatogonia - Sertoli-cells	Male sterility	
- Leydig cells	Hypogonadism, male infertility	
Infiltration of **leukozytes** in reproductive tract	Epididymitis, obstruction, immonologic infertility	Immunologic infertility, obstruction
Incorporation of virus genome in genome of spermatogonia		Risk of transmission to next generation

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Problems to define relevance

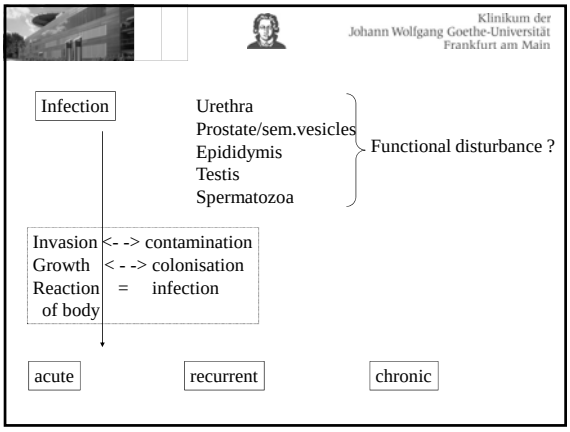
Prevalence of infection in a population

High → high predictive value of a positive test result

Low → low predictive value of a pos. test result

Length of exposure
Virulence of agent
Dose of agent
Immunologic response
Host factors

Infection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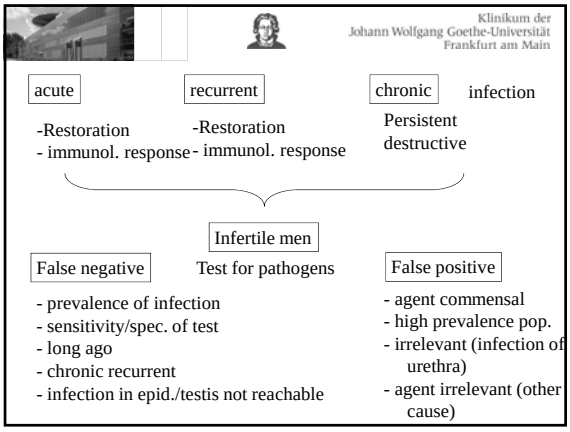
Infection
Urethra
Prostate/sem.vesicles
Epididymis
Testis
Spermatozoa
Functional disturbance ?
Invasion <- -> contamination
Growth < - -> colonisation
Reaction = infection
of body
acute
recurrent
chronic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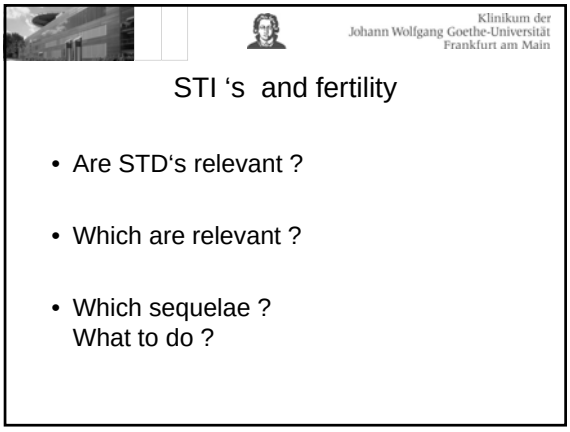
acute
recurrent
chronic
infection
-Restoration
- immunol. response
-Restoration
- immunol. response
Persistent
destructive
Infertile men
False negative
Test for pathogens
False positive
- prevalence of infection
- sensitivity/spec. of test
- long ago
- chronic recurrent
- infection in epid./testis not reachable
- agent commensal
- high prevalence pop.
- irrelevant (infection of urethra)
- agent irrelevant (other cause)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STI ‘s and fertility
• Are STD‘s relevant ?
• Which are relevant ?
• Which sequelae ?
What to do ?

Species	Disease	Etiologic agent
Bacteria	Syphilis	*Treponema pallidum*
	Gonorrhoea	*Neisseria gonorrhoeae*
	Ulcus molle	*Haemophilus ducreyi*
	Granuloma inguinale	*Calymmatobact. granulomatis*
	Lymphogranuloma venereum	*Chlamydia trachomatis L1-L3*
	Not-gonococcal urethritis / adnexitis	*C. trachomatis D-K; Mycoplasma spp.; Ureaplasma urealyticum*
	bacterial vaginosis	*Gardnerella vaginalis u.a.*
Viruses	Herpes genitalis	*Herpes-simplex-Virus 1/2*
	Genital ulcers (in HIV-infection)	*Zytomegalievirus*
	Verrucae vulgares, Condylomata acuminata, bowenoid papulosis	*Humane Papillomviren*
	Mollusca contagiosa	*Molluscum-contagiosum-Virus*
	Hepatitis	*Hepatitis-B-Virus, Hep. C Virus*
	AIDS	*HIV 1/2*
Yeasts	Balanitis, Vulvovaginitis, colpitis, urethritis	*Candida species*
Protozoa	urethritis, vulvovaginitis	*Trichomonas vaginalis*
Ectoparasites	pediculosis pubis	*Phthirus pubis*
	scabies	*Sarcoptes scabiei*

Species	Disease	Effect on male/female fertility
Bacteria	Syphilis	No Yes
	Gonorrhoea	Yes Yes
	Ulcus molle	No
	Granuloma inguinale	No
	Lymphogranuloma venereum	Unclear
	Not-gonococcal urethritis / adnexitis	Unclear Chl. Trach. Yes *Mycoplasma spp.,*
	bacterial vaginosis	No Yes
Viruses	Herpes genitalis	Unclear No
	Genital ulcers (in HIV-infection)	No
	Verrucae vulgares, Condylomata acuminata, bowenoid papulosis	No
	Mollusca contagiosa	No
	Hepatitis	No
	AIDS	Yes Yes
Yeasts	Balanitis, Vulvovaginitis, colpitis, urethritis	No
Protozoa	urethritis, vulvovaginitis	Unclear, probably negligible
Ectoparasites	pediculosis pubis	No
	scabies	No

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	scabies	No

	Syphilis	Gonok.	Chlamyd trachoma	HIV	HSV	Bakt. Vag.
Male infertility	-	+	+	+	-	--
Female infertility	-	+++	+++	+	-	-
Spontaneous abortion	-	-	-	-	+	-
Birth defects	+	-	-	-	+++	-
Fetal infection	+++	-	-	+ + +	+++	+
Preterm delivery	+++	++	++	-	+++	++
Growth restriction	+++	+	-	-	+++	-
Perinatal mortality	+++	-	-	+	++	-
Intrapatum infection	+	+++	+++	+++	+++	-
Infection via breastfeeding	-	-	-	+++	-	-

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Semen microbiology in fertile/infertile population

	Fertile population (n=144)	subfertile population (n=143)	Difference significant
Non-bacterial			
Ureaplasma urealyticum	7,6	12,5	N.S.
Mycoplasma hominis	1,4	2,9	N.S.
Both	3,,4	5,1	N.S.
C. Trachomatis	4,2	7,7	N.S.
Total	**16,6**	**27,2**	**P<0,05**
Bacterial			
Total	20,1	13,2	N.S.
Negative	68,7	72	N.S.

Human Reprod 12, 987ff, 1997

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Problems: C. trachomatis and male infertility

- Detection method
- Material investigated
- Detection: acute or prior infections
- Relevance of immunologic responses
- Relevance of co-infections
- Group sizes


STD and fertility

- Are STD‘s relevant ?
- Which are relevant ?
- Which sequelae ?
  What to do ?

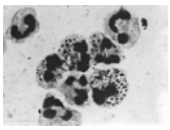

Relevant Diseases

- Urethritis (Gonorrhoe, Ureaplasmen)
- Adnexitis (C. trachomatis)
- Herpes genitalis
- Trichomonas vaginalis
- HIV-Infection


Relevant Diseases

- Urethritis (Gonorrhoe, Ureaplasmen)
- Adnexitis (C. trachomatis)
- Herpes genitalis
- Trichomonas vaginalis
- HIV-Infection

Gonorrhoe



- Urethritis no effect — Ness et al. 1997
- [strictures +] — Fievet et al. 1987, Dohle 2003

Gonorrhea

♂
- 2 yrs after unilateral epididymo-orchitis:
  → only 21 % sufficient semen quality
  → biopsy: bilateral testicular damage

♀
- Tubal occlusion in women
  → RR 2,4 – 2,7
  with history/serologic signs of prior gonorrhea
- Increased preterm birth (OR 2,9)

N.N. 1995
Grodstein et al. 1993

Gonococcal and chlamydia-infections

Coinfection with *C. trachomatis* often occurs among patients who have gonococcal infection; therefore, presumptive treatment of such patients for chlamydia is appropriate (see Gonococcal Infection, Dual Therapy for Gonococcal and Chlamydial Infections). The following recommended treat-

CDC 2010

Co-infection with *Chlamydia trachomatis* is common in patients with gonorrhoea. Treatment for gonorrhoea should routinely be followed with effective treatment for chlamydial infection or sensitive testing to exclude co-infection.

IUSTI 2001

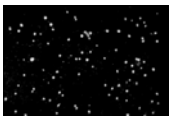
Gonococcal urethritis

- Cefixim 400 mg p.o. 97,4 % *oder*
- Ceftriaxon 250 mg i.m. 99,1 % *oder*

PLUS

- Azithromycin 1 g p.o. *oder*
- Doxycyclin 100 mg 2x/d 7 d

Chlamydia trachomatis and male infertility



- Deleterious effects: plausible
- Evidence: weak

Krause u, Bohring 2003, Cunninghang & Beagley 2008, Veznik et al. 2004

Men: evidence for deleterious effects

- 6/241 (2%) pos. DNA
  → decreased sperm count
- 244 infertile couples, 20 % pos. Chl.antibodies; OR 2,6 for infertility
- Association with inflammation
- Transport to the female tract

Idahl et al. 2007

Chlamydia and disease

- 17,764 men enrolled, retrospective 2001-05
  - 913 (5.14%): reproductive tract outcome
  - CT-positive men,

	cumulative incidence	Hazard ratio
– orchitis/epididymitis	4,28 %	1,38 (1,13-1,7)
– Prostatitis	1,41 %	
– Infertility	1,27 %	
– urethral stricture	0.13 %	
any outcome		1.37 (1.16-1.61)
infertility		1.36 (0.93-2.00)

Trei et al. 2008

Chlamydia and obstruction

- Obstructive azoospermia
  - 14 cases, 22 controls
- No C. trachomatis DNA
  - in testis or
  - epidydimis

Sripeda et al. 2010

Chlamydia-serology and prognosis

226 Paare	Male factor	DNA-demon stration	Tubal-factor	Chance of pregnancy	
IgG Man	-		-	+ ↓	2/3
IgA Man	-	+	-	+ ↓	1/3
IgG Woman			+		
IgA Woman		-		-	
CHSP 60 man			+	-	

Idahl et al. 2007

„...the chlamydial serology results .... were not indicative of reduced sperm function or subsequent fertilizing capacity." Eggert-Kruse et al. 2011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Chlamydia and female infertility

- Infertility, ectopic pregnancies and chronic pelvic pain, are important consequences of PID, and since sexually transmitted microorganisms are the cause of acute PID in the majority of cases, then PID represents the link between sexually transmitted diseases (STDs) and infertility.

N.N. 2002


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Therapy chlamydia

- Azithromycin 1 g p.o., single dose
- Doxycyclin 100 mg 2x/d for 7 d

- „Azithromycin and doxycycline are equally efficacious in achieving microbial cure and have similar tolerability. Further head-to-head trials comparing these antibiotics are unnecessary. Lau & Qureshi 2002


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Relevant Diseases

- Urethritis (Gonorrhoe, Ureaplasmen)
- Adnexitis (Chlamydia)
- Herpes genitalis
- Trichomonas vaginalis
- HIV-Infection

Acute epididymitis

Patient M.R.

- 29-yrs.
- Request for fertility status

Patient M.R.: Spermatogram

Volume	2,5
Spermconcentration (*10^6/ml) Total count	21,8
Motility a + b	4
Motility c	1
Motility d	95
Morphology (nl)	14
Leukozytes	9,8

History and physical examination

- 12 months ago: epididymitis
- Delayed diagnosis: chlamydia infection
- Epididymis both sides: thickened

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Patient M.R.: diagnosis and treatment

- Diagnosis:
  status after bilateral epididymitis
- Therapy
  - Diclofenac, Doxycylin, Vitamin E and C, Prednisone: no effect
  - Recommendation: ICSI
- Follow-up:
  after 18 months unchanged

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Relevant Diseases

- Urethritis (Gonorrhoe, Ureaplasmen)
- Adnexitis
- Herpes genitalis
- Trichomonas vaginalis
- HIV-Infection


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Ureaplasma/Mycoplasma

- Problem: Effect ?
  In-vitro: time- and dose-dependent
  - → Chromatin-Decondensation
  - → DNA damage
  - → abortion ?

Reichart et al. 2000


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Relevant Diseases

- Urethritis (Gonorrhoe, Ureaplasmen)
- Adnexitis durch C. trachomatis
- Herpes genitalis
- Trichomonas vaginalis
- HIV-Infektion


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Herpes simplex in men

- Demonstrated in spermatozoa
- Incidence 0 - 3 – 24 - 56 %
  PCR in-situ Hybridisierung
- Association to low sperm numbers and motility ?
- Pregnancies after aciclovir ?

