The General Practice Education Day
HealthEd / Generation Next
23rd July Brisbane

Male Infertility & Assisted Reproduction

Prof Robert I McLachlan FRACP, Ph.D, AM
Consultant Andrologist, Monash IVF Group
Principal Research Fellow, Hudson Inst. Med Res
Director, Andrology Australia

Declarations
- Equity interest in Monash IVF Group

Learning Objectives: GP perspective

- Systematic approach to male partner
  - identify treatable causes
  - co-morbidities
- Time- and cost-effective investigation
  expeditious diagnosis and treatment.
- Knowledge of evidence-based interventions
- Assisted Reproduction (ART)

What is Infertility?
- absence of conception
- after 1 year
- of regular, unprotected intercourse
- around the time of ovulation
  Consider individual circumstances
- couple’s level of concern
- desire for intervention
- age, co-existent problems

How many couples are affected?

- About 1:20 men are subfertile
- In ~60%, no identifiable cause
- 50% ART sole or contributory male factor
- ART accounts for ~4% of Australian births
Intracytoplasmic sperm injection (ICSI): 1992
effective bypass (not treatment) for male infertility

Providing viable sperm can be isolated in semen or testis, ART pregnancy rates in couples with severe male factor infertility are similar to other couples

Full assessment of the male partner

- Identify treatable disorders
- Provide a diagnosis
- Diagnose co-existent disease
- Consider genetic issues
- Counsel re ART safety (man & offspring)

Causes of male infertility

- Endocrine <1%
  - congenital
  - acquired

- Spermatogenesis 60%
  - idiopathic → genetic
    - acquired
    - drugs, toxins
    - infection

- Obstruction 30%
  - congenital
  - BCAV
  - acquired
  - vasectomy
  - STI

- Intercourse 7%
  - erectile & ejaculatory
  - anatomical
  - psychosexual

- Sperm antibodies 2%

Restoration of natural fertility

- Endocrine <1%
  - congenital
  - acquired

- Spermatogenesis 60%
  - idiopathic → genetic
  - acquired
  - drugs, toxins
  - infection

- Obstruction 30%
  - congenital
  - BCAV
  - acquired
  - vasectomy
  - STI

- Intercourse 7%
  - erectile & ejaculatory
  - anatomical
  - psychosexual

- Sperm antibodies 2%

Evaluation: clinical history

**General**
- General health
- Medications, drug use

**Reproductive history**
- Prior paternity
- Psychosocial issues (erectile, ejaculatory)
- Undescended testes
- Genital infection, trauma
- Previous pelvic surgery
- Symptoms of androgen deficiency
**Physical examination is essential**

GP, gynecologist, andrologist, endocrinologist

---

**Hypothalamo-pituitary-testicular axis**

**Hypothalamo-pituitary-testicular axis**

**Hypothalamo-pituitary problems**

rare but treatable

- **GnRH deficiency**
  - Isolated HH: congenital: Kallmann’s
  - Drugs: opiates, antipsychotics

- **Gonadotrophin deficiency**
  - Pituitary damage: prolactinoma, surgery
  - Sex steroid Rx: androgen abuse

---

**Causes of male infertility**

- **Endocrine <1%**
  - congenital: Kallmann’s
  - Drugs/disease: GnRH, LH, FSH, testosterone

- **Obstruction 30%**
  - congenital: BCAV
  - acquired: vasectomy

- **Intercourse 7%**
  - erectile & ejaculatory

- **Sperm antibodies 2%**

- **Semen analysis** describes variable defects in sperm:
  - number
  - motility
  - morphology (function)

- **SEVERE PHENOTYPE** → **ISOLATED DEFECT**

  - azoospermia → oligospermia
  - small testes → morphology
  - ↑ FSH ↓ inhibit B → failed fertilization

---

**Primary testicular failure = ‘Primary spermatogenic failure’**

Phenotypic description of heterogeneous disorders

Semen analysis describes variable defects in sperm

- number
- motility
- morphology (function)
Klinefelter’s Syndrome – 47,XXY

Commonest chromosomal disorder 1:600 males
Commonest cause of undiagnosed androgen deficiency
Almost all androgen deficient as adults - Benefit from replacement
70% escape diagnosis lifelong  Bojesen JCEM 2003

70% escape diagnosis lifelong  Bojesen JCEM 2003

Benefit from replacement

Klinefelter’s Syndrome: The most overlooked cause of androgen deficiency  St John B & McLachlan RI
Endocrinology Today 2015; 4(1): 8-14

