What is male fertility?
The ability to produce and deliver by normal sexual intercourse an ejaculate containing spermatozoa with the capability of causing conception in the partner at the normal rate of 20% per month

What is male fertility?
We now have the ability to produce pregnancies using assisted conception technology at a rate that exceeds the normal conception rate of 20% per month

Overcoming male fertility problems?
Bypassing nature's safeguards against faulty conceptions?
5 x Increase (0.39 – 1.94%) in de novo chromosome abnormalities in ICSI babies

<table>
<thead>
<tr>
<th>Ref</th>
<th>Fetuses</th>
<th>De novo</th>
<th>Inherited</th>
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<tr>
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<tr>
<td>Van Gold 1999</td>
<td>145</td>
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<td>Wennerholm 2000</td>
<td>1473</td>
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<td>4</td>
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<td>Bonduelle 2002</td>
<td>2175</td>
<td>16</td>
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</tr>
<tr>
<td>All ICSI</td>
<td>94465</td>
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Newborn

Bonduelle 2002
Human Reprod 17
2
5
149
Van Gold 1999
J Assit Reprod
1
57
Loft 1999
Human Reprod 14
3
101
Govaerts 1998
Human Reprod 13
-3
71
Van Opstal 1997
Human Reprod 12
5
115
Testart 1996
Human reprod 11
-3
6
Genetic abnormalities
Chromosome abnormalities (XY commonest)
CBAVD
Translocations
Y microdeletions
Environment and occupation
Hormone disrupters
Toxic substances Heavy metals e.g. Lead pesticides etc

Fertile
Subfertile
Infertile
Lifestyle
Food – obesity, lipids
Alcohol, drugs
Clothing
Warm baths
Stress
Diseases
Varicocele
Infections (chlamydia)
Antisperm antibodies
Acquired damage
Iatrogenic
Systemic

Sterile           fully fertile
What is male sterility in 2007?

- Absence of testicles
  - Agenesis
  - Castration
    - Social
    - Medical
    - Criminal
- Sertoli cells only
  - Spermatozoa can be obtained in approx 40-60% of men with an azoospermic ejaculate including those with XXY

The Skoptsy (self castrated) were the most despised of the many sects that broke from the Russian orthodox church.

Its members were peasants from the Russian heartland who turned their knives on themselves to become “eunuchs for the kingdom of heavens sake”

Short arm dicentric Y in a sterile man
Chandley et al 1986  Hum Genet 73:350
Non obstructive Azoospermia

Should we centrifuge the sample?

- 50/55 (91%) UK IVF clinic centrifuge semen for men with azoospermia
- 19/87 men who attended unit at Oxford has sufficient sperm recovered after centrifugation and careful examination of the sperm pellet to enable ICSI without the need for surgical sperm retrieval (PESA / TESA etc)


Outcome of testicular sperm recovery and ICSI in patients with non-obstructive azoospermia with a history of orchidopexy.


- 79 men with non-obstructive azoospermic men and a history of orchidopexy.
- Testicular spermatozoa were recovered in 41 patients (52%).
  - The mean age at orchidopexy of the patients was:
  - Sperm recovered - 10.6 years [95% c.i. 7.3-13.8]
  - No spermatozoa found 15.5 years (95% c.i.11.3-19.8)
- No differences were observed in the fertilisation rate, implantation rate and pregnancy rate between the orchidopexy group and a comparison group with unexplained azoospermia.
Induction of meiosis?


Fertility after death

If we become able to programme cells to undergo meiotic division then this will open the door to fertilisation using cells from other parts of the body and if so there may be no such thing as male sterility even after death!
Kaguya shows that imprinting normally blocks parthenogenesis.

**Reduced Fertility**

**Challenges**

- To identify specific fertility defects and correct them
- To predict the fertility potential so that treatment is cost effective

Infertility is a couple problem.

