

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
Nitrofurantoin
Phenytoin
Spironolactone
Sulfasalazine
Testosterone
Tricyclic antidepressants
Valproic acid

Physical examination

General

- Body habitus
- Gynaecomastia

- 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 (epididymal 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

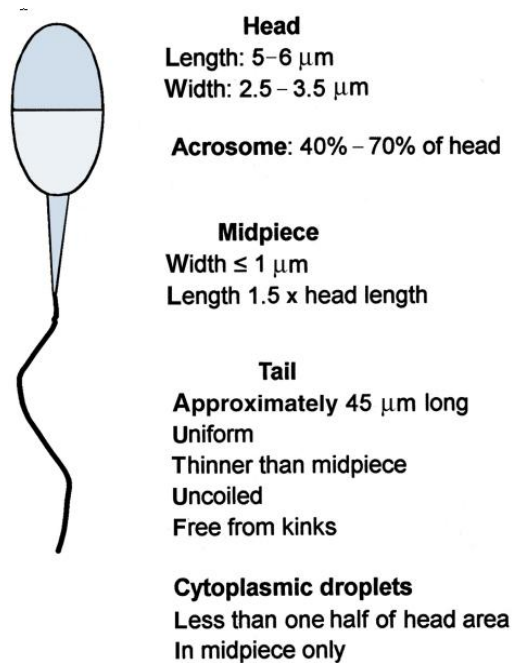
Updated WHO 2010 criteria

Parameter	Lower reference limit
Semen volume (mL)	1.5 (1.4–1.7)
Total sperm number (10^6 per ejaculate)	39 (33–46)
Sperm concentration (10^6 per mL)	15 (12–16)
Total motility (PR+NP, %)	40 (38–42)
Progressive motility (PR, %)	32 (31–34)
Vitality (live spermatozoa, %)	58 (55–63)
Sperm morphology (normal forms, %)	4 (3.0–4.0)
<i>Other consensus threshold values</i>	
pH	≥ 7.2
Peroxidase-positive leukocytes (10^6 per mL)	< 1.0
MAR test (motile spermatozoa with bound particles, %)	< 50
Immunobead test (motile spermatozoa with bound beads, %)	< 50
Seminal zinc ($\mu\text{mol}/\text{ejaculate}$)	≥ 2.4
Seminal fructose ($\mu\text{mol}/\text{ejaculate}$)	≥ 13
Seminal neutral glucosidase (mU/ejaculate)	≥ 20

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

Motility (WHO 1999)

- 1 Rapidly progressive
- 2 Slowly progressive
- 3 Non-progressive
- 4 Non-motile



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

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 3 Characteristic endocrine profiles of infertile men.

Condition	T	FSH	LH	PRL
Normal	Normal	Normal	Normal	Normal
Primary testis failure	Low	High	Normal/high	Normal
Hypogonadotropic hypogonadism	Low	Low	Low	Normal
Hyperprolactinemia	Low	Low/normal	Low	High
Androgen resistance	High	High	High	Normal