Kotronias et al. 1998
Kapranos et al. 2003
Krause et al. 2002

Viruses in ejaculate

Pathogen prevalence an	Leukozytospermie	Keine Leukozytospermie	
Pathogen	**LCS**	**Non-LCS**	**Total**
Any pathogen			
Prevalence	25/132 (18.9)	20/109 (18.3)	45/241 (18.7)
HPV			
Prevalence	3/70 (4.3)	5/109 (4.6)	8/179 (4.5)
C. trachomatis			
Prevalence	3/132 (2.3)	3/108 (2.8)	6/240 (2.5)
Range	10,000–460,000	8,300–590,000	8,300–590,000
CMV			
Prevalence	14/132 (10.6)	7/109 (6.4)	21/241 (8.7)
Range	110–580,000	3,200–12,000,000	110–12,000,000
HSV-1 and HSV-2			
Prevalence	4/132 (3.0)	5/109 (4.6)	9/241 (3.7)
Range	510–15,000	300–22,000	300–22,000
HHV-6			
Prevalence	5/132 (3.8)	4/109 (3.7)	9/241 (3.7)
Range	250–81,000,000	4,400–1,500,000	250–81,000,000
EBV			
Prevalence	1/132 (0.8)	0/108 (0)	1/240 (0.4)
Range	210		210
HBV			
Prevalence	0/132 (0)	0/109 (0)	0/241 (0)

Bezold et al. 2007

HPV in ejaculate

- 100 men with unprotected intercourse
  - 10/100 infected
    25 % of sperm heads infected
- 100 men without intercourse
  - No infection
- Motility infected 37,7 +/- 16,8
  non-infected 53,7 +/- 18,2
  controls 53,7 +/- 19

Foresta et al. 2010

Relevant Diseases

- Urethritis (Gonorrhoe, Ureaplasmen)
- Adnexitis durch C. trachomatis
- Herpes genitalis
- Trichomonas vaginalis
- HIV-Infektion

Trichomonas vaginalis

- In 25 % : only ejaculate positive
  J Infect Dis 189, 1926ff, 2004
- Infertile men: higher incidence ??
- Quality of ejaculate improved 1 month after therapy ??
- No negative effect on motility, sperm-mucus interaction
- Apparently no impact on female fertility

Soper 2004

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Relevant Diseases

- Urethritis (Gonorrhoe, Ureaplasmen)
- Adnexitis durch C. trachomatis
- Herpes genitalis
- Trichomonas vaginalis
- HIV-Infektion

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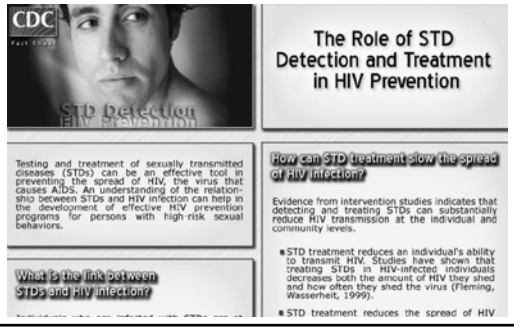
Relevance of STD: increase risk of HIV



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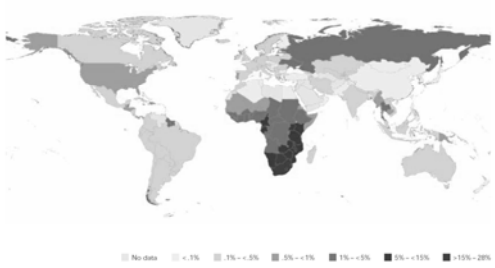
HIV infection prevalence 2009



UNAIDS Report 2010

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HIV in the male genital tract

- HIV-1 proviral DNA in spermatogonia
- Virus in ejaculate
- Intermitent „Shedding“
  → free in seminal plasma
  from prostate gland ?
- → Spermatozoen ?
  No infection of motile sperm
- → Lymphocytes
  Macrophages
  Monocytes
  Rete testis, Epididymis

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HIV infection in a semen donor

Semen variable	Before HIV infection (n=63)	After HIV infection (n=13)
Voplume (ml)	3,5	2,5
Concentration	74	110
% motility	49	41
% morphology	55	46
Total count	263	264
Total motile count	131	105

Van Leeuwen et al. 2004

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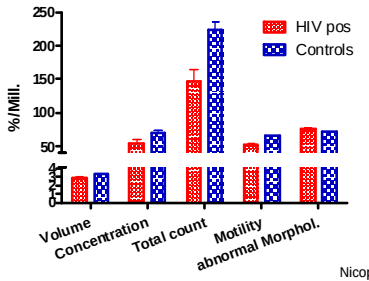
Ejaculate and HIV



Nicopoullos et al. 2004
Dulioust et al. 2002

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HAART and semen quality

- Only few studies
  - Zidovudine monotherapy: no effect
  - HAART: tendency to improvement
    (short follow up) HAART: increase of mitochondrial DNA
    In vitro: didanosine, zidovudine, saquinavir and indinavir; saquinavir: dose dependent decrease motility, decrease mitochondrial potential, increase acrosome reaction Ahmad et al. 2011

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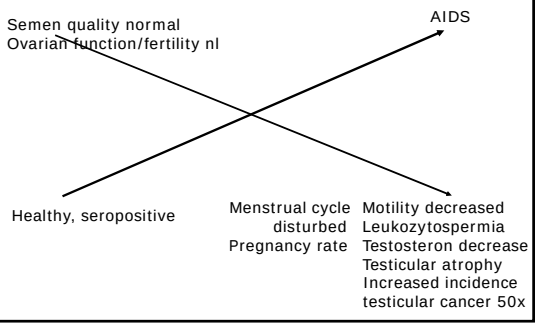
Relevance of stage of disease



HIV infection and reproduction

- 80 % HIV-pos. Couples had unprotected intercourse to achieve pregnancy
- Unprotected intercourse: 0,1- 0,2 % risk of HIV-infection per event man/woman
  - 100 000 copies: 1 zu 100
  - 100 copies: 3 zu 10 000

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Natural conception ?

- > 6 months no HIV-RNA im blood
- 62 serodiscordant couples
  - 22 HIV-pos. women
  - 40 HIV-pos. men
- 76 pregnancies, 68 births
- No seroconversion partner
- 1 HIV-pos. child
- 55 / 75 % HCV-pos: no infection

Barreira et al. 2007

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Natural conception ?

- Undetectable HIV in blood
- In semen: in 48 % (12/25) in more than one control:
  → viral shedding
  → 4/25 isolate > 5000 copies/ml
- 5 - 6 % in other studies

Sheth et al. 2009


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Treatment

- Counseling
- Antiretroviral therapy (< 1000 copies/ml)
  → significant improvement unrelated to CD4-count, ejaculate parameters, stimulation protocol
- Preparation of ejaculate: gradient centrifugation
  2x washs
  Swim-up
  PCR: use if HIV-RNA negative (~95 %)
- Use for IUI/ICSI

Zutlevics 2006


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ART in HIV-pos. men

- 18 studies
- 1239 couples: preparation of sperm
- 2794 IUI-cycles
  - 89 IVF-cycles
  - 188 ICSI cycles
- 539 pregnancies
- 474 births
- No seroconversion

Van Leeuwen et al. 2007


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ART in HIV-pos. men

- 245 couples, 439 cycles IUI
- 111/245 (45,4 %) pregnancy
- No seroconversion
- Prognostic relevant: maternal age and semen quality, rather than HIV factors
- Frozen sperm: significant negative impact on outcome

Nicopoullos et al. 2010

Diagnostics of infections and ART

Woman	Man
Phasecontrast preparation, vaginal pH	Spermatogram (if leukozytospermia mikrobiol. diagnostics)
Chlamydia Genamplification (cervical smear)	
Rubella HAH, eventually IgG	
Varizella-antibodies	
HBsAg, event. Anti-HBc Screening	HBsAg, Anti-HBcScreening
Anti-HCV	Anti-HCV
Anti-HIV	Anti-HIV

AWMF Leitlinie 15/040, 2004

STI‘s and Male Infertility

- Relevant:
  - Chlamydia, gonococci, HIV
  - Especially developing countries
- Unclear
  - Mycoplasma, Ureaplasmen Trichomonas, Viruses
- Consequences
  - Timely adequate therapy
  - HIV: counseling, assisted reproduction

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Genetically determined susceptibility to iatrogenic therapies

Yvonne Lundberg Giwercman, Ass Prof.

Faculty of Medicine
Dept. of Clinical Science

ESHRE
Stockholm 2011

Disclosure

The lecturer has no commercial and/or financial relationships with manufacturers of pharmaceuticals, laboratory supplies and /or medical devices.

Learning objectives

- Azoospermia is common after cancer treatment (10-20%)
- Inhibin B is a good marker for recovery of spermatogenesis
- Genetic variants can also be used as predictive tools for azoospermia.

Iatrogenic therapies

- ”First, do no harm”
- Conditions do not only result from medical errors e.g. mistakes made in surgery, the prescription or dispensing of the wrong therapy, but sometimes adverse effects of a medical treatment or combinations of treatments may be iatrogenic.
- For example, radiation therapy and chemotherapy frequently produce iatrogenic effects such as hair loss, anemia, vomiting infertility, etc.

High survival rate and risk of infertility

Childhood cancer

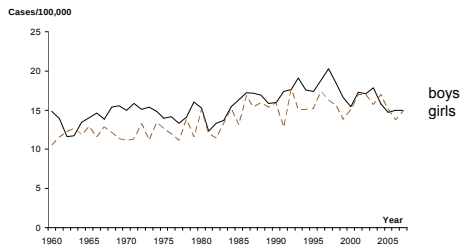
Facing heavy treatment.
Cryopreservation of testis tissue or not?

Testicular cancer

Received heavy treatment
Wants to have children when, or if, sperm production is restored.

Can genetic markers predict?

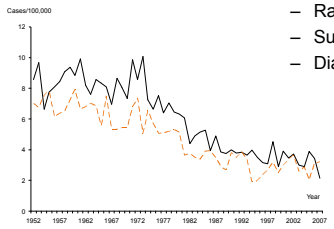
Childhood cancer incidence in Sweden



Swedish Childhood Cancer Registry

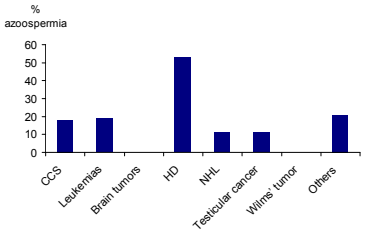
Mortality

- Chemotherapy
- Radiotherapy
- Surgical therapy
- Diagnostic tools



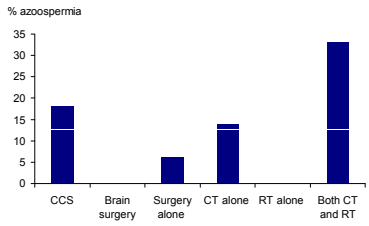
Swedish Childhood Cancer Registry

Diagnoses



Romerius P et al. Int J Androl 2011

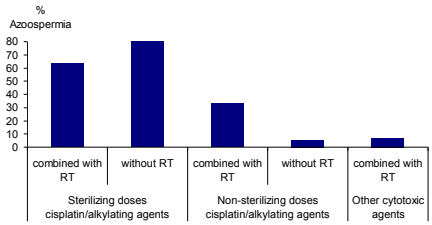
Therapy



If radiotherapy to the testes ⟶ 100% azoospermia

Romerius P et al. Int J Androl 2011

High risk treatment



Romerius P et al. Int J Androl 2011

Clinical markers

	OR	p	PPV (%)	NPV (%)
Subnormal Inhibin B	91	<0.001	66	98
Elevated FSH	89	<0.001	50	99
Subnormal total Testicular volume (≤24 mL)	17	<0.001	61	92

PPV = positive predictive value: still 35-50% have preserved sperm production
NPV = negative predictive value: risk of azoospermia only 1-2% if normal conc.

Romerius P et al. Int J Androl 2011

Can genetic variants be used in prediction?

Lundberg Giwercman Y et al. Hum Genet 1998.

Giwercman A et al. JCEM 2000.

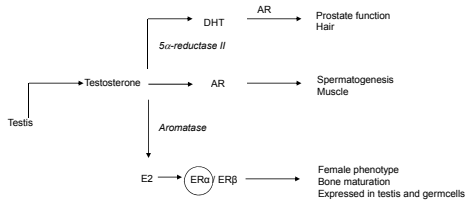
AR mutations are rare
1:10 000

Profound effects on phenotype

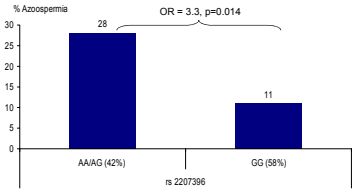
Polymorphisms are frequent
>1% of the population

Small effects on phenotype

Candidate genes

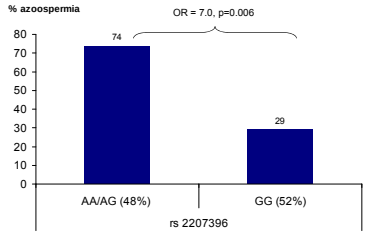


Estrogen receptor α



Romerius P et al. Pharm Genet & Genom, in press.

High-risk treatment



70% of those with azoospermia can be identified by using this SNP

Romerius P et al. Pharm Genet & Genom, in press.

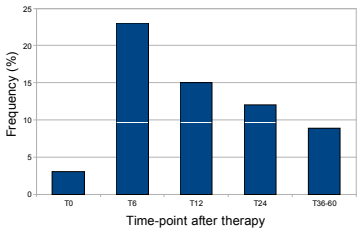
Summary childhood cancer

- ¾ survive
- 20% will have azoospermia
- FSH and inhibin B are good markers
- More than 70% are carriers of certain oestrogen receptor α variant, could be subjects for cryopreservation if prepubertal

Testicular Germ Cell Cancer

- incidence 6 / 100 000 men
- the most common cancer in men aged 20 – 40 years
- >95% cured
- associated with impaired sperm production and decreased fertility potential before diagnosis

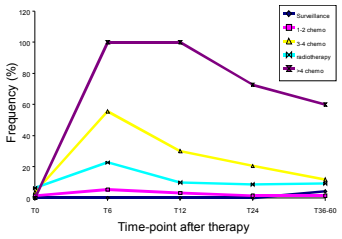
Azoospermia at different time-points



n=318

Eberhard J et al. Hum Repr 2004

Azoospermia due to oncological treatment



Eberhard et al. Hum Repr 2004

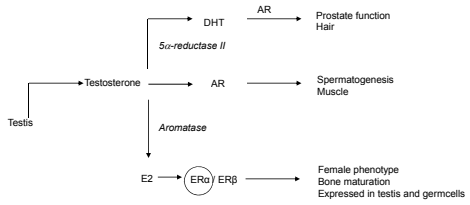
Inhibin B as predictor of azoospermia

Time of Inhibin B analysis	Inhibin B cut off level (ng/mL)	Sensitivity (%)	Specificity (%)	AUC
T6	64.5	100	60	0.84
T12	60.5	92	74	0.84
T24	68.4	81	71	0.82

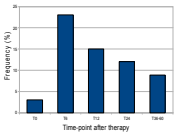
Normal range: <50 ng/mL

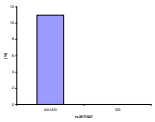
- Important for a patient to know whether he will be permanently infertile or sperm production will recover
- Can genetic markers predict?

Genetic markers



Estrogen receptor α again





GG carriers are safe, also if treated with high dose chemotherapy

n=202

Unpublished data.

General population

Young men from general population
prior to military service, n=305

rs2077647	**LH (IU/L)**	**p-value**	**FSH (IU/L)**	**p-value**
AA+AG / GG	**4.3 / 3.6**	**0.04**	**3.6 / 2.9**	**0.04**

Summary testicular cancer

- More than 95% survive
- 10% will have azoospermia
- Inhibin B is a good marker
- Estrogen receptor alfa variant predictive in all of cases.

Take home message

- Azoospermia is common after childhood cancer (20%) and testicular cancer treatment (10%)
- Inhibin B is a good marker for recovery of spermatogenesis
- Genetic variants can also be used as predictive tools for azoospermia.

