SEXUAL AND REPRODUCTIVE HEALTH

NOTES

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What's included: Ready-to-study anatomy, physiology and pathology notes of the human reproductive systems presented in succinct, intuitive and richly illustrated downloadable PDF documents. Once downloaded, you may choose to either print and bind them, or make annotations digitally on your iPad or tablet PC.

Free Bonuses: 'Gynecology' and 'Urology' chapters of Toronto Notes for reference and further detailed reading.

File List:

    - Pelvic Organ Prolapse
    - PERIMENOPAUSAL BLEEDING - Endometrial Adenocarcinoma
    - PERIMENOPAUSAL BLEEDING - Leiomyosarcoma
    - Urinary Incontinence (2p)
    - Vaginal Candidiasis (Thrush)
    - Vaginoses
    - Vulval Cancer
- **MCQS & CASES - Breast Disease**
- **MCQS & CASES - STIs, Penis & Testis Disorders**
- **Men's Health:**
    - Balanitis & Balanoposthitis
    - Benign Prostatic Hypertrophy
    - Congenital Penile Abnormalities
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    - Epididymo-Orchitis
    - Gynecomastia
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    - Peyronie's Disease
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    - Prostatitis
    - Scrotal Accumulations
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    - Torsion of the Testis
- **Sexual Health:**
    - 2 Alternative Differentials for Genital Malignancy
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    - Syphilis
- **TORONTO - Gynecology**
- **TORONTO - Urology**

System: MALE UROGENITAL

Pelvic Cavity:

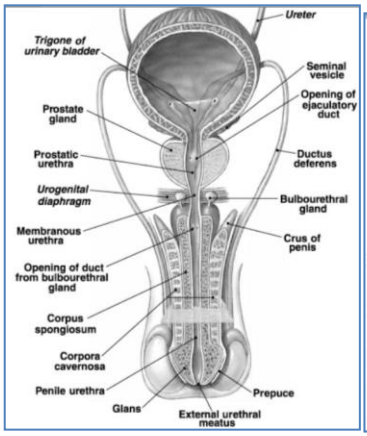
- **Male:**
  - Urinary Bladder (urinary system)
  - Rectum (digestive system)
- **Female:**
  - Urinary Bladder (urinary system)
  - Uterus (reproductive system)
  - Rectum (digestive system)

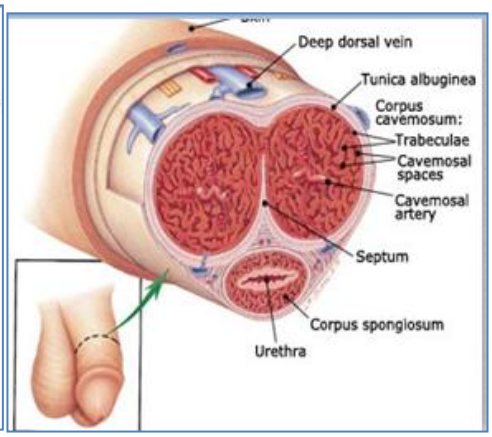
Normal Flora of the Genital Tract

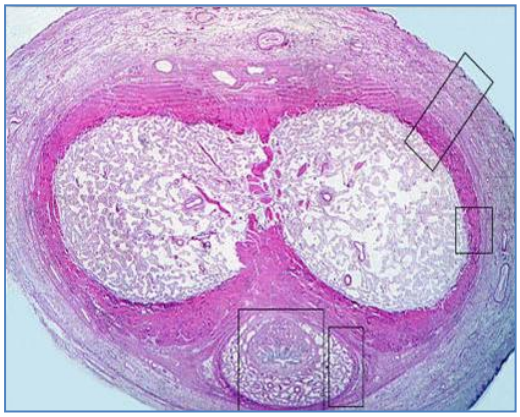
- **Male:**
  - **Urethra** – few organisms
  - *Staph. epidermidis*, Streptococci, *Uroplasma urealyticum*
- **Female:**
  - **Vagina: -** Very Large numbers of Bacteria: 108 – 109 bacteria/gram fluid
  - **Predominantly *lactobacillus*** (changes with age)
    - (Blue Gram Positive Rods)
    - → Produce lactic acid
    - → Protects against Bacterial Vaginosis & Yeast Infections.
  - Others – usually less than 10 organisms/gram fluid
  - Ratio of anaerobes to aerobes ~ 5:1

Review of Testis Anatomy & Physiology:

- **Normal Male Reproductive Anatomy:**
  - **Ducts** – (receive/transport gametes):
    - **1. Epididymis –** (5% of ejaculate)
    - **2. Ductus (vas) Deferens**
    - **3. Urethra -** (Prostatic → Membranous → Spongy (penile) → External Orifice)
  - **Penis:**
    - **2 Parts – Shaft & Glans Penis.**
    - **Corona –** Neck sulcus
    - **Erectile Tissues:**
      - **2x Corpus Cavernosum** – Central Arteries
      - **1x Corpus Spongiosum** – Central Urethra
    - **Tunica Albuginia –** Fibrous capsule encasing the Testis & Penis (NB: Does NOT encase the Epididymus)
    - **Urethra –** Transitional Epithelium
    - **Prepuce** (foreskin)

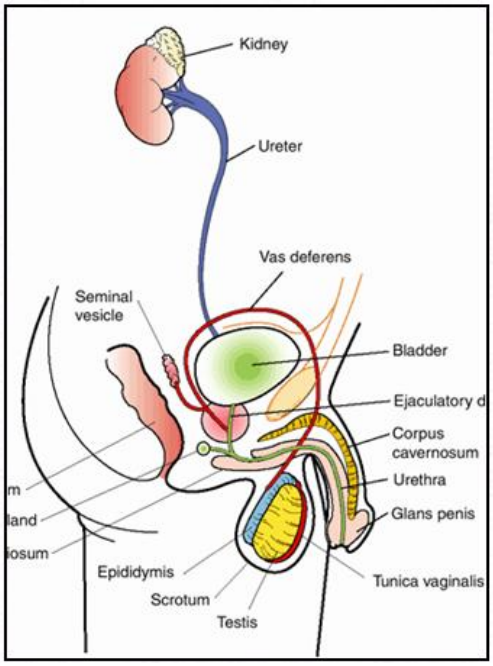


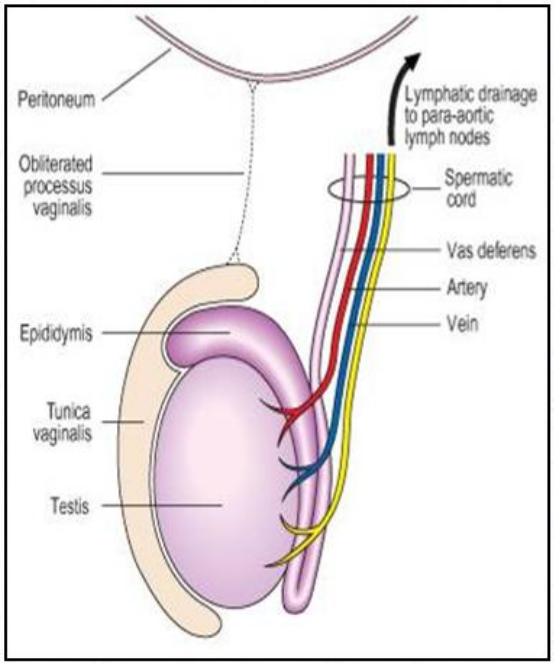




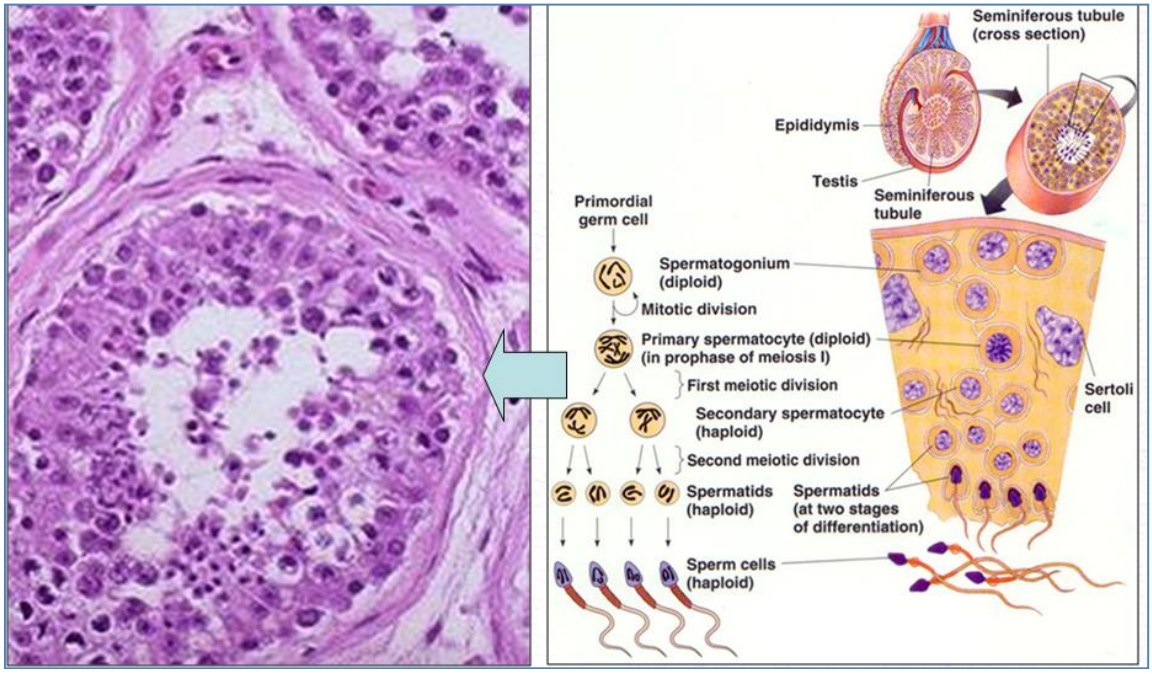
- **Testicles:**
  - **Testes - Gonads (produce gametes)**
    - **Testis (Albuginea of testes)**
      - **Seminiferous tubules** – sperm production
      - **Leydig Cells** – testosterone production
    - **Epididymis -** Highly coiled tubules.
  - **Spermatic Cord –** Spermatic Artery, Vein & Vas-Deferens (+ Lymphatics).
  - **Tunica Vaginalis –** Remnants of the foetal peritoneum dragged into the scrotum by descending testes.
    - **Obliterated Processus Vaginalis –** The obliterated peritoneal remnants from descending of the testes. NB: If not fully obliterated, can → Indirect Inguinal Hernias.
  - **Tunica Albuginia –** Fibrous capsule encasing the Testis & Penis (NB: Does NOT encase the Epididymus)
  - **Cremaster Muscle:** Lifts testicles closer to body when cold. (thermoregulation)
  - **Dartos Muscle:** Increases/decreases surface area of the scrotum (thermoregulation)

- **Accessory Glands:**
  - **Seminal vesicles -** (60% of ejaculate) – Reduces Acidity of Semen
  - **Prostate gland -** (30% of ejaculate) - Helps activate sperm & keep it viable
  - **Bulbourethral glands –** (5% of ejaculate) - Neutralises traces of urine in urethra.

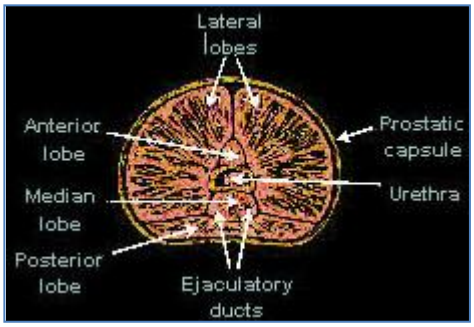




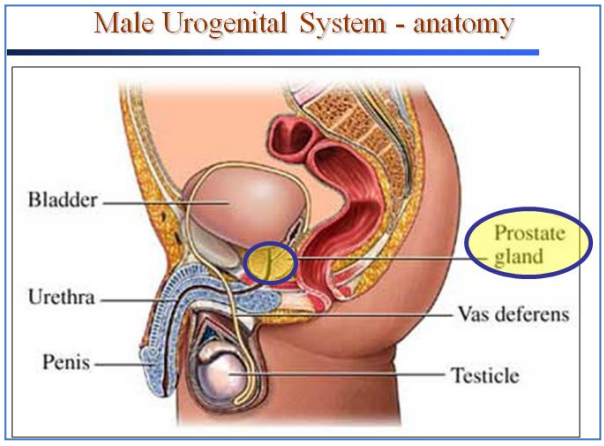
- **Sperm Manufacture & Transport:**
  - **Seminiferous Tubules –** Consist of:
    - **Sertoli Cells –** Make up the walls of the Seminiferous Tubules (+ Form the Blood-Sperm Barrier) (+ Produce Androgen-Binding Protein in response to **FSH** → Sperm Receptive to Testosterone)
    - **Germ Cells (Spermatogonia) –** Immature sperm at different stages of development and different levels within the Seminiferous Tubules. (NB: Only luminal spermatogonia have tails)
  - **Interstitial Leydig Cells –** (Outside the tubules) – Produce Testosterone in response to **LH**
  - **Epididymus –** Series of tubules where sperm undergo final maturation. (Pseudostratified columnar epithelium)
  - **Vas Deferens –** (Pseudostratified columnar epithelium + Surrounding smooth muscle)

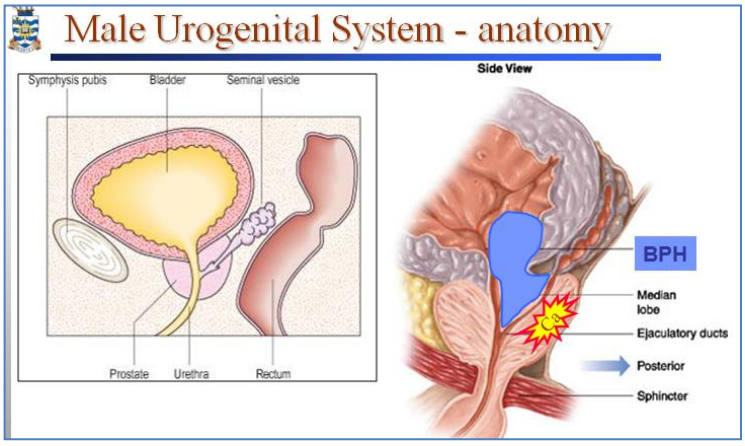


- **Revision of Normal Prostate:**
  - **Anatomy:**
    - 5 lobes (2 Laterals, Anterior, Median & Posterior)



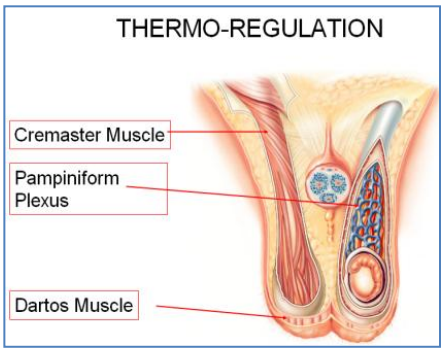
    - Inferior to Bladder, Posterior to Penis
    - Periurethral (Encases Urethra)
    - Also encases Ejaculatory Ducts from Seminal Vesicles



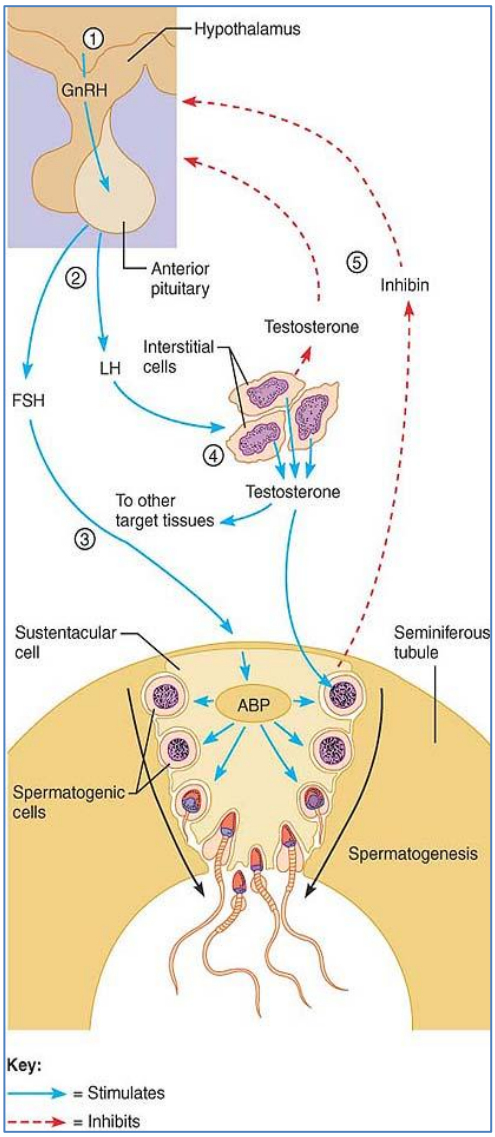


  - **Function:**
    - Adds bulk to Semen
    - Acid phosphatase - Proteolytic Enzyme - Maintains liquidity of prostate
    - Prostate Specific Antigen (PSA) – Proteolytic Enzyme - Maintains liquidity of prostate.
    - Hormone responsive - Androgens
  - **Normal Histology:**
    - Fibro-Muscular Organ – Plenty of Smooth Muscle Fibres
    - Glands *Normally* have a *Double Layer* Epithelium (NB: Prost.Ca. is a *Single Layer* Epithel.)

- **Normal Testis Physiology:**
  - **Thermoregulation:**
    - **Why descended?** – Spermatogenesis requires a lower temperature than core temperature.
    - **Cremaster Muscle:** Lifts testicles closer to body when cold. (thermoregulation)
    - **Dartos Muscle:** Increases/decreases surface area of the scrotum (thermoregulation)
    - **Pampiniform Plexus:** Network of blood vessels



  - **Spermatogenesis:**
    1) **Hypothalamus →GnRH →**
    2) **→ Ant.Pit**. → Releases **Gonadotropins (FSH & LH)**
       a. **FSH → Sertoli** (Sustentacular) Cells → Release Androgen-binding protein (ABP) → Makes sperm receptive to Testosterone.
       b. **LH → Leydig** (Interstitial) Cells → Produce Testosterone → ↑Spermatogenesis.
    3) **(NB: Testosterone → Neg. Feedback to Hypothalamus → ↓GnRH).**



Male Reproductive Processes:
Spermatogenesis & NeuroEndocrine Control

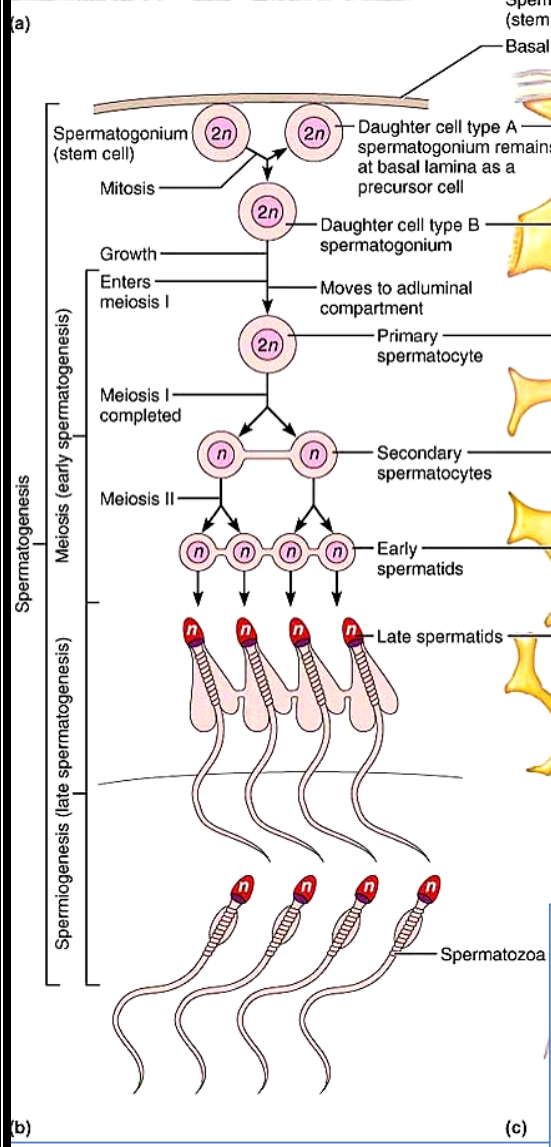
Spermatogenesis:

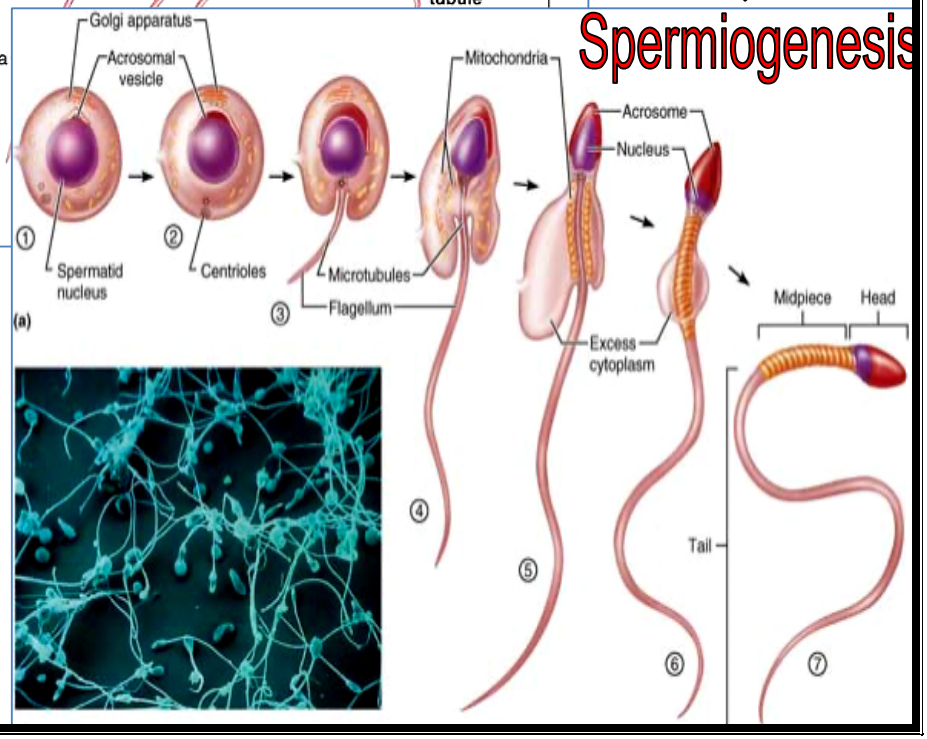
- The overall process of sperm formation – from **spermatogonium** (stem cells) **to spermatozoa** (sperm).
- Takes place inside the walls of the Seminiferous tubules
  - Walls of S.Ts are made of various sperm-forming cell types, all at different stages of development.

- **Mitosis:**
  - **#1 Spermatogonia (2n):**
    - The outermost tubule cells, in direct contact with the basal lamina.
    - Divide by mitosis into 2 spermatogonium.
      - Type A & Type B
        - Type A remains on the basement membrane – for future mitotic divisions.
        - Type B is pushed toward the lumen, where it becomes a **primary spermatocyte.**

- **Meiosis:**
  - **#$2_{(a)}$ Primary Spermatocyte (2n):**
    - Undergoes meiosis I, forming two smaller haploid cells called s**econdary spermatocytes.**
  - **#$2_{(b)}$ Secondary Spermatocytes (n):**
    - Continue into meiosis II producing 4 daughter cells called **spermatids**
  - **#3 Spermatids (n):**
    - Small, round cells with large nuclei.
    - Closer to the lumen of the Seminiferous tubule.

- **Spermiogenesis:**
    - Spermatids elongate
    - Shed excess Cytoplasmic baggage
    - Forms a tail (flagellum)
    - Result in potentially motile **spermatozoa (sperm)**
  - **# 4 Spermatozoa:**
    - **Head**:
      - Flattened nucleus → compacted DNA
      - Helmet-like **acrosome** on top of nucleus.
        - Contains hydrolytic enzymes for egg penetration.
    - **Mid-piece:**
      - Spiralled Mitochondria around contractile filaments of tail.
    - **Tail:**
      - **Flagellum** produced by the **centriole** near the nucleus
      - Whip-like movements of tail **propel** the sperm once **activated by prostate.**





Sustentacular Cells:

- **(Sertoli Cells)**
- Extend from basal lamina to the lumen of S.T.
- Bound by **tight-junctions:**
  - Defines the **basal & adluminal** compartments.
  - Forms the **blood-testes barier** →stops sperm's membrane antigens from escaping into bloodstream & activating immune system

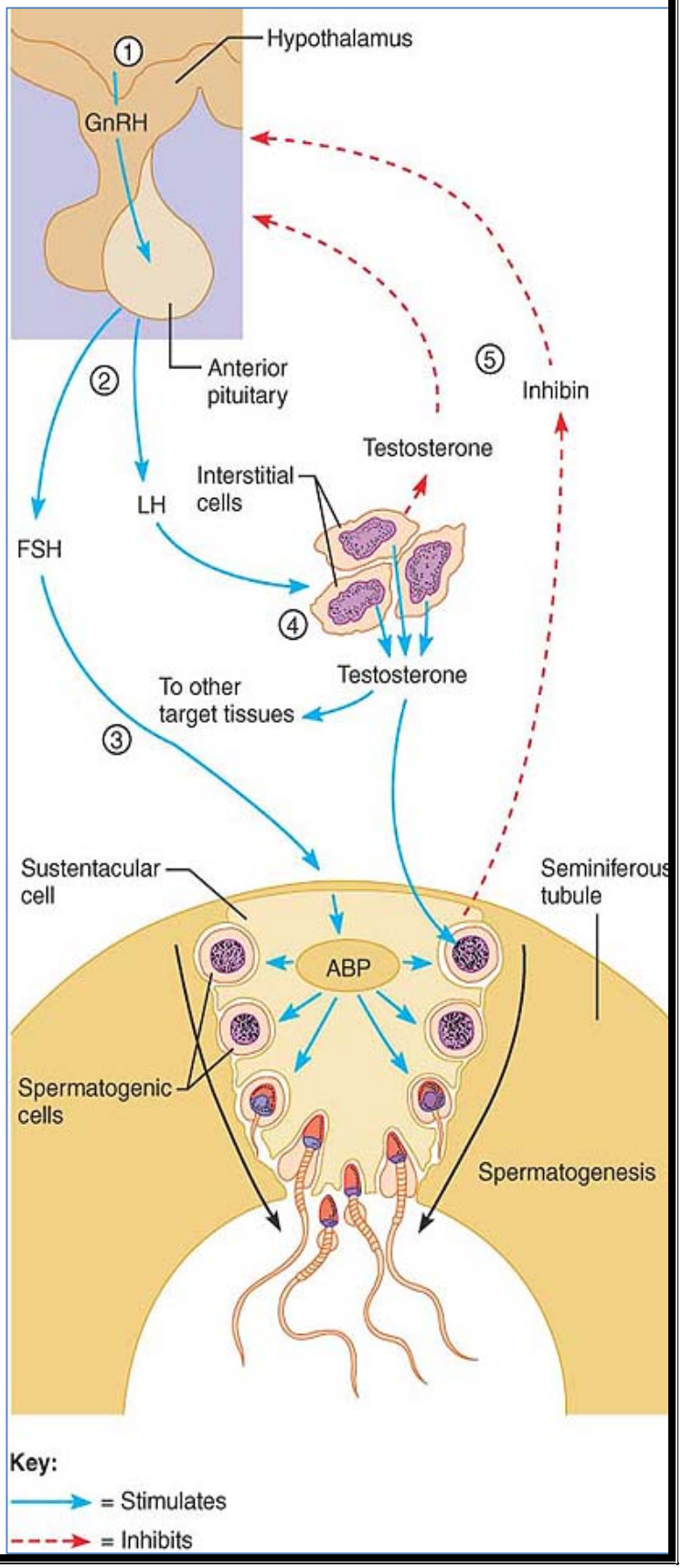
Hormonal Regulation:

NEUROENDOCRINE CONTROL:
"Brain-Testicular Axis"

1) **Hypothalamus** releases **GnRH (gonadotropin-releasing hormone)** which-
2) stimulates the release of gonadotropins: **FSH** (Follicle stimulating hormone) **& LH** (Luteinizing hormone).
3) **FSH:** stimulates sustentacular cells to release **Androgen-binding protein (ABP)** → Makes spermatagonium, spermatocytes, and spermatozoa **receptive to** the androgen: **Testosterone.**
4) **LH:** stimulates the **interstitial (Leydig) cells** [Basally external to Seminiferous tubules] to **produce testosterone** which **triggers & maintains spermatogenesis.**
5) **Testosterone** produced by Leydig (interstitial) cells **inhibits GnRH** production; as does **Inhibin**, produced by the sustentacular (sertoli) cells.

- When testosterone is at its peak → **sperm count is high (20Mil^{+})** → inhibin levels rise →GnRH decreases →FSH & LH levels decrease → Testosterone & ABP levels decrease → **spermatogenesis slows.**

-When **sperm count is low (20Mil $^{-}$)** → inhibin & testosterone levels are low → no negative feedback to hypothalamus → hyp. Releases GnRH → Ant. Pituitary releases LH & FSH → FSH stimulates sustentacular (sertoli) cells to produce ABP; LH stimulates the interstitial (Leydig) cells to produce testosterone →Testosterone + ABP stimulates spermatogenic cells → **Spermatogenesis increases.**



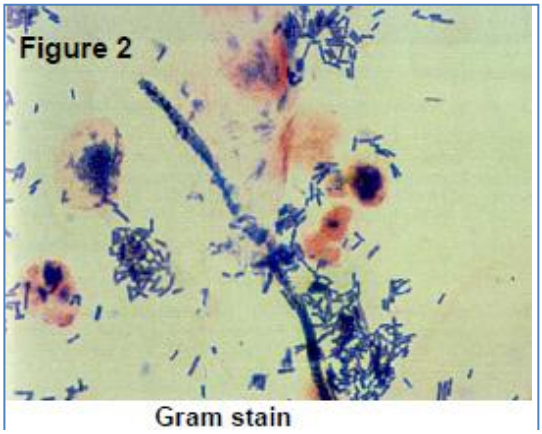
System: FEMALE REPRODUCTIVE SYSTEM

Pelvic Cavity:

- **Male:**
  - Urinary Bladder
  - Rectum
- **Female:**
  - Urinary Bladder
  - Uterus
  - Rectum

Normal Flora of the Genital Tract

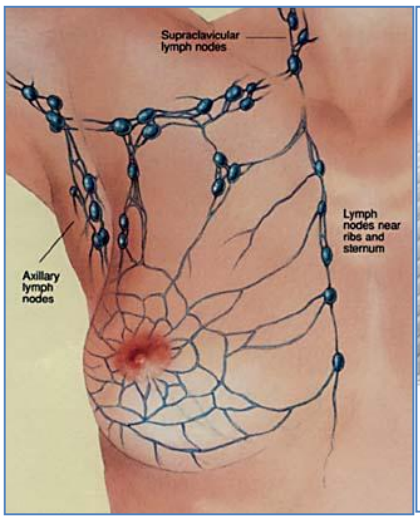
- **Male:**
  - **Urethra** – Few Organisms - (*Staph. epidermidis*, Streptococci, *Uroplasma urealyticum*)
- **Female:**
  - **Vagina** – High Numbers of Bacteria – (***Lactobacillus*** - Blue Gram Positive Rods, + Some Anaerobes)
    - → Produce lactic acid
    - → Protects against Bacterial Vaginosis & Yeast Infections.

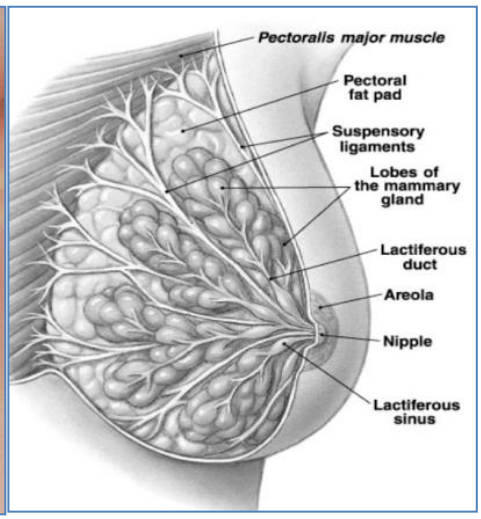


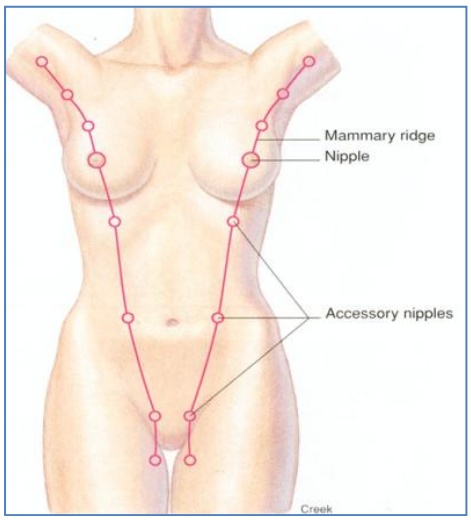
Gram stain

Revision of The Breast:

- **Anatomy:**
  - Attached to Pec-Major by Suspensory Ligaments
  - **Glandular Breast Tissue:**
    - Approx 20 lobes/lobules → Converge to Lactiferous Ducts → Lactiferous Sinuses → Nipple
  - **Lymphatic Drainage:**
    - Supraclavicular, Infraclavicular, Parasternal, Pectoral, Axillary, Central, Subscapular

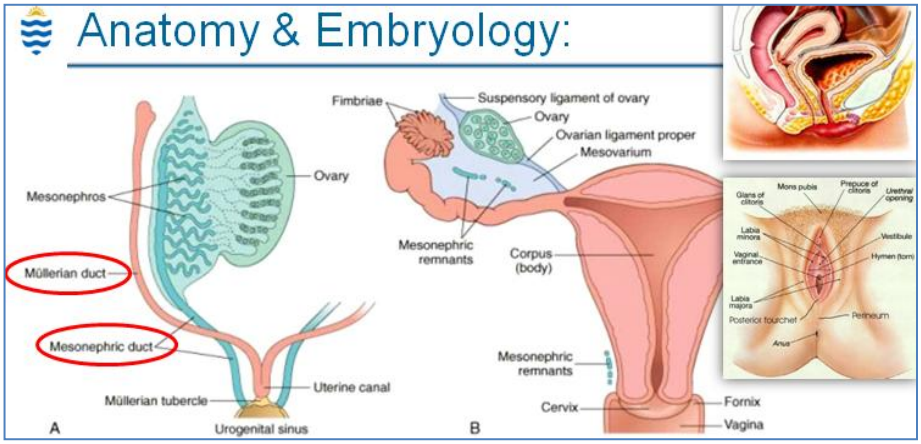




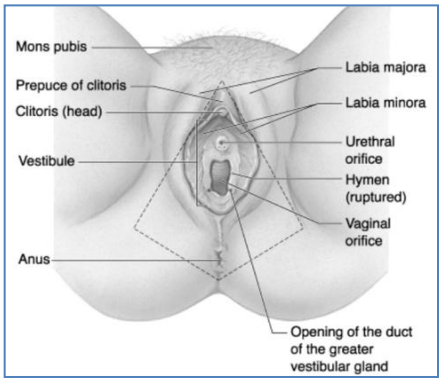


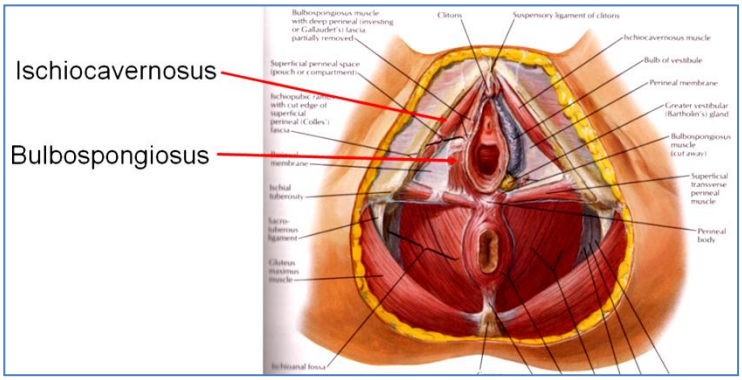
Review of Normal Female Reproductive Anatomy:

- **Embryology:**
  - **Female = The Default Sex** - (NB: The SRY Gene on the Y-Chromosome = the Male Determining Gene)

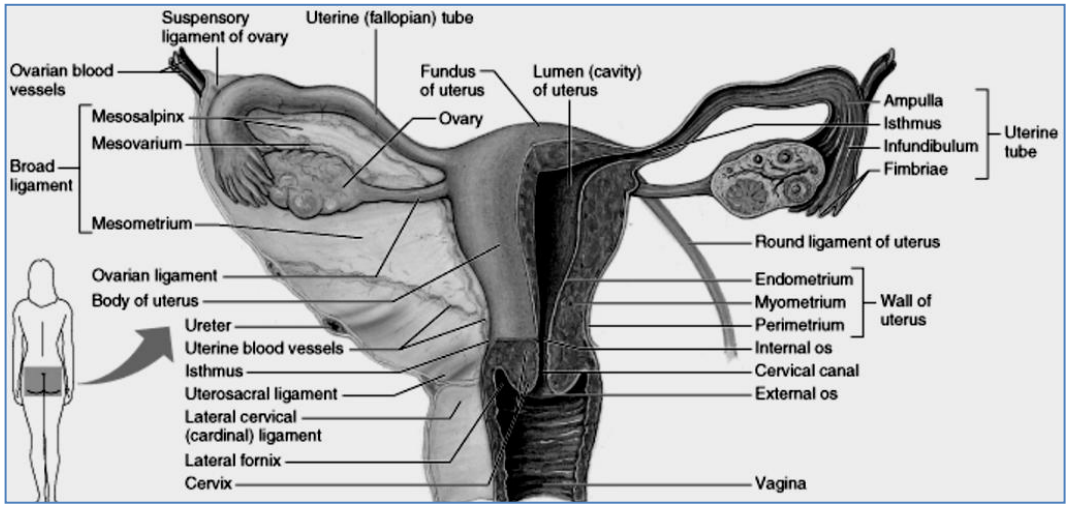


- **Anatomy:**
  - **Vagina/Vulva:**
    - Labia Majora & Minora
    - Clitoris & prepuce of clitoris
    - Urethral orifice

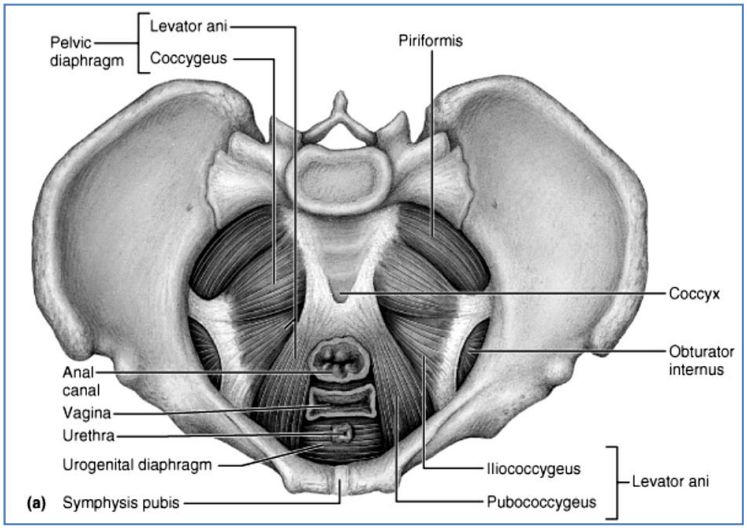




  - **Uterus -** Fundus (top / head), Body, Cervix (external os, canal, internal os), Lumen (internal cavity)
    - **Perimetrium** – Outer wall
    - **Myometrium** – Middle of wall
    - **Endometrium** – Inner wall
  - **Uterine (fallopian) Tubes**
    - Common site of fertilisation
    - Infundibulum – projections = fimbriae (closest to ovary) → Receives oocyte
  - **Ovaries (gonads)**
    - Produce female gametes (oocytes)
    - Secrete female sex hormones – (Oestrogen & Progesterone)
    - Held in place by ligaments & muscles

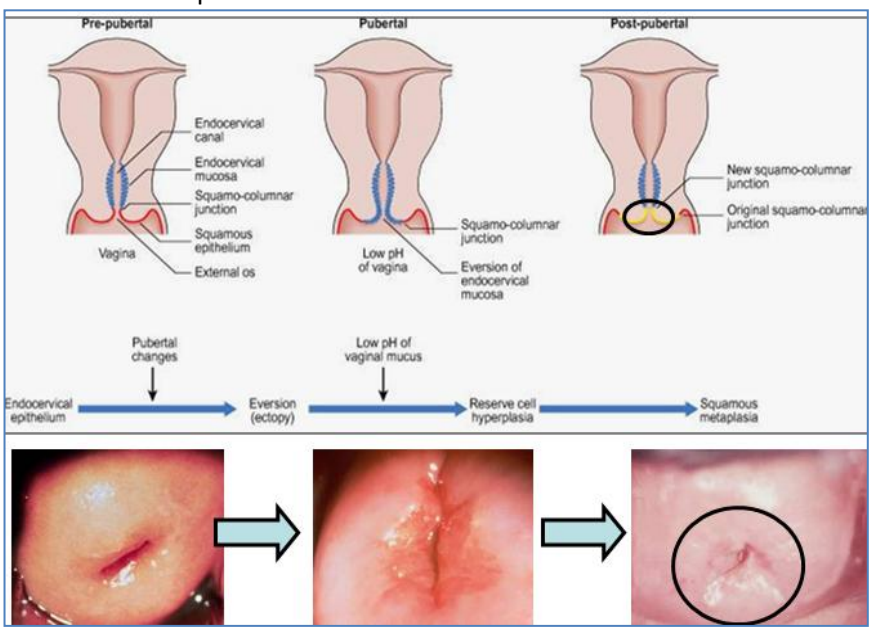


- **Blood Supply:**
  - **Internal iliac artery:**
    - Branches from common iliac artery.
    - Uterine Artery
    - Vaginal Artery
    - To external genitalia
  - **Ovarian Artery:**
    - To ovaries, uterine tubes and uterus
- **Pelvic Diaphragm:**
  - **Levator Ani (anterior half)**
    - Iliococcygeus
    - Pubococcygeus
  - **(posterior) Coccygeus** (ischiococcygeus)
  - **(posterior) Piriformis**



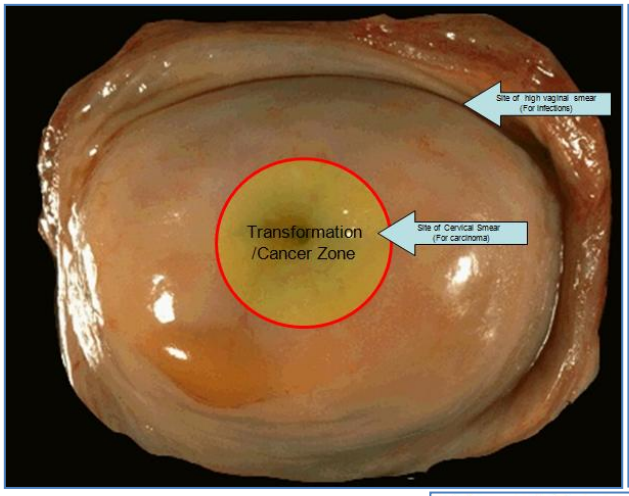
Background Information on the Cervix:

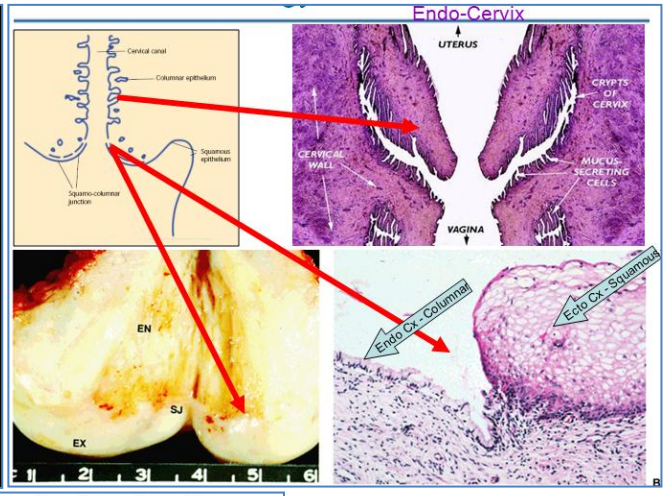
- **NB: The Transformation Zone – Commonest location of Cervical Cancer.**
  - **TZ =** The location of Transition from Squamous to Columnar Epithelium.
  - **NB:** During puberty, Columnar Epithelium Migrates out of the os → Exposed to Vaginal Acidity → Metaplasia to Squamous Epithelium
  - This is the area Predisposed to Cancer.

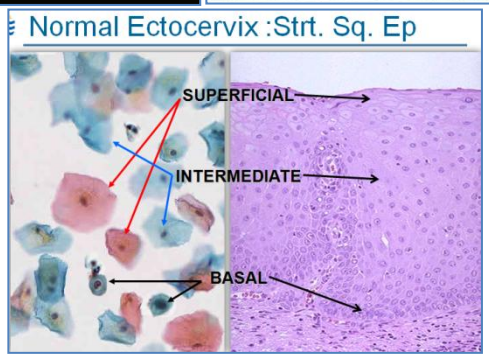


(Red = Squamous) (Blue = Columnar)

- **NB: The Normal Cervix – Anatomy & Histology:**
  - **Endocervix =** *Simple Columnar Epithelium*
  - **Ectocervix =** *Stratified Squamous Epithelium*

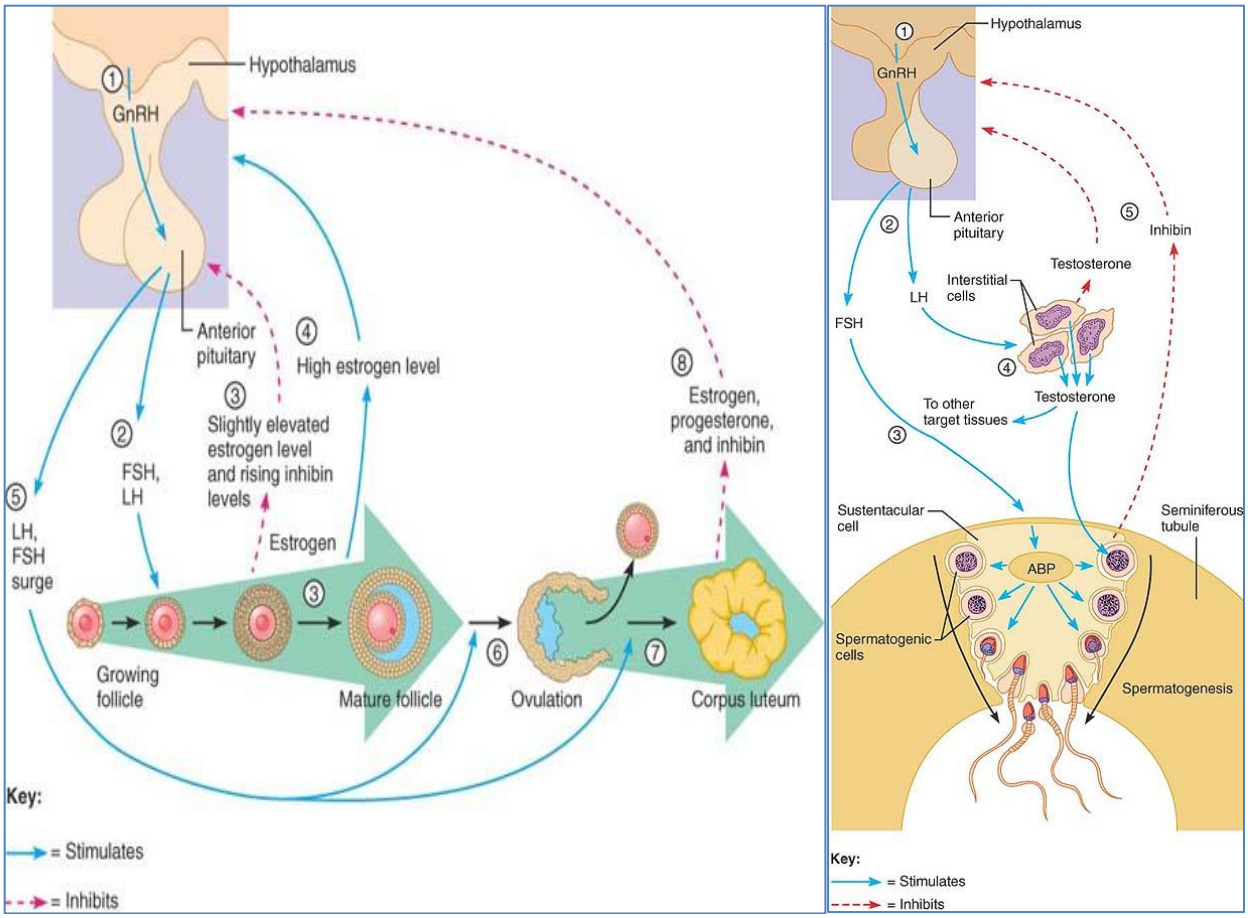






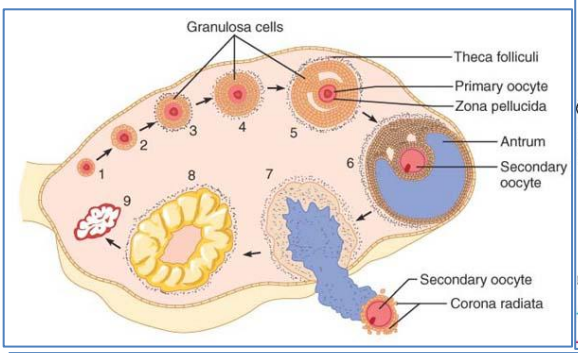
Review of Female Reproductive Physiology:

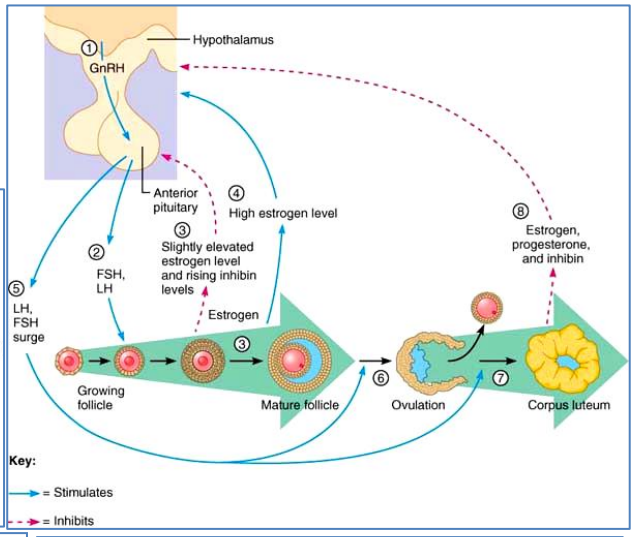
- **Puberty:**
  - A gradual series of events that transform a child into a sexually mature adult.
  - **Female:** Marked by first menstrual period (average age 13)
  - **(Male:** Marked by physical development of Male Sex Characteristics)
- **Initiation:**
  - Activation of **Hypothalamo-Pituitary-Gonadal Axis** → establishes regulation of gonadal function.
    - **At puberty** → ↓ Sensitivity of the hypothalamus to Inhibitory Steroid Hormones →↑GnRH →↑FSH & LH → ↑Gonadal Testosterone/Oestrogen/Progesterone → Sexual Maturation.

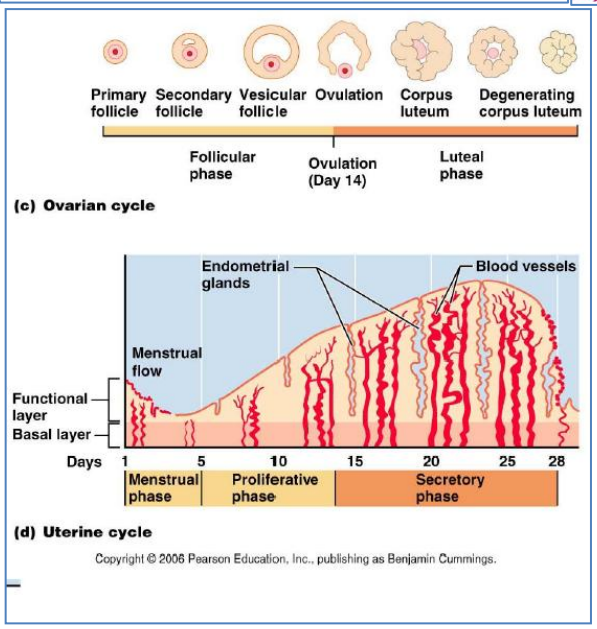


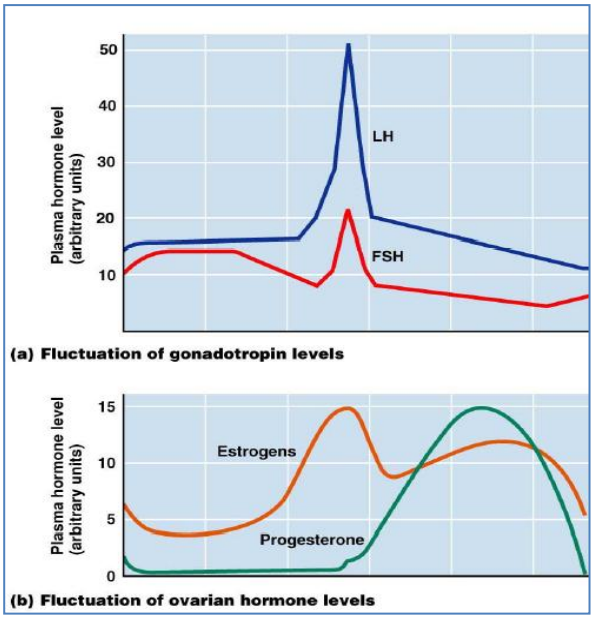
- **Menopause:**
  - **Menopause "occurs" when it has been a year since the last menstruation.**
  - Gradual process over 3-5yrs (between ages 46-54)
  - **Mechanism:** ↓Follicle Sensitivity to FSH → ↓Follicles Recruited →↓Oestrogen Levels Production → Symptoms:
    - ↓Ovulation
    - Irregular, Lighter Periods
    - Hot flushes
    - Palpitations
    - Insomnia, Depression
    - Breast Atrophy
    - Vaginal Dryness
    - **Osteoporosis**

- **The Female Reproductive Cycle:**
  - The monthly series of events associated with the maturation of an egg.
  - Typically 28 days long.
  - **Days 1-5: *Menstruation*:**
    - **Shedding of the Endometrium**
    - Low levels of all hormones (FSH, LH, Oest. & Prog).
  - **Days 5-14: The Follicular/Proliferative Phase:**
    - **Follicular Recruitment & Growth**
    - **+ Endometrial Proliferation**
    - Rising levels of Oestrogen as Follicle/s get larger.
  - **Day 14 (Mid-Cycle): *Ovulation*:**
    - Surge of FSH & LH → Ovulation into peritoneal cavity → Oocyte enters Fallopian Tubes.
    - **FERTILE**
  - **Days 14-28: The Luteal Phase:**
    - **Transformation of Follicle → Corpus Luteum**
    - Corpus Luteum Secretes Mainly Progesterone (& Some Oestrogen)
      - Degenerates (Unless pregnancy occurs →C.L. persists until the placenta can take over).
    - **FERTILE**
  - **Day 28: End of Cycle:**
    - **Corpus Luteum Degenerates** → No Oestrogen/Progesterone to sustain Thick Endometrium →Endometrial Arteries become Spastic & Tortuous → Menstruation.









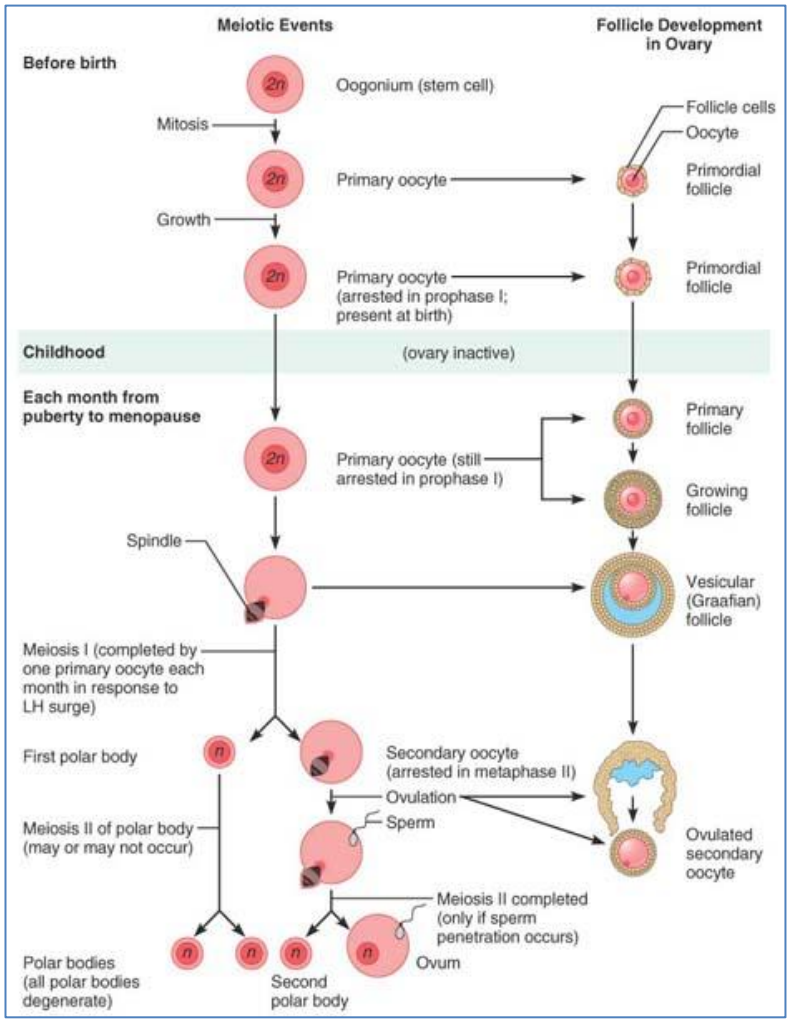
Meiosis (Female) – Oogenesis:

- It is thought that in general, the total number of eggs in a female is predetermined at birth.
- **Female gamete production = Oogenesis.**
    - Done through **meiosis**
        - Specialized cell division
        - Usually produces 4 haploid cells.

