Male Factor Infertility: investigation and management incl. Assisted Reproductive Treatments

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Declarations
- Equity interest in Monash IVF
- Consultant Healthscope Pathology Semen lab

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

Referral and 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

Male infertility
- About 1:20 men are subfertile
- In ~60%, no identifiable cause
- 50% ART sole or contributory male factor
- ART accounts for 3.4% of Australian births

How many couples are affected?

15%
Intracytoplasmic sperm injection (ICSI): 1992

- Effective bypass (not treatment) for male infertility

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

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ART approaches:

- **Only option**
- **Cost effective**

Evaluation: clinical history

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

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

Spermatogenesis requires FSH and testosterone action on healthy Sertoli & germ cells.

Hypothalamo-pituitary-testicular axis

- 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% gonadotrophin deficiency
  - congenital
  - acquired

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- Causes of male infertility

- Hypothalamo-pituitary-testicular axis
Primary testicular failure = ‘Primary spermatogenic failure’

Phenotypic description of heterogeneous disorders

Semen analysis describes variable defects in sperm - number and/or motility and/or morphology (function)

Descriptive diagnostic terms - ‘oligoasthenoteratospermia’

<table>
<thead>
<tr>
<th>SEVERE PHENOTYPE</th>
<th>ISOLATED DEFECT</th>
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<tbody>
<tr>
<td>azoospermia</td>
<td>oligospermia</td>
</tr>
<tr>
<td>small testes</td>
<td>morphology</td>
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<tr>
<td>↑ FSH ↓ inhibin B</td>
<td>failed fertilization</td>
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</table>

Klinefelter’s Syndrome – 47XXY

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 detection strategies a major challenge

Reject your stereotypical images of KS

Classical KS in textbooks

- Profound learning difficulties
- narrow shoulders
- reduced body hair
- horizontal pubic hairline
- gynecomastia
- abdominal obesity
- small testicular volume
- varicose veins

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

~10,000 missed KS males in Australia

Failure to systemically examine male genitalia: flaw in education & practice

Klinefelter’s syndrome: The most overlooked cause of androgen deficiency. St John B & McLachlan R1

Endocrinology Today 2015; 4(1): 8-14
### Laboratory investigations in male infertility

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

### 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*

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**Serum FSH reflects the state of sperm production**

**Normal:** obstruction  
**Elevated:** spermatogenic failure

*FSH levels in azoospermic men*

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**One in seven consecutive infertile men have evidence of androgen deficiency**

*Andersson, A. M. JCEM 2004*

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*Many cases of androgen deficiency go unrecognised*
One in seven consecutive infertile men have evidence of androgen deficiency - Andersson, A. M. JCEM 2004

Never start testosterone therapy without considering fertility. Testosterone has a contraceptive action.

Many cases of androgen deficiency go unrecognised.

Semen analysis is important but only a rough guide to fertility.

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

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!

Background rate of natural fertility in idiopathic male infertility is significant.

Chromosomal anomalies: numerical & structural

- Much more common in infertile men men
  - sex chromosomal: 4.2% (0.14%)
  - autosomal: 1.5% (0.25%)
  - Johnson Fertil & Steril 1998

- Relationship to sperm density
  - azoospermia: 13.7% numerical or structural
  - autosomal transloc / inversions
  - Van Assche Hum Reprod 1996

- Only a minority are clinically suspected

Clinical recommendation: cytogenetic 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

Courtesy C Krausz

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

% pregnant

0 20 40 60 80

0 1 2 3

Years

modified from Baker et al 1986

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

Involve 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

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**Insemination**

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

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

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**Monash IVF Clinical Pregnancy & Birth Rates**

Day 5 blastocyst transfers

<table>
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<tr>
<th>Female</th>
<th>Male</th>
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<td>&lt;25</td>
<td>30</td>
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<td>40-44</td>
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Decline in reproductive hormones and function

Female: Invariable (unaffected by health), sudden, severe

Male: Variable (follows general health), gradual and modest

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**Indications for ICSI**

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

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**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
Obstructive or ejaculation problems now managed by microinjection ICSI

- Epididymal obstruction of any cause
- Ejaculatory duct obstruction
- Prostate surgery or other bladder base problems
- Electro-ejaculation: spinal cord injury

Major changes to urology practice

Tubule heterogeneity in spermatogenic failure

‘Non-obstructive’ azoospermia

Sertoli cell only tubule

Tubule heterogeneity in spermatogenic failure

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

32 years  FSH 35 IU/L  Testes 4 ml

Testicular sperm in ~40% KS

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

Normal offspring

Micro-TESE Klinefelter syndrome

32 years  FSH 35 IU/L  Testes 4 ml
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

Courses for GPs

Accredited education provider through RACGP

<table>
<thead>
<tr>
<th>Course description</th>
<th>Type</th>
<th>RACGP QI Points</th>
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<tbody>
<tr>
<td>Younger male health, male infertility, testicular cancer, Klinefelter's, premature ejaculation, prostatitis</td>
<td>Online ALM (Free)</td>
<td>Category 1 PRPD points</td>
</tr>
<tr>
<td>Older male health, androgen deficiency, erectile dysfunction &amp; co-morbid disease, prostate disease</td>
<td>Online ALM (Free)</td>
<td>Category 1 PRPD points</td>
</tr>
<tr>
<td>Aboriginal and Torres Strait Islander males, tailored knowledge and skills to initiate dialogue and engagement</td>
<td>Male Health Education DVD (Free)</td>
<td>Category 2 Core points</td>
</tr>
<tr>
<td>Men's sexual and reproductive health</td>
<td>Distance education (Fee payable)</td>
<td>Contact the Coordinator</td>
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