70%

Assessment during infertility investigation
• Azoosperma
• FSH ↑
• LH ↑
• Testosterone ↓

Klinefelter’s iceberg

14% of men with azoosperma

~10,000 missed KS males in Australia
Failure to systemically examine male genitalia: flaw in education & practice

Not always!! may appear entirely normal and adequately virilised when clothed

From: Nieschlag and Behre, 2007

~10,000 missed KS males in Australia
Failure to systemically examine male genitalia: flaw in education & practice

From: Nieschlag and Behre, 2007

Reject your stereotypical images of KS

Classical KS in textbooks

Profound learning difficulties
narrow shoulders
reduced body hair
abdominal obesity
small testicular volume
varicose veins

From: Nieschlag and Behre, 2007

Not always!! may appear entirely normal and adequately virilised when clothed

Not always!! may appear entirely normal and adequately virilised when clothed

Classical KS in textbooks

Profound learning difficulties
narrow shoulders
reduced body hair
abdominal obesity
small testicular volume
varicose veins

From: Nieschlag and Behre, 2007

~10,000 missed KS males in Australia
Failure to systemically examine male genitalia: flaw in education & practice

From: Nieschlag and Behre, 2007

Klinefelter’s Syndrome: The most overlooked cause of androgen deficiency  St John B & McLachlan RI
Endocrinology Today 2015; 4(1): 8-14

From: Nieschlag and Behre, 2007

Not always!! may appear entirely normal and adequately virilised when clothed

Not always!! may appear entirely normal and adequately virilised when clothed

Classical KS in textbooks

Profound learning difficulties
narrow shoulders
reduced body hair
abdominal obesity
small testicular volume
varicose veins

From: Nieschlag and Behre, 2007

~10,000 missed KS males in Australia
Failure to systemically examine male genitalia: flaw in education & practice

From: Nieschlag and Behre, 2007

Klinefelter’s Syndrome: The most overlooked cause of androgen deficiency  St John B & McLachlan RI
Endocrinology Today 2015; 4(1): 8-14
Laboratory investigations in male infertility

- Serum FSH, LH and testosterone
- Semen analysis
- Testicular histology
- Genetic testing

Serum FSH reflects the state of sperm production

FSH levels in azoospermic men

Schoor et al J Urol 2002

Co-morbidities more prevalent in infertile men must be actively sought

1. Testicular cancer 2-10 fold risk
2. Androgen deficiency ~10%
3. Disorders impact reproductive health Numerous conditions and treatments Lifestyle

Presentation with infertility is a ‘window of opportunity’ to review male health

Semen analysis is important but only a rough guide to fertility

Troop number and speed must be combined with appropriate deployment and individual quality

Sperm concentration and motility Appearance (morphology) weak surrogate of ability

Semen analysis is important but only a rough guide to fertility

World Health Organization 2010 reference ranges
5% centile values of fertile men
Sperm conc >15 million/ml
A poor result must be repeated in 6 weeks

USE SPECIALIST LAB

Rough prediction of natural fertility potential

semen analysis does not test sperm function!
Chromosomal anomalies: numerical & structural

- Much more common in infertile men
  - Sex chromosomal:
    - Autosomal: 4.2% (0.14%)
    - Autosomal transloc / inversions: 1.5% (0.25%)
  - Autosomal:
    - Numerical or structural: 1.5% (0.25%)

- Relationship to sperm density
  - Azoospermia: 13.7%
  - Oligospermia: 4.6%

- Only a minority are clinically suspected

**Clinical recommendation:** cyto genetic analysis of all azoo- or oligospermic men

Y chromosome microdeletions: spontaneous loss of key spermatogenic on long arm

- Accounts for ~5% of severe male infertility

Bilateral congenital absence of the vas

- Absent Wolffian duct derivatives
- Mildest form of cystic fibrosis
- 1-2% of male infertility
- CFTR mutations
  - >80% hetero-compound heterozygotes
- Female CFTR status

Background rate of natural fertility in idiopathic male infertility is significant

- Significant variables:
  - Severity of semen defect
  - Duration of infertility
  - Female age & reproductive status - compounding effect

Empirical treatments in idiopathic male infertility: unproven or disproven

- ‘Alternative’ therapies widely used
  - Vitamin supplements
  - Antioxidants
  - Traditional therapies

Varicocele

- Well recognized association with infertility
- Recent systematic reviews suggest fertility benefit in selected cases
- Specialist input
Lifestyle and male infertility

