eshre
SCIENCE MOVING
PEOPLE
MOVING SCIENCE

Men in the middle

Paramedical Group

1

1 July 2012
Istanbul, Turkey

Men in the middle

Istanbul, Turkey
1 July 2012

Organised by
The ESHRE Paramedical Group

Contents

Course coordinators

Jolieneke Schoonenberg-Pomper (The Netherlands) and Helle Bendtsen (Denmark)

Course description

An advanced course for nurses and lab technicians focussing on the different aspects of male infertility.

Target audience

Nurses and lab technicians.

Scientific programme

Chair: Jolieneke Schoonenberg-Pomper (The Netherlands) / Co-chair: Helle Bendtsen (Denmark)

09.00 – 09.10	Introduction - **Jolieneke Schoonenberg-Pomper (The Netherlands)**
09.10 – 09.40	Diagnosing and treatment of male infertility – Elisabeth Carlsen (Denmark)
09.40 – 10.10	Sperm quality (WHO guidelines, ESHRE SIGA recommendations and European directive on tissue banking – **Lars Bjorndahl (Sweden)**
10.10 – 10.30	Discussion
10.30 – 11.00	Coffee break
11.00 – 11.35	Psychological aspects of male infertility (incl. sexuality and fertility Treatment) – **Tewes Wischmann (Germany)**
11.35 – 12.10	Sexual dysfunction in young males - **Maarten Albersen (Belgium)**
12.10 – 12.30	Discussion
12.30 – 13.30	Lunch
13:30 – 14:05	Nurses performing surgical sperm retrieval -**Heidi Birch (United Kingdom)**
14:05 – 14:40	Lab technicians performing IMSI - **Lucy Steiner (Austria)**
14:40 – 15.00	Discussion
15.00 – 15.30	Coffee break
15.30 – 16:00	Sperm quality and fertility – the clinical implications of environmental factors – **Martin Blomberg Jensen (Denmark)**
16:00 – 16:30	Banking sperm for men with cancer – **Allan Pacey (United Kingdom)**
16:30 – 17:00	Discussion

ESHRE – European Society of Human Reproduction and Embryology
By Jolieneke Schoonenberg-Pomper

What is ESHRE?

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

- promote interest in, and understanding of, reproductive science and medicine.
- facilitate research and dissemination of research findings in human reproduction and embryology to the general public, scientists, clinicians and patient associations.
- inform politicians and 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

The Paramedical Group (1/3)

The ESHRE Paramedical Group was established to assemble nurses, laboratory technicians and other support personnel active in the field of reproductive medicine and science.

The group serves as a platform for paramedics and organises specific sessions during the Annual Meeting and workshops.

ESHRE is one of the only organisations with a forum for paramedicals, who are represented in the Executive Board by Jolieneke Schoonenberg-Pomper.

The Paramedical Group (2/3)

- Established in 1987
- Meets 3 times a year
- Board Members:
  Jolieneke Schoonenberg-Pomper (chair)
  Heidi Van Ranst (past chair)
  Helle Bendtsen (chairman elect)
  Eline Dancet
  Inge Rose Jorgensen
  Helen J. Kendrew
  Cecilia Westin
  Uschi Van den Broeck

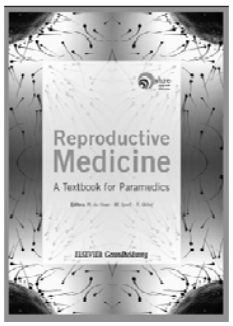
Paramedical Group (3/3)

- Nurses/Midwives
- Laboratory technicians
- Counsellors/Psychologists
- ESHRE certified clinical embryologists (Bsc level)

ESHRE Book for Paramedicals

ESHRE Book for Paramedicals

- First English textbook in Europe
- Free copy for every paramedical member
- Order it now - ask a member of staff



www.eshre.eu

ESHRE Campus 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 Journals

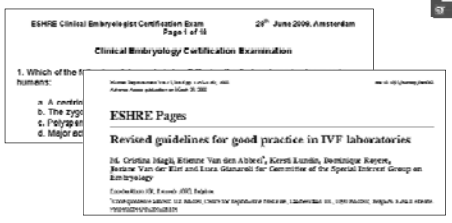
Human Reproduction with impact factor 4.357

Human Reproduction Update with impact factor 8.755

Molecular Human Reproduction with impact factor 3.506

ESHRE Activities

- Embryology Certification
- Guidelines
- Position papers



ESHRE COMMUNITY

RSS feeds for news in reproductive medicine

Since launch 12/2009: **1,927 Fans**

Since launch 12/2009: **434 Followers** (journalists, scientific organisations, patient societies, governmental bodies)

Retweets to MHR

Find a member

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

Paramedical Membership (1/3)

	ESHRE Members	Paramedical Members	%
2009	5.541	545	9,8
2010	5.659	596	10,5
2011	5.480	604	11,0
2012	5.664	644	11,4

Paramedical Membership (2/3)

	1 yr	3 yrs
Paramedical Member	€ 30	€ 90

1) Reduced registration fees* for all ESHRE activities:

Annual Meeting	€ 240	(€ 360)
General Workshops	€ 150	(€ 250)
Paramedical Workshops	€ 100	(€ 150)

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

* fees may vary

*fees may vary

ESHRE Membership – Benefits (3/3)

3) ESHRE Book for Paramedicals
- First English textbook in Europe
- Free copy for every paramedical member

4) ESHRE monthly e-newsletter

5) News Magazine 'Focus on Reproduction'

6) Paramedical Website 'Members only' access

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

Paramedical Group – Future Activities

Bringing evidence based innovations to your clinic

Leuven – Belgium 7 and 8 February 2013

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 2011 – Stockholm: 8,316 participants
ESHRE 2010 – Rome: 9,204
ESHRE 2009 – Amsterdam: 8,055

Future meetings:

ESHRE 2012 – Istanbul, 1-4 July 2012
ESHRE 2013 – London, 7-10 July 2013
ESHRE 2014 – Munich, 29 June-2 July 2014

ESHRE 2012, Istanbul, Turkey

When: **1 - 4 July 2012**
Where: **Istanbul Congress Centre, ICC**

Chair of conference: **Timur Gürgan**

Hotel and Travel:
Figür Congress Organisation
Mrs. Ebru Ersan
Tel: +90 212 381 46 38
Email: **ebruersan@figur.net**

For updates visit www.eshre.eu

Annual Meeting – Paramedical Programme

Sunday 1 July
Pre-Congress Course: Men in the middle

An advanced course for nurses and lab technicians focussing on the different aspects of male fertility

Annual Meeting – Paramedical Programme

Monday 2 July

11:45-12:45 Invited Session Nursing:
Female health care professionals in fertility services in Turkey
Ayse Aytoz (TK)

Psychosocial outcomes of IVF mothers during pregnancy and after delivery Eleanor Lowndes Stevenson (US)

Paramedical Oral Communication Sessions:
14:00-15:00 and 17:00-18:00

Annual Meeting – Paramedical Programme

Tuesday 3 July

08:30-09:30 Invited Session Laboratory:

The value of non-human primates as a model for human IVF Pierre Comizzoli (USA)

Do embryos talk to each other? Lessons from the bovine embryo model Ann van Soom (BE)

Annual Meeting – Paramedical Programme

Wednesday 4 July

14:00-15:00 Invited Session Nursing:
Midwifery research on the implementation of preconception care Ilse Delbaere (BE)

Establishing an online network for patients with recurrent pregnancy loss Lisbeth Egestad (DK)

Paramedical AGM

Monday 2 July at lunch

Yves Guns

Leonie van den Hoven

Contact

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

Male infertility - Diagnosis and treatment

Elisabeth Carlsen, M.D.
The Fertility Clinic, Rigshospitalet
Copenhagen, Denmark

Disclosures

I have no commercial and/or financial relationships with manufactures of pharmaceuticals, laboratory supplies and/or medical devices

Learning objectives

- When should male infertility be expected
- Confounders in the evaluation of semen quality
- Andrological examination- to whom and how
- Causes of male infertility
- Treatment of male infertility

Examination for male infertility

When should male infertility be expected?

- inability to conceive for more than 1 year
- a history or maldescensus or other urogenital disorders
- previous or current cancer treatment
- certain genetic disorders
- abuse of anabolic steroids

Evaluation of semen quality

- Analysis of 1-2 semen samples
- Semen analysis according to 2010 WHO guidelines:

lower cut-off values:

Semen volume	≥1,5 ml
Sperm concentration	≥ 15 mill/ml
Total sperm count	≥ 39 mill
Motile	≥ 40%
Progressive motile	≥ 32%
Morphology	≥ 4% (strict criteria)

WHO 2010

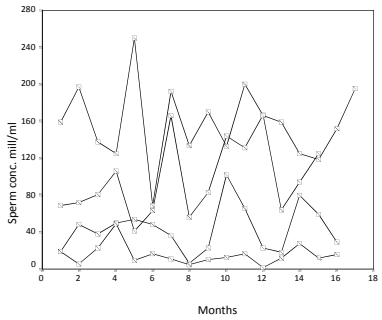
Intra-individual variations in semen parameters

Monthly semen samples from 27 men (median age 24.4) years for 17 months.

Intra-individual variation:

- Sperm concentration 61,9%
- Sperm motility 30,7%
- Sperm morphology 10.4%

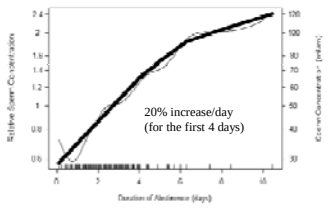
Carlsen et al. 2003



Potential confounders in the evaluation of semen quality

- Duration of abstinence
- Fever
- Ejaculatory frequency
- Other factors (medicine, stress)

Effect of duration of abstinence on sperm concentration



Carlsen et al 2005

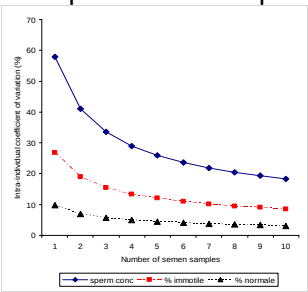
Effect of fever on semen quality

	Fever during mitotic proliferation (day –80 to -57)	Fever during meiotic division (day –56 to -33)	Fever during spermiogenesis (day –32 to -9)	Fever during sperm maturation (day -8 to 0)
Sperm concentration	5.5 (-21.7; 42.0) p=0.726	**-32.6 (-49.9; -9.2) p=0.010**	**-35.0 (-50.5; -14.6) p=0.002**	-0.3 (-38.7; 51.9) p=0.877
% normal spermatozoa	-2.8 (-7.5; 2.2) p=0.269	-4.3 (-9.0; 0.6) p=0.084	**-7.4 (-11.6; -3.0) p=0.001**	-1.4 (-8.7; 6.6) p=0.730
% immotile spermatozoa	2.7 (-10.5; 17.9) p=0.702	-6.4 (-18.7; 7.7) p=0.355	**20.4 (6.0; 36.8) p=0.004**	2.0 (-17.5; 26.1) p=0.856

% and 95% confidence interval

Carlsen et al 2003

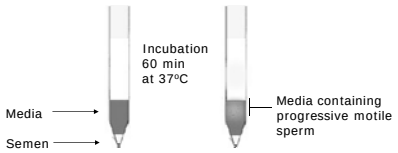
Intra-individual variation: effect of multiple semen samples



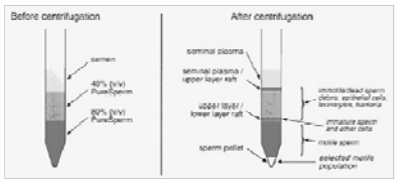
Diagnostic semen analysis

- Swim-up test
- Density gradient centrifugation

Swim-Up test



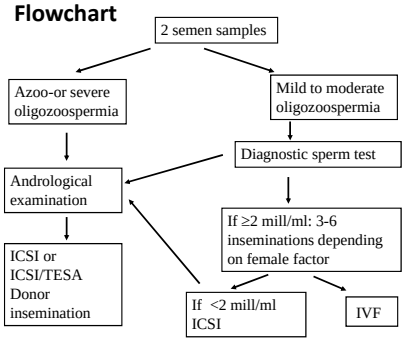
Density gradient centrifugation



Definitions

- Aspermia: no ejaculate
- Azoospermia: no spermatozoa in the ejaculate
- Oligozoospermia: less than normal number of spermatozoa in the ejaculate (<15 mill/ml)

Flowchart



Causes of male infertility

- Compromised sperm production
- Obstruction of sperm ducts
- Ejaculatory dysfunction
- Exogenous causes

Compromised sperm production

- Hormonal problems
  - Defect in GnRH release (Kallmann´s syndrome)
  - Pituitary tumors or hæmochromatosis
- Testicular dysfunction
  - Idiopathic
  - associated with maldescensus of the testis
- Genetic disorders
- Acquired disorders
  - Trauma/orchitis
  - Torsion of the testicle
  - Exogenous factors

Genetic disorders

- Klinefelter Syndrome (47, XXY)
- Chromosomal translocations
- Androgen receptor gen mutations
- Y chromosome microdeletions

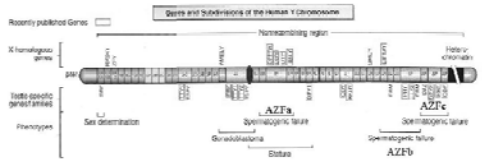
Klinefelter syndrome (47,XXY)

- 0,2% of newborn boys
- 11% of men with non-obstructive azoospermia
- small testes < 5 ml and often azoospermi
- Decreased virilisation
- hypergonadotropic hypogonadism

Y chromosome microdeletions

- Frequency:
  - 10% of men with non-obstructive azoospermi and 6% of men with severe oligozoospermia (ESHRE Capri Workshop Group, Hum Reprod Update 2007)
- Localization:
  - 3 AZF regions on Yq: AZFa, AZFb andAZFc
  - Newer modifications of the original classification including b2/b4 and gr/gr

The human Y chromosome



Lahn and Page, 1997

Obstructions of sperm ducts

- Previous genital infections
  - Chlamydia, gonorrhea
- Urogenital surgery
  - Vasectomy, reconstructive surgery
- Congenital aplasia of sperm ducts
  - Cystic fibrosis or cystic fibrosis gen mutations

Ejaculatory disorders

- Retrograde ejaculation
  - Neuropathy in diabetes
  - Previous pelvic or prostatic surgery
- Anejaculation
  - Neuropathy

Andrological examination

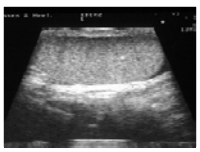
- Clinical examination
  - history
  - objective examination
  - ultrasound scan of the testis
- Laboratory tests
  - semen samples
  - Hormone analyses
  - Genetic analyses
- Diagnostic testicular biopsy in certain cases

History

- Previous maldescensus
- Infections/surgery
- Previous conceptions
- Medication

Objective examination

- Virilization
- Testicular size and location
- Ducts and epididymis
- Ultrasound scan



Laboratory tests

- Semen analysis
  - Urine analysis for retrograde ejaculation
- Hormone analysis
  - Inhibin B / FSH
  - LH
  - Testosterone
- Genetic analysis
  - Chromosome analysis
  - Y chromosome microdeletion analysis

Treatment of male infertility

- Elimination of environment and lifestyle factors
- Medical treatment
- Surgical treatment
- Assisted reproduction

Medical treatment

- Gonadotrophins (FSH/LH):
  - Hypogonadotropic hypogonadism (i.e. Kallmann Syndrome)
  - No evidence for an effect in case of testicular dysfunction
- Bromocriptine
  - Prolactinoma
- Tricyclic antidepressant agent (Imipramine®)
  - Retrograde ejaculation (caused by neuropathy)

Surgical treatment

- Re-fertilization
- Surgery for varicocele
- Surgery for prostatic cysts
- Testicular sperm extraction

Assisted reproduction

- Intrauterine insemination
  - Husbands semen
  - Donor semen
- In vitro fertilization
  - IVF
  - ICSI
- Obstructive azoospermia and in certain cases also non-obstructive azoospermia
  - TESA
  - PESA
- Pre-implantation gen analysis (PGD)

References

- WHO laboratory manual for the examination and processing of human semen (World Health Organization,2010)
- Carlsen, E, Andersson, A-M, Petersen, JH, Skakkebaek, NE (2003) History of febrile illness and variation in semen quality. Hum Reprod 18; 2089-2092.
- Carlsen, E. Swan, SH, Petersen, JH, Skakkebaek, NE (2005) Longitudinal changes in semen parameters in young Danish men from the Copenhagen area. Hum Reprod 20; 942-949.
- Intracytoplasmic sperm injection (ICSI) in 2006: evidence and evolution. Hum Reprod Update 2007;13; 515-26.
- Lahn, BT, Page DC (1997) Functional coherence of the human Y chromosome. Science 278; 675-80.

Sperm quality
- WHO guidelines
- ESHRE SIGA recommendations
- European directive on tissue banking

Lars Björndahl, MD PhD
Senior Consultant Laboratory Physician
Andrology Laboratory
Karolinska University Hospital, Huddinge, Stockholm, Sweden

July 1, 2012

Karolinska Institutet | KAROLINSKA

Declation of possible conflicts of interest

- I have no economical or financial interests in commmercial products or companies related to the topics of this presentation
- As an active member of SIG Andrology, working with the development of the Basic Semen Analysis Course and the External Quality Assurance Programme, I have co-authored a laboratory handbook based on WHO and ESHRE SIGA recommendations
  - *A Practical Guide to Basic Laboratory Andrology, Cambridge University Press, 2010*.

Learning Objectives

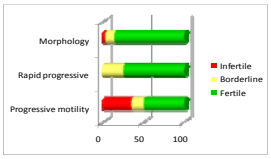
- A short introduction to male infertility and semen analysis
- New WHO manual
  - What is the main message?
  - What is new?
  - What is misunderstood?
- ESHRE-SIGA recommendations
  - Relation to WHO manual
  - Where are the main differences?
  - What can ESHRE-SIGA help with
- The EU directives on Cells and Tissues
  - Why are they here?
  - What is the impact on
    - Sperm preparation?
    - Sperm and testicular tissue cryopreservation?

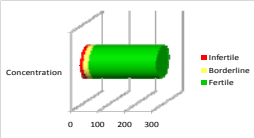
Fertility problems are different from all other disorders

ESHRE SIGA – Course on Basic Semen Analysis

What can be predicted from semen?

- There are not exact ”cut-offs”
  - Huge physiological (normal) variation
  - Overlapping distributions subfertile/fertile





- Correlation cf. Predictive Value
  - Comparison of groups vs. Estimate a couples chances

When is fertility really affected?


The New England Journal of Medicine

SPERM MORPHOLOGY, MOTILITY, AND CONCENTRATION IN FERTILE AND INFERTILE MEN

N Engl J Med 2001, 345: 1388-1393

Prediction of spontaneous conception based on semen parameters

Piotr Jedrzejczak,* Grazyna Taszarek-Hauke,* Jan Hauke,† Leszek Pawelczyk* and Antoni J. Duleba‡

*Division of Infertility and Reproductive Endocrinology, Poznan University of Medical Sciences, Poznan, †Institute of Spatial Management, Adam Mickiewicz University, Poznan, Poland, and ‡Department of Obstetrics and Gynecology, Yale University School of Medicine, New Haven, CT, USA

Int J Androl 2008: 31(5): 499-507

Summary: base semen analysis conclusions on a combination of several characterstics!