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- Aleksander Giwercman
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Cancer: impact of disease and therapy on male fertility

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SIG Andrology – Pre-congress course: 3 July 2011
Lifestyle and male reproduction
27th Annual Meeting - ESHRE 2011 - Stockholm, Sweden, 3-6 July 2011

Conflict of Interest

I have no commercial relationships or other activities that might be perceived as a potential conflict of interest.

Learning Objectives

- There is an increasing rate of cancer among young men in developed countries.
- Improving survival of young men with testis cancer and lymphomas is associated with high rates of infertility.
- Men with some cancers have damaged germ cells even prior to initiation of drug treatments.
- Chemotherapeutic agents have a wide range of effects on male germ cells.
- Chemotherapeutic agents can have effects on sperm while residing in the epididymis.
- Sperm returning after chemotherapy show damage to chromatin at least up to two years after drug treatment.
- Therefore sperm banking should be advised prior to treatment.

Paternal Occupations Affecting Incidence of Malformations in Progeny

Profession	Effect on offspring	Odds ratio
Janitor	hydrocephalus	5.04
	ventricular septal defects	2.45
	other heart defects	2.35
Forestry and Logging Worker	congenital cataract	2.28
	atrial septal defects	2.03
	syndactyly	2.03
Painter	spina bifida	3.21
	patent ductus arteriosus	2.34
	cleft palate	3.36
Printer	atresia of the urethra	4.50
	clubfoot	2.18
Plywood mill Worker	ductus arteriosus	2.52
	patent pyloric stenosis	4.12
	dislocated hip	2.71

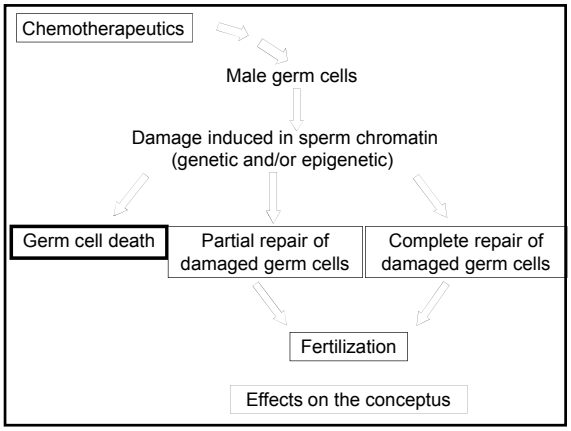
Olshan, Teschke, Baird. Paternal occupation and congenital anomalies in offspring. Am J Ind Med 1991; 20:447-75.

Associations between paternal exposures and adverse reproductive outcomes

Agent	Embryo/fetal loss*	Birth defects*	Childhood cancer*
Radiation	**0.9-1.5**	**1.4-5.6**	**N/T§**
Solvents	**0.9-2.3**	**N/T**	**1.7-7**
Anesthetic gases	**1.5-1.8**	**N/T**	**N/T**
Heavy metals	**0.9-2.3**	**1.5-249**	**3.5-7**
Smoking	**0.6-1.4**	**1.3**	**1.2-3.9**
Herbicides/pesticides	**N/T**	**5.7-405**	**2.4-7.1**
Cancer drugs	**N/T**	**4.1**	**N/T**

*Values represent the range of OR/RR (Odds Ratios/Relative Risk) found by different studies
§ N/T = not tested

Sawyer and Aitken, 2001



Male mediated developmental toxicity: chemotherapy, sperm chromatin, psychosocial and progeny outcome

Project 1: Impact of Combination Chemotherapy on Reproductive Health and Gamete Genetic Integrity in Humans

Project 3: Impact of Chemotherapeutic Regimens on Male Reproduction and Progeny Outcome in the Rat Model

Project 2: Risk Communication & Psychosocial Impact of Reproductive Sequelae Among Men Treated for Testicular or Lymphatic Cancers

The Team

Project 1:
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Animal Models

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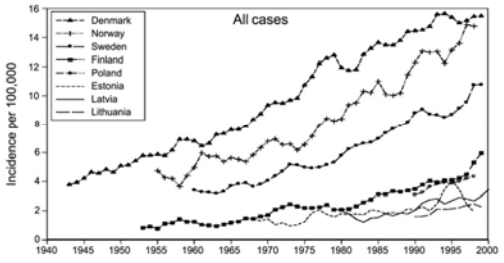
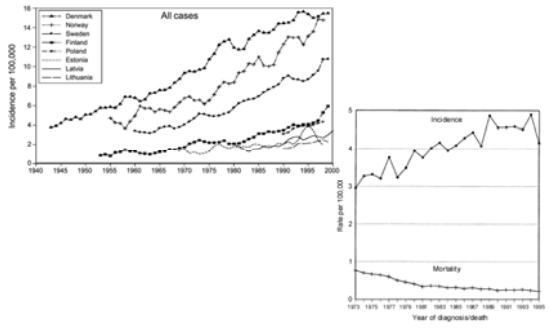
Grant # HGG-62294

Incidence of Testicular Cancer and Survival Rate



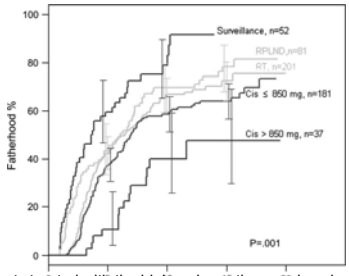
Testicular cancer incidence and rates of mortality in the United States.
http://www-seer.ims.nci.nih.gov/Publications/CSR7395

Incidence of Testicular Cancer and Survival Rate



Testicular cancer incidence and rates of mortality in the United States.
http://www-seer.ims.nci.nih.gov/Publications/CSR7395

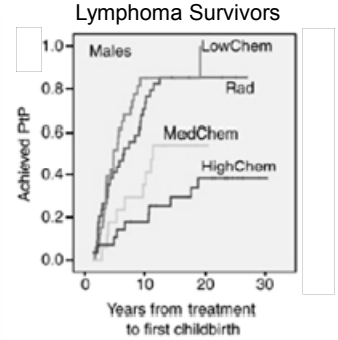
Paternity following Treatment for Testicular Cancer



Patients treated with the higher chemotherapy dose had the lowest chance of becoming fathers.

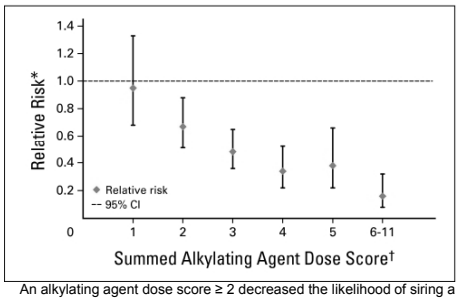
Brydøy et al., Journal of the National Cancer Institute (2005) 97):1580-1588

Post-treatment Parenthood in Hodgkins Lymphoma Survivors



C E Kiserud et al., *British Journal of Cancer* (2007) 96, 1442–1449

Fertility of Male Survivors of Childhood Cancers

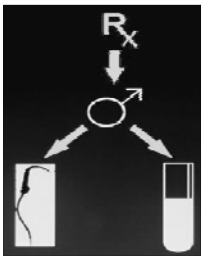


An alkylating agent dose score ≥ 2 decreased the likelihood of siring a pregnancy

Green DM et al., J Clin Oncol. 2010; 28(2): 332–339.

Evidence for Male-mediated Developmental Toxicity

- **Xenobiotics in the ejaculate can produce developmental toxicity**
- **Exposure of males to clastogens increases frequency of abnormal germ cells**
- **Sperm carrying chromatin abnormalities can fertilize an oocyte**



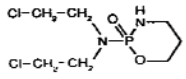
Germ cells Seminal fluid

Impact of Cancer Chemotherapy

• Actions of a single alkylating agent (cyclophosphamide) on sperm chromatin structure and consequences for progeny outcome

•Actions of combinations of agents used for treating testis cancer (BEP) (bleomycin, etoposide, cisplatin)

• Actions of combination of agents used for treating Hodgkin lymphoma (CHOP) (doxorubicin, cyclophosphamide, vincristine, prednisone)
pact of the chemotherapeutic regimens for testis cancer and Hodgkin lymphoma on sperm parameters and progeny outcome.

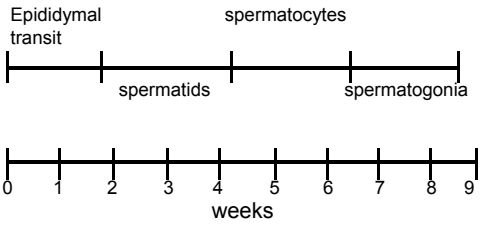


Cyclophosphamide

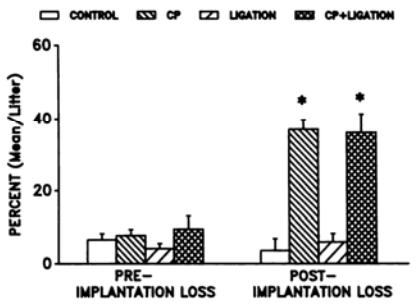
Anticancer Agent	Immunosuppressive Agent
(Non)-Hodgkin Lymphoma	Lupus Erythematosus
Lymphocytic Leukemia	Wegener's Granulomatosis
Breast Cancer	Graft-versus-Host Disease
Ovarian Cancer	
Lung Cancer	

- **Spermatogenesis**
- **Assessing semen: quantity/quality issue**
- **Animal models to study effects of chemotherapeutic drugs**

Effect of CPA on Spermatogenesis

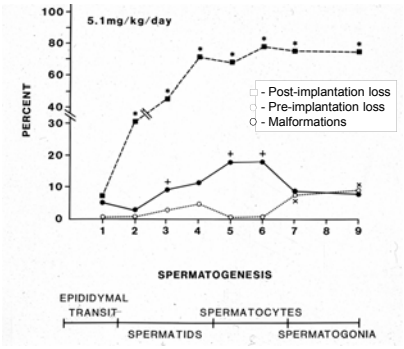


Effect of Cyclophosphamide and Efferent Duct Ligation (7 days) on Pre- and Post-implantation loss

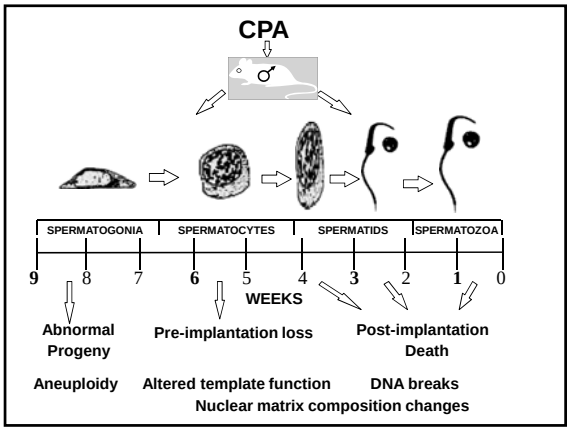


Qiu et al., Biol Reprod. 1992; 46:926-931

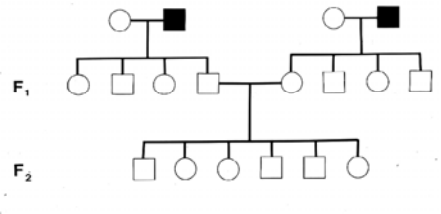
Chronic Paternal CPA affects Progeny

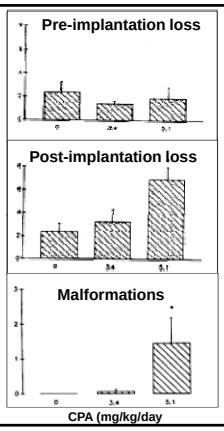


Effects of Paternal CPA on Skeletal Abnormalities in Offspring



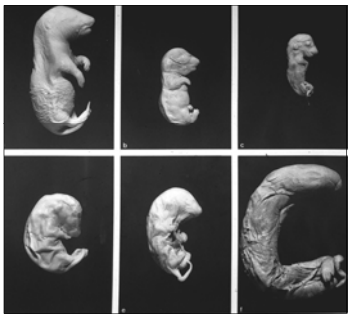
Are the effects of paternal CPA exposure on progeny outcome heritable?



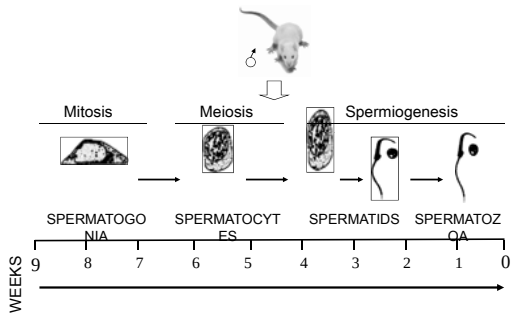


Paternal CPA affects the F_2 generation

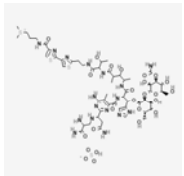
F_2 Fetuses after Paternal CPA Exposure



Chronic BEP Treatment of Male Rats

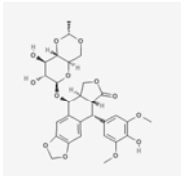


Drugs Used in the Management of Testis Cancer



Bleomycin

causes DNA strand breaks



Etoposide

: inhibits topoisomerase II

Cisplatin

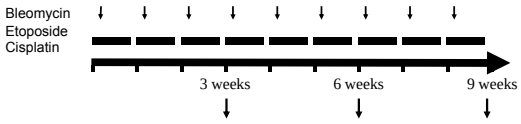
alkylates DNA, causing cross-links

Chronic BEP Treatment Regimen

Doses: 0X, 1/3X, 2/3X and 1X; n=10/group

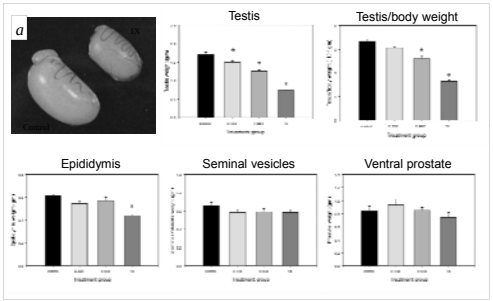
Human equivalent doses were determined for rats by converting for differences in surface area.

