Male infertility

Normal fertility depends upon:

- Spermatogenesis
- Epididymal maturation
- Coitus
- Transport through female genital tract
- Fertilisation
- Implantation

Except for implantation, all factors are influenced by male factors i.e. hypospadias for coitus, anti-sperm antibodies influence progression through female tract and fertilisation, etc.

Infertility defined as an inability to conceive after 12 months of unprotected intercourse. However, Won et al (1984) showed that rates of conception dependent upon female age

Chances of conception:

If fertile

- 20-25% per month
- 75% at 6 months
- 90% at one year

If infertile

- 1-3% per month
- 25% within 2 years of trying
- 33% at some time by intercourse alone

Male factors implicated in 50% of cases of infertility. 10-20% estimated to be purely due to male factors. Up to 10% of these thought to be associated with severe underlying medical abnormalities.

Top three causes of male infertility:

- Varicocele 38%
- Idiopathic 23%
- Obstruction 13%
- Endocrinopathy ~2%

Initial assessment of the infertile male

History

- Previous paternity
- Current attempts at paternity
  - Sexual frequency
  - Timing of intercourse re. female menstrual cycle
  - Use of lubricants
- Family history
  - UDT
  - Midline defects
  - Hypogonadonism
- Past medical history
  - Mumps orchitis
  - DM
  - Cystic fibrosis
  - Systemic disease
Cancer/chemotherapy
Past surgical history
   Orchidopexy
   Vasectomy/vasectomy reversal
   Varicocele repair
   Retroperitoneal surgery
   Bladder neck surgery
Drug history (including alcohol and nicotine – see table)
   NB. spermatogenesis takes 74 days – therefore sperm analysis
   reflect lifestyle 2.5 months ago
Occupational exposure
   Ionising radiation
   Chronic heat
   Benzene solvents
   Pesticides
   Dyes
   Herbicides
   Heavy metals

**Box 1** Drugs with potential adverse effects on male fertility.

- Alcohol
- Alkylating agents (e.g. cyclophosphamide)
- Allopurinol
- Antipsychotics
- Arsenic
- Aspirin (large doses)
- Caffeine
- Calcium-channel blockers
- Cimetidine
- Cocaine
- Colchicine
- Dibromochloropropane (pesticides)
- Diethylstilbestrol
- Lead
- Lithium
- Monoamine oxidase inhibitors
- Marijuana
- Medoxyprogesterone
- Nicotine
- Nitroturantoin
- Phenytoin
- Spiroprolactone
- Sulfasalazine
- Testosterone
- Tricyclic antidepressants
- Valproic acid

Physical examination
General
   Body habitus
   Gynaecomastia
Male infertility

Secondary sexual characteristics (facial & axillary hair etc.)
Genitals (standing and supine)
- Pubic hair
- Phallus size
- Hypospadias
- Chordee
- Peyronie’s plaques

Testes
- Location
- Size
- 80% testis volume = spermatogenesis
- Consistency
- Contour

Epididymis, vas and spermatic cord
- Presence (epidymal agenesis, bilateral vasal aplasia etc)
- Volume
- Varicocele
- Lipoma of cord

Digital rectal examination
- Prostate size, consistency and contour
- Midline prostate cysts
- Seminal vesicle dilatation

Semen analysis

Updated WHO 2010 criteria

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Lower reference limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Semen volume (mL)</td>
<td>1.5 (1.4–1.7)</td>
</tr>
<tr>
<td>Total sperm number (10^9) per ejaculate</td>
<td>39 (33–46)</td>
</tr>
<tr>
<td>Sperm concentration (10^6) per mL</td>
<td>15 (12–16)</td>
</tr>
<tr>
<td>Total motility (PR+NP, %)</td>
<td>40 (38–42)</td>
</tr>
<tr>
<td>Progressive motility (PR, %)</td>
<td>32 (31–34)</td>
</tr>
<tr>
<td>Vitality (live spermatozoa, %)</td>
<td>56 (55–63)</td>
</tr>
<tr>
<td>Sperm morphology (normal forms, %)</td>
<td>4 (3.0–4.0)</td>
</tr>
<tr>
<td>Other consensus threshold values</td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>≥ 7.2</td>
</tr>
<tr>
<td>Peroxidase-positive leukocytes (10^6) per mL</td>
<td>&lt; 1.0</td>
</tr>
<tr>
<td>MAR test (motile spermatozoa with bound particles, %)</td>
<td>&lt; 50</td>
</tr>
<tr>
<td>Immunobead test (motile spermatozoa with bound beads, %)</td>
<td>&lt; 50</td>
</tr>
<tr>
<td>Seminal zinc ((\mu\text{mol}/\text{ejaculate}))</td>
<td>≥ 2.4</td>
</tr>
<tr>
<td>Seminal fructose ((\mu\text{mol}/\text{ejaculate}))</td>
<td>≥ 13</td>
</tr>
<tr>
<td>Seminal neutral glucosidase ((\text{mU}/\text{ejaculate}))</td>
<td>≥ 20</td>
</tr>
</tbody>
</table>