Lifestyle and fertility
Obesity
Smoking
Drug use
Involves GPs
In health care

Assisted reproduction in male infertility

Overall strategy: treat the couple

Simple things first: timing of sex etc

Treatments
- Artificial insemination
- Conventional IVF
- Microinjection ICSI

Insemination

**Standard Insemination**
30,000 motile sperm compete

**Intracytoplasmic sperm injection**
single morphologically normal motile sperm selected

Monash IVF Clinical Pregnancy & Birth Rates
Day 5 blastocyst transfers

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Pregnancy Rate</th>
<th>Birth Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;25</td>
<td>40.0%</td>
<td>30.0%</td>
</tr>
<tr>
<td>25-29</td>
<td>30.0%</td>
<td>20.0%</td>
</tr>
<tr>
<td>30-34</td>
<td>20.0%</td>
<td>10.0%</td>
</tr>
<tr>
<td>35-39</td>
<td>10.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>40-44</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

Indications for ICSI

- Ejaculated sperm of ‘poor quality’
- Testicular or epididymal sperm (functional immaturity)
- Low sperm vitality (presumed DNA damage)
- IVF failed fertilisation (functional defect)

Decline in reproductive hormones and function
Female: invariable (unaffected by health), sudden, severe
Male: variable (follows general health), gradual and modest
Obstructive azoospermia and ART

Cost effective strategy: Vasectomy - infertility

- reversal surgery vs ICSI
- Fine needle aspiration from epididymis or testis.

Only strategy: Congenital absence of vas/ Cystic fibrosis

Excellent pregnancy rates: similar to age-matched female factor

Testicular sperm extraction - TESE

Focal spermatogenesis in >50% men

Technique

- Needle aspiration
- Open biopsy
  - Random ~50%
  - Micro dissection ~65%

-isolating sperm from testicular biopsy in azoospermia: in essence it's like........

Micro-TESE Klinefelter syndrome

Testicular sperm in ~40% KS

Low risk of abnormal sperm as the stem cell is usually 46, XY

Normal offspring
Key messages

1. **Systematic evaluation** of both partners
2. **GP initiated basic investigations** at presentation
3. **Spermatogenic failure** often idiopathic & untreatable
4. **Co-morbidities**: androgen deficiency, testis cancer
5. **Evidence-based treatment limited**: reliance on ART
6. **Lifestyle and older parenting** challenges

Clinical summary guides

Andrology Australia Health Professional Education - Accredited for GPs & PHCNs

<table>
<thead>
<tr>
<th>Title</th>
<th>Course description</th>
<th>Type</th>
<th>RACGP or ACRRM</th>
<th>PRPD points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reproductive health disorders in young adult males (younger male health)</td>
<td>Male infertility, Klinefelter’s syndrome, testis cancer, immature sperm &amp; prostatitis</td>
<td>Online ALM (Free)</td>
<td>Category 1</td>
<td>40 PRPD points</td>
</tr>
<tr>
<td>Reproductive health disorders in middle-aged and older males (older male health)</td>
<td>Case studies: Androgen deficiency, erectile dysfunction &amp; co-morbid disease, prostate disease</td>
<td>Online ALM (Free)</td>
<td>Category 1</td>
<td>40 PRPD points</td>
</tr>
<tr>
<td>Engaging Aboriginal and Torres Strait Islander males in different primary health care settings</td>
<td>Knowledge, skills and communication strategies to better engage Aboriginal and Torres Strait Islander men in primary care settings</td>
<td>Online ALM (Free)</td>
<td>Category 1</td>
<td>40 PRPD points</td>
</tr>
<tr>
<td>A lot of Aboriginal men sort of keep it to themselves</td>
<td>Tailored knowledge and skills to initiate dialogue and engagement</td>
<td>Online videos &amp; Male Health Education DVD (Free)</td>
<td>Category 2</td>
<td>2 Core points</td>
</tr>
<tr>
<td>Primary Health Care for Men</td>
<td>Knowledge, skills and communication strategies to assist primary health care nurses to better engage men in the primary health care setting</td>
<td>Online module (Free)</td>
<td>APNA endorsed</td>
<td>2 APNA Endorsed CPD hours</td>
</tr>
</tbody>
</table>

Evidence-based independent support to ~600 'grass roots' and national organisations

**www.andrologyaustralia.org**

120,000 pages view a month - #1 site

-------------------------

Federal Health Department defunded Andrology Australia from 1st July 2016

Blow to men’s health promotion and education for community and professional

Appeal for support to challenge this decision
Sign the petition ASAP

Raise awareness in your practices/waiting rooms

Write to local member or Senator

Know anyone in Cabinet??