- Bleomycin: 1.5mg/kg/week (i.p.)
- Etoposide: 15mg/kg/day (gavage)
- Cisplatin: 3mg/kg/day (gavage)



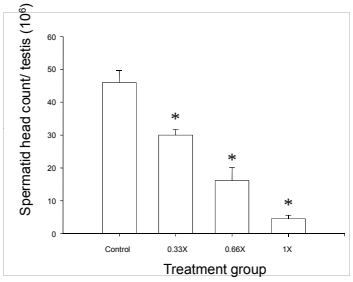
Mate to control, naturally cycling, females

Effects of BEP on Male Reproductive Organ Weights



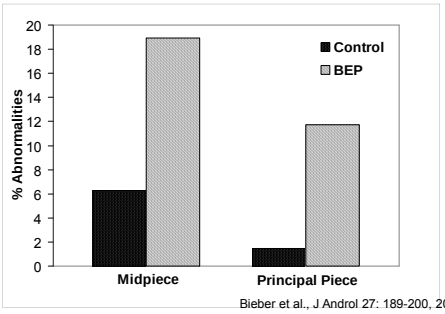
Bieber et al., J Androl 27: 189-200, 2006

Effects of BEP on Spermatid-Head Counts in the Testis



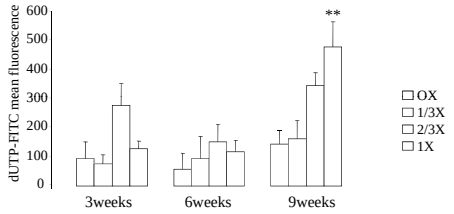
Bieber et al., J Androl 27: 189-200, 2006

Quantification of Morphological Abnormalities In Spermatozoa



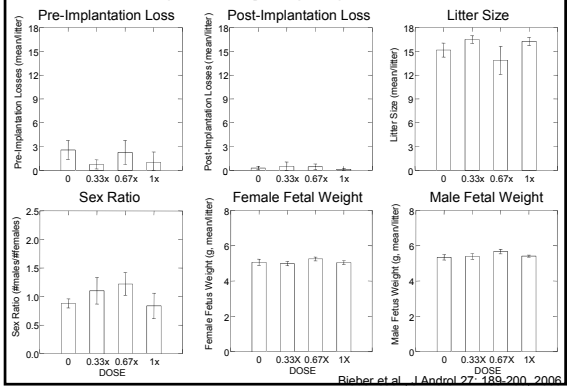
Bieber et al., J Androl 27: 189-200, 2006

Effects of BEP on Sperm Quality: TUNEL Assay



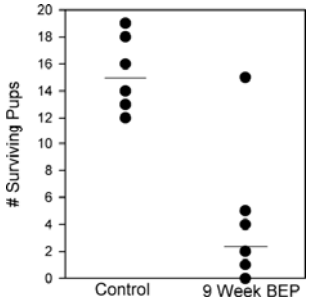
Delbès G et al., *J Androl.* 2007

Analysis of progeny outcome



Bieber et al., J Androl 27: 189-200, 2006

Numbers of pups per litter that survived past postnatal day 1



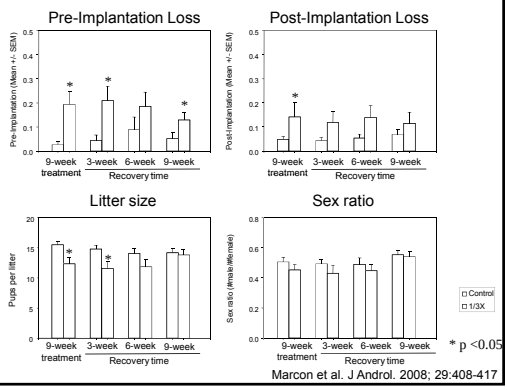
Bieber et al., J Androl 27: 189-200, 2006

Chronic treatment with BEP results in:

- **Decreased weights of the body, testes, and epididymides**
- **Abnormal testis histology**
- **Decreased spermatid head counts**
- **Significant effects on sperm motility, morphology, and quality**
- **No effects on pre- or post-implantation loss, litter size, or sex ratio**
- **Decreased post-natal survival**

Bieber et al., J Androl 27: 189-200, 2006

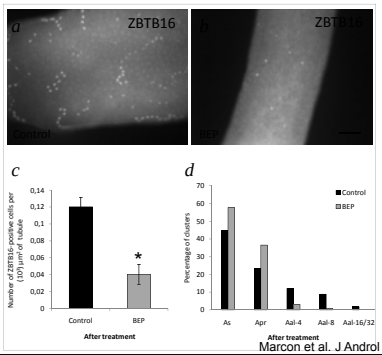
Progeny outcome after recovery



* p <0.05

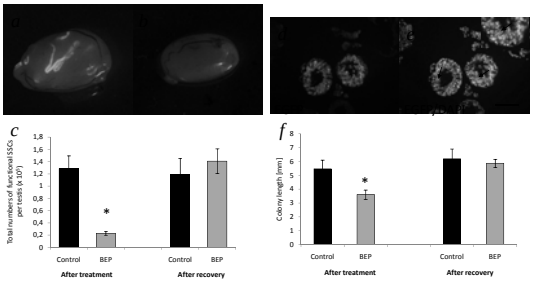
Marcon et al. J Androl. 2008; 29:408-417

BEP treatment affects the clonal organization of undifferentiated spermatogonia



Marcon et al. J Androl 2011 in press

BEP treatment decreases rat SSC activity and colony lengths



Marcon et al. Biol Reprod. 2010; 83:228-239.

Regimen for Non-Hodgkin Lymphoma (NHL): CHOP

Cyclophosphamide: alkylates DNA, causing cross links
Doxorubicin: inhibits topoisomerase II, generates free radicals
Vincristine: binds tubulin, depolymerizes microtubules
Prednisone: glucocorticoid

Objectives

- To evaluate the effects of treatment with CHOP on spermatogenesis, gamete genetic integrity, and progeny outcome in the rat.

2) To determine the effects of CHOP chemotherapy for NHL on sperm chromatin quality and the time course of recovery.

Experimental design

F x mg/kg = mg/m^2
F for rats is 6

species surface area
to body weight ratio

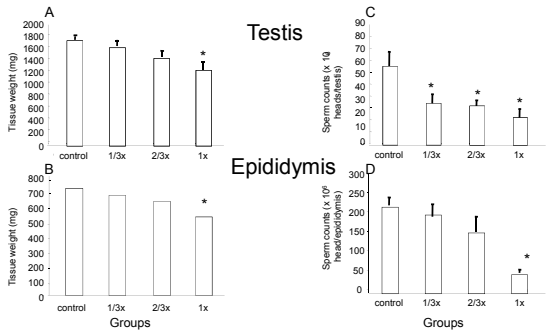
Standard regimen for patients		Experimental regimen for rats
Cyclophosphamide	750 mg/m^2	27 mg/kg
Doxorubicin	50 mg/m^2	1.8 mg/kg
Vincristine	1.4 mg/m^2	0.05 mg/kg
One injection i.v. every 3 weeks		One injection i.p. every 3 weeks
Prednisone	40 mg/m^2	1.47 mg/kg
	p.o. , 5 days	p.o., 5 days
6-8 cycles		4 cycles

12-weeks CHOP treatment

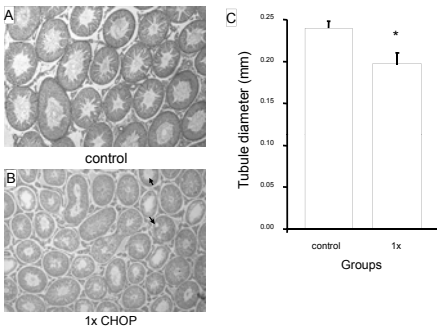
spermatids spermatocytes spermatogonia

CHOP regimen.

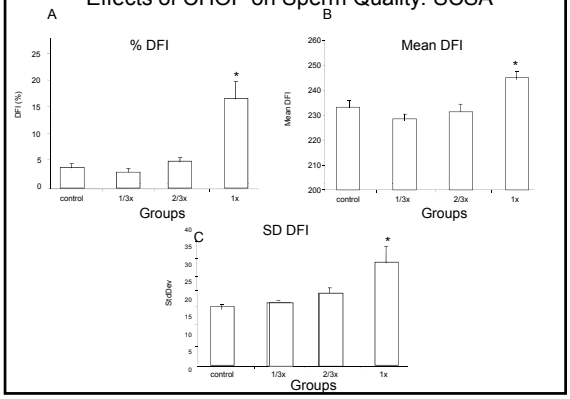
Effects of CHOP on Tissue Weights and Sperm Counts



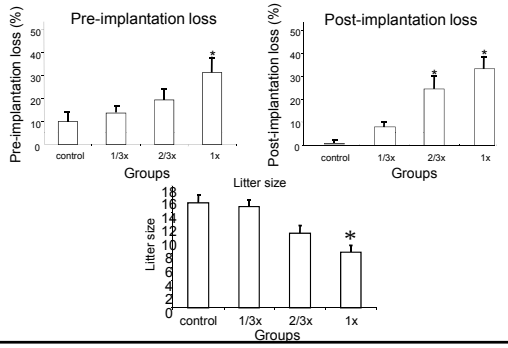
Effects of CHOP on Testicular Histology



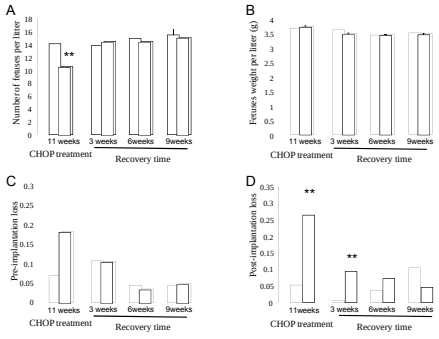
Effects of CHOP on Sperm Quality: SCSA



Effects of Paternal CHOP on Progeny Outcome



Effects of Paternal CHOP on Progeny Outcome Reversal Study



Male-Mediated Developmental Toxicity

• The treatment regimens for both testis cancer (BEP) and non-Hodgkin lymphoma (CHOP) have adverse effects on male germ cells and progeny outcome in the rat model.

• Both BEP and CHOP affect multiple parameters of sperm chromatin quality and function. BEP, but not CHOP, affects spermatogonial stem cells.

Sperm Quality: Chromatin Biomarkers

Sperm decondensation

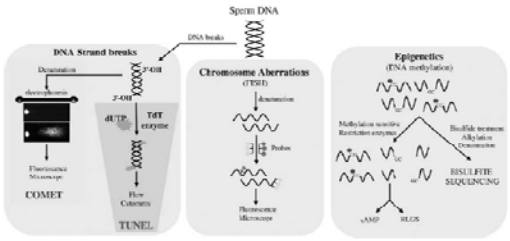
Breaks and cross-links and integrity of chromatin

Chromatin template function

Chromatin structure

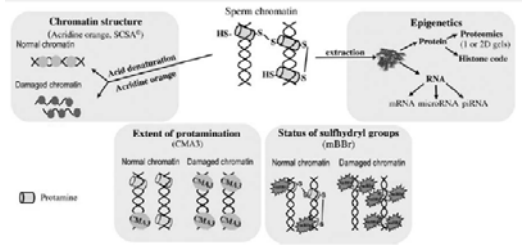
Chromatin epigenome

Sperm Quality: Chromatin Biomarkers



Delbes et el., Mol. Human Reprod. 2010

Sperm Quality: Chromatin Biomarkers



Delbes et el., Mol. Human Reprod. 2010

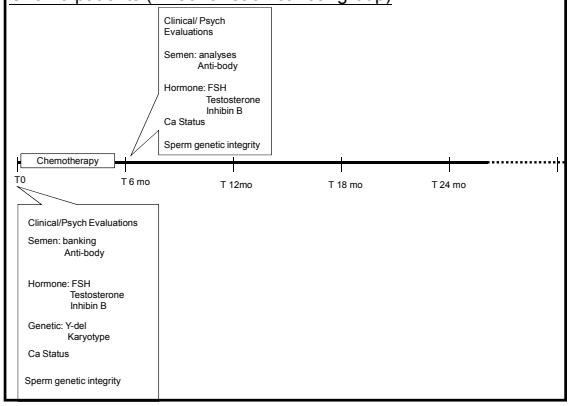
Male mediated developmental toxicity: chemotherapy, sperm chromatin, psychosocial and progeny outcome

Project 1: Impact of Combination Chemotherapy on Reproductive Health and Gamete Genetic Integrity in Humans

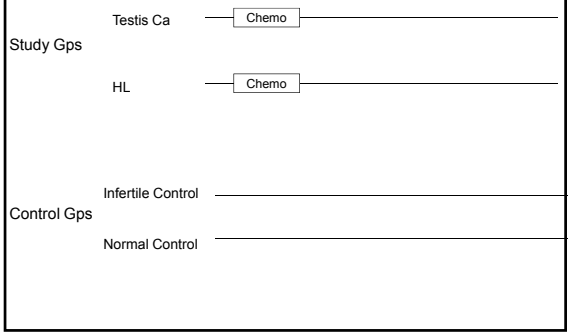
Project 3: Impact of Chemotherapeutic Regimens on Male Reproduction and Progeny Outcome in the Rat Model

Project 2: Risk Communication & Psychosocial Impact of Reproductive Sequelae Among Men Treated for Testicular or Lymphatic Cancers

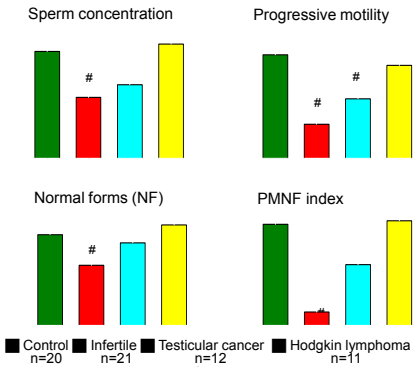
Chemo patients (N=30 for each cancer group)



Time Line

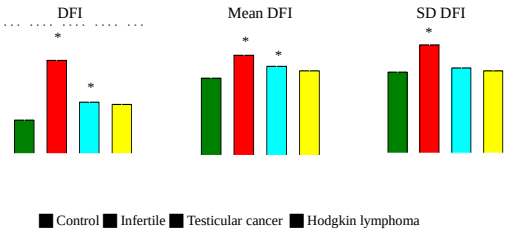


Semen Parameters



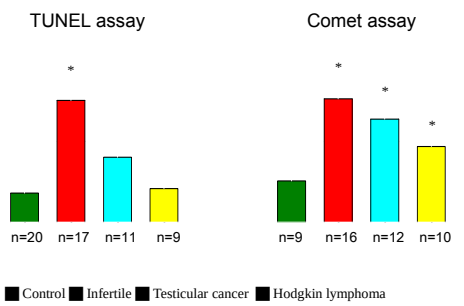
O'Flaherty et al. Hum Repro. 2008; 23:1044-1052

Acridine Orange Assay
Sperm chromatin structure assay® (SCSA®)



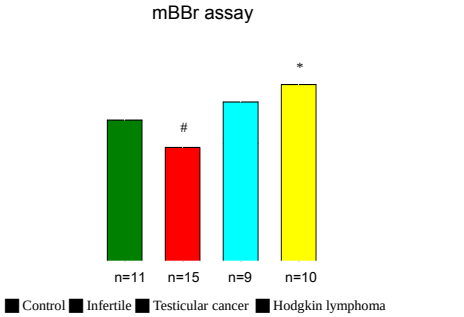
O'Flaherty et al. Hum Repro. 2008; 23:1044-1052