*MAR = Mixed antiglobulin reaction; PR = progressive; NP = non-progressive*

Motility (WHO 1999)
1. Rapidly progressive
2. Slowly progressive
3. Non-progressive
4. Non-motile
Male infertility

NB. Large variability in quality. Therefore at least two samples after 48-72 hours of abstinence. No one factor describes male fertility, but percentage of sperm with normal morphology best discriminator. > 48 million/ml with normal motility and morphology recently predictive of IVF success (Guzick 2001).

NB. morphology alone not predictive. Men with normal fertility can have up to 85% abnormal forms.

Distribution of male infertility by semen analysis

- Multiple abnormalities: 49%
- Normal: 14%
- Azoospermia: 14%
- Single abnormality
  - Low volume: 7%
  - Asthenospermia: 6%
  - Teratospermia: 4%
  - Oligospermia: 4%
  - Pyospermia: 2%

Further evaluation of male infertility should be directed towards the predominant semen finding

- Normospermia
- Low volume
- Azoospermia
- Oligospermia
- Asthenospermia

---

Head
Length: 5-6 μm
Width: 2.5 - 3.5 μm
Acrosome: 40% - 70% of head

Midpiece
Width ≤ 1 μm
Length 1.5 x head length

Tail
Approximately 45 μm long
Uniform
Thinner than midpiece
Uncoiled
Free from kinks

Cytoplasmic droplets
Less than one half of head area
In midpiece only
Male hormone evaluation
Incidence of clinically significant endocrinopathy presenting as infertility 2%
Standard assessment T, FSH, LH and PRL
Indicated in men with low sperm count, low volume or suspicion of endocrinopathy
Not required for men with asthenospermia, teratospermia, pyospermia, OAT

<table>
<thead>
<tr>
<th>Condition</th>
<th>T</th>
<th>FSH</th>
<th>LH</th>
<th>PRL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Primary testis failure</td>
<td>Low</td>
<td>High</td>
<td>Normal/high</td>
<td>Normal</td>
</tr>
<tr>
<td>Hypogonadotropic hypogonadism</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Normal</td>
</tr>
<tr>
<td>Hyperprolactinemia</td>
<td>Low</td>
<td>Low/normal</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Androgen resistance</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>Normal</td>
</tr>
</tbody>
</table>

FSH, follicle stimulating hormone; LH, luteinizing hormone; PRL, prolactin; T, testosterone.

FSH related to number of functioning germ cells
Maturation arrest (failed spermiogenesis) — normal FSH
One functioning testis — high FSH
Primary testis failure — high FSH

NB. FSH greater than 3x ULN indicative of testis failure. In presence of small testes, probably no value in performing testicular biopsy, unless attempting to retrieve sperm at same time for ICSI.
Testis biopsy

1. Not indicated in azoospermia if:
   (i) Normal testis volume AND
   (ii) Normal gonadotropins AND
   (iii) CBAVD
   Need genetic counselling vs. cystic fibrosis, then TESE

2. Not indicated in azoospermia if:
   (i) Small volume atrophic testes
   (ii) FSH > 3 x ULN
   Need genetic counselling vs. microdeletions/chromosomal abnormality, then TESE

3. Not indicated in azoospermia if:
   (i) Small volume atrophic testes
   (ii) FSH > 3 x ULN
   (iii) Y-gene microdeletion showing AZFa or AZFb defect (maturation arrest or sertoli-only – little chance of TESE finding sperm for ICSI)
**Normospermia**
If semen analysis normal, indicates normal spermatogenesis and spermiogenesis. However sperm still needs to penetrate cervical mucus, progress through endometrium and fallopian tubes, bind to and penetrate zona pellucida, release enzymes from acrosomal cap, penetrate oocyte and engage in transcription and translation. Following therefore may be performed. NB. Sperm viable for 5 days, ova viable in fallopian tube for 24 hours.