The WHO laboratory manual 2010

- Quality in semen analysis – *not controversial*
  - Awareness of sources of errors
  - Awareness of robust methods
  - Awareness of reliable equipment and materials
  - Standardization as a necessary step in quality development
- Reference limits – *highly controversial*
  - What is the problem with the suggested limits?

Semen Analysis Methods and Reference limits

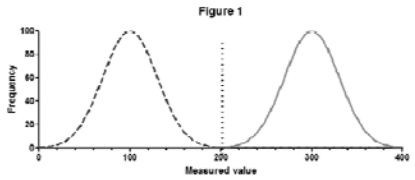
- Historical survey
  - John MacLeod – 1950
  - Rune Eliasson – 1970
  - WHO – 1980, 1987, 1992, 1999, 2010
  - David Mortimer – 1994
  - NAFA and ESHRE-SIGA – 1997/2002 (2010)
- Problems with the limits of WHO?
  - Recent fathers – **no men in subfertile couples**
  - Sharp limits are impossible – **unscientific and clinically unfair (unethical!)**

What is written in the WHO manual?

- Statistical tradition – a reference limit is a
  - threshold below which values are **not likely** to come from men in the reference population
  - But since the couple came to the clinic due to infertility we ALREADY KNOW THAT THE MAN IS NOT A RECENT FATHER!
  - **Therefore the WHO reference limits do not increase the "science" in male factor assessment.**

Three examples of reference ranges

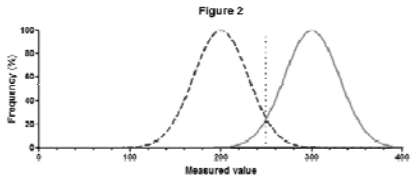
– Is the patient subfertile orfertile?



Björndahl: What is normal semen? On the use and abuse of reference ranges. Human Fertility 2011.

Three examples of reference ranges

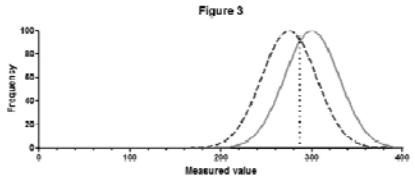
– Is the patient subfertile or infertile?



Björndahl: What is normal semen? On the use and abuse of reference ranges. Human Fertility 2011.

Three examples of reference ranges

– Is the patient subfertile or infertile?

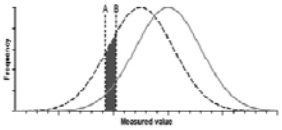


Björndahl: What is normal semen? On the use and abuse of reference ranges. Human Fertility 2011.

Interpretation of Laboratory Results

- WHO reference limits
  - Only from recent fathers
    - No data on men in subfertile couples
    - No change in biology or pathology
      - Men who were earlier "below" limits have not become more "fertile" just because WHO publish new data on recent fathers
    - A shifted decision limit based on WHO5 will mean that many men may be denied andrological investigation and evaluation.

Björndahl: What is normal semen? On the use and abuse of reference ranges. Human Fertility 2011.



ESHRE-SIGA recommendations 2011

- Follow WHO recommendations with a few changes
  - Maintained or Increased quality
  - Decreased or marginally increased workload
  - Ability to obtain data pertinent to ART laboratories
  - Avoid errors in the present edition of the WHO manual

ESHRE-SIGA recommendations

- Maintain assessment of four motility groups
  - Rapid, slow, non-progressive and immotile
    - Lack of rapid progressive sperm: strong negative factor for IVF-success
- Record all aspects of the morphology assessment and include in report
  - head, neck/midpiece, tail, and cytoplasmic residue
  - always calculate TZI (Teratozoospermia index) in addition to %Normal (or rather **%Typical** (morphology typical for sperm that can reach the site of fertilization)

ESHRE-SIGA recommendations

- Avoid *misleading nomenclature*
  - Oligozoospermia – give the number of sperm!
  - Asthenazoospermia – give the distribution in four motility categories
  - Teratozoospermia – give the % Typical and TZI
- Use only **ONE** method, staining etc
- Vitality staining only when *very few motile sperm*:
  - *WHO cut-off* when to use vitality test is not based on presence of immotile cells
  - WHO method to assess vitality is *not validated*

ESHRE-SIGA recommendations

- Avoid *unnecessary work*
  - Duplicate readings of morphology and vitality
  - Assessment of low sperm concentrations
    - See A Practical Guide to Basic Laboratory Andrology.
- Avoid *centrifugation* of all semen samples – first dilute
- Gradient centrifugation section contains *errors*
- *Don't use* WHO reference limits
  - Use a "three-level scale"

ESHRE-SIGA recommendations

Practical Guide to Basic Laboratory Andrology, Cambridge University Press, 2010

Characteristic	Units	Normal	Borderline	Pathological
Volume	ml	2.0–6.0	1.5–1.9	<1.5
Sperm concentration	10^6/ml	20–250	10–20	<10
Total sperm count	10^6/ejaculate	≥80	20–79	<20
Motility	% motile	≥60	40–59	<40
	% progressive	≥50	35–49	<35
	% rapid	≥25		
	progression grade	3 or 4	2	1 or 0
Morphology	% typical forms	≥14	4–13	<4
	TZI	≤1.60	1.61–1.80	>1.80
Vitality	% live (vital)	≥60	40–59	<40
Leukocytes	10^6/ml			>1.0
Antisperm antibodies	% binding	<50	50–79	≥80

ESHRE-SIGA offers to help…

- **Basic Semen Analysis Course**
  - 4½ day course with seminars and repeated practical training
  - Courses in English given in Stockholm and in Birmingham
  - All regions within the EU can get support (material and advice) to set up courses in local language
- **External Quality Assurance Scheme**
  - Testing the *four basic semen analysis techniques*
  - Providing service to *regions lacking* own schemes
  - Enabling regional schemes to *collaborate and harmonize*
- Contact **Lars.Bjorndahl@ki.se**

EU directives on Cells and Tissues

- **To protect donors and recipients of cells and tissues**
  - Testing before donation
  - Traceability after donation – up to 30 years
    - Media, critical equipment, medical problems for donors and recipients.
  - Competent Authorities and Tissue Establishments
    - Annual Reports
    - Reports on acute problems
- **To increase the availability of cells and tissues**
  - Spermatozoa and oocytes
  - Simplify distribution within the EU

EU directives on Cells and Tissues

- Gametes and embryos dominate quantitatively over all other types of cells and tissues
- Both man and woman are donors
  - Woman is the only recipient (of the embryo)
- The directives protect DONORS and RECIPIENTS, not the EMBRYO?
- Only when spermatozoa are **processed** or **stored**
  - IUI with spermatozoa that have not been processed is not included under the Directives
- All cells and tissues obtained directly from *epididymis* or *testis* is under the Directives

EU directives on Cells and Tissues

- Documented organization (Tissue Establishment)
- Documented routines (lots of…)
  - All operating procedures
    - Administration: donation, controls, documentation, signing etc
    - Laboratory: procurement, processing, testing, storage, distribution, and transport
  - Most demanding: storage of all *critical* data for 30 years traceability
    - Computer software may help
      - Will there be computers in the future that can read today's software and databases?

EU directives on Cells and Tissues

- *A summary of the results of a questionnaire on IT tools sent out to all members of SIGE and SIGA will be presented here at the meeting (responses are still coming in and therefore asummary is not yet available)*

thank you for your attention

Lars Björndahl, M.D. Ph.D. **Lars.Bjorndahl@ki.se**
Senior Consultant Laboratory Physician
Andrology Laboratory
Karolinska University Hospital, Huddinge, Stockholm, Sweden

References

L 102/48 EN Official Journal of the European Union 7.4.2004

DIRECTIVE 2004/23/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL
of 31 March 2004
on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells

L 38/40 EN Official Journal of the European Union 9.2.2006

COMMISSION DIRECTIVE 2006/17/EC
of 8 February 2006
implementing Directive 2004/23/EC of the European Parliament and of the Council as regards certain technical requirements for the donation, procurement and testing of human tissues and cells

L 294/32 EN Official Journal of the European Union 25.10.2006

COMMISSION DIRECTIVE 2006/86/EC
of 24 October 2006
implementing Directive 2004/23/EC of the European Parliament and of the Council as regards traceability requirements, notification of serious adverse reactions and events and certain technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells

References

– WHO 2010:
- http://www.who.int/reproductivehealth/publications/infertility/9789241547789/en/

– ESHRE-SIGA recommedations
- Barratt et al. (2011). Hum Reprod 26(12): 3207-3212.
- (2010). A Practical Guide to Basic Laboratory Andrology. Cambridge University Press.

– EU Directives 2004/23, 2006/17, and 2006/86
- http://eur-lex.europa.eu/Result.do?T1=V3&T2=2004&T3=23&RechType=RECH_naturel&Submit=Search
- http://eur-lex.europa.eu/Result.do?T1=V3&T2=2006&T3=17&RechType=RECH_naturel&Submit=Search
- http://eur-lex.europa.eu/Result.do?T1=V3&T2=2006&T3=86&RechType=RECH_naturel&Submit=Search

References

- Björndahl (2011). "What is normal semen quality? On the use and abuse of reference limits for the interpretation of semen analysis results." Hum Fertil (Camb) 14(3): 179-186.
- Guzick et al. (2001). "Sperm morphology, motility, and concen-tration in fertile and infertile men." N Engl J Med 345: 1388-1393.
- Jedrzejczak et al. (2008). "Prediction of spontaneous conception based on semen parameters." Int J Androl 31(5): 499-507.

UniversityHospital Heidelberg

Psychological aspects of male infertility (incl. sexuality and fertility treatment)

PD Dr. Dipl-Psych. Tewes Wischmann

Institute of Medical Psychology
Center for Psychosocial Medicine
Heidelberg, Germany

tewes.wischmann@med.uni-heidelberg.de

ESHRE
Istanbul (Turkey)
1 July 2012

Objectives

- ✓ Understanding of the psychological impact of infertility and of assisted reproductive technologies on men
- ✓ Knowledge of methodological considerations concerning studies on infertile men
- ✓ How to make infertility counselling more attractive for men
- ✓ Basic knowledge of special topics in counselling men

Introduction

A literature review showed that of 121 papers on infertility (published 1948-1985), 56% referred to women solely, 29% to both partners and only 15% exclusively to the man (Bents 1985)

In a well-known study, 49% of women but only 15% of men considered infertility the most upsetting experience of their lives (Freeman et al. 1987)

For 72.5% of the women and 61.8% of the men, psychological counselling as an aid to coping with involuntary childlessness was considered a viable proposition ($P < 0.001$) (Wischmann et al. 2001)

Childbearing intentions and births by couple desire

Couple Desires to Have Child	Percentage	Mean Intention Score[a] Wife	Husband	Percentage Had Child
Both No	21.1	1.51	1.58	13.0
Husband Yes	8.8	2.41	3.45	32.4
Wife Yes	10.0	3.60	2.59	30.1
Both Yes	60.1	5.87	5.87	66.8
All Couples	100.0	4.42	4.42	48.8

Source: National Survey of Families and Households, 1988–1993.

Notes: Married couples, neither sterilized, wife not pregnant and under 40 years old in 1988, no children from prior relationships, both spouses participated at NSFH1, at least one spouse responded at NSFH2; valid data for all variables in subsequent models ($N = 1,143$). Distributions are weighted to adjust for the NSFH sampling design and differential response rates.

[a]Intention score ranges from 1 (very sure intend not to have a child) to 7 (very sure intend to have a child).

(Thomson 1997, p. 347)

Key questions

1. *Do men suffer from infertility less than women or do they suffer at all* ("sturdy oaks")*?*
2. *What is the psychological impact of male factor infertility on men* ("shooting blanks")*?*

Methodological considerations (I)

The results of much of the available research supporting women's greater overt distress in response to infertility may well reflect differences in the ways in which men and women have been socialized to cope with negative affect

(Webb & Daniluk 1999)

The claim women react more adversely to infertility than their partners is overly influenced by outdated gender stereotyping and is unsupported by research data

(Edelmann & Connolly 2000, Fisher et al. 2010)

It is obvious that the introduction of ICSI has revolutionized the treatment of male factor infertility and thereby probably also improved the psychological well-being of males

(Holter et al. 2007)

Methodological considerations (II)

- Men may be more inclined to deny psychopathology
- Men and women may respond in different ways to stress, e. g. alcohol use or depression
- Any gender differences may reflect more general differences in response to stress rather than being specific to infertility (Edelmann & Connolly 2000)
- With statistical approaches that keep matched pairs, differences between men and women are much smaller than testing the samples as independent groups (Chamarnovich et al. 2009, Fisher & Hammarberg 2012)

Stigmatisation of male factor infertility

To be diagnosed with male factor infertility may result in secrecy surrounding diagnosis, sometimes to the point that women take the blame for the couples' infertility (Carmeli & Birenbaum-Carmeli 1994; van Balen 1996)

The relatives of the (formerly) infertile woman are more likely to be informed about successful treatment with donor insemination than the relatives of the man (Wischmann 2010)

Media reports on "the sperm decline" construct stereotypical masculinity and conflate male infertility with impotence (Gannon et al. 2004; q .v. Mikkelsen et al. 2010)

Stigmatisation of male infertility: a cohort effect?

In a study on 256 Danish infertile men the COMPI group found out that men with male factor infertility did not suffer more then man with infertility due to other causes

Most men in this study, including those with male factor infertility, were open about their fertility problems

Across all diagnostic groups, suffering increased over time when treatment was not successful indicating that suffering was not specific to male factor diagnosis or disproportionate for this group (Peronace et al. 2007, Fisher et al. 2010)

Social support and male factor infertility

When men are affected by infertility, the unfulfilled desire for a child and sexual dysfunction are often believed to be synonymous. (“You want me to pay your wife a little visit? This is a job for a real man!”) (Miall 1986; Throsby & Gill 2004)

Women with fertility problems tend to be pitied, whereas men are more likely to encounter insulting slurs on their manhood (Nachtigall et al. 1992, Lee 2003)

Medical treatment and male factor infertility

"Even the routine male fertility test is not a purely medical act, but has strong sexual connotations since it involves masturbation" (Meerabeau 1991, p. 405)

Religious beliefs might interfere with masturbation (Lee 2003, p. 77)

Among 210 men undergoing ICSI treatment, the ICSI procedure per se was not important for the perception of fatherhood. In 37% of the participants the reduced sperm quality negatively affected their perception of masculinity (Mikkelsen et al. 2010, p. i51)

Sexual disorders in infertile men

When an andrological factor is the sole cause of infertility, male probands in a recent study report appreciable impairments to their personal and sexual life quality even if they already have children (Smith et al. 2009)

A study on 206 infertile couples (compared to 190 fertile couples) could show that diagnosed male infertility correlated with the lowest average intimate life satisfaction, both in the groups of women and men (Drosdzol et al. 2009)

As many as 45.4% of 487 men interviewed at a reproductive medicine clinic reported that sex "by the clock" (timed intercourse) is stressful (Grieb et al. 1997)

After hearing the diagnosis, five out of 51 couples reported an „acute midcycle sexual dysfunction in the male partner“

(Drake & Grundet 1979, p. 542)

Every 9th of the subjects was unable to produce the sperm needed for a second semen analysis after having been told about sperm quality deficits identified in the first

(Saleh et al. 2003)

In one of 500 cases men are unable to produce a sperm probe before IVF (resulting in cycle cancellation)

(Emery et al. 2004)

More than twice as many men as in the overall population suffer from erectile dysfunctions. According to some studies, premature ejaculation is two to three times more common in infertile men than in the general population

(Shindel et al. 2008, Gurkan et al. 2009)

New onset erectile dysfunctions were reported by 26% of men after unsuccessful TESE compared with 0.4% of men in a group after successful TESE (Akbal et al. 2010)

Infertility treatment and counselling

Only 3 out of 51 studies concerning patients' perspective on fertility care had focused specifically on men's experience (Dancet et al. 2010)

Mental health support is sought by – and offered predominantly to – women

Although infertility is a couple problem, men and women generally experience treatment as observer and participant, respectively (the "patient's husband")

Man in particular indicate that they believe they can overcome their feelings alone (O'Donnell 2007)

Preparatory information: booklets

This factor would improve knowledge of and passage through an IVF cycle:	Women (n = 117)	Men (n = 101)
• Booklet of information about practical aspects	54%	50%
• Video about IVF	22%	**36%**
• Booklet about psychological aspects of IVF	39%	34%
• Bibliography about IVF	24%	29%
• Meetings with a psychologist	26%	22%
• Discussion group	24%	**8%**
• Information meeting with other couples	13%	13%

(Laffont & Edelmann 1994)

Expectations towards psychosocial support

Considered the professional psychosocial services as important	Women (n = 1169)		Men (n = 1081)	
• Course about childlessness	14.3%	13.9%	8.6%	8.9%
• Professionally led support group	11.7%	10.0%	5.4%	4.1%
• Psychologist	20.8%	18.7%	8.3%	7.5%
• Sex therapist	10.7%	8.9%	6.6%	5.7%
Would participate if these services were available				

(Schmidt et al. 2003)

Sources of information and support used

Source of information	% used	Mean rating of usefulness
• Discussion with staff	81	**4.39**
• Brochures from clinic	82	**4.14**
• Internet	54	3.55
• Books	47	3.46
• Family and friends	46	**3.39**
• Support group	19	**2.60**
Source of support		
• Partner	96	**4.59**
• Clinic staff	66	**4.13**
• Family member/s	48	3.55
• Friend/s	43	3.41
• Support group	17	**2.72**

(Hammarberg et al., 2010)

Improving uptake of psychosocial counselling

- Introduce the psychologic support before the medical process ("orientation meeting")
- Make personal and direct contact with the patients
- Present counselling as an integral component of the infertility treatment
- Offer free support to all patients regardless of their cause of their infertility

=> About one-half of the male patients took up psychologic group counselling (only 3% in individual/couple setting)

(Furman et al. 2010)

Making infertility counselling attractive for men

- Provide pretreatment educational brochures (for men) to enhance the participation rate of men
- Explain the potential benefits of infertility counselling for both partners
- Testimonials that reflect typical male concerns about counselling may encourage men to seek mental health support (O'Donnell 2007)

Preparatory information: Booklets

In a group of 250 men enrolling for a fertility workup, mailing of a leaflat with preparatory information about this procedure was associated with lower distress scores and a higher attendance rate compared to a group of men who did not receive this leaflat (Pook & Krause 2005)

Pre-Counselling checklists

FertiQoL


Psychosoziale Beratung bei unerfülltem Kinderwunsch:
die BKiD-Checkliste für Paare

Liebes Paar mit Kinderwunsch,

ich als Kind zu wünschen und darauf lange warten zu müssen: das wird von vielen Frauen und vor allem Frauen als starke psychische Belastung wahrgenommen. Häufig wird der Kinderwunsch Anderen gegenüber verheimlicht, da das Thema immer noch tabuisiert ist. Wenn dazu noch eine aufwändige und auch nicht in jedem Fall erfolgreiche medizinische Behandlung hinzukommt, kann diese Situation selbst ein ansonsten emotional stabiles Paar an den Rand der Belastungsfähigkeit bringen. Spätestens jetzt sollten Sie sich überlegen, eine psychosoziale Kinderwunschberatung in Anspruch zu nehmen, wie sie von den Beratungsstellen von BKiD angeboten wird. Die folgende BKiD-Checkliste kann Ihnen helfen, ob Sie diese Beratung aufsuchen sollten:

- „Als Paar haben wir kein anderes Thema mehr als den Kinderwunsch und die medizinische Behandlung."
- „Wenn ich Schwangeren oder Frauen mit Babys begegne, meide ich am liebsten die Straßenseite wechseln, Familienfeste belasten mich inzwischen ob."
- „Ohne eigenes Kind empfinde ich mein Leben als sinnlos."
- „Da der Befund bei mir liegt, denke ich darüber nach, meinen Partnerin freizugeben, damit ihrem Kinderwunsch in neuer Partnerschaft erfüllt werden kann."
- „Wir haben uns vom früheren

What to consider in couple counselling

• Be careful about appearing to take sides or subtly praise the female client

• Address man's ambivalence about help seeking

• Address masculine/feminine socialisation (e.g. conflict between work life and family life)

• Address man's discomfort with emotions

• Accept that men usually need more time in identifying their emotions and finding words for it than women

(Englar-Carlson & Shepard 2005)

"Feeling guilty" is not the same as "being guilty"

Identify allocation of blame on man and replace it with "accepting my part of the responsibility for our common problem" (Petok 2006)

Change attribution errors and unfavourable coping styles

Change man's internal attribution ("I'm a failure") to external attribution ("This blow of fate is our challenge")

Strengthen active and meaning based coping styles, replace passive and avoidance coping styles

Normalization of „toxic" emotions

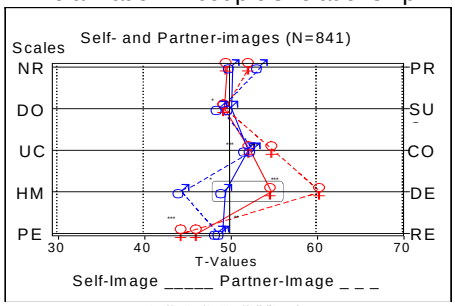
Regarding fathers-to-be with envy, or feelings of guilt due to the male factor, are common, comprehensible and acceptable.