Sperm DNA strand breaks



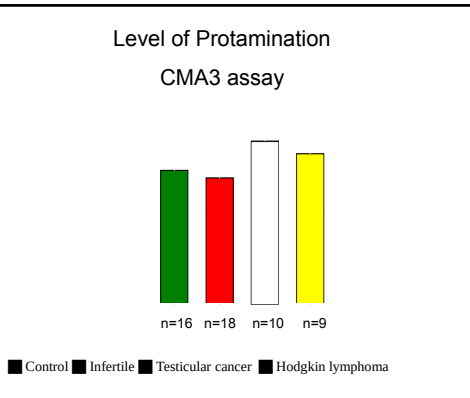
O'Flaherty et al. Hum Repro. 2008; 23:1044-1052

Reactive thiol groups



O'Flaherty et al. Hum Repro. 2008; 23:1044-1052

Level of Protamination

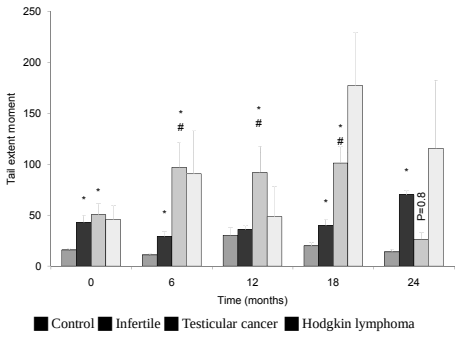


O'Flaherty et al. Hum Repro. 2008; 23:1044-1052

CONCLUSIONS

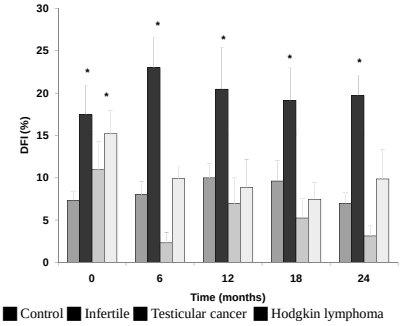
* Spermatozoa from cancer or infertile patients have lower sperm chromatin quality than in the control group.
* SCSA®, TUNEL and comet assays similarly predict sperm chromatin quality in infertile patients.
* In cancer patients, sperm chromatin anomalies can be identified best using the comet assay.
* Routine semen parameters fail to predict sperm chromatin quality.

Comet assay (Tail extent moment)



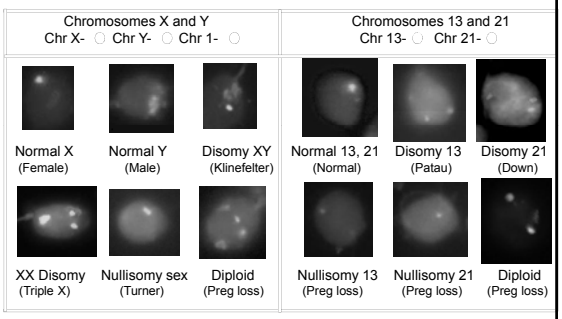
O'Flaherty et al. Fertil Steril. 2010; 94:1371-1379

Sperm chromatin structure assay® (SCSA®) %DFI

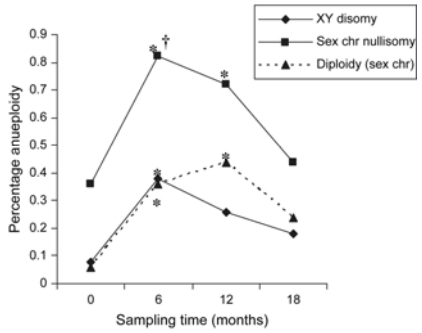


O'Flaherty et al. Fertil Steril. 2010; 94:1371-1379

FISH images



Aneuploidy Frequencies for the Sex Chromosome in Testis Cancer Subjects



Tempest et al. Fertil Steril. 2009 Jan;91(1):185-92

CONCLUSIONS

• Sperm generated post-chemotherapy maintain a significant degree of chromatin damage. Thus, survivors of TC and HL are at risk of having abnormal reproductive outcome.

• Proper counseling to these patients on reproductive risks and fertility preservation prior to chemotherapy is recommended.

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O'Flaherty et al. Fertil Steril. 2010; 94:1371-1379 .
Olshan et al. Am J Ind Med 1991; 20:447-475.
Tempest et al. Fertil Steril. 2009; 91:185-192.
Qiu et al., Biol Reprod. 1992; 46:926-931.
Sawyer and Aitken, 2001

Recreational drugs (smoking, alcohol and cannabis)

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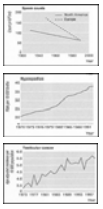
Queen's University Belfast
s.e.lewis@qub.ac.uk

SIGA, ESHRE, Stockholm 2011

Is male reproductive health under threat?



- **decreasing sperm counts**
- **congenital abnormalities**
- **testicular cancer**
- **inefficient reproduction**

•lifestyle hazards- in the environment

•recreational drugs (smoking, alcohol and cannabis) **.....**

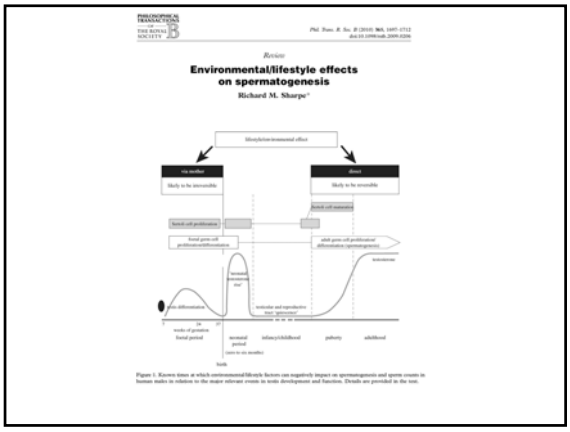
Are Lifestyle factors associated with semen quality?

Factors (evidence +, ++, +++)

- **Smoking (+++)**
- **Alcohol (++)**
- **Caffeine (+)**
- **Drugs (who me? ++)**

Endpoints (evidence +, ++, +++)

- **Sperm conc (+++)**
- **Sperm motility (++)**
- **Sperm motility by CASA (+)**
- **Sperm morphology (++)**
- **Sperm motility and acrosome reactions (++)**
- **Sperm chromosome abnormalities (+)**



Review

Environmental/lifestyle effects on spermatogenesis

Richard M. Sharpe*

Figure 1. Known times at which environmental/lifestyle factors can negatively impact on spermatogenesis and sperm counts in human males in relation to the major relevant events in testis development and function. Details are provided in the text.

Recreational drug number 1: cigarette smoking

- Impotence: 120,000 men/year
- ↓ Sperm counts
- ↓ Sperm motility
- ↓ Normal sperm morphology
- Mutations passed to children
- ↑ childhood cancers with smoking fathers

The sheer scale of smoke damage to fertility is shocking!

British Medical Association 12 February 2004

Smoking & Spermatogenesis

Smoking has a small –ve impact

(Vine et al, 1994; Vine , 1996)

Mechanism: Hypoxia- high metabolic requirements

50% of arterial blood goes to arterio- venous anastomoses in spermatic cord

(Maddocks et al 1993; Piner et al, 2002)

↓40% in sperm counts n sons by maternal smoking in utero SD1

(***Ramlau et al, 2007)***

↓10-17% in sperm counts of heavy smokers in adults

No effects

(***Martini et al, 2004, Marinelli et al, 2004)***

Slide 6

SD1 SallyD; 1/04/2010

Smoking & Semen Quality

- Is smoking an independent risk factor for poor semen quality or fertility?
- Impact may depend on both amount of exposure (cigarettes/day) and duration (pack years)
- Additive or synergistic Lifestyle factors may co-occur. SD2
  - Smoking and drinking? ("Pub" lifestyle, *Rubes et al., 1998*)
  - Abuse of alcohol and drugs? Unhealthy lifestyles, poor nutrition.
  - Smoking and vitamin C (protective?)

Are fertile men less susceptible to smoking and other lifestyle exposures?

- **The "Healthy Men Study" (HMS)**
  - Partners of pregnant women in a pregnancy outcome study
  - Exposure of interest: Disinfection byproducts (DBPs) in drinking water
  - Men lived in community with low DBPs, or high chlorinated DBPs or high brominated DBPs.
  - Exposure carefully characterized
  - Semen: Count/conc., morphology, and DNA damage (SCSA-%DFI) and immaturity (SCSA-%HDS)
  - No differences were found based on DBP exposures (Luben et al, 2007), adjusting for other factors.

With kind permission from Lavelle K, Perreault, S, Olshan, A, 2010

Analysis of Lifestyle Exposure factors in the 'Healthy Men Study' HMS

- **Smoking**: current, former or never; 0, 1-10, or >10 cigarettes/day, and years smoked (0, 1-5, 6-10 and >10). Pack years: /day /20 x years

Alcohol: calculated based on average drinks [beers (12 oz), wine (4 oz) and hard liquor (1oz)] and categorized by # drinks/week: 0-7, 8-15 and >15

- **Caffeine**: Based on Coffee (and other caffeinated drinks), mg caffeine/day was calculated and categorized: none, >0 to 150 (low), >150-300 (moderate) and >300 (high = 3 cups coffee).

With kind permission from Lavelle K, Perreault, S, Olshan, A, 2010

Slide 7

SD2 SallyD; 1/04/2010

Statistical Analysis in HMS

- Lifestyle exposure factors were examined (controlling for study site, age, income, education, abstinence interval, history of chronic or serious illness, body mass index (BMI), with other study exposures (smoking, alcohol, caffeine) as potential confounders.
- Multiple linear regression was used to estimate associations of each lifestyle exposure factor and each outcome. Full model (with all covariates) was evaluated for each covariate and only those that changed the parameter estimate of the exposure variable by at least 10% were retained. Age, sexual abstinence, income and study site were retained as obligate, along with any factor that met the criteria for confounding
- Semen outcomes were also dichotomized when possible for logistic regression: percent normal forms at <15%; and, SCSA %DFI at >30% according to the literature.

With kind permission from Lavelle K, Perreault, S, Olshan, A, 2010

Conclusion

The HMS findings show that, on average, men in this fertile cohort have above average semen quality and below average consumption of cigarettes and alcohol

Recreational drug number 2: Alcohol

- **↓ testosterone**
- **↓ impaired semen volume**
- **↓ sperm concentration**
- **↓ sperm motility**
- **↓ normal sperm morphology**
- **but the good news- its reversible!**

Donnelly, Lewis et al, Andrologia 1 43-47 1999
Vicari et al, J Endo Invest 25 473-476 2002
Muthusami et al, Fertility and Sterility 84 919-924 2005
Oliva et al, Rep Tox 22 599-605, 2006

Alcohol and Spermatogenesis

Alcoholism associated

- **with impotence and testicular atrophy**

Boyden et al, Endocrine Rev 1983

- **Spermatogenesis decreases ∞ alcohol intake**

Pajarinen et al, Alc Clin Exp Res 1996

- **XY aneuploidy (RR=1.38, CI 1.2-1)**

Robbins et al, Cyto Genet 2005

- **Synergistic effects of alcohol and smoking**

Mendiola , Agarwal et al, 2008

Alcohol and semen quality

Most studies do NOT show a significant effect on

- **sperm counts with moderate drinking**

(Marinelli et al, 2004; Martini et al, 2004)

in contrast in chronic alcoholics

- **impaired spermatogenesis**
- **reduced sperm counts**
- **reduced tstosterone levels**

(Villalta et al, 1997; Muthusami and Chinnaswamy, 2005, reviewed by Sharpe, 2010)

Alcohol, drugs, caffeine, tobacco, and environmental contaminant exposure: Reproductive health consequences and clinical implications

Sadeu, J. C.; Hughes, Claude L.; Agarwal, Sanjay; Foster, Warren G
Critical Reviews in Toxicology 40, 7, 2010 ,. 633-652

Cigarette smoking is strongly associated with adverse reproductive outcomes

High exposure to alcohol, drugs and caffeine are only weakly linked with negative outcomes

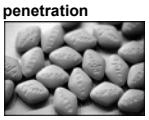
Recreational drug number 3

Phosphodiesterase-5 inhibitors such as sildenafil citrate and tadadafil

- between 1998- 2005, 1 billion scripts
- for impotence
- for sexual enhancement
- in treatment of diabetes
- in infertility clinics

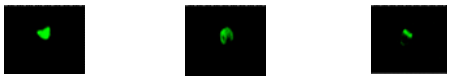
Phosphodiesterase-5 inhibitors Sildenafil citrate

- Use with Serotonin for temporary ejaculation failure during ART
  Lu et al, FS 2009
- Adjunct tool for ↑ Leydig function and contractility of epididymis
  Dimitriadas et al, Curr Pharma Design 2009
- ↑ sperm motility and viability, opp effects at higher doses
- ↓ sperm motility and viability with Tadafil
  Pomara et al, FS 2007
- Contradicted by Hellstrom et al, *Eur Urol 2008*
- No effects on volume, concentration, integrity or penetration
- Variable effects on capacitation
  Mostafa Int J Impotence 2008
- ↑↓ fertilizing ability
  Dimitriadis et al, Asian J Androl 2008



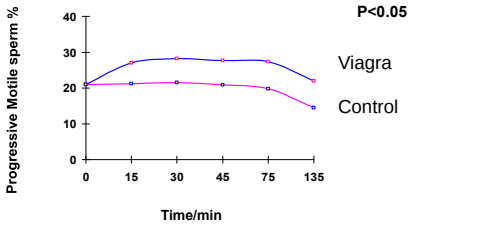
Methods to determine the direct effects of Viagra on sperm function

- Conc of 450ng/mL~ 100mg oral dose generously donated by Pfizer
- Quantitative motility 0-135 min using CASA
- Acrosome reaction by PNA-FITC



- *in vitro (n=45)*

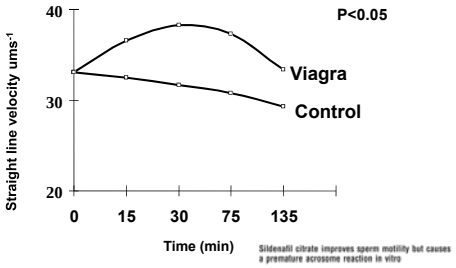
The direct effect of Viagra on sperm numbers



Sildenafil citrate improves sperm motility but causes a premature acrosome reaction in vitro

David R. J. Glenn, M.R.C.O.G., Carmel M. McVicar, Ph.D., Neil McClure, F.R.C.O.G., and Sheena E. M. Lewis, Ph.D.