**Sperm factors**
- **Anti-sperm antibody assay**
  Simplest and commonest is mixed antibody reaction, MAR (see above). Use rbc's bound with anti-human AB. Detects human IgG bound to sperm cell antigens.
- **Zona-pellucida binding assay**
  Animal ova cannot be used as zona pellucida prevents cross-species sperm penetration
  Thus uses human ova (cadveric/donated) – rarely performed
- **Zona-free hamster ova penetration assay**
  Assesses capacitation, acrosome cap reaction, oocyte penetration
  Normal penetration rates 10-30%. Abnormal suggests ICSI rather than conventional IVF
  If failed penetration may indicate inappropriate premature acrosome cap reaction – could do formal EM acrosome cap assay but still going to offer ICSI anyway
- **Chromatin integrity assay (TUNEL testing)**

**Female or mixed factors**
- **Post-coital sperm-mucus interaction testing**
  Done just before ovulation – thin mucus
  Normal test if 10-20 sperm/HPF (x400 magnification) and progressive motility – excludes cervical factor or deposition abnormality
  Persistently abnormal PCT suggests hyperviscous, unfavourable cervical mucus – refer for IUI

**Evaluation of ovulation**
- **Menstrual cycle**
  Body temperature
  Falls prior to ovulation, increases by 0.4 degrees between ovulation and menstruation
- **Hormone analysis** [Day 3 FSH, day 14 LH, day 21 progesterone indicates adequacy of follicle stimulation, ovulation, and corpus luteum function; PRL excludes hyperpituitarism]

**Anatomy**
- **Transvaginal USS**
Lap and dye

Asthenospermia

<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition (WHO 1999)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Rapidly progressive</td>
</tr>
<tr>
<td>2</td>
<td>Slowly progressive</td>
</tr>
<tr>
<td>3</td>
<td>Non-progressive</td>
</tr>
<tr>
<td>4</td>
<td>Non-motile</td>
</tr>
</tbody>
</table>

Defined as reduced sperm motility or progression

Causes

- Antisperm antibodies
  - Spermatozoal structural defects (absence of dynein arms in midpiece)
  - Immotile cilia syndrome
  - Prolonged abstinence
  - Varicocele
  - Infection (a/w leucocytospermia = high oxygen reactive species which can damage sperm)

Anti-sperm antibodies

- Found in 10% men with infertility cf. 2% fertile men
- Blood-testis barrier formed by tight junctions between Sertoli cells.
- Exists to prevent autoimmune destruction of germ cells displaying non-self antigens after meiosis
- Although conditions which disrupt blood-testis barrier (torsion, testicular fixation, infection) have been implicated in the development of anti-sperm antibodies, the only definite association is with obstruction [up to 60% pts after vasectomy (Fuchs 1983) and 30% with CBAVD (Patrizio 1992)]
- Antibodies may be IgA (from genital tract mucosal surfaces) or IgG (blood).
- Explains why serum tests may be negative. Direct tests such as MAR therefore required.

Management

1. Corticosteroids: not particularly good at supressing Ab formation.
   - One PC-RCT of intermittent steroids reported 30% pregnancy rate vs. 10% for placebo (Hendry 1990). Other trials no effect (Haas 1987)
2. Alternative is sperm processing and assisted conception
   - Chymotrypsin used to break of Fc component. Chymotrypsin-IUI better than conventional IUI, but not as good as ICSI

Immotile cilia syndrome

- Axoneme (microtubule rod which runs from head to tail) sperm defects associated with other ciliary abnormalities in respiratory tract leading to chronic sinusitis and bronchiectasis. Known as ICS. When associated with situs inversus = Kartagener’s syndrome. No specific treatment. Offer ICSI after adequate genetic counselling

Leucocytospermia

- Reactive oxygen species produced by wbcς a/w poor sperm motility. Also immature sperm cells (spermatids) which have poorly developed tails appear round on microscopy. Can be differentiated by specific stains. High confirmed
Male infertility

WBCs a/w infection/inflammation. Search for sources of infection, including urethral cultures for chlamydia & mycoplasma. Semen culture useless due to contamination – 83% positive in one study (Eggert-Kruse 1992)

Management (no evidence):
- Empirical antibiotics
- Anti-inflammatories
- Frequent ejaculation
- Prostate massage
- Sperm processing, then IUI,IVF or ICSI

Oligospermia
Sperm density< 20 million/ml
Usually a/w other sperm defects i.e. OAT
Isolated oligospermia rare

Causes
- Idiopathic
- Gonadotoxins
- Endocrine abnormality (e.g hyperprolactinoma)
- Varicocoele
- Genetic abnormality

If sperm counts < 10 million/ml, full hormonal evaluation recommended.
Isolated FSH elevation indicates failure of spermatogenesis rather than endocrinological abnormality

Management
- Exclude gonadotoxins
- Exclude endocrinopathy
- Repair varicocoele
- Consider IVF/ICSI after genetic testing for Y microdeletions (see azoospermia)

Varicocoele and Oligo-astheno-teratospermia (OAT)
Infertile men with varicoceles have reduced motility in 90% and oligospermia in 65%. Also immature forms and tapered sperm cells.