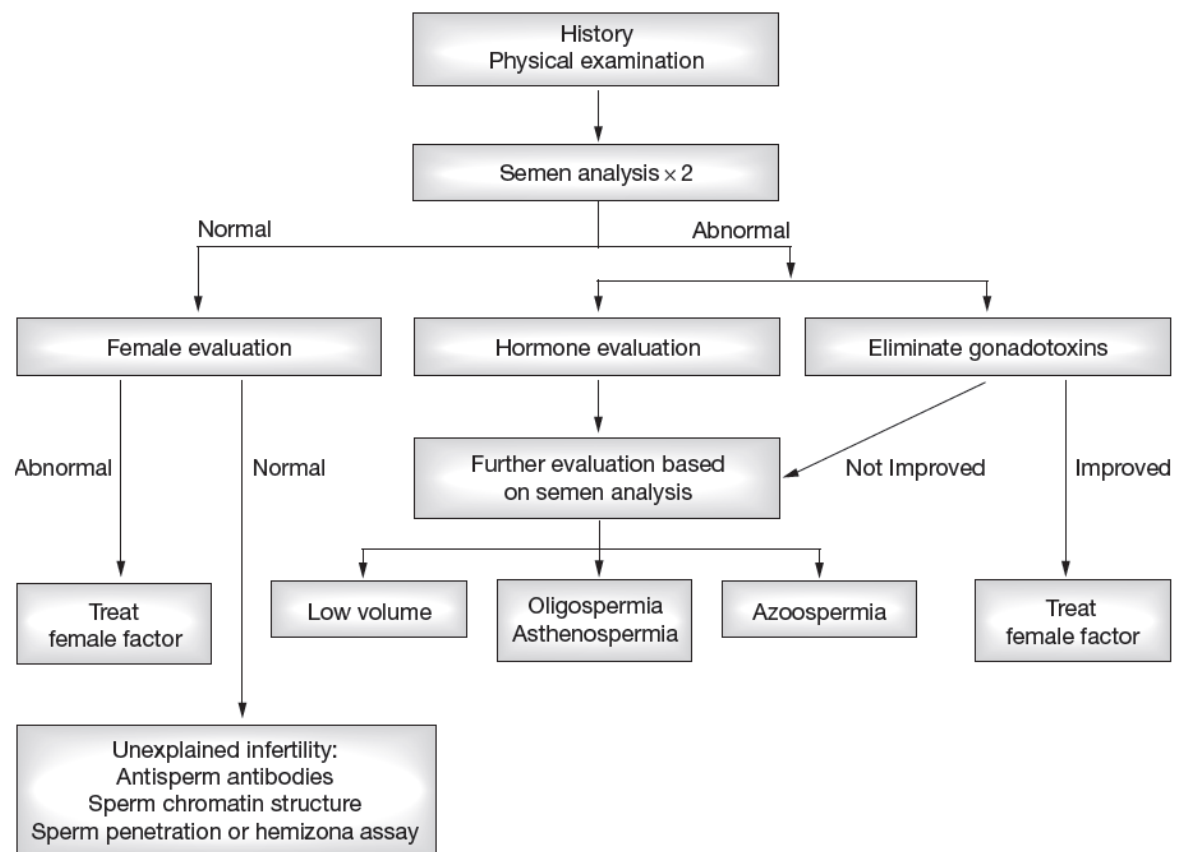
FSH, follicle stimulating hormone; LH, luteinizing hormone; PRL, prolactin; T, testosterone.

FSH related to number of functioning germ cells

- Maturation arrest (failed spermiogenesis)
- One functioning testis
- Primary testis failure

- normal FSH
- high FSH
- 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)


Biopsy

Johnsen score count

10	Complete spermatogenesis organised epithelium
9	many spermatozoa disorganised epithelium
8	< 10 spermatozoa
7	many spermatids
6	< 10 spermatids
5	many spermatocytes
4	< 10 spermatocytes
3	Spermatogonia
2	Sertoli cells only
1	No cells, tubular fibrosis



200 tubules



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)

Indicates DNA fragmentation. Associated with reduced fertility rates. Controversial relationship between DNA fragmentation index, pregnancy rates and spontaneous miscarriage.

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

Grade	Definition (WHO 1999)
1	Rapidly progressive
2	Slowly progressive
3	Non-progressive
4	Non-motile

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 suppressing 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 invertus = Kartagener's syndrome. No specific treatment. Offer ICSI after adequate genetic counselling

Leucocytospermia

Reactive oxygen species produced by wbcs 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

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)
- Varicocele
- 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 varicocele
- Consider IVF/ICSI after genetic testing for Y microdeletions (see azoospermia)

Varicocele and Oligo-astheno-teratospermia (OAT)

Infertile men with varicoeles 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 varicocele and degree of testicular atrophy a/w severity of effect
Varicocele repair a/w catch-up growth in patients with varicoeles 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

(Nieschlag). 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.

Study	Number of patients per arm		Pregnancy rate (%)	
	Control	Treatment	Control	Treatment
WHO ^a	109	129	16.7	34.8
Nieschlag <i>et al.</i> ³⁰	63	62	25.4	29.7
Madgar <i>et al.</i> ²⁹	25	20	10	60
Unweighted mean	—	—	17	41

^aThis 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)

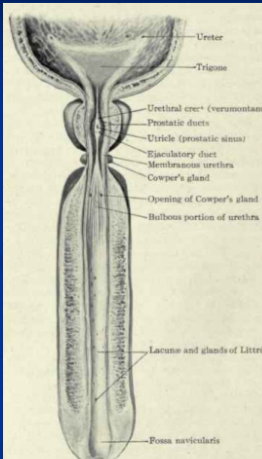
On the basis of above, varicocele repair recommended for men with palpable varicocele with low sperm counts.