1) **Foetal period** - the, **Oogonia** (diploid ovarian stem cells) multiply rapidly by mitosis, then enter a growth phase and lay in nutrient reserves as **Primary Oocytes**.
2) These **Primary Oocytes** then become **surrounded by** a single layer of **Follicle Cells** forming a **Primordial Follicle.**
3) **Primary Oocytes** (of the primordial follicles) then begin the **first meiotic division.** However, they are **arrested in prophase I.**
4) Female is born with approx. 2million primary oocytes. By puberty, 250000 primary oocytes are left.
5) **Puberty—Menopause:** Each month, a small number of **primary oocytes** are recruited in response to the LH surge midway through the menstrual cycle. (Luteinising Hormone) As these **primary oocytes** prepare to divide, a spindle forms on its edge, creating a small "nipple" where half of the chromosomes will be cast during division.
6) Only **one of the primary oocytes** is selected to **continue meiosis I.** Produces **2 haploid cells** (23 chromosomes each) **dissimilar in size**. The smaller cell is the "**first polar body"** (little->no cytoplasm) and the larger cell is the **secondary oocyte**. → The **secondary oocyte** is then arrested in **metaphase II** and **OVULATED.** (unequal Cytoplasmic divisions ensure that a fertilised egg has ample nutrients for its week-journey to the uterus.)
7) The **ovulated secondary oocyte MUST be penetrated by a SPERM for it to complete MEIOSIS II,** yielding one large **OVUM** and a **"Second polar body"**

***Note: -** The potential products of oogenesis are 3 small polar bodys and one large ovum. (3 polar bodies aren't always formed – first polar body often perishes before meiosis II)

-Only the **OVUM** is a ***functional gamete.***



Breast Cancer staging, prognosis, surgery and adjuvant treatment

Staging

- Investigations for staging
  - Mammogram if not already done
  - CXR
  - Bone scan
  - USS
  - CT/MRI
  - CT-guided needle biopsy
  - PET Scan
- Staging system and TNM system
  - Stage 0
    - DCIS
  - Stage I
    - Tumour <2cm and no nodes
  - Stage IIA
    - Tumour <2cm with axillary nodes OR
    - No breast tumour detectable but cancer cells in axillary nodes OR
    - Tumour 2-5cm and no nodal involvement
  - Stage IIB
    - Tumour 2-5cm with spread to axillary nodes OR
    - Tumour >5cm with no spread to axillary nodes
  - Stage IIIA
    - No tumour found in breast but with extensive clumping of axillary nodes or may involve retrosternal nodes OR
    - Cancer any size with clumping of axillary nodes
  - Stage IIIB
    - Tumour any size and has spread to chest wall and/or skin of breast AND
    - Clumping of axillary nodes and retrosternal node involvement
  - Stage IIIC
    - No sign of tumour in breast/tumour of any size and spread to chest wall and/or skin of breast AND
    - Subclavicular nodes involved AND
    - Axillary and retrosternal nodes may be involved
  - Stage IV
    - Metastatic spread
- Inflammatory breast cancer is considered at least stage IIIB

Prognosis

Stage	5-year survival rate
0	93%
I	88%
IIA	81%
IIB	74%
IIIA	67%
IIIB	41%
IIIC	49%
IV	15%

Reference: American Cancer Society 2011 Online at - http://www.cancer.org/Cancer/BreastCancer/DetailedGuide/breast-cancer-survival-by-stage

Stage	TNM	Description	5-year Survival
0	Tis N0 M0	Carcinoma in situ. No tumor is regional lymph nodes, No distant metastases	99%
I	T1 N0 M0	Tumor is less than or equal to 2 centimeters, No tumor is regional lymph nodes, No distant metastases	92%
IIA	T0 N1 M0 T1 N1 M0 T2 N0 M0	No evidence of primary tumor, metastases to movable ipsilateral nodes, No distant metastases. Tumor is less than or equal to 2 centimeters, metastases to movable ipsilateral nodes, No distant metastases. Tumor is between 2 and 5 centimeters, No tumor is regional lymph nodes, No distant metastases	82%
IIB	T2 N1 M0 T3 N0 M0	Tumor is between 2 and 5 centimeters, metastases to movable ipsilateral nodes, No distant metastases. Tumor is over 5 centimeters, No tumor is regional lymph nodes, No distant metastases.	65%
IIIA	T0 N2 M0 T1 N2 M0 T2 N2 M0 T3 N1, N2 M0	No evidence of primary tumor, metastases to fixed ipsilateral nodes, no distant metastases. Tumor is less than or equal to 2 centimeters, metastases to fixed ipsilateral nodes, No distant metastases. Tumor is between 2 and 5 centimeters, metastases to fixed ipsilateral nodes, no distant metastases. Tumor is over 5 centimeters, metastases to movable or fixed ipsilateral nodes, no distant metastases.	47%
IIIB	T4 Any N M0 Any T N3 M0	Tumor extends to chest wall, any nodal involvement, no distant metastases. Any primary tumor involvement, metastases to ipsilateral internal mammary nodes, no distant metastases.	44%
IV	Any T Any N M1	Any primary tumor involvement, any nodal involvement, distant metastases.	14%

Reference: Cancer Monthly Article with reference to Marc E. Lippman, *Breast Cancer*, in HARRISON'S PRINCIPLES OF INTERNAL MEDICINE, pt. 5 § 76, at 516-523 (Dennis L. Kasper, M.D. et al., eds, 16th ed 2005).

Treatment

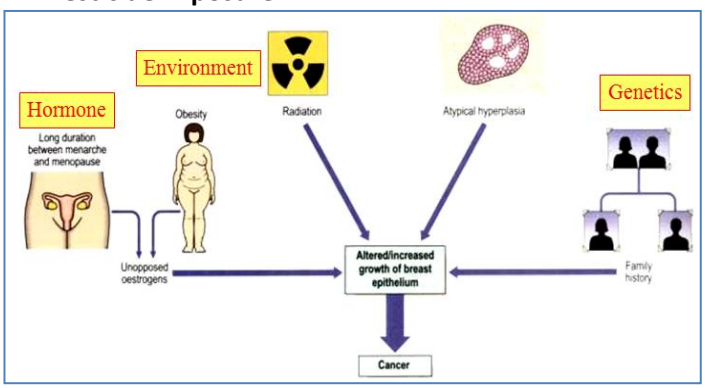
- DCIS
  - Breast conserving surgery
  - Radiotherapy post surgery
  - Possible node resection (rarely)
  - Hormonal therapy may be useful, side effects often out weight benefit
- Early breast cancer
  - Breast sparing surgery or mastectomy +/- breast reconstruction
  - Chemotherapy lowers risk of reoccurrence – given after surgery
  - Radiotherapy almost always given – sole agent or after chemo
  - Hormonal therapy of benefit solely or in combination with other agents
  - Targetted therapy (Herceptin) only suitable in some women
- Inflammatory breast cancer
  - If no lump in breast, begin with Chemotherapy
  - Mastectomy +/- nodal resection if responding well to chemotherapy +/- breast reconstruction
  - Radiotherapy is almost always used before or after surgery or as a replacement to surgery if response to chemotherapy is good.
  - Targeted therapy only suitable for some women
  - Hormonal therapy suitable for some women and can be used alone or with other agents
- Locally advanced breast cancer
  - Chemotherapy
  - Mastectomy for some, not all women.
  - Radiotherapy may be used before or after – local, axillary, neck and surrounding areas
  - Targeted therapies only suitable for some women
  - Hormonal therapies used if hormone sensitive and can be used alone or with other treatments
- Metastatic breast cancer
  - Hormonal are used as first treatment if hormone sensitive alone or with other agents
  - Chemotherapy for non-hormone sensitive cancers or in combination with hormone therapies for rapid-growing cancers particularly in liver or lung
  - Targeted therapies are only suitable for some women and are used with other treatments
  - Radiotherapy can be used to reduce size of tumours and secondaries in an effort to reduce pain, especially in bones
  - Surgery is not routinely used, but may be used to reduce symptoms at the sites of secondaries, such as bones, lung or brain and rarely liver.

Reference: Australian Government Cancer Australia online at: http://canceraustralia.nbocc.org.au/breast-cancer/treatment/treatment-options-by-breast-cancer-type

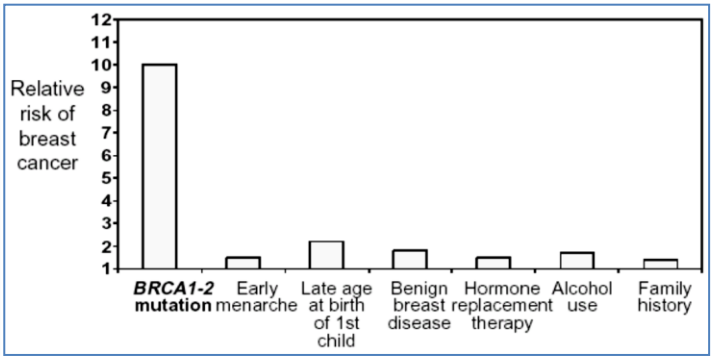
WOMENS HEALTH Pathology:

BREAST CANCERS:

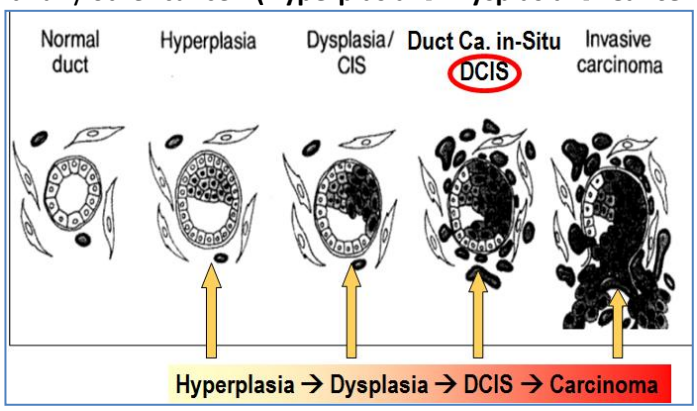
- ***Malignant* Neoplasms – BREAST CANCER: – (Irregular, Hard, Rough, Fixed)**
  - **Aetiology/Risk Factors:** (NB: know these for the exam – Eg. "List the risk factors.")
    - **Hormonal (Sporadic):**
      - **Gender** (99%F:1%M)
        - Affects ≈ 9% of Women
      - **Age** – Highest in 50-69yrs
      - **Parity** – Late Parity/Nulliparous Women have ↑Risk of Breast Ca.
        - (Early Parity & Breastfeeding → ↓ Risk of Breast Ca)
      - **Prolonged Oestrogen Exposure** – (Early Menarche, Late Menopause, HRT)
        - (NB: OCP Marginally ↑Breast Ca. Risk; BUT also ↓Endometrial Ca. Risk)
      - **Pre-Existing Fibrocystic Disease** – (Esp. *Proliferative* Subtype)
    - **Genetic (Familial):**
      - **ER-Negativity &/Or HER2-Positivity** → Cancer in Young Women
      - **Hereditary (Only 30% of Breast Cancers):**
        - ↑Risk with ↑# of 1st-Degree Relatives with Breast Ca.
        - ↑Risk with Presence of BRCA1 or BRCA2 Gene Mutations (Predisposed)
    - **Environmental:**
      - **Radiation Exposure**
      - **Pesticide Exposure**



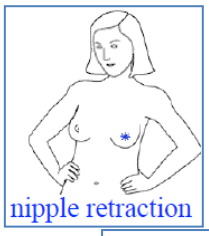
BRCA1 (FISH Technique)	BRCA2
52% of genetic type (2% overall)	32% of genetic type (1% overall)
Young age.	Not specific.
Risk of Ca – 40-90%	Risk of Ca 30-90%
High grade, necrosis, inflam (.. Medullary)	Low grade, NOS type. Scaring (..Schirrous)
Triple –ve (ER,PR, HER2)	ER positive.
F/H of ovarian, prostate, pancreas ca.	F/H of male breast ca (ovary, prostate also)
Chromosome 17q	Chromosome 13q.

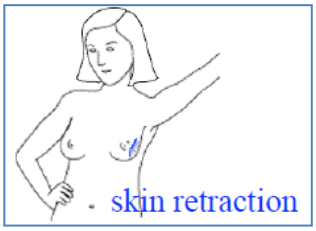


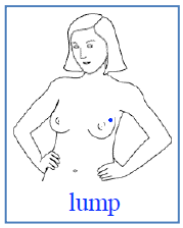
  - **Pathogenesis:**
    - **Carcinogenesis of Duct Epithelial Cells → :. "Ductal Carcinoma"**
    - As with any other cancer: **(Hyperplasia → Dysplasia → Cancer → Invasion)**

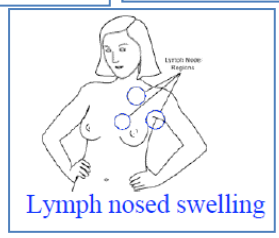


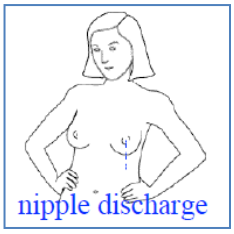
- **Clinical Features:**
  - **Common Signs & Symptoms:**



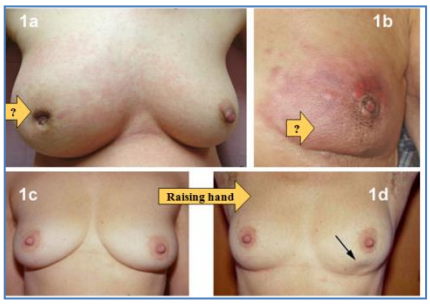


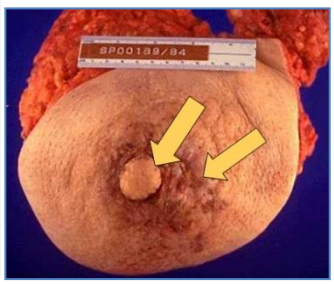


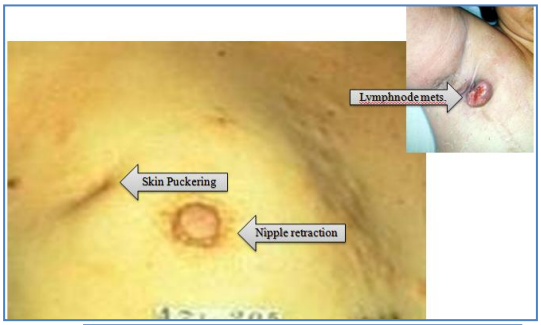


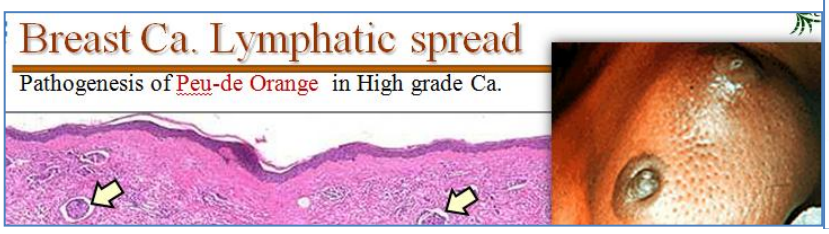


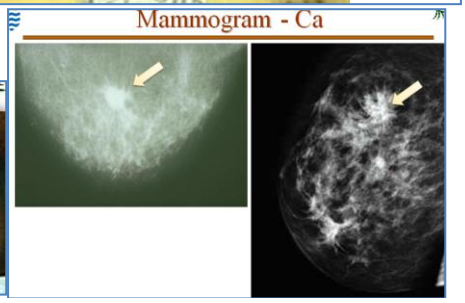
  - **Specific Features of DCIS (Ductal Carcinoma In Situ):**
    - **Presentation:**
      - **Bloody Nipple Discharge** (Intraductal papilloma still most common)
    - **Diagnosis:**
      - **Almost Exclusively detected by **Mammography**
    - **Complications:**
      - Localised; No distant metastasis ☺
      - Spreads through Ducts → Eventually becomes an **Invasive Duct Carcinoma**.
  - **Specific Features Of Ductal Carcinoma (Typical "*Schirrhous*" Type):**
    - **Presentation:**
      - **Nipple Retraction!!!**
      - **Skin puckering**
      - **Axillary Lymphadenopathy**
      - **Peu'de'Orange** – (Lymphoedema due to Lymphatic Infiltration by Ca. Cells)
    - **Quadrant Distribution:**
      - 50% occur in Upper-Outer Quadrant
      - 10% occur in each remaining Quadrants
      - 20% Sub-Areolar.
    - **Diagnosis – Triple Assessment:**
      - **1. Clinical History/Examination** (Firm, irregular, fixed lump)
      - **2. Imaging** (Mammography → Radial Fibrosis)
      - **3. Biopsy** (Malignant Adenocarcinoma)
    - **Complications:**
      - → Metastasis
      - → Death



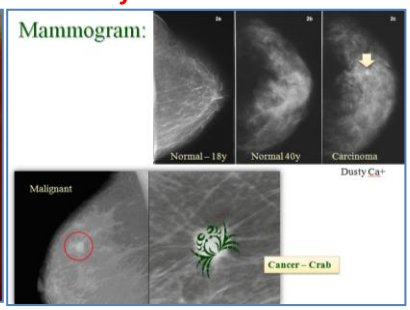




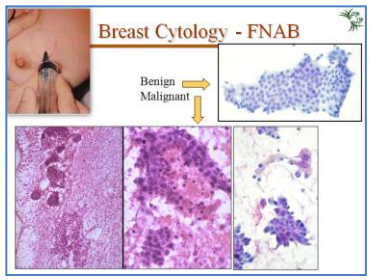




- **Diagnosis – "Triple Testing":**
  - Triple Assessment → Clinical, Imaging & Biopsy
  - **1. Clinical History First** (Firm, irregular, fixed lump + Lymphadenopathy, etc)
  - **2. Imaging – (Mammogram):**
    - **Mechanism:**
      - Low radiation dose (0.1rad)
      - Light compression by plates to stabilize and spread its interior structures.
    - **Very Sensitive; Low Specificity** – (Detects Lumps 1-2y before Physical Breast Exam)
      - (NB: This increases with age as breast density decreases)
    - **Recommended every 2yrs for Women 50-69yo.** – (Yearly for high risk Pts).
    - **Signs of Breast Ca = *Densities & Calcifications*.**

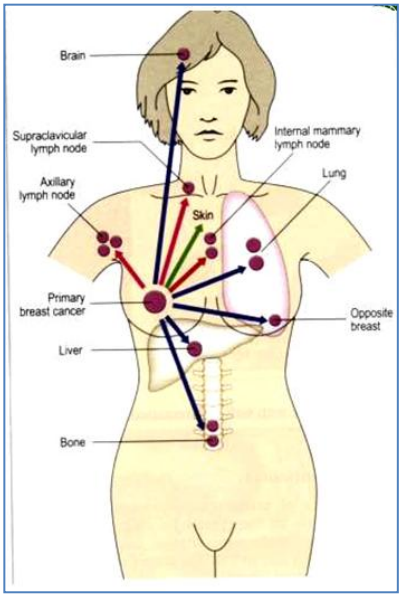


  - **3. Fine Needle Biopsy/Sectional Biopsy (Cytology):**
    - **Microscopy:** Dysplasia/Pleiomorphism
    - **Staining** – for *HER2 & ER Status* (Dictates Management & Prognosis)
    - **Gene Detection:** Familial BRCA1 & BRCA2 Gene Mutations

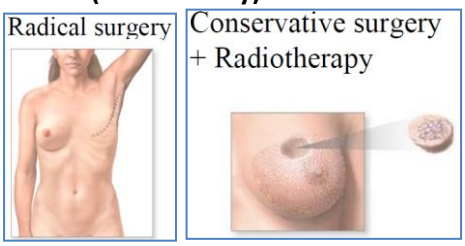


- **Calculating Prognosis:**
  - **Grading - Based on Tumour Markers (Low Grade → High Grade):**
    - **1. 'Luminal A' – (98% 5yr Survival):**
      - ER-Positive (Good Sign)
      - HER2-Negative (Good Sign)
      - **Responsive to Anti-Oestrogen (Tamoxifen) Therapy**
    - **2. 'Luminal B':**
      - ER-Positive (Good Sign)
      - HER2-Positive (Bad Sign)
      - **Responsive to Chemotherapy**
    - **3. 'Basal-Like'/'Triple Negative':**
      - ER-Negative (Bad Sign)
      - HER2-Negative (Good Sign)
      - But BRCA1 Positive (Bad Sign)
      - **Poor Prognosis + Young**
    - **4. 'HER2 Positive' – (16% 5yr Survival):**
      - ER-Negative (Bad Sign)
      - PR-Negative (Progest) (Bad Sign)
      - HER2-Positive (Bad Sign)
      - **Poor Prognosis + Early Brain Mets**
      - **NB: BUT has a Targeted Treatment ("Trastuzumab"/"Herceptin")**
    - (NB: ER = Oestrogen Receptor. Loss is Abnormal)
    - (NB: HER = Human Epidermal Growth-factor Receptor. Presence is Abnormal)
    - (NB: E-Cadherin = Cell Adhesion protein)
    - (NB: BRCA = Breast Ca. Antigen)

- **Staging:**
  - **Investigations for Staging:**
    - Mammogram/USS if not already done
    - CXR
    - CT/MRI/PET Scans
    - Bone scan
  - **Based on TNM System:**
    - **T –** (Size of Primary Tumour)
    - **N –** (# of Regional Lymph Nodes Involved)
    - **M –** (Metastases?)
  - **Stages:**
    - **0 –** DCIS
    - **1 –** T<2cm, N0, M0 98% 5YS
    - **2 –** T<5cm, N0, M0 85% 5YS
    - **3 –** T>5cm, N1, M0 50% 5YS
    - **4 –** T>5cm, N+, M+ 16% 5YS



- **Treatment – Surgical or Pharmacotherapy:**
  - **Surgery - May be Radical (Mastectomy) or Conservative (Local Excision + Chemo/Radio)**

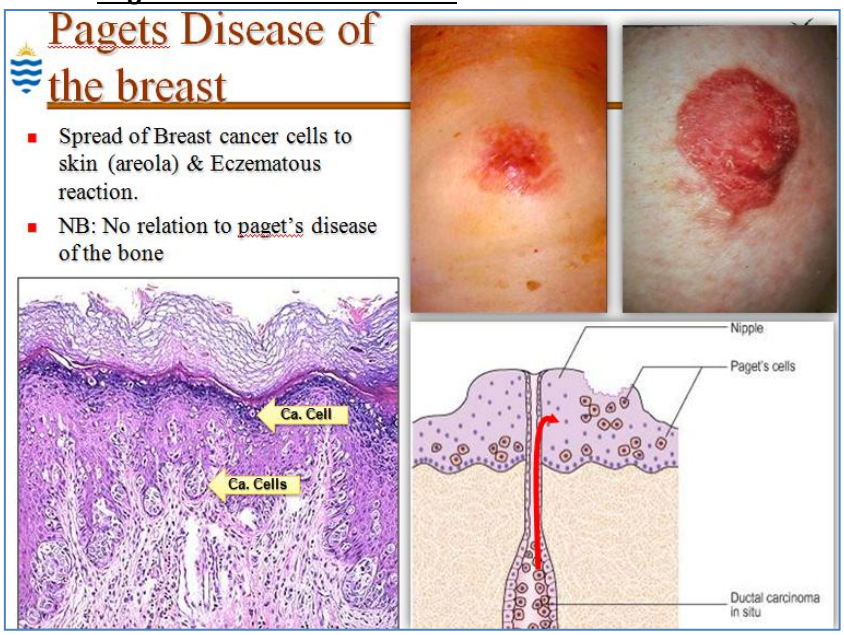


  - **Pharmacotherapy - Depends on Hormonal Status:**
    - Positive ER/PgR Status (Typically BRCA1) → Anti-Hormone Therapy (Tamoxifen)
    - Negative ER/PgR Status (Typically BRCA2) → Chemotherapy
    - **Eg. Tamoxifen – An ER Antagonist** → 45% Risk Reduction in ***ER-Positive*** Tumours.
    - **Eg. Herceptin – A HER2 Antagonist** → Used in ***HER2-Positive*** Tumours
  - ***If DCIS (Stage 0):***
    - Conservative Surgery + Radiotherapy
  - ***If Breast Cancer (Stage 1-4):***
    - Surgery – (Optional Conservative [*Stage 1-2*], OR Mastectomy [*Stage 1-3*] +/- L-Nodes)
      - (NB: If [*Stage 4*], surgery is only Palliative)
    - + Radiotherapy & Chemotherapy - (↓Risk of Reoccurrence & Metastases)
    - (+/- Hormonal therapy (**Tamoxifen**) if ER-Positive)
    - (+/- Targetted therapy (**Herceptin**) if HER2-Positive)

- **Screening & Prevention:**
  - **Population Screening Recommendations (UpToDate):**
    - **BSE** (Breast Self-Examination) advised Monthly from 18yo
    - **CBE** (Clinical Breast Examination) advised Annually from 25yo
    - ***Mammogram 1-2yrly from 40yo until old age (Recommended by UpToDate)**
    - ***+/- BRCA-Gene Testing for Pts with a FamHx of Breast/Ovarian Ca. (90% Sensitive)**
  - **Prevention of BRCA-Associated Cancers:**
    - **Breast:**
      - **Prophylactic Double Mastectomy:**
        - (≈ 90% Reduced Risk of Breast Ca.)
      - **+/- Prophylactic Oophorectomy (↓Oestrogen Stimulation):**
        - (≈95% Reduced Risk of Ovarian Ca.)
        - (≈50% Reduced Risk of Breast Ca.)
    - **Ovarian:**
      - **Prophylactic Oophorectomy (↓Oestrogen Stimulation)**
      - **Surveillance**

Rarer Breast Malignancies:

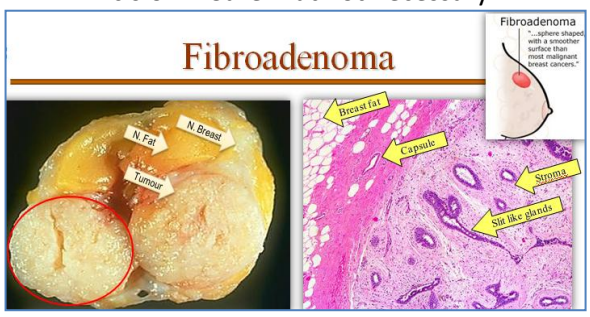
- **Paget's Disease of the Breast:**

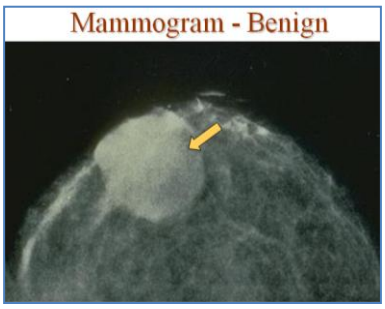


WOMENS HEALTH Pathology:
FIBROADENOMA

***Benign* Neoplasms: – (Round, Smooth, soft & Mobile)**

- ***FIBROADENOMA ("BREAST MOUSE"):**
  - **Aetiology:**
    - Benign Tumor of Intralobular Stroma (Loose Connective Tissue)
  - **Pathogenesis:**
    - Benign Tumor of Intralobular Stroma (Loose Connective Tissue) + Some Acinar (Gland) Proliferation
  - **Morphology:**
    - Capsulated, Firm, Homogenous, Grey, Nodular Tumour, *Without* Cysts.
  - **Clinical Features:**
    - **Most common *Benign Tumour* of the Breast**
      - NB: 50% Involute Spontaneously
      - NO risk of Malignancy.
    - **Presentation:**
      - Typically 20-40yrs
      - Typically Multiple & Bilateral
      - Palpable Mass Or Mammographic Density/s or Calicifications
      - Variable Size – Typically <5cm Rounded Tumour
      - Highly Mobile ("Breast Mouse")
      - Hormonal Stimulation - (May increase with pregnancy or HRT)
  - **Treatment:**
    - Excision = Cure. But not necessary.



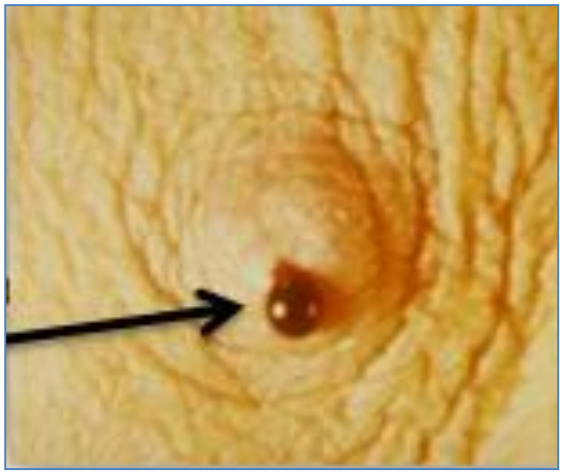


- **NB: "PHYLLODES TUMOUR"/"Cystosarcoma Phyllodes"/GIANT FIBROADENOMAS:**
  - **NB: Same as Fibroadenomas, except Typically occur in 50-60yrs (Cf. 20-40yrs for Fibroadenomas)**
  - **NB: "Phyllodes Tumour" is preferred due to Benign Nature.**
  - **Morphology:**
    - Capsulated, Firm, Homogenous, Grey, Nodular Tumour, *Without* Cysts.
    - ***PLUS*** *– "Phyllodes" ("Leaf-Like")* clefts and slits *throughout Tumour.*
  - **Clinical Features:**
    - Typically Benign **BUT Requires Excision** to avoid Local Recurrences.
      - Metastasis is Rare.
      - NB: can be premalignant in older people
    - NB: An expanding lesion :. No retraction
  - **Management:**
    - **Excision** to avoid Local Recurrences

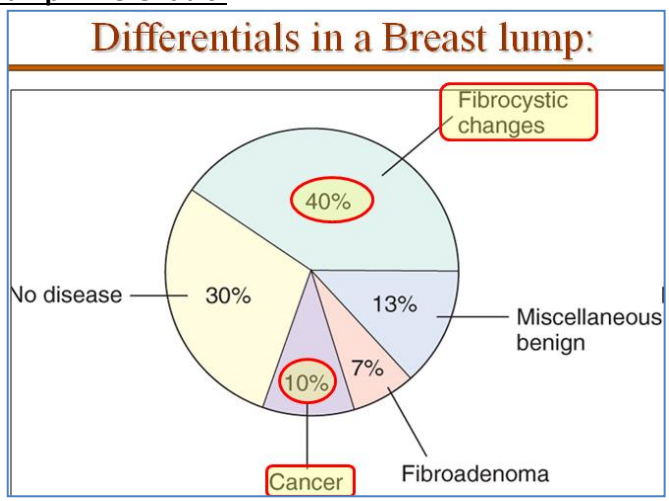
WOMENS HEALTH Pathology:
BREAST INTRADUCTAL PAPILLOMA

***Benign* Neoplasms: – (Round, Smooth, soft & Mobile)**

- **INTRADUCTAL PAPILLOMA:**
  - **Aetiology:**
    - Benign Tumor of Duct Epithelium
  - **Pathogenesis:**
    - Benign Tumor of Duct Epithelium → Papillary Projections *Within* a Dilated Duct
  - **Morphology:**
    - Solitary, Intra-ductal Papillary Proliferation.
    - Typically Occur in the Lactiferous Sinuses of the Nipple (:. Sub-Areolar)
  - **Clinical Features:**
    - Middle age, **Bloody Nipple Discharge**, Small Sub-Areolar Lump.
      - **(Commonest cause of Bloody Nipple Discharge)**
      - (Irregular, small, ***Sub-Areolar*** lump)
  - **Management:**
    - **Core Needle Biopsy**
    - **Excisional Biopsy** → Once Confirmed Intraductal Papilloma, no need for further Rx.
  - **Prognosis**:
    - Recurrent, but NO risk of malignancy. (rare)



WOMENS HEALTH Pathology:
TRIGGER PAGE - BREAST LUMPS

- **Breast Lump Differentials:**
  - 

- **Breast Lump Diagnostic Features:**

Clinical Presentation:	Most Common Dx:	DDx:
Single, Mobile Lump	*Fibroadenoma*	*Phyllodes Tumour (if >55yrs)*
Multiple, Irregular Lumpy Areas + Cyclical Pain	*Fibrocystic Change*	-
Firm, Tethered Lump	*Carcinoma*	-
Clear/Pus Nipple Discharge	*Duct Ectasia*	-
Bloody Nipple Discharge	*Duct Ectasia*	*Duct Papilloma* *Ductile Ca. In Situ (DCIS)*
Nipple Ulceration & Eczema	*Paget's Disease of the Breast*	*Nipple Adenoma*
Milky Discharge + Visual Changes + Headaches	*Prolactinoma*	*Pituitary Adenoma*

Breastfeeding:

The Importance of Breastfeeding:

- **Advantages of Breastmilk:**
  - Exactly suited to Bub's nutritional needs
  - It adapts to your baby's changing needs:
    - The 1st half of a feed is thirst-quenching & sugary, and the last half is rich, creamy and full of good fats.
    - Throughout lactation and as your baby has fewer feeds.
  - Breastmilk is hygienic.
  - Protects from infection
  - Protects against SIDS
  - Convenient & free(No bottles, sterilising, mixing, etc)
  - Aids development of:
    - Eyesight
    - Speech
    - Jaw and mouth development.
  - The taste of breastmilk changes with mum's diet, meaning a breastfed baby is likely to accept foods you like when you introduce solids.
  - Skin-to-skin contact provides a physical connection & stimulates oxytocins release.

Guidelines:

- Feed (Breast/bottle) Newborns every 2-3hrs (day & night) for the 1st 3mths. (Ie. >8x/Day)
- Feeds should last 20-30mins.
- Ensure baby is getting enough:
  - >5 wet heavy disposable nappies per 24hrs
  - or >6-8 wet normal nappies
- If bub is hungry all the time, try to increase milk production by expressing into a bottle between feeds and supplementing feeds with pre-expressed milk (or formula) in a bottle.

How long to Breastfeed?

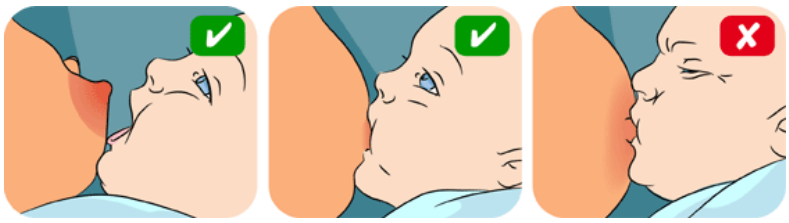
- Health authorities recommend mothers breastfeed exclusively for >6mths
- (The World Health Organization recommends breastfeeding until your child is two years and beyond, for as long as you and child desire.)
- Once you introduce solids, experts suggest it's best for your baby if you continue breastfeeding along with those solids until your baby is at least 12 months old.
- After that, it's really up to you and your baby how long you continue.

Don't expect too much of yourself – breastfeeding just doesn't work for everyone.

The basic feeding routine

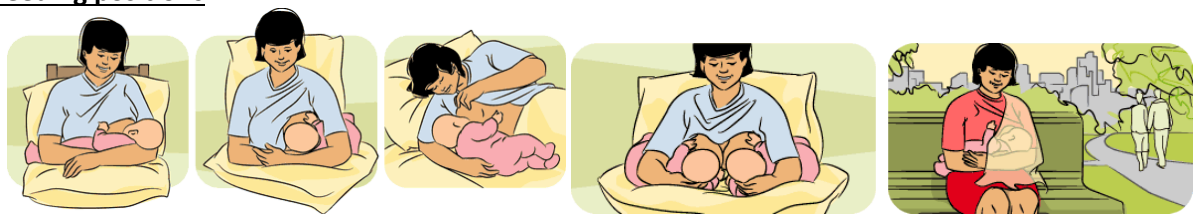
1) Comfy chair with good back support
2) Large glass of water on side (Avoid caffeine)
3) Bring baby up to breast. "Chin-To-Breast"
4) Aim the nipple upwards towards the hard palate.
5) Ensure nose is clear
6) Listen for the occasional swallow
7) Once bub is satisfied, give it a chance to burp (Sit her upright and gently rub/pat her back)
8) Change Nappy
9) If still hungry, offer the other breast.

Attaching to the breast



1. Hold bub chest-to-chest with nose in line with nipple. Brushing the nipple over bub's upper lip or cheek triggers the "Rooting Reflex" – turns head & opens mouth.
2. When bub's mouth is open, **bring bub to breast chin first**.
3. **Correct attachment:**
    - Most of the areola should be in bub's mouth (not just nipple sucking)
    - Chin tucked into the breast.
    - Nose clear
    - Deep and regular sucks + occasional swallowing.
4. If baby hasn't attached correctly, stop, and try attaching again.

Breastfeeding positions



1. **'front hold'** or **'cradle position'**.
2. **'underarm position'** or **'footy hold'**. (good for twins)
3. **'lying down'** (good for mums who've had caesareans).
4. **'twin hold'**.
5. **breastfeeding in public**

Breastfeeding Challenges:

- **Sore Nipples:**
    - Typically due to **malattachment**.
    - Solutions:
        - Nipple shields (short term only)
        - Express either by hand (the gentlest method) or breast pump
- **Nipple infections:**
    - Typically due to infiltration of cracked nipples by S.aureus or Candida
    - Solutions:
        - Moisturiser between feeds (Preventative)
        - Antibiotics/ointment (Antibacterial/Antifungal)
- **Blocked milk ducts:**
    - → Rapidly appearing tender lump in breast but otherwise feel well.
    - **Solutions:**
        - Feed frequently →empty affected breast.
        - Feed/Express from the affected breast first.
        - Gently massage the lump towards the nipple. (Even under hot shower)
        - Use a warm compress before the feed.
        - Ensure your bra isn't too tight.
    - **Complication = Mastitis** (Syx: Blockage persists for >12 hours + Onset of Malaise (Eg. Flu-like syx)
- **Mastitis**
    - = Abnomally **inflamed, sore, swollen or red breast** + MALAISE +/- chills.
    - Solution:
        - **See GP asap → For A**ntibiotics (NB: You can keep breastfeeding while taking these)
        - Continue feeding until syx have cleared, as Mastitis can → Breast Abscess if you stop breastfeeding during this time. (NB: The breastmilk is still safe for your baby).

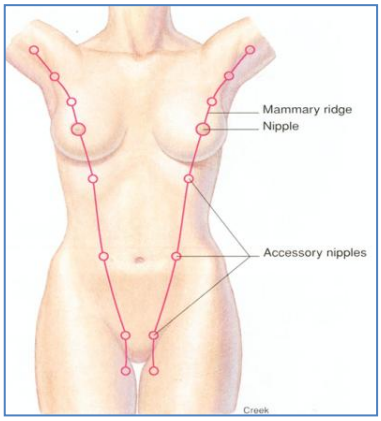
- **Engorgement/Oversupply:**
  - **Signs:**
    - **Engorgement (full, sore breasts)**
    - Baby might have a tummy ache or wind
    - Baby might cry a lot after feeds.
    - Your milk flows so quickly that bub can't swallow fast enough.
  - Solution:
    - **Watch and wait (Supply automatically adjusts to baby's demands** within a few weeks).
    - Or...
    - Feed from only one breast at each feed. Use the other breast for the next feed.
    - Expressing before feeds can make the flow less overwhelming for bub.
    - Ice-pack/cabbage leaf on the breast after breastfeeding to relieve pain.
- **Undersupply**
  - Signs that baby is NOT getting enough milk:
    - Less than 6-8 wet cloth nappies OR Less than 5 disposables in 24 hours
    - Has LESS than 1x bowel motion per day (if younger than 6-8 weeks old)
    - Failing to thrive (Ie. Not gaining enough weight; or Losing weight).
      - (Newborns normally lose <10% of birthweight in 1st week, but should be back to normal by day 14)
      - Infants should gain ~30g/day for 1st 3mths, then ~20g/day for next 9mths.
  - **Solutions:**
    - Give extra milk (Either your expressed breastmilk, or infant formula)
    - **Build up your supply by Breastfeeding/Expressing often**.
    - Give 'top-up' breastfeeds 20-30 minutes after a full feed.
- **Reflux:**
  - = Bub spits up a large volumes every feed
  - Causes:
    - Normal - common in 1st 6mths.
    - Abnormal – causing failure to thrive or is causing bub pain. (Typically pyloric stenosis)
  - Solutions:
    - If normal reflux:
      - Feed in a 'Head-up, Tail-down' position (Ie. Let gravity keep milk down)
      - Elevate head of bub's cot
    - If abnormal (projectile reflux, or failure to thrive):
      - Contact GP/Paediatrician.
- **Breast refusal**
  - Causes:
    - baby has a cold.
    - baby is uncomfortable or in pain.
    - baby is having trouble attaching.
    - baby is overstimulated/distracted (normal in older babies –Feed in a quiet place).
  - Solutions:
    - Typically only transient. (No need to give up breastfeeding)
    - Try new feeding positions
    - Express some milk into your baby's mouth
    - Play relaxing background music.
    - Feed in a rocking chair.
    - Offer a feed when baby is stirring from sleep or even still asleep.

<u>About bottle-feeding:</u>

- If you can't breastfeed, feeding options are:
  - 1. Expressed breastmilk in a bottle
  - 2. Infant formulas in a bottle **(Infant formulas are the ONLY safe alternative to breastmilk)**
- (Always prepare formula according to the instructions).

WOMENS HEALTH Pathology:
CONGENITAL BREAST DISORDERS

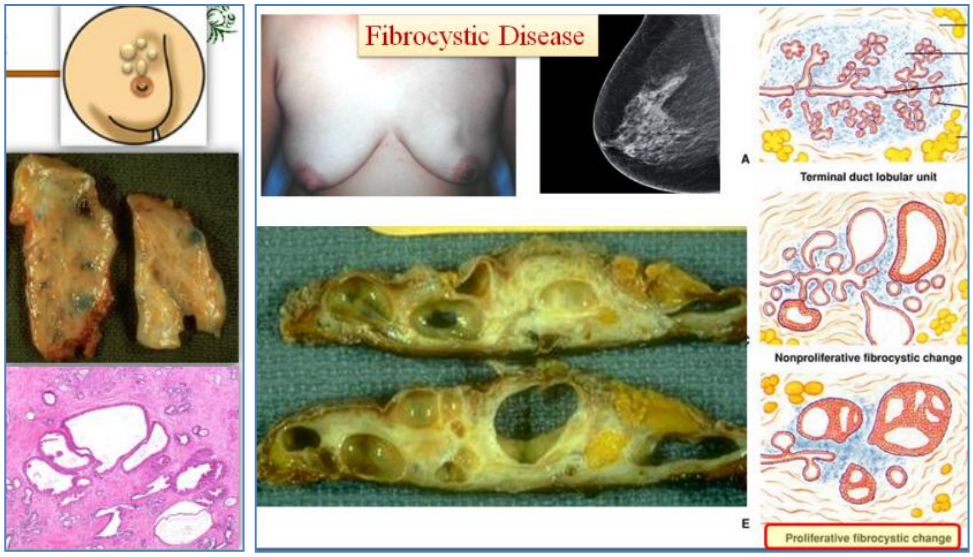
Congenital Breast Disorders:

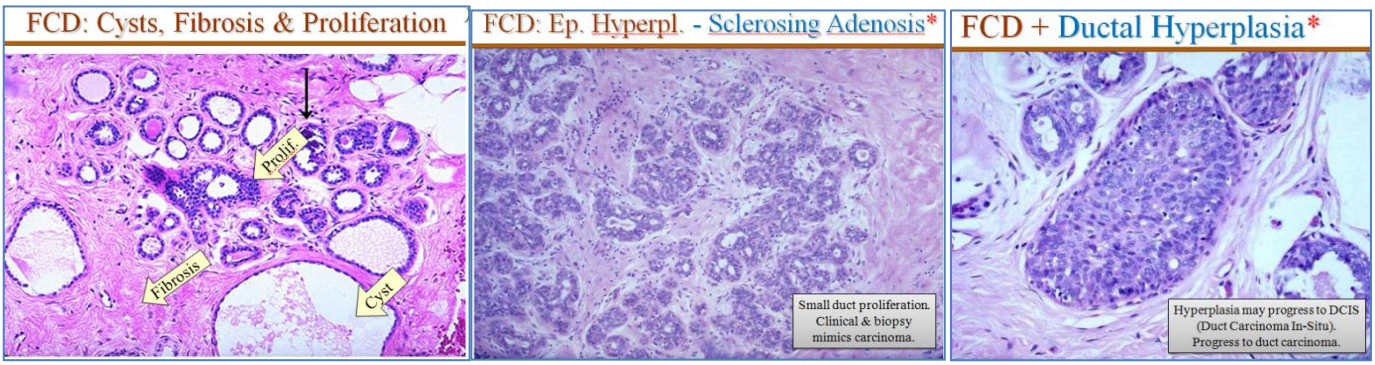
- **Aplasia:**
  - **(Eg. Turners** – 45XO – Ie. Monosomy X)
  - *ONLY IN FEMALES!!*
- **Breast Hypertrophy ("Macromastia"):**
  - **Juvenile Hypertrophy:**
    - Rare disease of Breast Connective Tissues → Breast Enlargement to >600g.
    - May be due to ↑Breast Sensitivity to Oestrogen, or ↑Basal Oestrogen Levels; or Both.
    - May occur before or during puberty.
  - **Gestational Hypertrophy:**
    - Physiologically occurs during Pregnancy
- **Accessory/Ectopic Breasts**:
  - (Along the milk line)
  - 

WOMENS HEALTH Pathology:
FIBROCYSTIC DISEASE

Proliferative Breast Conditions (Since breast responds to hormones):

- **FIBROCYSTIC DISEASE:**
  - **Aetiology:**
    - Hormone-Induced ***Acinar & Fibrous Hyperplasia***
  - **Pathogenesis:**
    - Oestrogens → ***Acinar & Fibrous Hyperplasia*** → Multiple, Bilateral, Irregular Lumpy Breasts.
    - (May be cyclical)
  - **Morphology:**
    - Grey-white Scar Tissue (Fibrosis)
    - Multiple Cystic Lesions.
    - **Proliferative:** When there is Epithelial Hyperplasia → ***PREMALIGNANT***
    - **Non-Proliferative:** No Epithelial Hyperplasia → Not Premalignant.
  - **Clinical Features:**
    - **Commonest (40%) cause of lumps in 20-40y.**
    - Multiple, Bilateral, Irregular "Lumpy Bumpy" Breasts.
    - (NB: UNLIKE Malignancy, they are multiple, bilateral, highly mobile)
    - Cyclical Pain/Discomfort.
    - Mammogram – Diffuse Fibrosis with Cystic Spaces
    - **Proliferative:** Epithelial Hyperplasia (>2 Cell Layers) → ***PREMALIGNANT → DCIS → Ca.***
    - **Non-Proliferative:** No Epithelial Hyperplasia → Not Premalignant.
  - **Management:**
    - **Optional Biopsy**
    - **Excision if Pre-Malignant**





Proliferative FCD: Epithelial Hyperplasia May → Dysplasia → DCIS – (once the cells fill the whole duct).

WOMENS HEALTH Pathology:
MASTITIS

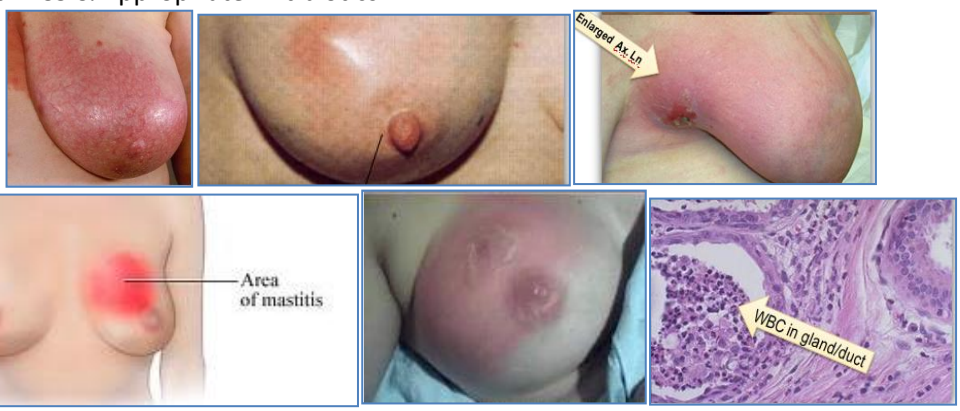
(NB: Inflammatory Breast Diseases are rare [<1%] in NON-Lactating Women. More commonly, an Erythematous, Swollen, Painful Breast is "Inflammatory Breast Cancer" until proven otherwise.)

ACUTE MASTITIS:

- **Aetiology:**
  - Acute Breast Infection (Typically Bacterial Skin Flora – **Staph.aureus**/Strep.pyogenes)
- **Pathogenesis:**
  - **99.9% - Lactational (First few weeks post-partum)** → Crack in Nipple = Entry Point → Bacterial Infection (*Staph. aureus*, Strep. Pyogenes) → Inflammation + Pain.
- **Morphology:**
  - Acute Inflammation, Swelling, Erythema & Pus.
  - May → Single/Multiple Abscesses.
- **Clinical Features:**
  - Initial Weeks Post-Partum.
  - Unilateral, Painful, Erythematous, & Swollen Breast
  - + Fever, Inflammation, Flu-Like Symptoms
  - (+/- Pus Discharge)
  - (+/- Nipple Cracks/Fissures)
- **Diagnosis:**
  - **Clinical Diagnosis** (Hard, Tender, Red, Swollen Area of one breast + Fever in a Nursing Mother)
    - (NB: Distinguishable from Engorgement which is Bilateral)
    - (NB: Breast USS can distinguish between Mastitis & Abscess)
  - (+/- Breastmilk Culture if Infection is Severe/Hospital-Acquired.)
- **Management:**
  - **Analgesia** (*Ibuprofen*)
  - **Cold Compresses**
  - **Improve Breast-Feeding Techniques** (Eg. Nipple Shields to stop Chapping)
    - (NB: Breastfeeding can continue during treatment)
  - **Antibiotics** (Anti-Staphylococcal; *Cephalexin*/*Dicloxacillin*/*Clindamycin*)

CHRONIC MASTITIS:

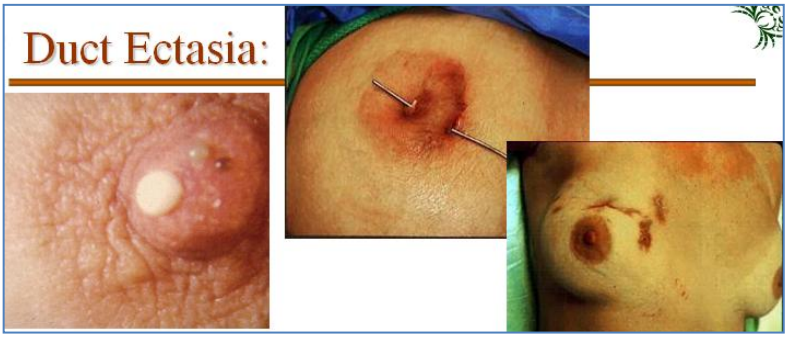
- **Aetiology – (NON-Lactational):**
  - Granulomatous (TB, Fungal, Silicone etc.)
  - Diabetic Mastopathy
- **Pathogenesis:**
  - Chronic Breast Infection (TB, Fungal, Immunocompromise) → Inflammation
- **Morphology:**
  - Localised Inflammation, Swelling & Erythema.
- **Clinical Features:**
  - Chronic
  - Localised Inflammation, Swelling & Erythema.
- **Management:**
  - Swab MCS & Appropriate Antibiotics

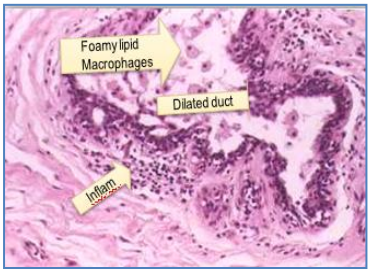


WOMENS HEALTH Pathology:
OBSTRUCTIVE BREAST DISORDERS

Obstructive Breast Disorders:

- **DUCT ECTASIA:**
  - **Aetiology:**
    - Nipple Outlow Duct Obstruction
  - **Pathogenesis:**
    - (*Remember – Kind of like *'Cystic Acne'* of the Nipple.)
    - Nipple Outlow Duct Obstruction → Stagnation of Breast Secretions → Inflammation
    - NB: Healing phase may → Fibrosis → may cause nipple inversion (a DDx of malignancy)
  - **Morphology:**
    - Dilation (Ectasia) of Lactiferous Ducts
    - Duct filled with Concentrated Secretions & Debris
  - **Clinical Features:**
    - Typically Multiparous Women 40-60yo.
    - **Symptoms/Signs:**
      - ***Poorly-Defined Periareolar Mass + Nipple Discharge.**
        - Nipple Discharge – (Serous/White/Frank Pus/or Frank Blood).
        - May → Fibrosis → Nipple Retraction/Inversion
      - NB: Pain is Uncommon
    - **Clinical Significance:**
      - *Fibrotic Response can → Firm, Irregular Periareolar Mass which may Mimic Invasive Carcinoma on Palpation & Mammogram!!*
  - **Management:**
    - **Diagnosis:**
      - FNA-Biopsy/Imaging to Investigate for DDx (Eg. Intraductal Papilloma)
    - **Treatment:**
      - Often Self-Limiting
      - +/- Antibiotics
      - (+/- Mammary Duct Excision)





- **GALACTOCOELE: (Obstruction of one of the ducts → accumulation of milk → Cyst)**
  - **Aetiology:**
    - Protein-Plug Obstruction to Duct Outlet
  - **Pathogenesis:**
    - Protein-Plug Obstruction to Duct Outlet → Obstruction → Accumulation of Milk → Cyst
  - **Morphology:**
    - **Macro:**
      - Smooth, Malleable breast lump filled with fluid
    - **Micro:**
      - Large Cystic space lined by normal duct epithelium
  - **Clinical Features:**
    - Centrally Located, NON-Tender Mass
    - No risk of infection since milk is sterile
    - Drainage is pointless as the Protein Plug remains and Milk Production Continues
  - **Treatment:** Self-Limiting Once Lactation Stops. (Drainage NOT Necessary, & recurs)

SPECIFIC GYNAECOLOGY NOTES:
AMENORRHOEA - HORMONAL CONTRACEPTIVES

Amenorrhoea:

- **Definition:**
  - Absence of a Menstrual period *In a woman of Reproductive Age*

Hormonal Contraceptives (Refractory/Extended Cycle Use/Progesterone-Only)

- **Aetiology:**
  - Retained effectiveness of ceased hormonal contraceptives (Eg. Depo Injection)
  - Extended cycle use of COCP (Skipping the "sugar pills")
  - Progesterone-Only Contraceptives (Depo-Provera/Mirena/Implanon)
- **Pathogenesis:**
  - Retained Effectiveness – Some hormonal contraceptives are still active in the blood after the drug is ceased (Esp. Depo – guaranteed for 3mths, but can last for <1yr)
  - Extended Cycle Use of OCP – Skipping "Sugar Pills" → Constant Oestrogen & Progesterone Levels → Amenorrhoea
  - Progesterone-Only Contraceptives – NB: The Major Side-Effect of POCs is Poor Menstrual Cycle Control (Ie. Irregular/Erratic/Prolonged/No Menstruation)
    - *The Exception:* Depo-Provera Injection → Thickens Cervical Mucus + Suppresses Ovulation (& therefore suppresses menstruation)

SPECIFIC GYNAECOLOGY NOTES:
AMENORRHOEA - HYPOTHALAMIC (ANOREXIA & FEM ATHLETES)

Amenorrhoea:

- **Definition:**
  - Absence of a Menstrual period *In a woman of Reproductive Age*

Hypothalamic (Anorexia/Female Athlete Triad)

- **Aetiology:**
  - Anorexia/Female Athlete Triad/Excessive Exercise
- **Pathogenesis:**
  - Insufficient caloric intake (or excessive caloric expenditure) → Energy Availability is Insufficient to maintain normal menstrual cycles.
- **Clinical Features:**
  - Excessively Low BMI
  - Female Athlete Triad (Fatigue, Amenorrhea, Osteoporosis)
  - Amenorhoea
- **Treatment:**
  - Exercise Moderation
  - Correction of Eating Disorders/Maintain Healthy Diet

SPECIFIC GYNAECOLOGY NOTES:
AMENORRHOEA - PHYSIOLOGICAL (PREGNANCY & LACTATION)

Amenorrhoea:

- **Definition:**
  - Absence of a Menstrual period *In a woman of Reproductive Age*

Physiological (Pregnancy & Lactation):

- **Aetiology:**
  - Pregnancy & Breast-Feeding
- **Physiology:**
  - **Pregnancy:** High levels of β-HCG (Similar to LH) → Sustains the Corpus Luteum, which maintains secretion of Progesterone → Suppresses Menstruation → **Amenorrhoea**.
  - **Breast Feeding:** High levels of Prolactin (Secreted by Ant.Pit due to Suckling) → Inhibits Ovulation (:. Inhibits subsequent menstruation) → **Amenorrhoea**

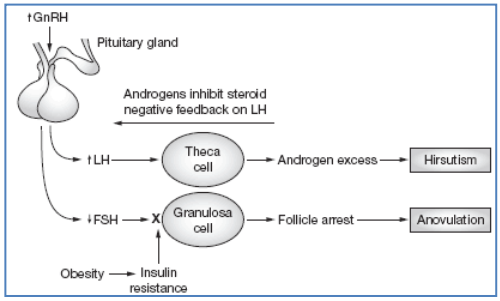
SPECIFIC GYNAECOLOGY NOTES:
AMENORRHOEA - POLYCYSTIC OVARIAN SYNDROME

Amenorrhoea:

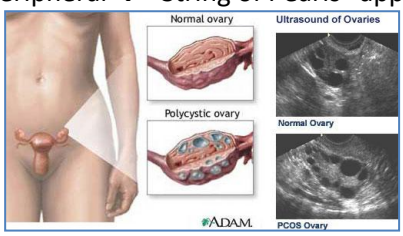
- **Definition:**
  - Absence of a Menstrual period *In a woman of Reproductive Age*

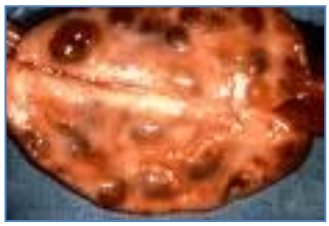
POLYCYSTIC OVARIAN SYNDROME (PCOS):

- **Aetiology:**
  - **Genetic – Sex-Limited Autosomal Dominant** (50% Chance of Inheritance if Female)
- **Pathogenesis:**
  - **Deranged Hypothalamo-Pituitary-Gonadal Axis Activity (↓FSH & ↑LH) →**
    - → ↑Thecal Cell Stimulation (Androgen Producers)
    - → ↓Follicular Maturation → Follicular Arrest



  - **→"Follicular Arrest":**
    - Follicles grow normally to the Mid-Antral stage, but then maturation ceases.
    - Follicles retain endocrine capacity, but over time the Granulosa Layer thins →
      - **→Ovaries Can't Convert Androgens (from Thecal Cells) to Oestrogen.**
        - **→ Hyperandrogenism (↑Testosterone).**
- **Morphology:**
  - Polycystic Ovaries – Abnormally high number of Developing Eggs → Cysts.
  - Cysts are peripheral → "String of Pearls" appearance.



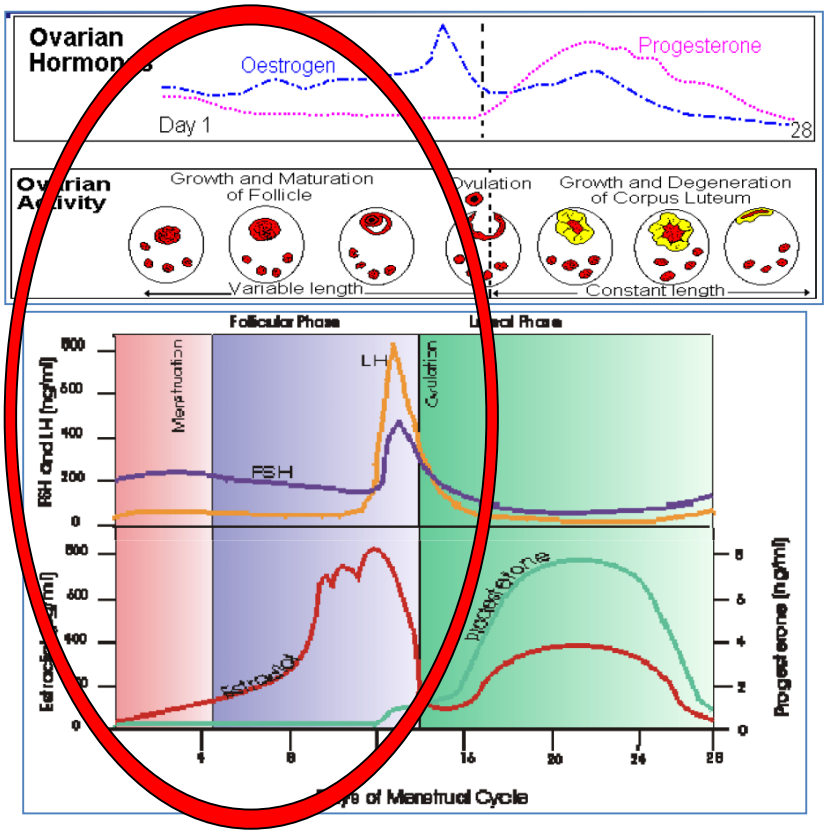


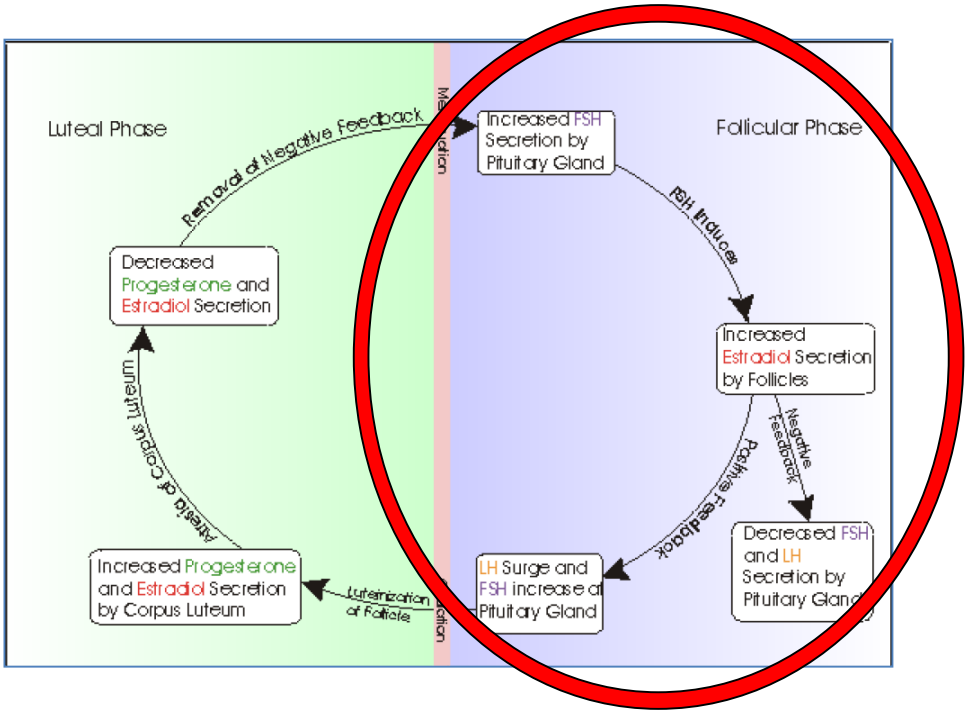
- **Clinical Features:**
  - **1. Infertility:** Due to Anovulation
  - **2. Menstrual Changes:** Amenorrhoea → Infertility
  - **3. Excess Testosterone:** Acne, Hirsutism (↑Hair), Deepening Voice
  - **4. Metabolic Syndrome ("Synd. X"):** Insulin Resistance (+/- Obesity, D2M, ↑Cholesterol)
- **Diagnosis:**
  - **Clinical:** (See Above)
  - **Pelvic Ultrasound:** Bilateral Polycistic Ovaries
  - **Blood Test:** ↑Serum Testosterone
  - **(DDX:** *Hypothyroidism, Congenital Adrenal Hyperplasia, Cushing's Syndrome***)**
- **Treatment:**
  - **#1. Immediate Concerns:** Hirsutism, Acne, Infertility
  - **#2. Long Term Consequences:** Metabolic (Diabetes/Obesity/↑Cholesterol), & Endometrial Ca
  - **How?**
    - **OCP/IUD/Anti-Androgens.** (Improves Hirsutism & Irregular Periods)
    - **Weight Loss** (Prevent Diabetes & Dyslipidaemia)
    - **Metformin** (Prevent Diabetes & Promotes Ovulation for ↑Fertility)
    - **+/- Hormonal Ovulatory Induction where fertility is desired.**
- **Prognosis:**
  - **→ ↑Risks of:** ***Endometrial Cancer & *D2M**

Week 10
Endocrinology Notes
Polycystic Ovary Syndrome / Contraception.