Polarization

A woman may want to talk about her pain and sadness, her partner may feel helpless and withdraw.

This circular pattern can result in polarization and isolation, at a time where both partners need each other the most (Shapiro 2009, Van den Broeck et al. 2010)

Polarization in couple's relationship



* p<.05 ** p<.01 *** p<.001 (Self-Images)

NR=negative response DO=dominant UC=uncontrolled HM=hypomanic PE=permeable
PR=positive response SU=submissive CO=compulsive DE=depressive RE=retentive

(from: Wischmann et al. 2002)

Bring forward the couple's communication

Identify dysfunctional role allocations ("depressive woman – helpless man") and make them more flexible

Do men suffer from infertility? Yes!

In keeping with masculinity norms, many husbands tend to suppress their emotions in an effort to support their wives (Petok 2006)

Withdrawal might be a way of protecting the woman from her partner's pain (Cousineau & Domar 2007)

Your count is zero

"One in seven couples today have a problem with fertility. While medical techniques for helping some couples continue to advance, for others there is no hope. For those of us in the latter category it is an inexpressible nightmare punctuated with operative procedures, probing personal questions, and frightful expenses. It is also the death of a dream." (Boyd 1988, p. 4)

Men in Non-Western vs. Western societies

Table II Mean T scores among antenatal clinic with their partn

SCL-90-R scales	Study group[a]
Somatization	53.6 (11.6)
Obsessive compulsive	57.9 (11.4)
Interpersonal sensitivity	59.7 (10.8)
Depression	58.7 (10.3)
Anxiety	56.2 (11.9)
Anger—hostility	55.7 (10.9)
Phobic anxiety	58.2 (11.1)
Paranoid ideation	59.8 (10.0)
Psychotism	58.9 (10.5)
Global severity index	59.7 (10.7)
PSDI[c]	56.9 (10.7)
Positive symptom total	58.2 (9.0)

[a]Value are unadjusted mean T scores (SD); resi
[b]Confidence interval.
[c]PSDI = Positive Symptom Distress Index.

Dyer et al. 2010
© Human Reproduction

Table IV. Differences from reference population in Symptom Checklist (SCL-90-R)

Symptom Checklist 90-R Scales	Women ($n = 562$)	Men ($n = 539$)
Somatization	$51.9 \pm 12.2^{***}$	$51.4 \pm 11.5^{***}$
Obsessive/compulsive	50.3 ± 11.4	$48.9 \pm 10.1^{*}$
Interpersonal sensitivity	$51.1 \pm 11.8^{**}$	49.7 ± 11.5
Depression	$51.9 \pm 12.2^{***}$	49.3 ± 10.6
Anxiety	$52.7 \pm 13.4^{***}$	50.7 ± 10.7
Anger-hostility	$51.2 \pm 11.9^{**}$	50.8 ± 11.2
Phobic anxiety	$51.5 \pm 14.7^{***}$	50.1 ± 11.7
Paranoid ideation	50.8 ± 11.9	$50.9 \pm 11.8^{*}$
Global severity index	$51.1 \pm 12.7^{*}$	49.2 ± 11.7
Positive symptom distress index	$51.6 \pm 10.2^{***}$	49.7 ± 7.8
Positive symptom total index	$51.2 \pm 12.4^{**}$	50.6 ± 12.0

Values are mean ± SD.
$^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$; reference population: mean = 50, SD = 10.
Psychoticism scale disregarded.

Wischmann et al. 2001
© Human Reproduction

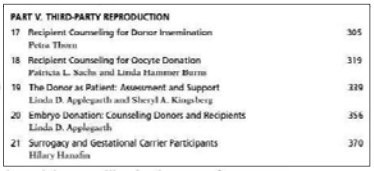
Male infertility: Impact of donor insemination

Counselling issues include managing the taboo, social stigma and legal uncertainties, the meanings attributed to the donor for the intended parents and the child, the donor's anonymity or identifiability as well as sharing the information with the child and significant others.

Human Fertility, June 2000; 12(2): 73-80

PSYCHOSOCIAL COUNSELLING

German guidelines for psychosocial counselling in the area of gamete donation



PART V. THIRD-PARTY REPRODUCTION

17	Recipient Counseling for Donor Insemination Petra Thorn	305
18	Recipient Counseling for Oocyte Donation Patricia L. Sachs and Linda Hammer Burns	319
19	The Donor as Patient: Assessment and Support Linda D. Applegarth and Sheryl A. Kingsberg	329
20	Embryo Donation: Counseling Donors and Recipients Linda D. Applegarth	356
21	Surrogacy and Gestational Carrier Participants Hilary Hanafin	370

(from: Covington & Hammer Burns 2006 ; Thorn & Wischmann 2009)

The position of the father after successful ART

Lesley and Louise Brown with her son Cameron and Professor Robert Edwards at Bourn Hall - 12 July 2008
© Bourn Hall

Counselling needs of fathers after ART

- The father of a son with congenital malformations after ICSI: Does he need psychosocial counselling?
- The father of 3-years old triplets after ART when all the social and financial resources have dried out: Does he need psychosocial counselling?
- The father of the adolescent girl after DI who has just given him a phone call that her blood test results revealed that he cannot be her biological father: Does he need psychosocial counselling?

Clinical experience says: Yes.
Research evidence says: We don‘t know.

Development of families after ART and DI

The “European Study of Assisted Reproduction Families” investigated 102 IVF families, 94 families after DI, 102 families after adoption and 102 families with spontanously conceived singletons.

Between the groups, there were no differences in the parent-child-relationship or in the various variables concerning the psychological development of the child

(Golombok et al. 1996, 2002, 2004)

Development studies: selection biases?

NB: The response rates in the primary “European Study” from 1996 were 76% for IVF families, 72% for families after adoption, just 65% for families with spontanously conceived singletons and only 47% for DI families

(Golombok et al. 1996; McWinnie 2001)

In the study on the DI adolescents (~18 years old), the response rate was 79% for mothers and 23% for fathers

(Owen & Golombok 2009)

"The culture has not yet provided positive examples of fathers of DI offspring, or images of strong father-child bonds in such families, as are now entering the media for same-sex parents" (Beeson et al. 2011, p. 8)

Long-term psychological effects of infertility

There are only small differences in the quality of life between involuntarily childless couples and parents

(Sydsjö et al. 2005, Sundby et al. 2007, Verhaak et al. 2007; Kraaij et al. 2008, Peterson et al. 2009)

NB: One third of the couples are non-responders

A study comparing women and men 4-5.5 years after successful and after unsuccessful IVF with a control group showed that quality of life in men seems more negatively affected by involuntary infertility than reported before:

Their scores in depression and psychological well-being were similar to the women in the unsuccessful IVF group

(Johannsson et al. 2010)

Summary

- In general, the emotional impact of infertility seems to be lower for men than for women (since women's loss of being pregnant is not experienced by men) (Mahlstedt 1985)
- At least men with male factor infertility suffer as much as women with female factor infertility, but research results are still inconclusive (Peronace et al. 2007, Holter et al. 2007)
- Male factor infertility seems to be more stigmatized than other infertility diagnoses
- Men do indeed experience pain related to their infertility but feel they have few acceptable outlets for the expression of their distresss (Elliott 1998, Webb & Daniluk 1999, Petok 2006)
- A significant selection bias has to be considered in studies on men and their reactions to infertility

Conclusions and Implications (I)

- Provide questionnaires to identify infertile men who need psychosocial support (e. g. FertiQoL or SCREENIVF)
- Sexuality: "Ask the specific questions" (Elliott 1998)
- Studies on invasive reproductive treatment measures on infertile men (e.g. MESA / TESE) are still missing, as well as studies on men who do not seek treatment (Fisher & Hammarberg 2012)
- The counselling needs of men and women after (successful or unsuccessful) treatment for male factor infertility have to be investigated
- The same implies to the counselling needs of families after donor insemination and to the development of children born after donor insemination

Conclusions and Implications (II)

- The "new" treatment options ICSI / MESA / TESE and also DI: Do they encourage and give hope or do they impede the grieving process in male factor infertility?
- Studies have to differentiate between the *psychological impact* of infertility on women and men and their respective *abilities to communicate* about this distress
- The influences of the doctor‘s gender and of the counsellor‘s gender on the infertile man‘s well-being and emotional adjustment during ART have to be studied
- More studies on infertile men in Non-Western societies have to be conducted (Fisher & Hammarberg 2012)

Key references

- Cousineau TM, Domar AD (2007): Psychological impact of infertility. *Best Pract Res Clin Obstet Gynaecol*, 21: 293–308.
- Edelmann RJ, Connolly KJ (2000): Gender differences in response to infertility and infertility investigations: Real or illusory. *B J Health Psychol*, 5: 365-375.
- Englar-Carlson M, Shepard DS (2005) Engaging Men in Couples Counseling: Strategies for Overcoming Ambivalence and Inexpressiveness. *The Fam J*, 13: 383-391
- Fisher J, Hammarberg K (2012): Psychological and social aspects of infertility in men: An overview of the evidence and implications for psychologically informed clinical care and future research. *Asian J Androl*, 14(1), 121-129
- Greil AL *et al.* (2010): The experience of infertility: a review of recent literature. *Sociol Health Illness*, 32: 140-162
- Jaffe J, Diamond MO (2010) *Reproductive Trauma.* American Psychological Association, Washington
- O'Donnell E (2007) Making room for men in infertility counseling. *Sex Reprod Menopause*, 5: 28-32
- Norré J, Wischmann T (2011): The Position of the fertility counsellor in a fertility team: A critical appraisal. *Hum Fertil* 14 (3), 154-159
- Petok WD (2006): The Psychology of Gender-Specific Infertility Diagnoses. In: Covington SH, Burns LH (2006, eds.): *Infertility Counseling. A comprehensive handbook for clinicans.* Cambridge University Press, Cambridge (2nd ed.), pp. 37–60.
- Thorn P, Wischmann T (2009): German Guidelines for Psychosocial Counselling in the Area of Gamete Donation. *Hum Fertil (Camb)*, 12: 73–80.
- Van den Broeck U *et al.* (2010): Counselling in infertility: individual, couple and group interventions. *Pat Educ Counsel* 81: 422-428.
- Wischmann T (2010): Sexual disorders in infertile couples. *J Sex Med,* 7: 1868–1876.
- Wischmann T (2012): Counselling and support for the infertile man, before, during and after treatment. *Hum Fertil (Camb)* (in print)
- Wischmann T *et al.* (2002): Couple Counseling and Therapy for the Unfulfilled Desire for a Child – The Two-Step Approach of the "Heidelberg Infertility Consultation Service". In Strauß, B: *Involuntarily childlessness.* Hogrefe International, Seattle, pp. 127-149.

Thank you for your attention!

SEXUAL DYSFUNCTIONS IN YOUNG MALES

… and the relationship between sexual dysfunction and infertility

UZ LEUVEN

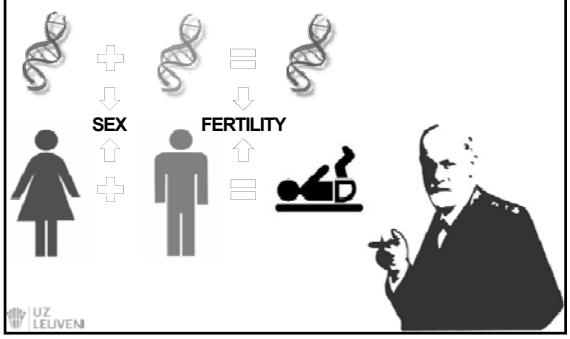
Maarten Albersen MD
"men in the middle" ESHRE 2012

---

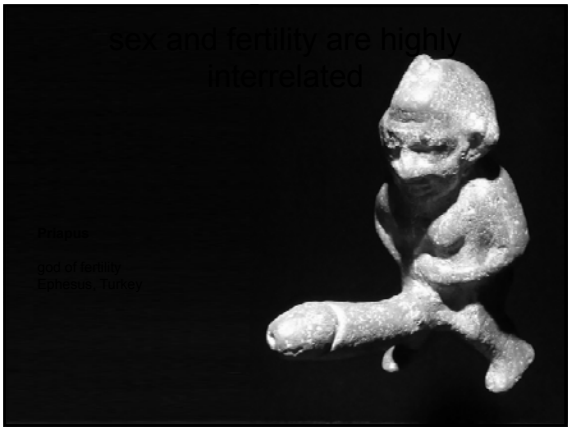
warning: presentation may contain some **bold** statements

UZ LEUVEN

"the meaning of life"



UZ LEUVEN



sex and fertility are highly interrelated

"*Sexuality and the desire for a child are strongly interconnected. The same applies to sexual disorders and the unfulfilled desire for a child.*"

"*Male infertility and impaired male health are intertwined with sexual functioning, both impacts on their reputation of virile males.*"

UZ LEUVEN

Wischmann, 2010, Brähler et al. 2001

introduction

MALE SEXUAL DYSFUNCTION

- congenital
- acquired
  - psychogenic
  - organic

UZ LEUVEN

introduction

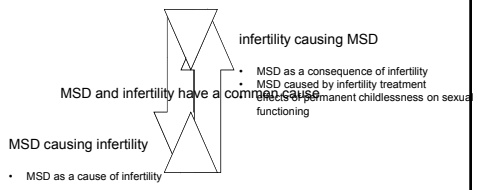
INFERTILITY

- congenital
- acquired
  - ~~psychogenic~~
  - organic

UZ LEUVEN

introduction

MALE SEXUAL DYSFUNCTION



INFERTILITY

UZ LEUVEN

introduction

MALE SEXUAL FUNCTION

libido
arousal
▽
erection
▽
orgasm
▽
ejaculation

UZ LEUVEN

introduction

MALE SEXUAL DYSFUNCTION

DIMINISHED LIBIDO (HSD)

▽

erection

▽

orgasm

▽

ejaculation

UZ LEUVEN

introduction

MALE SEXUAL DYSFUNCTION

libido
arousal

▽

ERECTILE DYSFUNCTION

▽

orgasm

▽

ejaculation

UZ LEUVEN

introduction

MALE SEXUAL DYSFUNCTION

libido
arousal

▽

erection

▽

ANORGASMIA

▽

~~ejaculation~~

UZ LEUVEN

introduction

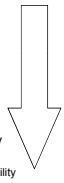
MALE SEXUAL DYSFUNCTION

libido
arousal
▽
erection
▽
orgasm
▽

PREMATURE- or ANEJACULATION

UZ LEUVEN

MALE SEXUAL DYSFUNCTION

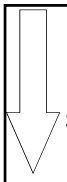


MSD causing infertility

- MSD as a cause of infertility

INFERTILITY

UZ LEUVEN



MSD as a cause of infertility

SEVERE ED

- rare in the young population
- psychogenic (1° or 2°) or congenital (1°)
- medication-induced
- iatrogenic
- trauma!

UZ LEUVEN

MSD as a cause of infertility

Table 7. Ambulatory surgery visits for males with infertility having commercial health insurance, count, rate[a]

	1994 Count	1994 Rate	1996 Count	1996 Rate	1998 Count	1998 Rate	2000 Count	2000 Rate	2002 Count	2002 Rate
As Primary Diagnosis										
Total	140	39	175	32	270	32	325	32	253	29
Age										
18–24	17	*	20	*	32	29	42	33	37	35
25–34	61	70	89	66	112	64	139	63	100	64
35–44	52	51	45	29	91	36	91	33	80	34
45–54	9	*	18	*	34	17	39	17	23	*
55+	1	*	3	*	10	*	14	*	13	*

Table 5. Population prevalence of erectile dysfunction, by age group

	Prevalence
Age	
50–54	26.0%
55–59	34.9%
60–64	46.9%
65–69	57.8%
70–76	69.4%

SOURCE: Adapted from Annals of Epidemiology, 10, Ansong KS, Lewis C, Jenkins P, Bell J, Epidemiology of ED: a community-based study in rural New York state, 293–299, 2000.