Theories include higher testicular temperature and reflux of metabolites from renal vein.

Size of varicocoele and degree of testicular atrophy a/w severity of effect
Varicocoele repair a/w catch-up growth in patients with varicoceles and loss of volume (Kass 1987, Paduch 1997). Semen parameters and subsequent fertility rates also shown to improve (Okuyama 1988; Salzhaer 2004).

**Improvement in seminal parameters is demonstrated in approximately 70% of patients after surgical varicocele repair.** Improvements in motility are most common, occurring in 70% of patients, with improved sperm densities in 51% and improved morphology in 44% of patients.

Controversy centred around effect of varicocele repair on pregnancy rates. Some early studies were uncontrolled, and one of the often quoted negative studies incorporated treatment of female factors in the ‘untreated’ arm.
Male infertility

Reviews of the literature have also conflicted. Schlegel 1997 reported PR of 33% in treated group vs. 16% in the untreated arm.

Table 4. Controlled trials addressing the treatment of palpable varicoceles.

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients per arm</th>
<th>Pregnancy rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Treatment</td>
</tr>
<tr>
<td>WHO²</td>
<td>100</td>
<td>120</td>
</tr>
<tr>
<td>Nieschlag et al.³⁰</td>
<td>63</td>
<td>62</td>
</tr>
<tr>
<td>Madjar et al.²⁹</td>
<td>25</td>
<td>20</td>
</tr>
<tr>
<td>Unweighted mean</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

*This study was conducted but never published. See reference³⁰ for details.

Evers et al (Cochrane review) however famously reported no difference. However multiple problems with Evers metaanalysis (4):

1. Patients with subclinical varicoceles were included
2. Patients with normal semen parameters included
3. Patients with severe oligospermia were excluded
4. Female factors were treated in ‘control’ arm

Recently Marmar re-evaluated the evidence to only include patients with oligospermia and a palpable varicocele, conclusively showing improved pregnancy rates in the treated arm (RR 2.87)

On the basis of above, varicocele repair recommended for men with palpable varicocele with low sperm counts.

NB. No evidence for azoospermia (although can result in detectable sperm count for ART)

No evidence for subclinical varicoceles

Low volume ejaculate (<1.5ml)
Causes
- Improper collection
- Low serum testosterone
- Retrograde ejaculation
  - Bladder neck surgery
  - Spinal cord injury
  - DM
- Ejaculatory duct obstruction*
- CBAVD*
- Anejaculation

* Associated with pH < 7.2 and Fructose < 120 mg/dL. CBAVD = azoospermia, but ejaculatory duct obstruction may be associated with low numbers of sperm following examination of sperm pellet after centrifuge.

Evaluation (see below)
- Hormone profile
- Semen analysis for pH and fructose
- Post-ejaculate urine sample
Retrograde ejaculation
10-15 sperm per HPF (x400)
Options include medical therapy vs. ART
May be due to anatomical (BNI/TURP) or neurological (DM/MS/retroperitoneal surgery) causes. Medical therapy not successful in anatomical BN disruption Phenylpropanolamine (75 mg bid), ephedrine (25 to 50 mg qid), pseudoephedrine (60 mg qid), and imipramine (25 mg bid) all tried. Few studies documenting efficacy
Should be given 7-10 days prior to planned ejaculation. Continuous therapy a/w tolerance and should not be recommended
If fails – sperm retrieval after centrifugation, washing and IUI. Urine pH can be toxic to sperm. Urinary alkalinisation recommended for 24 hours prior to planned ejaculation (Target pH 7.5). can use sodium bicarbonate 650mg qds or baking soda in water.
Male infertility

Anejaculation (emission failure)
Typically patients with spinal cord injury
70% patients respond to penile vibratory stimulation (usually those with lesions above T10 with intact bulbocavernosus reflex). Standard vibrators work fine. For failures (including those with lesions below T10), rectal probe electroejaculation works in approx 75%. Requires GA for those with partial sensate lesions. Watch out for autonomic dysreflexia (lesions above T6). Pre-treat with 20mg sublingual nifedipine prophylaxis 15 mins beforehand.
NB. Urine should be collected in all those with stimulated emission for centrifuge as retrograde ejaculation commonly seen. Sperm quality usually poor – probably due to stasis rather than stimulation itself. Thus most pts need IVF/ICSI as IUI typically unsuccessful.