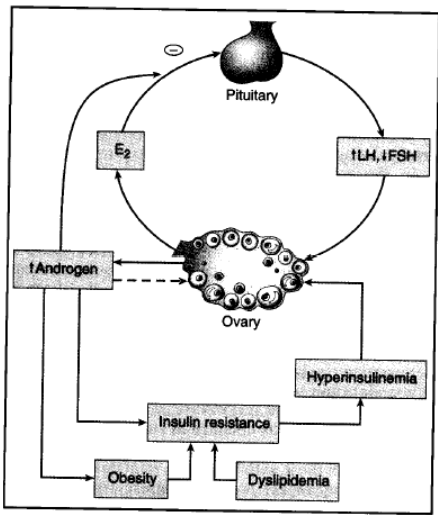
Polycystic Ovary Syndrome:

- **What?**
  - A multi-system reproductive/metabolic disorder caused by derangements in ovarian & hormonal activity.
  - It is the most common endocrine disorder in females. (Prevalence 4-12%)
  - It messes with the pre-ovulatory (Follicular) phase of the menstrual cycle.





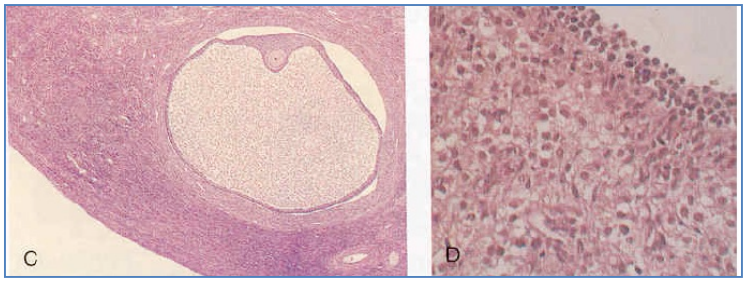
- **Cause:**
  - Unknown



- **Leads to:**
  - A wide range of endocrine abnormalities.
  - The leading cause of Infertility

- **Risk Factors:**
  - Gender – Only in females.
  - Obesity
  - Insulin Resistance (Insulin-Like Growth Factors usually promote follicular growth/maturation. Insulin Resistance→Hyperinsulinaemia → inhibits follicular growth/maturation.)
  - Family History (Highest risk among first-degree relatives)

- **Typical Features:**
  - **Ovarian Cycle Derangements:**
    - Oligomenorrhea/Amenorrhea (Irregular/few/absent menstruation)
    - Anovulation (resulting in enlarged ovaries with numerous Cystic Follicles)
    - Infertility (result of Anovulation) & Recurrent Miscarriage
  - **Endocrine Derangements:**
    - Hyperandrogenism → Irregular Menstruation (Can lead to Infertility)
    - Hirsutism (Excessive & Increased Body Hair)
    - Acne
    - Deepening Voice
    - Hyperinsulinaemia
  - **Associated Metabolic Dysfunction:**
    - Insulin Resistance
    - Dyslipidaemia
    - Obesity
  - **Polycystic Ovaries (Many cysts on the ovaries):**
    - Follicles grow normally to the Mid-Antral stage, but then maturation ceases.
    - Follicles retain their endocrine capacity, but over time the Granulosa Layer gets thin →
      - →Poor conversion of Androgens (Produced by the Thecal Cells) to Oestrogen.
        - → Hyperandrogenism.



- **Hormonal Derangements - Detailed:**

Increased	Decreased
↑Insulin (due to resistance)	
↑Androgens (Testosterone, Androstenedione & DHEAS)	↓Sex-Hormone-Binding-Globulin (SHBG - The Transporter for Oestrogen & Testosterone – required because they're lipid soluble sterols)
↑Oestrogen	
↑LH	↓FSH
↑Insulin-Like Growth-Factors I & II.	

- **Most Commonly Diagnosed –**
  - During puberty if regular cycles aren't established.
  - When the woman is trying to get pregnant – realizes she's infertile.

- **Treatment Goals:**
  - Reverse signs/symptoms of Androgen Excess
  - Establish cyclic menstruation
  - Restore Fertility
  - Improve Metabolic/Endocrine Disturbances
  - **Management:**
    - **#1. Immediate Concerns:**
      - Hirsutism
      - Acne
      - Anovulatory Infertility
    - **#2. Long Term Consequences:**
      - Metabolic Disturbances (Diabetes/Obesity)
      - Dyslipidaemia → Cardiovascular Disease
      - Chronic High Oestrogen → Endometrial Cancer
      - Hypertension
  - **How?**
    - Weight Loss (Prevent Diabetes & Dyslipidaemia)
    - Oral Contraceptive & Anti-Androgens.
      - Improves Hirsutism
      - Suppresses ovarian androgen production
      - Increases Sex-Hormone Binding Globulin (SHBG)
    - Screen for CVD Risk Factors
    - Ovulatory Induction where fertility is desired.
    - Metformin – Oral Hypoglycaemic (to prevent the hyperinsulinaemia)
      - Also causes ↑spontaneous ovulation.

SPECIFIC GYNAECOLOGY NOTES:
AMENORRHOEA - PREMATURE MENOPAUSE

Amenorrhoea:

- **Definition:**
  - Absence of a Menstrual period *In a woman of Reproductive Age*

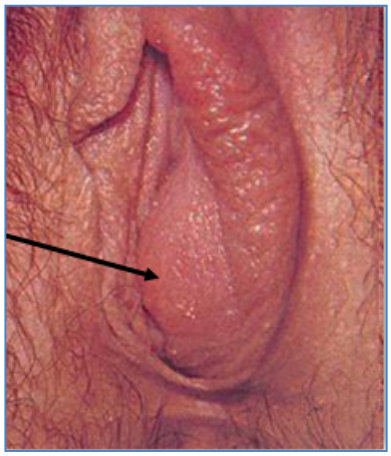
Premature Menopause:

- **Aetiology:**
  - Idiopathic/Autoimmune/Chemotherapy/Radiotherapy/Surgical Oophorectomy
- **Pathogenesis:**
  - Premature Ovarian Failure (No Follicles Left)→ ↓Oestrogen → ↑GnRH & ↑FSH
  - ↓Oestrogen → Amenorrhoea
- **Clinical:**
  - Menopausal Symptoms (Hot Flushes, Mood Swings, Vaginal Dryness, Dry Skin)
  - ↑Risk of Osteoporosis
- **Treatment:**
  - HRT – Combined Hormone Replacement Therapy

SPECIFIC GYNAECOLOGY NOTES:
BARTHOLIN GLAND CYST

Bartholin Gland Cyst (or Greater Vestibular Gland Cyst):

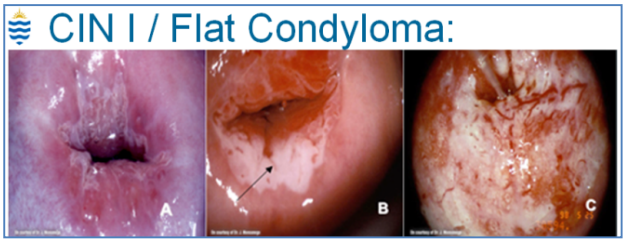
- **Aetiology:**
  - Physical Blockage of the Bartholin (Greater Vestibular) Gland
- **Pathogenesis:**
  - May result from Infection/Inflammation/Mucous Plug/other → Blockage of Greater Vestibular Gland
- **Morphology:**
  - **Macro:**
    - Range from Pea-Sized → Egg-Sized.
  - **Micro:**
    - Large Cystic Duct
- **Clinical Features:**
  - (Typically Women of Child-Bearing Age)
  - **Symptoms:**
    - Very Painful (→ Difficulty Walking)
    - Cysts may recur
  - **Complication:**
    - Secondary Infection of Cyst → Bartholin's Abscess
- **Treatment:**
  - Surgery → Create new duct opening



SPECIFIC GYNAECOLOGY NOTES:
CERVICAL CANCERS

Cervical Cancers: CIN 1 (LSIL) & CIN2-3 (HSIL):

- **Aetiology:**
  - **HPV Infection – Types 16, 18 & 45(& 31 & 33)**
    - (Direct Contact/Sexual Transmission – Highly Contagious)
  - **(Other Risk Factors** – Promiscuity, Family History, ↑Oestrogen Exposure, Smoking**)**
- **Pathogenesis:**
  - **HPV Infection (Almost Ubiquitous) →**
    - E6 Inhibits P53 (Tumour Suppressor Gene)
    - + E7 Inhibits RB (Tumour Suppressor Gene)
    - **→→Cell-Cycle Dysregulation → Dysplasia → Malignancy**
  - **+ Estrogens →**
    - Promoter (proliferation inducer)
    - (Ie. Early Menarche, late menopause, nulliparity, HRT, obesity & conditions of estrogen excess are Risk Factors)
- **Morphology:**
  - **LSIL: "*Low-grade Squam. Intraepithelial Lesion*" - (CIN1: Cervical Intraepithelial Neoplasia):**
    - **Macro:**
      - Small, Distinct, Clearly-Defined areas of Flat Leukoplakia
    - **Micro:**
      - *Koilocytosis - (Perinuclear Halo, Wrinkled Nucleus & Viral Inclusions)
      - *+ Mild* Nuclear Enlargement
      - Atypical cells in Basal region (Basal Layer is ≈Normal: Darker & ↓cytoplasm)
  - **HSIL: "*High-grade Sq. Intraepithelial Lesion*" - (CIN2-3: Cervical Intraepithelial Neoplasia):**
    - **Macro:**
      - **CIN2 -** Larger Areas of Flat Leukoplakia, But Still Distinct & Clearly-Defined.
      - **CIN3 –** Patchy, Poorly-Defined Leukoplakia + Areas of Haemorrhage.
    - **Micro:**
      - *Koilocytosis - (Perinuclear Halo, Wrinkled Nucleus & Viral Inclusions)
      - Complete Replacement of All Normal Cells with Dysplastic Squamous Cells



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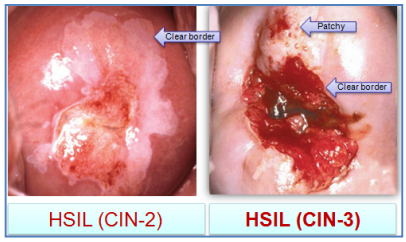
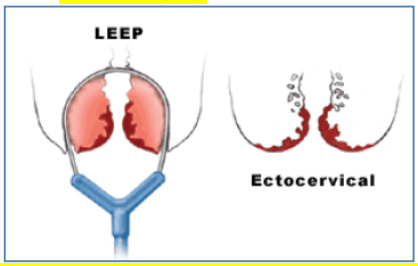
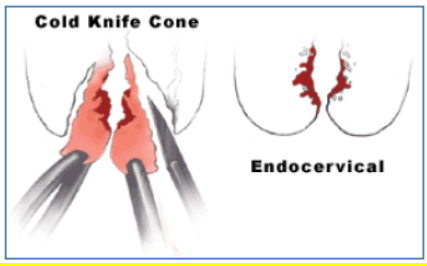


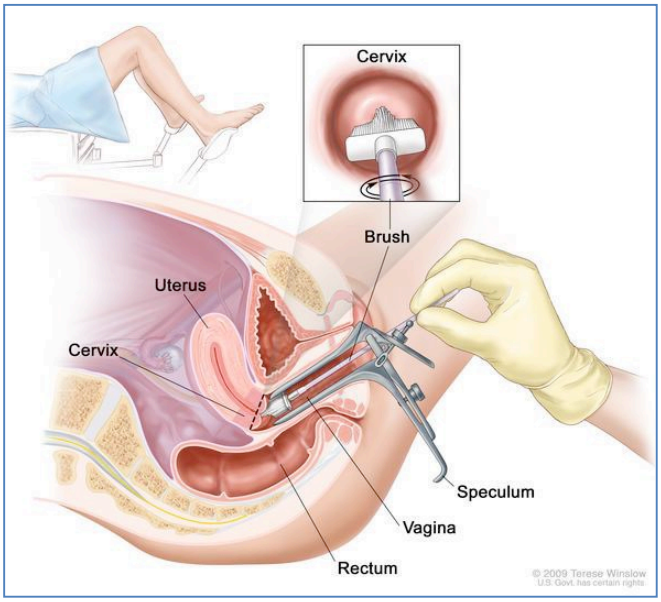
- **Clinical Features:**
  - Common, Ca. in women, 40-50y
  - **Symptoms:**
    - Usually Asymptomatic
    - But Post-Coital Bleeding in Advanced Disease.
- **Diagnosis:**
  - Colposcopy & Biopsy
  - (!!NB: Pap Smear is ONLY useful as a SCREENING TOOL FOR PREVIOUSLY NORMAL CERVIXES – NB: If you suspect cervical cancer, Colposcopy is the FIRST LINE INVESTIGATION!!!!)
- **Staging – CT/MRI:**
  - **Stage 1** (Cervix Only)
  - **Stage 2** (Beyond Cx)
  - **Stage 3** (Pelvic/Vaginal Involvement)
  - **Stage 4** (Abdomen/Lungs/Liver/Bone)

- **Treatment:**
  - **CIN 2 or 3 → Excision of Transformation Zone via:**
    - **"*LLETZ/LEEP*" – (Electrocautery)**
    - **or "*Cone Biopsy*" - (Cold Knife)**

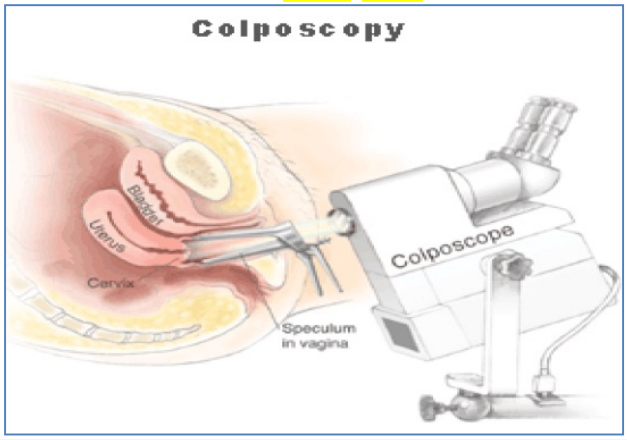




  - **Otherwise ***Total *Hysterectomy* (+/- *Oophorectomy*) + Lymph Nodes if High Grade**
    - + Radiotherapy (EBRT/Brachy) if High Grade & Stage.
    - + Chemotherapy if Advanced Disease.
- **Prognosis:**
  - ***NOT all CIN's → to Invasive Cancer:***
    - CIN1 >95% → Regression
    - CIN III <30% → Regression (:. 70% → Invasive Cancer)
  - **5y survival:**
    - **Stage 1 (Localised Disease) >80%,**
    - **Stage 4 (Metastatic Spread) ~10%.**
- **Prevention:**
  - **Gardasil Vaccine (Primary Prevention):**
    - **Gardasil = Quadrivalent :. Protects against Types 6, 11, 16 & 18.**
    - **Recommended for girls 9-13y**. (Approved for F:10-26yrs & M:9-15yrs)
    - **3x IM injections @ 0, 2 & 6mths**.
    - NB: Pap Smears should continue in both vaccinated and unvaccinated women.
  - **Pap Screening (Secondary Prevention):**
    - **Pap Screening → Prevents >90% of Cervical Cancer Deaths**
    - ****Recommendations:**
      - ***Every 2yrs**
      - ***Every Woman >18yrs OR As soon as Sexually Active → Even After Menopause***
      - ***Ideal Timing: Within the 1st Week AFTER Menstruation***
    - **Interpretation:**
      - An *Abnormal PAP Smear* is NOT Cancer! →Needs (Cosposcopy & Biopsy)
    - **Followup:**
      - If currently Normal → Repeat in 24mths
      - If currently LSIL, but PAP <1yr ago was normal → Repeat in 12mths
      - If currently LSIL, but last PAP was >1yr ago → COLPOSCOPY
      - If currently HSIL → COLPOSCOPY



- **Colposcopy:**
  - **For women with Identified LSIL/HSIL on Abnormal PAP-Smear**
  - →Visually assesses Abnormal Changes in the "Transformation Zone".
  - **1. Acetic Acid:** Abnormal cells stain White
  - **2. "Lugols Iodine":** Abnormal cells DO NOT stain brown (Ie. Stay white)
  - **3. → Punch Biopsy → Histology**
    - **If CIN 1** (LSIL) → Watch, Wait & Followup
    - **If CIN 2** (HSIL) → Treat (***LLETZ***/***Cone***)
    - **If CIN 3** (HSIL) → Treat (***LLETZ***/***Cone***)



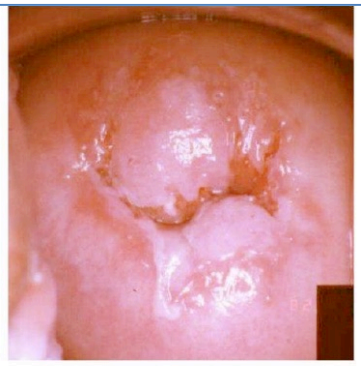
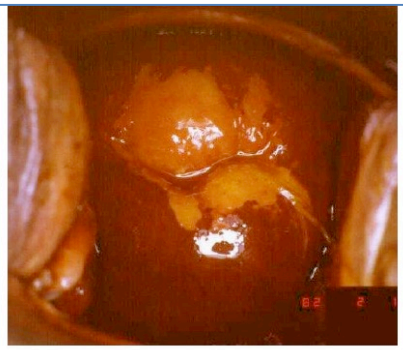


FIGURE 7.15: Moderately dense acetowhite lesions with irregular margins in the anterior and posterior lips (CIN 1).

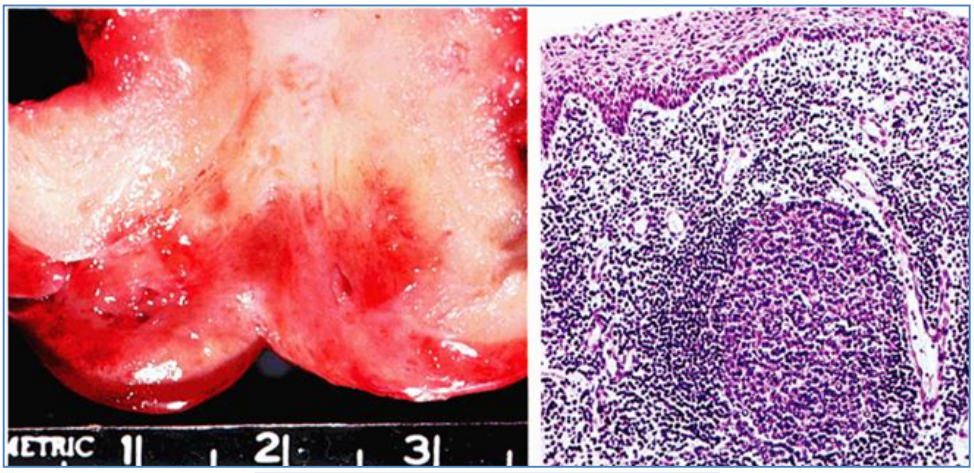


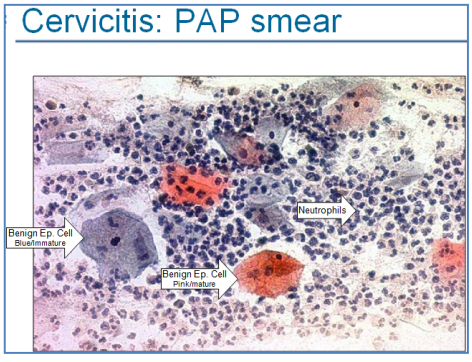
IGURE 7.29: A CIN 1 lesion with a mustard ellow iodine-negative area with irregular margins ee the appearance after acetic acid application in igure 7.15).

SPECIFIC GYNAECOLOGY NOTES:
CERVICITIS

CERVICITIS (Infection):

- **Aetiology:**
  - Secondary to Vaginal Infections
  - (NB: High Level of Sexual Activity is the Main Risk Factor)
- **Pathogenesis:**
  - Vaginal Infections (Eg. Chlamydia, Gonorrhoea, Trichomonas, Candida) → Inflammation of Cervix
- **Morphology:**
  - **Macro:**
    - Red, Inflamed, Swollen Cervix
    - +/- Discharge (Purulent or Mucoid)
  - **Micro:**
    - Inflammation & Oedematous Tissue
    - Plenty of Inflammatory Cells in Smear
- **Clinical Features:**
  - Very Common (50% of all women will have it >once in their life)
  - **Symptoms:**
    - Abnormal Vaginal Bleeding (Post Coital/Intermenstrual/Post Menopausal)
    - Vaginal Discharge (May be Gray/White/Yellow +/- Odour)
    - Dyspareunia
    - Pressure/Heaviness in the Pelvis.
  - **Diagnosis:**
    - Clinical Pelvic Examination
    - Pap Smear
    - Tests for Gonorrhoea &/or Chlamydia
- **Treatment:**
  - **Antibiotics – (*Azithromycin* or *Doxycycline*)**
- **Prognosis:**
  - If Infection due to HPV → ↑Risk of Cervical Cancer.





TRIGGER PAGE - DDX OF ABNORMAL PV BLEEDING

- **PV Bleeding in children –**
  - Precocious puberty
  - Foreign body in the vagina.
  - Molestation
  - Vaginitis
  - Tumour (rare)
- **Premenopausal women –**
  - Menstruation – menorrhagia/hypomenorrhoea (heavy/light)
  - Intermenstrual bleeding (spotting)
  - Dysfunctional uterine bleeding – common cause of menorrhagia and irregular bleeding. Due to hormonal imbalance and symptoms can be managed with OCP (may be due to PCOS).
  - Uterine fibroids (benign tumours of uterus)
  - Cervical cancer (often presents with contact bleeding – after intercourse)
  - Uterine cancer – irregular and often prolonged bleeding.
  - Endometritis/retained products of conception – in recently pregnant women who have delivered/miscarried.
  - Vaginal trauma/infections/lesions/cancer.
  - Condylomata acuminate of cervix
  - Pelvic inflammatory disease
  - Ovarian cysts
  - Birth control - An IUD (slight bleeding is usually normal), OCP.
  - Following pap smear.
- **Pregnant women –**
  - Vaginal bleeding occurs during 15-25% of 1st trimester pregnancies. Of these, half go on to miscarry and half bring foetus to term.
  - Rupture of small vein on outer rim of placenta
  - Miscarriage
  - Ectopic pregnancy
  - Placenta previa (placenta partially or completely overlying cervix) may bleed profusely.
  - Placental abruption (placenta sheared from wall of uterus)
- **Postmenopausal women –**
  - All vaginal bleeding in postmenopausal women should be medically assessed.
  - 30% unopposed oestrogen
  - 30% atrophic endometritis/vaginitis
  - 15% endometrial cancer
  - 10% endometrial/cervical polyps.
  - 5% endometrial hyperplasia
  - 10% other –
    - Vaginal dryness – trauma.
    - Drugs (eg. anticoagulant)
    - Inherited bleeding disorders

- **Diagnostic approach –**
  - Bleeding history -
    - Last episode of vaginal bleeding
    - LNMP
    - Regularity/cycle length.
    - Menorrhagia
    - Associated symptoms.

        - Previous episodes of abnormal bleeding
        - Postcoital bleeding
        - Intermenstrual bleeding
        - Pregnant/previous pregnancies
        - Present sexual activity
        - Use of birth control
        - No. of sexual partners
        - Medications
        - History of problems with clotting or bleeding disorders
        - Hx of recent surgeries or gynae procedures.
    - Physical examination
    - Pregnancy tests
    - Hormonal tests
    - FBC + clotting tests (maybe)
    - Thyroid (maybe)
    - Pap smear
    - Transvaginal USS
    - Treatment directed by cause.

Intermenstrual Bleeding

- **Definition:**
    - Vaginal bleeding (except postcoital) during the menstrual cycle other than menstruation.
- **Causes:**
    - **Pregnancy Related:**
        - Ectopic Pregnancy
        - Gestational Trophoblastic Disease
    - **Iatrogenic:**
        - Insufficient Dose of Combined Contraceptives
        - Side effect of Progesterone-Only Contraceptives
        - Intra-Uterine Device
    - **Cervical Causes:**
        - Cervicitis (Chlamydia/Gonorrhoea)
        - Cervical Polyps
        - Cervical Cancer
    - **Uterine Causes:**
        - Uterine Fibroids
        - Adenomyosis
        - Endometrial Cancer

Post-Coital Bleeding:

- **Definition:**
    - Non-menstrual bleeding that occurs immediately after sexual intercourse
- **Causes:**
    - Traumatic Sex (Particularly in Post-Menopausal Women due to Vaginal Dryness)
    - Infection (Bacterial Vaginosis/Cervicitis[Chlamydia, Gonorrhoea])
    - Vaginal Cancer
    - Cervical Cancer

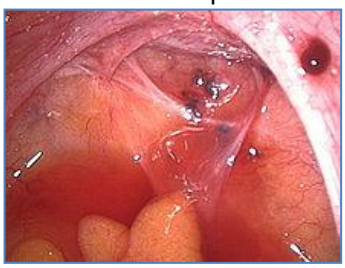
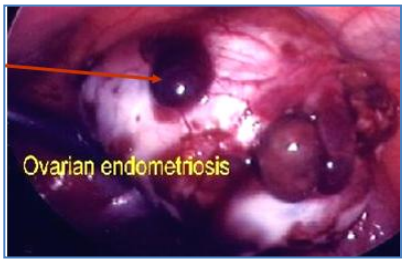
SPECIFIC GYNAECOLOGY NOTES:
DYSMENORRHOEA – ENDOMETRIOSIS

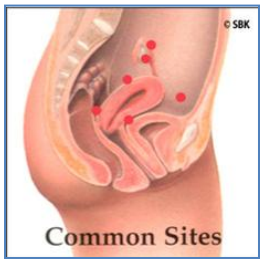
Dysmenorrhoea:

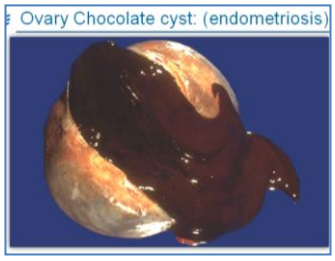
- **Definition:**
  - Excessively Painful Menstruation (Sharp/Throbbing/Dull/Nauseating/Burning/Shooting)
  - – May Precede Menstruation by several days
  - – Often Associated with Menorrhagia

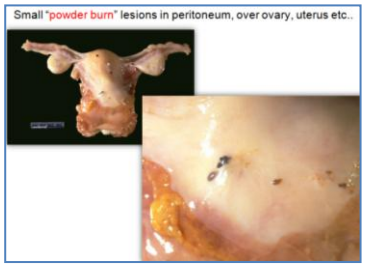
(Secondary Dysmenorrhoea) Endometriosis:

- **Aetiology:**
  - Retrograde Menstruation
  - (Or Vascular/Lymphatic Spread of Live Endometrial Tissue)
- **Pathogenesis:**
  - Spread of Live Endometrium beyond the Uterus →
    - → Pelvic Peritoneum
    - → Pouch of Douglas
    - → Ovaries/Fallopian Tubes
  - Chronic Cyclical Peritonitis → Pelvic, Abdominal & Lower-Back Pain/Cramping
- **Morphology:**
  - Small "Powder Burn" Lesions in Peritoneum, on Ovaries or on Uterus.
  - Dark Purple Nodules in Peritoneal Cavity
  - Ovarian "Chocolate Cysts"
- **Clinical Features:**
  - Dysmenorrhoea (Chronic & Cyclical Pelvic, Abdominal & Lower-Back Pain/Cramping)
  - Dyspareunia
  - Unexplained Chronic Pelvic/Lower-Back pain
- **Complications:**
  - **Pelvic Fibrosis/Frozen Pelvis →**
    - Infertility
    - Bowel Obstruction
  - ***Rupture of Endometriotic Cyst may** → Acute Abdomen (Emergency)
- **Treatment:**
  - **Surgical** – Laparoscopic Ablation of Endometrial Tissue
  - **Or Drugs:**
    - Oestrogen-Lowering Drugs (Aromatase Inhibitors)
    - Progesterone-Only OCP
    - **+ Analgesia**
- **Prognosis:**
  - **No Cure – But typically goes away after**
    - Pregnancy
    - Or Menopause.







SPECIFIC GYNAECOLOGY NOTES:
DYSMENORRHOEA - PHYSIOLOGICAL DYSMENORRHOEA

Dysmenorrhoea:

- **Definition:**
  - Excessively Painful Menstruation (Sharp/Throbbing/Dull/Nauseating/Burning/Shooting)
  - – May Precede Menstruation by several days
  - – Often Associated with Menorrhagia

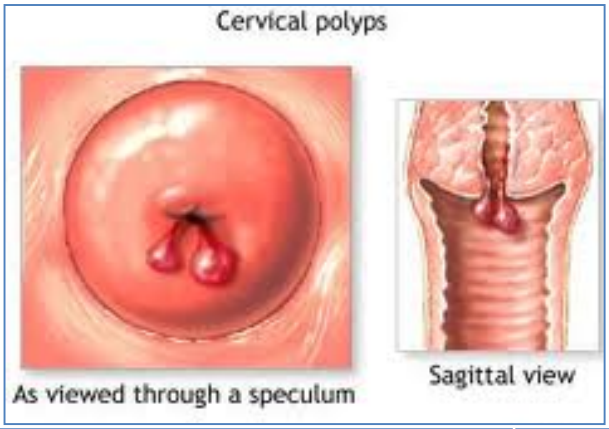
(Primary Dysmenorrhoea) Physiological Dysmenorrhoea:

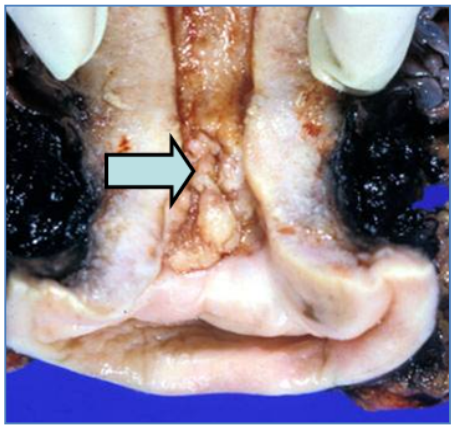
- Prostaglandins & Other Inflammatory Mediators →
  - → Constrict Blood Vessels in the Endometrium → Shedding
  - → Uterine Contractions → Ejection of Menstrual Products (+ Cramping Pain)

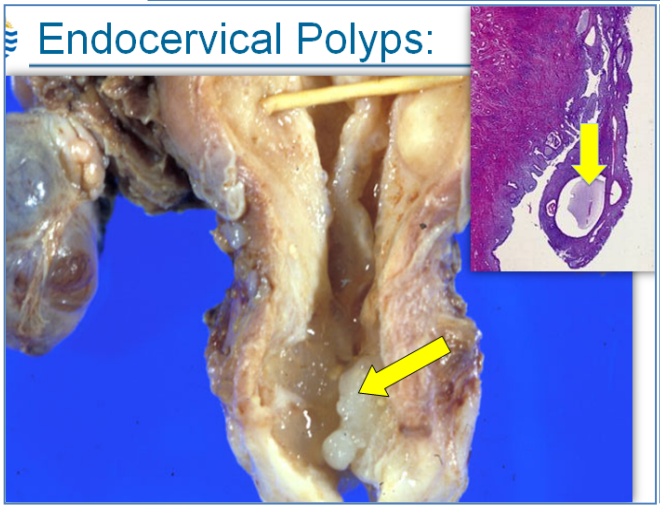
SPECIFIC GYNAECOLOGY NOTES:
ENDOCERVICAL POLYPS

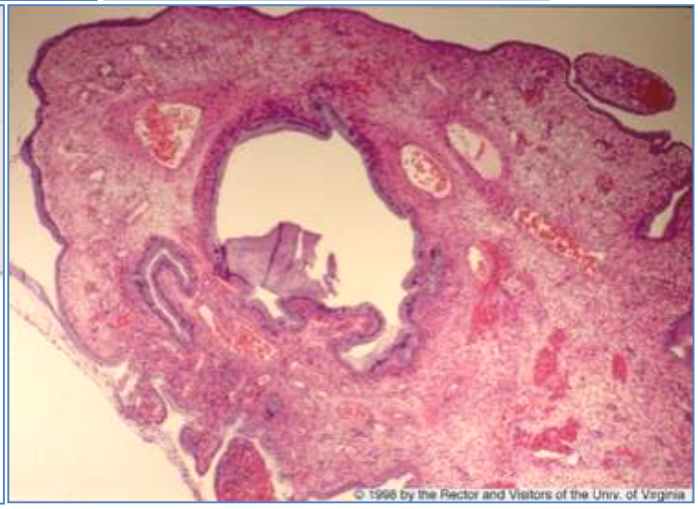
Endocervical Polyps (Benign Inflammatory Tumours):

- **Aetiology:**
  - Unknown – But Inflammatory Aetiology.
- **Pathogenesis:**
  - Inflammation → Hyperplasia of Endocervical Glands → Inflammatory Tumour
- **Morphology:**
  - **Macro:**
    - Finger-like Mucoid Polyps in Endocervical Canal
    - Usually <1cm Diameter.
    - May Project from the Cervical Canal (Visible on Pelvic Examination)
  - **Micro:**
    - Overgrowth of Benign Fibrous Stroma + Some Glands, covered by Squamous Epithelium.
- **Clinical Features:**
  - (Typically in Peri-Menopausal Women who have had Children)
  - **Symptoms:**
    - Irregular Inter-Menstrual Bleeding
    - Unusually Heavy Menstrual Bleeding (Menorrhagia)
    - Post-Coital Bleeding
- **Diagnosis:**
  - Pelvic Examination – (Red/purple projections from the cervical canal)
  - Cervical Biopsy
- **Treatment:**
  - Simple Surgical Excision/Strangulation of Polyp + Cauterisation of the Base.
- **Prognosis:**
  - 99% Benign







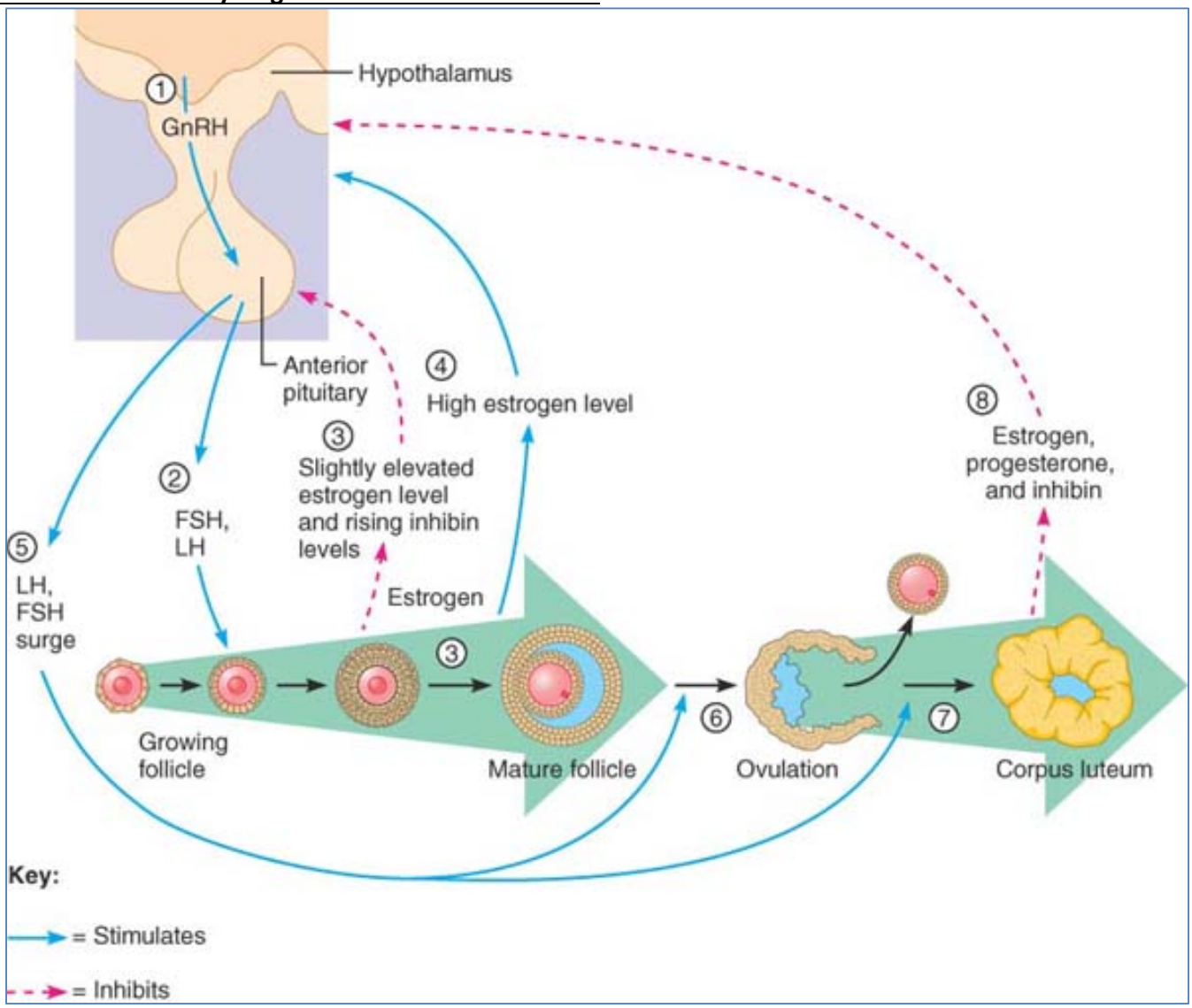


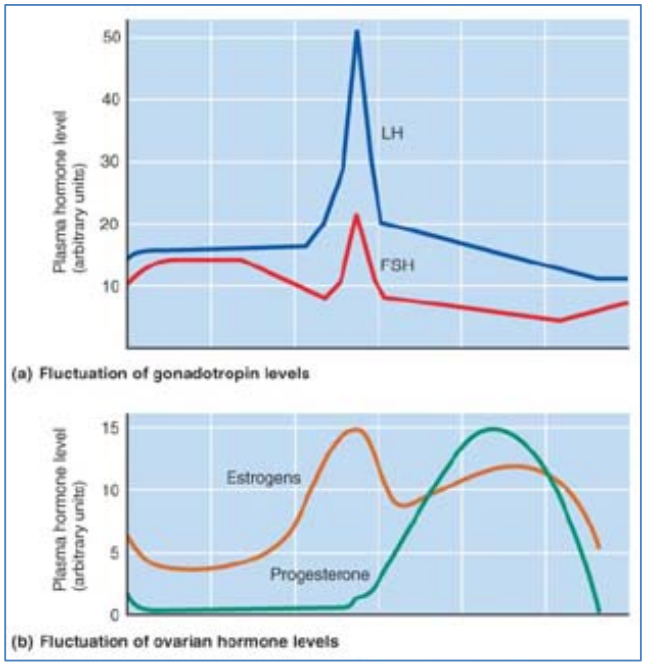
SPECIFIC GYNAECOLOGY NOTES:
MENOPAUSE

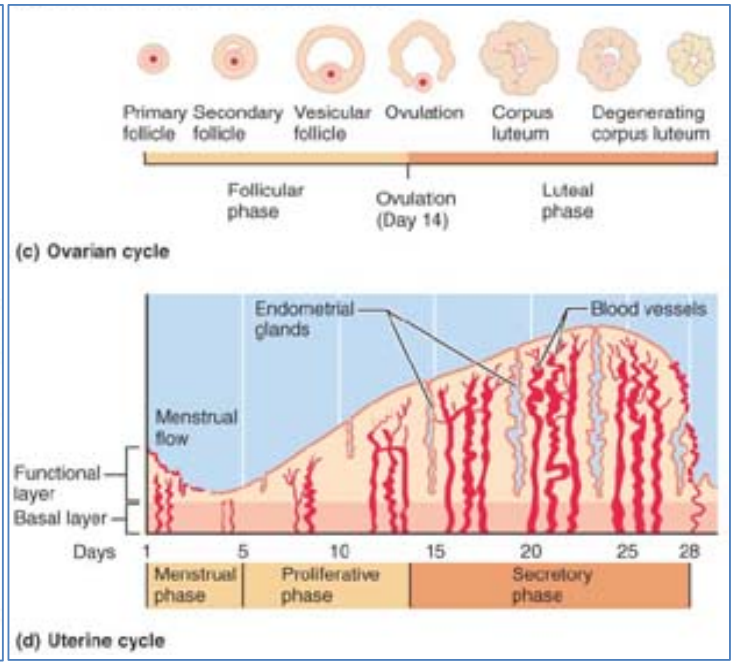
Menopause:

- **Terms:**
  - **"Menopause" = >12mths of Amenorrhoea since the Last Menstrual Period.**
    - (NB: And not accounted for by any other cause)
  - **"Pre-Menopause" = Early symptoms of Menstrual Irregularity**
  - **"Perimenopause" = From onset of *Pre-Menopausal Symptoms (Ie. >2skipped Cycles)*, to 12mths since the Last Menstrual Period.**
- **Types:**
  - **Physiological:** Spontaneous menopause ~45-55yrs
  - **Premature:** <40yrs (Due to Premature Ovarian Failure)
  - **Iatrogenic:** Medically Induced (Eg. Chemotherapy/Radiotherapy)
- **Mechanism:**
  - ↓Follicle Sensitivity to FSH → ↓Follicles Recruited →↓Oestrogen Levels Production → Progressive Oligomenorrhoea → Amenorrhoea
  - (NB: Gradual process over 3-5yrs)
- **Clinical Features:**
  - **Epidemiology:**
    - **Average ages:** 45-55
  - **Symptoms:**
    - **Menstrual Irregularity:**
      - Oligomenorrhoea (Irregular/Lighter Periods)
      - (Occasionally Intermittent Menorrhagia/DUB)
    - **Hormonal Symptoms - (NB: Can persist for <5yrs Post-"Menopause"):**
      - **Hot/Cold Flushes/Night-Sweats (Pathognomonic):**
        - 75% of Women
        - Onset @ Pre-Menopause (<2yrs before); Last for <2yrs after Menopause.
      - **Mood Changes:**
        - Mood Swings – Depression/Anxiety/Irritability
        - (+ Poor Concentration/Memory/Insomnia)
        - ↓Libido
      - **Associated Syx:**
        - Palpitations/Dizziness/Headaches
    - **Genitourinary:**
      - Vaginal Dryness →
        - Itching/Burning
        - Dyspareunia
      - Urethral Atrophy → ↑UTIs
      - ↓Ovulation → Infertility
  - **Anatomical Changes:**
    - **Uterus/Cervix:** Atrophy (NB: Any pre-existing Fibroids shrink as well)
    - **Vagina:** Dryness, ↑pH (and Lactobacilli ↓), Mucosal Atrophy, ↓Elasticity
    - **Vulva:** Atrophy
    - **Pelvic Floor:** ↓Muscle Tone (→ Uterovaginal Prolapse)
    - **Ovaries:** Atrophy, Stop producing follicles.
  - **Complications:**
    - ****Osteoporosis**** (Loss of Oestrogen-Mediated Ca-Deposition in Bone)
    - **↑Risk of Heart Disease** (Protective effects of oestrogen is lost)
- **Diagnosis:**
  - **Clinical Hx:**
    - Symptoms
    - Lifestyle Impact
  - **Examination:**
    - Complete Physical (incl. Breast & Pelvic)
  - **(Definitive Dx - ↑FSH & ↓Oestradiol = Ovarian Failure)**

Normal Menstrual Cycling & NeuroEndocrine Control:







- **Management:**
  - **Ix:**
    - FBC
    - LFTs
    - TFTs
    - Lipids
    - Coags
    - Bone-Mineral Density Scan (?Osteoporosis)
    - Mammogram & Pap Smear
  - **Non-Pharmacological Mx:**
    - Explain Menopause
    - Advise healthy lifestyle (Diet, Weight Loss, Weight-Bearing Exercise)
    - Reduce Caffeine, Smoking & Alcohol
    - Calcium & Vit-D Supplements
    - Advise Cold Drinks/Showers/Layered Clothing
    - (Phytoestrogens – [Soy/Chickpeas], Black Cohosh, St. John's Wort, etc)
  - **HRT (Pharmacological):**
    - **Strategy:**
      - **Duration:** Only for SHORT TERM Symptomatic Relief (Ie. 2-3yrs MAX)
      - **Smallest Dose:** Titrated to symptom relief
      - **Taper Doses:** To avoid "*Rebound Menopause*" when ceased
    - **Options:**
      - ****Combined Oest+Prog** (If Intact Uterus – To prevent Endometrial Cancer)
        - **Cyclical** – For *Peri-Menopausal*
        - **Continuous** – For *Post-Menopause*
      - **Oestrogen Only** (For women without a Uterus; Or Mirena Inserted)
      - **(Oral/Patch/SC-Implant)**

    - **Benefits:**
      - ↓Hormonal Symptoms (Flushes/Mood)
      - ↓Vaginal Dryness
      - ↓Risk of Osteoporosis
    - **Side Effects:**
      - Breakthrough Bleeding
      - Breast Tenderness
      - Headaches/Nausea/Mood Swings
      - Small ↑Risk of Cardiovascular Disease
      - Small ↑Risk of Breast & Colorectal Cancers
      - (↑ Risk of Endometrial/Ovarian Ca ONLY IF Unopposed Oestrogen Therapy)
      - Small ↑Risk of VTE & Stroke
    - **CONTRAINDICATIONS:**
      - Hx of Thromboembolism (DVT/PE/CVA)
      - Hx of Stroke
      - Unexplained Post-Menopausal Bleeding – (Suspected Endometrial/Breast Ca.)
      - Acute Liver Disease
      - Hx of Breast Cancer
      - Pre-Existing Cardiovascular Disease – (Incl. Hypertension & ↑Cholesterol)
      - Migraine Suffers
  - **+/- Bisphosphonates (*Eg. Alendronate [Fosamax]*):**
    - To prevent Osteoporosis
  - **+ Breast/Colon Cancer Screening:**
    - Annual Mammograms
    - Annual FOBT; 5yrly Colonoscopy
    - 2yrly Pap-Smears

Table 2. Benefits/Risks of Postmenopausal Hormone Replacement Therapy (HRT)

Variable	Effect	Benefit or Risk	Source of Data
Definite Benefits			
Symptoms of Menopause	Definite improvement	> 70-80% decrease	Observational studies and RCT
Osteoporosis	Definite increase in bone mineral density (BMD); probable decrease in risk of fractures	2-5% increase in BMD; 25-50% decrease in risk of fractures	Observational studies and limited data from RCT
Definite Risks			
Endometrial cancer	Definite increase in risk with use of unopposed E; no increase with use of combined E-P	Increase in risk by 8-10x with use of unopposed estrogen for >10 years; no excess risk with combined E-P	Observational studies and RCT
Venous Thromboembolism	Definite increase in risk	Increase in risk by 2.7x	Heart and Estrogen/Progestin Replacement Study (HERS) and Observational Studies
Probable Increase in Risk			
Breast Cancer	Probable increase in risk with long-term use (> 5 years)	Overall increase in risk by 1.35x with HRT use for > 5 years	Meta-analysis of 51 observational studies
Gallbladder Disease	Probable increase in risk	Increase in risk by 1.4x	HERS

SPECIFIC GYNAECOLOGY NOTES:
MENORRHAGIA - ADENOMYOSIS

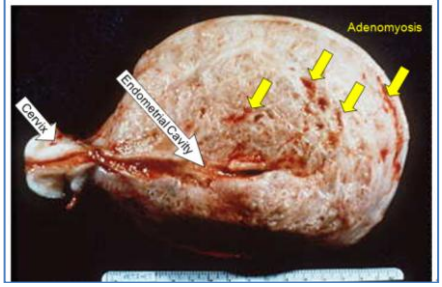
Menorrhagia:

- **Definition:**
  - Heavy periods/Heavy menstrual bleeding (>80mL during every period)(NB: Hard to measure)
- **Clinical Presentation:**
  - Unusually Heavy Periods (Changing pads/tampons *more than once every 4hrs*)
  - Long Periods: >7days (~5 days = normal)
  - Flooding of *blood NOT contained by pads/tampons*.
  - Blood clots >3cm diameter (NB: Small, stringy clots are normal)
  - Symptoms of Iron Deficiency Anaemia
  - **(NB: Common – 1 in 5 healthy women)**

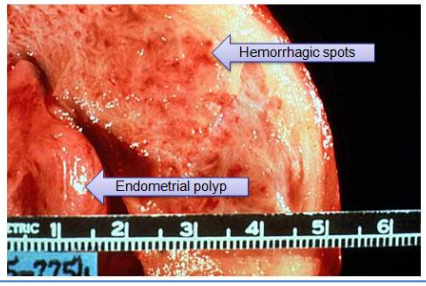
Adenomyosis

- **Aetiology:**
  - Hyperestrogenaemia
- **Pathogenesis:**
  - Hyperoestrogenaemia → Uterine Thickening (Endometrial Hyperplasia) & Invasion of Endometrium (Glands) into Myometrium (Muscle) → *Menorrhagia
- **Morphology:**
  - **Macro:**
    - Uterine Thickening (Endometrial Polyps/Thickening)
    - Haemorrhagic Spots on Endometrial Wall
  - **Micro:**
    - Endometrial Glands within the Myometrium.
    - NB: Glands are not normally present in the myometrium (Muscle layer)
- **Clinical Features:**
  - **Symptoms:**
    - *Menorrhagia (Long[8-14d] /Heavy Menstrual Bleeding)
    - Dysmenorrhoea: Intensely Painful Menstruation & Cramping
    - Dyspareunia
    - Heaviness & Dragging sensation.
  - **Diagnosis:**
    - Enlarged Uterus on Vaginal Ultrasound/MRI
- **Treatment:**
  - Progesterone-Only Contraceptive (OCP/Mirena/Implanon/etc)
  - Hysterectomy if Severe.
- **Prognosis:**
  - Symptoms abate with Menopause or Hysterectomy
  - Very rare progression to endometrial cancer.
- **Complications:**
  - Infertility
  - Carcinoma
  - Endometriosis

Uterus Adenomyosis:



Adenomyosis & Endometrial polyp:



(NB: Other Less-Common Causes: *Hyperthyroidism, IUDs, Bleeding Disorders, Endometrial Cancer*)

SPECIFIC GYNAECOLOGY NOTES:
MENORRHAGIA - DYSFUNCTIONAL UTERINE BLEEDING

Menorrhagia:

- **Definition:**
  - Heavy periods/Heavy menstrual bleeding (>80mL during every period)(NB: Hard to measure)
- **Clinical Presentation:**
  - Unusually Heavy Periods (Changing pads/tampons *more than once every 4hrs*)
  - Long Periods: >7days (~5 days = normal)
  - Flooding of *blood NOT contained by pads/tampons*.
  - Blood clots >3cm diameter (NB: Small, stringy clots are normal)
  - Symptoms of Iron Deficiency Anaemia
  - **(NB: Common – 1 in 5 healthy women)**

EG. DYSFUNCTIONAL UTERINE BLEEDING:

- **Aetiology:**
  - Excess oestrogen
- **Pathogenesis:**
  - Excess oestrogen → ↑Proliferation of Endometrium → Heavier periods
- **Clinical:**
  - Diagnosis of Exclusion – Ie. If no abnormality of the uterus is found, it is DUB.
- **Management:**
  - **Hormonal Contraception→ Amenorrhoea**

(NB: Other Less-Common Causes: *Hyperthyroidism, IUDs, Bleeding Disorders, Endometrial Cancer***)**

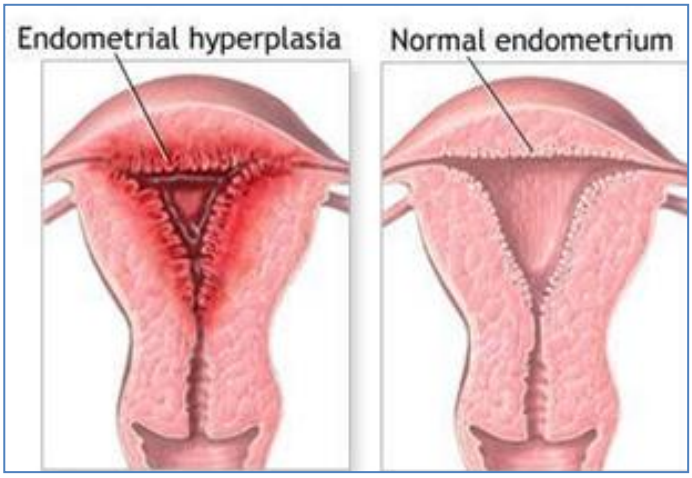
SPECIFIC GYNAECOLOGY NOTES:
MENORRHAGIA - ENDOMETRIAL HYPERPLASIA (POLYPS)

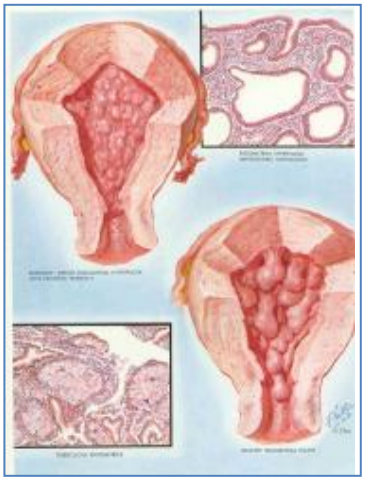
Menorrhagia:

- **Definition:**
  - Heavy periods/Heavy menstrual bleeding (>80mL during every period)(NB: Hard to measure)
- **Clinical Presentation:**
  - Unusually Heavy Periods (Changing pads/tampons *more than once every 4hrs*)
  - Long Periods: >7days (~5 days = normal)
  - Flooding of *blood NOT contained by pads/tampons*.
  - Blood clots >3cm diameter (NB: Small, stringy clots are normal)
  - Symptoms of Iron Deficiency Anaemia
  - **(NB: Common – 1 in 5 healthy women)**

ENDOMETRIAL HYPERPLASIA (POLYPS):

- **Aetiology:**
  - Hyperoestrogenaemia (Eg. Obesity, PCOS, Unopposed HRT)
  - (Ironically ***Tamoxifen*** [Oestrogen-R-Blocker] actually *stimulates* Endometrial Growth)
- **Pathogenesis:**
  - Hyperoestrogenaemia → Uterine Thickening (Endometrial Hyperplasia)
    - – (WITHOUT Invasion of Endometrium (Glands) into Myometrium (Muscle))
  - → *Menorrhagia (Long[8-14d] /Heavy Menstrual Bleeding)
- **Morphology:**
  - **Macro:**
    - Single or Multiple Polyps within the Uterine Cavity
  - **Micro:**
    - **Simple:** Irregular, Dilated, Cystic Glands
    - **Complex:** Crowding & budding of Glands
    - **Atypical:** Simple/Complex Changes + ***Atypical Changes in Cells*** *(Stratification, Pleomorphism, Enlarged Nuclei & ↑Mitotic Rate)*.
- **Clinical Features:**
  - **Symptoms:**
    - *Menorrhagia (Long[8-14d] /Heavy Menstrual Bleeding)
  - **Diagnosis:**
    - Endometrial Curettage Biopsy
    - Endometrium >5mm on USS
- **Treatment:**
  - ***Progesterone-Only Contraceptive*** (OCP/Mirena/Implanon/etc)
  - Or ***Hysterectomy***
- **Prognosis:**
  - Typically Benign (But ↑Risk of Malignancy with Atypical type.)