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

Low volume ejaculate (<1.5ml)

Seminal volume

Bulbourethral (Cowper's) and periurethral (Littre's) glands†	Neutral	No sperm	0.2 mL
Prostate secretions	Acid	No sperm	0.5 mL
Seminal vesicle*† (Fructose-rich)	Alkali	Few sperm	2 mL
Ampulla of vas & distal epididymis	Neutral	Many sperm	0.1 mL



* Seminal fluid contains substance responsible for coagulation of semen. PSA aids liquefaction after 5-25 mins
† Under androgenic control. Therefore low T a/w low semen volume

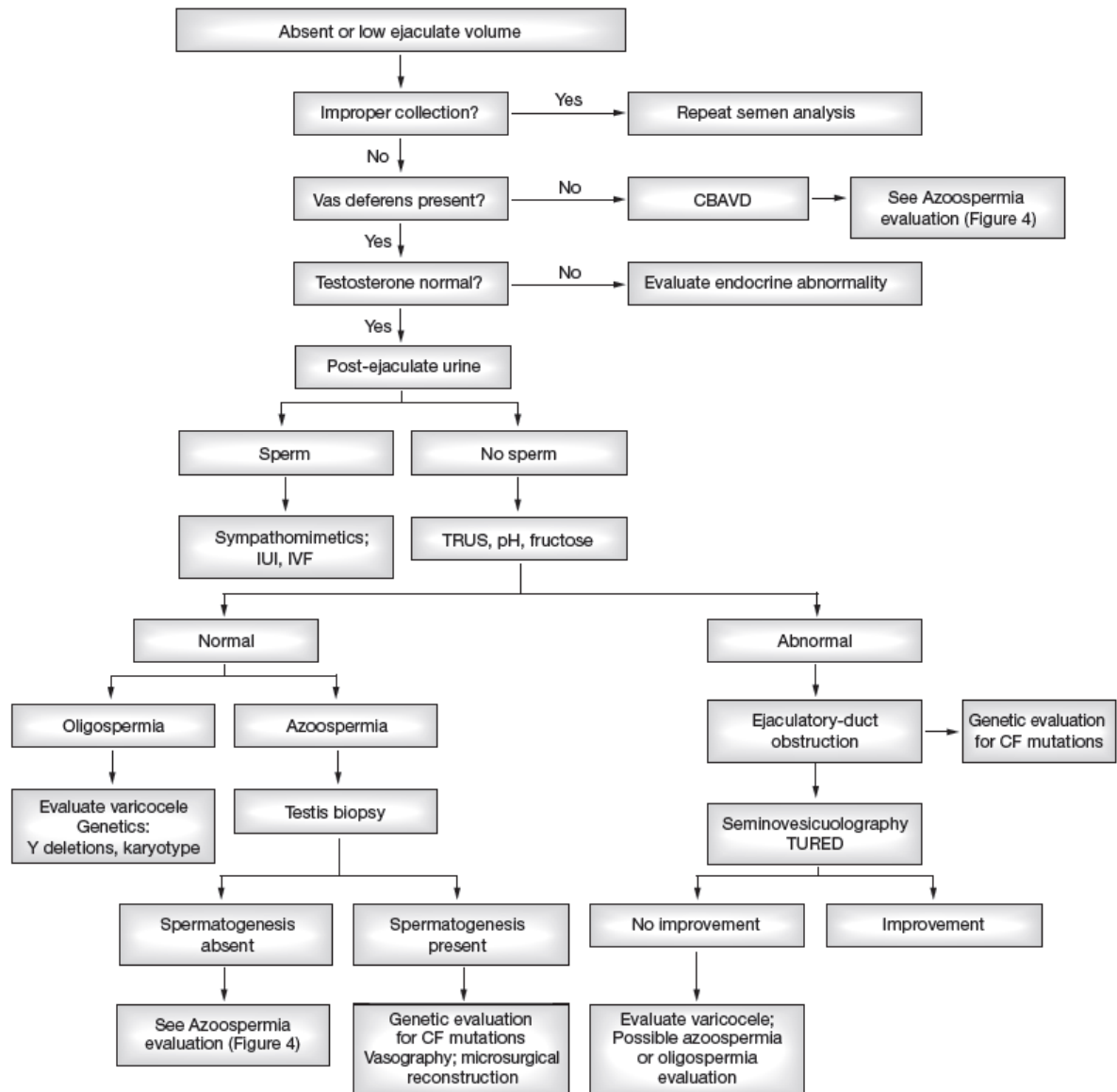
Causes

- 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 alkalisation recommended for 24 hours prior to planned ejaculation (Target pH 7.5). can use sodium bicarbonate 650mg qds or baking soda in water.