*The urologist should have some understanding of female problems*

<table>
<thead>
<tr>
<th>Male partner</th>
<th>Female Partner</th>
</tr>
</thead>
<tbody>
<tr>
<td>History</td>
<td>Significance of female age</td>
</tr>
<tr>
<td>Physical exam</td>
<td>History of problems that may cause Fallopian tube</td>
</tr>
<tr>
<td>Ultrasonography</td>
<td>occlusion</td>
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<tr>
<td>Semen Analysis</td>
<td>Understanding of</td>
</tr>
<tr>
<td></td>
<td>- ovulation induction</td>
</tr>
<tr>
<td></td>
<td>- interaction between male and female fertility</td>
</tr>
</tbody>
</table>
Couples who have been trying for a long time have a poor chance of spontaneous conception irrespective of test results

% chance of conception per month

Years trying without use of contraception

Examination of the man

The urologist is likely to be the only doctor who examines the man

- General virilisation
- Penis and foreskin (phimosis an balanitis)
- Testes position, size and consistency (hernia, hydrocele, epididymal cyst) (Ultrasound)
- Congenital absence of the vas deferens (low volume ejaculate)
- Varicocele
- (Prostate)

TESTICULAR VOLUME

ml = a x b x c x 0.52

cutpoint = 15 ml (both testicles)

Weidner Eurep 05
Testicular growth in an adolescent boy before and after varicocele ligation. He was one of 91 boys in a MRC longitudinal growth study.

From Hargreave 1994 Male Infertility 2nd Ed Springer

Effects of varicocele treatment in adolescents: a randomised study
Laven et al 1992 Fertil Steril 58:756

Right testis vol (ml) before and after treatment
Cumulative pregnancy rates over 12 months in couples with varicocele treated by intervention (ligation or embolization) or counselling alone

Nieschlag et al 1998

Varicocele

- Treatment of adolescent varicocele restores testicular growth in those with unilateral testicular hypertrophy
- Treatment of varicocele improves semen
- Treatment of varicocele for couples does not improve pregnancy rates (meta-analysis)

Treatment recommendations

Adolescents

- Treatment is recommended for adolescents who have progressive failure of testicular development documented by serial clinical examination
- Treatment is probably recommended for adolescents with ipsilateral testicular atrophy. Further clinical studies are needed with long-term follow up.

EAU guidelines 05
Penile Deformity

- Rare in younger men
- Associated with congenital abnormality
  - Hypospadias
  - Unilateral failure of development of genital tubule
- Commoner in older men
- Often little to find on examination of the flaccid penis
- Examination of erect penis
  - Digital (polaroid) photographs
  - Prostaglandin injection

Penile erection problems as a cause of infertility are very rare except after severe injury e.g. Paraplegia, Pelvic fracture

Predicting fertility potential from semen analysis

- Strict morphology
- Sperm function tests
  - Study of the whole ejaculate
  - Study of swim up or other selected sperm
  - Centrifugation

Poor Quality sperm

- Fertile men have upto 85% abnormal sperm forms in ejaculate (Strict criteria) WHO 1999
- Poor fertility (Hull et al 1985)
- High rates of DNA damage (Irvine et al 2000)
- High rates of aneuploidy
- High rates of pregnancy loss
- High rates of birth defects

Compared to viviparous vertebrates
Physiological and temporary variations in spermatozoa concentration

Genetic tests

- Klinefelters syndrome XXY and variants
- Translocations
  - Balanced
  - Unbalanced
- CBAVD and CF gene mutations
- Y microdeletions – Y genes
  - AZFc variable phenotype
  - AZFa and AZFb azoospermia

Prevalence of chromosome abnormalities in various male populations


TBH ESHRE 07

TBH EUREP06
CFTR Mutations in CBAVD

The more mutations that are screened the higher the percentage of men found to have mutations

<table>
<thead>
<tr>
<th>Country</th>
<th>No Patients</th>
<th>Mutations</th>
<th>% Both Alleles</th>
<th>Delta 508</th>
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<tbody>
<tr>
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<td>70</td>
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</table>

FSH is an indicator of the integrity of spermatogenesis. The higher the FSH the worse the damage but FSH cannot be used to predict complete azoospermia.
### Molecular tests

- Not yet in routine clinical practice
- One of the research challenges is to identify defects that are causative and specific
- It is likely that many abnormalities will simply reflect damaged metabolic processes common to all damaged tissues.