(NB: Other Less-Common Causes: *Hyperthyroidism, IUDs, Bleeding Disorders, Endometrial Cancer***)**

SPECIFIC GYNAECOLOGY NOTES:
MENORRHAGIA - GENERAL IX & MX

MENORRHAGIA:

- **Definition:**
  - Heavy periods/Heavy menstrual bleeding (>80mL during every period)(NB: Hard to measure)
- **Clinical Presentation:**
  - Unusually Heavy Periods (Changing pads/tampons *more than once every 4hrs*)
  - Long Periods: >7days (~5 days = normal)
  - Flooding of *blood NOT contained by pads/tampons*.
  - Blood clots >3cm diameter (NB: Small, stringy clots are normal)
  - Symptoms of Iron Deficiency Anaemia
  - **(NB: Common – 1 in 5 healthy women)**
- **Diagnostic Tests:**
  - **VE:**
    - Masses
  - **Trans-Vaginal USS:**
    - **(No Physical Abnormality = Dysfunctional Uterine Bleeding)**
    - **(Well-Defined Mass in Myometrium = Uterine Fibroid)**
    - **(Endometrial Thickening = Endometrial Hyperplasia)**
    - **(Myometrial Thickening = Adenomyosis)**
  - **Pipelle Endometrial Biopsy**
    - For Biopsy-Confirmation of Abnormal USS
  - **Hysteroscopy:**
    - For Biopsy-Confirmation of Abnormal USS
  - **Laparoscopy:**
    - If Menorrhagia + Pelvic Pain/Infertility/Ovarian Abnormality
- **Treating Menorrhagia:**
  - **Medical:**
    - **Progesterone-Only Contraceptive Tablets/IUDs (Most Effective):**
      - **MOA:** (Reduces Endometrial Proliferation → Lighter Periods)
      - **Pros:** →95% reduction in blood-loss; Contraception; Effective for 5years.
      - **Cons:** Irregular light bleeding in the initial months.
    - **Or Combined Oral Contraceptive Pill** (↓ blood loss by ~30%)
    - **+ NSAIDs – Eg. Aspirin** (↓ blood loss by ~30% + Relieve period pain)
    - **Iron Supplements for Anaemia**
  - **Surgical (NB: NOT for women planning for Children):**
    - Hysteroscopic Endometrial Ablation (<85% Effective; BUT 40% → INFERTILE)
    - Hysterectomy (Abdominal/Laparoscopic/Vaginal) (100% Effective; → 100% Infertility)

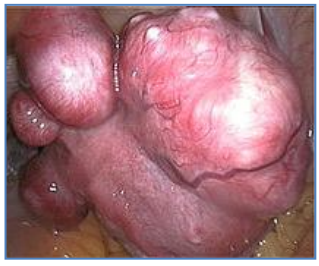
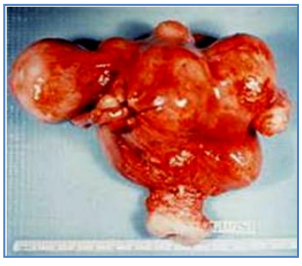
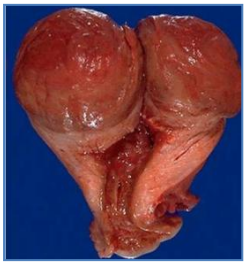
SPECIFIC GYNAECOLOGY NOTES:
MENORRHAGIA - UTERINE FIBROIDS

Menorrhagia:

- **Definition:**
  - Heavy periods/Heavy menstrual bleeding (>80mL during every period)(NB: Hard to measure)
- **Clinical Presentation:**
  - Unusually Heavy Periods (Changing pads/tampons *more than once every 4hrs*)
  - Long Periods: >7days (~5 days = normal)
  - Flooding of *blood NOT contained by pads/tampons*.
  - Blood clots >3cm diameter (NB: Small, stringy clots are normal)
  - Symptoms of Iron Deficiency Anaemia
  - **(NB: Common – 1 in 5 healthy women)**

Uterine LeioMYOMAS/FibroMYOMAS/LeiofibroMYOMA/"Uterine Fibroid" (Benign):

- **Aetiology:**
  - **Probably Multifactorial, BUT *Growth* is ++Oestrogen Dependent.**
- **Pathogenesis:**
  - Benign Tumourigenesis/Hyperplasia of the Smooth Muscle (Myometrium)
  - **+ Subsequent Growth is Strongly Oestrogen Dependent**
    - (:. Rapid increase during pregnancy; Regresses after menopause)
- **Morphology:**
  - **Macro:**
    - Multiple "Fibroids" – Round, Well-Circumscribed, White/Tan, Solid Nodules.
    - Size – Ranges from Microscopic → Grapefruit Sizes
  - **Micro:**
    - Whorls of Uniform Smooth Muscle cells (Spindle-Shaped), with Cigar-Shaped Nuclei.
    - Well Demarcated – But Not Encapsulated.
- **Clinical Features:**
  - **Epidemiology:**
    - <30% of women
    - Typically Perimenopausal.
  - **Symptoms:**
    - Asymptomatic if small
    - *Menorrhagia (Long[8-14d] /Heavy Menstrual Bleeding)
    - Dyspareunia
    - Abdo Mass/Bloating/Heaviness/Dragging Sensation/Constipation
    - Urinary Frequency & Urgency (Due to Pelvic Mass Compressing On Bladder)
  - **Diagnosis:**
    - Vaginal Ultrasound
    - (Bimanual Pelvic Examination – If Large Fibroids)
  - **Complications:**
    - Infertility/Miscarriage
    - Bleeding
    - Post-Renal Failure (Due to Ureteric Obstruction)
- **Treatment:**
  - Surgical Excision.
  - Hysterectomy if Symptomatic or Suspected Malignancy.
- **Prognosis:**
  - Benign

SPECIFIC GYNAECOLOGY NOTES:
OVARIAN CYSTADENOCARCINOMA

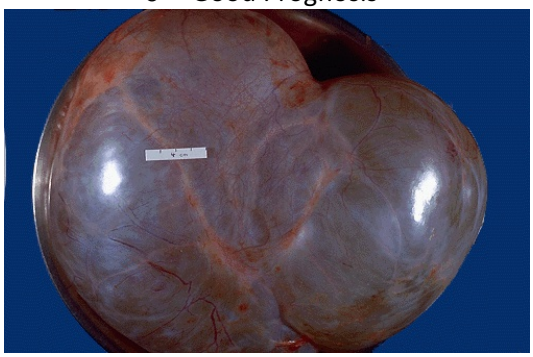
OVARIAN CANCER (CYSTADENOCARCINOMA - Malignant):

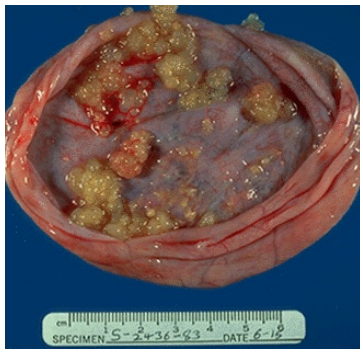
- **Aetiology:**
  - Unknown
  - **Risk Factors:**
    - Older >40yrs
    - BRCA1+/2+, & HNPCC
    - Oestrogen Exposure – (Early Menarche/Nulliparity/Late menopause)
    - Family History
    - Smoking
    - **(NB: OCP & Multiparity = Protective)**
- **Pathogenesis:**
  - Carcinogenesis of Ovarian Serous Epithelium
- **Morphology:**
  - Solid Tumour
- **Clinical Features:**
  - **Symptoms:**
    - (Early Stage-I/II = Asymptomatic)
    - Irregular Periods
    - Abdominal/Pelvic Pain/Discomfort
    - Bloating/Constipation.
    - Urinary Frequency/Urgency
  - **Signs:**
    - Abdominal Mass (Solid, Irregular, Fixed)
    - Weight Loss, Anorexia, Lethargy
    - Ascites
  - **Diagnosis:**
    - Physical Examination + PV
    - Trans-Vaginal USS
    - CT Abdo/Pelvis
    - *Confirmed by Surgery & Histology
    - ***NB: CA-125 useful only for Post-Diagnosis Monitoring.**
- **Treatment:**
  - **Surgery (Debulking)**
  - **+ Intensive Chemotherapy**
  - +/- Radiotherapy
- **Prevention (UpToDate):**
  - **UpToDate Advises NOT to screen for Ovarian Cancer. :O**
    - As Trans-Vag-USS & CA-125 are NOT Sensitive OR Specific Enough.
  - **BUT, in *High-Risk* Women, screen from 35yo with a COMBINATION of:**
    - Pelvic exam
    - Trans-Vaginal USS
    - CA-125 marker
  - ***+/- BRCA-Gene Testing for Pts with a FamHx of Breast/Ovarian Cancer. (90% Sensitive)**
    - **If Positive → Prophylactic BSO** (Bilateral Salpingo-Oophorectomy) – (Also ↓Breast Cancer)
      - **+/- Prophylactic Mastectomy** (Due to ↑↑Breast Ca Risk)
- **Prognosis:**
  - Malignant (15%)
  - **POOR Prognosis** - due to late detection:
    - **Stage 1** (Confined to Ovary/s) has 88% 5YS
    - **Stage 2** (Uterine Spread) has 60% 5YS
    - **Stage 3** (Peritoneal Spread) has 27% 5YS
    - **Stage 4** (Distant Mets) has <10 5YS
    - **(The vast majority are Stage 3 at Diagnosis)**

SPECIFIC GYNAECOLOGY NOTES:
OVARIAN CYSTADENOMA

OVARIAN CYSTADENOMA (Benign):

- **Aetiology:**
  - Unknown
- **Pathogenesis:**
  - Tumour of the Ovarian Surface Epithelium
- **Morphology:**
  - **Macro:**
    - May become very large (>20cm)
    - Multiple cysts containing clear fluid/mucous
    - Uni/Multi-Loculated
    - Little solid tissue
  - **Micro:**
    - Big Cyst lined by Cuboidal/columnar epithelium lining cysts
    - Cyst Lining may be Flat, or have Small Papillary Projections
    - Psammoma Bodies (Calcification) may be seen.
- **Clinical Features:**
  - Common & Benign (85%)
  - Young 20-45
  - **Prior to Rupture:** Abdominal Fullness, Heaviness, Pressure
  - **Upon Rupture:** Sudden, sharp Adnexal Pain → Followed by Dull, Aching → Pelvis/Vagina/Back/Thighs
  - **Diagnosis:**
    - Ultrasound
    - CT
    - Confirmed on Biopsy
  - **Complications:**
    - Commonest – Torsion (infarction, perforation, haemoperitoneum & autoamputation)
    - Infection
    - Perforation → Acute Abdomen
- **Treatment:**
  - **Analgesia –** Paracetamol or NSAIDs
  - **COCP –** To prevent follicle stimulation / Shrink existing cyst.
  - **Non-Medical –** Warm Bath/Hot Pack
  - (+/-Surgery (If large / Persistent / Life-Threatening))
- **Prognosis:**
  - Benign (85%)
  - Good Prognosis

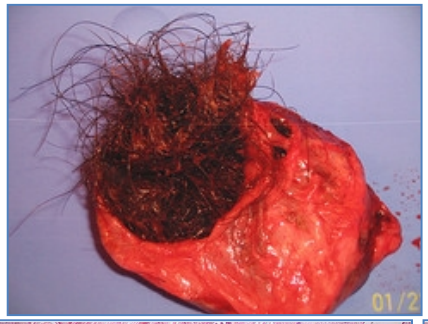
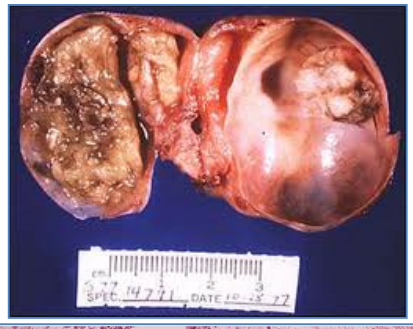
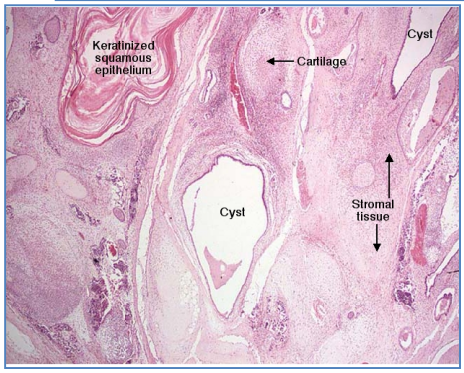


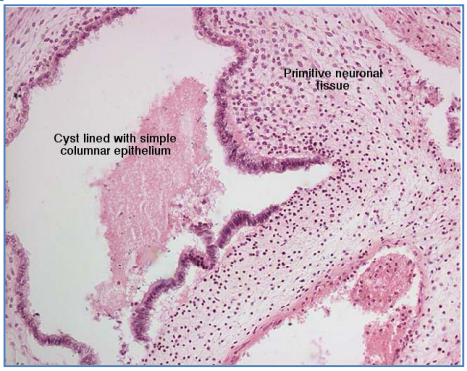


SPECIFIC GYNAECOLOGY NOTES:
OVARIAN TERATOMAS

Dermoid Cysts/Teratomas:

- **Aetiology:**
  - Often Congenital (Present @ Birth) – but slow-growing :. Presents later in life.
- **Pathogenesis:**
  - Abnormal Development of the Pluripotent Germ Cells in Testes(M)/Ovaries(F)
- **Morphology:**
  - **Macro:**
    - Hair, teeth, gingivae, neural tissue, fat, muscle, eye, retinal, glands etc.
    - May be cystic
  - **Micro:**
    - Multiple *Mature* Tissues in one tumour
    - Encapsulated
- **Clinical Features:**
  - **Symptoms:**
    - Abdominal/Pelvic Pain
  - **Diagnosis:**
    - Imaging → Biopsy → Histology
  - **Complications:**
    - Torsion of Ovary (→infarction, perforation, haemoperitoneum & autoamputation)
    - May → Paraneoplastic Syndrome (Eg. Hyperthyroidism, Morning Sickness)
- **Treatment:**
  - Surgery
- **Prognosis:**
  - Benign Tumour



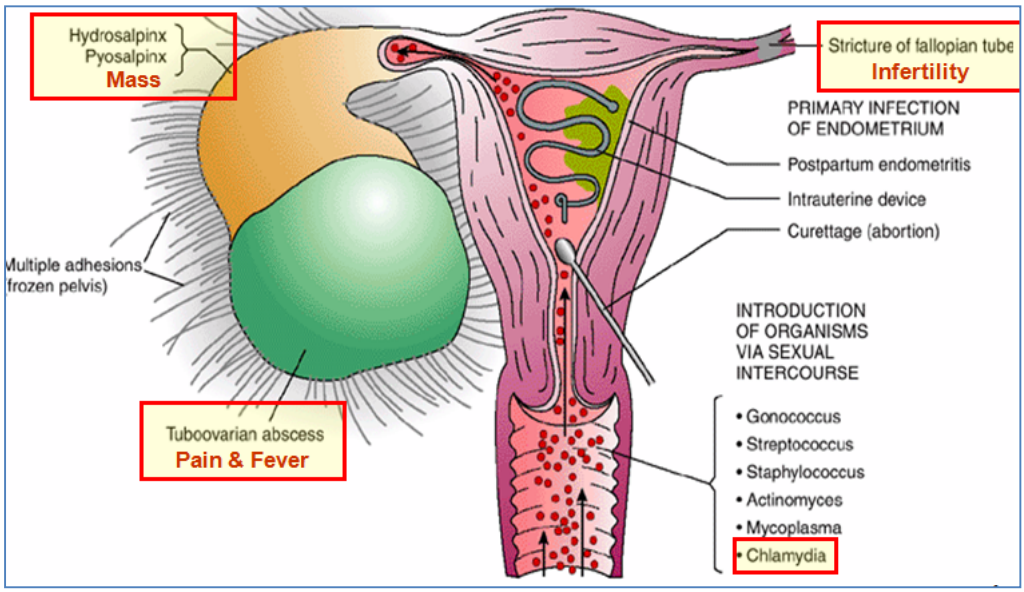
Teratocarcinomas:

- **Pathogenesis:**
  - Malignant Transformation of Benign Teratoma
- **Morphology:**
  - Typically a Squamous Cell Carcinoma
- **Treatment:**
  - Surgery + Chemotherapy
- **Prognosis:**
  - Malignant

SPECIFIC GYNAECOLOGY NOTES:
PELVIC INFLAMMATORY DISEASE

PELVIC INFLAMMATORY DISEASE (PID):

- **Aetiology:**
  - Typically Bacterial Infection (Often Sexually Transmitted) - (May also be Viral/Fungal/Parasitic)
  - **Commonest = 50% Chlamydia (C. Trachomatis) or 50% Gonorrhoea (N. Gonorrhoeae)**
    - (but also strep, staph, etc)
- **Pathogenesis:**
  - Prolonged/Chronic (Often Subclinical) Infection → Inflammation of the Uterus, Fallopian Tubes &/or Ovaries → Multiple Abscesses & Scar Tissue → Adhesions to Nearby Organs
- **Morphology:**
  - **Macro:**
    - Stricture of Fallopian Tube
    - Tubulo-ovarian abscesses
    - Dilatation/Cysts/Abscesses → Pelvic Mass
- **Clinical Features:**
  - (Typically Teenagers or New Mothers)
  - **Typical Symptoms:**
    - ***1.Chronic Pelvic Pain (+/- Lower Abdo, Dyspareunia)***
    - ***2.Fever***
    - ***3.Infertility*** – A result of Fallopian Tube Scarring/Obstruction.
    - ***4.Pelvic Mass*** – Due to Dilatations/Cysts/Abscesses
  - **Differentials –** Appendicitis, Ectopic, Ovarian Cysts/Tumour/Torsion.
- **Diagnosis:**
  - Clinical + Laparoscopy
  - NB: Early Detection is Imperative
- **Treatment:**
  - **Antibiotics – (*Azithromycin* / *Doxycycline*)**
  - **IVF for Conception.**
- **Prognosis:**
  - The *Infection* can be Cured, but Damage/Fibrosis/Infertility is Peramanent



SPECIFIC GYNAECOLOGY NOTES:
PELVIC ORGAN PROLAPSE

Definition:

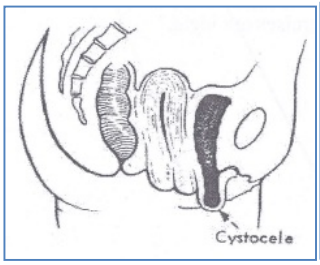
- **= "Protrusion of pelvic organs *Into/Out of* the Vaginal Canal – Due to incompetent pelvic structures"**

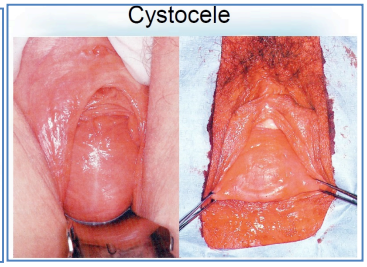
Aetiology:

- **Incompetent Pelvic Support Structures –** Relaxation/Weakness/Defect in Uterosacral Ligaments Due to:
  - Childbirth
  - Ageing
  - Menopause/Oestrogen Deficiency
  - Pelvic Surgery
  - ↑Intra-Abdominal Pressure (Obesity, Chronic Coughing, Constipation)

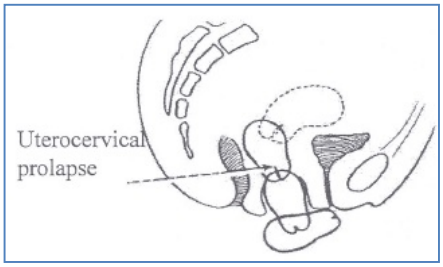
Pathophysiology:

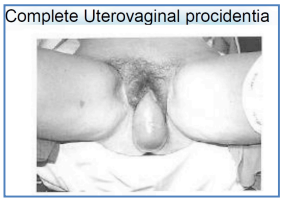
- **Incompetent Pelvic Support Structures → 3x Types of Prolapse:**
  - ***Anterior Prolapses:***
    - **Cystocoele/Cystourethrocoele:**
      - Prolapse of the Bladder &/or Urethra into the Vagina
      - → Urinary Frequency/Urgency/Nocturia/Stress Incontinence/Retention/UTIs

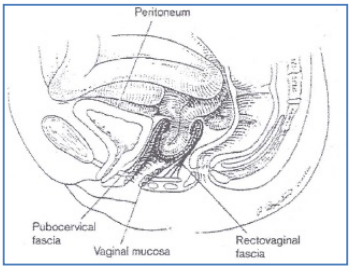


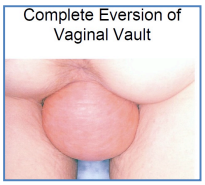


  - ***Uterocervical Prolapse:***
    - **Prolapse of the Uterus/Cercix/Vault (Following Hysterectomy)**
    - **3 Degrees:**
      - **1. Inside the Hymen**
      - **2. Up to the Hymen**
      - **3. Beyond the Hymen**

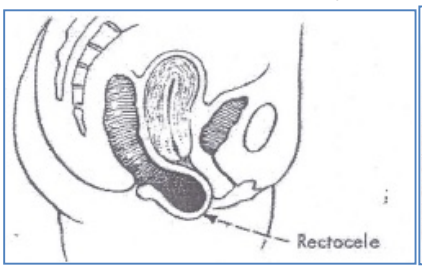


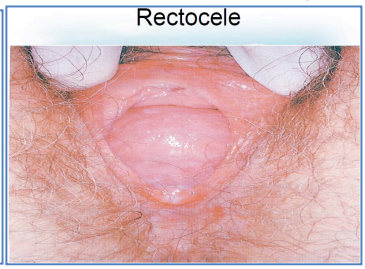


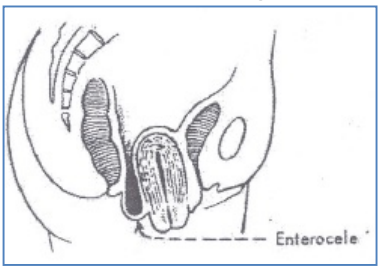




  - ***Posteroir Prolapses:***
    - **Rectocoele:**
      - Prolapse of the Rectum into the Vagina
      - → Constipation (Pt needs to reduce the rectocoele via the vagina to defecate)
    - **Enterocoele:**
      - Prolapse of the Intestines into the Vagina (Via the Pouch of Douglas)







Clinical Features:

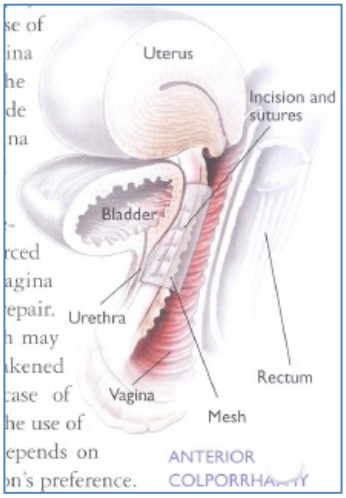
- **Symptoms:**
  - Heaviness/Fullness/Dragging Sensations – (Worse with Standing/Lifting; Better when Supine)
  - Referred Back Pain
  - Sexual Dysfunction/Dyspareunia
  - **Urinary:**
    - Urinary Frequency/Urgency/Nocturia/
    - Stress Incontinence
    - UTIs
    - Retention
  - Constipation
- **Signs:**
  - Palpable Mass/Bulge at Introitus
  - +/- Palpable Bladder (if retention)
  - +/- Signs of Incontinence

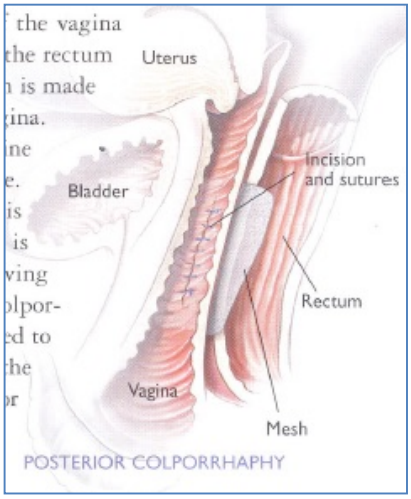
Diagnosis:

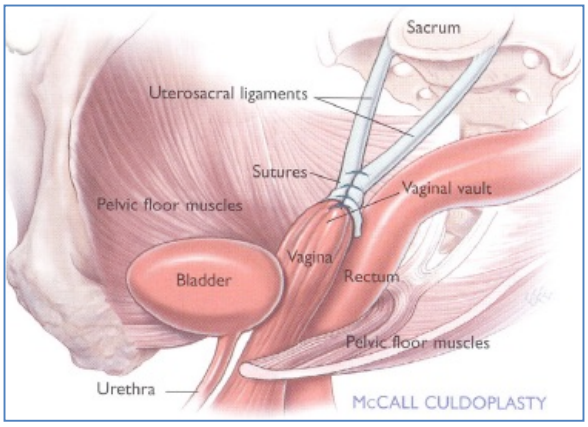
- **Clinical Dx** – Pelvic Examination
- **REFER TO GYNAECOLOGIST**
- **CT/MRI** – To Confirm + Pre-Surgery

Treatment:

- **Non-Surgical:**
  - Ring Pessary (if not suitable for surgery – eg. Old women)
  - Oestrogen Therapy
  - Pelvic Floor Exercises
  - Laxatives for Rectocoeles
- **Surgical Repairs:**
  - **"Anterior Repair/Sling"** (For Cystocoeles & Urethrocoeles)
  - **Hysterectomy** (For Utero/Cervico Prolapses
  - **Vault Sling Repair** (For Vault Prolapses)
  - **"Posterior Repair/Sling"** (For Rectocoeles & Enterocoeles)



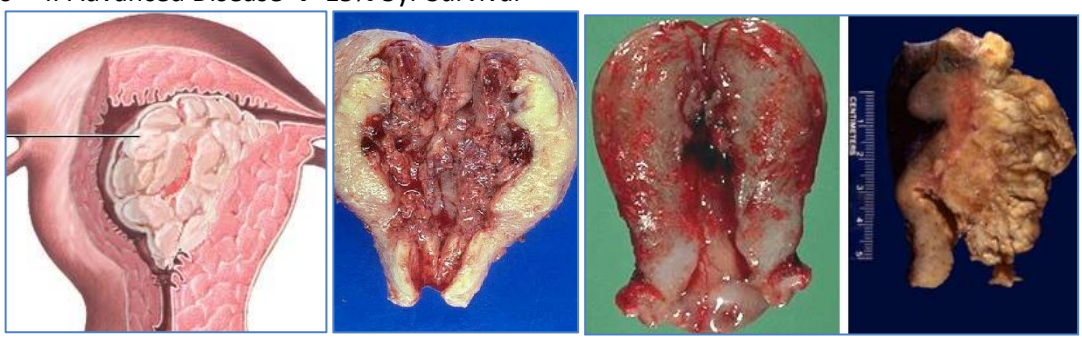




SPECIFIC GYNAECOLOGY NOTES:
ENDOMETRIAL ADENOCARCINOMA

ENDOMETRIAL ADENOCARCINOMA (Malignant "Endometrial Cancer"):

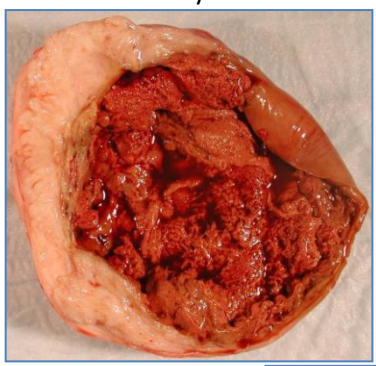
- **Aetiology:**
  - **Excessive Oestrogen Exposure**
  - **:. Risk Factors –**
    - **↑Oestrogen:** Early Menarche, Nulliparity, Late Menopause, Obesity, PCOS, & Prolonged Oestrogen Therapy (HRT), Tamoxifen
    - **Others:** Hypertension, Diabetes, Pelvic Radiation.
  - (Or progression from Endometrial Hyperplasia)
- **Pathogenesis:**
  - **Hyper-Oestrogenaemia** + Genetic Predisposition → Hyperplasia & Carcinogenesis of Endometrial Epithelium
- **Morphology:**
  - **Macro:**
    - Polypoid/Choleflower-Like Growth + Distended Uterus
    - Areas of Haemorrhage, Necrosis & Infiltration
  - **Micro:**
    - **Adenocarcinoma of Endometrial Glands:**
      - Numerous, Small, Back-to-Back Glands
      - Irregular & Dysplastic Cells
      - Little Stroma
- **Clinical Features:**
  - **Epi:**
    - Most Common Gynae. Cancers.
    - Mainly in postmenopausal, older women (>60yrs).
  - **Presentation:**
    - Post-Menopausal/Intermenstrual Bleeding
    - Lower Abdo Pain/Cramping
    - Syx of Anaemia
    - Thin White/Clear Vaginal Discharge
  - **Diagnosis:**
    - **Endometrial Aspiration (Via Pipelle) → Biopsy
    - **Endometrial Curettage → Biopsy
    - + Trans-Vaginal USS (>5mm Endometrial Thickness = Suspicious)
    - (+/- Hysteroscopy to eliminate Endometrial Hyperplasia/Polyps or Fibroids.)
- **Treatment:**
  - **Pre-Rx Staging (CXR/CT/MRI/PET)**
  - **Pre-Rx CA-125** (For monitoring)
  - **Total *Hysterectomy* + *Bilateral Salpingo-Oophorectomy* + Pelvic *Lymph Nodes Resected***
    - +/- *Radiotherapy*
    - +/- *Chemotherapy*
- **Prognosis:**
  - NB: Presents early with DUB :. Early Detection → 90% 5yr Survival
  - If Advanced Disease → 15% 5yr Survival

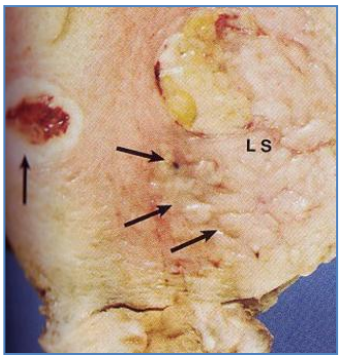


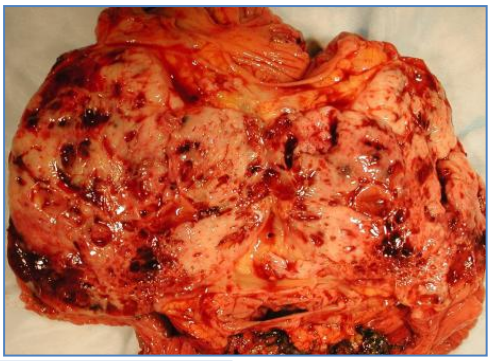
SPECIFIC GYNAECOLOGY NOTES:
LEIOMYOSARCOMA (MYOMETRIAL CANCER)

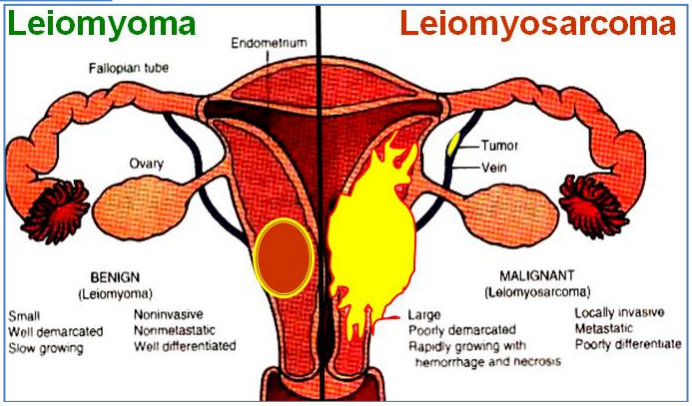
UTERINE LEIOMYOSARCOMA (Malignant *Myometrial* Tumour):

- **Aetiology:**
  - Unknown – Probably Genetic + Environmental
- **Pathogenesis:**
  - Connective Tissue Tumour of the Myometrium (Smooth Muscle layer of the Uterus)
  - **NB: NOT HORMONALLY DRIVEN**
  - (NB: Can also occur in Stomach, SI & Retroperitoneum)
- **Morphology:**
  - **Macro:**
    - Solitary, Large (>10cm), Poorly Circumscribed Tumour
    - Soft Fleshy Consistency
    - Yellow-Tan Colour
    - No Capsule + Invasion into the Myometrium
    - Haemorrhage & Necrosis
- **Clinical Features:**
  - Rare (1% of Uterine Cancers)
  - Typically 40-60yrs (Perimenopausal)
  - Typically present with Advanced Disease
  - **Presentation:**
    - *Dysfunctional Uterine Bleeding
    - Pelvic/Abdominal Pain
    - *Weight Loss, Lethargy, Weakness, Fever
    - Enlarged Uterus + may prolapsed into the vagina.
- **Diagnosis:**
  - Hysteroscopy & Biopsy
  - (Imaging is NOT sufficient)
- **Treatment:**
  - **Surgical – *Total Hysterectomy* +/- *Radiation* & *Chemotherapy*.**
- **Prognosis:**
  - Typically present with Advanced Disease
  - Aggressive & Can spread by any route → Poor Prognosis
  - <70% 5yr Survival









SPECIFIC GYNAECOLOGY NOTES:
URINARY INCONTINENCE

Urinary Incontinence:

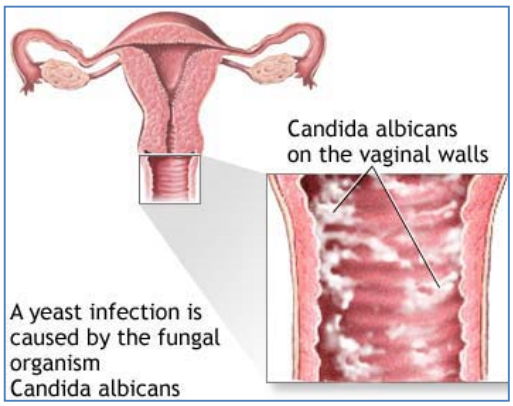
- **Epidemiology:**
  - Affects 13% of Men
  - Affects 37% of Women
  - F:M = 2:1
- **Definition:**
  - **Incontinence =** "The Involuntary Leakage of Urine sufficient to cause Social/Hygiene Problems"
- **Pathophysiology:**
  - **Continence Depends on 2 Things:**
    - 1. Compliant Reservoir (Bladder)
    - 2. Sphincter Competency (External Urinary Sphincter & Intact Pelvic Floor Supports)
  - **Types:**
    - ***Stress*:** **On Sudden ↑ in Intra-Abdominal Pressure (Coughing/Sneezing)**
      - **Severity -** (Usually only a few drops)
      - **Causes -** (Damage/Weakness of the Pelvic Floor, Urethra or Sphincter)
      - **Risk Factors -** (Child-Bearing, Pelvic Surgery, Menopause)
      - **Diagnosis –** (Urodynamics "Stress Test")
    - ***Urge*:** **Sudden Strong Urge to Void, but can't get to toilet soon enough.**
      - **Severity -** (Can empty the whole bladder)
      - **Causes -** (*Detrusor Instability*, Cystitis or Neurogenic)
      - **Risk Factors -** (UTIs, Poor Bladder Training, Neurological Detrusor Instability)
      - **Diagnosis –** (Urodynamics shows *Small Volume, Unstable Bladder*)
    - ***Overflow*:** **Bladder is too full (Retention/Overdistension) → Incontinence**
      - **Severity -** (Occasional Dribbles)
      - **Causes -** (LUT-Obstruction [Eg. BPH, Stricture], Hypotonic Bladder [Diabetes, Autonomic Neuropathy, Anticholinergic Drugs])
      - **Risk Factors -** (Old Age, Diabetic, Neurology)
      - **Diagnosis –** (Urodynamics shows *Large Volume, Immotile Bladder*)
    - ***Total/Constant*:** **Total loss of continence**
      - **Severity -** (Constant Dribbles – Requires Catheter)
      - **Causes -** (Sphincteric [Surgery, Neurology, Cancer], or Fistula bypassing Sphincter)
      - **Risk Factors -** (Pelvic Surgery, Nerve Damage, Metastatic Disease)
      - **Diagnosis –** (Clinical Diagnosis)
    - ***Functional/Transient*:** **Urine loss due to functional disorder (Immobility, Dementia)**
      - **Severity -** (Depends on functional disorder)
      - **Causes -** (Immobility, Cognitive Deficits)
      - **Risk Factors -** (Immobile [Eg. Para/Quadriplegic], Dementia/Retardation)
      - **Diagnosis –** (Clinical Diagnosis)
- **Assessment:**
  - **History:**
    - Type of Incontinence? – (Severity? How long? How often? In What Situations? Morbidity?)
    - Associated Syx? – (Dysuria [UTI], Faecal Incontinence, Menopausal, Prolapse)
    - Obstetric & Gynaecological Hx? – (#.Children, Pelvic Surgeries)
  - **Examination:**
    - Genitourinary Abnormalities – (Prolapse, Fistulae, Infection, Palpable Bladder, Sensation)
    - DRE – (Sensation, Anal Tone, Rectocoele)
  - **Investigations:**
    - **Voiding Diary:** Shows Triggers, Frequency, Severity & Morbidity
    - **Urinalysis:** Rules out Infection (Cystitis/UTI) & Renal Failure (From Urinary Retention)
    - **Urodynamics:** Differentiates Stress/Urge/Overflow Incontinence.
    - **Bladder USS:** Determines Pre & Post-Void Bladder Volumes (Urge Vs. Overflow)
    - **Cystoscopy:** Ix for Cystitis & Obstructive Uropathy
      - (Can also treat Detrusor Instability – [Botox], & Cystitis – [Steroid Injection]).

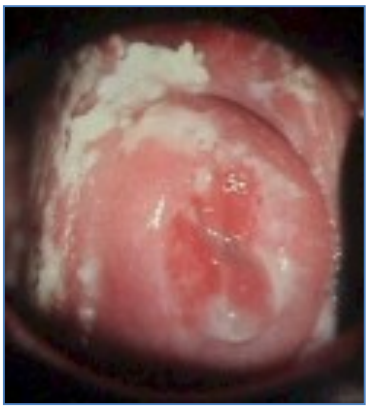
- **Treatment:**
  - **Stress Incontinence:**
    - (Weight Loss; Rx Chronic Cough)
    - Pelvic Floor Exercises
    - Topical Oestrogen Creams
    - +/- Surgery (Cystourethropexy Sling to elevate bladder neck)
  - **Urge Incontinence:**
    - Bladder Re-Training
    - Antispasmodics (*Oxybutinin ['Ditropan']*)
    - Anticholinergics
    - +/- Cystoscopy (for Detrusor Botox/Steroid Injection)
  - **Overflow Incontinence:**
    - Intermittent Self-Catheterization / Suprapubic
    - Surgery to Rx Urinary Retention – (Eg. TURP for BPH / Dilation of Stricture)
  - **Constant Incontinence:**
    - Surgical Correction & Urinary Diversion
  - **Functional Incontinence:**
    - Catheterisation/Pads/Condom Drainage
    - Nursing Care

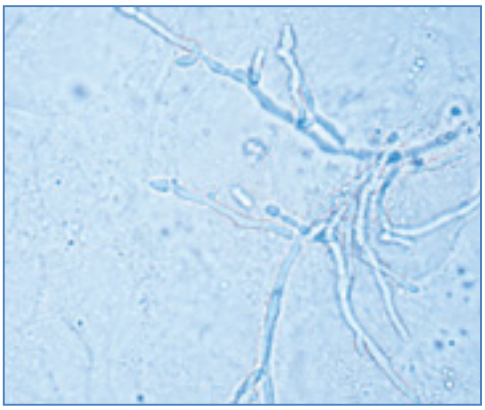
SPECIFIC GYNAECOLOGY NOTES:
VAGINAL CANDIDIASIS (THRUSH)

VAGINAL CANDIDIASIS/"THRUSH"/"YEAST-INFECTION":

- **Aetiology:**
  - Candida albicans overgrowth
- **Pathogenesis:**
  - Overgrowth of *Candia albicans* in the vagina secondary to...
    - Excessive douching → Loss of *Lactobacilli* → ↑pH & ↓Microbial Competition
    - Antibiotic use may → Loss of *Lactobacilli* → ↑pH & ↓Microbial Competition
    - Immunosuppression (Diabetes/HIV/Chemotherapy/Corticosteroids)
    - (High sugar intake if Oral Candidiasis)
  - →→Local inflammation & discomfort
  - (NB: Typically not an STI, however may be precipitated by some STI's – Eg. HIV → ↓Immune System)
- **Morphology:**
  - **Macro:**
    - Vaginal erythema
    - Furry white plaques on the vaginal wall
    - Pinpoint bleeding underneath candida plaques.
  - **Micro:**
    - Pseudohyphae and budding yeast cells
- **Clinical Features:**
  - Vaginal discharge - Thick, milky, curd-like & Odourless.
  - Vulval Pruritis/Burning/Soreness
  - Dyspareunia
  - Spotting
- **Diagnosis:**
  - Pelvic examination
  - Discharge MCS
- **Treatment:**
  - **Treat/Prevent precipitating factor/s.**
  - **+ Antifungals (*clotrimazole*/*nystatin*/*fluconazole*)**



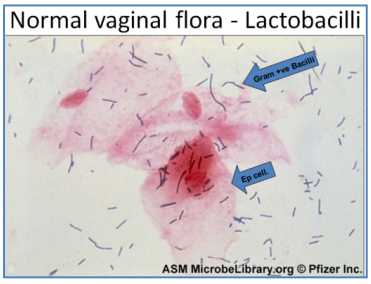


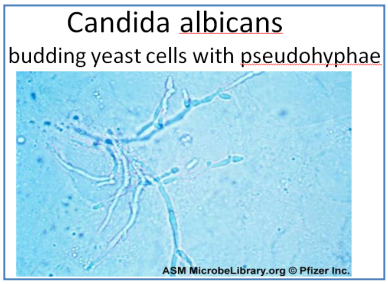


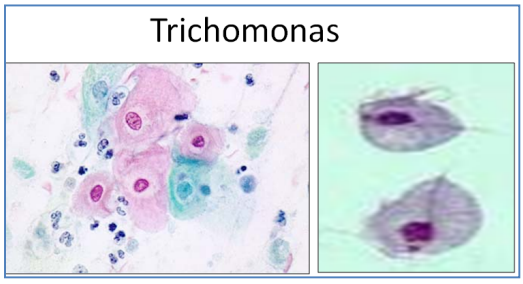
WOMENS HEALTH Pathology:
VAGINOSES (BACTERIAL, FUNGAL, PROTOZOAN)

VAGINITIS:

- **Aetiology:**
  - **50% = Bacterial** – Garnerella vaginalis
  - **30% = Fungal –** Candidia albicans
  - **20% = Protozoan** – Trichomonas vaginalis
- **Pathogenesis:**
  - **50% = Bacterial** – Garnerella vaginalis
    - Loss of Normal Vaginal Acidity *or* Loss of Normal Vaginal Flora (Lactobacillis) → Replaced by other Bacteria.
  - **30% = Fungal –** Candidia albicans
    - Typically only in Immunosuppressed (HIV, Diabetes, Corticosteroids, etc)
  - **20% = Protozoan** – Trichomonas vaginalis
    - Trichomonas = Bowel Flora → Infects Vagina & LUT
- **Morphology:**
  - **Micro:**
    - **Normal –** Blue, gram +ve Lactobacilli.
    - **Gardnerella** - "Clue cells" on Microscopy (Distinctive Bacteria-coated epithelial cells)
    - **Candida –** "Pseudohyphae" on Microscopy
    - **Trichomonas –** Pear-shaped, flagellate Protozoan on Microscopy
- **Clinical Features:**
  - **Typically → Vaginal Discharge + Odour + Dyspareunia:**
    - **50% - Gardnerella (Bacterial) =** Profuse Fishy, Grey-White Homogenous Watery Discharge, Pruritis, Dyspareunia & Dysuria.
    - **30% - Candida (Fungal) =** Curdy, white, sticky, cheezy discharge + furry white plaques + microbleeding beneath plaques. + vaginal & vulval pruritis → Excoriation
    - **20% - Trichomonas (Protozoa)=** Thin, frothy, yellow-green discharge, small, pruritis, dyspareunia, "strawberry vagina"
- **Diagnosis:**
  - **Clinical** – '*Is discharge Cervical or Vaginal?*', *Previous STIs?*, *Diabetic?*
  - **pH test** if Vaginal discharge (Reduced if Bacterial Vaginosis)
  - **Microscopy:**
    - ("Clue Cells" if Bacterial Vaginosis [Gardnerella])
    - ("Pseudohyphae" if Fungal Vaginosis [Candida])
    - ("Motile Flagellates" if Protozoan Vaginosis [Trichomonas])
  - **PCR for ?-Trichomonas.**
- **Treatment:**
  - Specific antimicrobials depending on pathogen.
    - **Gardnerella** - Oral ***Metronidazole*** BD for 1wk
    - **Candida** - Oral ***Fluconazole***
    - **Trichomonas** – Oral ***Metronidazole*** Stat Dose



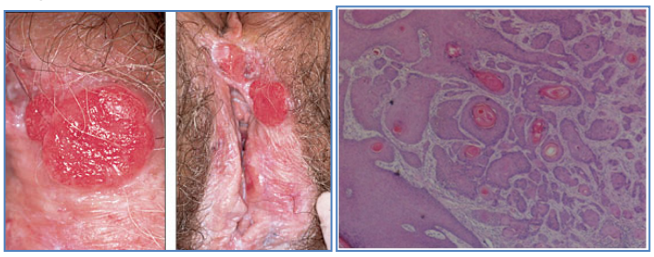




SPECIFIC GYNAECOLOGY NOTES:
VULVAL CANCERS

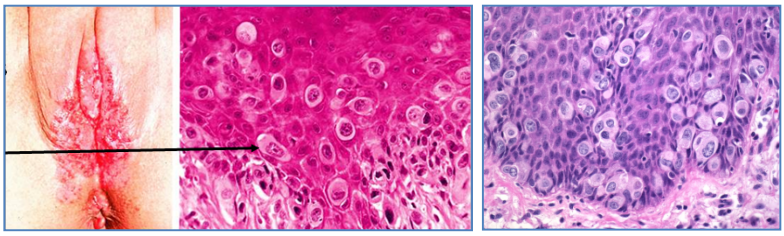
Vulval Cancer (Squamous Cell Cancer):

- **Aetiology:**
  - HPV-16 & -18
- **Pathogenesis:**
  - HPV-16 & -18 Infection → Dysplasia
  - (Lichen Sclerous can also → Vulval Cancer)
- **Morphology:**
  - **Macro:**
    - Unifocal Lesion on Labia Majora
  - **Micro:**
    - **SCC** – Pleomorphic Squamous Cells + **Epithelial Keratin Pearls**
- **Clinical Features:**
  - Typically Post-Menopausal Women
  - **Symptoms:**
    - Unifocal Lesion/Lump/Ulcer on Labia Majora
    - Itching/Irritation
    - Local Bleeding/Discharge
    - Dyspareunia
  - **Diagnosis:**
    - Pelvic Exam / Pap Smear / Colposcopy
    - →Biopsy
- **Treatment:**
  - **Surgery – (*Wide Local Excision*)**
    - (or Radical Vulvectomy + Lymph Node Resection)
  - **+/- *Radiotherapy***
  - **+/- *Chemotherapy***
- **Prognosis:**
  - Spreads via Lymphatics. May → Pelvic Lymph Nodes
  - **Stage 1-3 ≈75% 5yr Survival**



Paget's Disease of Vulva (Adenocarcinoma):

- **Aetiology:**
  - HPV-16 & -18
- **Pathogenesis:**
  - HPV-16 & -18 Infection → Dysplasia
- **Morphology:**
  - **Macro:**
    - Red & White Scaly Plaques on Vulva
  - **Micro:**
    - Typically an *In-Situ* Adenocarcinoma of the *Apocrine Glands,* However, may be Invasive.
- **Clinical Features:**
  - **Epidemiology:** Typically Older Women (50-60yrs)
  - **Symptoms:**
    - Painful & Itchy Red & White Scaly Plaques. – (May be mistaken for Eczema)
    - NB:Has a Predilection for Apocrine Gland Areas (Ie. Perineum, Vulva, Axilla, Scrotum & Penis)
  - **Diagnosis:**
    - Failed Steroid Therapy for Eczema.
    - Biopsy
- **Treatment:**
  - Wide Surgical Excision
- **Prognosis:**
  - Size = Prognosis



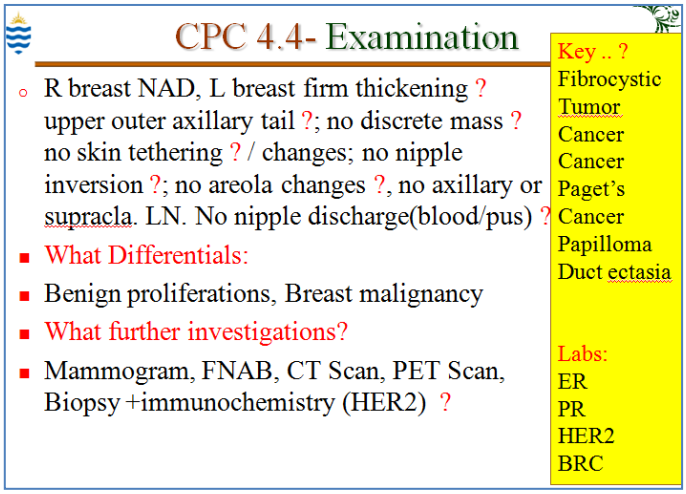
MCQS & CASES - Breast Disease

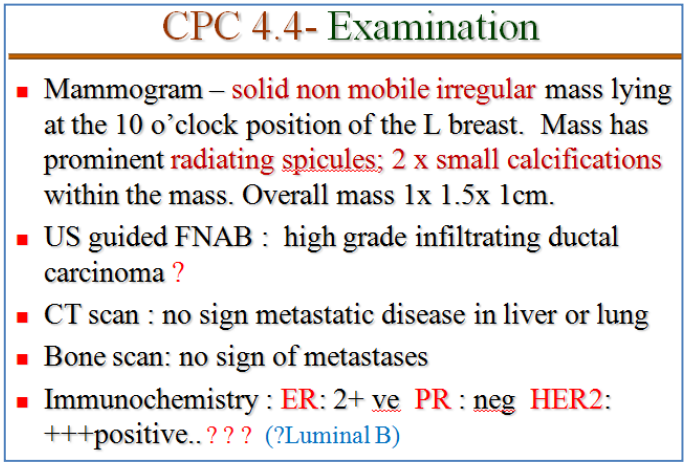
CPC Case:

1.

- **Mrs. M.J. is a 42y primary school teacher, from Weipa returned for follow-up consultation.**
  - **Sore R breast, not improving on oral antibiotics.**
  - History: Miscarriage 3wk, week later sore R breast.
    - Hot, red area, pain 4/10.
    - No – Fever, Nipple discharge, retraction or trauma.
    - Had Past H of mastitis. Responded to antibiotics. (not now)
    - Smoker 5-10/day for 22y. Stopped when pregnant.
    - Palpable, tender, enlarged LN in Rt axilla.
  - Differential Diagnosis - ???
    - Mastitis, Insect bite, Dermatitis, infection, lymphoma, Duct ectasia, Breast malignancy

2.

- **Mrs. JM, 45y woman, primary school teacher, living in Weipa. 'I have noticed a odd change in my left breast when I was showering last week'**
  - History:
    - Duration. Noticed it 8 days ago ?
    - What: 'My left breast feels a bit thicker – just here' (points to upper outer breast)
    - Pain? No - ?
    - Nipple discharge: No - ?
    - Trauma to breast: No - ?
    - Menstrual cycle: regular - ?
    - Mastalgia: not usually ?
  - Differential Diagnosis - ???
  - 

  - 

STIs, Penis & Testis Disorders

CPC Case:

15 year old student, pain in groin

- **PC:**
  - J.S. is a 15y male, high school student. He presents at 23h30 to the ED with his mother, looking worried and embarrassed, and asks if he can see the attending doctor. He has a pain in his groin.
- **HxPC:**
  - Left scrotal pain, 10 hours, fever, ?viral.
  - Pain increasing 2-5/10. took paracetamol.
  - Urine normal, no dysuria, no discharge, no blood.
  - Similar attack a year ago. Resolved with antibiotics.
- **DDx:**
  - 1. Exclude Torsion
  - 2. Epididymo-orchitis
- **ProvDx:**
  - Epididymo-orchitis

CPC4.4:Testes: Common presentations.

Torsion	12y boy, woke up in the night with sudden severe scrotal pain. O/E tender, swollen testes high up in the scrotal sac does not allow to touch.
Seminoma	35y man, dragging sensation in scrotum since 6 weeks. O/E enlarged, smooth, non tender, firm testes on one side.
Ep.Orchitis	28y man, severe aching pain in the left groin radiating to the scrotum since 3 days with associated fever and rigors. O/E a 4 cm, hot, swollen, tender, (left epididymis & testis).
Hernia	35y man, smoker, chronic cough, presents with recurrent attacks of sharp pain in right groin with small painful bulge, disappears on laying down.
Bowen/EQ	68y male, erythematous, irregular, raised papule on penis/glans since 6 months.

DD: Scrotal pain in Young:

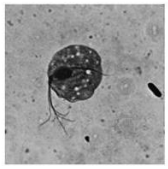
Diagnosis	History	Features
Torsion of the testis	Sudden, severe pain in testes (may start in iliac fossa) sudden, exertion, onset may have nausea, vomiting.	Discolouration of scrotum; exquisitely tender testis, riding high
Torsion of the appendix testis	More gradual onset of testicular pain	Focal tenderness at upper pole of testis; "blue dot" sign – necrotic appendix.
Epididymo orchitis	Onset insidious; fever, vomiting, urinary symptoms;	Red, tender, swollen hemiscrotum; posteriolateral to testis. Pyuria.
Incarcerated inguinal hernia	Past History of intermittent inguinoscrotal bulge, with associated irritability (hernia)	Firm, tender, irreducible, inguinoscrotal swelling
Hydrocele (hematocele, spermatocele)	Swollen hemiscrotum in well, settled baby	Soft, non-tender swelling adjacent to testis; transilluminates brightly.
Henoch Schonlein purpura	Painful scrotal oedema, with purpuric rash over scrotum + buttocks and lower limbs, arthritis, abdominal pain with GI bleeding, and nephritis	may be difficult to distinguish from testicular torsion in absence of other features
Mumps Orchitis	Child with fever, headache, and malaise. ear pain (lower lobe), cheek swelling (parotits) 1wk later scrotal pain & swelling.	Unilateral (70%), oedematous swollen.

Symptoms - Pathogenesis

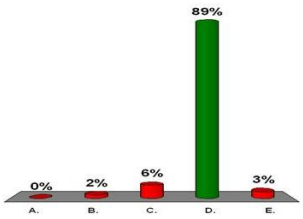
- Acute Pain - trauma, torsion, infection (STD)…
  (duration, Severity; relieving/precipitating factors)
- Urgency – UTI, Prostate.
- Dysuria – UTI, nephrolithiasis
- Urethral discharge – UTI, STD,
- Urinary stream – Prostate, UTI, obstruction,
- Haemtauria – Stone, tumors.
- Fever - Inflammation UTI, Orchitis, PID.
- Bowel habit change – PID, IBD
- Sexual history - STD
- Back/pelvic pain – Tumours, metastasis, injury.
- Appetite, Weight, Fatigue – malignancy, endocrine.
- Painless swelling in young – neoplasm* malignant*

Quiz Questions:

A 28 year old female, greenish vaginal discharge, wet film showed oval motile organisms. What is the likely causative organism?

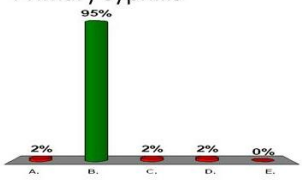


A. Candida albicans
B. Chlamydia trachomatis
C. Gardnerella vaginalis
D. Trichomonas vaginalis
E. Neisseria gonorrhoea



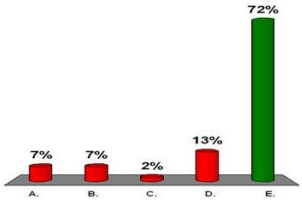
A 35 yr old female, vulval prurutis, erythema, dysuria and white vaginal discharge. Image shows wet film appearance. ? Most likely diagnosis

A. Gonorrhoea
B. Candidiasis
C. Bacterial vaginosis
D. Trichomoniasis
E. Primary syphilis



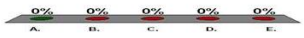
A 55 yr old male presents with red oedematous, painful scrotal swelling; pain relieved by scrotal elevation. What is the most likely causative organism?

A. Chlamydia trachomatis
B. Haemophilus ducreyi
C. Staphylococcus aureus
D. Neisseria gonorrhoea
E. Escherichia coli



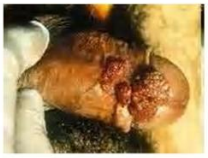
A 25 yr old male, painless ulcerative lesion with exudate on the penis. Which of the following is the most appropriate first line diagnostic procedure?

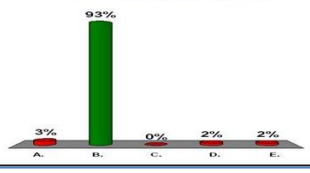
A. Dark ground microscopy of exudate
B. Culture and sensitivity of the exudate
C. Gram stain of the exudate
D. Wet film microscopy of exudate
E. Negative staining of the exudate



A 40 yr old male, painless cauliflower like outgrowths with itching and irritation. Biopsy of these lesions shows 'koilocytes" Causative organism?

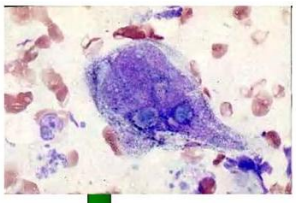
A. Herpes simplex virus
B. Human papilloma virus
C. Cytomegalo virus
D. Treponema pallidum
E. Chlamydia trachomatis

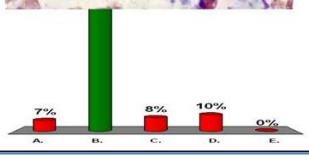




A 45 yr old female, painful, recurrent, multiple genital ulcers around labia and vulva. Image shows a smear taken from the ulcer. What diagnostic feature is seen in the image?

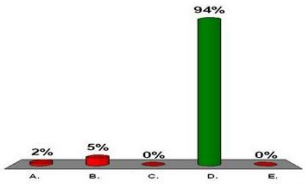
A. Donovan bodies.
B. Multinucleated giant cell.
C. Intracytoplasmic inclusion bodies.
D. Cowdry type B inclusion bodies.
E. Negri bodies.





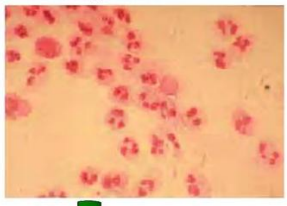
A 32 yr old female, profuse watery vaginal discharge with fishy odour. Gram stain of discharge shows decreased number of lactobacillii & squamous epithelial cells studded with gram negative bacilli. What is the likely diagnosis?

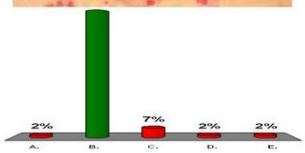
A. Gonorrhoea
B. Trichomoniasis
C. Secondary syphilis
D. Bacterial vaginosis
E. Chlamydial infection



A 48 yr old male, dysuria and urethral discharge; Culture of discharge shows no growth. Image shows gram stain of the discharge. What is the most likely causative organism?

A. Treponema pallidum
B. Chlamydia trachomatis
C. Neisseria gonorrhoea
D. Calymmatobacterium granulomatosis.
E. Haemophilus ducreyi.



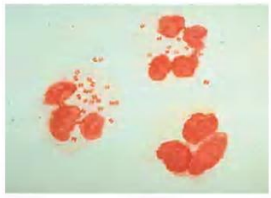


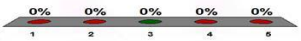
A 20-year-old man presents with dysuria, urgency, and urethral discharge. Physical examination shows suppurative urethritis, with redness and swelling at the urethral meatus. Which of the following is the most likely etiology of urethritis in this patient?