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 (utricle, 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 Klinefelter'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 vasal aplasia	18%
Unilateral vasal aplasia	12%
Ejaculatory duct	1%

~ 30% of men have absence of one or both vasa. Unilateral vasal 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 prostatic 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 vasal 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

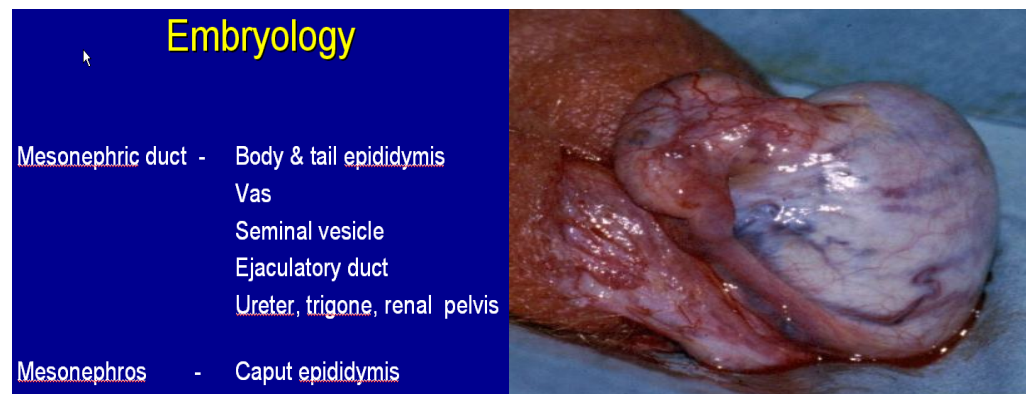
Seminal vesicle agenesis in 50%

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



Vasovasostomy

6% men request vasectomy reversal

Improved pregnancy rates if

Microsurgical technique

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%

Years of Obstruction	Patency (%), Sperm Present	Pregnancy (%)
<3	86/89 (97)	56/74 (76)
3-8	525/600 (88)	253/478 (53)
9-14	205/261 (79)	92/209 (44)
≥15	32/45 (71)	11/37 (30)

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 azoospermia

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
 be passed on to offspring if ICSI utilised. Therefore

Endocrine causes relatively rare but important to diagnose. Also Kallman's
 only reliably reversible cause of non-obstructive azoospermia.

Cryptorchidism

Unilateral (treated or untreated) 13% azoospermia
 Bilateral untreated 90% azoospermia
 Bilateral treated 45% azoospermia

Name	Freq.	Karyotype	Inheritance	Features	Mx infertility
Klinefelter's	1:600	47 XXY	Sporadic Non-disjunction at meiosis 1	Small firm testes, gynaecomastia, high serum gonadotrophins	Donation ICSI for mosaics*
Sex reversal syndrome	?	46 XX male	Sporadic	As above but short stature	Donation
XYY syndrome	1:1000	47 XYY	Sporadic non- disjunction at meiosis 1	Tall stature, aggression, criminality Normal gonadotrophins	Donation, ART for oligospermia*
Noonan's	?	46 XY	Sporadic	Like Turner's. Webbed neck, UDT small testes	Donation

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

Y-gene microdeletions

Y microdeletions

Y gene microdeletions

Y chromosome 11q position
I
AZF a – b – c (severity) →

Genes RBW, DAZ, DBY, XXX

Commonest AZFc (Daz gene)

No phenotype abnormality

All male offspring have Y deletions

Obstructive azoospermia – no deletions

>1200 (>700 personally) PATIENTS tested:
ONE ISOLATED GENE DELETION FOUND

AZFa Sertoli-only defects
AZFb Maturation arrest
AZFc Severe oligospermia

TESE unsuccessful
TESE unsuccessful
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 (hypogonadotropic 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