The direct effects of Viagra on the quality of sperm motility



Sildenafil citrate improves sperm motility but causes a premature acrosome reaction in vitro

Alterations in sperm motility after acute oral administration of sildenafil or tadalafil in young, infertile men

Giorgio Pomara, M.D.,[a] Girolamo Morelli, M.D.,[a] Domenico Canale, M.D.,[b] Paolo Turchi, M.D.,[c] Carolina Caglieresi, Ph.D.,[b] Cecilia Moschini, Ph.D.,[b] Giovanni Liguori, M.D.,[d] Cesare Selli, M.D.,[a] Enrico Macchia, M.D.,[b] Enio Martino, M.D.,[b] and Francesco Francesca, M.D.[a]

TABLE 1

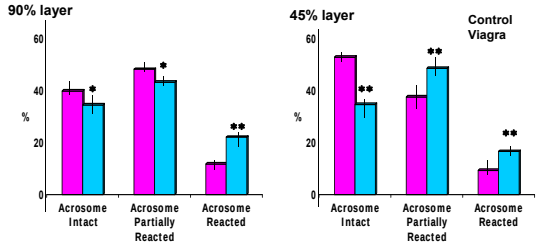
Seminal parameters in basal conditions and after either sildenafil or tadalafil.

Seminal parameters	Basal	Sildenafil	Tadalafil
Volume (mL)	2.9 ± 0.4 (2.8)	2.4 ± 0.4 (2.1)	2.7 ± 0.5 (2.1)
pH	7.9 ± 0.2 (8.0)	7.9 ± 0.2 (7.8)	7.9 ± 0.1 (7.8)
Sperm count (million per mL)	29.1 ± 6.0 (17.4)	31.5 ± 5.9 (22.1)	28.6 ± 5.9 (17.3)
Rapid progressive motility (%)	11.9 ± 2.1 (10.5)	18.8 ± 2.7 (18.5)	8.6 ± 1.8 (6.0)
Total progressive motility (%)[a]	28.6 ± 3.4 (28.5)	35.5 ± 3.3 (37.0)	24.2 ± 3.2 (21.5)
Normal forms (%)	23.7 ± 6.1 (11.0)	24.8 ± 3.8 (16.0)	23.6 ± 4.2 (15.5)

Note: All data are mean ± SE (median).
[a] Class a (rapid) + b (slow) progressive motility.

Pomara. Sildenafil, tadalafil, and seminal parameters. Fertil Steril 2007.

The direct effects of Viagra on the acrosome reaction



Burger, Hellstrom et al, 2000- no effects on any sperm parameters

Phosphodiesterase11 regulation of spermatozoa physiology

Wayman et al, Pfizer Global R and D, 2005

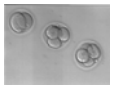
Ejaculated sperm from PDE11-/-
- **↓sperm conc, prog motility and viability**
- **Pre- ejaculated sperm had premature capacitation**
- **Data consistent with human data**

Eli Lilly and Co, Tadadafil www.fda.gov/ 2007

Dogs given Tadadafil for 6-12 months
→ alterations in seminferous epithelium and subsequent effects on spermatogenesis

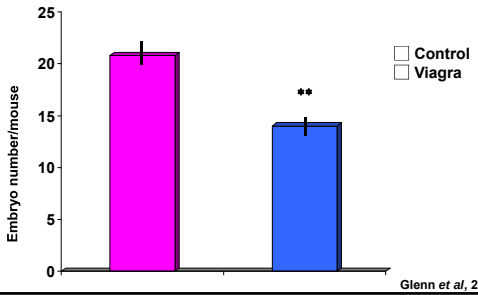
To determine effects of one dose of Viagra on embryo development

- **Case study by Tur Kaspa et al, 1999**
- **Same action as Pentoxifylline??**
- **Animal model**
- **Effects on fertilization**
- **Effects on embryo cleavage rates**



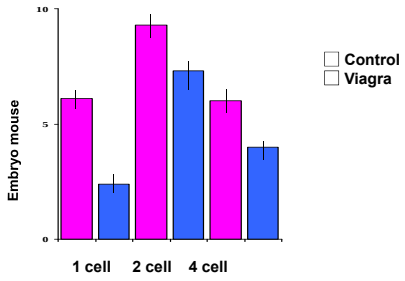
Sildenafil citrate (Viagra) impairs fertilization and early embryo development in mice

The effects of one dose Viagra on embryo yield



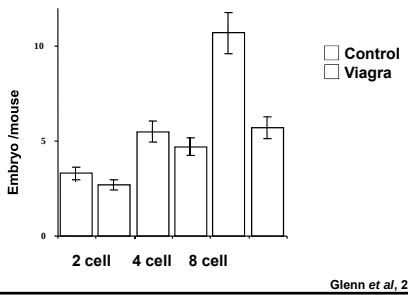
Glenn *et al*, 2004

The effects of Viagra on embryo numbers and stage at Day 2



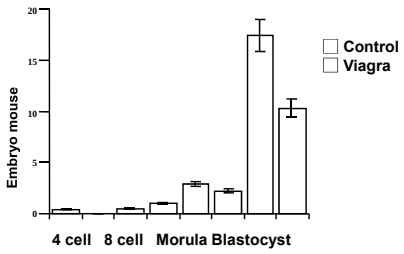
Glenn *et al*, 2004

The effects of Viagra on embryo numbers and stage at Day 3



Glenn *et al*, 2004

The effects of Viagra on embryo numbers and stage at Day 4



Glenn *et al*, 2004

Developmental toxicity of orally administered sildenafil citrate (Viagra) in SWR/J mice

Abou- Tarboush et al, 2001

Sildenafil citrate to 285 pregnant mice

at 1-50mg on 7-9,10-12 or 13-15 days gestation

- No maternal toxicity
- No external, internal or skeletal malformations
- 40mg→ fetal growth suppression at all times
- 25-40mg at 13-15 days → embryo-fetal toxicity

Recreational Drug No 4

(Cannabis - δ-9-tetrahydrocannabinol; THC)

Cannabis and Male Fertility

↑ sexual behaviour in humans

↓ sexual behaviour in animals

↓↑ effects on spermatogenesis

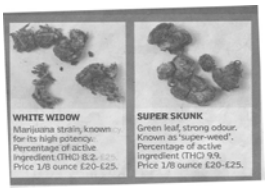
Highly variable effects on motility

Increased chromatin condensation

Damage to developing sperm

Cannabis and endocrine profiles - animal studies

- Suppression of LH and accumulation of THC in testis
  Ho et al, 1970
- Acute and chronic doses both decrease testosterone
  List et al, 1997; Harclerode et al, 1978
- No changes in FSH, no direct oestrogenic effect
  Ruh et al, 1997; Fernandez- Ruiz et al, 1997
- Reduced nucleic acid and protein synthesis
- In Leydig cells
  Jakubovic et al 1979; Husain et al 1979

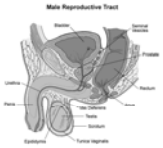


Potency of THC on the streets

The Observer 18 January 2004

Are endocannabinoids present in the male reproductive system?

Cannabinoid (CB1) receptors are present in

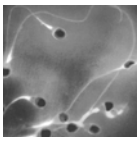


Testis
Gerard et al, 1991

Vas deferens
Pertwee et al, 2002

Epididymis

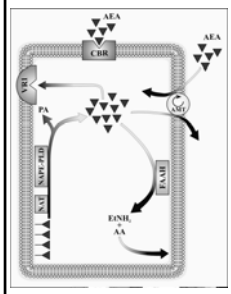
Prostate
reviewed by Schuel et al, 2002



Sea urchin sperm
Chang et al, 1993

Human sperm
Schuel et al, 2002

The endocannabinoid system in sperm



Sperm have

CBR receptors
Vanilloid (TRPV1) receptors
AEA
NAPE-PLD
AMT
FAAH

Bull sperm study by Maccarrone et al, 2005

Endocannabinoid Effects on Sertoli Cells

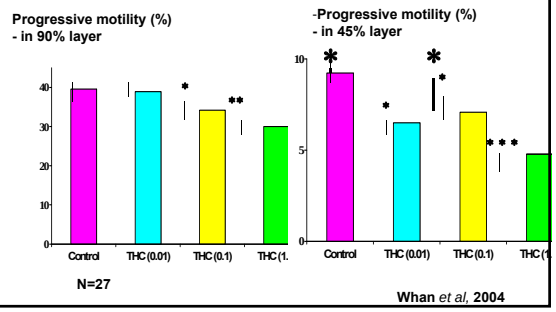
- **Sertoli cells have CB1R and CB2R and can degrade AEA**
- **FAAH activity ↓ with Sertoli cell age**
- **AMT↓ with age but ↑ by NO donors**
- **↑AEA can force Sertoli cells into apoptosis**
- **FSH activates FAAH via mRNA and PrS to prevent this**

Maccarrone et al, 2003

Therapeutic and Recreational Concentrations of THC

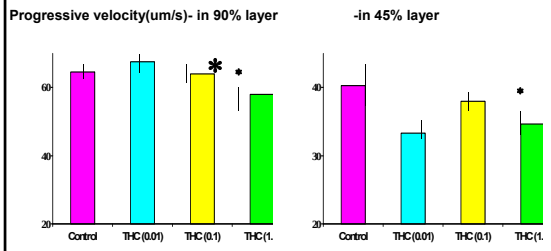
- 0.001μg/mL ~ therapeutic
- 0.01 μg/mL ~ recreational
- 1. 5 μg/mL ~recreational

Direct effects of THC on sperm motility



Whan *et al*, 2004

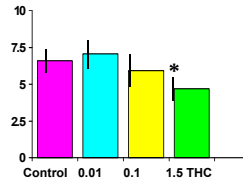
Direct effects of THC on sperm motility



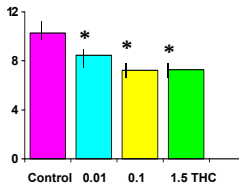
Whan *et al*, 2004

Direct effect of THC on the Acrosome Reaction

Acrosome reacted sperm in 90% layer (%)



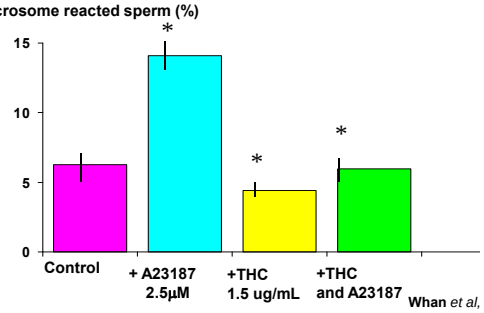
Acrosome reacted sperm in 45% layer (%)



Whan *et al*, 2004

Direct effect of THC on the Induced AR

Acrosome reacted sperm (%)



Whan *et al*, 2004

What are the mechanisms of action?

i) Reduced ATP by impaired mitochondrial function

Cannabinoids inhibit the respiration of human sperm

Potent inhibitors of mt O_2 / min/10^8 sperm

Δ^9-Tetrahydrocannabinol disrupts mitochondrial function and cell energetics

↓ mt membrane potential by JC-1
uncoupling of electron transport

What are the mechanisms of action?

ii) 2nd messenger systems- Ca^{2+} channels

Cellular and Molecular Mechanisms Underlying Learning and Memory Impairments Produced by Cannabinoids

→G protein mediated inhibition of Ca^{2+} channels

THE EFFECTS OF CANNABINOIDS ON THE BRAIN

→ Shrinkage of neurons
→ DNA fragmentation in hippocampus

Alcohol & Alcoholism Vol. 35, No. 2, pp. 126–133, 2000

REVIEW

ARE ANANDAMIDE AND CANNABINOID RECEPTORS INVOLVED IN ETHANOL TOLERANCE? A REVIEW OF THE EVIDENCE

B. L. HUNGUND[2,3]* and B. S. BASAVARAJAPPA[1]

Involvement of 2-arachidonoyl glycerol in the increased consumption of and preference for ethanol of mice treated with neurotoxic doses of methamphetamine

MD Gutierrez-Lopez[1]*, N Llopis[1]*, S Feng[2], DA Barrett[2], E O'Shea[1]† and MI Colado[1]†

Cannabinoids lead to voluntary EtOH consumption and preference in animals!

Conclusions

- **Recreational drugs may impair male reproduction, either singly or together**
- **It is difficult to determine the impact of any one factor separate from other factors as men often use several recreational drugs together**
- **Very little is currently known about the mechanisms behind observed associations, how lifestyle factors may interact, and whether some men are inherently more vulnerable than others**

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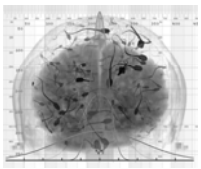
ENI

r&d office

Good Sperm, Good Brain?

The Connection Between Semen Quality & Intelligence



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eshre European Society of Human Reproduction and Embryology

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Linda S Gottfredson, University of Delaware
Geoffrey Miller, University of New Mexico
Arand Pierce, NMVA Health Systems, University of New Mexico

Learning Objectives

- Understand why intelligence and semen quality may both be influenced by common genetic factors that influence overall survival fitness
- Understand the biologic commonalities of sperm and neuron function that may be influenced by pleiotropic mutations of those common genetic factors that affect overall fitness

Background/Hypothesis

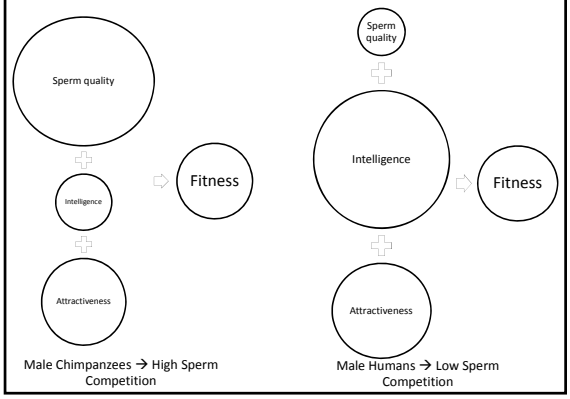
- Survival adaptations
  - Low heritability, low phenotypic and genetic variation between individuals of a species

- Survival fitness (*f*)
  - The statistical propensity to survival and reproductive success, under ancestrally normal conditions
  - In courtship, fitness indicators have higher variation, and advertise highly heritable traits promising good genes and good health
    - These indicators are so costly that only high-fitness individuals can maintain them

Background/Hypothesis

- "…During human evolution, mate choice by both sexes focused increasingly on intelligence as a major component of biological fitness – both for its heritable genetic benefits and its relevance to parenting ability. Many human-specific behaviors (such as conversation, music production, artistic ability, and humor) may have evolved principally to advertise intelligence during courtship."

Miller GF, 2000



Background/Hypothesis

- If intelligence is a prominent component of survival fitness, is there a correlation between sperm quality and intelligence?