UZ LEUVEN

Source: NIH report on urologic diseases in the US (website)

MSD as a cause of infertility

ANORGASMIA, ANEJACULATION
(premature ejaculation)

- Psychogenic, medication or organic (trauma!)
  antidepressants diabetes, pelvic frx, SCI

Prevalence in a population of men enrolled in an ART program for severe male factor infertility in 2010: anejaculation or retrograde ejaculation:

5,7%

UZ LEUVEN

Franco et al. univ. of Rome, unpublished data. ESSM 2010

MSD as a cause of infertility

AGE:

Table 1 – Men's demographics and background data stratified by sexual problem

	Erectile problems N (%)	Premature ejaculation N (%)	Other ejaculation problems N (%)	Reduced sexual desire N (%)	Penile deformities N (%)
Age					
<19	55 (1.1)	42 (2.4)	3 (1.0)	3 (1.5)	5 (2.7)
20–29	[illegible]	475 (27.1)	[illegible]	[illegible]	[illegible]
30–39	932 (18.0)	540 (31.0)	95 (31.9)	46 (23.5)	13 (7.1)
40–49	872 (16.9)	404 (23.3)	39 (13.1)	44 (22.4)	15 (8.2)
50–59	1044 (20.2)	166 (9.5)	34 (11.4)	48 (24.5)	42 (23.0)
60–69	1171 (22.7)	102 (5.9)	35 (11.7)	[illegible]	68 (37.2)
70–79	350 (6.8)	13 (0.7)	15 (5.0)	6 (3.1)	19 (10.4)
≥80	26 (0.5)	3 (0.2)	3 (1.0)	–	–
Marital					
Married	3257 (63.1)	913 (52.4)	128 (43.0)	128 (65.3)	135 (73.8)
In a relationship	735 (14.2)	333 (19.1)	71 (23.8)	22 (11.2)	10 (5.5)
Single	1013 (19.6)	471 (27.1)	91 (30.5)	37 (18.9)	34 (18.6)
Divorced	159 (3.1)	24 (1.4)	8 (2.7)	9 (4.6)	4 (2.2)
Co-morbidities					
None	3158 (61.2)	1572 (90.3)	227 (76.2)	142 (72.4)	138 (75.4)
Cardiovascular	1012 (19.6)	59 (3.4)	35 (11.7)	16 (8.2)	24 (13.1)
Diabetes	375 (7.3)	22 (1.3)	4 (1.3)	4 (2.0)	12 (6.6)
Urologic	284 (5.5)	41 (2.4)	11 (3.7)	8 (4.1)	5 (2.7)
Neurologic	103 (2.0)	6 (0.3)	6 (2.0)	2 (1.0)	2 (1.1)
Psychiatric conditions	148 (2.9)	27 (1.6)	9 (3.0)	9 (4.6)	–
Psychological distress	61 (1.2)	10 (0.6)	5 (1.7)	7 (3.6)	–
Previous medical contact					
No	3261 (63.1)	1432 (82.3)	216 (72.5)	139 (70.9)	105 (57.4)
Yes	1903 (36.9)	309 (17.7)	82 (27.5)	57 (29.1)	78 (42.6)

UZ LEUVEN

Papaharitou et al. 2006

MSD as a cause of infertility

PE:

	PE?	Control of Ejaculation	How often do you feel control?	Frustrate You?	Frustrate Partner?
Male Partner Mean Age 34±7	50%	24% Poor, 57% Fair, 19% Good	Always 4% Usually 33% Sometimes 47% Rarely 13% Never 3%	40%	30%
	PE?	Control of Ejaculation	How often can he control?	Frustrate You?	How often are you satisfied?
Female Partner Mean Age 30±5	29%	38% Poor, 37% Fair, 25% Good	Always16% Usually 59% Sometimes 18% Rarely 13% Never 4%	16%	Always 27% Usually 48% Sometimes 15% Rarely 9% Never 0%

UZ LEUVEN

Shindel et al. SMSNA 2006: personal communication

MSD as a cause of infertility

Infertility: A label of choice in the case of sexually dysfunctional couples

Ujjwal A. Nene*, Kurus Coyaji, Hemant Apte

Although most couples in the present study felt pressure because of their childlessness, they never revealed the problem of sexual dysfunction to others. Couples preferred 'infertility' as a label to avoid stigma when the man was sexually dysfunctional.

Practice implication: COUNSELING!!
treat MSD wherever possible.

UZ LEUVEN

MALE SEXUAL DYSFUNCTION

infertility causing MSD

- MSD as a consequence of infertility
- MSD caused by infertility treatment
- effects of permanent childlessness on sexual functioning

INFERTILITY

UZ LEUVEN

infertility causing MSD

MSD as a consequence of infertility

- **diminished libido**
- **erectile dysfunction**
- **delayed or anorgasmia**
- **premature -, delayed - or anejaculation**

UZ LEUVEN

infertility causing MSD

STRESS & ANXIETY:

- 11% of men has moderate depressive symptoms
- 12% of men has severe depressive symptoms

UZ LEUVEN

Shindel et al. 2008

infertility causing MSD

SEAR (Self-Esteem and Relationship Quality Scale):

• Sexual relationship quality	**29.4** (0–**97**)
• Self-Esteem	31.6 (0–92)
• Confidence	30.6 (0–95)
• Overall relationship	**25.7** (0–**89**)
• Total	29.4 (0–98)

comparison:

SEAR scores in men with severe ED: ± 35 !!!

UZ LEUVEN

Shindel et al. 2008

infertility causing MSD

ED:

22%

Sexual dysfunction in the female partner was a positive predictor of erectile dysfunction in the male partner.

UZ LEUVEN

Shindel et al. 2008

infertility causing MSD

ED: PSYCHOGENIC!

Erection upon masturbation (not for semen collection!), erection during REM sleep (erection with other sexual partners?)

UZ LEUVEN

infertility Dx & Tx causing MSD

- **semen analyses**
- **post coital tests**
- **timed intercourses**
- **ART techniques**

PERFORMANCE
A N X I E T Y

UZ LEUVEN

infertility Dx & Tx causing MSD

PERFORMANCE
A N X I E T Y

SEX for PLEASURE ≠ SEX for CONCEPTION

RELAXING	**PERFORMANCE**
FREE CHOICE	**OBLIGATION**
QUALITY	**QUANTITY**
"WHENEVER"	**"NOW!!!"**

UZ LEUVEN

infertility Dx & Tx causing MSD

PERFORMANCE
A N X I E T Y

SEXUAL POWER

⇧

REPRODUCTIVE CAPACITY ⇨ MASCULINE IDENTITY
SEDUCTIVE POWER
chance of reproduction

⇩

WORK POWER

UZ LEUVEN

infertility Dx & Tx causing MSD

PERFORMANCE
A N X I E T Y ⇨ (NOR)EPINEPHRINE

⇩

- **diminished libido**
- **erectile dysfunction**
- **delayed or anorgasmia**
- **delayed or anejaculation**
- **premature ejaculation**

UZ LEUVEN

infertility Dx & Tx causing MSD

Male Sexual Dysfunction

Effect of Testicular Sperm Extraction Outcome on Sexual Function in Patients With Male Factor Infertility

Cem Akbal, Naşide Mangır, Hasan Hüseyin Tavukçu, Özay Özgür, and Ferruh Şimşek

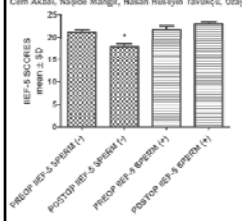


Figure 1. Mean IIEF-5 scores of both groups before and 6 months after TESE.* indicates statistically significant.

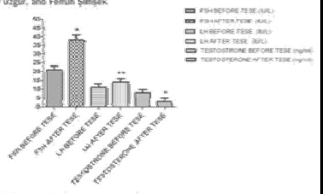


Figure 2. Hormonal profiles of the patients who reported new-onset ED. * indicates statistically significant; **, statistically insignificant.

management

COUNSELING

PDE5-inhibitors

Journal of endocrinological investigation
Volume 26, Issue 3 Suppl, 2003, Pages 72-76

Stress, sexual dysfunctions, and male infertility.

Lenzi, A., Lombardo, F., Sallacone, P., Gandini, L., Jannini, E.A.

Department of Medical Physiopathology, 1st University of Rome La Sapienza, Rome, Italy.

Involuntary childlessness is considered to be a chronic stressor for couples suffering from infertility. Stress itself may interfere with spermatogenesis and fertility rate. The long period of diagnostic and treatment procedures may also have a negative impact on the sex life of the infertile couple. In fact, we observed in such patients a higher frequency of male sexual disturbances expressed as erectile dysfunction, ejaculatory disorders, loss of libido and a decrease in the frequency of intercourse. We tried to partially overcome these sexual symptoms by administration of 50 mg of a type-V phosphodiesterase inhibitor (sildenafil) to two selected groups: patients collecting semen for artificial insemination and male partners of couples before post-coital testing. The results of this uncontrolled pilot study suggest that sildenafil is effective in increasing compliance of male patients facing infertile couple management procedures, and also in improving some sperm parameters, above all the number of sperm penetrating the cervical mucus.

UZ LEUVEN

MALE SEXUAL DYSFUNCTION

▽

MSD and infertility have a common cause

△

INFERTILITY

UZ LEUVEN

MSD and infertility have a common cause

- congenital/genetic disorders
- trauma / neurological disorders

UZ LEUVEN

genetic disorders

Klinefelter

Kallmann

UZ LEUVEN

trauma & neurological disease

SPINAL CORD INJURY !

depending on the level of injury:

- **complete, high lesion**: psychogenic erections are lost **but reflex erections remain intact**
- **Low lesions**, expecially to the cauda equina, **substantially reduce erectile capacity**

  Erection ≠ intercourse!!
- After complete spinal-cord injury **only 4% of men with high lesions and 18% of men with lower lesions** (conus and equina) are **able to ejaculate**
- **Poor sperm quality** after spinal-cord injury is a further confounding factor.
- even in complete injury: **38% is able to experience orgasm**! (unexplained)

UZ LEUVEN

trauma & neurological disease

ED:

PDE5-inhibitors

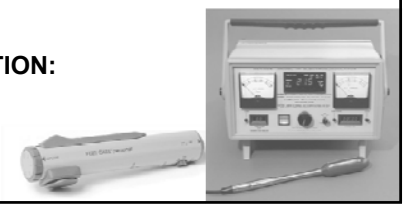
intracavernous injections of vaso-active substances

penile prosthesis

EJACULATION:

vibro-ejaculation

electro-ejaculation



UZ LEUVEN

trauma & neurological disease

other neurological diseases:

- MS
- PELVIC SURGERY
- PERIPHERAL NEUROPATHY (diabetes)

UZ LEUVEN

conclusion

MIND

sexual dysfunction

infertility

BODY

UZ LEUVEN


15th CONGRESS OF THE EUROPEAN SOCIETY FOR SEXUAL MEDICINE
6 - 9 December 2012, RAI Amsterdam Convention Centre, The Netherlands
Deadline for Abstract Submission: 3 September 2012
www.essm.org

Nurses performing Surgical Sperm Recovery

ESHRE Pre congress course

Istanbul 2012

Heidi Birch
Director of Nursing Services
Midland Fertility Services

Midland Fertility Services

Scope of Presentation

- Explain the relevant male anatomy
- Discuss the indications for SSR
- Explain the screening process/tests required
- Discuss the differences between PESA and TESA technique
- Explain the training protocol for nurses who wish to undertake SSR

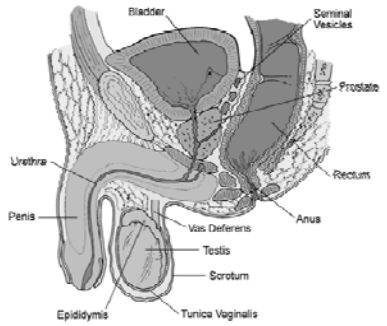
Midland Fertility Services

Learning Outcomes

- Have an understanding of the male anatomy
- Be able to identify who the procedure is suitable for
- Understand which screening tests are required and why
- Understand and be able to explain to a patient the differences between TESA and PESA and what is involved for the patient.

Midland Fertility Services

Male Reproductive Tract



Midland Fertility Services

Indications for SSR

1. **Testicular failure** – There are several causes including previous trauma, surgery, infection, hormonal problems. In some cases there is a genetic predisposition and in a few cases the cause is unknown
2. **Obstruction in the tubes carrying the sperm**. This may be as a result of previous surgery e.g. vasectomy or infection. Absence of the Vas can be a result of a genetic cause such as CF
3. **Retrograde Ejaculation** – usually associated with diabetics
4. **Spinal injury or other nerve damage**
5. **Failure of Miss Palmer!!**

Midland Fertility Services

Miss palmer

Midland Fertility Services

Screening tests

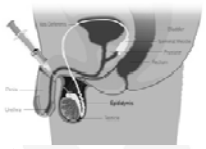
- Medical History
- Physical examination
- FSH, LH and testosterone
- CF and Karyotype

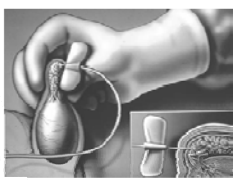
Midland Fertility Services

Pesa

- Infiltrate using up to 10 mls lidocaine around the spermatic cord
- Insulin needle on a 1ml syringe is passed into the epydidymis and suction applied
- Process repeated up to 5 times until adequate sperm is recovered
- Sperm is frozen

Midland Fertility Services





Midland Fertility Services

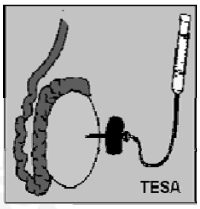
TESA

- Local analgesia as with PESA
- White butterfly with suction from a 20ml syringe
- Core of tissue containing seminiferous tubules is obtained
- Procedure is repeated up to 5 times until adequate sperm is obtained
- Sperm is frozen for future use

Midland Fertility Services

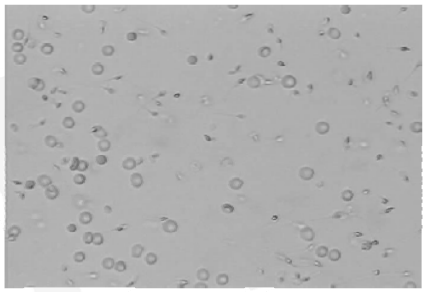
Midland Fertility Services

Biopsy Gun



White butterfly and 20ml syringe

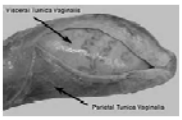
Midland Fertility Services



Midland Fertility Services

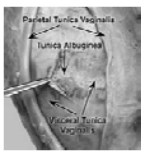
Open Biopsy

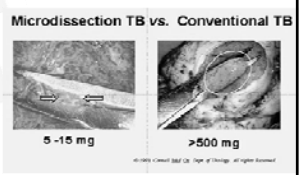
- Not currently carried out by Nurses
- Local analgesia as with PESA
- Cut is made through the skin and layers are separated



Midland Fertility Services

- Cut is made into the tunica vaginalis
- Sample is taken





Midland Fertility Services

Training protocol - selection of appropriate trainee

- Registered RGN with 2 years experience as a fertility nurse specialist
- Observed a minimum of 10 procedures
- Feel competent in his/her ability to commence training and want to extend her role
- The head of department views her to have adequate experience to take on training

Midland Fertility Services

- The testes are easily palpable and greater than 12mls volume
- Any previous TESAs/PESAs were uncomplicated
- factors such as varicocele, bleeding disorder, diabetes or retractile testes

Midland Fertility Services

Training

- Each unit should have protocols produced by the team for all procedures performed by practitioners. The protocol should cover: the location; equipment required; description of the procedure that each practitioner should adhere to and should be updated and form part of the quality system.
- Supervision should be mandatory until the individual has been assessed competent by a senior nurse or clinician. You must audit you practice on a monthly basis and should keep accurate records of this

Midland Fertility Services

Training Continued

During the training and assessment process you will: -

- Demonstrate the ability to anaesthetise the spermatic cord, (training initially on the anatomical model).
- Perform 10 needle biopsies supervised by a doctor.
- Keep an individual log of SSR's performed for one year for assessment by your superior
- At the end of training period feel confident and adequately prepared to undertake this extended role.
- Provide written agreement that she/he and the consultant in charge are happy with her level of competence.

Midland Fertility Services

Know our limitations

A doctor should attend if: -

- There is difficulty with anaesthetising the spermatic cord
- After repeated samples (5) there is no sperm
- The patient experiences an unusual amount of pain
- Excessive amount of bleeding or swelling

Midland Fertility Services

Surgical Sperm Recovery with ICSI:
January 2006 - December 2011

	PESA			TESA			Total		
Age	All	<38	>=38	All	<38	>=38	All	<38	>=38
Total Cycles	123	88	35	191	141	50	314	229	85
Cycles to Egg Recovery	116	86	30	190	140	50	306	226	80
Successful Recoveries	116	86	30	189	140	49	305	226	79
Embryo transfers	99	71	28	154	113	41	253	184	69
Clinical pregnancies	31	27	4	53	45	8	84	72	12
Pregnancy rate per cycle started (%)	25.2	30.7	11.4	27.7	31.9	16.0	26.8	31.4	14.1
Pregnancy rate per egg collection (%)	26.7	31.4	13.3	27.9	32.1	16.0	27.5	31.9	15.0
Pregnancy rate per embryo transfer (%)	31.3	38.0	14.3	34.4	39.8	19.5	33.2	39.1	17.4

Midland Fertility Services

Thank you Any Questions?

Midland Fertility Services

Lab Technicians Performing IMSI

Sarah Lucy Steiner MSc
STERIGNOST Klagenfurt, Austria

Pre-congress course 1 „Men in the Middle“
ESHRE Istanbul 2012

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

Learning Objectives

- Does morphology have an impact on ART outcome?
- When, why and how to perform IMSI?
- Original IMSI technique and possible improvements?
- What to look for - MSOME classification
- DNA strandbreak – free sperm preparation
- The importance of sperm maturity
- What are vacuoles and are they important?

Birth of One Healthy Baby

Andrological Prerequisites:

- Presence of viable sperm — Creus et al.2000
- Morphologically normal sperm — Berkovitz 1999,Bartoov 2003

- Sperm DNA integrity — Greco 2005,Zini 2008
- Chromosomal stability — Calogero 2001,Burrello 2003

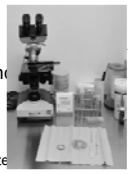
Natural fertilization barriers are removed by ICSI
concerns about increased risk of
birth defects, genetic and epigenetic abnormalities.

OPTIMIZE SPERM PREPARATION
SPERM SELECTION

Van Waart et al.(2001): Predictive value of normal sperm morphology in intrauterine insemination (IUI): a structured literature review.

Grow et al.(1994): Sperm morphology as diagnosed by strict criteria: probing the impact of teratozoospermia on fertilization rate and pregnancy outcome in a large in vitro fertilization population.

Routine sperm morphology assessment is conducted on random cells of initial semen samples and does not reflect the morph quality of the single spermatozoon selected for microinjection into an oocyte.



Queiroz et al.(2006): Sperm sample morphology is not correlate quality of the single sperm used in ICSI cycles.

Impact of Sperm Morphology - Contra

- **French et al.(2009**): Largest (according to authors) retrospective study on the influence of sperm morphology in ICSI

Fertilization rate, clinical PR, IR, birth and abortion rate (10%) were the same for all groups from 100% teratozoospermia to samples with good morphology.

- **Bonetti et al.(2005):** Sperm morphology does not impair embryo quality in ICSI cycles.
- **Nagy et al.(1995):**The result of intracytoplasmic sperm injection is not related to any of the three basic sperm parameters.

M.Montag (2009): Even in ejaculates with a high proportion of abnormal Sp. sufficient but few normal sperm are available for ICSI.

Virro et al. (2004): The establishment of a pregnancy even with compromised ejaculated (dysfunctional and/or with high rates of DNA fragmentation) may be attributed to the corrective role of selecting a single spermatozoon for ICSI.

Impact of Sperm Morphology - Pro

- Papers on significant role in ICSI outcome: **Bartoov et al.(2001, 2002, 2003), Tesarik et al.(2002)**
- Deformities of the midpiece section of the spermatozoon assessed under high magnification microscopy has been linked to centrosomal dysfunction **Ugajin et al.(2010)**
- **De Vos et al.(2003):** Influence of individual sperm morphology on fertilization, embryo morphology, and pregnancy outcome of intracytoplasmic sperm injection

  Retrospective study, 662 consecutive ICSI cycles

Ejaculated sperm	Normal nucleus	Abnormal nucleus
Oocytes injected	4,406	418
Fertilization rate	72,5 ± 25,1	64,4 ± 38,0✔
Embryo quality	73.6 ± 29,8	72,5 ± 35,2
Nr.of transfers	1226	41
Female age	34,1 ± 5,4	32,3 ± 6,7
PR	37,0	22,0✔
Clinical PR	33,0	22,0✔
IR	19,0 ± 31,7	11,2 ± 23,2✔
Live birth rate	14,9 ± 28,4	7,9 ± 18,1✔

✔ - significantly different De Vos et al.(2003)

Bartoov 2002
MSOME: Motile Sperm Organellar Morphology Examination

Bartoov 2003
IMSI: MSOME and ICSI
Intracytoplasmic Morphologically Selected Sperm Injection
Real Time Fine Sperm Morphology Assesment

Letter to New England Journal of Medicine
B.Bartoov (2001)
„selection of spematozoa with normal nuclei improves pregnancy rate with intracytoplasmic sperm injection"

To prove a paper by Berkovitz et al.(1999) who observed that the ultramorphology of subcellular organelles, viewed by transmission and scanning electron microscopy, has an impact on ICSI outcome

IMSI vs ICSI:

Bartoov et al.(2003):
pregnancy rate was significantly increased in IMSI (66%) as compared with routine ICSI (30%), implantation rate was even the three-fold (9.5% vs. 27.9%).