### Proteomics and Spermatogenesis


Automated molecular techniques will bring down the cost of testing and make it practical to perform many molecular tests on blood or sperm samples to identify defects known to be associated with reduced fertility.
Sperm banking

Adolescents more likely to produce sperm if not accompanied by mother!
Bahadur et al Human reproduction 17:2654-2656

Live birth with sperm cryopreserved for 21 years prior to cancer treatment:
Department of Reproductive Medicine, St Mary's Hospital, Manchester, M13 9JH, UK and Department of Clinical Oncology, Christie Hospital, Manchester, UK Human Reproduction, Vol. 19, No. 6, 1448-1449, June 2004

Advances in cancer treatment have led to significant improvements in the likelihood of reaching remission and long-term survival for men. Chemo- and radiotherapy-induced infertility are significant treatment side effects. Cryopreservation before the start of treatment enables sperm to be stored, thereby preserving the man’s potential fertility. Here, we describe the successful use (with ICSI) of sperm cryopreserved prior to cancer treatment, for a total of 21 years. We believe this to be the longest period of sperm cryopreservation, resulting in a live birth, so far reported in the literature.

Seager technique - The First European baby

Veterinary technique adapted for Humans
Fertility problems as a consequence of Urological procedures

- Orchidopexy and hernia repair in infancy
  - be careful of the vas
- Epididymal cysts
  - be careful of bilateral cysts in young men
- Pelvic surgery
  - advise about sperm recovery
- Renal transplantation
  - may damage the vas

Treatment for male fertility problems 1900 - 1980

- All men with poor sperm analysis
- Empiric treatments
  - e.g. Replacement therapy for pituitary insufficiency
  - Well defined subgroups

Treatment for male fertility problems 1980 – 2007

- All men with poor sperm analysis
- Assisted conception
  - Empiric treatments
  - Well defined subgroups

Louise Brown
25/7/1978

No treatment possible - not possible to recover any sperm from the testicle
IVF - ICSI for male factor infertility is an admission of failure to be able to treat the underlying male problem.

Mission statement of the Andrologist – treatments for male fertility problems that enable safe natural fertility.

- Specific safe treatment
- Assisted conception
- Well-defined subgroups
- Treatment possible but only with great risks to the future child
- No treatment possible - not possible to recover any sperm from the testicle

Irrational belief

Therapy with Testicular Extracts

- Increased physical strength, mental abilities and appetite by self-injection of animal testicle preparations

Don’t let women prefer dildos to you! Megadik will bring you to your sexual dreams! You just have to trust this excellent preparation! Soon you’ll be the only one girls will want! Megadik is your real cure!
Research treatments to improve spermatogenesis

- Molecular therapy for specific defects
  - Not very practical as most men with poor spermatogenesis have multiple molecular defects i.e. there is not a single lesion that accounts for the disorder

- Gene transfer research
  - Gene Therapy
    - Altering the germline
    - Supporting the germline

- Transplant therapy
  - Repopulating the testis with germ cells
  - Transplant between individuals
  - Stem cells
  - Into animals

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<table>
<thead>
<tr>
<th>Donor</th>
<th>Recipient</th>
<th>colonisation</th>
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<td>No</td>
<td>2002 Nagano, Panusko, Brinster: 381:1484</td>
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</tbody>
</table>

DEAF by design

Empowering genetic diagnosis to avoid having a baby with a disability is controversial enough. But a minority of deaf people would consider testing to ensure that they had a deaf child. Carina Denne finds out why.
Male Infertility

Tim Hargreave, Urological Surgeon, Edinburgh
Senior Fellow, Dept of Oncology, Edinburgh University
Chair, Scientific and Ethical Review Group UNDP / UNFPA / WHO / World Bank
Special programme of Research, Development and Research Training in Human Reproduction, WHO, Geneva
Co-editor “Andrology for the Clinician” (Published Springer 2006)
Y Micro-deletions as a cause of male infertility were first identified in my patients

All slides used in this lecture will be made viewable and downloadable from
www.urologyedinburgh.co.uk - from the home page follow the link to lectures