Courtesy of R Arden

Subjects

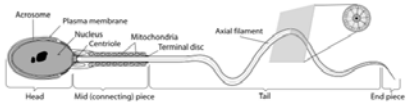
- The Center for Disease Control Vietnam Experience Study
  - Multidimensional health assessment of American veterans of the Vietnam War
  - A random sample of enlisted men who entered the U.S. Army from 1965 to 1971, 7,924 Vietnam and 7364 non-Vietnam veterans participated in a telephone interview.
  - A random subsample of 2,490 Vietnam and 1,972 non-Vietnam veterans also underwent a comprehensive health examination, including medical examination, laboratory tests, and a psychological evaluation.
  - A Subset of 425 men submitted semen samples
    - Mean Age: 38
    - 355 white
    - 48 black
    - 16 Hispanic
    - 4 Asian/Pacific Islander
    - 2 Native American/Native Alaskan
  - Data published in the *Journal of the American Medical Association* in numerous publications circa 1988

Intelligence metrics (*g*)

- *g* = the general factor of mental ability
- Principal axis factoring of five tests to extract *g*
  - Verbal and Arithmetic tests
    - Army Classification Battery
  - Spatial awareness tests
    - Information and Block Design subtests of the Wechsler Adult Intelligence Scale – Revised
  - Reading comprehension
    - Subtest of the Wide Range Achievement Test

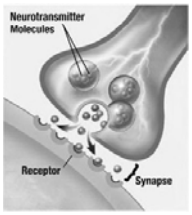
Semen quality metrics

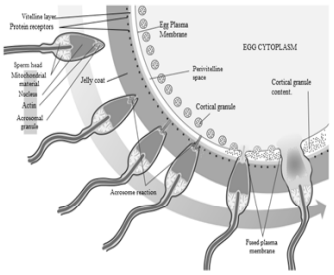
- Sperm concentration (millions of sperm per ml of semen), $\log_{10}$ transformed
- Sperm count (millions of sperm in the total ejaculate) $\log_{10}$ transformed
- Sperm motility (percentage of motile sperm)



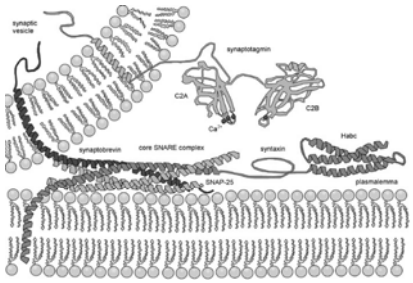
Results

- Significant but modest positive correlations between intelligence and 3 key indices of semen quality:
  - Log sperm concentration (r=.15, p=0.002)
  - Log sperm count (r=.19, p<0.001)
  - Sperm motility (r=.14, p=.002)
- Correlations controlled for:
  - Sexual abstinence (no. of days prior to sample)
  - Age
  - Body Mass Index
  - Drinking alcohol (drinks per month)
  - Smoking (cigarettes per day)
  - Drugs: marijuana or hard drugs (past & current use examined separately)
  - Service in Vietnam





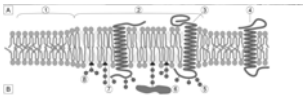
Proof of Concept:
Strikingly similar constellations of genes are involved in the regulation of sperm and neural function
(Pierce et al., 2009)



- SNAREs are concentrated at presynaptic terminals of neurons, as well as the acrosomal region of sperm (Rizo et al. 2002, Tomeset al. 2005)
- SNAREs also mediate hypothalamic release of gonadotropin releasing hormone, thyrotropin releasing hormone, and growth hormone
  - Possible effect on other traits of fitness

Other commonalities

- Glial cell line derived neurotrophic factor (GDNF) (Meng et al., 2000)
- Tight genetic regulation of polyunsaturated fatty acids of plasma membrane
  - Spatial compartmentalization of membrane microdomains of lipids and proteins (lipid rafts) coordinates the sequences of signal transduction required for spermatogenesis, maturation, capacitation, acrosomal reaction (AR) and ultimately fertilization (Lenzi et al., 2000)



More commonalities

- Sperm, retinal photoreceptor cells, and olfactory sensory neurons employ conserved cyclic nucleotide gated calcium ion channels
  - Many of these channels in sperm are T-type voltage-gated Ca2+ ion channels involved in AR regulation (Florman et al., 1998; Stamboulian et al., 2004)

More commonalities

- Other odorant gene family receptors are sperm-specific, directly regulating sperm motility and chemotaxis via activation of $Ca_V3.2$ ($\alpha 1_H$) Ca2+ ion channels (Spehr et al. 2003, Babcock 2003)
  - The *CACNA1H* gene encodes this ion channel, which is heavily expressed in the neocortex as well. Various mutations have been implicated in case studies of childhood absence seizures (Chen et al., 2003) and idiopathic generalized epilepsy (Heron et al., 2004)

Implications

- If most genes have pleiotropic effects on several traits (e.g. sperm and neuron function), then most mutations will harm several traits in parallel and create positive genetic correlations among traits, as manifest in an *f* (fitness) factor (Arden, 2009)

The real question

- Is the *g* factor a special case of a more general fitness factor *f* that captures individual differences in general phenotypic quality? (Houle, 2000)

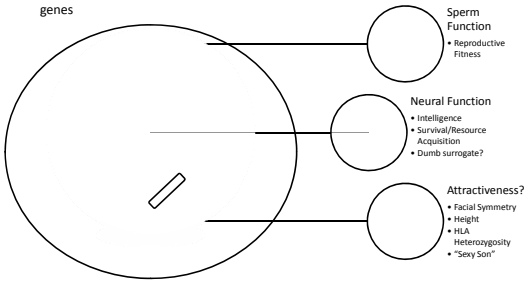
f → *g* → 

$f \rightarrow g$?

- Numerous studies link *g* with better longevity, attractiveness, health, etc. (Batty et al., 2007; Bates, 2007)
- *f,* like *g,* is likely not traceable to single genetic loci with Mendelian inheritance
  - "The data imply that the genes causing the high heritability of IQ do not code for different levels of psychometric intelligence per-sé but are pleiotropic—expressed in many systems, and acting on fitness in the same direction, positive or negative in all the systems in which they are expressed" (Bates, 2007)

Quantitative traits: Phenotypic traits that vary in degree according contributions of multiple genes as well as the environment

Mutations acting on pleiotropic genes will result in correlations between the traits affected by those genes



Overall Mutation Load = Overall Fitness?

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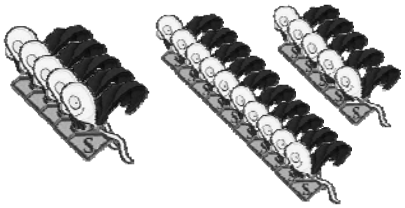
EXERCISE: FIT SPERM?



Diana Vaamonde, B.S., M.S., Ph.D.
University of Cordoba
No potential conflict of interest.

Exercise: Fit Sperm ????

1. Prior considerations
2. Physical Exercise vs. Physical Activity
3. Physical Exercise/Training Load Variables
4. Background: Exercise vs. reproductive system
5. Endocrine system and reproductive system
6. Recent research (Intensity, Volume, and Modality)
7. Exercise: bad sperm????
8. Take home message and challenges

Is Exercise Health???

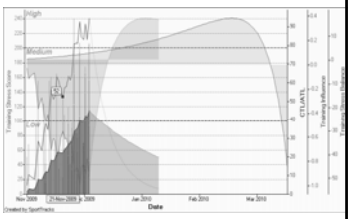
Physical Exercise vs. Physical Activity

Both terms refer to the voluntary movements you do that burn calories (energy expenditure)

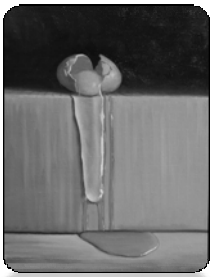
- Physical activities are activities that get your body moving.
- Exercise is a form of physical activity that is planned, structured and done to improve at least one aspect of physical fitness*** that is, strength, flexibility or aerobic endurance.

Physical Exercise/Training Load Variables

- Intensity:
- Volume:
- Frequency:
- Type of exercise:
  - Strength
  - Endurance



Background: Exercise vs. Reproductive System

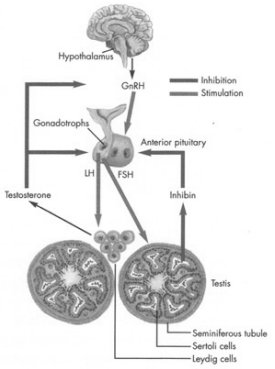


Elite FEMALE Athletes

- Hormonal decrease
- Delayed menarche
- Oligomenorrhea
- Amenorrhea
- Inadequate luteal phase
- Anovolutary cycles

Shangold, 1984; Cumming et al., 1985;
De Souza et al.,1991, 1994; Loucks, 2001

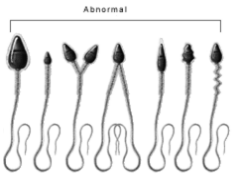
Endocrine system
and
Reproductive System



Disrupting agents of endocrine and reproductive homeostasis

and…

An extenuating physical exercise may provoke alterations on the reproductive system.
(Cumming et al., 1985; Shangold, 1984)



Adequate assessment of male reproductive potential

- Hormonal analysis
- Semen analysis
- Fertilizing capacity assessment

Semen Analysis

- Complete sexual abstinence: 3–6 days
- Questionnaire.
- Time between sample collection and delivery: under 30 minutes
- Physical parameters: volume*
- Microscopical qualitative parameters:
  - Sperm concentration and total sperm number*
  - Sperm Velocity (a, b, c, d)*
  - Sperm Morphology *

What is known…

- Hormonal Responses
  - Marathon
  - Cyclists
  - Swimmers
- Semen Response
  - Marathon
  - Cyclists
  - Swimmers
- VOLUME THRESHOLD (De Souza and Miller, 1993)

Recent research

Intensity

Volume

Modality

Intensity

International Journal of Sports Medicine

Design

16 Subjects

8 (CG)	8 (EG)
Control Group	**Experimental Group**

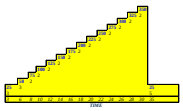
Vaamonde et al., 2006. Reproductive profile of physically active men after exhaustive endurance exercise. *Int J Sports Med*. 2006;27(9):680-9

Intensity

Training parameter: 2 weeks of cycle ergometer exercise to exhaustion.

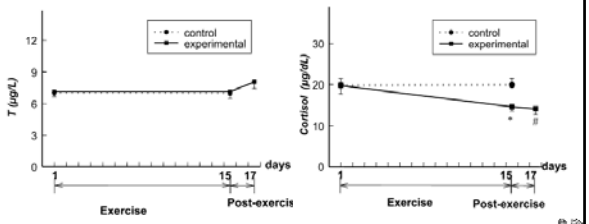
Design

Training



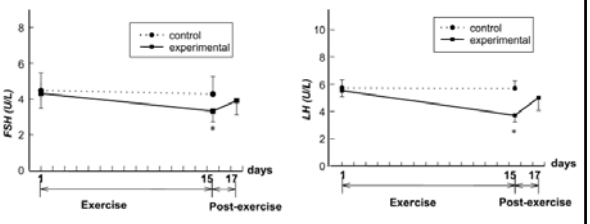
Hormonal and semen analysis

Testosterone and Cortisol



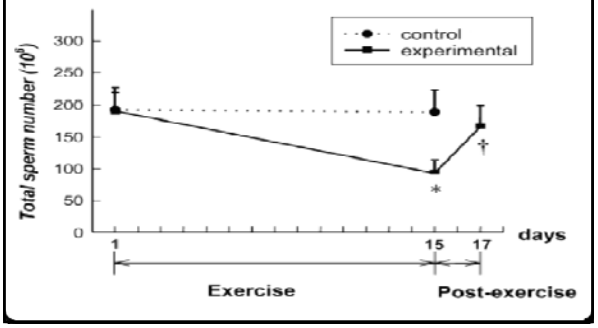
Vaamonde et al., 2006.

FSH and LH

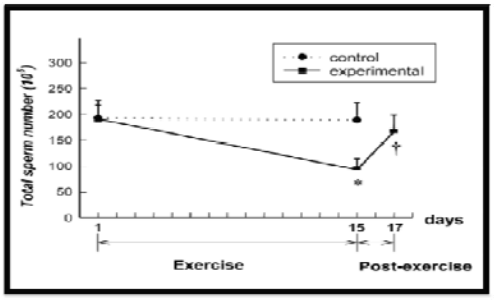


Vaamonde et al., 2006.

Sperm Concentration, ejaculate volume, total sperm number

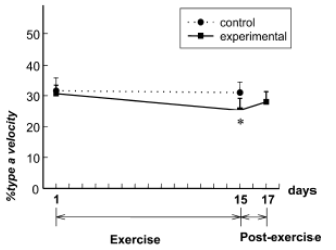


Sperm Concentration, ejaculate volume, total sperm number



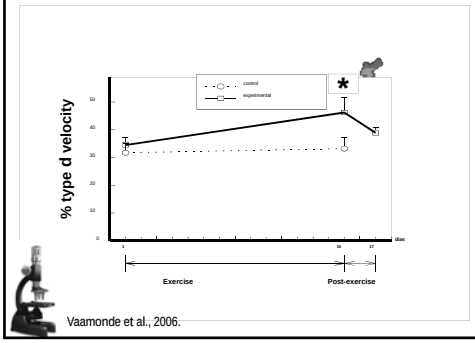
Vaamonde et al., 2006.

Type "a" Velocity



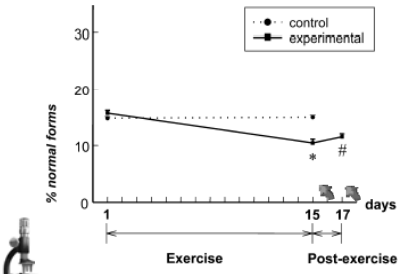
Vaamonde et al., 2006.

Type"d" Velocity



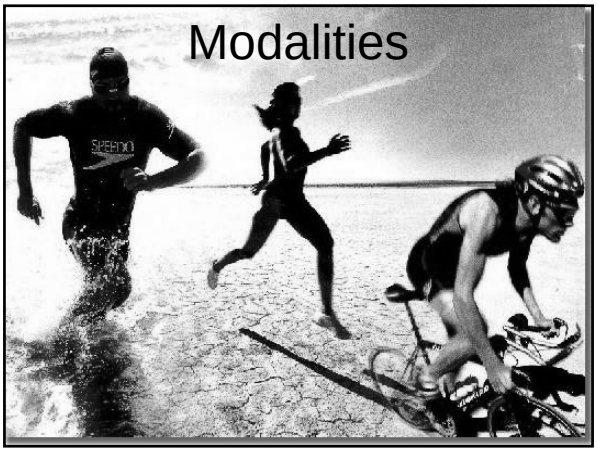
Vaamonde et al., 2006.