Berkovitz et al.(2005): dramatic increase in abortion rate from 10% (no spermatozoa with normal nuclei) to 57% if no normal spermatozoon for ICSI was available.

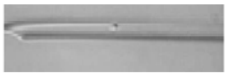
Meta – Analysis Souza-Setti et al.(2010)

All published studies analyzing the relationship of IMSI/ICS I outcomes – only three includeed:
Bartoov et al.(2003) – at least two previous ICSI failures
Berkovitz et al.(2006) - at least two previous ICSI failures
Antinori et al.(2008) – 3 years of infertility, randomly allocated to ICSI/IMSI

↑ Top quality embryos, IR, PR, ↓ miscarriage rate	In favor of IMSI

Fertilization rate: no significant difference

200x



400x

6600x

Advantages of IMSI

select sperm without vacuoles

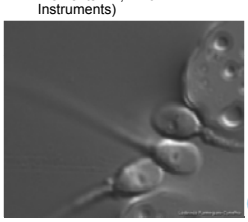
unstained, real time
Integrated in a micromanipulation system – direct injection into mature oocytes
As standardised guidelines are available, intra-observer and inter-observer variability are reduced

MSOME Criteria

Normal Sperm
Bartoov et al.(2003)

LENGTH 4,75 ± 0,28µm
WIDTH 3,28 ± 0,20µm
Smooth
Symmetric
Oval shape
Homogeneity of the nuclear mass with only one small vacuole (less than 4% of the nuclear area)
maximum vacuole diameter: 0.78±0.18 µm

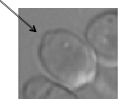
- Evaluation by transparent celluloid forms fitting these criteria
- Measurement with digital imaging software (NIS Elements BR, Nikon Instruments)



Hierarchy of morphologically evaluated "second best" sperm cells
Bartoov (2002)

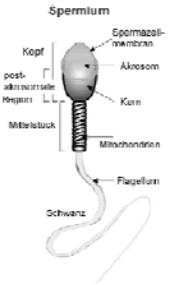
Choice	Nuclear malformations
1	large oval
1	small oval
2	wide forms (> 3.7 µm width)
2	narrow forms (< 2.9 µm width)
3	regional disorders
4	large vacuoles + normal shape/size
5	abnormal forms + large vacuoles

Regional nuclear shape malformation: extrusion or invagination of the nuclear chromatin mass



6 Subcellular Structures

- **Acrosome**: lack, vesiculated, partial
- **Postacrosomal Lamina**: lack,vesiculated
- **Tail:** lack, coiled, broken, multi,short
- **Shape**: small oval, large oval, narrow (<2,9µm in width), wide (>3,7µm)
- **Neck**: abaxial, disorder, cytoplasmic droplet
- **Mitochondria**:lack, partial disorganization



IMSI Classification Vanderzwalmen Pierre

grade I, normal form and absence of vacuoles

grade II, normal form and maximum of two small vacuoles

grade III, normal form and more than two small vacuoles or at least one large vacuole

grade IV, large vacuoles in combination with abnormal head shapes or other abnormalities

New approach to perform a spermocytogram:
„MSOME is a much stricter criterion than Kruger analysis alone“ Oliviera et al.(2008)

Zech et al.(2007): previous implantation failure with ICSI ET D3, 307 sperm selected:

I: 5 %
II: 61,5%
III: 28%
IV: 5,5%

	BC
I u.II	45%
III	9,3%
IV	0,4%

26 couples, two previous implantation failures 19/26
only IMSI transfers: PR 47%,
6 mixed transfers: 4 pregnancies

I: 6%
56%
43%
9%

	BC	quality
ICSI	20 %	6%
IMSI	38 %	16%

Cassuto et al.(2007)

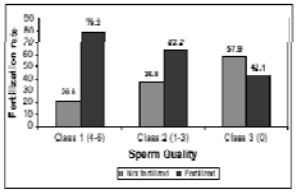
205 MII oocytes injected only 23% class I

Combination of head abnormalities and vacuoles resulted in 82,3% fertilization failure

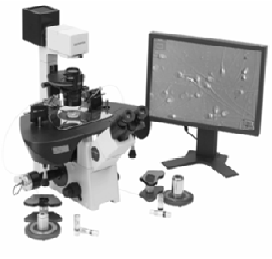
Embryo quality decreased for Class II and III

BC	quality
37% (I)	15%
26% (II)	9%
16% (III)	0%

A new real-time morphology classification for human spermatozoa: a link for fertilization and improved embryo quality.
Cassuto et al.(2009)
SICSI – scored intracytoplasmic sperm injection
Normal **head** score = 2 + Lack of **vacuole** score = 3 + Normal **base** score = 1 = (Total score = 6) for a morphologic "normal top" spermatozoon.



Cassuto. Classification for morula sperm cells. Fertil Steril. 2009.



- Inverted microscope (Nikon, Leica, Zeiss, Olympus etc.) with micromanipulation tools as for ICSI
- Hoffmann modulation contrast (HMC)

Plastic dishes!
removes the need to transfer between dishes, and saves time and money.

- Nomarsky differential interference contrast (DIC)

Glassbottom dishes, but better contrast

Adjust for Köhler illumination!

- 60x or 100x objective and condensor
  Dry or oil immersion?
  Oil immersion has a higher resolution. Dry is easier to handle.
  Oil can be messy and may contaminate air- objectives on the microscope
- The 60x objective offers greater brightness and greater depth of focus than the 100x objective.
  The field-of-view is better with the 60x objective, which is particularly useful when observing rapidly moving sperm.

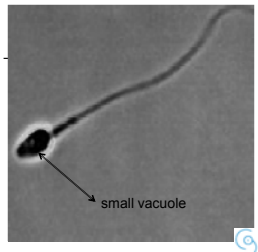
❖ Digital camera (sensor with high-sensitivity pixels that match the resolution of the optics, good frame rate)

❖ Digital zoom function for higher Magnification
(often not used in the IMSI procedure - therefore IMSI is then performed at x600 times magnification!)

❖ USB connection

❖ Monitor with high resolutiuon

❖ Imaging software for storing images for future reference and tools for morphological measurements



Resolving power of the optical magnification system is determined by four image properties:
Berkovitz et al.(2005)

Optical resolution, which depends on microscope optics and the light source
Image contrast, which is provided by Nomarski DIC optics
Maximal optical magnification**,** which defines the objective magnification – 100x,
the magnification selector – 1,0x,1,5x,2,0x and the video coupler magnification- 0,99
Magnification of the video system - ccd chip diagonal dimension 8mm and televison monitor dimension 355,6mm

FINAL DIGITALLY ENHANCED MAGNIFICATION: 100 X 1.5 X 0.99 X (355.6MM/8MM) = 6600 x

Sperm Preparation: Swim-up and Two-layer Density Gradient

Both methods allow the selection of sperm with lower nuclear vacuolization and presumably less DNA-fragmentation than the whole ejaculate
Sakkas et al.(2000)

Both sperm processing methods, swim-up and density gradient centrifugation, allow the selection of sperm with lower nuclear vacuolization and presumably lower DNA fragmentation than the whole ejaculate.
Monqaut et al.(2011)

Final concentration for IMSI:
4000 motile sperm cells in 4ul

Zech Selector

Ebner et al.(2010,2011)
Easy sperm processing technique allowing exclusive accumulation and later usage of DNA-strandbreak-free spermatozoa

DNA damage was significantly removed in the Zech selectors

Motility is likely to be the parameter that seems to be of utmost importance as the Zech-selector strictly separates spermatozoa according to their motility/velocity and not their morphology.

Other authors have found a correlation between sperm motility and DNA-integrity:
Van den Bergh et al.(1998), Avendan~o & Oehninger (2011).

Physiological answer:

- Nuclear and motochondrial DNA can be harmed by strand breaks, any impact on the mitochondrial type could cause alterations in ATP production.
- Mutations or deletions within mitochondrial DNA have also been associated with reduced sperm motility Ozmen et al.(2007)
- Positive correlation ($P < 0.001$) between DNA fragmentation index (DFI) and sperm midpiece defects Speyer et al.(2010).

Limited field-of-view: two options

PVP

PVP has a detrimental action on:
Plasma membrane

– Acrosomal & mitochondrial membranes
Deterioration of: – axonemal tubules – Chromatin – Fibrous sheath – Accessory fibres
Baccetti et al. (1995)

Daily subcutaneous injections of polyvinyl-pyrrolidone-vasopressin in a woman with diabetes insipidus for six years led to a papular dermatosis. Polyvinylpyrrolidone was detected in biopsy material
La Chapelle et al. (1966)

or

„Physiologic IMSI“

- Hyaluronic Acid (HA) is present in the extracellular matrix of the cumulus oophorus at the time of fertilization - additional selection criteria - hyaluronan binding
- Easier to select sperm- more sperm in one place, no need to move dish a lot, higher number of sperm can be analyzed in less time, no or reduced forward motility, so easier to catch
- „Physiologic IMSI“ - HA is biodegradable, removes fear of possible negative effects of PVP

"Physiologic ICSI": Hyaluronic acid (HA) favors selection of spermatozoa without DNA fragmentation and with normal nucleus, resulting in improvement of embryo quality

Lodovico Parmegiani, B.Sc., Graciela Estela Cognigni, M.D., Silvia Bernardi, B.Sc., Enzo Troilo, B.Sc., Walter Ciampaglia, M.D., and Marco Filicori, M.D.
Reproductive Medicine Unit, GynePro Medical Centers, Bologna, Italy

Human Zona Pellucida and Hyaluronic Acid are comparable in selection power for sperm with normal chromatin structure
Yagei et al.(2008)

HA-bound spermatozoa show a 5.4-fold reduction on chromosomal aneuploidies
Jakab *et al.*(2005)

One ready-to-use system : SPERM SLOW ™ (MediCult)

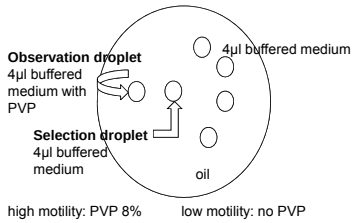
Most studies show an improved clinical outcome of physiological ICSI using HA-viscous medium or a HA-dish (pICSI).
Worrilow et al. (2007,2010), Nasr-Esfahani et al.(2008), Parmegiani et al.(2010).

Immature sperm show diminished plasma membrane remodelling and Zona-binding ability, aneuploidies, rate of lipid peroxidation and consequential DNA fragmentation.

Furthermore, HA may also be used to speed up the selection of spermatozoa with normal nucleus during IMSI because HA-spermatozoa have a significantly higher probability (P = 0.013) of presenting a normal nucleus (14.5%) – according to MSOME criteria – than spermatozoa immersed in PVP (11%).

PHYSIOLOGIC IMSI
Parmegiani et al.
(2010)

The creation of small bays extruding from the rim of the droplets may facilitate the assessment of motile sperm, as sperm heads are "trapped". Follow the motile sperm cell by moving the microscopic stage in the x, y and z directions for at least 20s, Berkovitz et al.(2005)

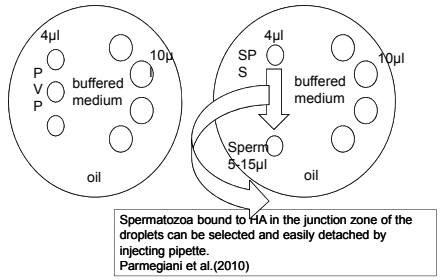


high motility: PVP 8% low motility: no PVP

Bartoov/Berkovitz/Eltes (2003)

Glassbottom Dish:
No optical aberrations, equally divided temperature but no CE-marks for clinical use
(plastic dish Research Instruments)

- PVP
- SPERM SLOW 10min before



Spermatozoa bound to HA in the junction zone of the droplets can be selected and easily detached by injecting pipette.
Parmegiani et al.(2010)

Temperature

❖ Peer et al.(2007)

2h at 37°C: increase in vacuoles and decrease in the morphologic integrity of the sperm nuclei

2h at 21°C: no significant morphological changes

(note: sperm was only washed and the whole pellet used, results may be different for DF-free preparation techniques)

❖ Hammadeh et al.(2001): rise of 25% to 91% of sperm with uncondensed chromatin after incubation at 37°C for 24h

⇒ low temperature in the IMSI dish if possible

Time Factor

Most criticised factor of the IMSI procedure!

Antinori et al.(2008): 60-120min
Bartoov and Berkovitz: 1,5h-5h, average time 2h for 20 sperm (2 per oocyte)

❖ Prolonged manipulation time post-separation from seminal fluid (capacitation) (Bartoov and Berkovitz)

❖ If you immobilize sperm after selection, don´t wait to long before injecting it into the oocyte:

Sperm-associated oocyte-activating factor is released from the spermatozoon within 30 minutes after injection as a result of the sperm-oocyte interaction,
Dozortsev et al. (1997)

❖ Time-frame for injecting oocytes is very important

Vacuoles and Craters

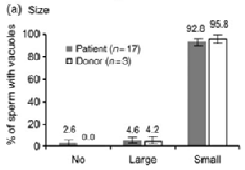
Nagayoshi et al.(2009)

- **95,9% of human sperm show crater defects (CD)** of varying size.
- The frequency of CDs is the same throughout spermatogenesis. In the shaping of the nucleus during spermiogenesis, the number of craters increased while their size diminished as cells moved through the epididymis.
- (no CDs in mouse sperm, 1% in boar sperm)
- Nuclear vacuoles are irregular entities in the condensed chromatin and are due to variably localized aberrations of nuclear decondensation during the histones-to-protamine exchange, **Calvin et al. (1971)**
- These vacuole-like structures dis- appear as the spermatozoon matures in the epididymis or at the time of the acrosome reac-tion, **Kacem et al. (2010)**

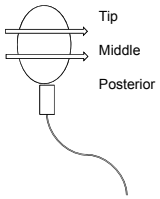
Watanabe et al.(2009)
No relationship between chromosome aberrations and vacuole-like structures on human sperm heads

TUNEL and sperm chromosome assay

17 patients, 3 donors, vacuoles were found in >90% normal shaped sperm in all semen samples examined



Vacuoles with a diameter of 1.5 µm and visible at 400× magnification were classified as 'large'; smaller vacuoles were classified as 'small'.
Location: mainly at the tip and middle area of nuclei, LNV were mainly found at the tip of the sperm (97%).



97 TUNEL-positive in 12 sperm samples
- ❖ 80.4% positive fluorescent signal in the tip or the middle of the nucleu
- ❖ 19.6% intense fluorescence was observed within the posterior area of the nucleus, where the vacuoles were rarely found
- ❖ fluorescence was rarely detected around large and smaller vacuoles

⇨ DNA fragmentation was not caused selectively in normal-shaped sperm with large vacuoles

No difference in fertilization and BZ-forming rate following ICSI with normal shaped SPERM heads showing three different sizes of CDs (human sperm in mouse oocytes)

Gianpiero D. Palermo et al. (2011) Thoughts on IMSI

"Crater" characterization for IMSI

N° of (%)	Large	Small	None	ICSI
Oocytes injected	23	63	20	256
Fertilization	14(60.9)	54(85.7)	16(80.0)	167 (70.8)
Blastocyst Development	7(50.0)	28 (54.9)	4(25.0)	85 (51.0)

DNA Fragmentation

Basic sperm parameters	
Concentration	63,5 ± 26,3
Motility	56,9 ± 1,7
Morphology	3,4 ± 3,2

VACUOLES	CONTROL
576	486
23 (3,9)	22 (4,5)

Basic sperm parameters	
Concentration	45,9 ± 17
Motility	56,5 ± 9,1
Morphology	4,2 ± 1,5

Tunel

Basic sperm parameters	
Concentration	79,5 ± 56,7
Motility	52,9 ± 5
Morphology	4,0 ± 2

VACUOLES	CONTROL
697	592
68 (9,8)	61 (10,3)

Chromosomal Content

x,y,13,15,16,17,18,21,22

VACUOLES	CONTROL
623	575
10 (1,5)	7 (1,1)

Franco Jr. et al.(2008): Significance of large nuclear vacuoles (LNV) in human spermatozoa: implications for ICSI

Table 1: DNA fragmentation values in sperm with LNV and normal nucleus

DNA fragmentation	**Nr of LNV**	**Normal nucleus**
positive	111	65
negative	271	345

P>0,0001

Table 2: Denatured and double-stranded DNA evaluated by acridine orange fluorescence in sperm with LNV and normal nucleus

DNA fragmentation	**Nr of LNV**	**Normal nucleus**
positive	252	117
negative	119	237

P>0,0001

Garolla et al. (2008):
Mitochondrial function, DNA status, and chromosome number of individual sperm cells isolated using a new apparatus able to magnify the sperm image up to 13,000.

⟹

Highly increased mean values for impaired DNA integrity and DNA fragmentation in spermatozoa with LNV of severely oligozoospermic men when compared to those with normal nuclear content and higher aneuploidy rates in sperm with vacuoles.

Oliveira, Garolla, and Vanderzwalmen (2008):
Lower mitochondrial membrane potential, a higher incidence of chromosomal abnormalities, and greater DNA damage

Oliviera et al.(2011):
Infertile men with male factor presented, a significantly higher percentage of spermatozoa with large nuclear vacuoles and a lower percentage of normal spermatozoa than fertile men

Berkovitz et al. (2005) reported a significant negative correlation between the size of LNV and chromatin stability assessed by SCSA.

Boitrelle et al. (2011): 30 normal "top" sperm and 30 spermatozoa with a large sperm-head vacuole
Degree of chromatin condensation (aniline blue staining) and DNA fragmentation (TUNEL assay) were assessed.

	LNV	Normal nucleus
Chromatin condensation	36,2±1,9%	7,6±1,3%,
DNA fragmentation	1,3±0,4%	0,7±0,4%
Aneuploidy	2,2±0,7%	1,1±0,5%

Pedrix et al. (2011):

	LNV	normal nucleus
Chromatin condensation	77,6 ± 2,54%	26,5±2,57%
DNA fragmentation	8,6±1,09%	1,7±0,65%

Chromosomal Content

Spermatozoa free of nuclear morphological malformations were found to be significantly associated with the lower incidence of aneuploidy in derived embryos Figueira et al.(2011)

first IVF treatment in conjunction with preim- plantation genetic screening (PGS) for aneuploidy – FISH (X, Y, 13, 16, 18, 21, 22)

ICSI vs. IMSI:

- lower risk of sex chromosome aneuploidy ICSI:23,5%, IMSI:15%
- lower risk of sex chromosome abnormalities
- more chaotic embryos in the ICSI group ICSI:27,5% IMSI:18,8%
- Less cancellation in Imsi PGS cycles

chromosomally normal embryos, rather than an increase in embryo morphology quality, could explain the increased pregnancy and implantation rates in IMSI cycles that sometimes may not be related to a significant improvement in the quality of embryo morphology.