Ejaculatory duct obstruction
Rare – accounts for 1-5% of obstructive cases of male infertility
May be congenital (utricile, mullerian or wolffian duct cysts, congenital atresia) or acquired (calculus, cyst, infection a/w prior surgery)
Oligospermia/azoospermia with
- Low volume (<1.5 mL)
- Low pH (<7.2)
- Low fructose (120 mg/dL)
- Low or absent coagulation (PSA predominates)
Characteristic TRUS findings
- Dilated seminal vesicles (ULN 1.5cm in TV plane) best indicator
- Hypoechoic areas/cyst reported but low specificity
- Calcium casting acoustic shadow
NB. Aspiration of dilated seminal vesicles at time of TRUS makes diagnosis and obviates need for testis biopsy
Because TRUS overdiagnoses up to 50% of patients, vasography recommended prior to TURED. Also good for equivocal cases on TRUS
TURED
- Improved semen parameters in 75%
- Pregnancy rate 25%
- No controlled trials of sham treatment
- Complications in 10%
  - Haematuria
  - Thin ejaculate
  - Epididymitis
**Azoospermia**  
Absence of sperm in ejaculate  
Ensure adequacy of examination  
x2 samples after at least 48-72 hours abstinence  
Centrifuge pellet and examine  
Due to failed spermatogenesis or obstruction.  
10-20% of cases of male infertility: 50% obstructive, 50% non-obstructive  
Obstructive may be congenital or acquired; non-obstructive may be testicular or non-testicular:  

### Non-obstructive  
**Testicular**  
- Chromosomal abnormality (e.g. Kleinfelter's)  
- Y gene microdeletions  
- Idiopathic  
- UDT  
- Gonadotoxins  
- Chemo/RT  
- Viral orchitis  
- Torsion  

**Non-testicular**  
- Hypogonadotrophic hypogonadism (Kallman's syndrome)  
- Hyperprolactinoma  
- Idiopathic gonadotropin deficiency  
- Gonadotropin suppression  
  - Pituitary tumour  
  - Drugs (alcohol, anabolic or glucocorticoid steroids)  
  - Systemic illness (cancer/uraemia)  

### Obstructive  
**Congenital**  
- CBAVD*  
**Acquired**  
- Vasectomy  
- Trauma (renal Tx, pelvic trauma)  
- Infection  
- Ejaculatory duct obstruction*  

* a/w low volume ejaculate  

Testicular volume proportional to amount of spermatogenesis  
FSH proportional to number of functioning germ cells  
Therefore 3 crucial elements to investigation of azoospermia  
- Testicular examination  
- Identification of vasal aplasia (in 30% of cases – see below)  
- FSH measurement  

NB. FSH greater than 3x ULN indicates severe failure of spermatogenesis
Obstructive azoospermia
If testes normal, vasa present and FSH normal, highly likely to be obstructive.
Site of obstructive azoospermia in 321 men (Ralph et al)
  Intratesticular  16%
  Epididymal     51%
  Bilateral vasa aplasia  18%
  Unilateral vasa aplasia  12%
  Ejaculatory duct  1%

~ 30% of men have absence of one or both vasa. Unilateral vasa aplasia should be managed as for CBAVD
Most series recommend diagnostic testicular biopsy +/- vasography in men with obstructive azoospermia and palpable vasa. Retrograde vasography via prostactic utricle a/w high risk of UTI, epididymitis and further fibrosis, therefore contraindicated. Because direct proximal puncture is also a/w risk of further fibrosis most andrologists recommend testis biopsy, sperm harvesting, vasography and immediate reconstruction (vaso-vasostomy or vaso-epididymostomy) in one sitting.