1. Borrelia recurrentis
2. Chlamydia trachomatis
3. Haemophilus ducreyi
4. Neisseria gonorrhoeae
5. Treponema pallidum

24y male, dysuria, discharge ? Diagnosis

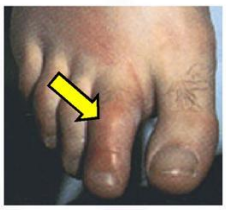
A. Chlamydial Urethritis
B. Syphilis
C. Gonorrhoea
D. Reiters syndrome
E. E.coli - UTI

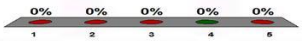




24y male, dysuria, discharge ? Diagnosis

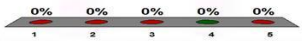
A. Chlamydial Arthritis
B. Syphilis
C. Gonorrhoea
D. Reiters syndrome
E. E.coli - Arthritis





25y male, painless papule with ulcer. Cytology darkfield microscopy: ? Diagnosis

1. Human Papilloma virus
2. Chlamydia trachomatis
3. Mycobacterium
4. Treponema pallidum
5. Neisseria gonorrhoeae.

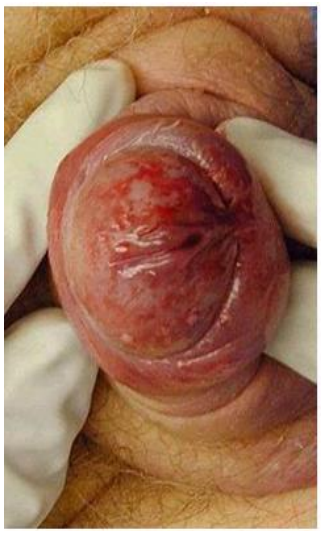


MENS HEALTH Pathology:
BALANITIS & BALANOPOSTHITIS

BALANITIS & BALANOPOSTHITIS:

- ***Balanitis*** = Inflammation of the Glans Penis Only
- ***Balanoposthitis*** = Inflammation of the Glans & Prepuce
- **Aetiology:**
  - **Many Possible Causes:**
    - **Infection – Staph, E.coli, Gonorrhoea, Candida**
    - Environmental Irritation
    - Physical Trauma
  - **Risk Factors:**
    - Phimosis
    - Underwashing of Underneath Foreskin
    - Overwashing of Underneath Foreskin
    - Poorly-Controlled Diabetes (Candida)
- **Morphology:**
  - Redness of Glans (Balanitis & Balanoposthitis)
  - Redness of Glans & Prepuce (Balanoposthitis)
- **Clinical Features:**
  - **Symptoms:**
    - 1. Small, Red Erosions on the Glans
    - 2. Redness of Glans (Balanitis & Balanoposthitis)
    - 3. Redness of Glans & Prepuce (Balanoposthitis)
    - 4. Pain
  - **Complications:**
    - May → Phimosis (Scarring of Preputial Ring)
- **Management:**
  - **Antibiotics**
  - **↑Self-Hygeine**

Balanitis



Balanoposthitis

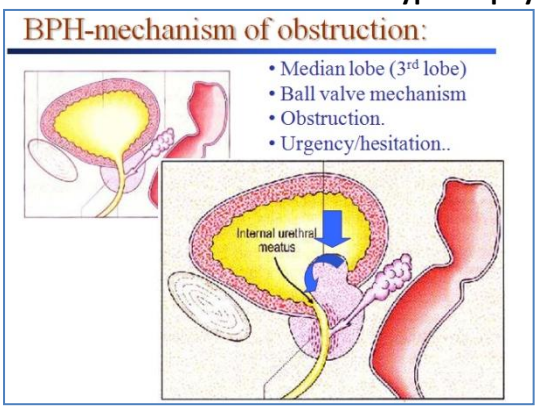
MENS HEALTH Pathology:
BENIGN PROSTATIC HYPERTROPHY

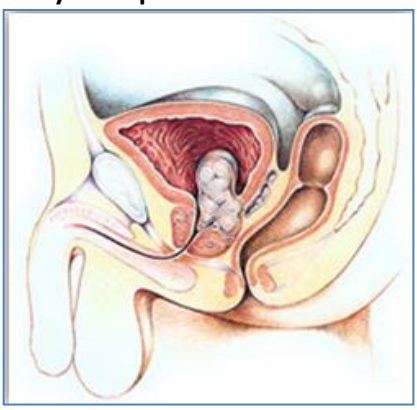
Prostate Diseases:

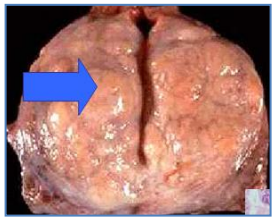
- **Typical Locations of Prostate Disease:**

Enlargement:	Disease:	Aetiology:	Morphology:	Clinical:
Diffuse (All Lobes)	Prostatitis	Infective (Inflammation)	Red, Oedematous & Inflamed	Rectal Pain, Dysuria, Obstructive Uropathy
Median Lobe (:. Obstructs Urine)	BPH	Hormone-Mediated Hyperplasia	Smooth, Firm & Nodular Hyperplasia. Median Groove is Preserved.	Urinary Voiding Symptoms (Nocturia, Urgency, Hesitancy, Dribbling, Incomplete voiding). PSA Usually Normal.
***Lateral/Posterior* Lobe** (:. No Urine Obstruct)	Prostate Ca.	Neoplasia	Adenocarcinoma. Hard, Stony, Irregular, Fixed Masse/s. Loss of Median Groove.	Usually Asymptomatic. No Urinary Voiding Syx. Late → Osteoblastic Lesions, Weight Loss, Metastatic Complications. Elevated PSA.

- **BPH – (BENIGN PROSTATIC HYPERTROPHY):**
  - **Aetiology:**
    - **Non-Neoplastic Hormone-Induced Hyperplasia**
    - **Old Age – (**75% among men aged 70-80years**)**
  - **Pathogenesis:**
    - **Hormone-Induced (Androgen) Hyperplasia (NB: Castration → no BPH):**
  - **Morphology:**
    - **Smooth, Firm & Nodular Hyperplasia.**
      - Median Groove is Preserved.
      - Encroaches Into Bladder → ***Ball-Valve Mechanism*** → **Urinary Retention**
    - **Bladder Wall Hypertrophy & Hydronephrosis**



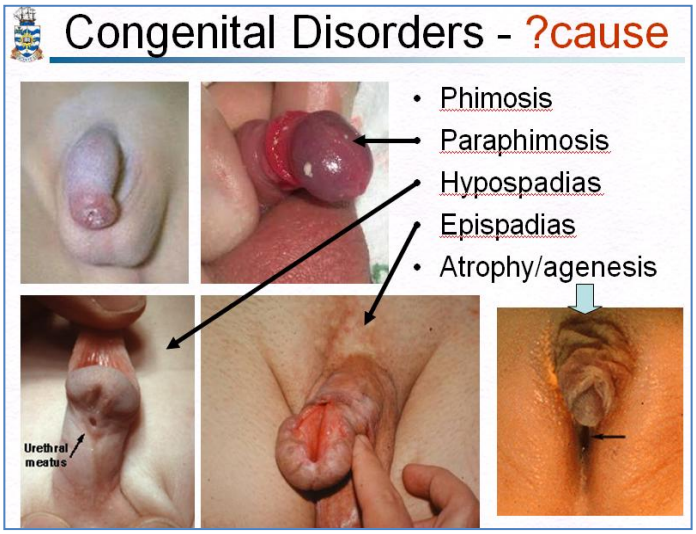




  - **Clinical Features:**
    - **Lower Urinary Obstruction Symptoms – (***Urgency, Frequency, Dribbling, Nocturia, ↓Flow***)**
  - **Treatment:**
    - ***Finasteride*** **(5-α-Reduct. Inhibitor)**
    - **Surgery (*TURP*)** = Trans-Urethral Resection of the Prostate **(NB: Can → Impotence)**
  - **Complications:**
    - **UTI** → Cystitis → Inflammation.
    - **Bladder Diverticuli** → (May even rupture → Uroperitoneum).

SPECIFIC PAEDIATRICS NOTES:
CONGENITAL PENILE ABNORMALITIES

- **Phimosis:**
  - **What?**
    - Foreskin is ***Too Tight*** retract over Glans.
  - **Why?**
    - Congenital
    - Or Repeated Infection → Fibrosis/Scarring of Preputial Ring.
  - **Outcome?**
    - Phimosis Interferes with Cleanliness → Secondary Infections and Carcinoma
- **Paraphimosis:**
  - **What?**
    - Foreskin becomes trapped behind the Glans Penis & Cannot be Pulled Back.
  - **Why?**
    - Congenital Phimosis
    - Or Foreskin is Retracted for Too Long → Oedematous → Difficult Reduction
  - **Outcome?**
    - Can → Ischaemia of Glans Penis → Gangrene → Loss of Penis
    - (:. Medical Emergency)
- **Hypospadias & Epispadias:**
  - **What?**
    - Malformation of Urethral Groove/Canal/Opening – Either on Ventral Surface (*Hypospadias – Most Common*) or on the Dorsal Surface (*Epispadias*)
  - **Why?**
    - Congenital
    - (NB: Statistically associated with Cryptorchidism)
  - **Outcome?**
    - Can → Urinary Obstruction → ↑Risk of UTI +/- Ascending.
    - Also → Abnormal Ejaculation and Insemination.
- **Penile Atrophy/Agenesis:**
  - **What?**
    - Male born without a Penis
  - **Why?**
    - Congenital (1/6000000)
    - Often Secondary to *Testicular Agenesis* → No Testosterone → No Male Organs
  - **Outcome?**
    - Absence of Urinary Outlet → Requires Surgical Redirection of Urethra
    - If Testicles are Present → Normal Male Appearance
    - If Testicles are Absent → Maintained Pre-Pubescent Appearance



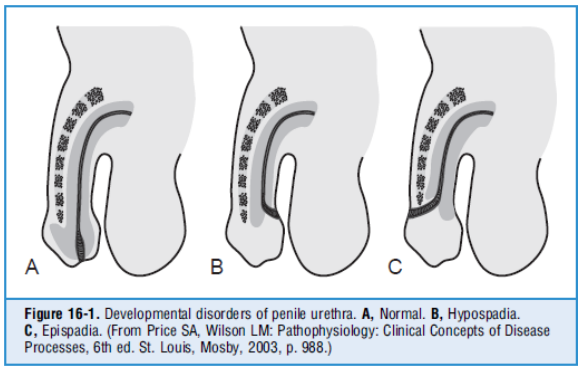
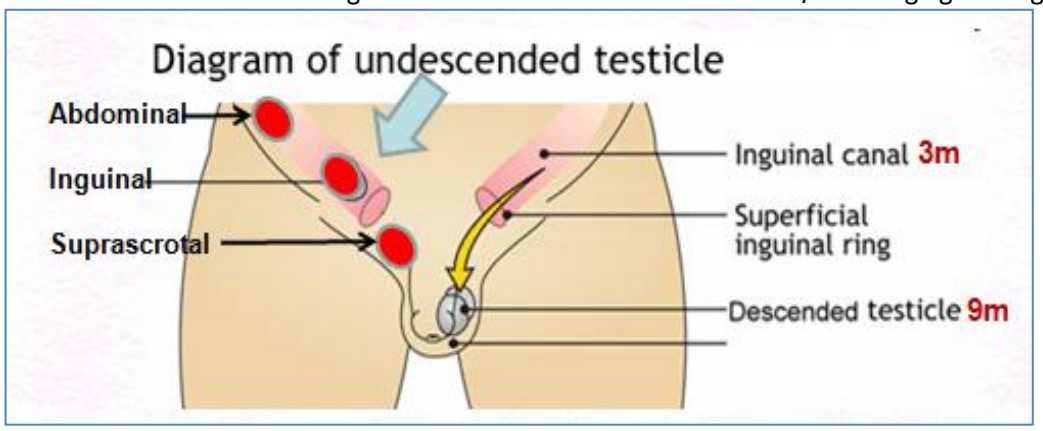


Figure 16-1. Developmental disorders of penile urethra. **A,** Normal. **B,** Hypospadia. **C,** Epispadia. (From Price SA, Wilson LM: Pathophysiology: Clinical Concepts of Disease Processes, 6th ed. St. Louis, Mosby, 2003, p. 988.)

SPECIFIC PAEDIATRICS NOTES:
CRYPTORCHIDISM

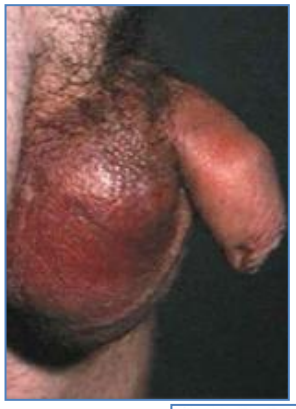
- **Cryptorchidism:**
  - **Aetiology:**
    - Unknown
  - **Pathogenesis:**
    - Failure of the Intra-Abdominal Testes to descend into scrotal sac
  - **Clinical Features:**
    - Testicle is undescended (Absent from the scrotum)
      - NB: 90% are palpable in inguinal canal
    - Usually unilateral
    - **Completely Asymptomatic* – Always incidental discovery.
    - Most Inguinal Testes descend spontaneously by 1yr, & those that remain require surgical correction before histological deterioration sets in at 2yrs
    - **Complications:**
      - GREATLY INCREASED RISK OF TESTICULAR CANCER (3-5x)
      - May → Sterility
      - Testes in Inguinal Canal are Vulnerable to Trauma/Crushing against ligaments.

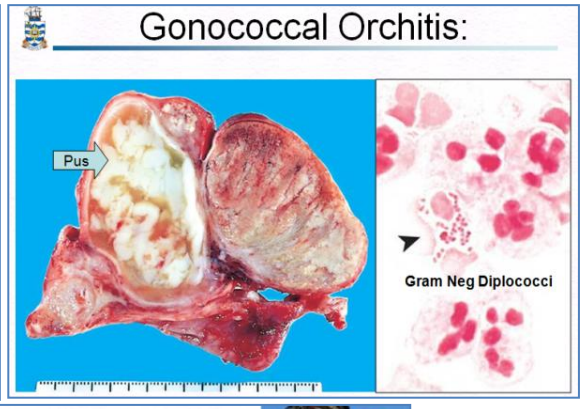


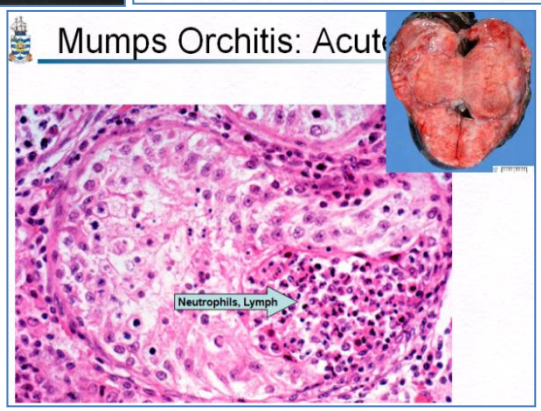
MENS HEALTH Pathology:
EPIDIDYMO-ORCHITIS

EPIDIDYMO-ORCHITIS:

- **Aetiology:**
  - ***Non-Gonnoccal** (*Chlamydia*) – (Most Common ~50%)
  - **Gonococcal** (*Neisseria gonorrhoeae*)
  - (Children – *Mumps*)
- **Pathogenesis:**
  - Infection of the Epididymus & Testis (Via Urethra or Haematogenous) → Inflammation of Epididymus & Testis → Pain + Infective Symptoms
- **Morphology:**
  - **Macro:**
    - Swollen, hot, acute inflammation, oedema
  - **Micro:**
    - Just Oedema, & neutrophilic inflammation + some necrosis
- **Clinical Features:**
  - **Symptoms:**
    - Gradual Onset SEVERE Testicular Pain – Unilateral +/- Radiation to Inguinal Area
    - Erythema/Oedeam of the scrotum
    - Urethritis, Dysuria, & Discharge
    - Fever, Urethritis, Dysuria
- **Diagnosis:**
  - **Doppler Ultrasound** - Exclude torsion/trauma
  - **FBC** – Infection?
  - **Microbiology** - MCS, Elisa, PCR, etc
- **Treatment:**
  - **Antibiotics**
  - **Analgesia**



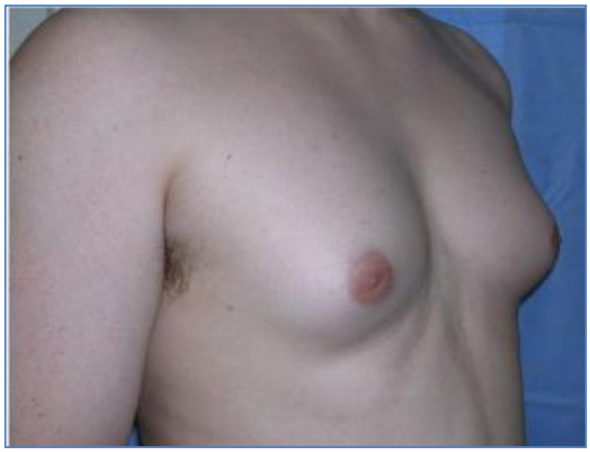




MENS HEALTH Pathology:
GYNECOMASTIA

GYNECOMASTIA:

- **Aetiology:**
  - Imbalance of Oestrogens (Breast Stimulants) & Androgens (Breast Retardants)
    - Puberty
    - Old Age
    - Hepatic Cirrhosis, Alcohol,
    - Testicular Atrophy, Testicular Cancer
    - Anabolic Steroids,
    - Klinefelter's XXY Syndrome,
    - Hyperthyroidism,
    - Anti-Testosterone Treatment for Prostate Ca.
- **Pathogenesis:**
  - Imbalance of Oestrogens (Breast Stimulants) & Androgens (Breast Retardants) → Hypertrophy of Rudimentary Breast Tissue in Male Breast
- **Morphology:**
  - **Macro:**
    - Adolescent-Female-Like Breasts
  - **Micro:**
    - Duct (Epithelial) & Stromal (Fibrous) Hyperplasia
    - NB: NO acini
- **Clinical Features:**
  - Breast enlargement in men.
- **Management:**
  - **Anti-Oestrogens**
  - **Breast Reduction Surgery**



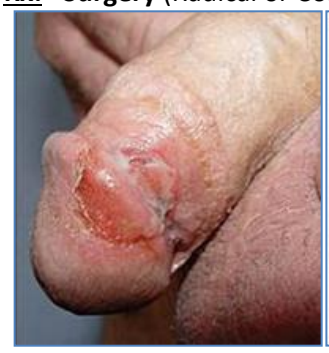
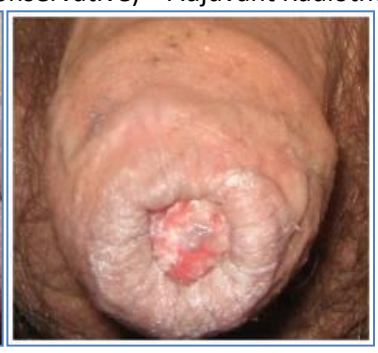
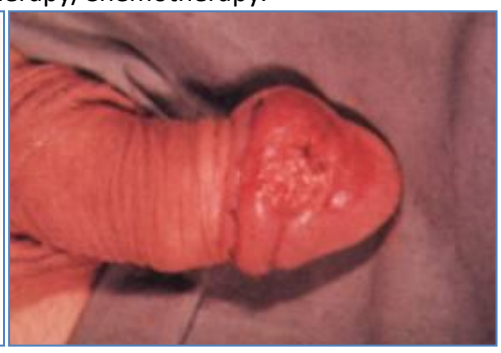
MENS HEALTH Pathology:
PENILE DYSPLASIA & CANCER

DYSPLASIAS OF THE PENIS:

- **Erythroplasia of Queyrat:**
  - = Dysplasia on the Glans Penis
- **Bowen's Dysplasia:**
  - = Dysplasia on the Shaft of the Penis
- **Aetiology:**
  - HPV Types 16 & 18 – The Cancer Ones! (Cf. 6/11 – Genital Warts, & 18/45 – Cervical Ca.)
- **Pathogenesis:**
  - Virus-Induced DNA damage → Dysplasia
- **Morphology:**
  - Red patch
  - Indurated on Palpation
- **Clinical Features:**
  - Asymptomatic
  - Chronic - present for long time.
  - **Complications:**
    - Dysplasia is Premalignant → Can → Squamous Cell Carcinoma.


CARCINOMA OF THE PENIS:

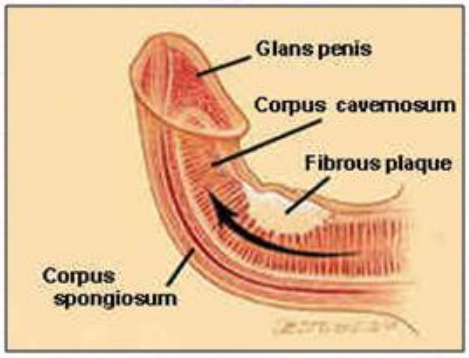
- **Aetiology:**
  - HPV Types 16 & 18 – The Cancer Ones!
  - Risk Factors – Phimosis, Poor Hygeine
  - (NB: Some evidence to suggest Circumcision is Preventative)
- **Pathogenesis:**
  - Virus-Induced DNA damage → Dysplasia →
    - → Erythroplasia or Leukoplasia
      - → Carcinogenesis
- **Morphology:**
  - **Macro:**
    - Malignant Ulceration
  - **Micro:**
    - Well-Differentiated Squamous Cell Ca.
    - Epithelial pearls
- **Clinical Features:**
  - **Syx:** Redness, Irritation, Ulceration
  - **Complications:** Spreads to Inguinal & Iliac Lymph Nodes First → Metastasis
- **Rx:** ***Surgery** (Radical or Conservative) + Adjuvant Radiotherapy/Chemotherapy.

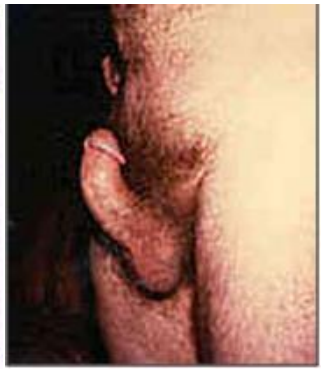




MENS HEALTH Pathology:
PEYRONIE'S DISEASE

PEYRONIE'S DISEASE:

- **Aetiology:**
  - Unknown
  - NB: 25% Association with Dupuytren's Contracture
- **Pathogenesis:**
  - Focal Fibrosis & Contraction of the Tunica Albuginea → Bent Penis
- **Morphology:**
  - **Macro:**
    - Bent Penis
- **Clinical Features:**
  - Bent Penis
  - Painful Erection
  - Recurs after surgical removal

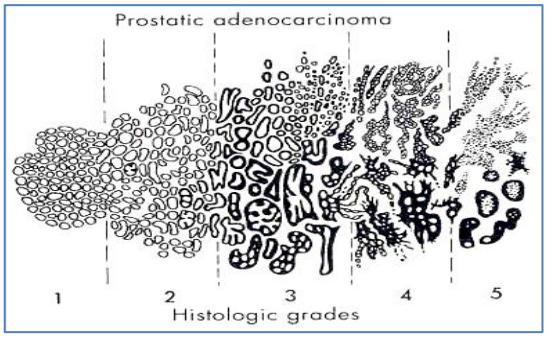




MENS HEALTH Pathology:
PROSTATE CANCER

PROSTATE ADENOCARCINOMA:

- (Most common cancer in elderly males. Rare before 50yrs, but seen in >70% of men over 70yrs)
- **Aetiology:**
  - Aetiology unknown - Hormones, genes & environment most likely.
  - (***NOT*** BPH)
- **Pathogenesis:**
  - Initially PIN (Prostatic Intraepithelial Neoplasia) – *Multilayered* – Not yet cancer
  - Then Adenocarcinoma – *Single-Layered* - Cancer
- **Morphology:**
  - *Lateral/Posterior Lobe* (:. No Urine Obstruct)
  - Hard, Stony, Irregular, Fixed Masse/s.
  - Loss of Median Groove.
- **Clinical Features:**
  - **Symptoms:**
    - Usually Asymptomatic.
    - Urinary Voiding Syx.
    - Late → Weight Loss, Metastatic Complications.
- **Diagnosis:**
  - **Elevated PSA = *BAD*: Poor Sensitivity, Poor Specificty.**
    - 4.0ng/L = Upper Limit of Normal
    - Elevated in: Prostate Damage, Malignancy, Post Ejeculation, Post DRE, Non-Pathology
  - **Positive Biopsy = Reasonable: Poor Sensitivity, High Specificity**
  - **DRE = Reasonable: Reasonable Sensitivity, Reasonable Specificity**
    - Normally = soft, rubbery, with a median groove.
    - Malignancy = hard, gritty, fixed tumor + Loss of median groove.
  - **Imaging (US/CT/MRI) = Good: Good Sensitivity if Macroscopic, Good Specificity**
- **Grading - Gleason Scale (1-5):**



- **Treatment:**
  - **Watch & Wait** (If elderly with multiple comorbidities)
  - **Surgical** (Radical/Partial Prostatectomy) NB: → Impotence & Incontinence.
  - **Radiotherapy** (External Beam, or Brachy)
  - **Chemotherapy** (Hormonal – Antitestosterone Drugs)
  - **Palliative Chemo + Analgesia** (If advanced/metastatic)
- **Prevention:**
  - **Screen 2yrly for 50^{+}yrs**
  - **Screening Procedures – (**Digital Rectal Exam (DRE), PSA**)**.

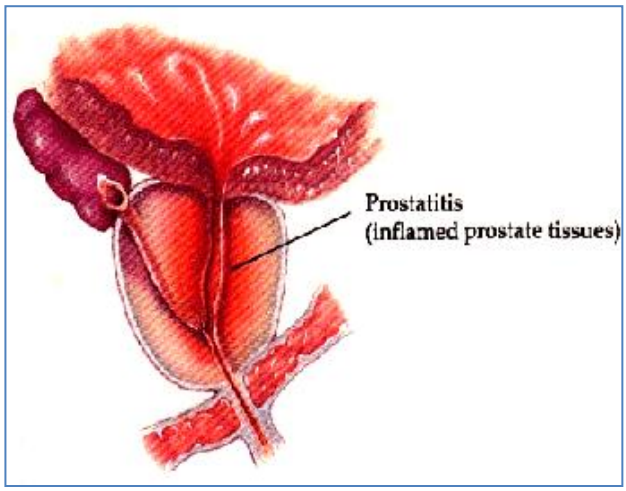
MENS HEALTH Pathology:
PROSTATITIS

Prostate Diseases:

- **Typical Locations of Prostate Disease:**

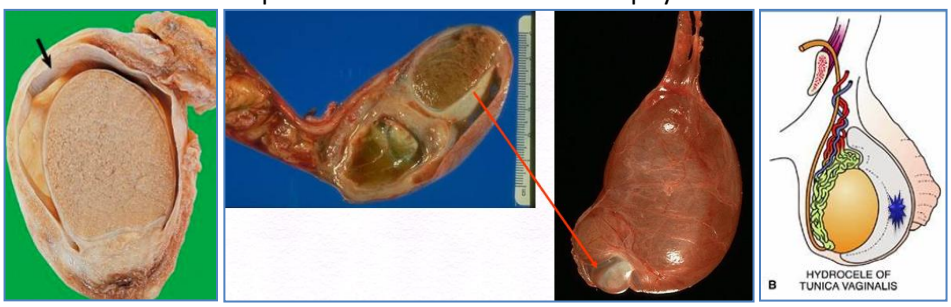
Enlargement:	Disease:	Aetiology:	Morphology:	Clinical:
Diffuse (All Lobes)	Prostatitis	Infective (Inflammation)	Red, Oedematous & Inflamed	Rectal Pain, Dysuria, Obstructive Uropathy
Median Lobe (:. Obstructs Urine)	BPH	Hormone-Mediated Hyperplasia	Smooth, Firm & Nodular Hyperplasia. Median Groove is Preserved.	Urinary Voiding Symptoms (Nocturia, Urgency, Hesitancy, Dribbling, Incomplete voiding). PSA Usually Normal.
***Lateral/Posterior* Lobe** (:. No Urine Obstruct)	Prostate Ca.	Neoplasia	Adenocarcinoma. Hard, Stony, Irregular, Fixed Masse/s. Loss of Median Groove.	Usually Asymptomatic. No Urinary Voiding Syx. Late → Osteoblastic Lesions, Weight Loss, Metastatic Complications. Elevated PSA.

- **PROSTATITIS:**
  - **Aetiology:**
    - Infective – Bacterial
  - **Pathogenesis:**
    - **Acute suppurative prostatitis:**
      - E.coli, rarely Staph or N. gonorrhoeae
    - **Chronic non-specific prostatitis:**
      - Recurrent acute → fibrosis, lymph + plasma.
    - **Granulomatous prostatitis-**
      - BPH, infarction, post TURP, idiopathic, TB, or allergic(eosinophilic).
  - **Clinical Feature:**
    - Similar to BPH – (Urinary Obstruction/Dysuria/Frequency/etc)
    - + Rectal Pain
    - + Fever, Malaise
  - **Management:**
    - Antibiotics

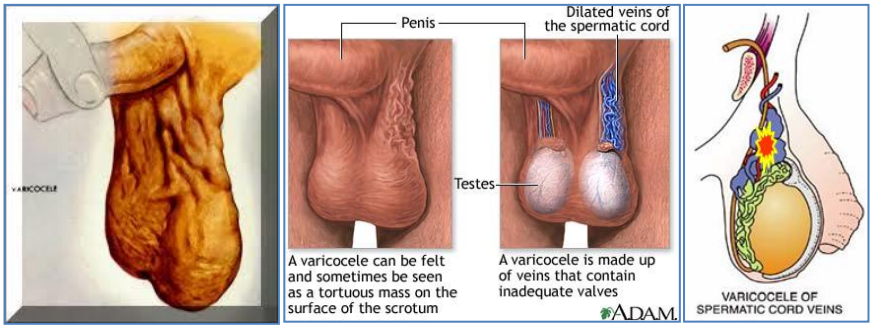


MENS HEALTH Pathology:
SCROTAL ACCUMULATIONS

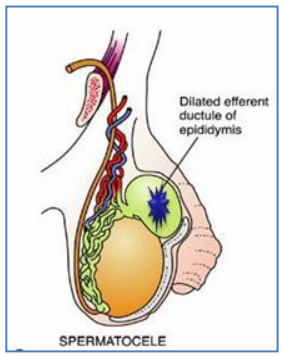
- **Fluid Accumulations – 4 types:**
  - **Hydrocoele:**
    - **What?** – Clear Serous Fluid accumulation in Tunica Vaginalis (Surrounding Testis)
    - **Why?** – Congenital (Incomplete Obliteration of Processus Vaginalis); or 2^{o} to Infection.
    - **Outcome?** – Displaced Testes & Testicular Atrophy if Untreated.



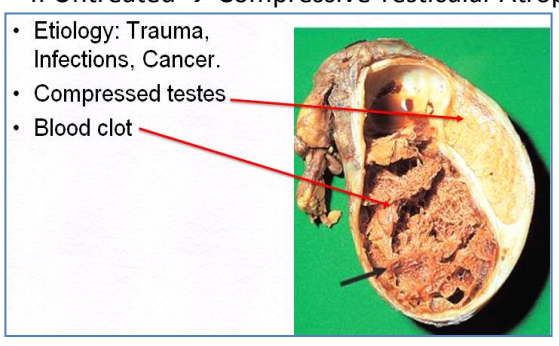
  - **Varicocoele**
    - **What?** – Engorged spermatic cord veins (Pampiniform plexus)
    - **Why?** – Incompetent Valves in Pampiniform Plexus → Varicosity
    - **Outcome?** – Common cause of infertility/oligospermia



  - **Spermatocoele**
    - **What?** – Sperm-Filled Cyst on the Head of the Epididymis
    - **Why?** – Epididymis dilatation due to Trauma/Infection
    - **Outcome?** – Treatment not necessary unless Large or Pt. Discomfort. NB: Surgery may lead to Infertility in that Testicle.



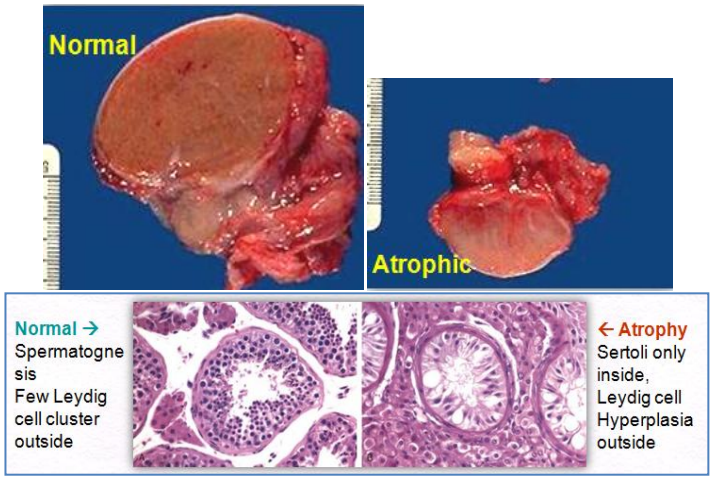
  - **Haematocoele**
    - **What?** – Blood in the tunica vaginalis
    - **Why?** – Any trauma/tumours→ Bleeding
    - **Outcome?** – If Untreated → Compressive Testicular Atrophy



MENS HEALTH Pathology:
TESTICULAR ATROPHY

Testes Atrophy:

- **Aetiology:**
  - Hypopituitarism
  - Chronic Alcoholism
  - Chronic Liver Disease
  - Chemotherapy/Radiation
  - Chronic Anabolic Steroid Use.
- **Pathogenesis:**
  - No Spermatogenesis, Atrophy of Sertoli Cells, & Leydig Cell Hyperplasia
- **Morphology:**
  - Shrunken Testicle
- **Clinical Features:**
  - **Complications:**
    - High risk of Testicular Cancer



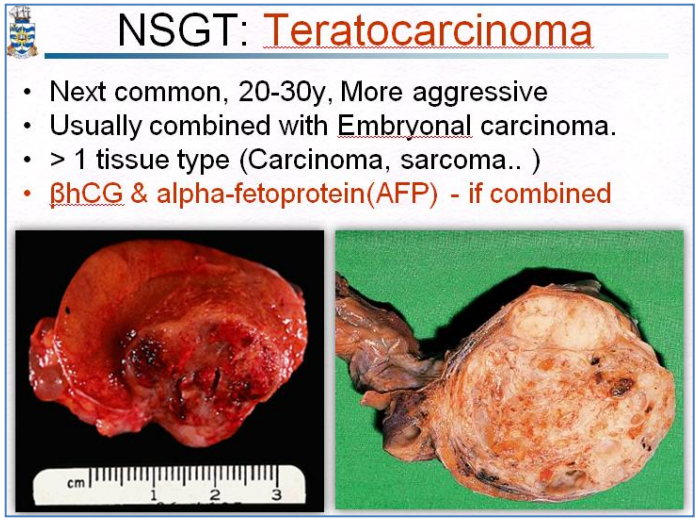
MENS HEALTH Pathology:
TESTICULAR TUMOURS

Tumours of the Testis:

- **95% Germ Cell Tumours:**
  - **Aetiology:**
    - Idiopathic/Undescended Testes/Oestrogens
  - **Common Clinical Features:**
    - **Symptoms:**
      - *Painless* Enlargement – (Typically Unilateral)
      - May → Hydrocoele
    - **Complications:**
      - Metastasis → Retroperitoneal Masses
      - Gynaecomastia

  - ***Seminoma* - 40% - (Adults):**
    - **Pathogenesis:**
      - Malignant Transformation of Germ Cells (Spermatogonia)
    - **Pertinent Clinical Features:**
      - **Epi:** Commonest in 30-50yrs
    - **Dx:** No serological Tumour Markers for Seminoma
    - **Rx:** Surgery, Radiation, Chemotherapy
    - **Prog:**
      - Behaves like a benign tumour grossly, but is Malignant.
      - Malignant, but Highly Responsive to Treatment
      - Great Prognosis – 40-50yrs
      - 90% Cure Rate

  - ***Non-Seminoma Germ-cell Tumours (NSGT) - Embryonal Carcinoma* - 25% - (Children):**
    - **Pathogenesis:**
      - Malignant Transformation of Yolk-Sac Cells
    - **Pertinent Clinical Features:**
      - **Epi:** Children <4yrs
    - **Dx:** Elevated AFP (Alpha-Fetoprotein) & hCG Tumour Markers
    - **Rx:** Surgery + Chemotherapy
    - **Prog:**
      - Highly Malignant
      - Metastasis Common
      - Poor Response to Treatment (Cf. Seminoma)

  - **NB: Teratocarcinoma - multiple types of tissue**
    - 

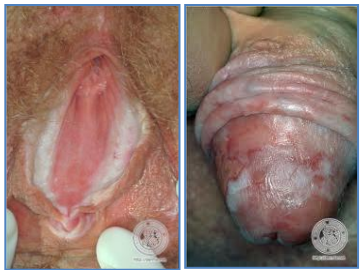
MENS HEALTH Pathology:
TORSION OF THE TESTIS

- **Torsion of the Testis:**
  - **Aetiology:**
    - 90% - Congenital Free-Floating Testis – ("Bell Clapper Deformity")
    - Precipitated by exertion, contraction of the cremaster muscle, or at rest.
  - **Pathogenesis:**
    - Twisting of spermatic cord on its axis → Obstructs Venous Outflow → Ischaemia → Gangrenous & Haemorrhagic Necrosis of testis → Dark, blackish discoloration
  - **Morphology:**
    - **Macro:**
      - Dark, blackish discoloration of Testis
    - **Micro:**
      - Haemorrhagic Necrosis
  - **Clinical Features:**
    - Typically in either <1yrs or in Teenagers.
    - **Symptoms:**
      - Acute Onset Extreme Unilateral Testicular Pain (Relieved upon Passive Elevation)
      - Swollen, Hard, Retracted Testis.
  - **Diagnosis:**
    - Doppler Ultrasound (No Blood flow)
    - Absent Cremasteric Reflex
    - Positive Sign = Elevation of scrotum relieves pain
  - **Complications:**
    - Loss of Testicle
  - **Treatment:**
    - **Surgical Emergency <6hrs** (NB: <12hrs → 50% chance of Saving the Testis)
    - **Manual Detorsion with Analgesia**
    - **Orchidectomy of Dead Testicle** to prevent Gangrenous Infection

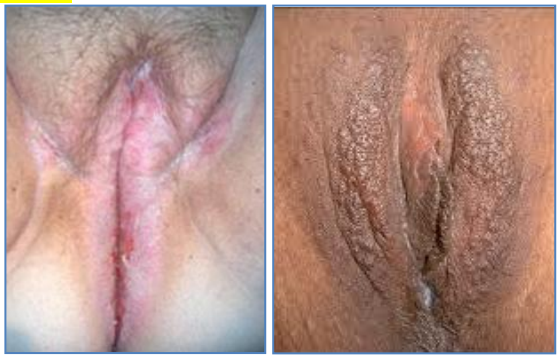
UNISEX UROGENITAL Pathology:
DIFFERENTIALS FOR MALIGNANCY

2 Differentials for Malignancy:

- **LICHEN SCLEROSUS:**
  - **Pathogenesis:**
    - Autoimmune → Atrophy
  - **Morphology:**
    - **Macro:**
      - White Patches on Skin
      - Scarring on/around Genital Skin.
  - **Clinical Features:**
    - (Typically Peri-Menopausal Women)
    - Typically Affects Vulva & Perineum
    - Glistening Ivory-White Plaques
    - May be Itchy
    - Thinning, Shrinkage & Traction of Genital Area → Dyspareunia, Dysuria, Dyschezia.
  - **Treatment:**
    - ***Potent Topical Steroids*** (2-3mths)
    - ***+/- Cryotherapy***
  - **Prognosis:**
    - Higher Risk of Cancer



- **LICHEN SIMPLEX CHRONICUS (NEURODERMATITIS):**
  - **Aetiology:**
    - Chronic Infection
  - **Pathogenesis:**
    - Chronic Infection → Chronic Pruritis → Constant Scratching → Hyperkeratosis (Hypertrophy), aka. Acanthosis.
  - **Morphology:**
    - Thick, Leathery, Brownish Skin
  - **Clinical Features:**
    - Chronic Pruritis
    - Thick, Leathery, Brownish Skin
  - **Treatment:**
    - Itch Relief
    - **Topical Steroids**



Infectious Disease Notes

Bloodborne Viral Diseases. HIV And The Immunocompromised Host

Weekly Overview:

- **Human Retroviruses:**
  - HIV (Human Immunodeficiency Virus)
  - HTLV (Human T-Cell Lymphotropic Viruses)
- **Other Blood-Borne Viruses:**
  - Human Herpes Viruses:
    - EBV (Epstein-Barr Virus)-(Infectious Mononucleosis)
    - Cytomegalovirus
    - HHV-6 (Human Herpesvirus 6)
    - HHV-7 (Human Herpesvirus 7)
    - HHV-8 (Human Herpesvirus 8)
  - TT Virus

- **Mims 2nd Ed**
  - HIV pp 242-250
  - HTLV1 &2 pp339-340
  - EBV pp349-351
  - CMV pp347-348
  - Kaposi's Sarcoma p248

Bloodborne viruses, HIV and the Immunocompromised Host

Human Retroviruses:

(ie. Those which have reverse transcriptase)

- **HIV-1 (Human Immunodeficiency Virus 1):**
  - Responsible for AIDS
- **HIV-2 (Human Immunodeficiency Virus 2):**
  - Less common
- **HTLV-1 (Human T-Cell Lymphotropic Virus 1):**
  - Can cause T-Cell leukaemia
- **HTLV-2 (Human T-Cell Lymphotropic Virus 2):**
  - Less common
- **Human Foamy Virus:**
- **Human Placental Virus/es**
- **Human Genome Viruses**

HUMAN RETROVIRUSES	
virus	**comment**
HTLV1	endemic in West Indies and SW Japan; transmission via blood, human milk; can cause adult T cell leukemia, and HTLV1-associated myelopathy, also known as tropical spastic paraparesis
HTLV2	uncommon, sporadic occurrence; transmission via blood; can cause hairy T cell leukemia and neurological disease
HIV-1, HIV-2	transmission via blood, sexual intercourse; responsible for AIDS, HIV-2 West African in origin, closely related to HIV-1 but antigenically distinct
human foamy virus	causes foamy vacuolation in infected cells; little is known of its occurrence or pathogenic potential
human placental virus(es)	detected in placental tissue by electron microscopy and by presence of reverse transcriptase
human genome viruses	nucleic acid sequences representing endogenous retroviruses are common in the vertebrate genome, often in well-defined genetic loci; acquired during evolutionary history; not expressed as infectious virus; function unknown; perhaps should be regarded as mere parasitic DNA

HUMAN RETROVIRUSES:
HIV – (HUMAN IMMUNODEFICIENCY VIRUS):

The Origins of HIV:

- **HIV-l and HIV-2 have sequence homology with corresponding viruses in African primates:**
  - :. It is Likely that HIV originated in African Primates → Crossed over to Humans.
- **Possibility of Further Transmissions:**
  - The original virus still exists in African Primates (& Is *STILL EVOLVING*)
  - :. Further transmission of similar viruses to Humans is Very Possible.
  - (If it has done it once, it will do it again)

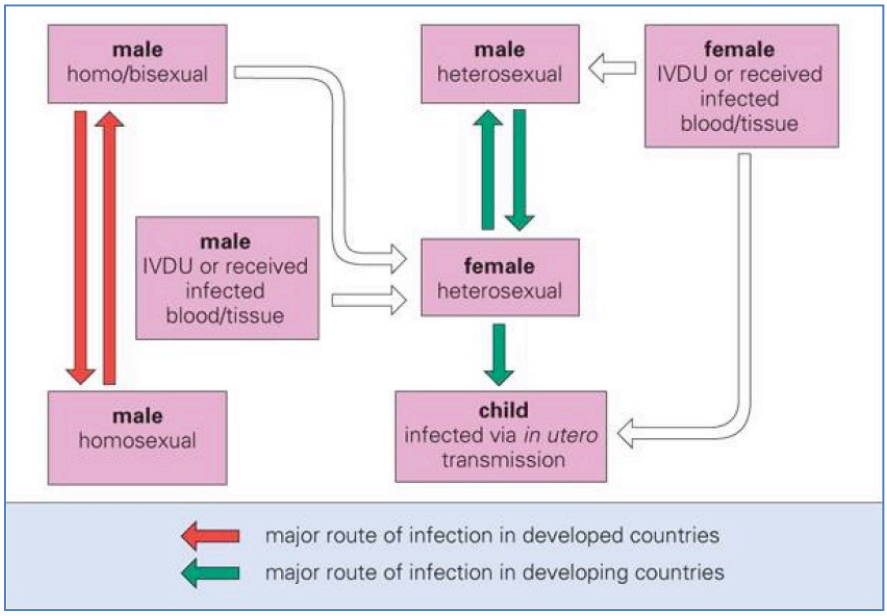
Epidemiology of HIV:

- **Sub-Saharan = Most Affected:**
  - 2/3 of all HIV cases
  - (24.7 million people in 2006.)
  - **75%** of all AIDS-Related Deaths occurred in sub-Saharan Africa
- **Developing Countries:**
  - High Prevalence
- **Developed Countries:**
  - Low Prevalence – (But Incidence is Increasing)
- **(HIV-2):**
  - Less virulent infection
  - Perinatal transmission is less common
  - Most common in West Africa

Transmission:

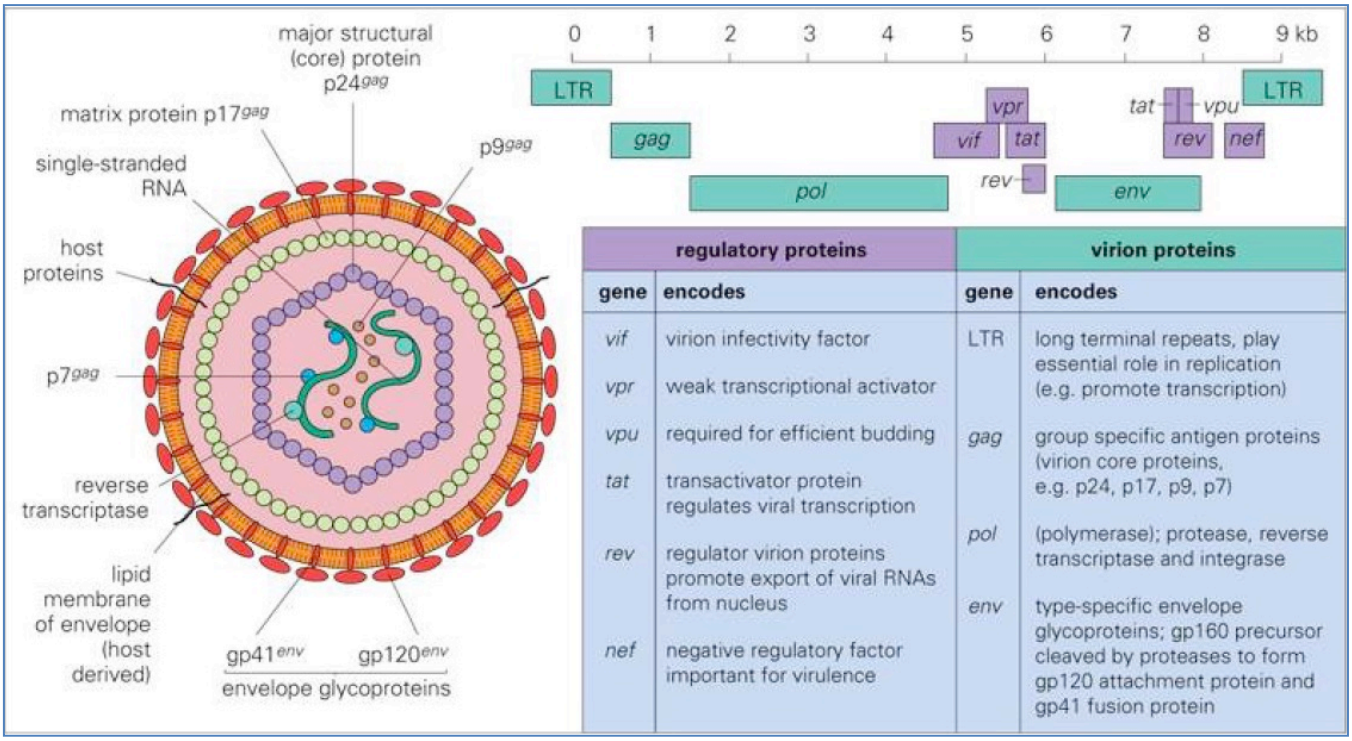
- **Sexual Transmission:**
  - 75% of transmission worldwide
  - **Risk Factors that Increase Chance of Sexual Transmission:**
    - **Trauma/Inflammation** - (The Virus must attach to CD4 receptors; Therefore presence of inflammatory cells @ Site of Inoculation vastly increases risk of transmission)
    - **Sexually Transmitted Diseases** (Eg. Gonorrhea, Chlamydia, trichomoniasis or vaginosis) – Because they lead to Inflammation in the Genital Region.
    - **Higher risk with Anal Sex rather than Vaginal or Oral Sex:**
      - Vagina is Stratified Squamous (Greater Barrier Protection)
      - Rectum is Simple Columnar (Less Barrier) + Anal Sex commonly causes bleeding.
  - **Developing Countries:**
    - Males→Females Transmission (heterosexual transmission)
    - Vertical Mother→Child transmission.
    - IV Drug use
    - Blood Transfusion
  - **Developed Countries:**
    - Male→Male Transmission (Homosexuality)
    - IV Drug use
- **Parenteral Transmission (Blood Transfusion/IV-Needle Sharing):**
  - Depends on Titre in the Blood & the Amount of Blood Transferred. (Determines the number of Infectious Doses Contained)
- **Perinatal:**
  - Transplacental infection is becoming one of the most important routes of transmission
  - Breastmilk.

- ***NB: Transmission is Surprisingly Difficult*:**
  - Risk of Percutaneous Exposure is ≈ 0.3%
  - Risk of Mucous Membranous Exposure ≈ 0.09%
  - **Factors =** *Amount of Blood & Titre of Virus*.



Structure of the HIV Virion & Contents:

- **Dicosahedral capsid**
- **2x *Separate Strands* of ssRNA**
- **Envelope with Glycoproteins (Incl. Gp120** – important for adhesion & entry to CD4 T-Cells)
- **Contains Reverse Transcriptase Enzymes:**
  - Necessary for Reverse Transcription of ssRNA genome into DNA to Integrate into host Genome.
- Gag ,Pol, Env – Open Reading Frames in Genome



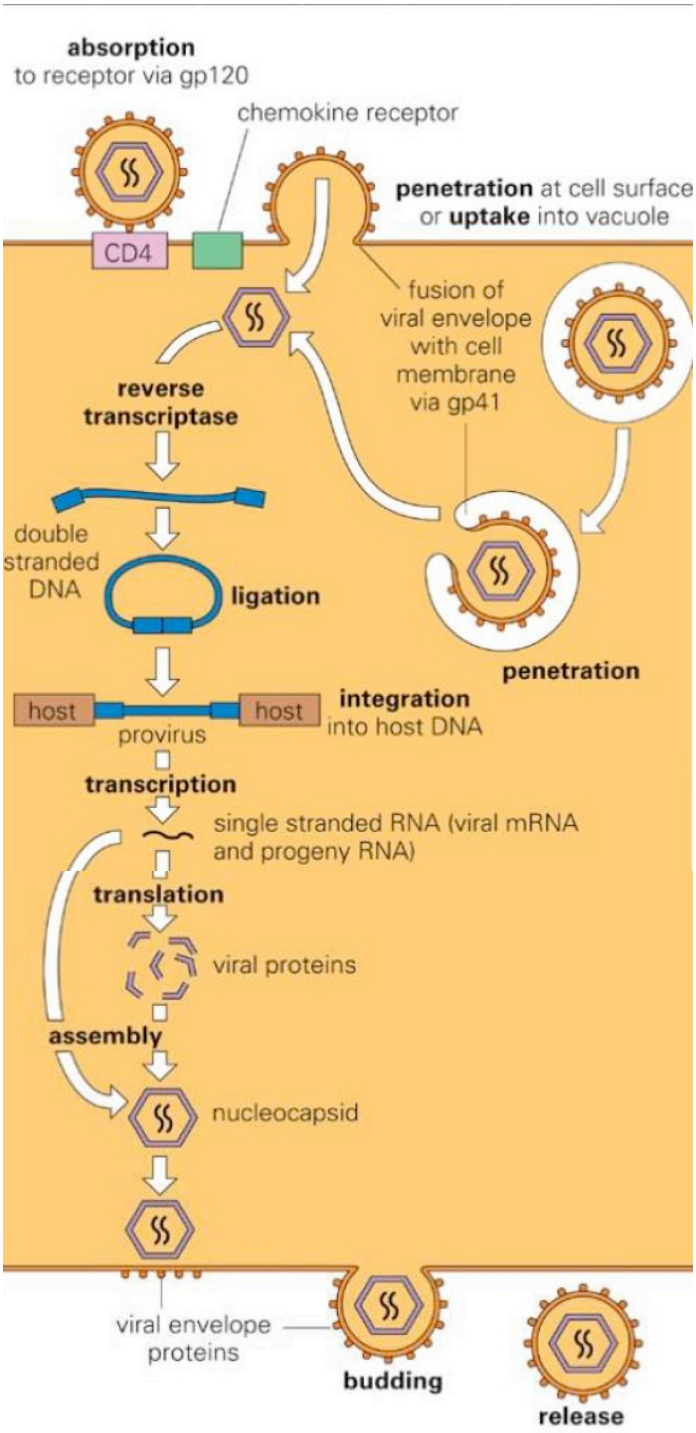
regulatory proteins		virion proteins	
gene	**encodes**	**gene**	**encodes**
vif	virion infectivity factor	LTR	long terminal repeats, play essential role in replication (e.g. promote transcription)
vpr	weak transcriptional activator		
vpu	required for efficient budding	*gag*	group specific antigen proteins (virion core proteins, e.g. p24, p17, p9, p7)
tat	transactivator protein regulates viral transcription		
rev	regulator virion proteins promote export of viral RNAs from nucleus	*pol*	(polymerase); protease, reverse transcriptase and integrase
		env	type-specific envelope glycoproteins; gp160 precursor cleaved by proteases to form gp120 attachment protein and gp41 fusion protein
nef	negative regulatory factor important for virulence		

Reverse Transcriptase Enzyme:

- **Necessary for DNA Production from the Positive-ssRNA in the Virus.**
  - Reverse Transcription of Positive-ssRNA genome into DNA to Integrate into host Genome.
    - → Produces ssDNA from ssRNA
    - Then →Produces dsDNA from ssDNA
- **NB: *Highly Error-Prone* → High Mutation Rate → Production of *QUASISPECIES*:**
  - Quasispecies = Mutant/Recombinant Viral Genomes
  - Quasispecies are constantly subject to Genetic Variation, Competition & Selection.
  - → Assists virus to persist in the host. (Overwhelms the Immune Response)

Process of HIV Infection (@ The Cellular Level):

- **GP120** on Virus Binds to CD4 Receptors
- **Fusion of Viral Envelope** with Cell Membrane → Uptake into cell.
- **Reverse Transcriptase:**
  - → Produces ssDNA from ssRNA
  - Then →Produces dsDNA from ssDNA
- **dsDNA→ Migrates to the Nucleus → Integrates into Host Genome**:
  - :. HIV Uses host DNA-Replication for Reproduction.
  - Is Transparent to the Immune System.
  - Virus replicates with DNA Replication or Cellular Protein Synthesis.
  - Can also be *transported* by migrating cells into other areas of the body – eg. Crossing the BBB.
- **Genes Transcribed & Translated** → Viral proteins
- **Assembly**
- **Budding** → Released

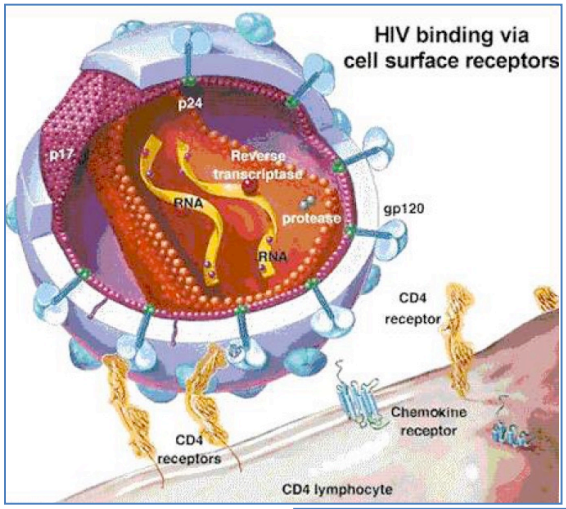


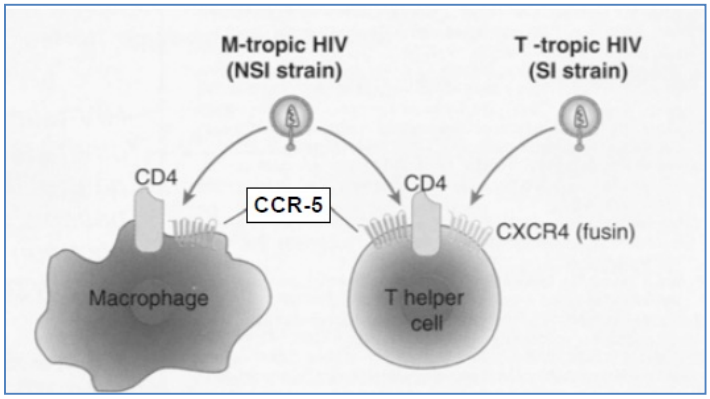
Susceptible Cells

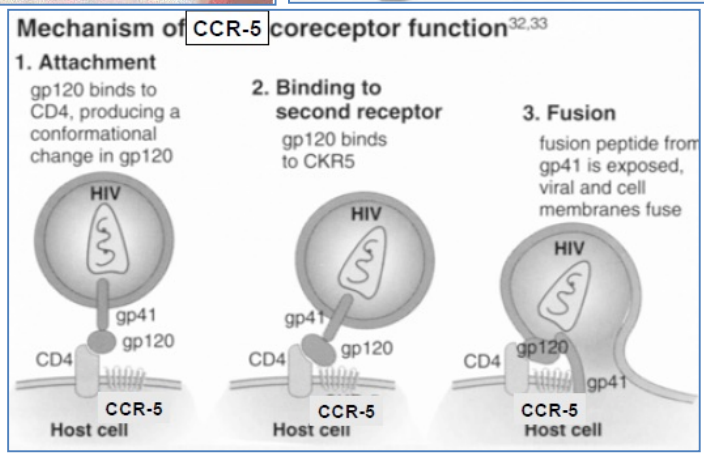
- ****T-Helper Cells**
- **But Also:**
  - **B lymphocytes**
  - **Macrophages/Monocytes**
  - **Dendritic cells**
  - **Microglia (In CNS)**

Major HIV Receptors:

- **1. The *CD4 molecule* – (on CD4-Th-cells)**
- **2. Chemokine Receptors - (act as *Co-Receptors* for the HIV):**
  - **T-cell Tropic strains:** use the ***CXCR-4 chemokine*** receptor
    - Preferentially Infect T-Cells
  - **Macrophage-Tropic strains:** use the ***CCR-5 chemokine*** receptor
    - Preferentially Infect Macrophages
    - (**NB:** Macrophages can readily cross the BBB → Infect Glial Cells → Produce cytokines → wipe out the neurons → AIDS Dementia)







Typical timescale of HIV infection

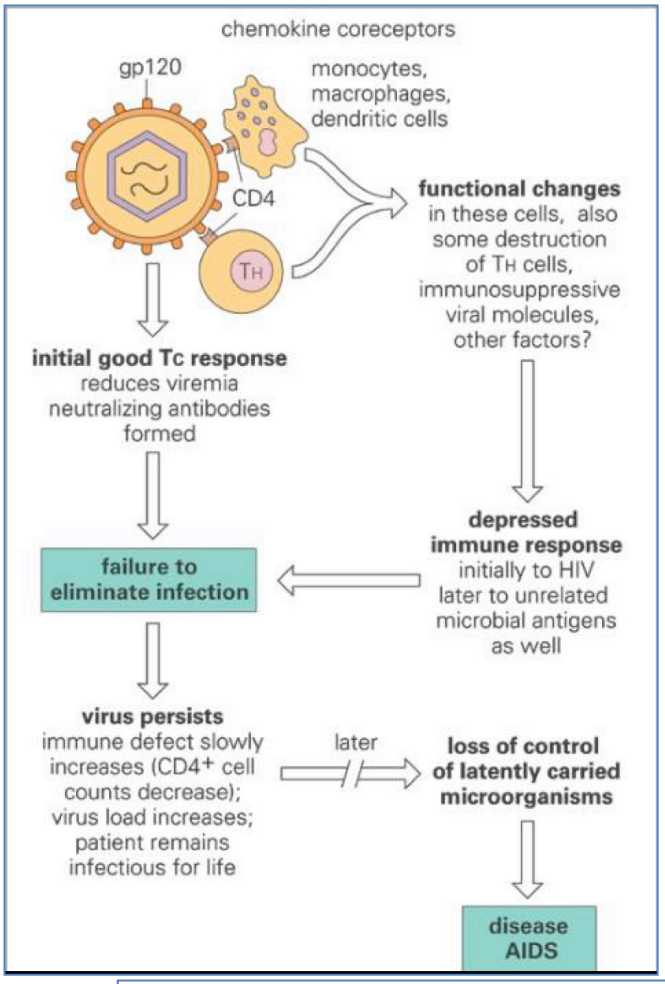
- **1-2 months:**
  - Acute infection
  - Following the acute infection, Antibody titres rise **(*Detectable after 2.5mths*)**
- **2-4 Years:**
  - Asymptomatic infection
- **8 years:**
  - Symptomatic infection
- **10-12 years:**
  - Advanced infection (If no intervention)

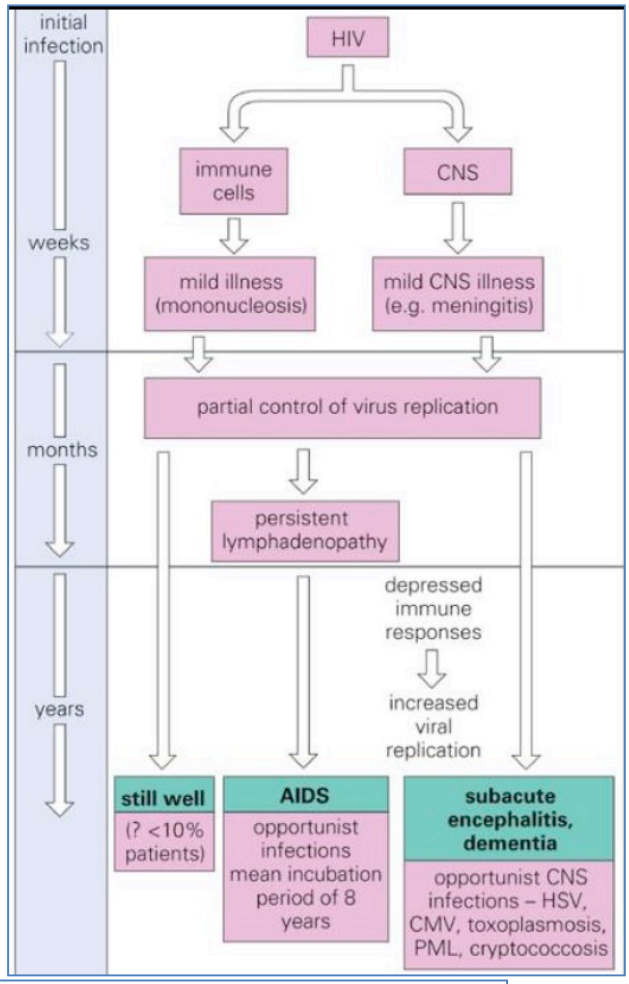
Pathogenesis of AIDS:

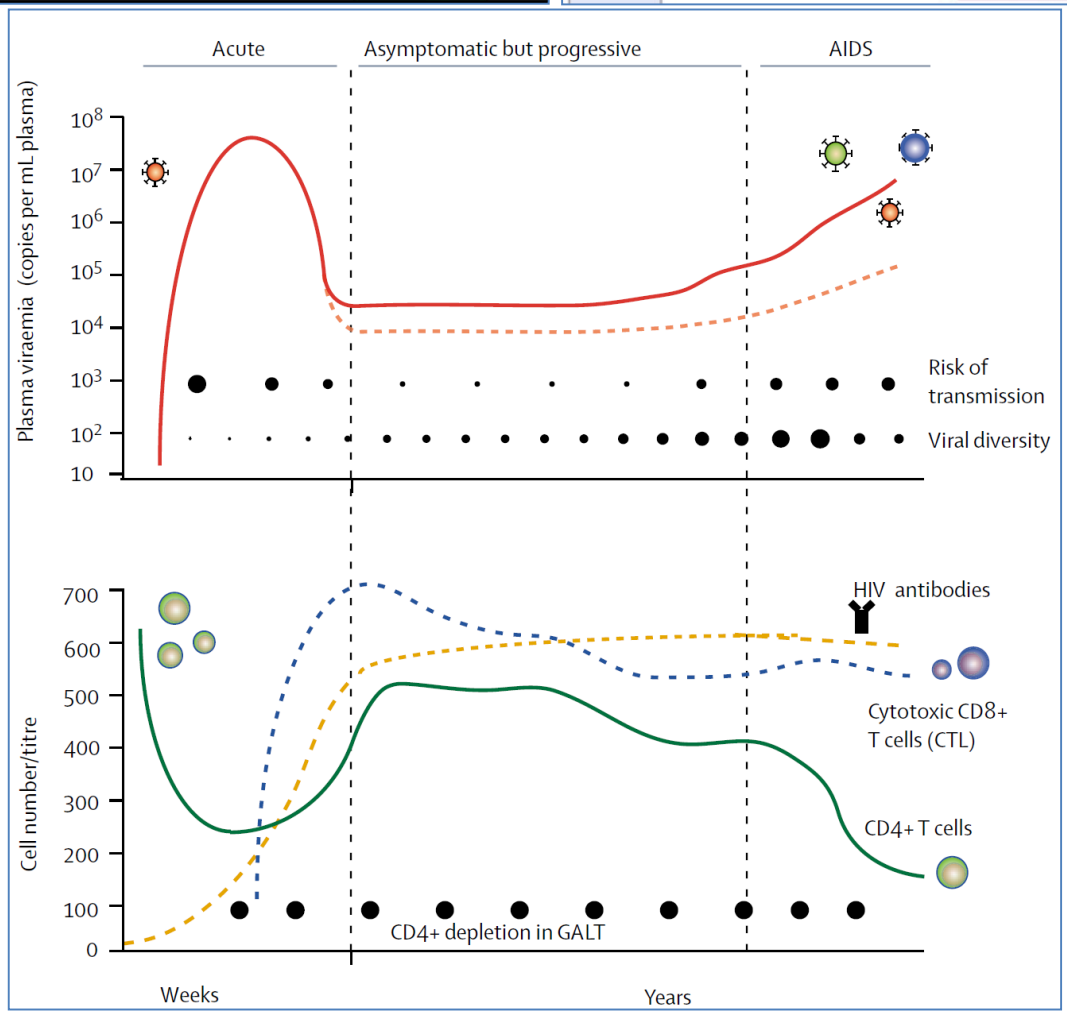
- **1. Acute Infection:** (High Risk of Transmission)
  - **Symptoms:**
    - Flu-Like Symptoms
    - Maculopapular Rash (AKA: Immuno-Thrombocytopaenic Purpura)
  - **Characterised by:**
    - High plasma Viraemia (red line, top)
    - Massive Depletion of CD4/CCR5 Low CD4 ***Memory Cells*** in the ***Mucosal Associated Lymphoid Tissues (MALT).*** (green line, bottom)
      - Loss of Memory Cells requires constant immune activation → Hyperactive immune system
      - During this period, many Quasispecies will be made (due to high polymerase error rate & Rapid CD4-Cell Turnover)
    - Absence of HIV-1 specific antibodies (orange line, bottom).
  - **Viraemia drops as cytotoxic CD8+ Tlymphocytes (CTL) develop:**
    - (blue line, bottom)
    - An individual ***Viral-Load Set Point*** is reached during chronic infection.
      - (***Viral set points*** differ greatly among individuals (eg, red dotted line, top) and predict disease progression.)
  - **NB: Takes weeks-months for antibodies to rise.**

- **2. Chronic (Asymptomatic) Infection:**
  - Ineffective cell mediated immune responses lead to the chronic stage of the infection
  - There is Chronic Immune Activation → CD4+ T-cell Depletion (Driven into Apoptosis)
  - Viral diversity increases throughout the disease (closed circles, top).
  - As CD4-T-Cells are Depleted, Viral Titre Rises.
  - Eventually, the virus produces more quasispecies, than the amount of specific CD8-T-cells the body can produce.