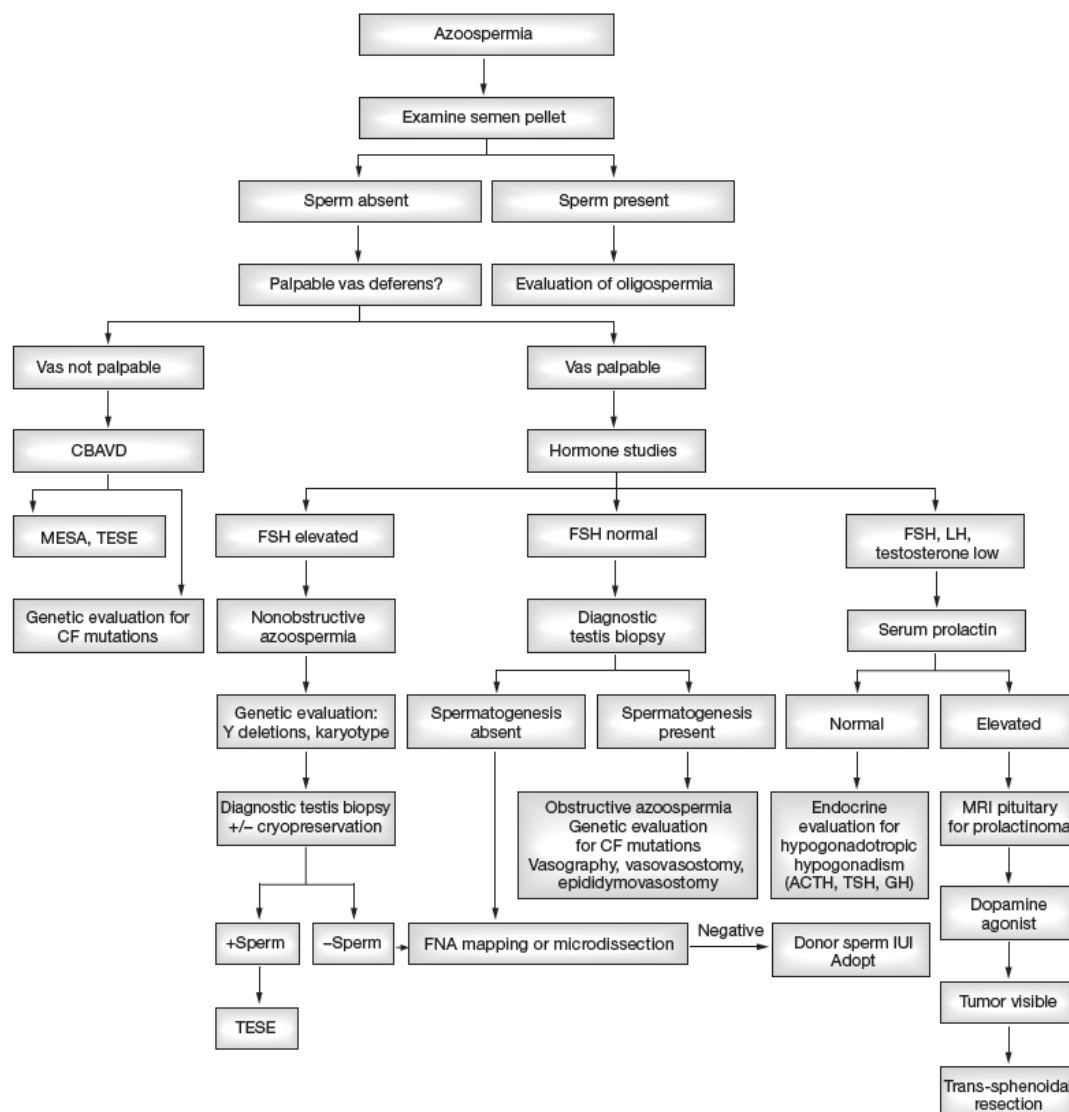
Micropenis (50%)

Testicular atrophy

Delayed puberty

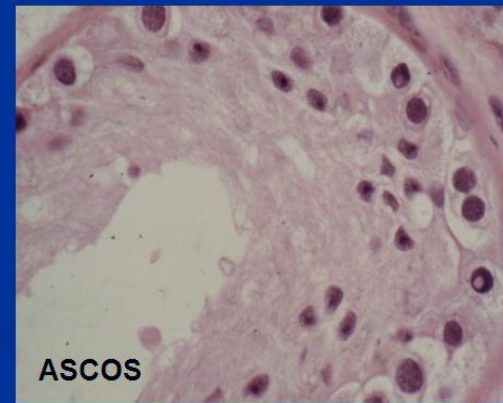
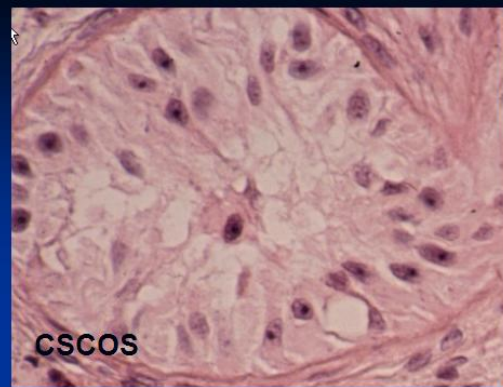
Rx is with androgens to stimulate virilization, but inhibits spermatogenesis

Gonadotrophin Rx (HCG 2000IU tds for 3-6 mo. followed by FSH 75IU tds) for spermatogenesis.



Sertoli-cell only

- Absence of germ cells
- Congenital or acquired
- Congenital due to failure of germ-cell migration – identical to normal testis architecture except no germ cells
- Acquired much more degenerative in appearance
- ACSOS
 - Cytokeratin positive
 - Immature forms sometimes
 - Occasional islands of spermatogenesis
 - ? Successful retrieval in 50%
 - TESE/mapping usually required
 - Pre-harvest genetic counselling mandatory
- NO spermatogenesis in CSCOS



Assisted reproduction

<i>Technique</i>	<i>Abbreviation</i>
Intrauterine insemination	IUI
In-vitro fertilization	IVF
Intracytoplasmic sperm injection	ICSI
Microsurgical epididymal sperm aspiration	MESA
Percutaneous sperm aspiration	PESA
Testicular sperm extraction	TESE
Testicular sperm aspiration	TESA