- The observation of spermatozoa at high-magnification in translocation carriers cannot be used to select sperm cells with a balanced chromosomal content. **Casutto et al. (2011)**
- Data from several studies suggest that abnormal sperm morphology does not necessarily translate into abnormal chromosomal content. **Rosenbusch (1992), Viville (2000)**
- FISH centromeric probes for chromosomes X, Y, 10, 11, and 17 to evaluate human sperm shape and chromosomal aberrations (n=15): 10% of sperm with disomic nuclei were categorized as normal by strict morphology
  ⇒ at sperm dimensions or shape are not reliable attributes in selection of haploid sperm for ICSI

Celik-Ozenci et al.(2004)

DNA Fragmentation

- Hormonal
- Temperature
- Oxidants
- Toxins
- Idiopathic
- Genetic?
- Developmental?

- **Concept of "Abortive apoptosis" − Cell enters and then escapes apoptosis Sakkas *et al.*(2003)**
- Wilding et al.(2011): 64,8% of sperm selected for ICSI showed abnormalities at IMSI magnification and increase in DNA fragmentation (TUNEL analysis

- is increased in poor-quality semen samples
- causes failed fertilisation
- impaired pre-implantation development
- worse pregnancy outcome

Evenson et al. (1999), Carrell et al.(2003), Seli et al.(2004), Borini et al.(2006), Velez de la Calle et al.(2008), Zini et al.(2008)

- two double strand breaks, each on different chromosomes, are sufficient to promote reciprocal translocations Richardson et al.(2000)
- single defects may be repaired by the oocyte Sakkas et al.(2010)

However, 67% of couples with high DNA damage had normal offspring
↑Intervention from IUI to IVF to ICSI, the less impact sperm DNA damage has on early fertility check points
BUT in IVF and ICSI pregnancy loss: DNA damage has a moderate positive effect (OR=2.5)
Zini et al. (2010)

Late Paternal Effect

Tesarik et al.(2004): 18 infertile couples, previous failed attempts, sperm with increased DNA fragmentation.

In 8 couples: no perceptible deterioration of zygote morphology. However, a late paternal effect is not associated with morphological abnormalities at the zygote and early cleavage stages.

Fernandez-Gonzalez et al.(2008): Aberrant growth, premature aging, abnormal behaviour and mesenchymal tumors

Zini et al.(2008): Evidence is emerging that embryos with high DNA sperm damage are associated with early pregnancy loss. ICSI success may be affected but only at a later stage.

It was clearly shown that DNA-damaged sperm (regardless of degree of damage) have the ability to fertilise the oocyte, while blastomere number and blastocyst development are very much related to the degree of DNA damage.
Upadhya et al.(2010), Ahmadi et al.(1999)

Sources of sperm tested for strand breaks are inhomogeneous. The vast majority of studies analysed DFI from processed ejaculates, whereas others worked with neat semen. When assuming that sperm processing accumulates DNA intact sperm, the ‚normalising' effect of the semen preparation procedure has been neglected.
Ebner et al.(2011).

Proposed Indications for IMSI:

- previous ICSI implantation failure (2times)
- bad embryo quality the last time
- history of miscarriages
- severe teratozoospermia
- OAT
- high DFI (DNA Fragmentation Index)
- vacuoles
- female age? oocyte repair capacity
- male partners >35
- surgically retrieved sperm
- macrocephalic sperm
- globozoospermia
- spermiogramm
- embryologists´training

(badly adjusted microscope x400)

Previous Implantation Failures:

Positive outcome with IMSI: **Bartoov et al.(2003), Berkovitz et al.(2005),Hazout et al.(2006), Antinori et al.(2008),Franco et al.(2008)**

Oliveira et al.(2011)
No statistically significant differences: fertilisation, implantation and pregnancy/cycle.

Although not statistically significant:
rates of miscarriage (IMSI:15.3% vs ICSI:31.7%)
ongoing pregnancy (IMSI:22% vs ICSI:13%) and
live births (IMSI:21% vs ICSI:12%)

showed a trend towards better outcomes in the IMSI group. In addition, analysis of subpopulations with or without male factor showed similar results which confirm the beneficial effects of IMSI in couples with poor reproductive prognoses.

ICSI Versus IMSI in Sibling Oocytes

Subsequent treatment with ICSI after one failed attempt: 44,2% !
ART failures are multifactorial (1,166/2,640) and cannot be simply blamed on the spermatozoon.
Gianpiero D. Palermo et al.(2011)

Bartoov/Berkovitz/Eltes (2003): 50 couples – previous ICSI implantation failure: subsequent ICSI or IMSI cycle

	IMSI	ICSI
PR	66%	30%
IR	27,9±26,4%	9,5±15,3%
Top blastocysts	45±28,2%	31,0±19,5%
MR	9%	33%

Severe Male Factor

Balaban et al.(2011):
ICSI/IMSI the same in an unselected patient group, but In the subgroup of severe male factor: benefit with IMSI, especially when the concentration< 1x106 Mio/ml

Souza Setti et al.(2011):

- First analysis: 500 couples, no female factor
48,8% OAT
31,6% Teratozoospermia
19,6% Asthenozoospermia fertilization rate higher in IMSI, but no difference in high quality embryos, OR, IR and miscarriage rate

- Second analysis: 244 couples
Only OAT patients
First group: WHO 1999 Second group: WHO 2010
Fertilization rate was higher for IMSI in both groups, but IR and PR (2,5times) were only higher in the WHO 2010 group

Who 2010/1999

Figuera et al.(2010):
IMSI vs ICSI: No significant differences except for fertilization rate, which was significantly higher in the IMSI group (68.0% vs 73.0%).

- **WHO 1999** oligoastenozoospermic patients: positive influence of IMSI on the fertilization rate
- **WHO 2010** oligoastenozoospermic patients: close relationship between IMSI and fertilization rate, determinant to the likelihood of implantation and pregnancy occurrence.

CONCLUSION: With the introduction of new cut-off points, oligoasteno-zoospermic males, who may largely be responsible for the subfertility of the couple, can be more accurately identified. Moreover, in those patients, IMSI treatment could result in improved outcomes.

<5 × 106/mL concentration and normal sperm morphology of <4% according to Kruger's strict criteria
The mean time employed to collect normal appearing spermatozoa (according to MSOME criteria) was
7.7 ± 3.1 min for ICSI and 108.3 ± 29.9 min for IMSI ($P < 0.001$).

Gianpiero D. Palermo et al. (2011) Thoughts on IMSI

No. of (%)	ICSI	IMSI
Cycles	16	17
Maternal age (M years ± SD)	34.9 ± 3	35.2 ± 3
2PN	40/48 (83.3)	42/49 (85.7)
Top quality day 2 embryos	27/40 (67.7)	29/42 (68.2)
Embryos transferred (M ± SD)	2.5 ± 0.8	2.5 ± 0.5
Delivery	6 (37.5)	5 (29.4)
Live birth	8/40 (20.0)	7/42 (16.7)

Advanced Maternal Age?

Takeuchi et al.(2009) sibling oocytes study

First attempt – 347 couples
Three age groups: I: <35
II: 35-39
III: >40
No significant difference btw. ICSI and IMSI irrespective of maternal age except for age group II which had a significantly higher IR with IMSI

Conclusion: No benefit for advanced maternal age and in first attempts

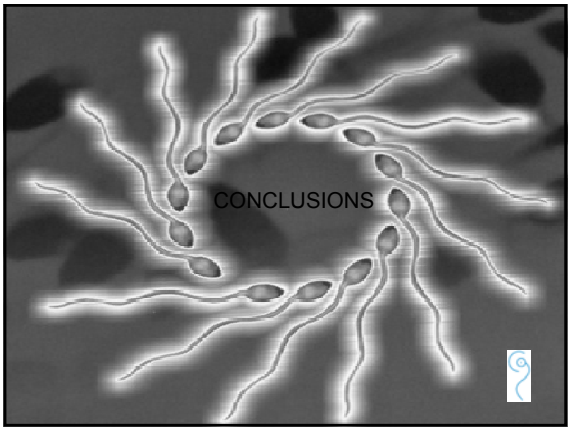
❖ **Surgically retrieved sperm**: helps select immature sperm with higher developmental capabilities, sibling oocytes,43 pairs,
PR ICSI: 28,6 IMSI:45,5%
There appears to be a beneficial effect Takeuchi et al.(2009)

❖ **Macrocephalic sperm head syndrome:** is associated with aneuploid and polyploid sperm content.
Polyploid or diploid spermatozoa can be eliminated by IMSI ($p<0.05$),but no euploid spermatozoa was found by IMSI thus IMSI is not the solution.
Hammoud et al.(2008)
Chelli et al.(2010) 3h for selection, two patients (North Africa)

❖ **Globozoospermia:**
classic spermiogamm 100% globozoospermia, IMSI:1% of the sperm cells seemed to show a small bud of acrosome
Succesful birth! (no AOA necessary)
Sermondale et al.(2011):

❖ 134 Second trimester pregnancies:
Late spontaneous abortions/death: no difference
But: ICSI group had a significantly higher risk (7,09% vs 2,8%) of major congenital malformations
Berkovitz et al.(2007)

❖ Follow-Up Study 2005-2010 Cassuto et al.(2011)
Only women <39 1028 children born
578 (56%) after IMSI 450 (44%) after ICSI
From birth to 3 years of age
No significant differences in terminated pregnancies due to foetal malformations or genetic disorders
But: major congenital malformations and genetic disorders was 24/578(4,15%) in ICSI vs. 8/450 (1.77%) in IMSI



Why Different Results?

- A well-adjusted standard injection microscope with a 40× Hofmann contrast objective allows the identification of sperm with irregularities in the sperm head which represent sperm vacuoles if viewed at higher magnification. This led us to conclude that experienced embryologists probably already select morphologically intact spermatozoa for ICSI. This may also explain why IMSI does not necessarily lead to a better treatment outcome in some laboratories M.Montag et al. (2009).
- Different sperm processing techniques Peer et al.(2007)
- Qualitative data on sperm sometimes missing in published literature – questionable if IMSI is required for high-quality sperm

"IMSI as a Valuable Tool for Sperm Selection During ART "

Monica Antinori, Pierre Vanderzwalmen and Yona Barak

In : "Biennial Review of Infertility, Volume 2" New York Inc. Springer-Verlag; June 2011

The introduction of IMSI has fostered a deeper understanding of those mechanisms that interfere with male fertility potential in both natural and assisted reproduction. ART treatments can no longer be considered mere "shots in the dark" they must become a decisive therapy, with much more weight being given to the first attempt.

The lack of standardization in terms of basic techniques and morphological evaluation criteria, its routine application available in only a few ART units due to man-hours and high costs involved - all these factors create skepticism regarding IMSI's cost-effectiveness.

Sperm quality affects ICSI results in terms of blastocyst formation and pregnancy rate

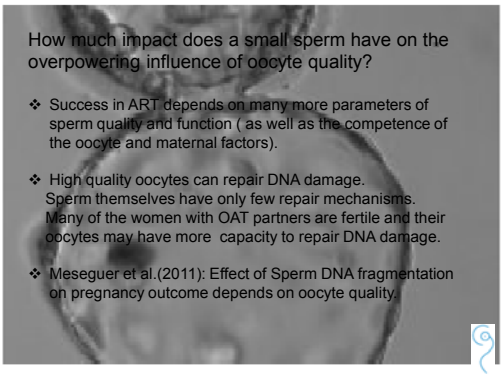
But:

No direct association of chromosomal abnormalities or presence of DNA strand breaks with sperm head defects as assessed by IMSI

The presence of vacuoles does not necessarily reduce sperm competence

We conclude.....that a 16× factor magnification does not bring any advantage in the quest to find spermatozoa devoid of surface irregularities and significantly lengthens the search time required. The presence of vacuoles does not flag spermatozoa with fragmented DNA or aneuploidy. Finally, the putative correlation between vacuolar size and genomic integrity was not confirmed.

Thoughts on IMSI
Gianpiero D. Palermo et al.(2011)



How much impact does a small sperm have on the overpowering influence of oocyte quality?

- Success in ART depends on many more parameters of sperm quality and function (as well as the competence of the oocyte and maternal factors).
- High quality oocytes can repair DNA damage. Sperm themselves have only few repair mechanisms. Many of the women with OAT partners are fertile and their oocytes may have more capacity to repair DNA damage.
- Meseguer et al.(2011): Effect of Sperm DNA fragmentation on pregnancy outcome depends on oocyte quality.

Security of IMSI?

- Decreases in fertilization rates in at least one private clinic that introduced IMSI for at least 6 months until technicians gained more experience in IMSI
- Junca et al.(2010): 2004-2008
  Pregnancies: 1841 ICSI 458 IMSI
  NS: miscarriage rate, intrauterine a. perinatal death, congenital abnormality, sex ratio
  Only significance: difference in birth weight, more babies <2500g in IMSI
- Otherwise no difference to ICSI or better outcome

- Expensive equipment to reach the necessary magnification
- Experienced embryologists - training (work in pairs?)
  one clear advantage: train the sensibility of the embryologist to minor malformations of the sperm
- Time-consuming process – oocytes might suffer...
- No clear indication to suggest IMSI to the patient, so is it ok to charge the patient more money for IMSI?
- In regard to long-term safety we should avoid hypothetical fertilisation by DNA damaged and chromosomal unbalanced spermatozoa – combine methods of selection that are available today - follow-up studies needed – if possible, every laboratory should see what works best for their situation

Laboratory STERIGNOST

EMBRYOLOGY
Dr.Susanne Bulfon-Vogl
Dr.Ciska Leberl
Dr.Elena Iacovelli
Sarah Lucy Steiner,MSc

GYNECOLOGY
Dr.Alexander Boschi
Dr.Alexander Stadler
Dr.Martin Kaimbacher

REFERENCES Ahmadi A, Ng SC (1999a) Fertilizing ability of DNA-damaged spermatozoa. J Exp Zool 284:696–704.
Ahmadi A, Ng SC (1999b) Developmental capacity of damaged spermatozoa. Hum Reprod 14:2279–2284.
Antinori M, Licata E, Dani G, et al. Intracytoplasmic morphologically selected sperm injection: a prospec- tive randomized trial. Reprod Biomed Online. 2008;16(6):835–41.
Avendan˜o C, Oehninger S (2011) DNA fragmentation in morphologically normal spermatozoa: how much should we be concerned in the ICSI era? J Androl 32:356–363.
Baccetti B (2004) Microscopical advances in assisted reproduction. J Submicrosc Cytol Pathol 36:333–339
Balaban B, Yakin K, Alatas C, Oktem O, Isiklar A, Urman B (2011) Clinical outcome of intracytoplasmic injection of spermatozoa morphologically selected under high magnification: a prospective randomized study. Reprod Biomed Online 22:472–476
Bartoov B, Berkovitz A, Eltes F. Selection of sperma- tozoa with normal nuclei to improve the pregnancy rate with intracytoplasmic sperm injection. N Engl J Med. 2001;345(14):1067–8.
Bartoov B, Berkovitz A, Eltes F, Kogosowski A, Menezo Y, Barak Y. Real-time fine morphology of motile human sperm cells is associated with IVF-ICSI outcome. J Androl. 2002;23(1):1–8.

Bartoov B, Berkovitz A, Eltes F, et al. Pregnancy rates are higher with intracytoplasmic morphologically selected sperm injection than with conventional intra- cytoplasmic injection. Fertil Steril. 2003;80(6):
1413–9.
Bartoov B. Is fine morphology of the human sperm nuclei affected by in vitro incubation at 37 degrees C? Fertil Steril. 2007;88(6):1589–94.
Berkovitz A, Eltes F, Yaari S, et al. The morphologi- cal normalcy of the sperm nucleus and pregnancy rate of intracytoplasmic injection with morphologically selected sperm. Hum Reprod. 2005;20(1):185–90
Boitrelle F, Ferfouri F, Petit JM, Segretain D, Tourain C, Bergere M, Bailly M, Vialard F, Albert M, Selva J (2011) Large human sperm vacuoles observed in motile spermato- zoa under high magnification: nuclear thumbprints linked to failure of chromatin condensation. Hum Reprod 7:1650–1658.
Borini A, Tarozzi N, Bizzaro D, Bonu MA, Fava L, Flamigni C, Coticchio G (2006) Sperm DNA fragmentation: paternal effect on early post-implantation embryo development in ART. Hum Reprod 21:2876–2881.
Calvin HI, Bedford JM. Formation of disulphide bonds in the nucleus and accessory structures of mam- malian spermatozoa during maturation in the epididymis. J Reprod Fertil Suppl. 1971;13 Suppl
13:65–75.

Carrell DT, Liu L, Peterson CM, Jones KP, Hatasaka HH, Erickson L, Campbell B (2003) Sperm DNA fragmentation is increased in couples with unexplained recurrent pregnancy loss. Arch Androl 49:49–55.
Cassuto NG, Bouret D, Plouchart JM, Jellad S, Vanderzwalmen
P, Balet R, Larue L, Barak Y (2009) A new real-time morphology classification for human spermatozoa: a link for fertilization and improved embryo quality. Fertil Steril 92:1616–1625.
Celik-Ozenci C, Jakab A, Kovacs T, Catalanotti J, Demir R, Bray-Ward P, Ward D, Huszar G (2004) Sperm selection for ICSI: shape properties do not predict the absence or presence of numerical chromosomal aberrations. Hum Reprod 19:2052–2059.
De Vos A, Van De Velde H, Joris H, Verheyen G, Devroey P, Van Steirteghem A. Influence of individual sperm morphology on fertilization, embryo morphol- ogy, and pregnancy outcome of intracytoplasmic sperm injection. Fertil Steril. 2003;79(1):42–8.
Dozortsev D, Rybouchkin A, De Sutter P, Dhont M (1995) Sperm plasma membrane damage prior to intracytoplasmic sperm injection: a necessary condition for sperm nucleus decondensation. Hum Reprod 10:2960–2964.
Ebner Th., Filicori M., Tews g.,Parmegiani L.(2011): A plea for a more physiological ICSI, in: andrologia, invited review.
Evenson DP, Larson KL, Jost LK (2002) Sperm chromatin structure assay: its clinical use for detecting sperm DNA fragmentation in male infertility and comparisons with other techniques. J Androl 23:25–43.

Fernandez-Gonzalez R, Moreira PN, Perez-Crespo M, et al. Long-term effects of mouse intracytoplasmic sperm injection with DNA-fragmented sperm on health and behavior of adult offspring. Biol Reprod. 2008;78(4):761–72.
Figueira, R.d.C/Brage, D. P./Souza Setti, A./Iaconelli, A. Jr./Borges, E. Jr. (2011): Morphological nuclear integrity of sperm cells is associated with preimplantation genetic aneuploidy screening cycle outcomes, in: Fertil. Steril., 95(3), 990-993
Greco E, Scarselli F, Iacobelli M, Rienzi L, Ubaldi F, Ferrero S, Franco G, Anniballo N, Mendoza C, Tesarik J (2005) Effi- cient treatment of infertility due to sperm DNA damage by ICSI with testicular spermatozoa. Hum Reprod 20:226–230.
Hazout A, Dumont-Hassan M, Junca AM, Cohen BP, Tesarik J (2006) High-magnification ICSI overcomes paternal effect resistant to conventional ICSI. Reprod Biomed Online 12:19–25.
Franco Jr JG, Baruffi RL, Mauri AL, Petersen CG, Oliveira JB, Vagnini L. Significance of large nuclear vacuoles in human spermatozoa: implications for ICSI. Reprod Biomed Online. 2008;17(1):42–5.
French DB, Sabanegh ES Jr, Goldfarb J, Desai N (2010) Does severe teratozoospermia affect blastocyst formation, live birth rate, and other clinical outcome parameters in ICSI cycles? Fertil Steril 93:1097–1103.
Garolla A, Fortini D, Menegazzo M, et al. High-power microscopy for selecting spermatozoa for ICSI by physiological status. Reprod Biomed Online. 2008;17(5):610–6.