- **3. AIDS (Symptomatic):** (High Risk of Transmission)
  - The *Terminal* Stage of the Disease.
  - There are too many HIV Quasispecies for the CD8-Tc-Cells & Antibodies to deal with.
  - **How HIV Causes Immunosuppression:**
    - **CD4 Depletion Via:**
      - Direct CD4-T-Cell Lysis
      - Cytotoxic T-Cells kill CD4-T-Cell
      - Apoptosis of CD4-T-Cell
      - Infected CD4-T-Cells can fuse together →form *'Syncitia'* → Removed by Spleen.
      - (Ie. Predominantly via the Immune Response, not the Virus)
    - **CD4 Depletion → Immunosuppression By:**
      - ↓IFNy Production
      - ↓Antibody Production
      - ↓Antibody Isotype Switching
      - ↓Macrophage Activation
      - ↓CD8-T-Cell Activation
    - **→→Loss of the Adaptive Immune System → Opportunistic Infections.**
  - **HIV can lead to Death of Neurons (AIDs Dementia). How?:**
    - Infected Macrophages can cross the BBB → Infect Glial Cells (Esp. Astrocytes)→ Glia Produce TNF cytokines → Kill Neurons → AIDS Dementia
- **(NB: CD4:CD8 ratios can be a good marker for disease progression)**

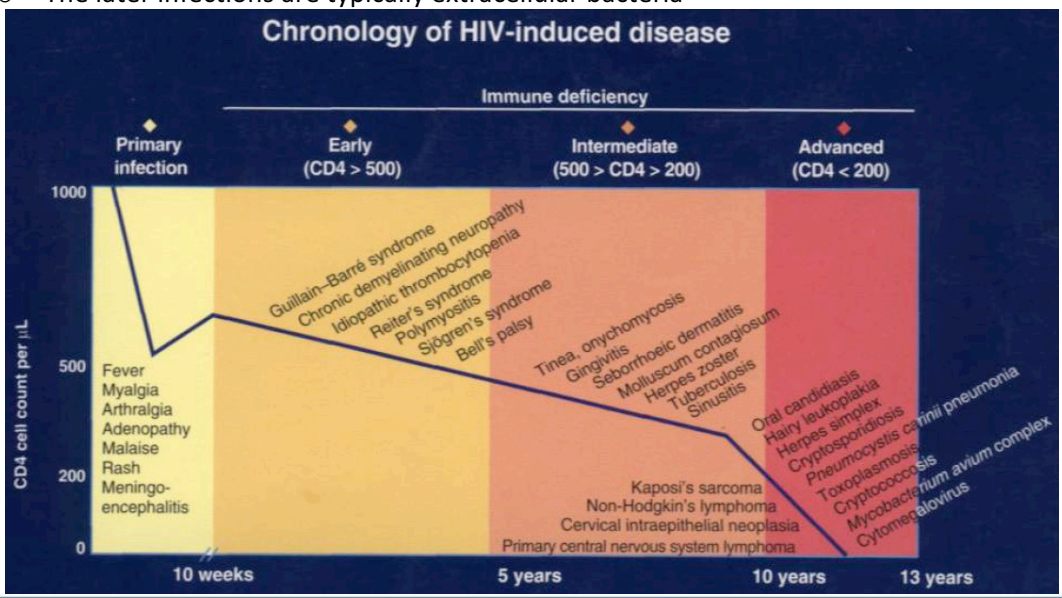






Opportunistic Infections & Tumours in AIDS:

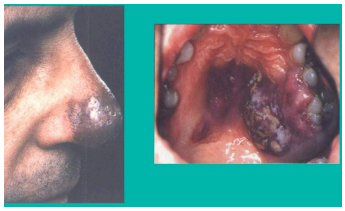
- Loss of CD4 Cells →↓ production of IFNγ → ↑Intracellular Viral/Bacterial Infections.
- **What do the common opportunistic infections associated with AIDS have in common?**
  - Infections where IFNγ (from Th-Cells) is really important to protection are the first infections seen (Ie. Those with intracellular viruses/bacteria).
  - The later infections are typically extracellular bacteria



OPPORTUNIST INFECTIONS AND TUMORS IN AIDS	
viruses	disseminated CMV (including retina, brain, peripheral nervous system, gastrointestinal tract) HSV (lungs, gastrointestinal tract, CNS, skin) JC virus (brain – PML) EBV (hairy leukoplakia, primary cerebral lymphoma)
bacteria*	mycobacteria (e.g. *Mycoplasma avium, M. tuberculosis* – disseminated, extrapulmonary) *Salmonella* (recurrent, disseminated) septicemia
protozoa	*Toxoplasma gondii* (disseminated, including CNS) *Cryptosporidium* (chronic diarrhea) *Isospora* (with diarrhea, persisting more than one month)
fungi	*Pneumocystis jiroveci* (pneumonia) *Candida albicans* (esophagitis, lung infection) *Cryptococcus neoformans* (CNS) histoplasmosis (disseminated, extrapulmonary) *Coccidioides* (disseminated, extrapulmonary)
tumors	Kaposi's sarcoma** B cell lymphoma (e.g. in brain, some are EBV induced)
other	wasting disease (cause unknown) HIV encephalopathy

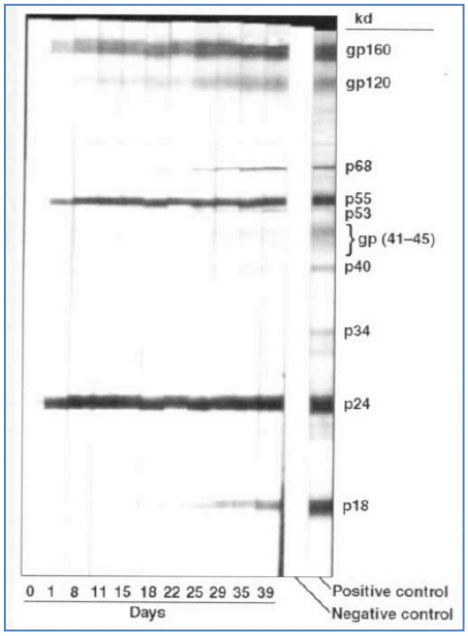
*also pyogenic bacteria (e.g. *Haemophilus, Streptococcus, Pneumococcus*) causing septicemia, pneumonia, meningitis, osteomyelitis, arthritis, abscesses etc.; multiple or recurrent infections, especially in children
**associated with HHV8, an independently-transmitted agent; 300-times as frequent in AIDS as in other immunodeficiencies

- **Kaposi's Sarcoma:**
  - **Produced by Human Herpes Virus 8 (But *Strongly Associated with HIV*)**
    - → Causes massively vascularised tumours
  - Is transmitted sexually
  - Is 300x as prevalent in AIDs than other Immunodeficiencies.



Diagnostic assays

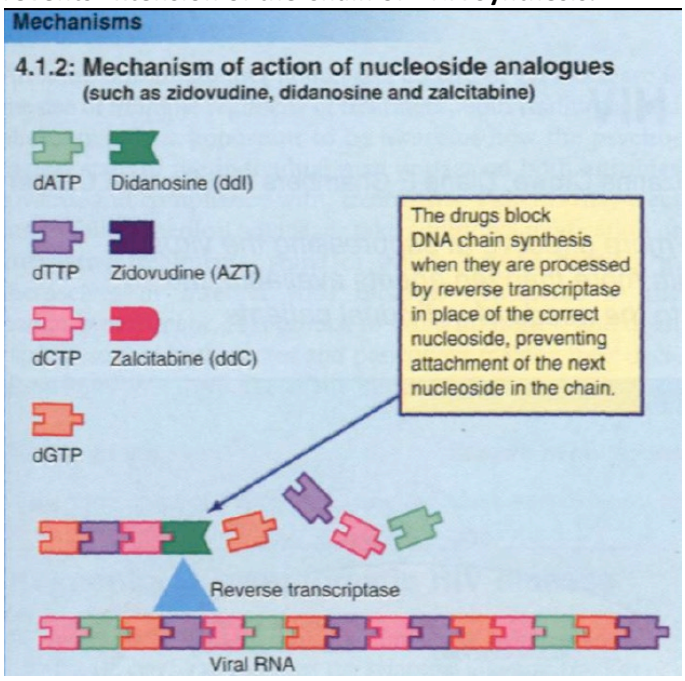
- **Antibody Detection:** (Only detectable *After* the Acute Response):
  - ELISA
  - Western blotting
  - Rapid agglutination or immunochromatography (RDTs)
- **Antigen detection:** (The Presence of Antigen will Parallel the Viraemia – Ie. Detectable In the Acute & Terminal Phases – NB: You won't detect antigen in the intermediate phase)
  - ELISA for p24
  - Western Blotting (Identifies Virus Proteins) – *More Specific than ELISAs*.
    - Take the virus, break it up into various proteins.
    - Proteins separated on basis of size by electrophoresis
    - Transfer to nitrocellulose
    - Blot patient's serum onto the nitrocellulose (Antibody reactions can be identified)



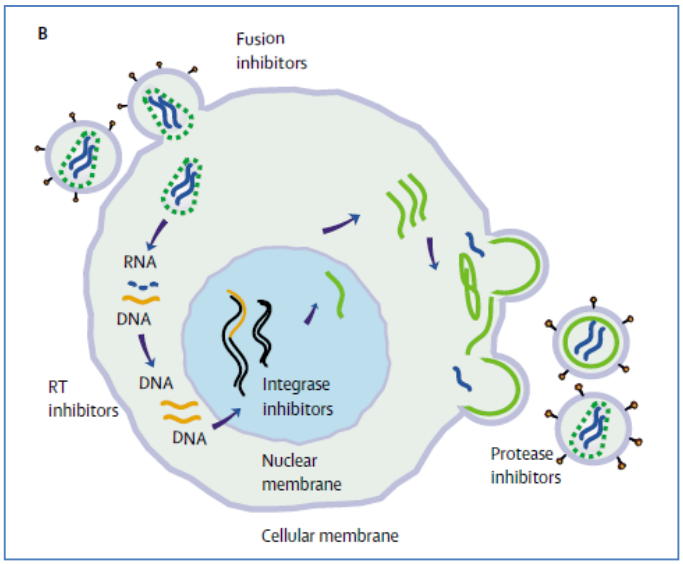
- **Genome Detection:**
  - PCR (Detects DNA)
  - RT-PCR ("viral load" – able to monitor progression of AIDS treatment)(Detects RNA)
- **Viral isolation**

HIV Drug Options:

- **Fusion Inhibitors:**
  - **Eg. CCR5 Inhibitors:**
    - Prevent HIV from fusing with the Cellular Membrane
- **Reverse Trancriptase Inhibitors (RTI's)**
  - **Nucleoside Reverse Trancriptase Inhibitors (NRTIs)** – (Blocks addition of purines/purymadines to DNA)
    - Zidovudine (azidothymidine, AZT)
    - Didanosine (dideoxyinosine, ddi)
    - Zalcitabine (dideoxycytidine, ddC)
    - Lamivuridine (3TC) (complementary resistance spectrum to AZT)
    - → **Prevents Extension of the Chain of DNA Synthesis.**



  - **Non-Nucleoside Reverse Trancriptase Inhibitors (NNRTIs):**
    - Targets the Non-Nucleoside-Binding Site of the HIV's Reverse Transcriptase → Inhibits RT Activity.
- **Protease inhibitors** – (Next generation of drugs):
  - Prevents cleavage of Inactive Poly-Proteins into Active Viral Proteins.
  - → Assembly of ineffective (Non-Infective) viruses.



HUMAN RETROVIRUSES:
HTLV – (HUMAN T-LYMPHOTROPIC VIRUSES):

Origin:

- Thought to have originated in Monkeys → Crossed over to Humans (Similar to HIV)

"T-Lymphotropic":

- = The virus Preferentially Replicates in T-cells

Presentation:

- **HTLV-1:**
  - **2x Associated Syndromes of HTLV-1:**
    - **Adult T-Cell Leukemia (ATL)**
      - Cancer of the T-Cells
    - **HTCL Associated Myelopathy (Tropical Spastic Paraparesis)**
      - Infection of the Spinal Cord by HTLV → Paraparesis (weakness of the legs)
- **HTLV-2:**
  - **1x Associated Syndrome of HTLV-2:**
    - **Hairy Cell Leukaemia (HCL)**
      - Cancer of the B-Cells
      - (Not Caused by HTLV-2, but *only Associated*)
- **(Ie. Both Are Oncogenic)**

Transmission:

- IV Drug Use
- Blood transfusion
- Breast feeding
- Sexual intercourse
- (Intrauterine transmission is rare)

Pathogenesis of HTLV-1 & HTLV-2:

- The viral protein called "Tax-Protein" → inhibits p53 (Fail to switch the cell off)
  - p53 is involved in apoptosis of cells
- Also insert into host chromosome → viral protooncogene expression (Switches on cell replication)
  - → TUMOURs (NB: Since it only infects T-Cells, it produces T-Cell Tumours)

OTHER BLOOD BORNE VIRUSES:
***HERPES VIRUSES* (EBV / CMV / HHV 6,7,8) & TT-Virus:**

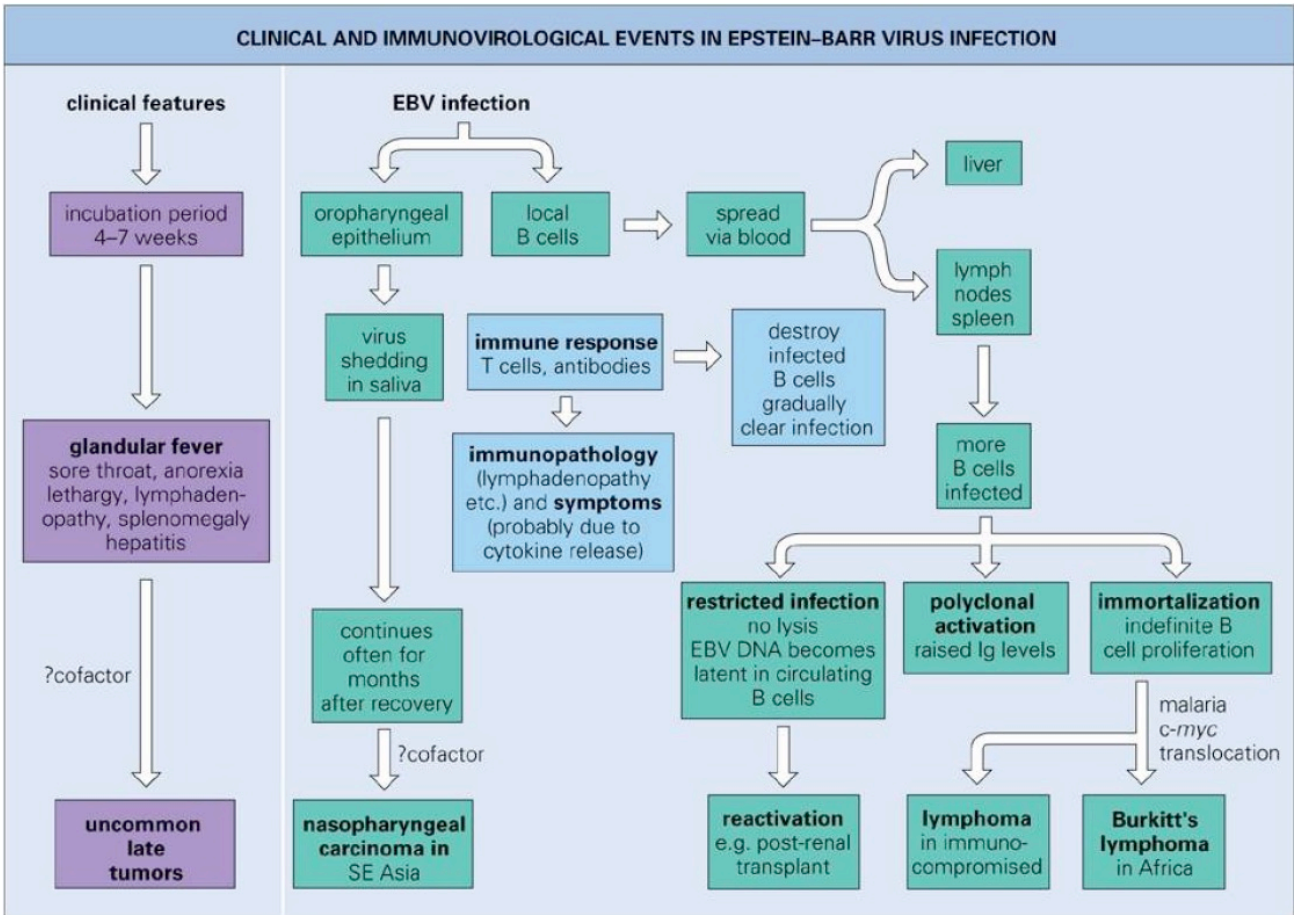
HUMAN HERPES VIRUSES

Herpes Viruses – In General:

- **Treatment:**
  - Most are treatable by ***Aciclovir*** – an Antiviral
- **Latency:**
  - Herpes Viruses can remain latent in Body Cells.
  - Structural Proteins are *Not* Produced during this phase.
- **Immuno-Modulation:**
  - **Can Inhibit '*TAP*' protein in infected cells** → Prevents Presentation of Viral Peptides on MHC-I.
    - → Avoids Immune Recognition → Avoids Apoptosis.
  - **EBV can also Directly Inhibit Apoptosis by T-Cells.**

Epstein Barr Virus (EBV):

- **Exhibits B-Cell Tropism:**
  - Preferentially Infects B-cells
  - (Via the CR2, a co-receptor complex)
- **Transmission:**
  - Oral Salivary Transmission (Ie. "Kissing Disease"/Glandular Fever)
    - Or Poor Hygeine
  - (or Blood-Blood Transmission)
- **Epidemiology:**
  - Endemic Virus + Change in Behaviour (Eg. Teenagers Kissing)
  - Or Endemic Virus + Change in Climate (Eg. People stay indoors → ↑Transmission)
- **Presentation of EBV-Related Syndromes:**
  - **Clinical Features:**
    - **→"Infectious Mononucleosis" (Glandular Fever):**
      - ↑Proliferation of Non-Specific Memory B-Cells → Raised titres of different Abs.
      - **Symptoms:**
        - **Glandular Fever Triad:**
          - Fatigue (Anorexia/Lethargy)
          - Pharyngitis (Sore Throat)
          - Generalised Lymphadeopathy
        - **Later/Rarer Symptoms:**
          - Splenomegaly
          - Hepatitis/Jaundice
    - **Some are Asymptomatic**
  - **EBV is an Oncogenic Herpesvirus → Tumours:**
    - **→Burkitt's Lymphoma:**
      - Latent Viruses in B-cells may →Indefinite B-cell Proliferation → *Burkitt's lymphoma*.
      - (Association with Malaria)
    - **→Hodgkin's Lymphoma:**
      - EBV may also transform B-cells cells to produce *Hodgkin's Lymphoma*
    - **→Nasopharyngeal Carcinoma:**
      - If the Primary EBV Infection was in the Oropharyngeal Epithelium.
  - **Cancers Result from Gene Translocation:**
    - Virus changes the cell → Protoncogene relocation into the IgM gene
    - Cell doesn't require the virus anymore to become a tumour ("Hit & Run" Phenomenon)
  - **NB: Cancers are More Prevalent in Immunocompromised:**
    - Eg. AIDs Patients
    - Eg. Malaria-Endemic Areas
    - Eg. Developing Countries



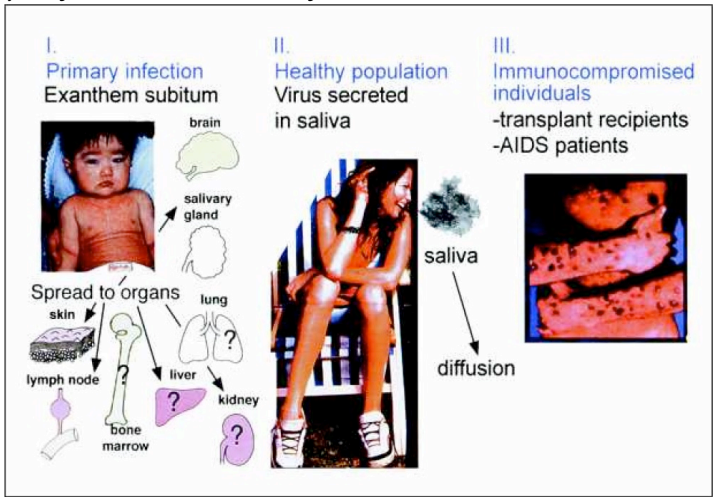
Know this diagram.

Cytomegalovirus

- **What is it?**
  - A Herpes Virus
  - dsDNA
  - A *Lytic Virus*.
- **Epidemiology:**
  - Very common Herpes Virus infection
- **Infection:**
  - Infects Monocytes, Dendritic Cells & Bone Marrow Progenitor Cells
  - →Infected Cells exhibit ***Gigantism*** ("Cytomega" = Big Cells)
  - **(*NB: Once Infected, you have it FOR LIFE*)** – (Stays latent → Can Recrudesce)
- **Presentation:**
  - Usually asymptomatic
  - Immunocompromised may get an interstitial pneumonia, focal cerebral lesions and retinitis.
- **Immune Evasion:**
  - Inhibits MHC-I Presentation of Viral Peptides.
  - Also produces MHC-I Analogues to Avoid NK-Cell-Mediated Attack.
- **Transmission Depends on Site of Infection:**
  - Salivary Glands — Virus in Saliva
  - Renal Tubules — Virus in Urine
  - Genitals — Sexual Transmission
  - Breast Tubules — Virus in Breast Milk
  - Lymphocytes — (Helps spread the virus *Throughout the Body*)
  - **(:. Transmission Requires close, intimate contact with person Shedding the Virus)**
  - **(Can be easily spread in children in places like child-care/daycare places.)**
- **Congenital Cytomegalovirus Disease:**
  - CMV May cross the placenta →Foetal Abnormalities
  - → Permanent mental retardation/hearing loss/etc

Human Herpes Virus Type 6:

- **Epidemiology:**
  - **The virus is Ubiquitous (Everywhere) - (Most are already infected with the virus)**
  - Most closely related to CMV
- **Transmission:**
  - Virus Shed in Saliva
- **Infection:**
  - **It has a Trophism for CD4 T cells**
    - Replicates in CD4-T-Lymphocytes
  - Latency and recurrence occur (Recurrence Especially in Immunosuppressed Patients)
- **Presentations:**
  - **Infants:**
    - **Glandular Fever-like Symptoms:**
      - Fever-induced seizures
        - (NB: HHV6 = The most common cause of Febrile Seizures in Infancy)
      - Rash
      - Irritability
      - Otitis media
      - GI upset
      - Encephalitis
  - **Immunocompetent:**
    - Usually Asymptomatic
    - May cause Infectious mononucleosis (Glandular Fever) symptoms.
  - **Immunocompromised:**
    - A Common Opportunistic Infection (in AIDS patients and transplant recipients)
    - Prominent Infectious mononucleosis (Glandular Fever) symptoms.
    - *May → fatal disseminated infection*.



- **Diagnosis:**
  - Culture
  - Or Serology

HHV-7

- Also a very common virus
- May be responsible for very high fever in young children

Human Herpes Virus 8:

- **Presentation:**
  - Associated with ***Kaposi's Sarcoma***
- **Transmission:**
  - Sexual Transmission
  - Transfusion
  - IV Needle Sharing
- **Factors in Pathogenesis of Kaposi's Sarcoma:**
  - **HHV8 Infection** precedes the development of the tumours
  - **Cytokines** Produced by Infected Cells play an important role in the development of lesions.
    - Growth Regulated Oncogene Alpha (GRO-a)
    - IL-8
    - HIV-1 Tat Protein
  - ***AIDS patients have a 20,000x risk of *Kaposi's Sarcoma***
    - ↑Virus → ↑Tumours
    - ↓CD8 Function → ↓Cellular Immunity → ↑Tumours (Due to interaction between the 2 viruses + the immunosuppression)
    - (Hypothesized that one of the HIV proteins drives Tumour Growth)

TT VIRUS:

TT virus (Torque Teno):

- **What is it?**
  - Torque Teno virus (TTvirus)
  - ssDNA viruses
  - Genus *Anellovirus*
- **Epidemiology:**
  - Almost Ubiquitous (Prevalence can be up to 90%)
- **Transmission:**
  - May be transmitted by blood transfusion (No point screening, since almost everyone has it)
- **Presentation?:**
  - Not Associated with Disease
  - May Produce Immunosuppression under certain circumstances
- **Pathogenesis:**
  - Probably replicates in T-cells and produces immunosuppression under certain circumstances

Antiretroviral drugs currently approved by US Food and Drug Administration:

- **Five drug classes, Targeting three viral steps:**
  - **entry,**
  - **reverse transcription**
  - **or protease**
- Availability of these drugs in resource-limited countries is subject to country specific licensing agreements.

	Entry	Reverse transcriptase			Protease
		Nucleoside	Nucleotide	Non-nucleoside	
Single compound tablets	Enfuvirtide	Abacavir	Tenofovir	Delaviridine	(Fos)-Amprenavir
		Didanosine		Efavirenz	Atazanavir
		Emtricitabine		Nevirapine	Darunavir
		Lamivudine			Indinavir
		Stavudine			Nelfinavir
		Zalcitabine			Ritonavir
		Zidovudine			Saquiravir
					Tipranavir
Fixed-dose combination tablets		Abacavir/lamivudine (Epzicom)			Lopinavir/ritonavir
		Zidovudine/lamivudine (Combivir)			
		Tenofovir/emtricitabine (Truvada)			
		Abacavir/lamivudine/zidovudine (Trizavir)			
		Tenofovir/emtricitabine/efavirenz (Atripla)			

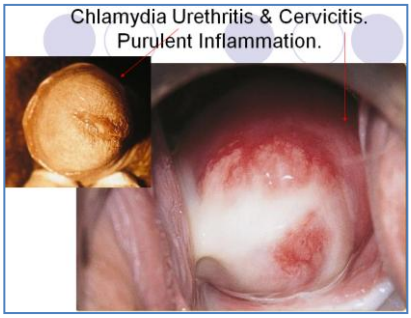
Antiretrovirals currently in phase II/III of clinical development

	Drug	Mechanism	Activity against PI and RT resistant strains
Maraviroc	MVC	CCR5 inhibitor	Yes, but not X4 variants
Vicriviroc	SCH D		Yes, but not X4 variants
Etravirine	TMC-125	Non-nucleoside reverse transcriptase inhibitor	Yes, also NNRTI-resistant strains
	TMC-278		Yes, also NNRTI-resistant strains
n/a	MK-0518	Integrase strand transfer inhibitor	Yes
n/a	GS-9137		Yes

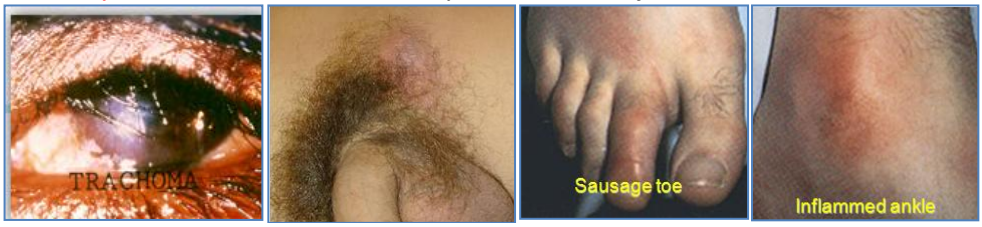
UNISEX UROGENITAL Pathology:
STIS – CHLAMYDIA

*CHLAMYDIA (Notifiable Disease):

- **Aetiology:**
  - Chlamydia Trachomatis
- **Pathogenesis:**
  - Vaginal, Anal, Oral & Vertical Transmission.
  - **Obligate Intracellular Replication** – (Ie. Replicate like Viruses → Shed by Infected cell lysis)
- **Morphology:**
  - **Micro:** Obligate Intracellular Bacteria → Chlamydial Intracellular Reticulate Bodies
- **Clinical Features:**
  - **Symptoms:**
    - **Males –** The COMMONEST cause of Urethritis.
      - (May also → Epididymitis, Orchitis, Prostatitis & Proctitis)
      - (NB: A *Non-Gonococcal Urethritis:* Ie. Clear, Watery Discharge)
    - **Females –** Asymptomatic, or Urethritis.
      - (May → Cervicitis, Salpingitis/***PID***)
    - **Neonates:**
      - Neonatal conjunctivitis (similar to Gonorrhea)
      - Chlamydial pneumonia



- **Diagnosis:**
  - **Sample for PCR:**
    - ***1st Catch Urine (Unisex)...or***
    - **Women – Endocervical/High-Vaginal Swab**
    - **Men – Swab of Urethral Discharge**
    - **+/- Throat Swabs:**
  - **→ Antigen Detection Tests – PCR**
  - **→ Gram stain & Immunoflourescence -** Intracytoplasmic inclusion bodies – Replicate intracellularly
  - ***(NB: All Females <25 are screened for Chlamydia) – (Via Non-Invasive PCR)***
- **Complications:**
  - *Trachoma* – (Chlamydial Conjunctivitis)
  - *Lymphogranuloma Venereum* - (Lymphatic Chlamydial infection) → Groin Abscesses/Buboes → May become ulcerative.
  - ***PID*** – can → Infertility, ↑Risk of Ectopic Pregnancy, Chronic Pelvic Pain
  - *Reiter's Syndrome Triad* - Reactive Poly-Arthritis + Conjunctivitis + Urethritis



- **Treatment:**
  - **1 Dose *Azithromycin* 1g**
  - or ***Doxycycline*** 10days 100mg BD

Contraceptive Options Summary

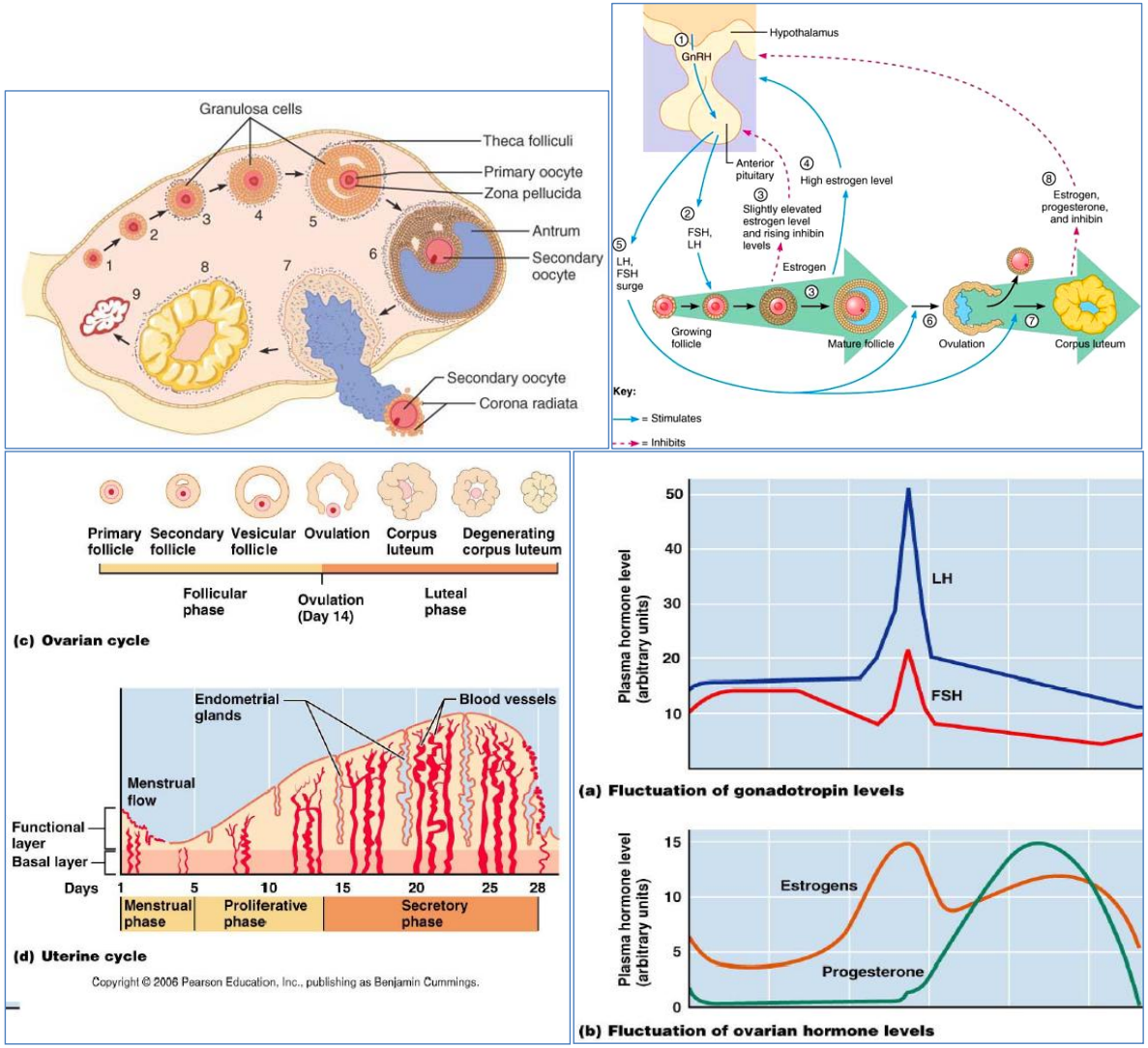
	Combined Pill (Global Oest+Prog)	Minipill – Prog. Only (Systemic Prog)	Depo-Provera (Systemic Prog)	Implanon SC (Systemic Prog)	Mirena IUD (Local Prog)	Copper Rod IUD (Non-Hormonal)	Condoms (Barrier)	Family Planning (Non-Hormonal)	Tubal Ligation (Surgical)	Vasectomy (Surgical)
MOA:	Inhibits Ovulation Thickens Cx Mucus	Inhibits Ovulation Thickens Cx Mucus	Inhibits Ovulation Thickens Cervical Mucus	Inhibits Ovulation Thickens Cx Mucus	Thickens Cx Mucus (↓Endometrial Growth)	Causes Sterile Endometritis (Hospitable Uterus)	Barrier – Prevents Insemination	Avoiding Coitus During Most Fertile Periods (D8-19)	Barrier – Prevents Oocyte from entering Uterus	Barrier – Prevents Sperm from mixing with Ejaculate.
Duration of Action:	24hrs	22hrs	3 Months	3 Years	5 Years	3-5 Years	Per-Usage	11 Days	Permanent	Permanent
Efficacy:	Excellent-Moderate 0.1-5% Failure	Excellent-Moderate 0.1-5% Failure	Excellent <0.3% Failure	Excellent <0.2% Failure	Excellent <0.1% Failure	Good <1% Failure	Moderate-Poor 3-15% Failure	Poor <25% Failure	Excellent <0.5% Failure	Excellent <0.5% Failure
Reversibility:	Yes – 24hrs	Yes – 22hrs	Yes – 3-9mths	Yes – 1 Cycle	Yes – 1 Cycle	Yes – 1 Cycle	Yes – Instantly	Yes – 11 Days	No	No
Spontaneity:	Excellent	Excellent	Excellent	Excellent	Excellent	Excellent	Poor	Poor	Excellent	Excellent
Pros: (Off-label usage)	Effective if used properly. Controls Periods (if skip sugar pills). Reduced cramping. Protects against ovarian & endometrial Ca. (a Rx for Acne) (a Rx for PCOS)	Effective if used properly. Inhibits Ovulation NOT Affected by Antibiotics Safe for Smokers >35 Safe for Lactating Women	Highly Effective Inhibits Ovulation NOT Affected by Antibiotics LOW dependence on user – 3mthly injections. High Spontanaeity Moderate Duration Safe for Lactating Women	Highly Effective Inhibits Ovulation NOT Affected by Antibiotics NOT dependent on user – Once off Insertion High Spontanaeity Easily Removed & Reversed Long Lasting Safe for Lactating Women	Highly Effective & Long-Lasting NOT Affected by Antibiotics NOT dependent on user – Once off Insertion High Spontanaeity Easily Removed & Reversed Safe for Lactating Women (a Rx for Menorrhagia)	Highly Effective NOT Affected by Antibiotics NOT dependent on user – Once off Insertion High Spontanaeity Easily Removed & Reversed Safe for Lactating Women No hormonal side effects	Easily Available STI Protection (HIV, HPV, Chlamydia, Gonorrhoea) No hormonal side effects Safe for Lactating Women	100% natural (No exogenous hormones/devices)	<100% Effective 1-off Procedure → Permanent Lifelong Contraception No hormonal side effects NO User Dependence	<100% Effective 1-off Procedure → Permanent Lifelong Contraception No hormonal side effects NO User Dependence Reversible Father can freeze sperm at the blood bank if unsure about future children.
Cons:	Highly User Dependent – DAILY Tender Breasts, Weight Gain Nausea, Headaches. Inhibits Lactation **Drug Interactions:** Antibiotics, Barbiturates, Antiepileptics, St.John's Wort.	Highly User Dependent - Taken SAME TIME EVERYDAY Tender Breasts, Irregular Spotting NOT protective for ovarian/endometrial ca's.	POOR Reversibility of Contraception AND SIDE EFFECTS– up to 9mths Require repeat GP visits for injections 3mthly. Weight Gain	Painful SC Insertion Transient initial spotting Tender Breasts, Headaches.	Invasive/Painful Insertion Ovulation still occurs Menstruation still occurs (but lighter & shorter) Transient initial spotting	Invasive/Painful Insertion Ovulation still occurs Menstruation still occurs (AND is HEAVIER & MORE PAINFUL)	Not Very Effective (Can break/slip off) Poor Spontaneity	HIGHLY UNRELIABLE Poor Spontaneity (when fertile) Highly dependent on couple.	NOT Reversible Surg/Anaesthetic Risks Expensive	Surg/Anaesthetic Risks Expensive Doesn't stop the woman from getting pregnant via other means.
Contraindications:	Smokers >35yrs Breast Feeding Epilepsy Vascular Risk Factors POOR COMPLIANCE	Previous Ectopic Pregnancy POOR COMPLIANCE	-	-	-	Primigravid/para Iron Deficiency Anaemia	Latex Allergy	Couples who cannot afford unwanted pregnancies.	Any contraindications to surgery or anaesthesia.	Any contraindications to surgery or anaesthesia.
Suitability:	For Compliant, Non-Breast-Feeding, Non-Smoking, Non-Epileptic Pts who want reversible & reliable contraception.	For HIGHLY Compliant pts who have contraindications to the COCP. (Ie. Breast-Feeding, Smoking, Epilepsy, Vasculopaths)	Pts who want low-maintenance, reliable, medium-term contraception who DONT WANT an IUD or an Implant.	Pts who require LOW-Maintenance, Reliable, Long-Term Contraception ...AND/OR... Are Breast-Feeding/ don't tolerate oest.	Pts who require LOW-Maintenance, Reliable, Long-Term contraception ....AND/OR.... Have Menorrhagia	Older Multiparous pts who require LOW-Maintenance, Non-Hormonal, Reliable, Long-Term contraception	Advisable for all sexual encounters with random partners. Also a good adjunct for any other contraceptive.	For Couples who don't mind accidental pregnancy.	For women who are 100% sure they want no more children.	For couples who are ≈ certain they don't want future children. (But Artificial Insemination is an option)

Oestrogen MOA:

- (Initially included in oral contraceptives for better cycle control (Stabilise endometrium & reduce breakthrough/intermenstrual bleeding).
- Slightly Elevated Oestrogen → Negative feedback on **Ant.Pituitary** → ↓FSH & LH
  - ↓FSH → Inhibits follicular development
  - ↓LH → Inhibits Ovulation

Progesterone MOA:

- High Progesterone → Negative feedback to the **Hypothalamus** → ↓GnRH → ↓FSH & LH
  - ↓FSH → Inhibits follicular development
  - ↓LH → Inhibits Ovulation
- ALSO → Thickens cervical mucus → Inhibits sperm from crossing cervix.



Take Charge!

Your choice of contraceptive methods

The Pill Combined oral contraceptive	IUS Intrauterine system	IUD Intrauterine Device	Barrier Method Condom	Female sterilisation Tubal Ligation	Natural Method Calendar / Withdrawal	Injection	Implant	Combined Patch
								
How it works								
Contains two types of hormones - estrogen & Progestogen Prevents Ovulation. [1]	Progestin-delivering implant introduced into the womb. Continuously releases small amounts of progestin. Thickens cervical mucus in the neck of the uterus, making it difficult for sperm to enter. [2] Suppress growth of the lining of uterus (endometrium) [1]	A device placed in the uterus with copper coil. Cause a chemical change that damages sperm & egg before they can meet. [1]	Thin sheath over erect penis traps sperm. Prevents sperm entry into the vagina.	Fallopian tubes occluded (closed), cauterised (burned), or cut. Prevents egg from reaching the uterus.	Selecting "infertile" dates for intercourse (calendar method). Withdrawal of penis before ejaculation (withdrawal method).	Injection is administered every 2-3 months. Stops release of eggs from ovaries. [1] Thickens cervical mucus.	A rod that is placed under the skin of the upper arm Releases progestin continuously into the blood stream. [1] Prevents ovulation.	A small thin, square of flexible plastic worn on the body. Continuously releases 2 hormones – a progestin and an estrogen into the body, directly through the skin into the bloodstream. [1] Prevent releases of eggs from the ovaries (ovulation).
Failure rate								
0.1 – 5% [2]	0.1% [2]	0.6 – 0.8% [2]	3 - 14% [2]	0.5% [2]	Calendar method (9-25%) [2] Withdrawal method (4-19%) [2]	0.3% [2]	0.2% [2]	0.9% [2]
Reversibility								
Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Dependence on User								
Highly dependent	No (inserted by doctor)	No (inserted by doctor)	Highly dependent on partner	No (operated by doctor)	Highly dependent	No (injected by doctor)	No (inserted by doctor)	Highly dependent
Contraceptive duration								
Daily	5 Years	3 - 5 Years	Per Usage	Permanent	NA	2 -3 months	3 Years	3 weeks
Main advantages								
Very effective if taken as indicated. Reduced bleeding pattern (No pill free period) [1] Fewer menstrual cramps. [1] Protects against ovarian & endometrial cancer.* Contains the new progestin Drospirenone which counter-act water retention caused by the estrogen, thereby preventing weight gain due to water retention. [4] Quick return of fertility after stopping. Can be used for treatment of symptoms of severe Pre-menstrual syndromes –Premenstrual Dysphoric Disorder (PMDD) (Only for product YAZ) Can be used for treatment of moderate acne (Only for product YAZ)	Highly effective & very reliable. Shorter, lighter & less painful periods. Menses reduces over time. Convenient, once fitted usually unfelt & unnoticed. Easily inserted & removed. Long-lasting. Protect against iron-deficiency anemia. [1] Do not require daily intake of oral contraceptives. Reduces non-compliance issue.	Highly effective. Convenient, once fitted usually unfelt and unnoticed. Easily inserted and removed if necessary. Long-lasting	Easily available Helps protect against sexually transmitted disease (e.g. HIV) No hormonal side effects Use as when required.	Highly effective. A one-time surgery as day/outpatient or in-hospital procedure. No hormonal side effects. No compliance issue.	Does not require strict dosing regimens or insertion of devices.	Does not require daily intake of contraceptive medication. Lower risk of forgetting to stick to dosing regimen. Long-acting compared to the pill.	Does not require daily intake of contraceptive medication. Long-lasting Reduce non-compliance issue.	Does not require daily intake of contraceptive medication. Convenient.
Main drawbacks & Precautions								
Side effects such as nausea, mild headaches, breast tenderness may occur but are usually not serious. Missed pill reduces contraceptive efficacy. Transient change in vaginal bleeding.	Spotting & intermenstrual bleeding within the first few months. Change of unnoticed slippage or expulsion. Involves a minor procedure.	Change of unnoticed slippage or expulsion. Recommended to regularly feel for string to check placement. Risk of PID (Pelvic Inflammatory Disease), possibly with resultant infertility (especially in women with many partners). [1] May increase menstrual bleeding and cramping. [1] Involves a minor procedure.	Not very reliable. Can break or slip off during sexual intercourse. Inhibits spontaneous love making. Possible allergy to latex or other condom material and/or spermicide. Requires care on removal to avoid spills.	Common risks of surgery & anaesthesia. Not reversible if couple change their mind. Expensive.	Higher failure rates. Inhibits spontaneous love-making during fertile dates. Need close co-operation between couple.	Repeat visits to the clinic are required for injections. Changes in vaginal bleeding. Some weight gain or mild headaches may occur. Any side effects may persist for some time as the medication remains in the body for a long time (unlike pill where one can stop taking it immediately). Takes a longer time for return of fertility compared to the pill. May take an average of 4 months longer than usual to get pregnant after stopping contraception. [1] Can be painful due to injection.	Spotting and intermenstrual bleeding. Hormones circulate systemically like the pill. May cause headaches, mood changes & breast tenderness.	Pregnancy rates may be slightly higher among woman weighing 90kg or more. [1] Skin irritation or rash may occur when patch is applied. Changes in vaginal bleeding. Headaches, nausea, breast tenderness, abdominal pain may occur.
Suitability								
Not recommended for women with high blood pressure, heart problems, diabetes, high cholesterol/blood fats, liver, kidney or gall bladder disease, epilepsy or jaundice. Not recommended for smokers above age 35. [1]	For women who seek long-term contraception. Also for women who suffer from heavy menstrual bleeding. Best suits women who have completed their family. Alternative for women who for some reasons are not suitable candidates for the pill, eg. Breast-feeding mothers.	For women who seek long-term contraception. Not suitable for women at risk of STDs (teenagers, women with multiple partners). Not a method of choice for women who have not given birth or women with anaemia. [2]	Good to protect against STDs. Not fully reliable for people who are likely to use it incorrectly or inconsistently.	Suitable for women who have completed their families. Not suitable for women with doubts about future desire for children or in fear of infertility.	Suitable for couples who do not mind accidental conception. Highly unreliable in preventing conception.	Suitable for women at reproductive age group and whether or not they have children.	Suitable for women at reproductive age group and whether or not they have children. Suited for women who want long term contraception. Suitable for women who are breast feeding & those who do not tolerate estrogen. [2]	Suitable for women who cannot remember to take the pill correctly. Not very suitable for women who weigh 90kg or more Women will be exposed to about 60% more estrogen if use patch than if they use a typical birth control pill containing 35 micrograms of estrogen. Increased estrogen may increase the risk of side effects. [3] The risk of venous thromboembolic events (blood clots in the legs and/or the lungs) may be increased with patch use compared with use of birth control pills. [3] Not recommended for smokers above age 35. [1]

The information provided is for educational purposes only. Please consult your doctor to discuss the most suitable contraceptive method for your family planning.

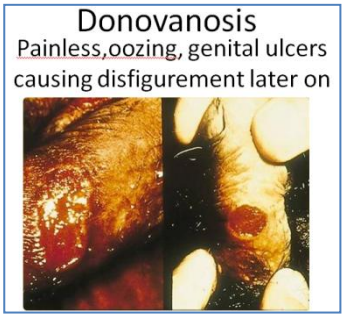
References:

* These non contraceptive health benefits related to the use of combination birth control pills are supported by studies that mostly used oral contraceptives formulations containing high doses of estrogen. • 1. Family Planning, a global handbook for providers, a WHO Family planning 2007 • 2. Asia Pacific council on Contraception (http://www.apcpc.net/) • 3. Ortho-McNeil-Janssen Pharmaceuticals, Inc. 2009 (http://www.orthoevra.com/is-patch-safety-sideeffects.html) • 4. B Schultz-Zehden, E Boschitsch, Treatment Endocrinol 2006;5(4):251-56.

UNISEX UROGENITAL Pathology:
DONOVANOSIS

DONOVANOSIS:

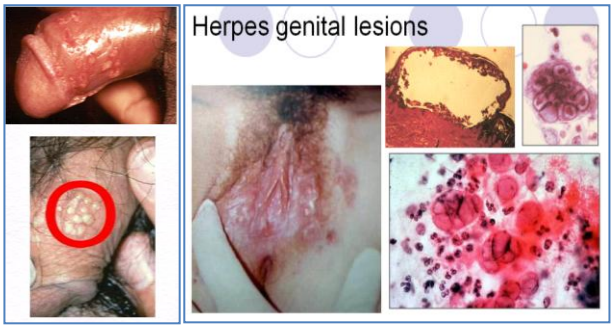
- **Aetiology:**
  - Klebsiella Granulomatis (Gram Neg)
- **Pathogenesis:**
  - Direct Contact Transmission with OPEN sores.
- **Morphology:**
  - **Macro:**
    - Painless, Oozing, Red Ulcers with Characteristic *Rolled Edges* of Granulation Tissue.
  - **Micro:**
    - Donovan Bodies = Intracellular Rod-Shaped, Oval Organisms seen inside Phagocytes
- **Clinical Features:**
  - **Symptoms:**
    - → Chronic, painless, **offensive, oozing** genital ulcers (Cf. Syphilis = dry) + genital disfigurement. (Lesions occur on Penis, Labia, or Perineum)
    - NB: **NO Lymphadenopathy** (Cf. Syhpilis = Lymphadenopathy Present)
- **Diagnosis:**
  - Scrape → Microscopy (Donovan Bodies)
  - Swab → PCR
  - + Rule out Syphilis (RPR, VDRL, TPHA)
- **Complications:**
  - Genital Disfigurement
- **Treatment:**
  - ***Doxycycline***/***Azithromycin***/Erythromycine



UNISEX UROGENITAL Pathology:
STIS - GENITAL HERPES

GENITAL HERPES SIMPLEX:

- **Aetiology:**
  - **HSV2** in Genital Herpes **(12.5% Prevalence!!)**
  - (HSV1 in Coldsores; but can still cause genital infections) **(70% Prevalence!!)**
- **Pathogenesis:**
  - **Contact Transmission**
  - **1.Lives in Neurons → Latent....2.Reactivation → Travels down Axon into Skin → Lesions.**
- **Morphology:**
  - Papular/Vesicular lesions on external Genitalia
- **Clinical Features:**
  - 2F:1M
  - **Symptoms:**
    - **Course:**
      - **<3wks Incubation**
      - **Prodrome –** Paraesthesia, Itching, Redness
      - **Symptoms last for <2wks if untreated.**
        - Clusters of PAINFUL, ITCHY, Papules/Vesicles on External Genitalia
        - Vesicles may Rupture → Painful Ulcerations
      - **Recrudescences:**
        - Typically milder than 1st presentation
        - 1-2 day prodrome (Paraesthesia)
    - **+/- Proctitis/Cervicitis**
    - (NB: *ANY genital ulcer, scabbed, red-edged, multiple, and painful = Think Herpes!*)
- **Diagnosis:**
  - **Clinical Diagnosis**
  - **Swab Vesicle → HSV 1&2 PCR**
  - **Tzanck Smear** (Typical intranuclear inclusion bodies & multi-nucleated giant cells)
  - HSV Serology (limited use)
- **Treatment (NO CURE; Symptomatic & Suppressive Therapy ONLY):**
  - ***Valaciclovir*/Famciclovir/Aciclovir – (Nucleside Analogue Anti-Virals) (BD 10 days)**
    - NB: "Suppressive Therapy" → 50% Reduction in Transmission.
  - **Analgesia – Lignocaine Gel**
  - **Counselling & Sex-Education**
    - 90% of HSV2 will have recurrences >5x/year
    - (NB: HSV1 have annual recurrences)
  - **Advise Abstinence in the Prodrome or when Lesions are Present.**
    - BUT NB: *Asymptomatic Viral Shedding Still Occurs!!!!*

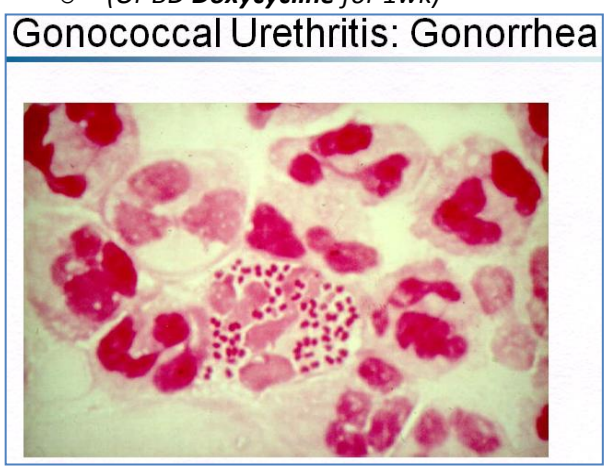


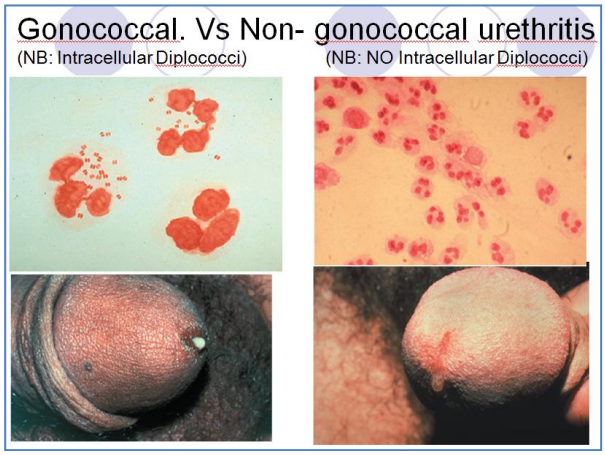
- **DDXs of Genital Ulcers:**
  - **Infection:** Herpes/Syphilitic Chancre/Donovanosis/Lymphogranuloma Venereum
  - **Trauma:** Mechanica/Chemical
  - **Allergic:** Contact Wet Dermatitis

UNISEX UROGENITAL Pathology:
STIS – GONORRHOEA

*GONORRHOEA (Notifiable Disease):

- **Aetiology:**
  - Neisseria Gonorrhoeae (Gram Negative)
- **Transmission:**
  - **Horizontal via Direct Sexual Contact:**
  - **Vertical – (During childbirth; not trans-placental [like syphilis & hep B])**
- **Pathogenesis:**
  - **Virulent**, Fastidious (Delicate), aerobic, gram negative diplococcic.
    - ***Pili*** – anchors to urethral epithelium → Resists Flushing → Infiltrates Epithelium
    - ***Gonococcal Toxin*** – Endotoxin
    - ***Protease*** – Destroys secretory IgA
- **Morphology:**
  - **Macro -** Inflamed Urethra + Thick, Milky-white Discharge
  - **Micro -** Intracellular Diplococci on Gram Stain (Typically inside neutrophils)
- **Clinical Features:**
  - **Symptom Onset within <1wk of Infection.**
  - **Men** → Acute **Gonococcal Urethritis** + Dysuria + Discharge (Thick & milky)
  - **Women** → Acute **Gonococcal Cervicitis** + Vaginal Discharge. (May also be Asymptomatic in Women) + (NB: Can → PID in females)
- **Diagnosis:**
  - **Clinical:**
    - **NB: Differentiating Gonococcal Urethritis Vs Non-Gonnoccal Urethritis:**
      - **Gono** – Thick, milky, Penile discharge. Gram Negative Diplococci on gram stain of discharge.
      - **Non** – Thin, watery discharge. No organisms on Gram Stain. (Typically Chlamydia).
  - **Sample for PCR:**
    - ***1st Catch Urine (Unisex)...or***
    - **Women – Endocervical Swab**
    - **Men – Swab of Urethral Discharge**
  - **Men + Women – Throat Swabs**
- **Complications:**
  - *PID* (Females)– can → Infertility
  - *Urethral Stricture* → Urinary Obstruction → Hydronephrosis
  - *Epididymitis, Prostatitis*
  - *Endocarditis*
  - *Gonococcal Arthritis*
  - *Ocular Infections, Neonatal Conjunctivitis*
- **Treatment:**
  - Stat Dose IM ***Ceftriaxone*** + Stat Dose PO ***Azithromycin***
  - *(Or BD **Doxycycline** for 1wk)*

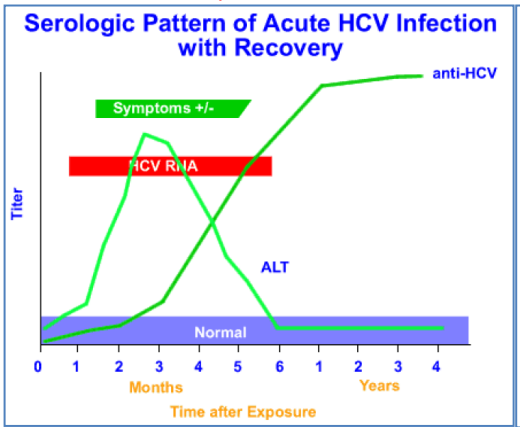


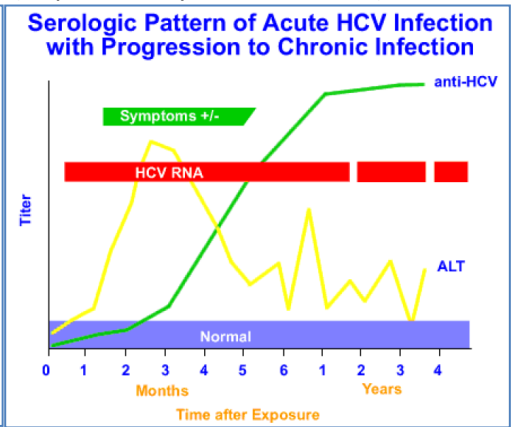


UNISEX UROGENITAL Pathology:
STIS - HEP C

HEP C (Acute/Chronic)

- **Aetiology:**
  - Hepatitis C Virus
- **Transmission:**
  - **Blood (Eg. IVDU):** As little as 0.0001 mL of blood can transmit the infection
  - **Body fluids (Eg. Sexual):** (Incl. Cervical Secretions and Semen)
  - **Vertical** (Uncommon)
- **NB: Epidemic Potential:**
  - No Vaccines
- **Pathogenesis:**
  - Viral Infection (Horizontal/Vertical) →Virus Replicates in the Liver
    - NB: Virus is NOT directly Cytopathic; Damage is due to CD8-T-Cell Attack.
  - → Cellular (CD8) Immune Attack on Infected Hepatocytes
  - → ***Chronic, Low-Grade Inflammation*** → **Eventually leads to Fibrosis → Cirrhosis**
- **Morphology – Mostly Chronic:**
  - Chronic '*Peri-Portal*' Inflammatory Infiltrates
  - Necrosis, Apoptosis & Fibrosis → Cirrhosis
  - (Hep C – Mild Fatty Change [Microvesicular Steatosis])
- **Clinical Features:**
  - **10% →Acute with Recovery –** (Mild Viral Illness + Jaundice)
    - *May have* Non-Specific Viral Symptoms (Nausea/Anorexia/Fatigue)
    - *May have* Jaundice
  - **90% →Chronic with Extrahepatic & Intrahepatic Manifestations:**
    - Asymptomatic for years (Usually Incidental Diagnosis)
    - May have Sporadic Mild Viral Illnesses + Jaundice
    - +/- Arthritis
    - +/- Glomerulonephritis
  - **END STAGE (CIRRHOSIS):**
    - 20-30% → *Cirrhosis* (within 10-30yrs)
    - 5% → *Hepatocellular Carcinoma* – (Hep C Directly inactivates P53)



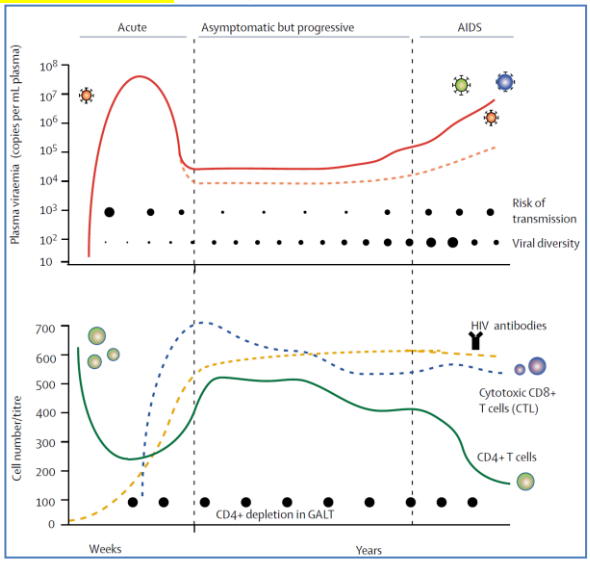


- **Investigations:**
  - **Usually discovered on Routine LFTs – (**Mildly ↑ ALT/AST**)**
  - **Hep C Serology – (**(+) Anti-HCV**)**
  - **Hep C PCR – (**(+) HCV-RNA**)**
- **Treatment:**
  - **Post-Exposure/Acute (Eg. Needlestick):**
    - ***IFN***
    - ***Ribavirin***
  - **Supportive Treatment:** in established disease.