Recent drive to offer IVF, often with ICSI, can overlook cheaper alternatives, i.e. varicocele repair (Schelegel 1997), vas reversal, redo vas reversal, vasoepididymostomy 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

Angelman and Beckwith-Wiedemann syndromes

Soft signs such as developmental delay

Infertility in male offspring (Y microdeletions)

Anatomy and physiology

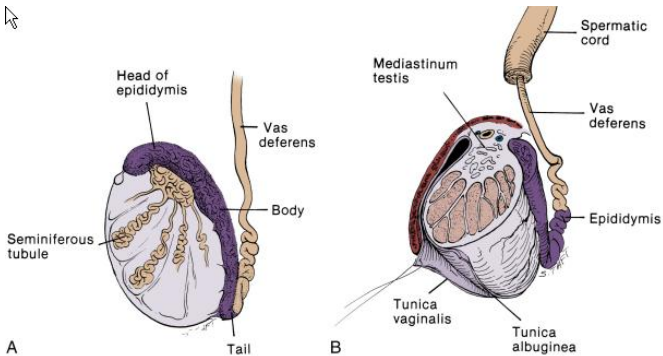
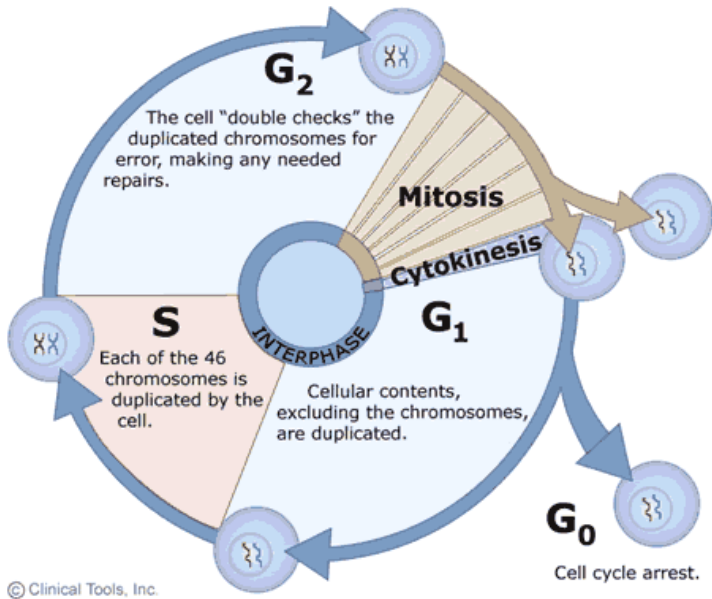
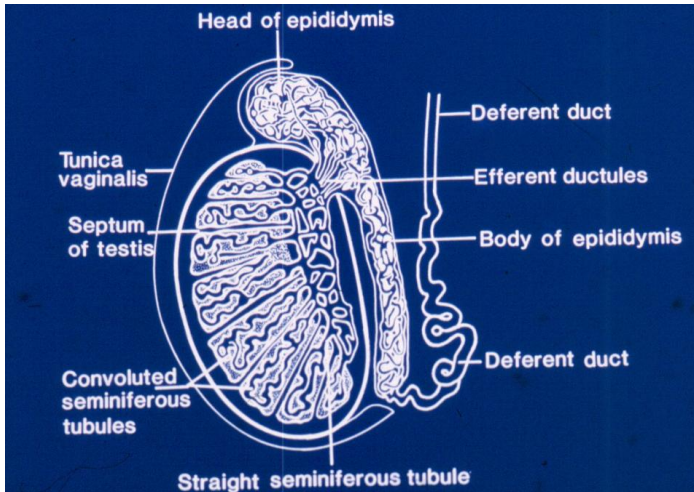


Figure 2-43 Testis and epididymis. A, One to three seminiferous tubules fill each compartment and drain into the rete testis in the mediastinum. Twelve to 20 efferent ductules become convoluted in the head of the epididymis and drain into a single coiled duct of the epididymis. The vas is convoluted 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.