CBAVD
0.5% post-mortem series
1% infertile men
18% obstructive azoospermia (further 12% with unilateral vasa aplasia)
~80% of azoospermic men with CBAVD (and 30% with idiopathic obstruction) have genetic mutation in cystic fibrosis transmembrane conductance regulator (CFTR) on chromosome 7 – epithelial chloride transport
  Δ F508 common and severe
  R117H less common and mild
Seminal vesicle agenesis in 50%
Renal anomalies in 20% (should all have renal tract USS)
Genetic counselling mandatory following diagnosis
Suitable for MESA/TESE if assisted conception requested
NB. 95% of men with cystic fibrosis are azoospermic

Embryology

Vasovasostomy
6% men request vasectomy reversal
Improved pregnancy rates if
  Microsurgical technique
Male infertility

Sperm at cut end of vas
Short duration since vasectomy
Young female partner
Overall patency rate ~80% and ~ 60% pregnancy rate
Sperm may take up to 2 years to appear in semen
Discuss cryopreservation (for IUI, IVF, ICSI) in case VV/VE unsuccessful
Complications
Granuloma, occasionally leading to:
- Testis atrophy
Obstruction after successful vas reversal 10%
Redo vas reversal a/w patency rates of 27%-57%

<table>
<thead>
<tr>
<th>Years of Obstruction</th>
<th>Patency (%)</th>
<th>Sperm Present (%)</th>
<th>Pregnancy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3</td>
<td>86/89 (97)</td>
<td>56/74 (76)</td>
<td></td>
</tr>
<tr>
<td>3-8</td>
<td>52/500 (88)</td>
<td>253/478 (53)</td>
<td></td>
</tr>
<tr>
<td>9-14</td>
<td>205/261 (79)</td>
<td>92/209 (44)</td>
<td></td>
</tr>
<tr>
<td>≥15</td>
<td>32/45 (71)</td>
<td>11/37 (30)</td>
<td></td>
</tr>
</tbody>
</table>

From Belker et al, J Urol 1991

Vasoepididymostomy
Vasoepididymostomy if at VV
- No sperm
- Thick or creamy secretions
- Swollen indurated epididymis
May be a/w CF gene abnormalities
Originally side-to-side ‘fistula’ (Martin 1909)
Replaced by microsurgical anastomosis to single epididymal tubule – intussusception technique (Chan 2002). In experienced hands, patency rates of 80% and pregnancy rates of 30-35% (Kolettis 1997)

Non-obstructive azoosperma
Usually indicated by small testes, presence of vasa, and high FSH
Genetic abnormalities leading to failed spermatogenesis account for up to one third of cases:
- Chromosome abnormalities 12-18%
- Y gene microdeletions 7-18%
Important as genetic disorders (particularly y-gene microdeletions) may passed on to offspring if ICSI utilised. Therefore
Endocrine causes relatively rare but important to diagnose. Also Kallman’s only reliably reversal cause of non-obstructive azoosperma.
Cryptorchidism
- Unilateral (treated or untreated) 13% azoosperma
- Bilateral untreated 90% azoosperma
- Bilateral treated 45% azoosperma
Male infertility

<table>
<thead>
<tr>
<th>Name</th>
<th>Freq.</th>
<th>Karyotype</th>
<th>Inheritance</th>
<th>Features</th>
<th>Mx infertility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kleinfelter's</td>
<td>1:600</td>
<td>47 XXY</td>
<td>Sporadic</td>
<td>Small firm testes, gynaecomastia, high serum gonadotrophins</td>
<td>Donation ICSI for mosaics*</td>
</tr>
<tr>
<td>Sex reversal syndrome</td>
<td>?</td>
<td>46 XX male</td>
<td>Sporadic</td>
<td>As above but short stature</td>
<td>Donation</td>
</tr>
<tr>
<td>XYY syndrome</td>
<td>1:1000</td>
<td>47 XYY</td>
<td>Sporadic</td>
<td>Tall stature, aggression, criminality Normal gonadotrophins</td>
<td>Donation, ART for oligospermia*</td>
</tr>
<tr>
<td>Noonan's</td>
<td>?</td>
<td>46 XY</td>
<td>Sporadic</td>
<td>Like Turner's. Webbed neck, UDT small testes</td>
<td>Donation</td>
</tr>
</tbody>
</table>

* Higher incidence of chromosomal and medical abnormalities. Kleinfelter's mosaics have 30-50% of chance of finding normal sperm

Y-gene microdeletions

- AZFa: Sertoli-only defects, TESE unsuccessful
- AZFb: Maturation arrest, TESE unsuccessful
- AZFc: Severe oligospermia, TESE successful in ~25% cases

Patients need counselling that male offspring will inherit defects and also be oligospermic.
**Box 2** Current indications for genetic testing of infertile men.