UNISEX UROGENITAL Pathology:
STIS – HIV

*HIV (Notifiable Disease):

- **Aetiology:**
  - HIV
- **Transmission:**
  - **Blood** (IVDU, Transfusion)
  - **Body Fluids** (Sexual – Particularly Anal Sex)
  - **Vertical** (Cross-Placental & Breastmilk)
- **Pathogenesis:**
  - **Lymphotrophic** – Preferentially infects CD4-T-Cells → Integrates into Genome → Uses host DNA-Replication for Reproduction.
  - CD4-T-Cell Lysis → CD4-T-Cell Depletion (incl. Memory T-Cells) →**Immunosuppression By:**
    - ↓IFNy Production
    - ↓Antibody Production
    - ↓Antibody Isotype Switching
    - ↓Macrophage Activation
    - ↓CD8-T-Cell Activation
- **Clinical Features:**
  - **Symptoms:**
    - **1-2 months:**
      - **Acute infection** (Flu-like symptoms + Maculopapular Rash (ITP))
      - Following the acute infection, Antibody titres rise **(*Detectable after 2.5mths*)**
    - **2-4 Years:**
      - **Asymptomatic** Chronic Infection – (Equilibrium between T-Cells & Viral Mutation Rate)
    - **8 years:**
      - **Symptomatic** Chronic Infection – (Disequilibrium – HIV Quasispecies outnumber T-Cell Diversity → Body starts to lose the battle)
    - **10-12 years:** (If no intervention)
      - **AIDS** - Advanced infection – (T-Cell Depletion)
- **Diagnosis:**
  - Serology (Ab Detection)
  - Viral PCR (Ag Detection)
- **Complications:**
  - ↑Infections
  - ↑Cancer (Esp. **Kaposi's Sarcoma**),
- **Treatment:**
  - **Fusion Inhibitors – (Eg. CCR5 Inhibitors) -** Prevent binding of HIV to Cell
  - ***Reverse Trancriptase Inhibitors*** **(RTI's)** – (Blocks addition of nucleotides to DNA)



LECTURE:

Bloodborne viruses, HIV and the Immunocompromised Host

Human Retroviruses:

(ie. Those which have reverse transcriptase)

- **HIV-1 (Human Immunodeficiency Virus 1):**
  - Responsible for AIDS
- **HIV-2 (Human Immunodeficiency Virus 2):**
  - Less common
- **HTLV-1 (Human T-Cell Lymphotropic Virus 1):**
  - Can cause T-Cell leukaemia
- **HTLV-2 (Human T-Cell Lymphotropic Virus 2):**
  - Less common
- **Human Foamy Virus:**
- **Human Placental Virus/es**
- **Human Genome Viruses**

HUMAN RETROVIRUSES	
virus	**comment**
HTLV1	endemic in West Indies and SW Japan; transmission via blood, human milk; can cause adult T cell leukemia, and HTLV1-associated myelopathy, also known as tropical spastic paraparesis
HTLV2	uncommon, sporadic occurrence; transmission via blood; can cause hairy T cell leukemia and neurological disease
HIV-1, HIV-2	transmission via blood, sexual intercourse; responsible for AIDS, HIV-2 West African in origin, closely related to HIV-1 but antigenically distinct
human foamy virus	causes foamy vacuolation in infected cells; little is known of its occurrence or pathogenic potential
human placental virus(es)	detected in placental tissue by electron microscopy and by presence of reverse transcriptase
human genome viruses	nucleic acid sequences representing endogenous retroviruses are common in the vertebrate genome, often in well-defined genetic loci; acquired during evolutionary history; not expressed as infectious virus; function unknown; perhaps should be regarded as mere parasitic DNA

HUMAN RETROVIRUSES:
HIV – (HUMAN IMMUNODEFICIENCY VIRUS):

The Origins of HIV:

- **HIV-l and HIV-2 have sequence homology with corresponding viruses in African primates:**
  - :. It is Likely that HIV originated in African Primates → Crossed over to Humans.
- **Possibility of Further Transmissions:**
  - The original virus still exists in African Primates (& Is *STILL EVOLVING*)
  - :. Further transmission of similar viruses to Humans is Very Possible.
  - (If it has done it once, it will do it again)

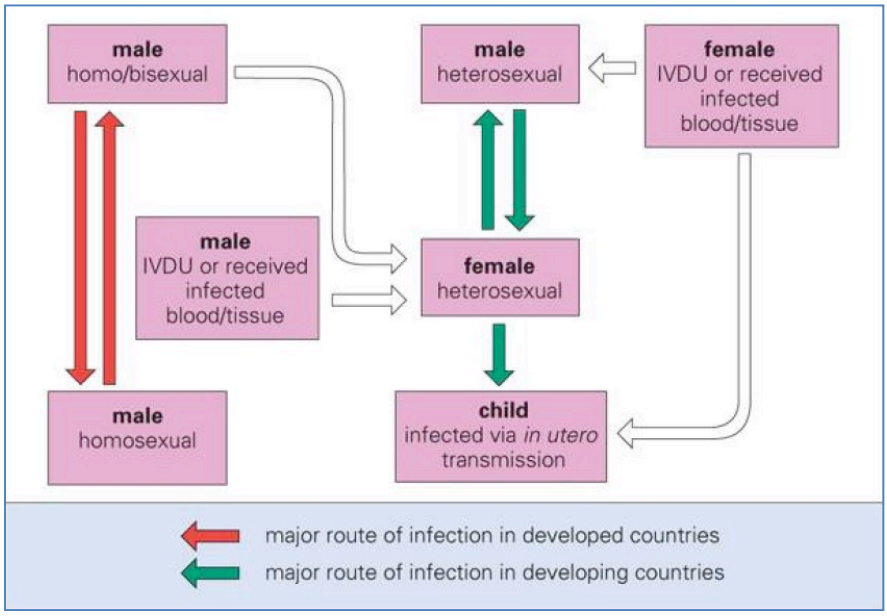
Epidemiology of HIV:

- **Sub-Saharan = Most Affected:**
  - 2/3 of all HIV cases
  - (24.7 million people in 2006.)
  - **75%** of all AIDS-Related Deaths occurred in sub-Saharan Africa
- **Developing Countries:**
  - High Prevalence
- **Developed Countries:**
  - Low Prevalence – (But Incidence is Increasing)
- **(HIV-2):**
  - Less virulent infection
  - Perinatal transmission is less common
  - Most common in West Africa

Transmission:

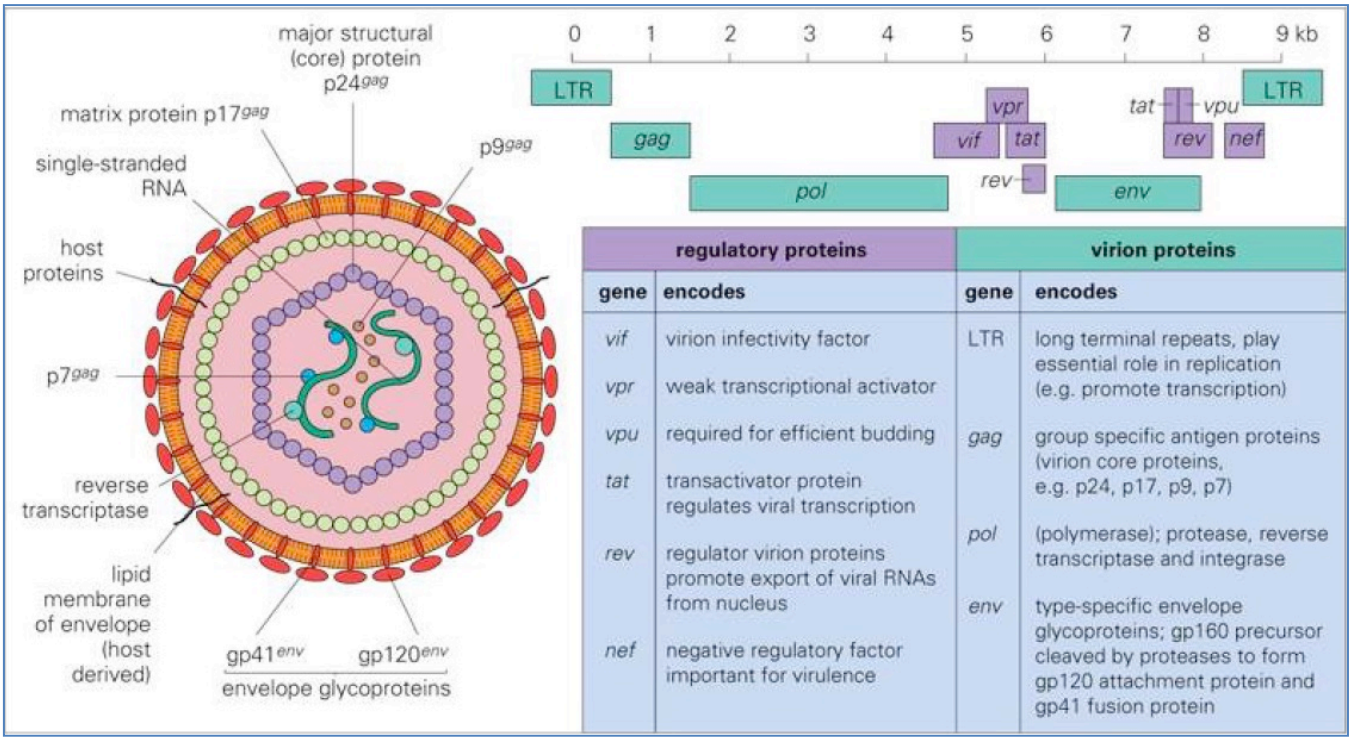
- **Sexual Transmission:**
  - 75% of transmission worldwide
  - **Risk Factors that Increase Chance of Sexual Transmission:**
    - **Trauma/Inflammation** - (The Virus must attach to CD4 receptors; Therefore presence of inflammatory cells @ Site of Inoculation vastly increases risk of transmission)
    - **Sexually Transmitted Diseases** (Eg. Gonorrhea, Chlamydia, trichomoniasis or vaginosis) – Because they lead to Inflammation in the Genital Region.
    - **Higher risk with Anal Sex rather than Vaginal or Oral Sex:**
      - Vagina is Stratified Squamous (Greater Barrier Protection)
      - Rectum is Simple Columnar (Less Barrier) + Anal Sex commonly causes bleeding.
  - **Developing Countries:**
    - Males→Females Transmission (heterosexual transmission)
    - Vertical Mother→Child transmission.
    - IV Drug use
    - Blood Transfusion
  - **Developed Countries:**
    - Male→Male Transmission (Homosexuality)
    - IV Drug use
- **Parenteral Transmission (Blood Transfusion/IV-Needle Sharing):**
  - Depends on Titre in the Blood & the Amount of Blood Transferred. (Determines the number of Infectious Doses Contained)
- **Perinatal:**
  - Transplacental infection is becoming one of the most important routes of transmission
  - Breastmilk.

- ***NB: Transmission is Surprisingly Difficult*:**
  - Risk of Percutaneous Exposure is ≈ 0.3%
  - Risk of Mucous Membranous Exposure ≈ 0.09%
  - **Factors =** *Amount of Blood & Titre of Virus*.



Structure of the HIV Virion & Contents:

- **Dicosahedral capsid**
- **2x *Separate Strands* of ssRNA**
- **Envelope with Glycoproteins (Incl. Gp120** – important for adhesion & entry to CD4 T-Cells)
- **Contains Reverse Transcriptase Enzymes:**
  - Necessary for Reverse Transcription of ssRNA genome into DNA to Integrate into host Genome.
- Gag ,Pol, Env – Open Reading Frames in Genome



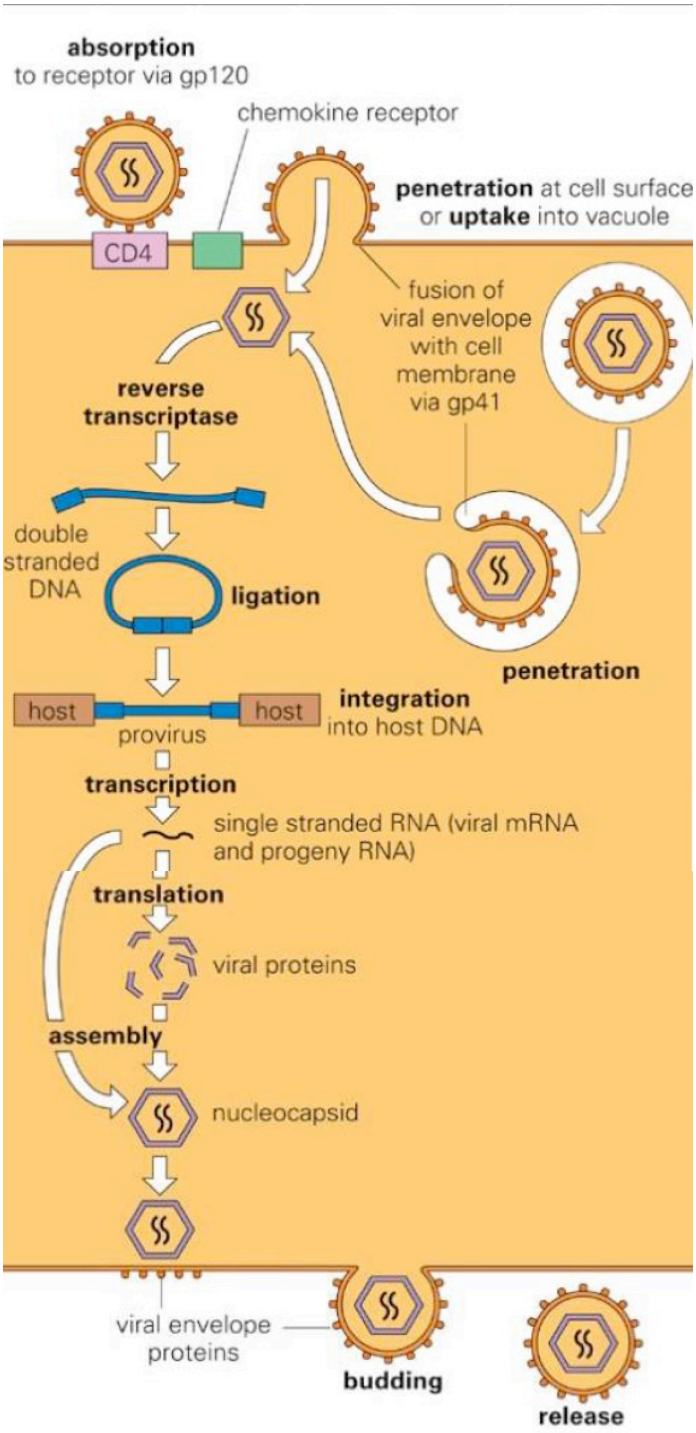
regulatory proteins		virion proteins	
gene	**encodes**	**gene**	**encodes**
vif	virion infectivity factor	LTR	long terminal repeats, play essential role in replication (e.g. promote transcription)
vpr	weak transcriptional activator		
vpu	required for efficient budding	*gag*	group specific antigen proteins (virion core proteins, e.g. p24, p17, p9, p7)
tat	transactivator protein regulates viral transcription		
rev	regulator virion proteins promote export of viral RNAs from nucleus	*pol*	(polymerase); protease, reverse transcriptase and integrase
		env	type-specific envelope glycoproteins; gp160 precursor cleaved by proteases to form gp120 attachment protein and gp41 fusion protein
nef	negative regulatory factor important for virulence		

Reverse Transcriptase Enzyme:

- **Necessary for DNA Production from the Positive-ssRNA in the Virus.**
  - Reverse Transcription of Positive-ssRNA genome into DNA to Integrate into host Genome.
    - → Produces ssDNA from ssRNA
    - Then →Produces dsDNA from ssDNA
- **NB: *Highly Error-Prone* → High Mutation Rate → Production of *QUASISPECIES*:**
  - Quasispecies = Mutant/Recombinant Viral Genomes
  - Quasispecies are constantly subject to Genetic Variation, Competition & Selection.
  - → Assists virus to persist in the host. (Overwhelms the Immune Response)

Process of HIV Infection (@ The Cellular Level):

- **GP120** on Virus Binds to CD4 Receptors
- **Fusion of Viral Envelope** with Cell Membrane → Uptake into cell.
- **Reverse Transcriptase:**
  - → Produces ssDNA from ssRNA
  - Then →Produces dsDNA from ssDNA
- **dsDNA→ Migrates to the Nucleus → Integrates into Host Genome**:
  - :. HIV Uses host DNA-Replication for Reproduction.
  - Is Transparent to the Immune System.
  - Virus replicates with DNA Replication or Cellular Protein Synthesis.
  - Can also be *transported* by migrating cells into other areas of the body – eg. Crossing the BBB.
- **Genes Transcribed & Translated** → Viral proteins
- **Assembly**
- **Budding** → Released

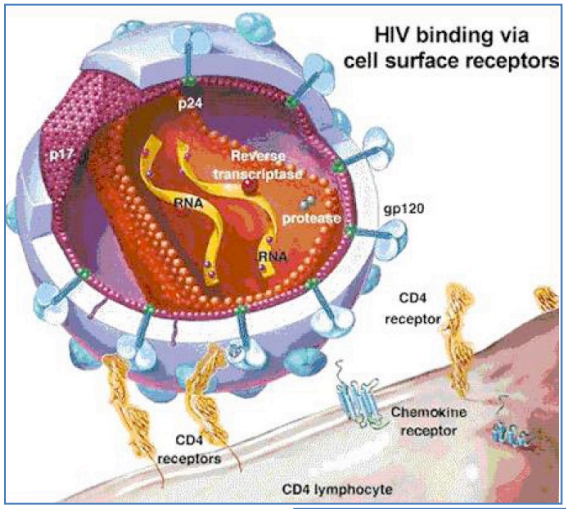


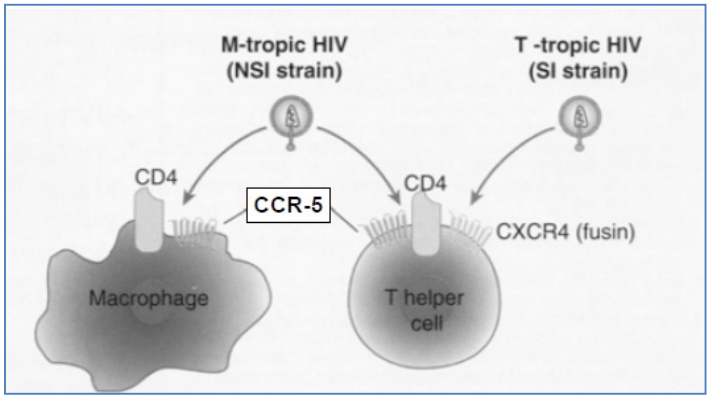
Susceptible Cells

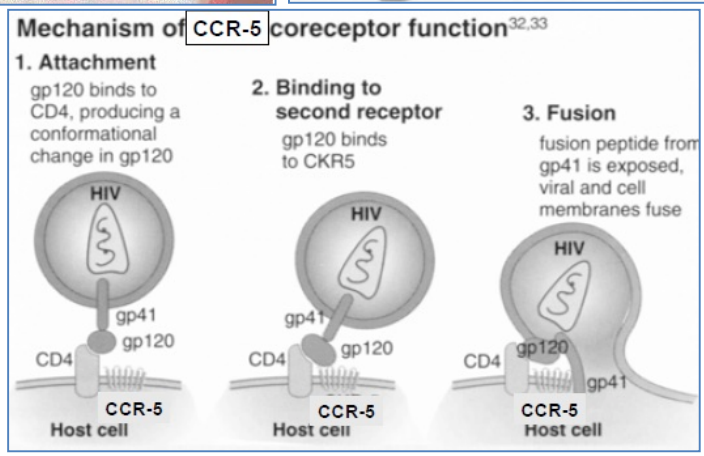
- ****T-Helper Cells**
- **But Also:**
  - **B lymphocytes**
  - **Macrophages/Monocytes**
  - **Dendritic cells**
  - **Microglia (In CNS)**

Major HIV Receptors:

- **1. The *CD4 molecule* – (on CD4-Th-cells)**
- **2. Chemokine Receptors - (act as *Co-Receptors* for the HIV):**
  - **T-cell Tropic strains:** use the ***CXCR-4 chemokine*** receptor
    - Preferentially Infect T-Cells
  - **Macrophage-Tropic strains:** use the ***CCR-5 chemokine*** receptor
    - Preferentially Infect Macrophages
    - (**NB:** Macrophages can readily cross the BBB → Infect Glial Cells → Produce cytokines → wipe out the neurons → AIDS Dementia)







Typical timescale of HIV infection

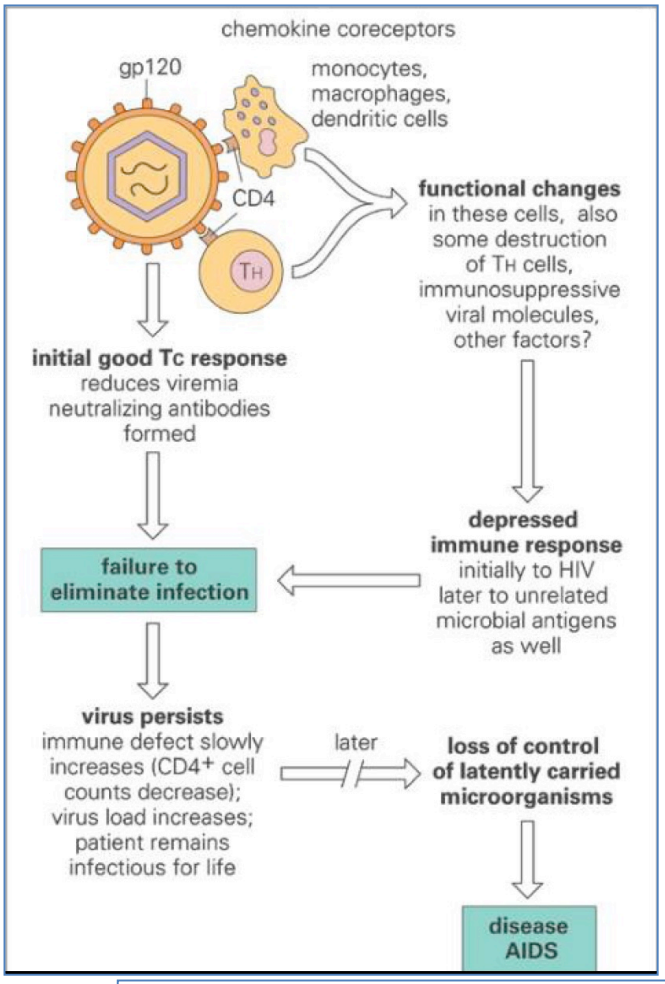
- **1-2 months:**
  - Acute infection
  - Following the acute infection, Antibody titres rise **(*Detectable after 2.5mths*)**
- **2-4 Years:**
  - Asymptomatic infection
- **8 years:**
  - Symptomatic infection
- **10-12 years:**
  - Advanced infection (If no intervention)

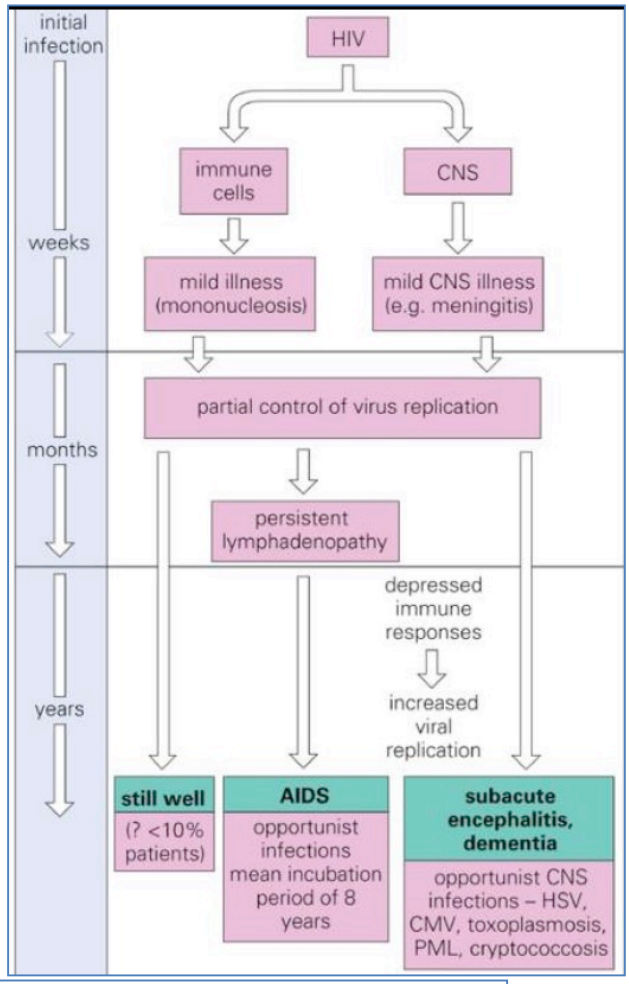
Pathogenesis of AIDS:

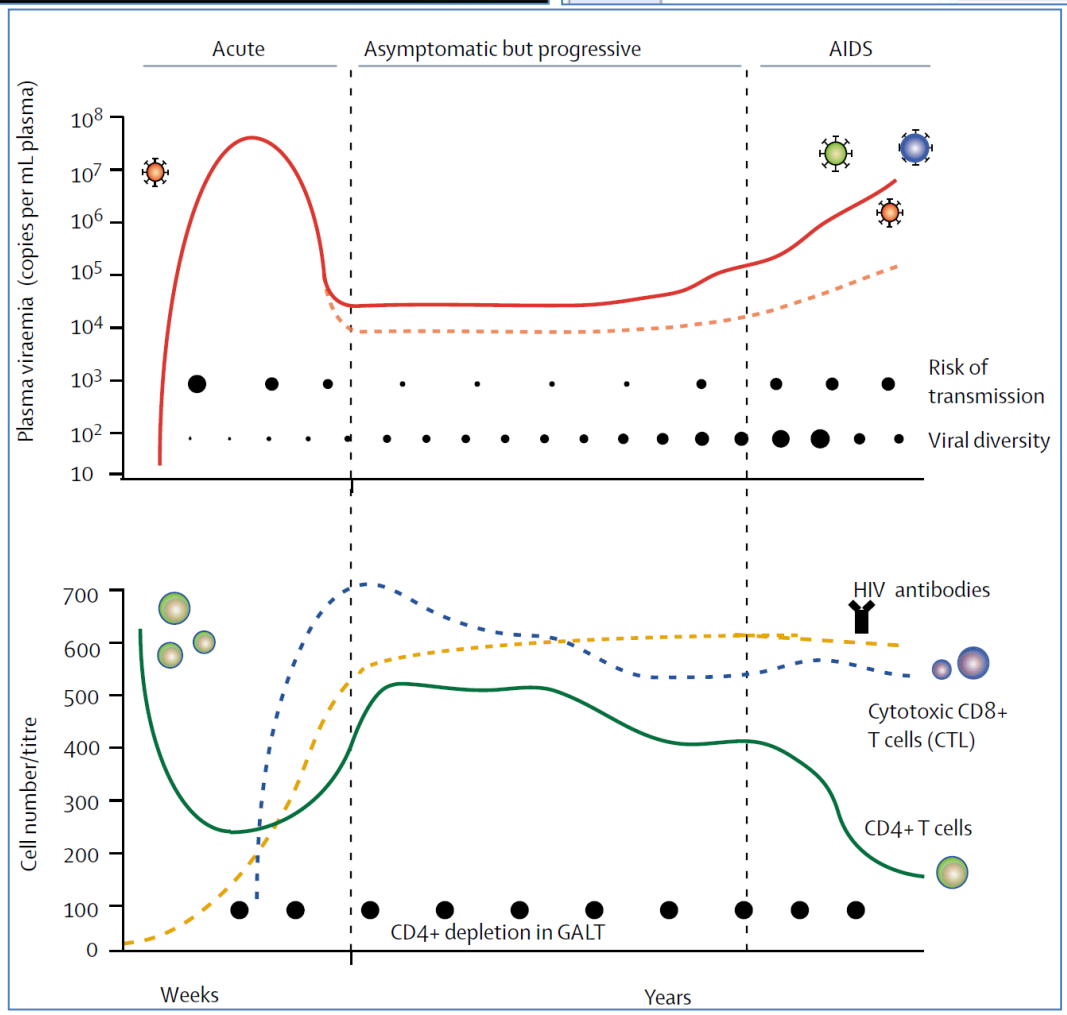
- **1. Acute Infection:** (High Risk of Transmission)
  - **Symptoms:**
    - Flu-Like Symptoms
    - Maculopapular Rash (AKA: Immuno-Thrombocytopaenic Purpura)
  - **Characterised by:**
    - High plasma Viraemia (red line, top)
    - Massive Depletion of CD4/CCR5 Low CD4 ***Memory Cells*** in the ***Mucosal Associated Lymphoid Tissues (MALT).*** (green line, bottom)
      - Loss of Memory Cells requires constant immune activation → Hyperactive immune system
      - During this period, many Quasispecies will be made (due to high polymerase error rate & Rapid CD4-Cell Turnover)
    - Absence of HIV-1 specific antibodies (orange line, bottom).
  - **Viraemia drops as cytotoxic CD8+ Tlymphocytes (CTL) develop:**
    - (blue line, bottom)
    - An individual ***Viral-Load Set Point*** is reached during chronic infection.
      - (***Viral set points*** differ greatly among individuals (eg, red dotted line, top) and predict disease progression.)
  - **NB: Takes weeks-months for antibodies to rise.**

- **2. Chronic (Asymptomatic) Infection:**
  - Ineffective cell mediated immune responses lead to the chronic stage of the infection
  - There is Chronic Immune Activation → CD4+ T-cell Depletion (Driven into Apoptosis)
  - Viral diversity increases throughout the disease (closed circles, top).
  - As CD4-T-Cells are Depleted, Viral Titre Rises.
  - Eventually, the virus produces more quasispecies, than the amount of specific CD8-T-cells the body can produce.

- **3. AIDS (Symptomatic):** (High Risk of Transmission)
  - The *Terminal* Stage of the Disease.
  - There are too many HIV Quasispecies for the CD8-Tc-Cells & Antibodies to deal with.
  - **How HIV Causes Immunosuppression:**
    - **CD4 Depletion Via:**
      - Direct CD4-T-Cell Lysis
      - Cytotoxic T-Cells kill CD4-T-Cell
      - Apoptosis of CD4-T-Cell
      - Infected CD4-T-Cells can fuse together →form *'Syncitia'* → Removed by Spleen.
      - (Ie. Predominantly via the Immune Response, not the Virus)
    - **CD4 Depletion → Immunosuppression By:**
      - ↓IFNy Production
      - ↓Antibody Production
      - ↓Antibody Isotype Switching
      - ↓Macrophage Activation
      - ↓CD8-T-Cell Activation
    - **→→Loss of the Adaptive Immune System → Opportunistic Infections.**
  - **HIV can lead to Death of Neurons (AIDs Dementia). How?:**
    - Infected Macrophages can cross the BBB → Infect Glial Cells (Esp. Astrocytes)→ Glia Produce TNF cytokines → Kill Neurons → AIDS Dementia
- **(NB: CD4:CD8 ratios can be a good marker for disease progression)**

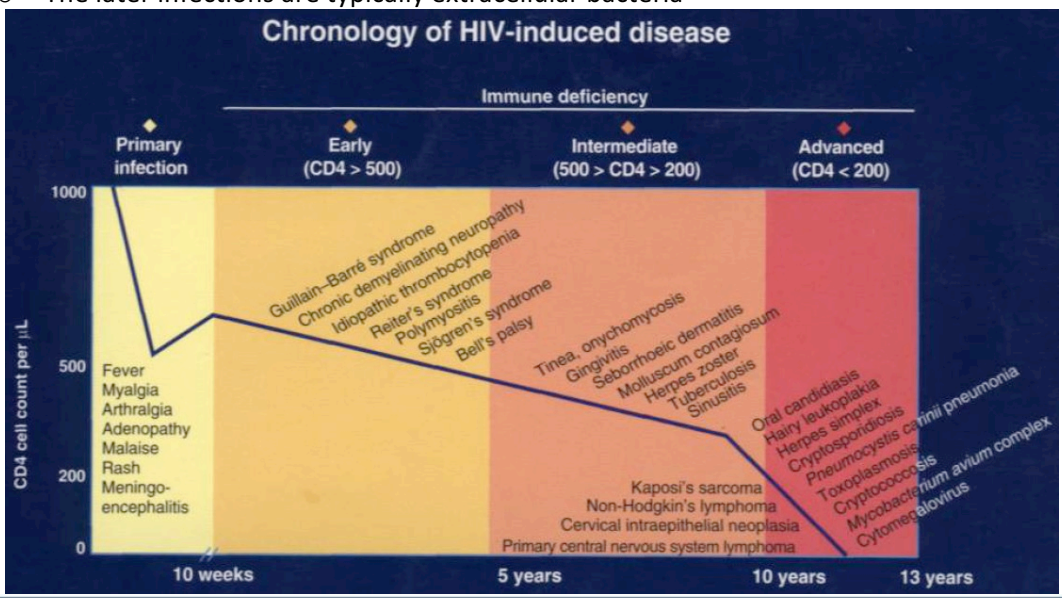






Opportunistic Infections & Tumours in AIDS:

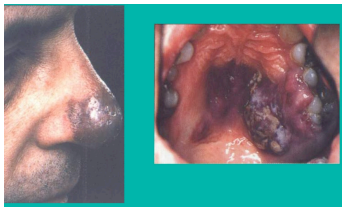
- Loss of CD4 Cells →↓ production of IFNγ → ↑Intracellular Viral/Bacterial Infections.
- **What do the common opportunistic infections associated with AIDS have in common?**
  - Infections where IFNγ (from Th-Cells) is really important to protection are the first infections seen (Ie. Those with intracellular viruses/bacteria).
  - The later infections are typically extracellular bacteria



OPPORTUNIST INFECTIONS AND TUMORS IN AIDS	
viruses	disseminated CMV (including retina, brain, peripheral nervous system, gastrointestinal tract) HSV (lungs, gastrointestinal tract, CNS, skin) JC virus (brain – PML) EBV (hairy leukoplakia, primary cerebral lymphoma)
bacteria*	mycobacteria (e.g. *Mycoplasma avium, M. tuberculosis* – disseminated, extrapulmonary) *Salmonella* (recurrent, disseminated) septicemia
protozoa	*Toxoplasma gondii* (disseminated, including CNS) *Cryptosporidium* (chronic diarrhea) *Isospora* (with diarrhea, persisting more than one month)
fungi	*Pneumocystis jiroveci* (pneumonia) *Candida albicans* (esophagitis, lung infection) *Cryptococcus neoformans* (CNS) histoplasmosis (disseminated, extrapulmonary) *Coccidioides* (disseminated, extrapulmonary)
tumors	Kaposi's sarcoma** B cell lymphoma (e.g. in brain, some are EBV induced)
other	wasting disease (cause unknown) HIV encephalopathy

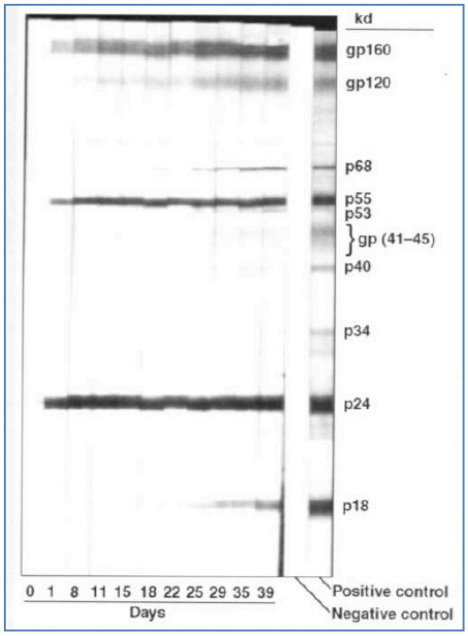
*also pyogenic bacteria (e.g. *Haemophilus, Streptococcus, Pneumococcus*) causing septicemia, pneumonia, meningitis, osteomyelitis, arthritis, abscesses etc.; multiple or recurrent infections, especially in children
**associated with HHV8, an independently-transmitted agent; 300-times as frequent in AIDS as in other immunodeficiencies

- **Kaposi's Sarcoma:**
  - **Produced by Human Herpes Virus 8 (But *Strongly Associated with HIV*)**
    - → Causes massively vascularised tumours
  - Is transmitted sexually
  - Is 300x as prevalent in AIDs than other Immunodeficiencies.



Diagnostic assays

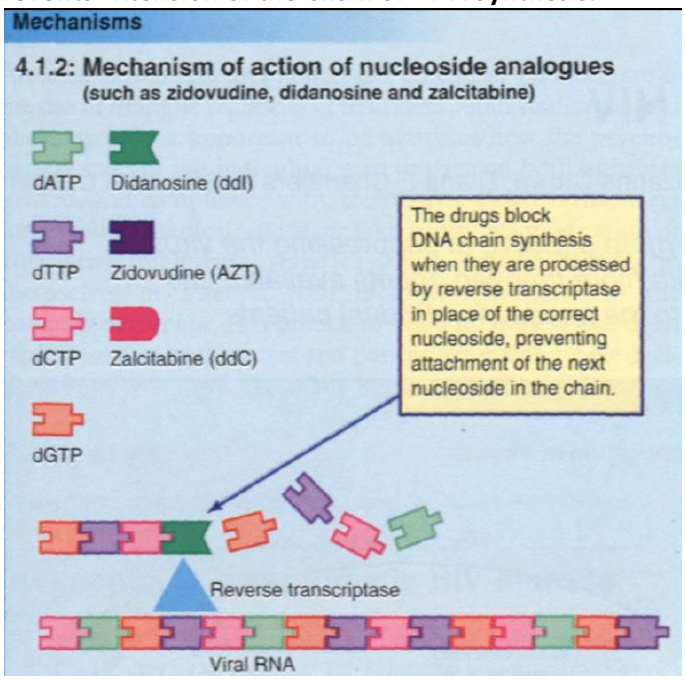
- **Antibody Detection:** (Only detectable *After* the Acute Response):
  - ELISA
  - Western blotting
  - Rapid agglutination or immunochromatography (RDTs)
- **Antigen detection:** (The Presence of Antigen will Parallel the Viraemia – Ie. Detectable In the Acute & Terminal Phases – NB: You won't detect antigen in the intermediate phase)
  - ELISA for p24
  - Western Blotting (Identifies Virus Proteins) – *More Specific than ELISAs*.
    - Take the virus, break it up into various proteins.
    - Proteins separated on basis of size by electrophoresis
    - Transfer to nitrocellulose
    - Blot patient's serum onto the nitrocellulose (Antibody reactions can be identified)



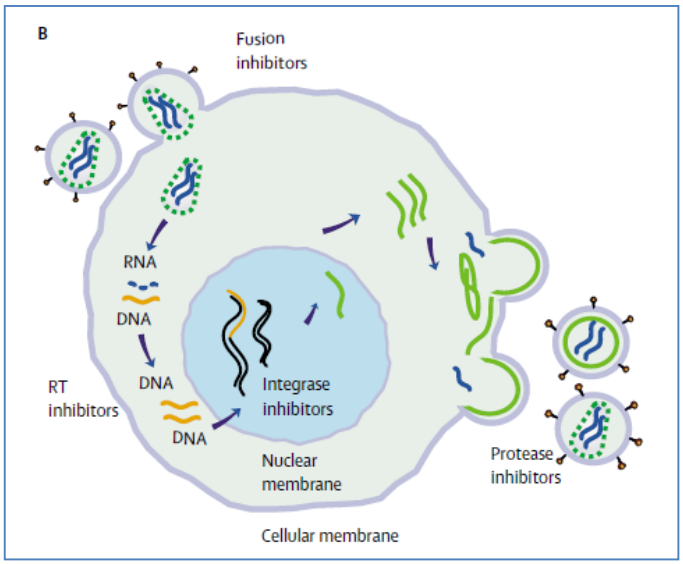
- **Genome Detection:**
  - PCR (Detects DNA)
  - RT-PCR ("viral load" – able to monitor progression of AIDS treatment)(Detects RNA)
- **Viral isolation**

HIV Drug Options:

- **Fusion Inhibitors:**
  - **Eg. CCR5 Inhibitors:**
    - Prevent HIV from fusing with the Cellular Membrane
- **Reverse Trancriptase Inhibitors (RTI's)**
  - **Nucleoside Reverse Trancriptase Inhibitors (NRTIs)** – (Blocks addition of purines/purymadines to DNA)
    - Zidovudine (azidothymidine, AZT)
    - Didanosine (dideoxyinosine, ddi)
    - Zalcitabine (dideoxycytidine, ddC)
    - Lamivuridine (3TC) (complementary resistance spectrum to AZT)
    - → **Prevents Extension of the Chain of DNA Synthesis.**



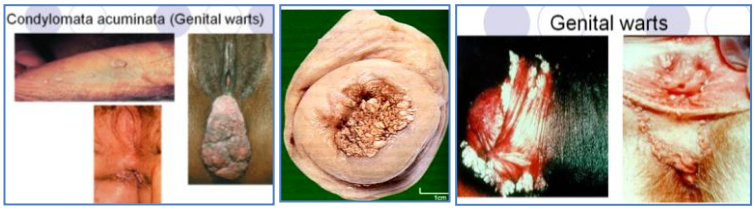
  - **Non-Nucleoside Reverse Trancriptase Inhibitors (NNRTIs):**
    - Targets the Non-Nucleoside-Binding Site of the HIV's Reverse Transcriptase → Inhibits RT Activity.
- **Protease inhibitors** – (Next generation of drugs):
  - Prevents cleavage of Inactive Poly-Proteins into Active Viral Proteins.
  - → Assembly of ineffective (Non-Infective) viruses.



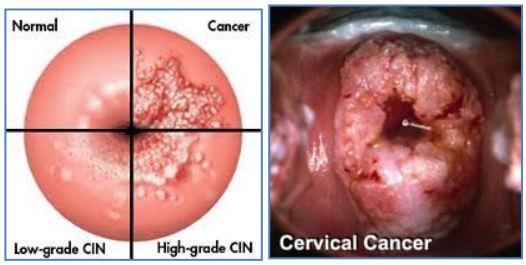
UNISEX UROGENITAL Pathology:
STIS - HUMAN PAPILLOMA VIRUS

HUMAN PAPILLOMA VIRUS:

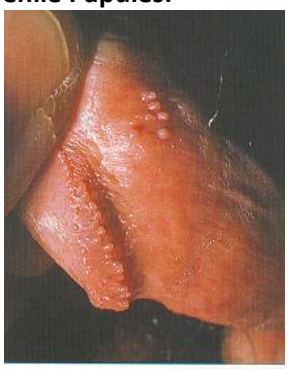
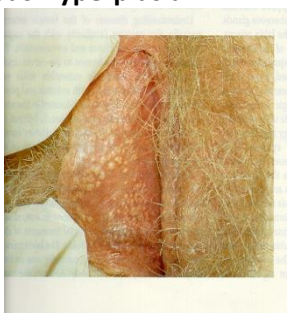
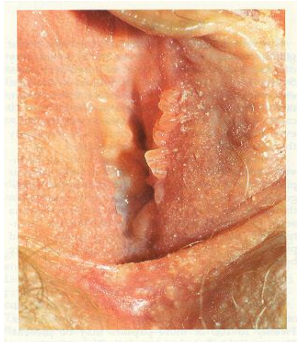
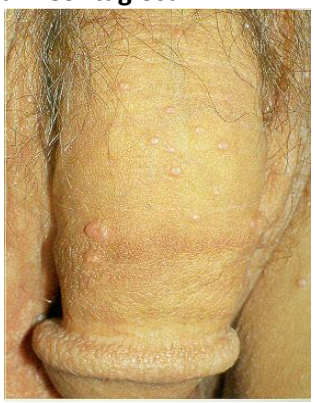
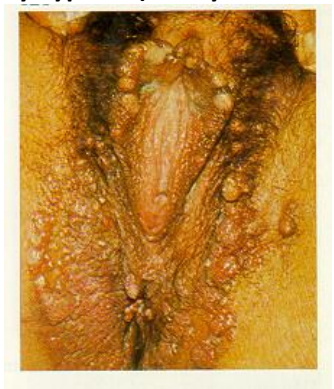
- **Aetiology:**
  - ***HPV Types 6 & 11*** → Genital Warts (Preventable by ***Gardasil)***
  - ***HPV Types 16, 18 & 45*** → Cervical Cancer (Somewhat preventable by ***Gardasil***)
- **Transmission:**
  - (Direct Contact/Sexual Transmission – Highly Contagious)
- **Pathogenesis:**
  - Contact & Fomite Transmission
  - **3mth Incubation Period**
  - HPV Infection → Cell-Cycle Dysregulation → Benign Overgrowth
- **Morphology:**
  - **Macro:**
    - **Genital/Cervical Warts (6/11) -** Warty Papillomas – External Genitalia/Oral/Anal.



    - **Cervical Ca (16/18/45)** – Abnormal looking cervix (Loss of normal smoothness, obvious dysplasia)



  - **Micro:**
    - **Genital/Cervical Warts (6/11) – *"Koilocytosis"*** = Cells with "halo" cytoplasm
    - **Cervical Ca (16/18/45)** – *Squamous Cell Carcinomas*, or *Adenocarcinomas*
- **Clinical Features:**
  - **Symptoms:**
    - Infection is long-term, latent, and usually asymptomatic.
    - **Genital Warts (6/11)** → Painless, papillary outgrowth on external genitalia
    - **Cervical Ca (16/18/45)** → Abnormal Vaginal Bleeding, Dyspareunia, Weight-Loss, Fatigue, Pelvic Pain (May be Asymptomatic)
- **Diagnosis:**
  - ***Papsmear &/or Cervical Biopsy***
  - DNA detection
  - Tam Pap (Self-sampling HPV DNA test)
- **Complications:**
  - *Cervical Cancer* - Metastasis
- **Treatment:**
  - **Genital Warts (6/11)** – ***Podophylin*** Cream, *Aldara (**Imiquimod**)* Cream, ***Excision*** or ***Cryotherapy*** – BUT Will Recur.
    - **+ Counselling**
    - **+/- Refer to Gynae if –** Extensive, Chronic/Recurrent, Cervical or Rectal.
  - **Cervical Ca (16/18/45)** – Surgical Excision +/- Chemotherapy +/- Radiotherapy
- **Prognosis:**
  - **Genital Warts (6/11) – Benign**
    - 70% clear by 12mths (NB: Warts may disappear, but virus may persist)
  - **Cervical Ca (16/18/45) - Malignant**

- **Differential Diagnoses:**
  - **Pearly Penile Papules:**
    - 
  - **Sebaceous Hyperplasia:**
    - 
  - **Vestibular Papillae:**
    - 
  - **Molluscum Contagiosum:**
    - 
  - **Secondary Syphilis (Condylomata Lata):**
    - 

UNISEX UROGENITAL Pathology:
INFERTILITY

Infertility Definition:

- **Generic:** "Failure to conceive following >1yr of regular unprotected sex during fertile periods"
- **Primary:** "As above – but in a Nulligravid woman"
- **Secondary:** "As above – but in a uni/multi-parous woman"

Infertility – Epidemiology:

- Incidence = 20%
- Male Causes = 40%
- Female Causes = 40%
- Combined M&F = 20%

Evaluation of Infertility:

1. **Male Factor** – ***Adequate functional & motile sperms?***
   a. **Sperm Concentration:** Normal = >20million/mL (<20M/mL = Oligospermia; No sperm = Aspermia)
   b. **Motility:** Normal = >50% are forward progressive.
   c. **Morphology:** Normal = >30% normal morphology
2. **Ovulation** – ***Is ovulation occurring?***
   a. **Menstrual History:** Normal = 28 +/- 7days
   b. **Cervical Mucus Studies** (@ Day 12-14)
   c. **Ultrasound Scan** (Follicle Monitoring @ Day 10)
   d. **Hormonal Assays** (Oestrogen @ Day 12, LH Levels @ Day13 , Progesterone @ Day21)
   e. **Laparoscopy** (looking for ruptured ovarian follicle & Luteum @ Day 21-23)
3. **Cervical Function** – ***Can the sperm get through the cervix?***
   a. **Post-Coital Test (PCT)** (Intercourse on D12-13 → Examine Cervical Secretions @ 8hrs → >10 Actively Motile Sperms per High-Power Field = Satisfactory)
4. **Tubal Function**– ***Can the sperm & egg meet?***
   a. **Hystero-salpingography** (Radiological Dye) (Both @ D7-10)
   b. **Laparoscopy + Blue Dye** (Naked Eye) (Both @ D7-10)
   c. **Falloscopy** (Hysteroscopic examination of proximal fallopian tubes)
   d. **Salpingoscopy** (Laparoscopic examination of distal fallopian tubes)
5. **Uterine Function** – ***Can Implantation occur and be manintained?***
   a. **Ultrasound Scan** (Endometrium Normal? Or Fibroids/Polyps/Congenital) (@ Day 7-10)
   b. **Hysteroscopy** (Endometrium Normal? Or Fibroids/Polyps/Congenital) (@ Day 7-10)

ART – Assisted Reproductive Technologies *(NB: <30% Success Rate)*:

- **Ovulation Induction** (Using exogenous hormones to induce ovulation)
- **Luteal Phase Support** (Supplemental Progesterone *Post-ovulation* → Prevents early Menstruation)
- **IUI – Intrauterine Insemination** (Direct insemination into the uterus - Bypasses Cervical Barriers)
- **IVF-ET – InVitro Fertilisation & Embryo Transfer** (Fertilisation outside the body → Direct Embryo Transfer into Uterus)
- **GIFT –** Gamete intra fallopian transfer (sperm & egg artificially injected into fallopian tubes)
- **ZIFT** – Zygote intra fallopian transfer (fertilised egg transferred into the fallopian tubes)
- **ICSI – IntraCytoplasmic Sperm Inection** (Sperm directly injected into Oocyte *In-Vitro*)
- **TESA – Testicular Epididymal Sperm Aspiration** (Bypasses any semen/ejaculatory problems)
- **(Surrogacy/Adoption)**

Infertility - Female Causes:

- **Endometriosis:** ***(NB: 40-60% of women conceive within 18mths of surgery)***
- **Pelvic Inflammatory Disease (PID):**
- **Polycystic Ovarian Syndrome (PCOS):**
- **Hypothalamic Amenorrhoea** **(Underweight/Eating Disorders/Female Athlete Triad)**
- **Other Causes:**
    - **Advanced Maternal Age (>35)/ Menopause (~>45)**
    - **Smoking (Reduces Fertility by 60%)**
    - **Chemotherapy/Radiotherapy**
    - **Turner's Syndrome**
    - **Ovarian Cancer**
    - **Anti-Sperm Antibodies**

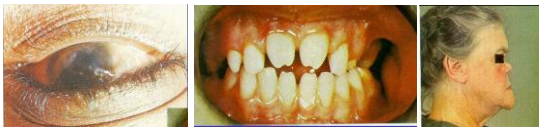
Infertility - Male Causes:

- **Pre-Testicular Problems:**
    - **Pituitary Failure ("*Hypogonadotrophic Hypogonadism*")**
    - **Strenuous Riding (Cycling/Horseriding)**
    - **Chemotherapy/Radiotherapy**
    - **Anabolic Steroids**
    - **Impotence**
- **Testicular Problems:**
    - **Klinefelters Syndrome**
    - **Testicular Cancer**
    - **Cryptorchidism**
- **Post-Testicular Problems:**
    - **Vas-Deferens Fibrosis (Chlamydia/Gonorrhoea)**
    - **Vas-Deferens Occlusion (Cystic Fibrosis)**
    - **Vas-Deferens Compression by Varicocoele**
    - **Retrograde Ejaculation (Bladder Neck Sphincter Dysfunction – Eg. BPH, Prostate Surgery, Spinal Injury, Diabetic Neuropathy, Hypertension)**
- **Sperm Problems:**
    - **Eg. Low Sperm Count (Oligospermia <20M sperm/mL; Aspermia 0.sperm/mL)**
    - **Eg. Low Sperm Motility**
    - **Eg. Abnormally-Shaped Sperm**

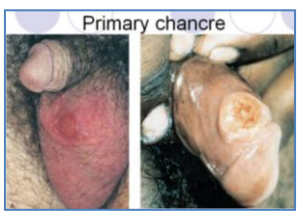
UNISEX UROGENITAL Pathology:
STIS – SYPHILIS

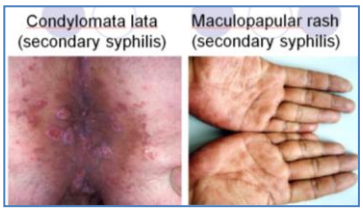
*SYPHILIS (Notifiable Disease):

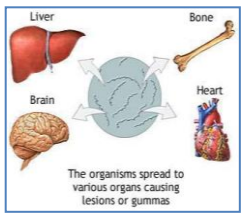
- **Aetiology:**
  - Treponema Pallidum (Spirochaete)
- **Transmission:**
  - Contact, Sexual, & Blood (IVDU) Transmission.
  - **!!Vertical – 100% Transmission if mother is untreated!!**
- **Pathogenesis:**
  - **Four Stages** – *Primary, Secondary, Latent, Tertiary (CVS/Neurosyphilis)*
- **Clinical Features:**
  - ***Primary Syphilis:***
    - **10d-10wks Post-Infection** →Painless Chancre (ulcer) + Lymphadenopathy
  - ***Secondary Syphilis –*** (NB: Most contagious during secondary syphilis)***:***
    - **4-8wks Post-Chancre** → Characteristic Rash (Palms, Feet), Lymphadenopathy, Hepatosplenomegaly, Flu-like Illness & "Condylomata Lata" (Wart-like Growths)
  - ***Latent Syphilis:***
    - **Mths-Lifetime Post-Secondary-Stage** → Asymptomatic but positive serology
    - ¼ of cases → Tertiary Syphilis (Most remain latent for life)
  - ***Tertiary Syphilis:***
    - **>1yr Post-Infection** → Formation of *'Gummas'* (Highly-Destructive → bones, skin, nervous tissue, heart & arteries) → Serious complications are Cardiovascular (Aneurysms) & Neurosyphilis (Dementia/Psychosis/Paresis/etc)
- **Diagnosis:**
  - **Dark-Field Microscopy**
  - **Serology (May remain +ve for years after recovery)**
    - **1. TPHA:** *T. pallidum* haemagglutination assay
    - **2. FTA-AB:** Fluorescent Treponemal Antibody Absorption
    - **3. VDRL:** Venereal Disease Research lab tests.
    - **4. RPR – Diagnostic Standard:** Rapid Plasma Reagin
- **Complications:**
  - *Neurosyphilis* → Meningitis, paresis, personality change, ataxia, dementia.
  - *Cardiovascular Syphilis* → Typically Syphilitic Aortitis → Aneurysm
  - ***Congenital Syphilis – 25% Miscarriage; 25% Neonatal Death; The rest are DEFORMED!!***
    - → **Early Congenital Syphilis:**
      - Snuffles – Profuse Runny Nose
      - Cutaneous Lesions (Often on Palms and Soles)
    - →**Late Congenital Syphilis:**
      - Frontal bossing
      - Short maxilla
      - High palatal arch
      - Deafness