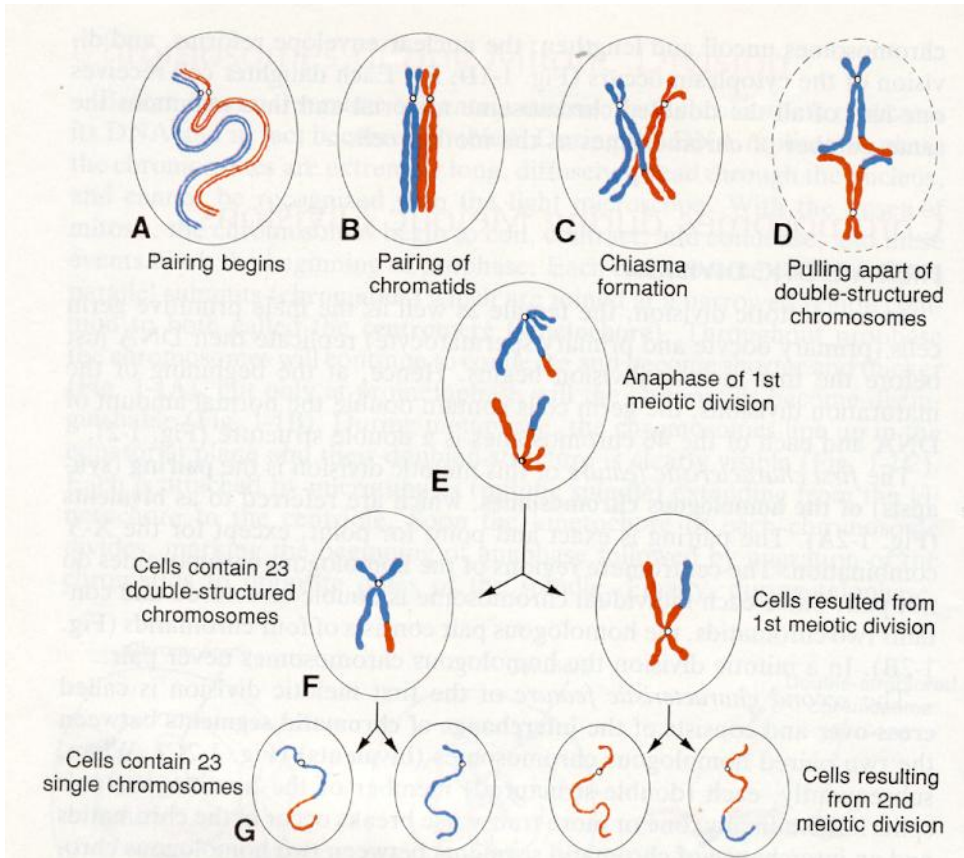
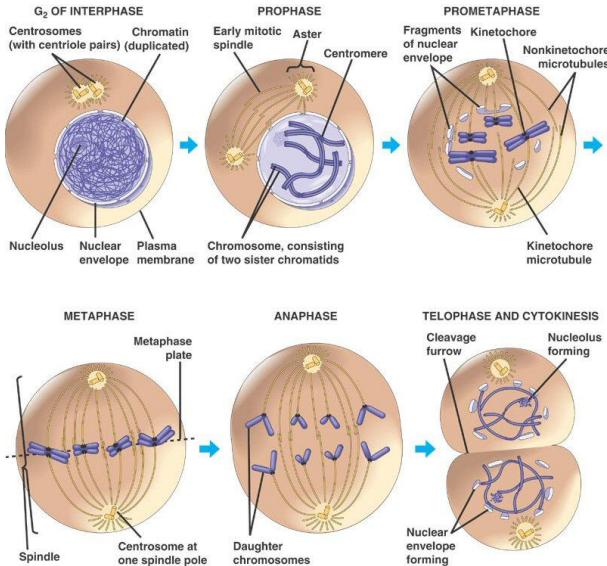
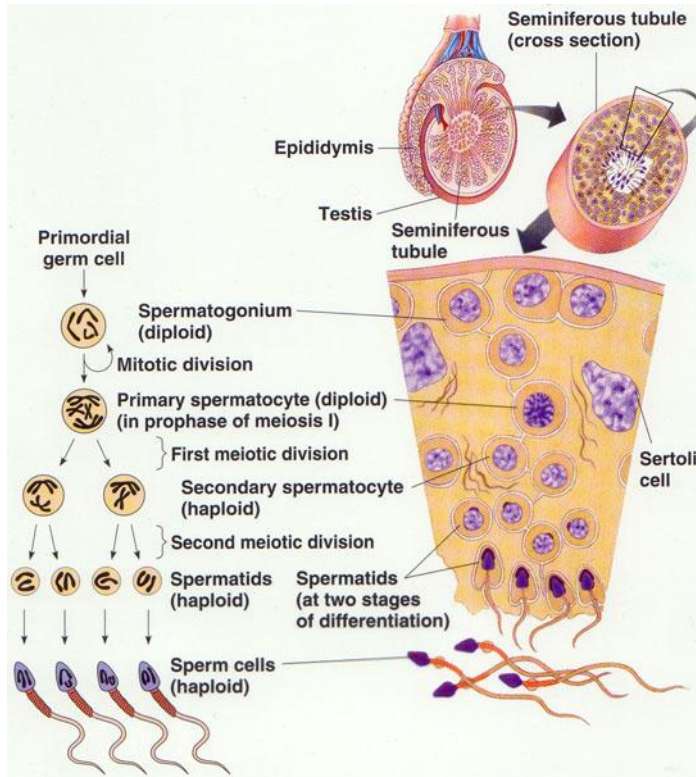