- A semen analysis with sperm concentrations <10 million sperm/ml, in a couple considering *in vitro* fertilization (IVF) and intracytoplasmic sperm injection (ICSI) (Y microdeletion assay and karyotype analysis)
- A semen analysis showing no sperm with evidence of testis atrophy, in a couple considering testis sperm extraction with IVF and ICSI (Y microdeletion assay and karyotype analysis)
- A semen analysis showing no or low sperm concentration with at least one absent vas deferens on physical examination (cystic fibrosis gene mutations)
- A semen analysis showing no sperm with evidence of normal spermatogenesis (cystic fibrosis gene mutations)
- A couple with other syndromes or conditions suggested by personal or family histories (e.g. Kallman syndrome KAL 1–3)
Kallman’s syndrome (hypogonadotrophic hypogonadism with anosmia)
Isolated failure of gonadotropin production with otherwise normal pituitary function
Uncommon
X-linked (most common), AD and AR forms
X-linked leads to loss/mutation of KAL1, responsible for migration of LH secreting neurones to medial hypothalamus
Phenotype
Long arms and legs cf. body
Craniofacial abnormalities
Gynaecomastia
UDT
Micropenis (50%)
Testicular atrophy
Delayed puberty
Rx is with androgens to stimulate virilization, but inhibits spermatogenesis
Gonadotrophin Rx (HCG 2000IU tds for 3-6 mo. followed by FSH 75IU tds) for spermatogenesis.
Assisted reproduction

<table>
<thead>
<tr>
<th>Technique</th>
<th>Abbreviation</th>
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</thead>
<tbody>
<tr>
<td>Intrauterine insemination</td>
<td>IUI</td>
</tr>
<tr>
<td>In-vitro fertilization</td>
<td>IVF</td>
</tr>
<tr>
<td>Intracytoplasmic sperm injection</td>
<td>ICSI</td>
</tr>
<tr>
<td>Microsurgical epididymal sperm aspiration</td>
<td>MESA</td>
</tr>
<tr>
<td>Percutaneous sperm aspiration</td>
<td>PESA</td>
</tr>
<tr>
<td>Testicular sperm extraction</td>
<td>TESE</td>
</tr>
<tr>
<td>Testicular sperm aspiration</td>
<td>TESA</td>
</tr>
</tbody>
</table>

Recent drive to offer IVF, often with ICSI, can overlook cheaper alternatives, i.e. varicoceole repair (Schelegel 1997), vas reversal, redo vas reversal, vasosepididymostomy all more cost-effective (cost per live birth) than ICSI. However IUI, IVF and ICSI all have a role.

Intrauterine insemination
Used to bypass cervical mucus
Sperm must be processed to remove PGs (very irritant to uterus) and bacteria. Often a/w ovarian hyperstimulation to improve pregnancy rate
Indications
  - Deposition abnormality (hypospadias)
  - Cervical factor
Severe dyspareunia
Severe psychosexual abnormality
HIV male/non HIV female (HIV on WBC and free in seminal plasma – no HIV transmission in 500 babies (Semprini 2004)

Requirements
5-10 million/ml motile sperm (up to 50% loss after processing)

Outcome
Pregnancy rates of up to 30% for 4 cycles (Guzick 1999)
Multiple gestation in up to 30%

IVF and ICSI
Ovarian hyperstimulation with clomiphene and transvaginal egg harvest
Petri dish fertilisation, 2-3 day growth, followed by transcervical blastocyst implantation. One third of implanted embryos survive

IVF Less than 5 million/ml sperm
ICSI one sperm required
Pregnancy rate 20-30% per cycle, significantly related to age [37% in women <35 yrs, 10.7% in those >40 yrs]

Sperm retrieval
Obstruction
MESA or PESA – equivalent pregnancy rates
MESA more invasive, but more sperm, therefore can be frozen
PESA easy, but may need to be performed again
No difference in pregnancy rates after ICSI with fresh vs. frozen

Non-obstructive
Failure to retrieve sperm in up to 50% of men
Nomograms designed but cannot distinguish which pts will have sperm
Number of approaches:
  Sperm preservation at time of diagnostic biopsy
  If sperm present at biopsy
    Open/microsurgical TESE
    If no sperm present at biopsy
      FNA mapping, followed by TESE directed to positive ‘site’

Genetic considerations
Overall rates of major birth defects with ICSI (3.3%) – similar to intercourse
Chromosomal abnormality 3x expected rate (2.9%) (Bonduelle 2002)
Also increased
  Hypospadias
  Angelmann and Beckwith-Wiedemann syndromes
  Soft signs such as developmental delay
  Infertility in male offspring (Y microdeletions)
Anatomy and physiology