Sperm Morphology



Vaamonde et al., 2006.

Modalities



FERTILITY AND STERILITY

Response of semen parameters to three training modalities.

Vaamonde D[a], Da Silva Grigoletto ME[b], García-Manso JM[c], Vaamonde-Lemos R[a], Swanson RJ[d], Oehninger SC[e]

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[b]Andalusian Center of Sports Medicine. Córdoba – Spain

[c]Physical Education Department, School of Physical Activity and Sport Sciences, University of Las Palmas de Gran Canaria – Spain

[d]Department of Biological Sciences, Old Dominion University and Eastern Virginia Medical School, Norfolk, VA – USA.

[e]The Jones Institute for Reproductive Medicine, Department of Obstetrics and Gynecology, Eastern Virginia Medical School, Norfolk, VA – USA

Fertil Steril. 2009; 92(6):1941-6Nov 14.

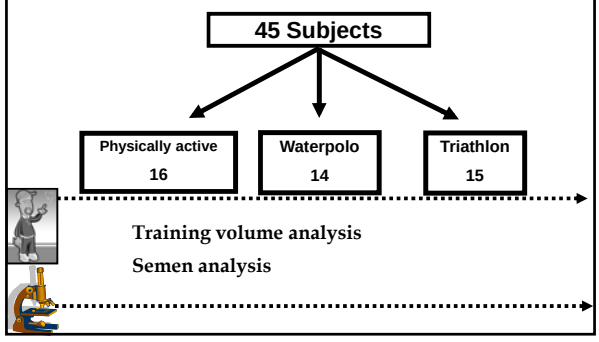
Modality

Methods

- Exclusion criteria
  - Any condition possibly impairing reproduction
- Inclusion criteria
  - Not exclusion criteria,
  - Minimum practice of 3 hours/week
  - VO2max ≥ 40 ml/min/kg.

Modality

Methods



Methods

Modality

	Physically Active	Water Polo	Triathletes
Subjects	16	14	15
Age (years)	19.0 ± 1.8[bc]	25.5 ± 3.2[ac]	33.1 ± 3.5[ab]
Weight (kg)	73.1 ± 8.3[b]	79.9 ± 10.7[ac]	74.5 ± 7.6[b]
Height (cm)	175.9 ± 4.2	180.1 ± 5.2	175.3 ± 3.7
Body fat (%)	15.6 ± 3.0	13.2 ± 3.5	7.0 ± 2.9
VO2max (ml/min/kg)	45.2 ± 4.2	54.2 ± 4.9	64.0 ± 5.1
Years of training	1.6 ± 0.7	4.0 ± 1.1	8.1 ± 3.2
Number of sessions/week	3.3 ± 0.4	5.0 ± 0.0	9.9 ± 1.8
Duration of session (min)	60.0 ± 0.0	90.0 ± 0.0	122.6 ± 62.7[#]
Sports category	Local	Regional	International

[a] Significant differences (p< 0.05) compared to physically active subjects
[b] Significant differences (p< 0.05) compared to water polo players
[c] Significant differences (p< 0.05) compared to triathletes
[#] Mean of all sessions (cycling, swimming, running)

Results

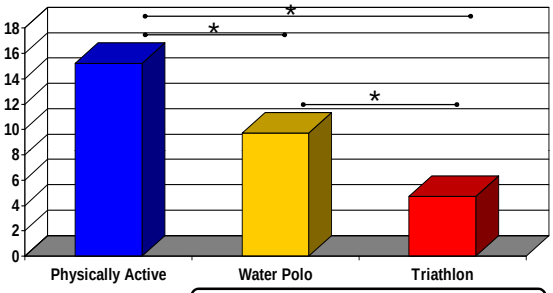
Modality

	Physically Active	Water Polo	Triahtletes	
Volume (mL)	**3.2 ± 0.9**	**3.4 ± 1.3**	**2.9 ± 0.9**	P>0.05
Sperm concentration (106/mL)	**61.0 ± 23.0[c]**	**58.0 ± 24.4[c]**	**48.2 ± 14.7[ab]**	**P<0.05**
Total sperm number (10[6])	**191.8 ± 73.4[c]**	**196.6 ± 85.4[c]**	**141.3 ± 58.0[ab]**	**P<0.05**
% Type "a" Vel.	**31.1 ± 9.7[b]**	**23.6 ± 8.8[ac]**	**31.4 ± 8.7[b]**	**P<0.05**
% Type "b" Vel.	**25.6 ± 9.1[c]**	**28.8 ± 12.3[c]**	**18.9 ± 7.6[ab]**	**P<0.05**
% Type "a+b" Vel.	**56.7 ± 6.5**	**52.5 ± 11.1**	**50.3 ± 8.9**	P>0.05
% Type "c" Vel.	**10.4 ± 5.0**	**14.3 ± 6.6**	**11.9 ± 6.3**	P>0.05
% Type "d" Vel.	**33.0 ± 7.1[c]**	**33.3 ± 11.3**	**38.4 ± 7.2[a]**	**P<0.05**

[a] Significant differences (p< 0.05) compared to physically active subjects
[b] Significant differences (p< 0.05) compared to water polo players
[c] Significant differences (p< 0.05) compared to triathletes
[#] ANOVA with repeated measures and Sidak *post hoc* test for multiple comparisons

Results

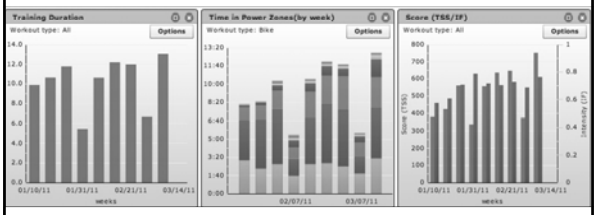
Modality



*Significant differences (p< 0.05) ANOVA and Sidak *post hoc* test

WP and TA reached both statistical and clinical significance (reference value of 14%)

Training Volume …



Correlation between cycling kilometers and sperm morphology in elite triathletes

Vaamonde D[1], Da Silva-Grigoletto ME[2], Cunha Filho JS[3] , Garcia-Manso JM[4], Suarez Serra R[5].

[1]School of Medicine- Universidad de Córdoba, Spain.
[2]Andalusian Center of Sports Medicine –Junta de Andalucía. Córdoba, Spain
[3]Insemine Centro de Reprodução Humana and Hospital de Clinicas de Porto Alegre. Porto Alegre, Brazil
[4]School of Physical Education- Universidad de Las Palmas de Gran Canaria, Spain
[5]Centro Iberoamericano de Reproduccion Asistida, Uruguay

Presented at ESHRE 2009

Training Volume

Methods

Fifteen male triathletes.

Subjects´ demographics

Age (years)	33.1 ± 3.5
Weight (kg)	74.5 ± 7.6
Height (cm)	175.3 ± 3.7
Body fat (%)	7.0 ± 2.9
VO2max (ml/min/kg)	64.0 ± 5.1
Years of training	8.1 ± 3.2
Number of sessions/week	9.9 ± 1.8
Duration of session (min)	122.6 ± 62.7

Training Volume

Methods

Training was carefully analyzed, especially with regards to weekly volume expressed as total volume or volume in each modality.

Training Volume

Methods

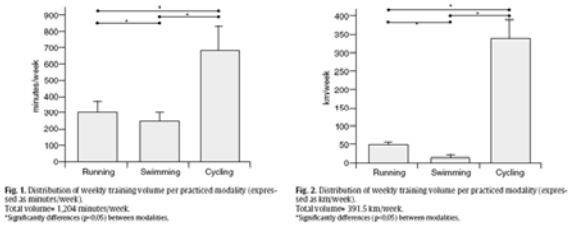


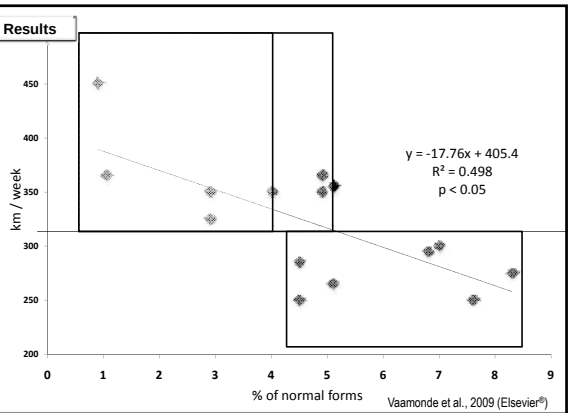
Fig. 1. Distribution of weekly training volume per practiced modality (expressed as minutes/week).
Total volume= 1,204 minutes/week.
*Significantly differences (p<0.05) between modalities.

Fig. 2. Distribution of weekly training volume per practiced modality (expressed as km/week).
Total volume= 391.5 km/week.
*Significantly differences (p<0.05) between modalities.

Elsevier®

Vaamonde et al., 2009

Results



Vaamonde et al., 2009 (Elsevier®)

Training Volume

Conclusions

A high cycling volume, especially over 300km/week, is detrimental to sperm morphology.

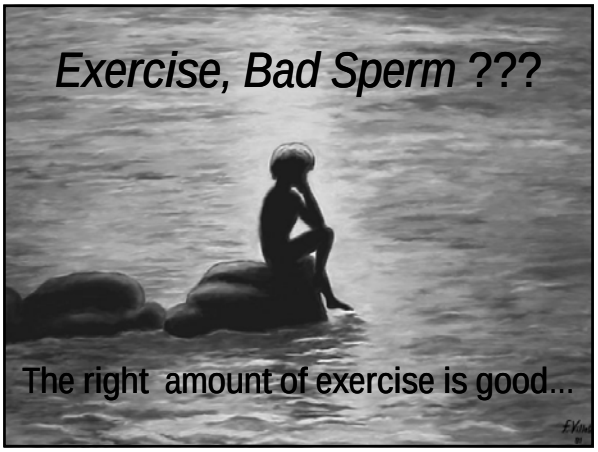
Training Volume, Intensity and Modality

High-load physical exercise, whether intensity or volume may alter male reproductive function

- De Souza et al. (1994,1997), Hackney (1996); Vaamonde et al., 2009: volume
- Vaamonde et al., 2006: intensity

Triathletes show worse semen parameters than physicaly active subjects or water polo players.

- Vaamonde et al., 2009: modality



PHYSICALLY ACTIVE SUBJECTS SHOW BETTER SEMINOLOGICAL PARAMETERS THAN SEDENTARY SUBJECTS

Vaamonde D[1], Da Silva-Grigoletto ME[2], Swanson RJ[3], Cunha Filho JS[4], Oehninger S[5].

[1]School of Medicine- Universidad de Córdoba
[2]Andalusian Center of Sports Medicine –Junta de Andalucía
[3]Biology Department, Old Dominion University
[4]Insemine Centro de Reproducao Humana
[5]Centro Iberoamericano de Reproducción Asistida, Jones institute for Reproductive Medicine

METHODS · Criteria

- Exclusion criteria

- Inclusion criteria
  - Not exclusion criteria

  - minimum practice of 2-4 hs/week
  - VO_2max ≥ 40 ml/min/kg } PA group

  - not practicing any physical activity
  - VO_2max < 40 ml/min/kg } SE group

METHODS · Subjects

	Sedentary	Physically Active
Subjects	15	16
Age (years)	19.0 ± 1.8	19.2 ± 1.9
Weight (kg)	73.1 ± 8.3	73.8 ± 9.1
Height (cm)	175.9 ± 4.2	176.14± 5.2
Body fat (%)	15.6 ± 3.0	13.2 ± 3.5
VO2max (ml/min/kg)	36.9 ± 3.2	51.1 ± 4.9

RESULTS

	Sedentary	Physically Active	
% Type "a+b" Velocity	56.7 ± 4.5	60.94 ± 5.03	***P* < 0.05**
% normal forms (morphology)	14.40 ± 1.15	15.54 ± 1.38	***P* < 0.05**

Unpaired student T-test
Values are Mean and Standard Deviation

CONCLUSION

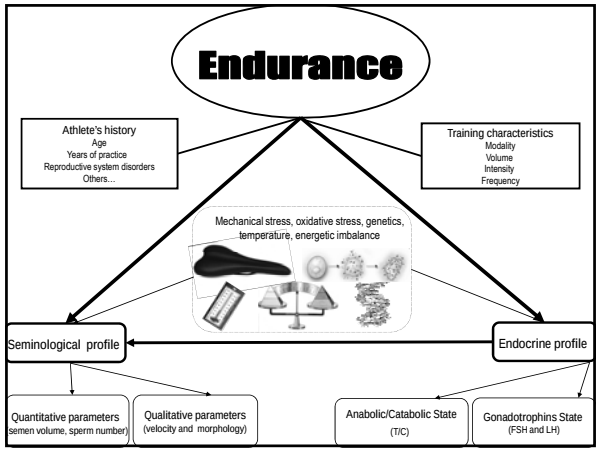
Moderate exercise seems to benefit endocrine and sperm production processes with regards to sedentary subjects

- Regular endurance exercise
  - Catabolic and stress-related hormones (Haber et al. 1997b, Rivier & Rivest 1991, Sussh et al. 1988)
  - Anabolic hormones
- Moderate exercise favors a more anabolic state

What's happening?

High-load physical exercise, seems to interfere with endocrine and spermatogenic processes

Manna et al. (2004): exercise alters sperm cell lineages and antioxidant enzymes. Antioxidant administration



TAKE HOME MESSAGE AND CHALLENGES

- Moderate exercise seems to improve hormonal milieu and semen
- High-load exercise (volume/intensity) may have adverse effects
  - Key mechanism
  - How to palliate
    - Antioxidants
    - Training modification

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Many thanks…

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Mark your calendar for the upcoming ESHRE campus workshops!

- Early pregnancy disorders: integrating clinical, immunological and epidemiological aspects
  23-26 August 2011 - Copenhagen, Denmark
- The management of infertility – training workshop for junior doctors, paramedicals and embryologists
  7-8 September 2011 - St. Petersburg, Russia
- Basic genetics for ART practitioners
  9 September 2011 - Bucharest, Romania
- The whole man
  22-23 September 2011 - Sevilla, Spain
- Accreditation of a Preimplantation Genetic Diagnosis Laboratory
  3-4 October 2011 - Athens, Greece
- Human reproductive tissues, gametes and embryos: Innovations by science-driven culture and preservation systems
  9 October 2011 - Cairns, Australia
- Comprehensive preimplantation screening: dynamics and ethics
  13-14 October 2011 - Maastricht, The Netherlands
- Endometriosis and IVF
  28-29 October 2011 - Rome, Italy
- Endoscopy in reproductive medicine
  23-25 November 2011 - Leuven, Belgium
- What you always wanted to know about polycystic ovary syndrome
  8-10 December 2011 - Sofia, Bulgaria

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