Jakab A, Sakkas D, Delpiano E, Cayli S, Kovanci E, Ward D, Revelli A, Huszar G (2005) Intracytoplasmic sperm injection: a novel selection method for sperm with normal frequency of chromosomal aneuploidies. Fertil Steril 84: 1665–1673.
Junca AM, Dumont M, Cornet D, Douard S, De Mounzon J, Prisant N. Is intracytoplasmic morpho- logically selected sperm injection (IMSI) detrimen- tal for pregnancy outcome? Fertil Steril. 2010;94: S31.
Kacem O, Sifer C, Barraud-Lange V, et al. Sperm nuclear vacuoles, as assessed by motile sperm organel- lar morphological examination, are mostly of acrosomal origin. Reprod Biomed Online. 2010;20(1):132–7.
Meseguer M, Santiso R, Garrido N, Garcı´a-Herrero S, Remoh´ı J, Fernandez JL (2011) Effect of sperm DNA fragmentation on pregnancy outcome depends on oocyte quality. Fertil Steril 95:124–128.
Nagy ZP, Liu J, Joris H, et al. The result of intracyto- plasmic sperm injection is not related to any of the three basic sperm parameters. Hum Reprod. 1995; 10(5):1123–9.
Nasr-Esfahani MH, Razavi S, Vahdati AA, Fathi F, Tavalaee M (2008) Evaluation of sperm selection procedure based on hyaluronic acid binding ability on ICSI outcome. J Assist Reprod Genet 25:197–203.
Oliveira, J. B./Cavagna, M./Petersen, C. G./Mauri, A.L./Massaro, F. C./Silva L. F./Baruffi, R. L./Franco, J. G. Jr. (2011): Reprod. Biol. Endocrinol. 9, 99

Ozmen B, Caglar GS, Koster F, Schopper B, Diedrich K, Al-Hasani S (2007) Relationship between sperm DNA damage, induced acrosome reaction and viability in ICSI patients. Reprod Biomed Online 15:208–214.
Parmegiani L, Cognigni GE, Bernardi S, Troilo E, Ciampaglia W, Filicori M (2010a) 'Physiologic ICSI': hyaluronic acid (HA) favors selection of spermatozoa without DNA frag- mentation and with normal nucleus, resulting in improve- ment of embryo quality. Fertil Steril 93:598–604.
Parmegiani L, Cognigni GE, Ciampaglia W, Pocognoli P, Marchi F, Filicori M (2010b) Efficiency of hyaluronic acid (HA) sperm selection. J Assist Reprod Genet 27:13–16.
Parmegiani L, Cognigni GE, Filicori M (2010c) Risks in inject- ing hyaluronic acid non-bound spermatozoa. Reprod Biomed Online 20:437–438
Palermo Gianpierro D.,Hu jennifer C.Y., Rienzi Laura et al.(2011): Thoughts on IMSI.publshed at Springer Link
Pedrix, A./Travers, A./Chell,i M. H./Escalier, D./Do Rego, J. L./Milazzo, J. P./Mousset- Simeon, N./Mace, B./Rives, N. (2011): Assessment of acrosome and nuclear abnormalities in human spermatozoa with large vacuoles, in: Hum. Reprod. 26, 47-58.
Peer S, Eltes F, Berkovitz A, Yehuda R, Itsykson P, Bartoov B (2007) Is fine morphology of the human sperm nuclei affected by in vitro incubation at 37 degrees C? Fertil Steril 88:1589–1594.Ramos L, Wetzels AM (2001) Low rates of DNA fragmenta- tion in selected motile human spermatozoa assessed by the TUNEL assay. Hum Reprod 16:1703–1707.

Richardson C, Jasin M (2000) Frequent chromosomal translo- cations induced by DNA double-strand breaks. Nature 405:697–700.
Sakkas D, Manicardi GC, Bizzaro D. Sperm nuclear DNA damage in the human. Adv Exp Med Biol. 2003;518:73–84.
Tanaka A, Nagayoshi M, Awata S, Tanaka I, Kusunoki H, Watanabe S. Are crater defects in human sperm heads physiological changes during spermiogenesis? Fertil Steril. 2009;92(3):S165.
Takeuchi T, Colombero LT, Neri QV, Rosenwaks Z, Palermo GD. Does ICSI require acrosomal disrup- tion? An ultrastructural study. Hum Reprod. 2004; 19(1):114–7.
Seli E, Gardner DK, Schoolcraft WB, Moffatt O, Sakkas D (2004) Extent of nuclear DNA damage in ejaculated spermatozoa impacts on blastocyst development after in vitro fertilization. Fertil Steril 82:378–383.
Souza Setti, A./Ferreira, R.C./Paes de Almeida Ferreira Braga, D./de Cássia Sávio Figueira, R./Iaconelli, A. Jr./Borges, E. Jr. (2010): Intracytoplasmic sperm injection outcome versus intracytoplasmic morphologically selected sperm injection outcome: a meta-analysis, in: Reprod Biomed Online, 21(4), 450-455
Speyer BE, Pizzey AR, Ranieri M, Joshi R, Delhanty JD, Serhal P (2010) Fall in implantation rates following ICSI with sperm with high DNA fragmentation. Hum Reprod 25:1609–1618.

Svalander P, Jakobsson AH, Forsberg AS, Bengtsson AC, Wikland M (1996) The outcome of intracytoplasmic sperm injection is unrelated to 'strict criteria' sperm morphology. Hum Reprod 11:1019–1022.
Tesarik J, Greco E, Mendoza C. Late, but not early, paternal effect on human embryo development is related to sperm DNA fragmentation. Hum Reprod. 2004;19(3):611–5.
Tesarik J, Mendoza C, Greco E. Paternal effects act- ing during the first cell cycle of human preimplanta- tion development after ICSI. Hum Reprod. 2002;17(1):184–9.
Upadhya D, Kalthur G, Kumar P, Rao BS, Adiga SK (2010) Association between the extent of DNA damage in the spermatozoa, fertilization and developmental competence in preimplantation stage embryos. J Turkish-German Gynecol Assoc 11:182–186.boi
Vanderzwalmen P, Hiemer A, Rubner P, et al. Blastocyst development after sperm selection at high magnifica- tion is associated with size and number of nuclear vacuoles. Reprod Biomed Online. 2008;17(5):617–27
Van den Bergh M, Emiliani S, Biramane J, Vannin AS, Englert Y (1998) A first prospective study of the individual straight line velocity of the spermatozoon and its influences on the fertilization rate after intracytoplasmic sperm injection. Hum Reprod 13:3103–3107.

Van Waart, J./Kruger, T. F./Lombard, C. J./Ombelet, W. (2001): Predictive value of sperm morphology in intrauterine insemination (IUI): a structured literature view, in Hum. Reprod. 7 (5), 495-500
Velez de la Calle JF, Muller A, Walschaerts M, Clavere JL, Jimenez C, Wittemer C, Thonneau P (2008) Sperm deoxyri- bonucleic acid fragmentation as assessed by the sperm chro- matin dispersion test in assisted reproductive technology programs: results of a large prospective multicenter study. Fertil Steril 90:1792–1799.
Virro MR, Larson-Cook KL, Evenson DP (2004) Sperm chro- matin structure assay (SCSA) parameters are related to fertilization, blastocyst development, and ongoing pregnancy in in vitro fertilization and intracytoplasmic sperm injection cycles. Fertil Steril 81:1289–1295
Watanabe S, Tanaka A, Fujii S, Misunuma H. No rela- tionship between chromosome aberrations and vacu- ole-like structures on human sperm head. Hum Reprod. 2009;24 Suppl 1:i94–6.
Wilding M, Coppola G, di Matteo L, Palagiano A, Fusco E, Dale B (2011) Intracytoplasmic injection of morphologically selected spermatozoa (IMSI) improves outcome after assisted reproduction by deselecting physiologically poor quality spermatozoa. J Assist Reprod Genet 28:253–262.

Worrilow KC, Huynh HT, Bower JB, Anderson AR, Schillings W, Crain JL (2007) PICSI vs. ICSI: statistically significant improvement in clinical outcomes in 240 in vitro fertiliza- tion (IVF) patients. Fertil Steril 88(Suppl. 1):s37.
Worrilow KC, Eid S, Matthews J, Pelts E, Khoury C, Liebermann J (2010) Multi-site clinical trial evaluating PICSI, a method for selection of hyaluronan bound sperm (HBS) for use in ICSI: improved clinical outcomes. Hum Reprod 25(Suppl. 1):i7.
Zech NH, Bach M, Neyer T, Stecher A, Zintz M, Petra Baborova, Uher P, Vanderzwalmen P. Blastocyst formation after intracytoplasmic morphologically selected sperm injection (IMSI) according to the morphological integrity of human sperm nuclei.
Fertil Steril 2007; 88(Suppl 1): P-86Zini, A./Boman, J. M./Belzile E./Ciampi, A. (2008): Sperm DNA damage is associated with an increased risk of pregnancy loss after IVF and ICSI: systematic review and meta-analysis, in: Hum. Reprod. 23, 2663-2668.
Zini A, Sigman M. Are tests of sperm DNA damage clinically useful? Pros cons J Androl. 2009;30(3): 219–29.

Rigshospitalet
GROWTH REPRODUCTION

Sperm quality and fertility –
the clinical implications of environmental factors

Martin Blomberg Jensen, MD
Department of Growth and Reproduction, Rigshospitalet, Copenhagen, Denmark

Rigshospitalet
GROWTH REPRODUCTION

Disclosure

No conflicts of interest

Rigshospitalet
GROWTH REPRODUCTION

Learning objectives

- Environmental influence may be important for male reproductive function
- Influence at different time points may influence reproductive function differently
- Early influence and Testicular dysgenesis syndrome
- Vitamin D: an example on adult exposure

Environmental influence on semen quality at various time points





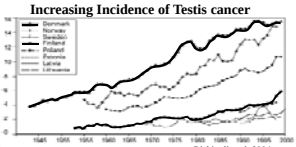

- Changes in diet
- Medication
- Endocrine disruption chemicals
- Pollutants
- Outdoor/Indoor life
- Sunshine
- and much more



Evidence for environmental influence on male reproductive disorders

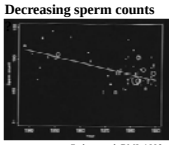
- Rapid changes in particular geographical areas support an environmental influence on reproductive function
- Migration studies and environmental exposure in animals corroborate that environmental exposure is important for male reproductive function
- Several confounders exist such as socioeconomic changes will influence fertility rates, but supposedly less towards the incidence of Testis Cancer

Increasing Incidence of Testis cancer



Richiardi et al. 2004

Decreasing sperm counts

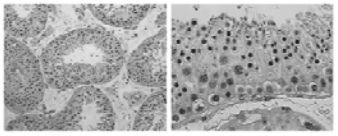


Carlsen et al. BMJ, 1992

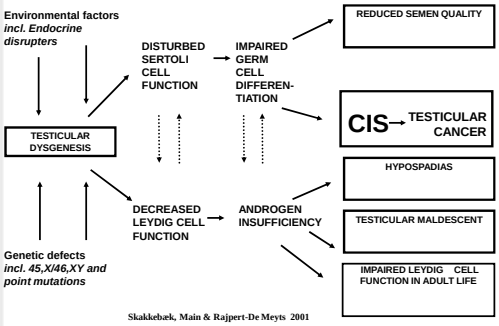
Environmental exposure targets and time ?

A simplified model

- Sertoli cell number determines sperm counts
- Sertoli cells do not proliferate after puberty
- Putative environmental exposure affecting sperm counts may thus be important during the fetal and perinatal period
- Spermatozoa are passively transported to the epididymis
- Here, they maturate and become motile
- Indicating that exposure affecting sperm motility and morphology may be relevant throughout life.

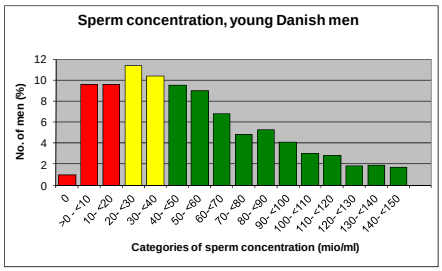


Testicular Dysgenesis Syndrome fetal origin



Skakkebæk, Main & Rajpert-De Meyts 2001

Sperm concentration in > 3000 young men from the general population



Similar results from Edinburgh, Hamburg and Leipzig

Jørgensen et al, 2006

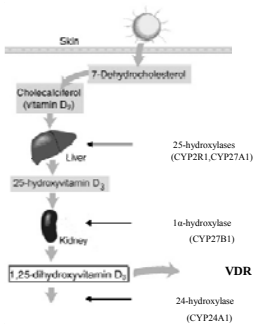
What about exposure in adulthood ?

Why Vitamin D and male reproduction ?

- Calcium is important for sperm maturation and capacitation (Yoshida 2008)
- Vitamin D deficiency is common in the western world
- Vitamin D deficiency has been associated with male infertility and impaired semen quality in rodents (Kwicinski 1989/Uhland 1992)
- VDR Knock out >>>impaired male fertility (Kinuta 2000/Boullion 2008)
- VDR is expressed in human spermatozoa (Aquila 2008/Corbett 2006 /Nangia 2007)
- Extra-renal VD metabolism

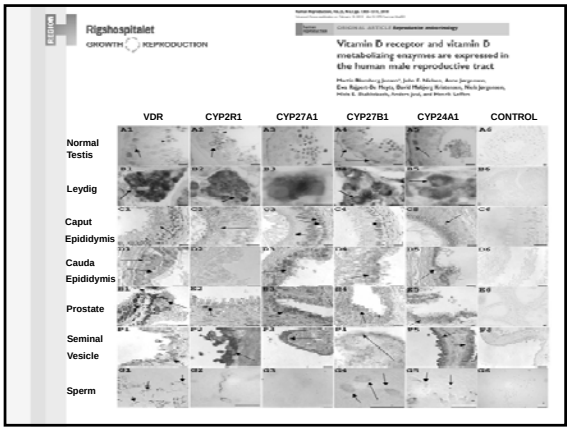
Rigshospitalet
GROWTH REPRODUCTION

Vitamin D physiology

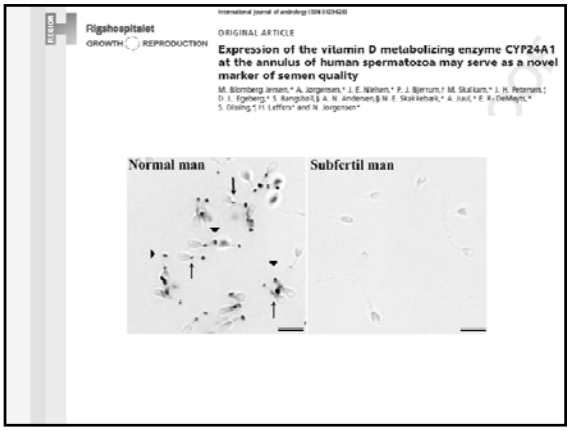


Prosser and Jones Trends Biochem 2004

Rigshospitalet
GROWTH REPRODUCTION



Rigshospitalet
GROWTH REPRODUCTION



Rigshospitalet
GROWTH REPRODUCTION

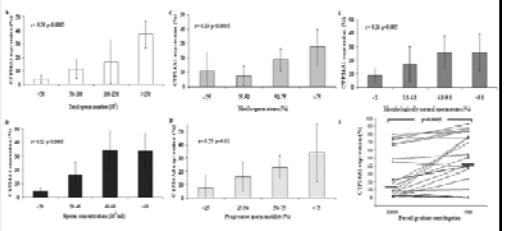
CYP24A1 expression in normal and subfertile men

Variable Median (5-95 percentile)	Subfertile men	Normal men	P-value
Included men (N)	84	53	-
Age (years)	33 (19-45)	19 (18-24)	0.001
Semen volume (ml)	4.1 (2.6-7.7)	3.9 (2.2-6.2)	-
Total sperm number (10^6)	47 (0.2-454)	192 (52-640)	<0.0005
Sperm concentration (10^6/ml)	9 (0.2-69)	52 (11-197)	<0.0005
Motility (ABC %)	54 (5-82)	70 (45-89)	<0.0005
Morphologically normal (%)	2.8 (0-5)	7.0 (1-16)	<0.0005
25-hydroxyvitamin D(nmol/l)	45 (9-104)	41(13-80)	-
CYP24A1-positive sperm (%)	**1 (0-68)**	**25 (0-85)**	**<0.0005**

Blomberg Jensen IJA 2012

Rigshospitalet
GROWTH REPRODUCTION

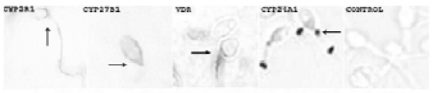
CYP24A1 expression and semen quality

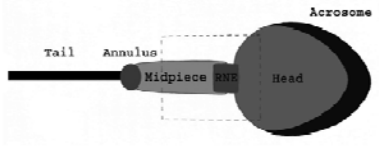


Blomberg Jensen IJA 2012

Rigshospitalet
GROWTH REPRODUCTION

VDR and VD metabolizing enzymes co-localize in the neck of human spermatozoa

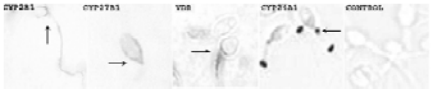


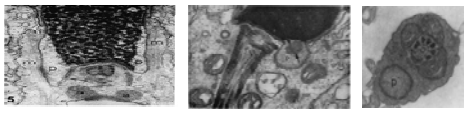


Spermatozoa transcriptionally silent

Rigshospitalet
GROWTH REPRODUCTION

VDR and VD metabolizing enzymes co-localize in the neck of human spermatozoa





Nuclear redundant envelope (RNE)

Calreticulin, calcium binding protein present in acrosome and neck (RNE)

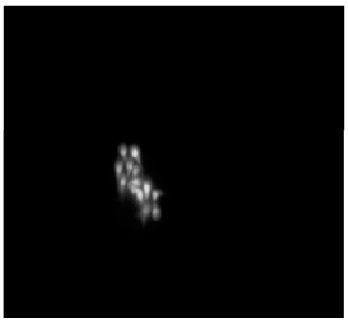
Calcium is an important messenger in spermatozoa

Franklin 1967

Naaby-Hansen 2001

Rigshospitalet
GROWTH REPRODUCTION

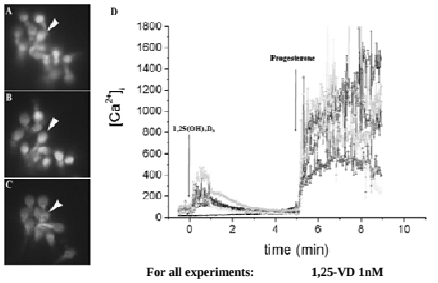
Vitamin D increases intracellular calcium In human spermatozoa



Rigshospitalet
GROWTH REPRODUCTION

ORIGINAL ARTICLE Andrology

Vitamin D is positively associated with sperm motility and increases intracellular calcium in human spermatozoa

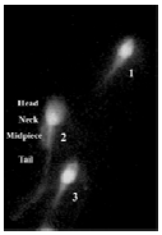


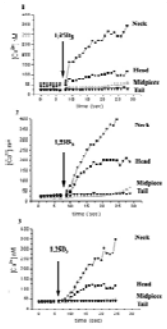
For all experiments: **1,25-VD 1nM**

Progesterone 10 uM

Rigshospitalet
GROWTH REPRODUCTION

Spatio-temporal calcium increase

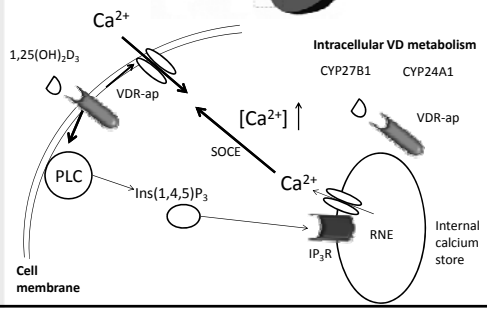




Blomberg Jensen IJA 2012

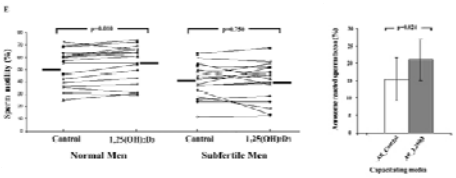
Rigshospitalet
GROWTH REPRODUCTION

Proposed mechanism of action



Rigshospitalet
GROWTH REPRODUCTION

Vitamin D induces sperm motility and the acrosome reaction



Blomberg Jensen IJA 2012

Rigshospitalet
GROWTH REPRODUCTION

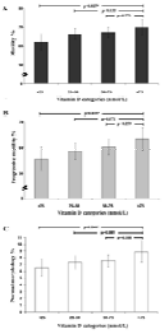
VD serum levels and semen quality

Cross sectional study 300 normal men

Adjustment for calcium level reinforced the association between VD serum level and sperm motility.