Figure 1-2. Schematic representation of the first and second meiotic divisions. **A**, The homologous chromosomes approach each other. **B**, The homologous chromosomes pair and each member of the pair consists of two chromatids. **C**, The intimately paired homologous chromosomes interchange chromatid 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

Bulbourethral (Cowper's) and periurethral (Littre's) glands	Neutral	No sperm	0.2 mL
Prostate secretions	Acid	No sperm	0.5 mL
Seminal vesicle* (Fructose-rich)	Alkali	Few sperm	2 mL
Ampulla of vas & distal epididymis	Neutral	Many sperm	0.1 mL

Hypothalamus-Pituitary-Testis Axis

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

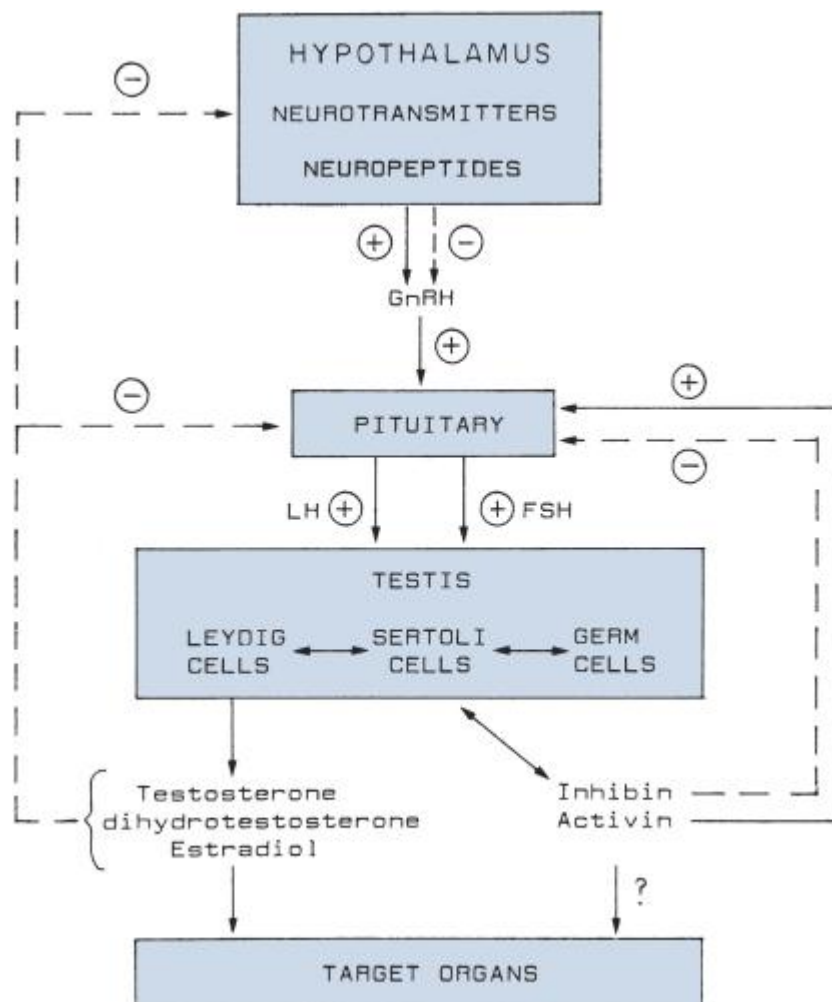
Seasonal	Highest in spring	Pineal gland
Circadian	Highest in early hours	Suprachiasmatic nucleus
Pulsatile	Peaks every 90-120 mins	

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:

Assay	Utility	Comments
Total testosterone	Low/intermediate	Variable normal ranges; below 200 ng/dL very likely to be hypogonadal; above 600 ng/dL unlikely to be
Free testosterone		
Dialysis	High	Difficult to do; requires β H-T
Ultrafiltration	High	
Analog	Poor	Commonly available in N/A
Calculated free	Intermediate	Requires SHBG and T measurements
Bioavailable testosterone		
Ammonium sulfate	High	Easier to do than free T; excellent precipitation assay; good correlation with symptoms
Calculated bioavailable	Intermediate	Requires SHBG and T measurements
Free androgen index		
Testosterone/SHBG	Poor	Requires SHBG and T measurements
Salivary testosterone	Undetermined	Uncertain value