Figure 2-43: Testis and epididymis. A. One to three seminiferous tubules fill each compartment and drain into the rete testis in the mediastinum. Twelve to 25 efferent ductules become convoluted in the head of the epididymis and drain into a single coiled duct of the epididymis. The vasa are convoluted in its first portion. B. Cross section of the testis, showing the mediastinum and septations continuous with the tunica albuginea. The parietal and visceral tunica vaginalis are confluent where the vessels and nerves enter the posterior aspect of the testis.
Male infertility

Figure 1-2. Schematic representation of the first and second meiotic divisions. A, The homologous chromosomes approach each other. B, The homologous chromosomes pair and each member of the pair consists of two chromatids. C, The intimately paired homologous chromosomes interchange chromatid fragments (cross-over). Note the chiasma. D, The double-structured chromosomes pull apart. E, Anaphase of the first meiotic division. F and G, During the second meiotic division the double-structured chromosomes split at the centromere. At completion of the division the chromosomes in each of the four daughter cells are different from each other.
Meiosis #1  Duplication of chromosomes in S phase (46 doubled chromosomes). Line up in doubled pairs (as opposed to mitosis) except sex chromosomes. First meiotic division after chiasma formation to form secondary spermatocyte containing 23 doubled chromosomes.

Meiosis #2  Doubled haploid chromosomes line up. Cell divide to form spermatids containing 23 single chromosomes.

NB. Maturation from spermatids to spermatozoa known as spermiogenesis – under influence of androgens, unlike remainder of spermatogenesis

<table>
<thead>
<tr>
<th>Source</th>
<th>pH</th>
<th>Sperm</th>
<th>Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bulbourethral (Cowper's) and periurethral (Littre's) glands</td>
<td>Neutral</td>
<td>No sperm</td>
<td>0.2 mL</td>
</tr>
<tr>
<td>Prostate secretions</td>
<td>Acid</td>
<td>No sperm</td>
<td>0.5 mL</td>
</tr>
<tr>
<td>Seminal vesicle* (Fructose-rich)</td>
<td>Alkali</td>
<td>Few sperm</td>
<td>2 mL</td>
</tr>
<tr>
<td>Ampulla of vas &amp; distal epididymis</td>
<td>Neutral</td>
<td>Many sperm</td>
<td>0.1 mL</td>
</tr>
</tbody>
</table>
**Hypothalamus-Pituitary-Testis Axis**

Hypothalamus receives input from higher centres, including amygdala, olfactory and visual cortex. GnRH release displays three types of rhythmicity:

- **Seasonal**: Highest in spring
- **Circadian**: Highest in early hours
- **Pulsatile**: Peaks every 90-120 mins

LH and FSH from anterior pituitary (vasopressin and oxytocin from posterior)

Negative feedback:

- **Primary feedback via testosterone** (unclear whether acts unchanged or via oestradiol/dihydrotestosterone)
- Inhibin B selectively inhibits production of FSH by impairing transcription of its beta subunit (activins have opposite action)

Testosterone circulates in 3 forms:

- Bound to sex hormone binding globulin (SHBG) 60%
- Bound to albumin 38%*
- Non-bound (free) 2%*

* SHBG-bound testosterone generally not bioavailable. As SHBG increases with ageing it may be important to use different assays to measure the bioavailable testosterone. More accurate alternatives to total testosterone:
<table>
<thead>
<tr>
<th>Assay</th>
<th>Utility</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total testosterone</td>
<td>Low/intermediate</td>
<td>Variable normal ranges; below 200 ng/dL very likely to be hypogonadal, above 800 ng/dL unlikely to be</td>
</tr>
<tr>
<td>Free testosterone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dialysis</td>
<td>High</td>
<td>Difficult to do, requires sH-T</td>
</tr>
<tr>
<td>Ultrafiltration</td>
<td>High</td>
<td></td>
</tr>
<tr>
<td>Analog</td>
<td>Poor</td>
<td>Commonly available in NIA</td>
</tr>
<tr>
<td>Calculated free</td>
<td>Intermediate</td>
<td>Requires SHBG and T measurements</td>
</tr>
<tr>
<td>Bioavailable testosterone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ammonium sulfate</td>
<td>High</td>
<td>Easier to do than free T, excellent precipitation assay, good correlation with symptoms</td>
</tr>
<tr>
<td>Calculated bioavailable</td>
<td>Intermediate</td>
<td>Requires SHBG and T measurements</td>
</tr>
<tr>
<td>Free androgen index</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Testosterone/SHBG</td>
<td>Poor</td>
<td>Requires SHBG and T measurements</td>
</tr>
<tr>
<td>Salivary testosterone</td>
<td>Undetermined</td>
<td>Uncertain value</td>
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</tbody>
</table>