Now, we have started a randomized clinical trial including 360 infertile men with VD insufficiency (< 50nM)

www.clinicaltrials.gov



Blomberg Jensen hum reprod 2011

Rigshospitalet
GROWTH REPRODUCTION

Take home messages

- **Several environmental factors influence reproductive performance during different time points in life**
- **Sertoli cell number and function is predictive for number of spermatozoa**
- **Sperm motility and normal sperm morphology depend besides optimal spermatogenesis on maturation in the epididymis**
- **Vitamin D levels fluctuate with season and may influence sperm quality**
- **Vitamin D is metabolized in human spermatozoa**
- **VDR mediates rapid calcium release from an intracellular storage in the neck of human spermatozoa**
- **Vitamin D induces sperm motility and the acrosome reaction**
- **Expression of CYP24A1 may serve as marker for semen quality**
- **VD serum levels are positively associated with semen quality**
- **The clinical potential of vitamin D is being tested !**

Rigshospitalet
GROWTH REPRODUCTION

Acknowledgements

Department of Growth and Reproduction, Rigshospitalet

Anders Juul

Niels Erik Skakkebæk

Henrik Leffers

Niels Jørgensen

Ewa Rajpert-De Meyts

John Nielsen

Anne Jørgensen

Maria Skalkam

All the technical staff

Dept. of Physiology, University of Copenhagen

Steen Dissing

Dept. of Clinical biochemistry, Holbæk

Poul Bjerrum

Torben E. Jessen

Fertility Dept., Rigshospitalet

Anders Nyboe Andersen

Susanne Bangsbøll

Dept. of Biostatistics, University of Copenhagen

Jørgen Holm Petersen

Funding: Novo Nordisk Fonden and Danielsens fond.

The University Of Sheffield.

Banking sperm for men with cancer

Allan Pacey
University of Sheffield
Sheffield Teaching Hospitals

The University Of Sheffield.

British Fertility Society

Association of Biomedical Andrologists

A.Pacey@Sheffield.ac.uk
http://www.twitter.com/allanpacey

Outline

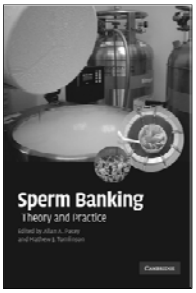
Fertility issues in survivors from adolescent cancers

A.A. Pacey*

- Referring the patient
- Obtaining a specimen
- Freezing and Storage
- Natural fertility of cancer survivors
- Assisted conception in the adult survivor
- Future technologies

Pacey (2007) Cancer Treatment Reviews 33: 646-655

Outline



- Referring the patient
- Obtaining a specimen
- Freezing and Storage
- Natural fertility of cancer survivors
- Assisted conception in the adult survivor
- Future technologies

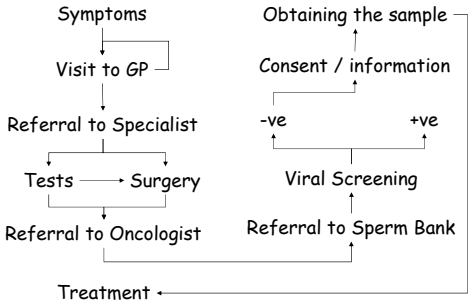
Pacey & Tomlinson (2009) Cambridge University Press

Referring the patient

The Medical Rollercoaster

Symptoms
↓
Visit to GP
↓
Referral to Specialist
↓
Tests → Surgery
↓
Referral to Oncologist
↓
Treatment

The Medical Rollercoaster



Are men offered sperm banking?

- 91% of oncology doctors in the USA think sperm banking should be offered to men at risk but only mention it to <25%. (Schover *et al.*, 2002).
- Number of men banking sperm in Spain is lower than expected given the incidence of cancer in men of reproductive age (Meseguer *et al.*, 2006).
- Problems in communication between doctors and patients in Canada were identified as a major deterrent to banking sperm (Achille *et al.*, 2006)
- 21% of oncologists were unaware of the local protocols for sperm banking (Gilbert *et al.*, 2011) and made assumptions about patient need based on age, sexual orientation ..etc

Eiser & Pacey (2011) Human Fertility 14: 208-217

Decisions about banking sperm

- Need to be seen against the background of men's experiences *prior to diagnosis*.
- Most were overwhelmed with the amount of information they were given on diagnosis and half of the men were pessimistic about future fertility.
- Decision to bank was sometimes facilitated by partners and in younger men by their fathers.
- All emphasised the importance of the oncologist in organising sperm banking and men went along with this advice.
- Few men had a clear understanding of why they were offered banking, the possible impact on treatment and how they would use banked sperm.

Eiser *et al.*, (2011) Human Reproduction 26: 2791- 2798

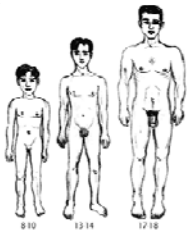
Decisions about banking sperm

"I think we just thought well we're here so I think we just said yes. One of them cases that if you're advising it we'll do it. I think it was like a no brainer really. I didn't even understand what you bank it for, I didn't understand the system. I didn't know – maybe I thought it would just come back on its own, I don't know. Maybe they told me and I was just a bit naïve or didn't take things on board or realise"

Eiser *et al.*, (2011) Human Reproduction 26: 2791- 2798

Obtaining a specimen

Age at Spermache



Spermache occurs at a:

- Median age of 13.4 (range 11.7-15.3 years of age.
- Median Testicular volume 11.5 ml (4.7 - 19.6ml)
- Pubic hair distribution (tanner stage) 2.5 (range 1 - 5).
- Median height of 160.4 cms (range 151.7 - 175.9).

Spermache is an early pubertal event

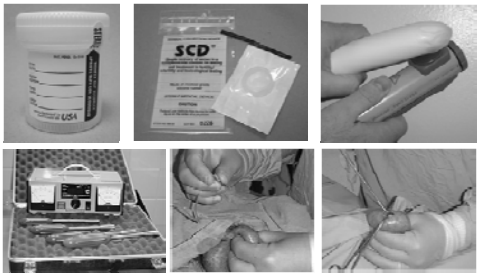
Nielsen *et al.*, (1986) *J Clin Endocrinol Metab.* **62:** 532-535

Initial Sample Quality

Disease	n	Age (years) Mean ± SEM	Sperm Count (x10^6/ml) Mean ± SEM
Hodkin's	36	16.44 ± 0.34	55.56 ± 7.30
Non-Hodkin's	6	16.83 ± 0.70	91.67 ± 22.72
Osteosarcoma	51	16.38 ± 0.24	59.14 ± 6.75
Ewings Sarcoma	24	16.67 ± 0.40	49.41 ± 9.01
ALL	7	17.43 ± 0.48	57.43 ± 23.15
AML	3	14.33 ± 0.67	18.00 ± 11.14
Testicular cancer	17	17.82 ± 0.31	31.94 ± 4.81
Leukemia	23	16.68 ± 0.35	38.96 ± 8.31
Lymphoma	11	16.17 ± 0.52	66.67 ± 15.55
Other	27	16.96 ± 0.29	36.41 ± 8.88
Healthy donors	71	22.89 ± 0.34	84.51 ± 3.39

Bahadur *et al.*, (2002) *Human Reproduction* 17: 3157-3161

Issues of sample production



Pacey & Tomlinson (2009) Cambridge University Press

Pornography and the NHS

- 36% of UK fertility clinics supply pornography to patients.
- 77% of NHS employees are female and should never have to work in an environment that endorses pornography.
- The NHS is suggesting a man should sexually objectify another woman and it encourages "adultery of the mind"
- Average spend on magazines was £21.32 per year.
- Use of hospital space for specimen collection is wasteful.

http://www.2020health.org

Benefits of Erotica


EDITORIAL

Using Erotica in Government-Funded Health Service Clinics

- Erotic videos are use in the assessment of sexual function in both males and females.
- Men using 'visual erotic material' were more relaxed and achieved ejaculation easier than those who did not.
- Men watching 'Sexual stimulating videotapes' provided better quality ejaculates than those who did not.
- No evidence that exposure of normal men to erotica results in aggressive or violent behaviour.

Wylie and Pacey (2011) *J Sex Med* 8: 1261-1265

The Obscene Publications Acts 1959 and 1964

In determining whether a prosecution would be in the public interest, the principal factors include:

- the degree and type of obscenity together with the form in which it is presented;
- the type and scale of any commercial venture;
- whether publication was made to a child or the possibility that such publication would be likely to take place

These are real issues for those providing semen storage to minors

Attorney General, in a Parliamentary Written Answer on 16 June 1997

Freezing and Storage

Preserving male fertility

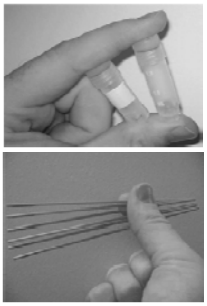

1949


1951

1953

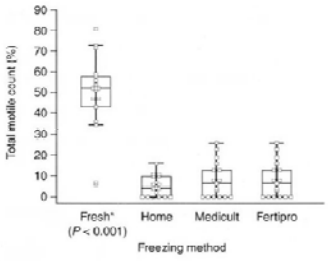
Pacey (2007) Cancer Treatment Reviews 33: 646-655

Freezing and storage



Pacey & Tomlinson (2009) Cambridge University Press

Effects of Storage



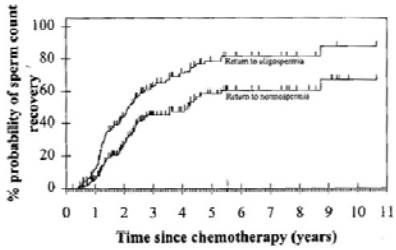
Nijs & Ombelet (2001) *Human Fertility* 4: 158-163

And then .....

Seasons change .....

After treatment ...

Natural fertility after cancer treatment



Lampe *et al.*, (1997) *J. Clin. Oncol.*, **15**: 239 - 245

Natural fertility after cancer treatment

	Number	Azoospermia	Oligozoospermia	Normozoospermia
Leukemia	13	46%	8%	46%
Lymphoma	128	59%	14%	27%
Testicular	102	12%	38%	50%
Benign	13	16%	23%	61%
Other	58	34%	33%	33%
All	314	37%	25%	38%

Bahadur *et al.*, (2002) *Human Reproduction* 17: 3157-3161

Fertility monitoring

- For most was not seen as important and was an intrusion in their everyday lives, unlike oncology follow-up which was important.
- Men were reluctant to take time of work or run the risk of having to explain the reason to their employers.
- Men tended to have semen analysis when they were establishing a new relationship or planning to start a family.
- A common deterrent to fertility testing was anxiety about the result. Men preferred not to know if their semen quality was poor.
- Information about recovered fertility was welcome, even in men who did not want any more children because it contributed to restored feelings of masculinity.

Eiser *et al.*, (2011) Human Reproduction 26: 2791- 2798

Fertility monitoring

"Again I don't see how you can get them to come in, people are quite ignorant of a lot of things, myself included, and I sort of ignored two letters because I couldn't be bothered, how you could have got, again, I don't think you could have changed my mind at that time, it was my own, when that letter came through a few month ago, I thought oh yeah, well I'll look at this and see what's what, it was my own inquisitiveness I suppose as to why I actually responded to it, if you sent me one next year I may well look at it and think no, I'm not interested or I haven't got time because I'm now settled and I know where I am, as for trying to get people in I really don't see how you could encourage people to come in, I don't.

Eiser *et al.*, (2011) Human Reproduction 26: 2791- 2798

Multivariate Logistic Regression

Odds Ratio predicting non-attendance

	OR (95% CI)	Significance
No treatment side effects	5.72 (2.10-15.56)	0.001
Experience of banking sperm	1.82 (1.17-2.82)	0.007
Attitudes to disposal	1.56 (1.01-2.42)	0.048

Pacey *et al.*, (2012) submitted

Natural fertility

For Males

Chances of being a father by the age of 35 years old:

64%

General population

63%

Cancer survivors

Magelssen *et al.*, (2008) *Human Reproduction* 23: 178-186

Childhood Cancer Survivor Study

Relative Risk of ever siring a pregnancy was 0.56 (95% CI 0.49-0.63) compared to siblings

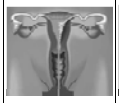
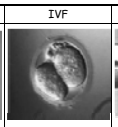
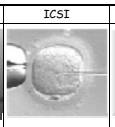
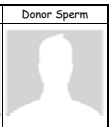
Green *et al.*, (2010) *J. Clin. Oncol.*, 28: 332-339

Contraception

Its important

Assisted conception

Conception and semen quality

Timed intercourse	IUI	IVF	ICSI	Donor Sperm
				
>15 x 10^6 sperm/ml >32% motile	>5 x 10^6 motile sperm	>1 x 10^6 motile sperm	1 to 1 x 10^6 sperm	azoospermia

European Data in 2007

No of cycles:	134,261	117,318	232,844	24,339
Pregnancy rate:	8.5%	32.4%	33.0%	12.4%

De Mouzon *et al.*, (2007) *Human Reproduction* **25:** 1851-1862

Success after long-term storage

Exclusive: Parents of the deep-freeze boy talk to the Mail

THE BABY AGED 23

Daily Mail 25th May 2004

Success after long-term storage

Successful sperm storage for 28 years

Joseph Feldschuh, M.D., James Brassel, M.D.,* Nancy Durso, M.D.,[b] and Allen Levine, M.D.**

*Lilant Laboratories, New York, New York; [b]Mid-Atlantic Fertility Center, Bethesda, Maryland; and *Orange OB/GYN Associates, New York, New York

Objective: To report on two instances of successful long-term cryopreservation resulting in live births.
Design: Case report.
Setting: The patient stored his sperm at a private sperm banking facility, and his partner underwent artificial insemination at an obstetrics/gynecology practice for one pregnancy and at a fertility center for the other.
Patient(s): One man who stored his sperm before treatment for cancer.
Intervention(s): Storage of sperm under liquid nitrogen in a cryovial cushion system. Intrauterine insemination in which the semen was thawed, washed with human tubal fluid (HTF), and inseminated.
Main Outcome Measure(s): Successful pregnancy resulting in live birth.
Result(s): Artificial insemination with semen cryopreserved for 21 and 28 years resulted in two live births.
Conclusion(s): This case report describes the to-date longest known successful cryopreservation of sperm, with two live births resulting from IUI. Successful long-term semen storage can be very beneficial for men facing impaired fertility or sterility early in life, so that they have sufficient time to make appropriate family planning decisions. (Fertil Steril® 2005;84:1017.e3–4. ©2005 by American Society for Reproductive Medicine.)
Key Words: Semen storage, cryopreservation, intrauterine insemination

Feldschuh et al., (2005) *Fertility and Sterility* **84:** 1017

Usage of frozen samples

Reference	Country	Age Range (years)	Years	Number banked	% utilised
Lass (1998)	UK	15-56	1989-1997	225	2.7%
Lass (2001)	UK	14-55	1989-2000	306	3.6%
Kelleher (2001)	Australia	n/a	1978-2000	833	7.7%
Blackhall (2002)	UK	16-44	1978-1990	122	27.0%
Ragni (2003)	Italy	15 -53	1986-2001	686	5.2%
Agarwal (2004)	USA	n/a	1982-2001	318	9.7%
Chung (2004)	USA	13-58	1993-2003	164	3.7%
Magelssen (2005)	Norway	15-45	1983-2002	422	6.9%
Meseguer (2006)	Spain	15-58	1991-2004	184	16.3%
Chang (2006)	Taiwan	13-45	1995-2004	75	4.0%
Girasole (2006)	USA	14-76	1994-2004	31	6.5%
van Casteren (2008)	The Netherlands	14-57	1983-2004	557	7.5%
Crha (2009)	Czech Republic	13-64	1995-2006	559	5.0%
Selk (2009)	Canada	n/a	2002-2005	367	8.4%
Ping (2010)	China	18-37	2003-2008	30	6.7%

Eiser & Pacey (2011) Human Fertility 14: 208-217

Problem areas

Problem areas

- Identifying males at risk and offering them fertility preservation options
- Obtaining sperm from post-pubertal males who cannot, will not or are too ill too masturbate
- Fertility preservation for pre-pubertal individuals
- Long-term funding and storage
- Access to Assisted Conception Services if they are needed

Pacey & Tomlinson (2009) Cambridge University Press

Summary

- Oncologists need to identify men at risk of infertility and offer them sperm banking as part of routine care.
- Men need access to information and support in order to make informed consent.
- Across most cancer types, there are sufficient sperm to bank.
- Many men recover their fertility after treatment and as such contraception is an important issue for young men.
- A range of Assisted Conception techniques are available to help men become fathers, either with their fresh or frozen sperm.
- Some new technologies are on the horizon, but we need to realistic about their chances of success.

Thank You!

The University Of Sheffield.

British Fertility Society

ABA Association of Biomedical Andrologists

A.Pacey@Sheffield.ac.uk
http://www.twitter.com/allanpacey

Mark your calendar for the upcoming ESHRE Campus events

- Basic Semen Analysis Course in Greek Language
  4-7 September 2012 - Athens, Greece
- Basic Genetics for ART practitioners
  7 September 2012 - Rome, Italy
- Regulation of quality and safety in ART – the EU Tissues and Cells Directive perspective
  14-15 September 2012 - Dublin, Ireland
- Basic Semen Analysis Course in Spanish language
  18-21 September 2012 - Galdakano,Vizcaya
- GnRH-antagonists in ovarian stimulation
  28 September 2012 - Hamburg, Germany
- The best sperm for the best oocyte
  6-7 October 2012 - Athens, Greece
- Basic Semen Analysis Course in Italian language
  8-11 October 2012 - Rome, Italy
- Accreditation of a preimplantation genetic diagnosis laboratory
  11-12 October 2012 - Istanbul, Turkey
- Endoscopy in reproductive medicine
  21-23 November 2012 - Leuven, Belgium
- Evidence based early pregnancy care
  29-30 November 2012 - Amsterdam, The Netherlands

www.eshre.eu
(see "Calendar")

Contact us at info@eshre.eu

eshre
SCIENCE MOVING
PEOPLE
MOVING SCIENCE

NOTES

NOTES

NOTES

NOTES

NOTES

NOTES

NOTES

NOTES