- **Treatment:**
  - ***Azithromycin***/***Doxycycline***
  - Or Single Dose ***IM Penicillin-G***







Continue Reading For Bonus Supplementary Study Materials…

GY Gynecology

Dalia Bibr, Katie Bies, Christine Edwards, and **James CM Wang,** chapter editors
Hasaan Chaudhry and **Nardin Samuel,** associate editors
Alex Cressman and **Shany Gertzbein,** EBM editors
Dr. Sari L. Kives, Dr. Ally Murji, and **Dr. Fay Weisberg,** staff editors

Basic Anatomy Review

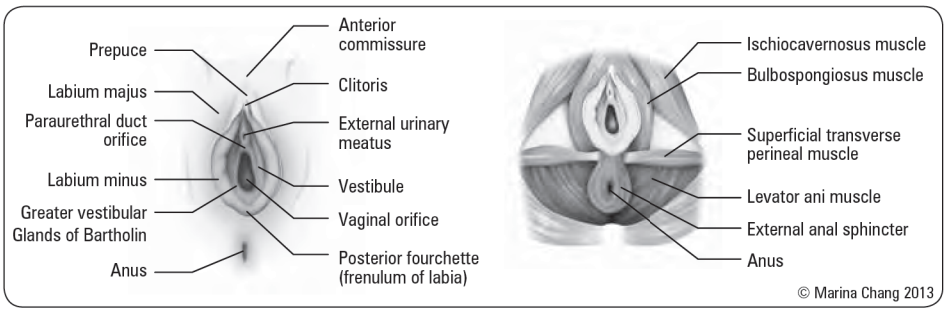


Figure 1. Vulva and perineum

A. EXTERNAL GENITALIA

- referred to collectively as the vulva
- blood supply: internal pudendal artery
- sensory innervation: pudendal nerve
- lymphatic drainage: inguinal nodes

B. VAGINA

- muscular canal extending from cervix to vulva, anterior to rectum and posterior to bladder
- lined by rugated, stratified-squamous epithelium
- upper vagina separated by cervix into anterior, posterior, and lateral fornices
- blood supply: vaginal branch of internal pudendal artery with anastamoses from uterine, inferior vesical, and middle rectal arteries

C. UTERUS

- thick walled, muscular organ between bladder and rectum, consisting of two major parts:
  - uterine corpus
    - blood supply: uterine artery (branch of the internal iliac artery)
  - cervix
    - blood supply: cervical branch of uterine artery
- supported by the pelvic diaphragm, the pelvic organs, and 4 paired sets of ligaments
  - round ligaments: travel from anterior surface of uterus, through broad ligaments, and inguinal canals then terminate in the labia majora
    - function: anteversion
    - blood supply: Sampson's artery (branch of uterine artery running through round ligament)
  - uterosacral ligaments: arise from sacral fascia and insert into posterior inferior uterus
    - function: mechanical support for uterus and contain autonomic nerve fibres
  - cardinal ligaments: extend from lateral pelvic walls and insert into lateral cervix and vagina
    - function: mechanical support, prevent prolapse
  - broad ligaments: pass from lateral pelvic wall to sides of uterus; contain fallopian tube, round ligament, ovarian ligament, nerves, vessels, and lymphatics
- infundibulopelvic ligament: continuous tissue that connects ovary to pelvic wall
  - contains the ovarian artery, ovarian vein, ovarian plexus, and lymphatic vessels
- position of the uterus
  - anteverted (majority)
  - retroverted

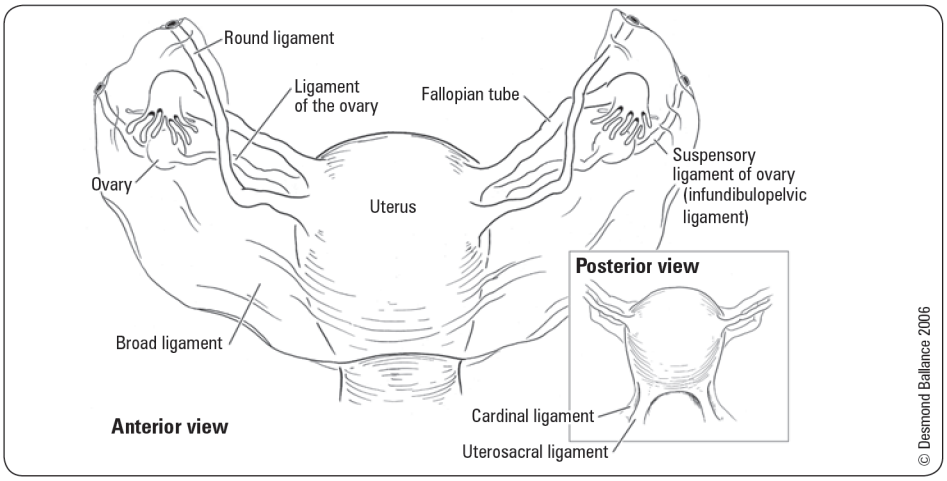


Figure 2. External genital organs

Acronyms

β-hCG	beta-human chorionic gonadotropin
AFP	alpha-fetoprotein
AIS	androgen insensitivity syndrome
ASCUS	atypical squamous cells of undetermined significance
AUB	abnormal uterine bleeding
BMI	body mass index
BSO	bilateral salpingo-oophorectomy
BV	bacterial vaginosis
CAH	congenital adrenal hyperplasia
CMV	cytomegalovirus
D&C	dilatation and curettage
DES	diethylstilbestrol
DHEA	dihydroepiandrosterone
DMPA	depo-medroxyprogesterone acetate or Depo-Provera®
DUB	dysfunctional uterine bleeding
DVT	deep venous thrombosis
EPC	emergency postcoital contraception
FSH	follicle stimulating hormone
GA	gestational age
GIFT	gamete intrafallopian transfer
GnRH	gonadotropin-releasing hormone
GTD	gestational trophoblastic disease
GTN	gestational trophoblastic neoplasia
HERS	heart and estrogen/progestin replacement study
HMG	human menopausal gonadotropin
HPO	hypothalamic-pituitary-ovarian
HPV	human papillomavirus
HRT	hormone replacement therapy
HSG	hysterosalpingography
HSIL	high grade squamous intraepithelial lesion
HSV	herpes simplex virus
IBD	inflammatory bowel disease
ICSI	intracytoplasmic sperm injection
ITP	immune thrombocytopenic purpura
IUD	intrauterine device
IUI	intrauterine insemination
IVDU	intravenous drug use
IVF	*in vitro* fertilization
IVM	*in vitro* maturation
JRA	juvenile rheumatoid arthritis
LDH	lactate dehydrogenase
LEEP	loop electrosurgical excision procedure
LH	luteinizing hormone
LHRH	luteinizing hormone releasing hormone
LMP	last menstrual period
LN	lymph node
LNMP	last normal menstrual period
LSIL	low grade squamous intraepithelial lesion
LVSI	lymphovascular space involvement
MRKH	Mayer-Rokitansky-Küster-Hauser
NK	natural killer
OCP	oral contraceptive pill
OGTT	oral glucose tolerance test
PCOS	polycystic ovarian syndrome
PCR	polymerase chain reaction
PG	prostaglandin
PID	pelvic inflammatory disease
PMDD	premenstrual dysphoric disorder
PMN	polymorphonuclear neutrophils
PMS	premenstrual syndrome
RPR	rapid plasma reagin
SCC	squamous cell carcinoma
SERMs	selective estrogen receptor modifiers
SHBG	sex hormone binding globulin
SHG	sonohysterography
SSRI	selective serotonin reuptake inhibitors
STI	sexually transmitted infections
TAH	total abdominal hysterectomy
TET	tubal embryo transfer
TH	total hysterectomy
TOT	tension-free obturator tape
TSH	thyroid stimulating hormone
TVT	tension-free vaginal tape
TZ	transformation zone
VDRL	venereal disease research laboratory
VIN	vulvar intraepithelial neoplasia
VTE	venous thromboembolism
vWD	von Willebrand's disease
W/D	withdrawal
WHI	Women's Health Initiative
ZIFT	zygote intrafallopian transfer

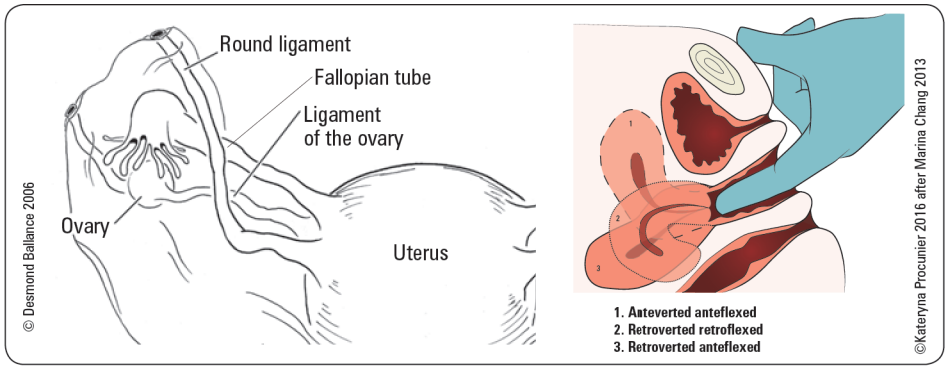


Figure 3. Positioning of uterus

Determination of uterine position by clinical exam
- If cervix faces anteriorly (under the urethra and less easily accessible), i.e. toward vaginal orifice, more likely RETROVERTED UTERUS
- If cervix faces posteriorly (easily accessible), i.e. toward sacrum or rectum, more likely ANTEVERTED UTERUS
- If uterus palpable on bimanual exam, more likely ANTEVERTED UTERUS

D. FALLOPIAN TUBES
- 8-14 cm muscular tubes extending laterally from the uterus to ovary
- interstitial, isthmic, ampullary, and infundibular segments; terminates at fimbriae
- mesosalpinx: peritoneal fold that attaches fallopian tube to broad ligament
- blood supply: uterine and ovarian arteries

"Water Under the Bridge"
The ureters run posterior to the uterine arteries

E. OVARIES
- consist of cortex with ova and medulla with blood supply
- supported by infundibulopelvic ligament (suspensory ligament of ovary)
- mesovarium: peritoneal fold that attaches ovary to broad ligament
- blood supply: ovarian arteries (branches off aorta), left ovarian vein (drains into left renal vein), right ovarian vein (drains into inferior vena cava)

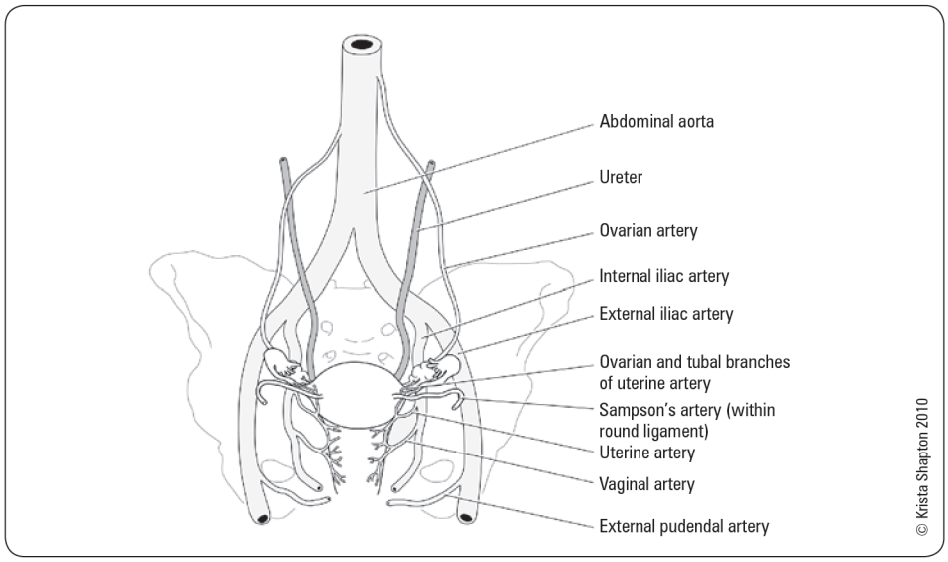


Figure 4. Vascular supply

Stages of Puberty
"Boobs, Pubes, Grow, Flow"
Thelarche, Pubarche, Growth spurt, Menarche

Menstruation

Stages of Puberty

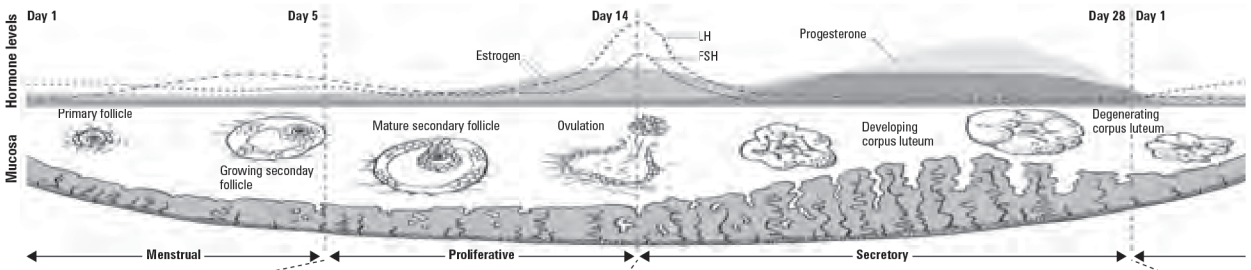
- see Pediatrics, P31
- adrenarche: increase in secretion of adrenal androgens; usually precedes gonadarche by 2 yr
- gonadarche: increased secretion of gonadal sex steroids; ~age 8 yr
- thelarche: breast development
- pubarche: pubic and axillary hair development
- menarche: onset of menses, usually following peak height velocity and/or 2 yr following breast budding

Tanner Stage

Thelarche
I. None
II. Breast bud
III. Further enlargement of areola and breasts with no separation of contours
IV. 2° mound of areola and papilla
V. Areola recessed to general contour of breast – adult

Pubarche
I. None
II. Downy hair along labia only
III. Darker/coarse hair extends over pubis
IV. Adult type covers smaller area, no thigh involvement
V. Adult hair in quantity and type; extends over thighs

Menstrual Cycle



	FOLLICULAR/PROLIFERATIVE PHASE (Variable Duration)			LUTEAL/SECRETORY PHASE (Fixed Duration - 14 days)		
	Early	**Mid**	**Late**	**OVULATION**	**Early-Mid**	**Late**
Initiating Events	↓ E and ↓ P (from end of previous cycle)	↑ FSH acts on ovarian granulosa cells	Growing follicles continue to secrete E	Sudden switch from negative to positive feedback (E and P now ↑ FSH & LH)	Switch back to negative feedback	No fertilized oocyte
HPO Axis	↑ GnRH pulse frequency ↑ FSH ↑ LH pulse frequency	↑ E from follicles (ovary)		↑↑ LH pulse amplitude (LH surge)	↓ LH	
Hormones			↑ E from follicles, especially from dominant follicle	E peaks → LH surge → ovulation	↑ P from corpus luteum	↓ P secondary to degeneration of corpus luteum
Feedback on HPO Axis		Negative feedback E → ↓ FSH, ↓ LH		Positive feedback: E and P → ↑ FSH, ↑ LH	Negative feedback P → ↓ FSH, ↓ LH	
Ovaries	↑ FSH → follicular growth in 3-30 follicles	↑ follicular growth (by reducing atresia) → ↑ E	Dominant follicle persists, remainder undergo atresia Granulosa cells luteinize → produce P	~36 h after LH surge, dominant follicle releases oocyte; corpus luteum (remnant of dominant follicle) produces P		Cessation of P from corpus luteum
Endometrium	Menses from P withdrawal (from end of previous cycle)		E builds up endometrium		P stabilizes endometrium	Withdrawal of P → menses
Cervical Mucus	Cervical mucus: Clear, ↑ amount, Spinnbarkeit 8-10 cm, more stringy					Opaque, scant amount, Spinnbarkeit 1-2 cm

E = estrogen; FSH = follicle-stimulating hormone; GnRH = gonadotropin-releasing hormone; HPO = hypothalamic-pituitary-ovarian; LH = luteinizing hormone; P = progesterone

Figure 5. Events of the normal menstrual cycle

Characteristics
- Menarche 10-15 yr
- Average 12.2 yr
- Entire cycle 28 ± 7 d with bleeding for 1-6 d
- 25-80 mL blood loss per cycle

Estrogen
ESTROGEN is the main hormone in the follicular/proliferative phase and is stimulated by FSH. As the level increases it acts negatively on FSH. The majority of estrogen is secreted by the dominant follicle

Estrogen effects
- On the follicles in the ovaries
  - Reduces atresia
- On the endometrium
  - Proliferation of glandular and stromal tissue
- On all target tissues
  - Decreases E receptors

Progesterone
PROGESTERONE is the main hormone in the luteal/secretory phase and is stimulated by LH. Increased progesterone acts negatively on LH and is secreted by the corpus luteum (remnant of dominant follicle)

Progesterone effects
- On the endometrium
  - Cessation of mitoses (stops building endometrium up)
  - "Organization" of glands (initiates secretions from glands)
  - Inhibits macrophages, interleukin-8, and enzymes from degrading endometrium
- On all target tissues
  - Decrease E receptors (the "anti-estrogen" effect)
  - Decrease P receptors

Premenstrual Syndrome

- synonyms: "ovarian cycle syndrome," "menstrual molimina" (moodiness)

Etiology
- multifactorial: not completely understood; genetics likely play a role
- CNS-mediated neurotransmitter interactions with sex steroids (progesterone, estrogen, and testosterone)
- serotonergic dysregulation – currently most plausible theory

Diagnostic Criteria for Premenstrual Syndrome
- at least one affective and one somatic symptom during the 5 d before menses in each of the three prior menstrual cycles
  - affective: depression, angry outbursts, irritability, anxiety, confusion, social withdrawal
  - somatic: breast tenderness, abdominal bloating, headache, swelling of extremities
- symptoms relieved within 4 d of onset of menses
- symptoms present in the absence of any pharmacologic therapy, drug or alcohol use
- symptoms occur reproducibly during 2 cycles of prospective recording
- patient suffers from identifiable dysfunction in social or economic performance

Premenstrual Syndrome
Physiological and emotional disturbances that occur 1-2 wk prior to menses and last until a few days after onset of menses; common symptoms include depression, irritability, tearfulness, and mood swings

Treatment
- goal: symptom relief
- psychological support
- diet/supplements
  - avoid sodium, simple sugars, caffeine, and alcohol
  - calcium (1,200-1,600 mg/d), magnesium (400-800 mg/d), vitamin E (400 IU/d), vitamin B_6
- medications
  - NSAIDs for discomfort and pain
  - spironolactone for fluid retention: used during luteal phase
  - SSRIs: used during luteal phase x 14 d or continuously
  - OCP: primarily beneficial for physical/somatic symptoms
  - danazol: an androgen that inhibits the pituitary-ovarian axis
  - GnRH agonists if PMS is severe and unresponsive to treatment (may use prior to considering definitive treatment with BSO)
- mind/body approaches
  - regular aerobic exercise
  - cognitive behavioural therapy
  - relaxation, light therapy biofeedback, and guided imagery
- herbal remedies (variable evidence)
  - evening primrose oil, black cohosh, St. John's wort, kava, ginkgo, agnus castus fruit extract
- BSO if symptoms severe

Premenstrual Dysphoric Disorder

Definition
- official diagnosis in the DSM-5
- described as a more severe form of PMS with specific diagnostic criteria
- treatment with SSRIs (first line), and Yaz® OCP (highly effective)

Differential Diagnoses of Common Presentations

Abnormal Uterine Bleeding

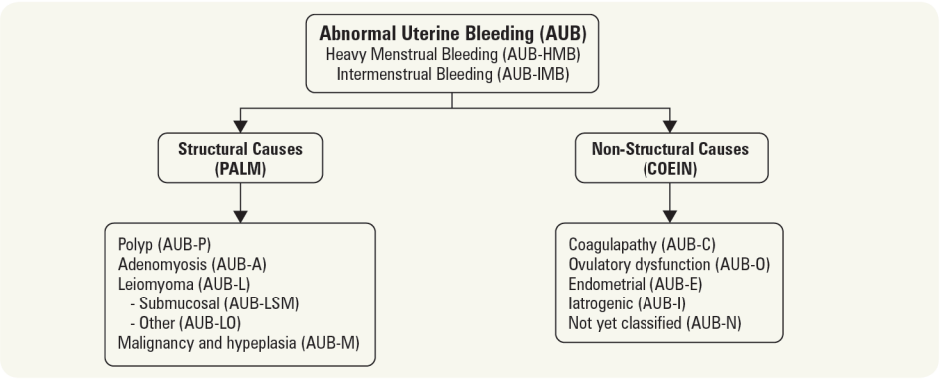


Figure 6. Differential diagnosis of abnormal uterine bleeding

- see *Disorders of Menstruation*, GY10
- menstrual bleeding should be evaluated by ascertaining: frequency/regularity of menses, duration, volume of flow, affects on quality of life and timing (inter or premenstrual or breakthrough)
- classified as
  - regular: cycle to cycle variability of <20 d
  - irregular: cycle to cycle variability of ≥20 d
  - heavy menstrual bleeding: ≥80 cc of blood loss per cycle or ≥8 d of bleeding per cycle or bleeding that significantly affects quality of life
  - postmenopausal bleeding: any bleeding that presents >1 yr after menopause; must rule out endometrial cancer

Postmenopausal bleeding is endometrial cancer until proven otherwise

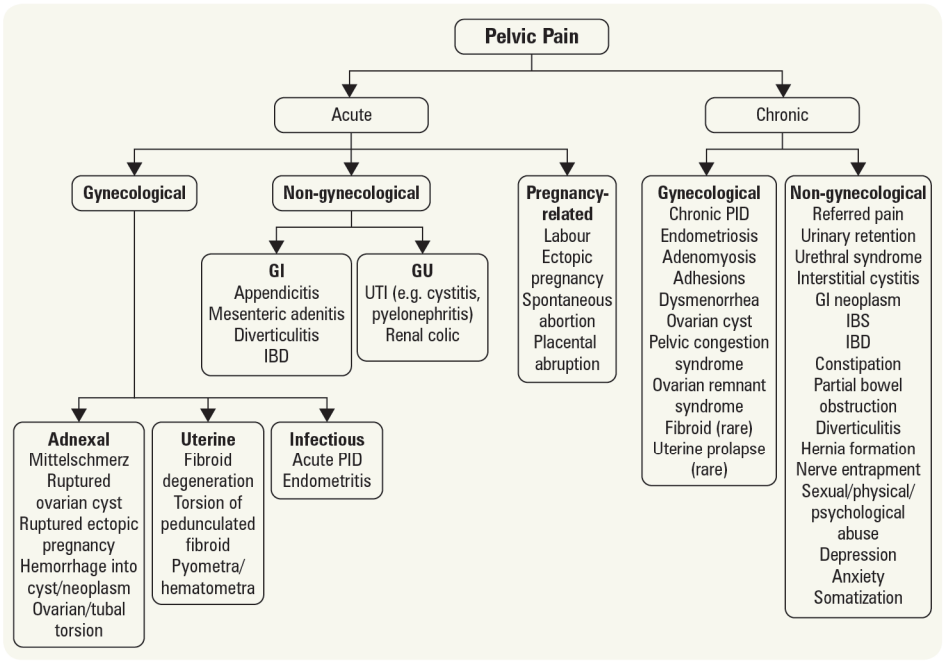
Dysmenorrhea

- see *Disorders of Menstruation*, GY13
- primary/idiopathic
- secondary (acquired)
  - endometriosis
  - adenomyosis
  - uterine polyps
  - uterine anomalies (e.g. non-communicating uterine horn)
  - leiomyoma
  - intrauterine synechiae
  - ovarian cysts
  - cervical stenosis
  - imperforate hymen, transverse vaginal septum
  - pelvic inflammatory disease
  - IUD (copper)
  - foreign body

Vaginal Discharge/Pruritus

- see *Gynecological Infections*, GY25
- physiologic discharge and cervical mucus production
- non-physiologic
  - genital tract infection
  - vulvovaginitis: candidiasis, trichomoniasis, BV, polymicrobial superficial infection
  - chlamydia, gonorrhea
  - pyosalpinx, salpingitis
  - genital tract inflammation (non-infectious)
  - local: chemical irritants, douches, sprays, foreign body, trauma, atrophic vaginitis, desquamative inflammatory vaginitis, focal vulvitis
  - neoplasia: vulvar, vaginal, cervical, endometrial
  - systemic: toxic shock syndrome, Crohn's disease, collagen disease, dermatologic (e.g. lichen sclerosis)
  - IUD, OCP (secondary to progesterone)

Pelvic Pain



20% of chronic pelvic pain patients have a history of previous sexual abuse/ assault; remember to ask about it

Pyometra
Pus within the uterine cavity

Hematometra
Blood within the uterine cavity

Hydrometra
Fluid within the uterine cavity

Hematocolpos
Blood within the vagina

Figure 7. Approach to pelvic pain

Pelvic Mass

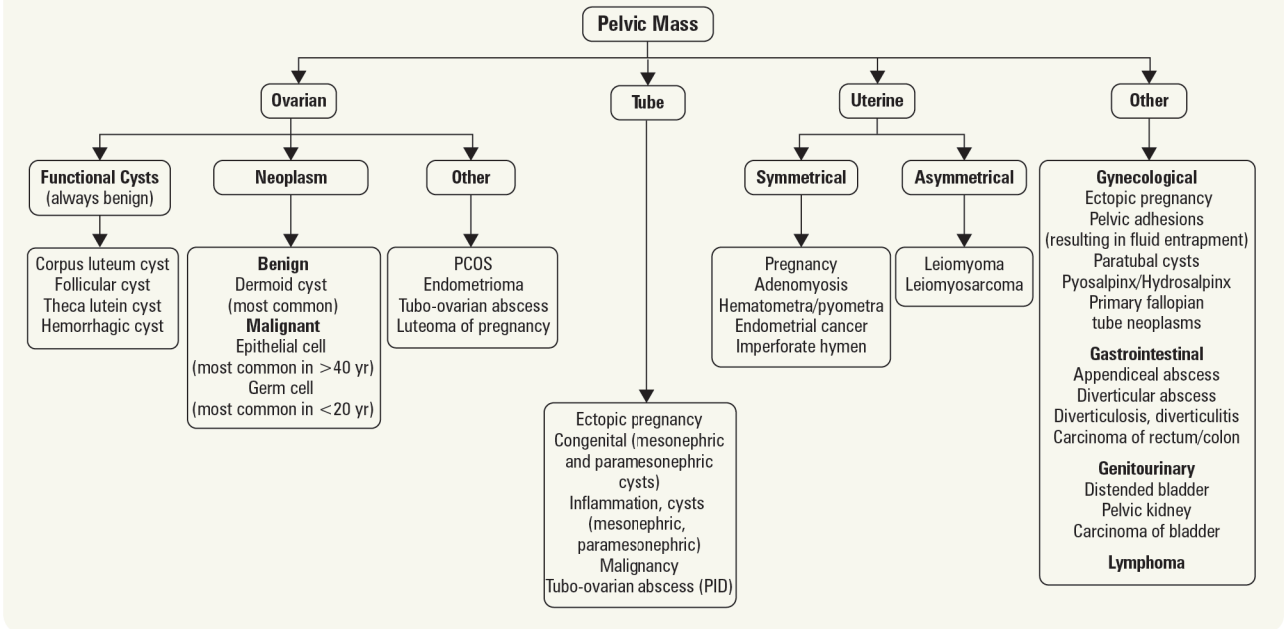


Figure 8. Differential diagnosis of pelvic mass

Dyspareunia

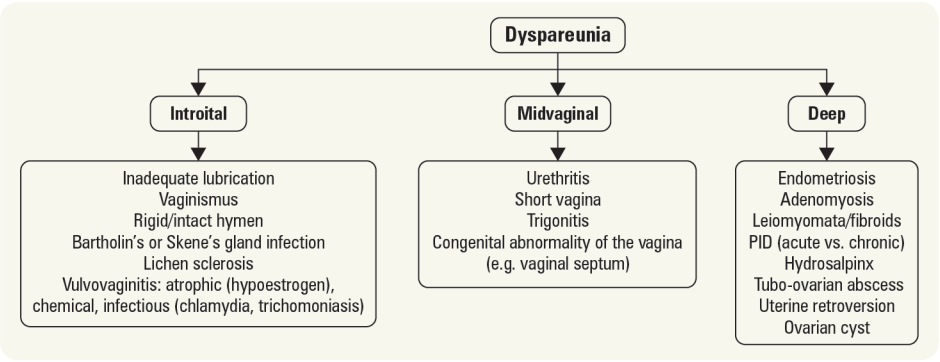


Figure 9. Approach to dyspareunia

First and Second Trimester Bleeding

Approach to the Patient with Bleeding in T1/T2

History
- risk factors for ectopic pregnancy (see *Ectopic Pregnancy*, GY21)
- previous spontaneous abortion
- recent trauma
- characteristics of the bleeding (including any tissue passed)
- characteristics of the pain (cramping pain suggests spontaneous abortion)
- history of coagulopathy
- gynecological/obstetric history
- fatigue, dizziness, syncopal episodes due to hypovolemia, fever (may be associated with septic abortion)

Bleeding in Pregnancy Definitions
- First trimester bleeding: vaginal bleeding within the first 12 wk
- Second trimester bleeding: 12-20 wk

Differential Diagnosis
- Physiologic bleeding: spotting, due to implantation of placenta – reassure and check serial β-hCGs
- Abortion (threatened, inevitable, incomplete, complete)
- Abnormal pregnancy (ectopic, molar) (see *Hydatidiform Mole*, GY49)
- Trauma (post-coital or after pelvic exam)
- Genital lesion (e.g. cervical polyp, neoplasms)

Physical
- vitals (including orthostatic changes)
- abdomen (symphysis fundal height, tenderness, presence of contractions)
- perineum (signs of trauma, genital lesions)
- speculum exam (cervical os open or closed, presence of active bleeding/clots/tissue)
- pelvic exam (uterine size, adnexal mass, uterine/adnexal tenderness)

Investigations
- β-hCG (lower than expected for GA in spontaneous abortion, ectopic pregnancy)
- U/S (confirm intrauterine pregnancy and fetal viability)
- CBC
- group and screen

Treatment
- IV resuscitation for hemorrhagic shock
- treat the underlying cause

Common Investigations and Procedures

Imaging

Ultrasound (U/S)
- transabdominal or transvaginal U/S is the imaging modality of choice for pelvic structures
- transvaginal U/S provides better resolution of uterus and adnexal structures
  - detects early pregnancy if β-hCG ≥1,500 (β-hCG must be ≥6,500 for transabdominal U/S)
- may be used to identify pelvic pathology
  - identify ectopic pregnancy, intrauterine pregnancy
  - assess uterine, adnexal, cul-de-sac, ovarian masses (e.g. solid or cystic)
  - determine endometrial thickness, locate/characterize fibroids
  - monitor follicles during assisted reproduction
  - assess endometrial lining in postmenopausal women

Every woman of childbearing age presenting to ER with abdominal or pelvic pain should have β-hCG measured

Endometrial Biopsy

- performed in the office using an endometrial suction curette (pipelle) guided through the cervix to aspirate fragments of endometrium
  - pre-treatment with misoprostol (Cytotec®) if nulliparous or postmenopausal
- more invasive procedure (D&C) may be done in the office or operating room ± hysteroscopy
- indications
  - AUB/PMB
  - cancer screening (e.g. following specific cervical cytology results (i.e. AGUS) or in high-risk women)

Hysterectomy

Indications

- uterine fibroids
- endometriosis, adenomyosis
- uterine prolapse
- pelvic pain
- AUB
- cancer (endometrium, ovaries, fallopian tubes, cervix)

Complications

- general anesthetic
- bleeding
- infection
- injury to other organs (ureter, bladder, rectum)
- loss of ovarian function (if ovaries removed, iatrogenic menopause)

Approaches

1. vaginal vs. abdominal
   - indications for vaginal approach: mobile uterus, uterine size <12 wk
   - advantages of vaginal approach: less pain, faster recovery time, allows for simultaneous repair of rectocele/cystocele/enterocele, improved aesthetics
2. open vs. laparoscopic-assisted
   - advantages of laparoscopy: less pain, faster recovery, improved aesthetics, shorter hospital stay
   - unless contraindicated or unavailable laparoscopic hysterectomy is the standard of care
3. robotic
   - similar advantages to laparoscopy
   - more dexterous

Approaches to Hysterectomy

- Abdominal hysterectomy: uterus removed via transverse or vertical laparotomy
- Vaginal hysterectomy: uterus removed via vagina; no visualization or entry into abdomen unless laparoscopic-assisted
- Laparoscopic/Robotic: uterus removed via vagina or morcellation

Table 1. Classification of Hysterectomy

Classification	Tissues Removed	Indications
Subtotal Hysterectomy	Uterus	Inaccessible cervix (e.g. adhesions) Patient choice/preference
Total Hysterectomy (extrafasical simple hysterectomy/type 1)	Uterus, cervix, uterine artery ligated at uterus	Uterine fibroids Endometriosis Adenomyosis Menorrhagia DUB
Total Hysterectomy (extrafasical simple hysterectomy/type 1) + Bilateral Salpingo-Oophorectomy (TAH/BSO)	Uterus, cervix, uterine artery ligated at uterus, fallopian tubes, ovaries	Endometrial cancer Malignant adnexal masses >45 yr old Consider for endometriosis
Modified Radical Hysterectomy (type 2)	Uterus, cervix, proximal 1/3 parametria, uterine artery ligated medial to the ureter, mid point of uterosacral ligaments and upper 1-2 cm vagina	Cervical cancer (up to stage IBI)
Radical Hysterectomy (type 3)	Uterus, cervix, upper 1/3-1/2 vagina, entire parametria, uterine artery ligated at its origin from internal iliac artery, uterosacral ligament at most distal attachment (rectum)	Cervical cancer

Disorders of Menstruation

Amenorrhea

Differential Diagnosis of Amenorrhea

Table 2. Differential Diagnosis of Primary Amenorrhea

With Secondary Sexual Development		Without Secondary Sexual Development	
Normal breast and pelvic development	*Normal breast, abnormal uterine development*	*High FSH (hypergonadotropic hypogonadism)*	*Low FSH (hypogonadotropic hypogonadism)*
Hypothyroidism Hyperprolactinemia PCOS Hypothalamic dysfunction	Androgen insensitivity Anatomic abnormalities • Müllerian agenesis, uterovaginal septum, imperforate hymen	Gonadal dysgenesis • Abnormal sex chromosome (Turner's XO) • Normal sex chromosome (46XX, 46XY)	Constitutional delay (most common) Congenital abnormalities • Isolated GnRH deficiency • Pituitary failure (Kallman syndrome, head injury, pituitary adenoma, etc.) Acquired • Endocrine disorders (type 1 DM) • Pituitary tumours • Systemic disorders (IBD, JRA, chronic infections, etc.)

Table 3. Differential Diagnosis of Secondary Amenorrhea

With Hyperandrogenism	Without Hyperandrogenism
PCOS Autonomous hyperandrogenism (androgen secretion independent of the HPO axis) • Ovarian: tumour, hyperthecosis • Adrenal androgen-secreting tumour Late onset or mild congenital adrenal hyperplasia (rare)	Hypergonadotropic hypogonadism (i.e. premature ovarian failure: high FSH, low estradiol) • Idiopathic • Autoimmune: type 1 DM, autoimmune thyroid disease, Addison's disease • Iatrogenic: cyclophosphamide drugs, radiation Hyperprolactinemia Endocrinopathies: most commonly hyper or hypothyroidism Hypogonadotropic hypogonadism (low FSH): • Pituitary compression or destruction: pituitary adenoma, craniopharyngioma, lymphocytic hypophysitis, infiltration (sarcoidosis), head injury, Sheehan's syndrome Functional hypothalamic amenorrhea (often related to stress excessive exercise and/or anorexia)

Functional hypothalamic amenorrhea is the most common cause of secondary amenorrhea

Investigations

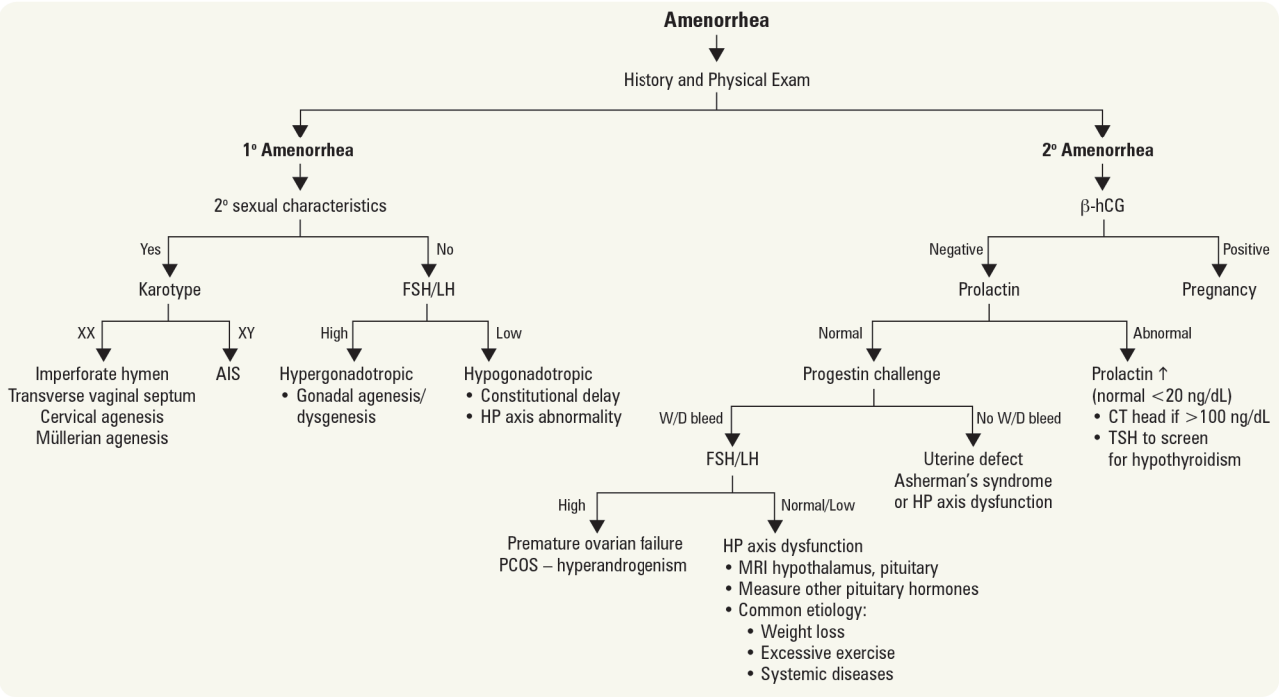


Figure 10. Diagnostic approach to amenorrhea

- β-hCG, hormonal workup (TSH, prolactin, FSH, LH, androgens, estradiol)
- progesterone challenge to assess estrogen status
  - medroxyprogesterone acetate (Provera®) 10 mg PO OD for 10-14 d
  - any uterine bleed within 2-7 d after completion of Provera® is considered to be a positive test/withdrawal bleed
    - withdrawal bleed suggests presence of adequate estrogen to thicken the endometrium; thus withdrawal of progresterone results in bleeding
    - if no bleeding occurs, there may be inadequate estrogen (hypoestrogenism), excessive androgens, or progesterones (decidualization)
- karyotype: indicated if premature ovarian failure or absent puberty
- U/S to confirm normal anatomy, identify PCOS

Prolactinoma Symptoms
Galactorrhea, visual changes, headache

Treatment

Table 4. Management of Amenorrhea

Etiology	Management
1° AMENORRHEA	
Androgen insensitivity syndrome	• Gonadal resection after puberty • Psychological counselling • Creation of neo-vagina
Anatomical • Imperforate hymen • Transverse vaginal septum • Cervical agenesis	• Surgical management
Müllerian dysgenesis (MRKH syndrome)	• Psychological counselling • Creation of neo-vagina with dilation • Diagnostic study to confirm normal urinary system and spine
2° AMENORRHEA	
Uterine defect • Asherman's syndrome	• Evaluation with hysterosalpingography or sonohysterography • Hysteroscopy: excision of synechiae
HP-axis dysfunction	• **Identify modifiable underlying cause** • Combined OCP to decrease risk of osteoporosis, maintain normal vaginal and breast development (NOT proven to work)
Premature ovarian failure	• Screen for DM, hypothyroidism, hypoparathyroidism, hypocorticolism • Hormonal therapy with estrogen + progestin to decrease risk of osteoporosis; can use OCP

Hyperprolactinemia	• MRI/CT head to rule out lesion
	• If no demonstrable lesions by MRI
	  • Bromocriptine, cabergoline if fertility desired
	  • Combined OCPs if no fertility desired
	• Demonstrable lesions by MRI: surgical management

Polycystic ovarian syndrome	• See *Polycystic Ovarian Syndrome*, GY25

Primary Amenorrhea
No menses by age 13 in absence of 2° sexual characteristics or no menses by age 15 with 2° sexual characteristics or no menses 2 yr after thelarche

Secondary Amenorrhea
No menses for >6 mo or 3 cycles after documented menarche

Oligomenorrhea
Episodic vaginal bleeding occurring at intervals >35 d

2° amenorrhea is pregnancy until proven otherwise

Abnormal Uterine Bleeding

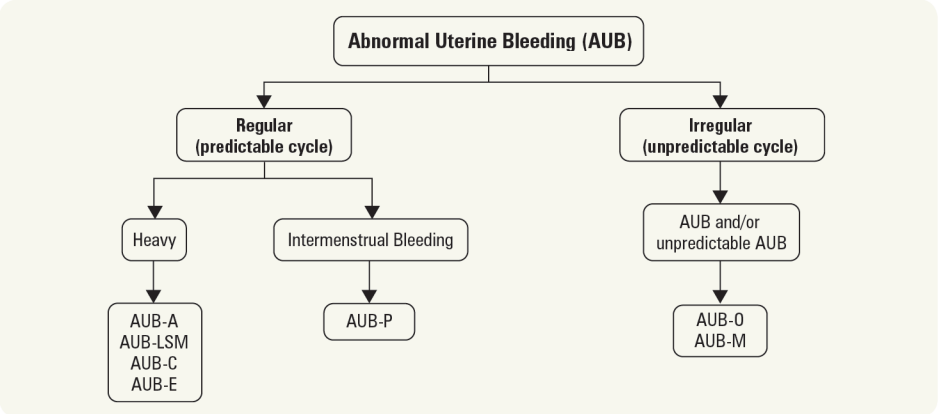


Figure 11. Diagnostic approach to abnormal uterine bleeding

Approach

- is it regular?
  - predictable vs. unpredictable cycle
- is it heavy
- is it structural?
  - PALM
- is it non-structural?
  - COEIN

Abnormal Uterine Bleeding
Change in frequency, duration, or amount of menstrual flow

Table 5. AUB – Etiologies, Investigations, and Management

Etiology	Investigations	Management
	STRUCTURAL	
Polyps (AUB-P)	Transvaginal Sonography Saline Infusion Sonohysterography MRI	Polypectomy (triage based on symptomatic,polyp size, histopathology & patient age)
Adenomyosis (AUB-A)	Transvaginal Sonography MRI	see *Adenomyosis*, GY15
Leiomyoma (AUB-L) • **Submucosal (AUB-LSM)** • **Other (AUB-LO)**	Transvaginal Sonography Saline Infusion Sonohysterography Diagnostic Hysteroscopy	see *Leiomyomata (fibroids)*, GY15
Malignancy & Hyperplasia (AUB-M)	Transvaginal Sonography Endometrial Biopsy - consider biopsy in women >40 yr to exclude endometrial cancer	Dependent on diagnosis
	NON-STRUCTURAL	
Coagulopathy (AUB-C)	CBC, coagulation profile (especially in adolescents), von Willebrand Factor, Ristocetin Cofactor, Factor VIII	Dependent on diagnosis Lifestyle modification
Ovulatory dysfunction (AUB-O)	Bloodwork: β-hCG, ferritin, prolactin, FSH, LH, serum androgens (free testosterone, DHEA), progesterone, 17-hydroxy progesterone, TSH, fT4 pelvic ultrasound	see *Infertility*, GY23
Endometrial (AUB-E)	Endometrial Biopsy	see *Endometriosis*, GY13
Iatrogenic (AUB-I)	Transvaginal Sonography (rule out forgotten IUD) Review OCP/HRT use Review meds (especially neuroleptic use)	Remove offending agent
Not yet classified (AUB-N)	–	–

*Ferrous gluconate 300 mg PO TID will raise Hb 10 points per wk

Dysfunctional Uterine Bleeding
Abnormal bleeding not attributable to organic (anatomic/systemic) disease
DUB is a diagnosis of exclusion
Anovulatory AUB often used synonymously with DUB

AUB in women >40 yr requires an endometrial biopsy to rule out cancer even if known to have fibroids

Determine if patient is hemodynamically stable prior to any other task

Treatment

- resuscitate patient if hemodynamically unstable
- treat underlying disorders
  - if anatomic lesions and systemic disease have been ruled out, consider DUB
- medical
  - mild DUB
    - NSAIDs
    - anti-fibrinolytic (e.g. Cyklokapron®) at time of menses
    - combined OCP
    - progestins (Provera®) on first 10-14 d of each month or every 3 mo if oligomenorrheic
    - Mirena® IUD
    - danazol
  - acute, severe DUB
    - replace fluid losses, consider admission
    - a) estrogen (Premarin®) 25 mg IV q4h x 24 h with Gravol® 50 mg IV/PO q4h or anti-fibrinolytic (e.g. Cyklokapron®) 10 mg/kg IV q8h
    - b) any OCP with minimum 50 µg estradiol 1 tab PO q4h x 24 h with Gravol® 50 mg IV/PO q4h
      - taper to 1 tab tid x 2 d → bid x 2 d → OD
    - after (a) or (b), maintain patient on monophasic OCP for next several months or consider alternative medical treatment
  - clomiphene citrate
    - consider in patients who are anovulatory and who wish to get pregnant
- surgical
  - endometrial ablation; consider pretreatment with danazol or GnRH agonists
    - if finished childbearing
    - repeat procedure may be required if symptom reoccur especially if <40 yr
  - hysterectomy: definitive treatment

Dysmenorrhea

Etiology
- see *Differential Diagnoses of Common Presentations*, GY6

Table 6. Comparison of Primary and Secondary Dysmenorrhea

	Primary Dysmenorrhea	Secondary Dysmenorrhea
Features	Menstrual pain in absence of organic disease Begins 6 mo-2 yr after menarche (once ovulatory cycles established)	Menstrual pain due to organic disease Usually begins in women who are in their 20s, worsens with age May improve temporarily after childbirth
Signs and Symptoms	Colicky pain in abdomen, radiating to the lower back, labia, and inner thighs beginning hours before onset of bleeding and persisting for hours or days (48-72 h) Associated symptoms: N/V, altered bowel habits, headaches, fatigue (prostaglandin-associated)	Associated dyspareunia, abnormal bleeding, infertility
Diagnosis	Associated dyspareunia, abnormal bleeding, infertility Rule out underlying pelvic pathology and confirm cyclic nature of pain	Bimanual exam: uterine or adnexal tenderness, fixed uterine retroflexion, uterosacral nodularity, pelvic mass, or enlarged irregular uterus (findings are rare in women <20 yr) U/S, laparoscopy and hysteroscopy may be necessary to establish the diagnosis Screening for infections (vaginal and cervical cultures) and Papanicolaou smear may be required
Treatment	PG synthetase inhibitors (e.g. Anaprox®): should be started before onset of pain OCP: suppress ovulation/reduce menstrual flow	Treat underlying cause

Primary Dysmenorrhea
Menstrual pain in absence of organic disease

Secondary Dysmenorrhea
Menstrual pain due to organic disease

Endometriosis

Etiology
- not fully understood
- proposed mechanisms (combination likely involved)
  - retrograde menstruation (Sampson's theory)
    - seeding of endometrial cells by transtubal regurgitation during menstruation
    - endometrial cells most often found in dependent sites of the pelvis
  - immunologic theory: altered immunity may limit clearance of transplanted endometrial cells from pelvic cavity (may be due to decreased NK cell activity)
  - metaplasia of coelomic epithelium
    - undefined endogenous biochemical factor may induce undifferentiated peritoneal cells to develop into endometrial tissue
  - extrapelvic disease may be due to aberrant vascular or lymphatic dissemination of cells
    - e.g. ovarian endometriosis may be due to direct lymphatic flow from uterus to ovaries

Epidemiology
- incidence: 15-30% of pre-menopausal women
- mean age at presentation: 25-30 yr
- regresses after menopause

Risk Factors
- family history (7-10x increased risk if affected 1st degree relative)
- obstructive anomalies of the genital tract (earlier onset) – resolve with treatment of anomaly
- nulliparity
- age >25 yr

Sites of Occurrence
- ovaries: 60% patients have ovarian involvement
- broad ligament, vesicoperitoneal fold
- peritoneal surface of the cul-de-sac, uterosacral ligaments
- rectosigmoid colon, appendix
- rarely may occur in sites outside abdomen/pelvis, including lungs

Endometriosis is classified according to a scoring system standardized by the American Society for Reproductive Medicine; score is based on location and extent of disease

Endometriosis
The presence of endometrial tissue (glands and stroma) outside of the uterine cavity

Endometrioma
Endometriotic cyst on surface of ovary

Differential Diagnoses
- Chronic PID, recurrent acute salpingitis
- Hemorrhagic corpus luteum
- Benign/malignant ovarian neoplasm
- Ectopic pregnancy

Recurrence Rates
Medical therapy: 30-50%
Conservative surgery: 14-40%

Clinical Features

- may be asymptomatic and can occur with one of 3 presentations

1. **pain**
   - menstrual symptoms
     - cyclic symptoms due to growth and bleeding of ectopic endometrium, usually precede menses (24-48 h) and continue throughout and after flow
     - secondary dysmenorrhea
     - sacral backache with menses
     - pain may eventually become chronic, worsening perimenstrually
     - deep dyspareunia
   - bowel and bladder symptoms
     - frequency, dysuria, hematuria
     - cyclic diarrhea/constipation, hematochezia, dyschezia (suggestive of deeply infiltrating disease)
2. **infertility**
   - 30-40% of patients with endometriosis will be infertile
   - 15-30% of those who are infertile will have endometriosis
3. **mass** (endometrioma)
   - ovarian mass can present with any of above symptoms or be asymptomatic

- physical
  - tender nodularity of uterine ligaments and cul-de-sac felt on rectovaginal exam
  - fixed retroversion of uterus
  - firm, fixed adnexal mass (endometrioma)
  - physical findings not present in adolescent population

There may be little correlation between the extent of endometriosis and symptomatology

Classic Triad of Endometriosis
- Dysmenorrhea
- Dyspareunia (cul-de-sac, uterosacral ligament)
- Dyschezia (uterosacral ligament, cul-de-sac, rectosigmoid attachment)

A sharp, firm, and exquisitely tender "barb" on the uterosacral ligament is a classic feature of endometriosis

Investigations

- definitive diagnosis requires
  - direct visualization of lesions typical of endometriosis at laparoscopy
  - biopsy and histologic exam of specimens (2 or more of: endometrial epithelium, glands, stroma, hemosiderin-laden macrophages)
- laparoscopy
  - mulberry spots: dark blue or brownish-black implants on the uterosacral ligaments, cul-de-sac, or anywhere in the pelvis
  - endometrioma: "chocolate" cysts on the ovaries
  - "powder-burn" lesions on the peritoneal surface
  - early white lesions and clear blebs
  - peritoneal "pockets"
- CA-125
  - may be elevated in patients with endometriosis

Treatment

- **surgical** confirmation of disease is NOT required prior to starting medical management. Asymptomatic endometriosis does not require treatment. Management depends on certainty of the diagnosis, severity of symptoms, extent of disease, desire for future fertility, and impact to GI/GU systems (e.g. intestinal obstruction)
- medical
  - NSAIDs (e.g. naproxen sodium – Anaprox®)
  - 1st line
    - cyclic/continuous estrogen-progestin (OCP)
    - **progestin** (IM medroxyprogesterone (Depo-Provera®) or oral dienogest (Visanne®)
    - Mirena® IUS
  - 2nd line
    - 2nd line: GnRH-a example: leuprolide (Lupron®): GnRH agonist (suppresses pituitary)
      - side effects: hot flashes, vaginal dryness, reduced libido
      - can use ≥12 mo with add-back progestin or estrogen
    - danazol (Danocrine®): weak androgen
      - side effects: weight gain, fluid retention, acne, hirsutism, voice change
- surgical
  - conservative laparoscopy using laser, electrocautery ± laparotomy
    - ablation/resection of implants, lysis of adhesions, ovarian cystectomy of endometriomas
  - definitive: bilateral salpingo-oophorectomy ± hysterectomy
  - ± follow-up with medical treatment for pain control not shown to impact on preservation of fertility
  - best time to become pregnant is immediately after conservative surgery

Laparoscopic Surgery for Endometriosis
Cochrane DB Syst Rev 2014;4:CD011031
Purpose: To assess the effectiveness and safety of laparoscopic surgery for the treatment of painful symptoms and subfertility associated with endometriosis.
Selection Criteria: RCTs in which effectiveness and safety of laparoscopic surgery was compared with any other laparoscopic or robotic intervention, holistic or medical treatment, or diagnostic laparoscopy only.
Results: 10 RCTs, 973 participants. Laparoscopic surgery was associated with decreased overall pain compared with diagnostic laparoscopy at 6 and 12 mo (OR 6.58, 95% CI 3.31-13.10; OR 10.00, 95% CI 3.21-31.17). Laparoscopic surgery was also associated with an increased live birth or ongoing pregnancy rate compared with diagnostic laparoscopy (OR 1.94, 95% CI 1.20-3.16) and increased pregnancy rate (OR 1.94, 95% CI 1.25-2.86). Compared to diagnostic laparoscopy plus medical therapy (GnRHa plus add-back therapy), laparoscopic ablation resulted in a greater number of participants reporting no pain at 12 mo (OR 5.63, 95% CI 1.18-26.85) although there was no difference in overall pain relief at 12 mo comparing laparoscopic ablation to laparoscopic excision.
Conclusions: Moderate quality evidence suggests that laparoscopic surgery to treat mild and moderate endometriosis reduces overall pain and increases live birth and ongoing pregnancy rates. There was insufficient evidence on adverse events to allow any conclusions regarding safety.

Adenomyosis

- synonym: "endometriosis interna" (uterine wall may be diffusely involved)

Adenomyosis
Extension of areas of endometrial glands and stroma into the myometrium

Epidemiology
- 15% of females >35 yr old; found in 20-40% of hysterectomy specimens
- mean age at presentation: 40-50 yr old (older age group than seen in endometriosis)
- adenomyosis is a common histologic finding in asymptomatic patients

Clinical Features
- often asymptomatic
- menorrhagia, secondary dysmenorrhea, pelvic discomfort
- dyspareunia, dyschezia
- uterus symmetrically bulky, usually <14 cm, mobility not restricted, no associated adnexal pathology
- Halban sign: tender, softened uterus on premenstrual bimanual exam

Investigations
- clinical diagnosis
- U/S or MRI can be helpful
- endometrial sampling to rule out other pathology

Final diagnosis of adenomyosis is based on pathologic findings, but predictably identified on MRI

Treatment
- iron supplements as necessary
- analgesics, NSAIDs
- OCP, medroxyprogesterone (Depo-Provera®)
- GnRH agonists (e.g. leuprolide)
- Mirena® IUS
- low dose danazol 100-200 mg PO OD (trial x 4 mo)
- definitive: hysterectomy (no conservative surgical treatment)

Leiomyomata (Fibroids)

Epidemiology
- diagnosed in approximately 40-50% of pre-menopausal women >35 yr
- more common in African Americans, where they are also larger and occur at earlier age
- common indication for major surgery in females
- minimal malignant potential (1:1,000)
- typically regress after menopause; enlarging fibroids in a postmenopausal woman should prompt consideration of malignancy
  - 50% of leiomyosarcomas originate from within fibroids

Pathogenesis
- estrogen stimulates monoclonal smooth muscle proliferation
- progesterone stimulates production of proteins that inhibit apoptosis
- degenerative changes (occur when tumour outgrows blood supply)
  - fibroids can degenerate, become calcified, have scarcomatous component or obtain parasitic blood supply

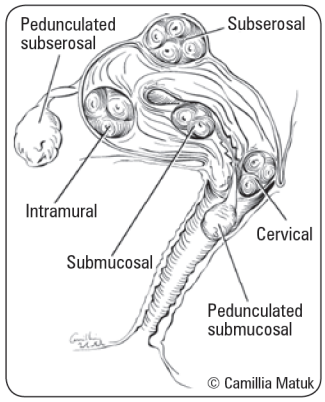


Figure 12. Possible anatomic locations of uterine leiomyomata

Leiomyomata/Fibroids
Benign smooth muscle tumour of the uterus (most common gynecological tumour)

Clinical Features
- majority asymptomatic (60%), often discovered as incidental finding on pelvic exam or U/S
- abnormal uterine bleeding (30%): dysmenorrhea, menorrhagia
- pressure/bulk symptoms (20-50%)
  - pelvic pressure/heaviness
  - increased abdominal girth
  - urinary frequency and urgency
  - acute urinary retention (extremely rare but surgical emergency!)
  - constipation, bloating (rare)
- acute pelvic pain
  - fibroid degeneration
  - fibroid torsion (pedunculated subserosal)
- infertility, recurrent pregnancy loss
- pregnancy complications (potential enlargement and increased pain, obstructed labour, difficult C-section)

Submucosal leiomyomata are most symptomatic (bleeding, infertility)

Investigations

- bimanual exam: uterus asymmetrically enlarged, usually mobile
- CBC: anemia
- U/S: to confirm diagnosis and assess location of fibroids
- sonohysterogram: useful for differentiating endometrial polyps from submucosal fibroids, or if intracavitary growth
- endometrial biopsy to rule out uterine cancer for abnormal uterine bleeding (especially if age >40 yr)
- occasionally MRI is used for pre-operative planning (e.g. before myomectomy)

The effect of pregnancy on fibroid size is variable

Treatment

- only if symptomatic, rapidly enlarging, menorrhagia, menometrorrhagia, or intracavitary
- treat anemia if present
- conservative approach (watch and wait) if
  - symptoms absent or minimal
  - fibroids <6-8 cm or stable in size
  - not submucosal (submucosal fibroids are more likely to be symptomatic)
  - currently pregnant due to increased risk of bleeding (follow-up U/S if symptoms progress)
- medical approach to treat AUB-L
  - antiprostaglandins (ibuprofen, other NSAIDs)
  - tranexamic acid (Cyklokapron®)
  - OCP/Depo-Provera®
  - GnRH agonist: leuprolide (Lupron®), danazol (Danocrine®)
    - short-term use only (6 mo)
    - often used pre-myomectomy or pre-hysterectomy to reduce fibroid size
    - reduced bleeding
  - ulipristal acetate: a partial progesterone receptor agonist
- interventional radiology approach
  - uterine artery embolization (occludes both uterine arteries) → shrinks fibroids by 50% at 6 mo; improves menorrhagia in 90% of patients within 1-2 mo; not an option in women considering childbearing
- surgical approach
  - myomectomy (hysteroscopic, transabdominal, or laparoscopic): preserves fertility
  - hysteroscopic resection of fibroid and endometrial ablation for menorrhagia
  - hysterectomy (see *Hysterectomy*, GY9)
  - note: avoid operating on fibroids during pregnancy (due to ↑ vascularity and potential pregnancy loss); expectant management usually best

Ulipristal Acetate vs. Leuprolide Acetate for Uterine Fibroids
NEJM 2012;366:421-432
Study: Phase III, double-blind RCT of the efficacy and side-effect profile of ulipristal acetate versus those of leuprolide acetate for the treatment of symptomatic uterine fibroids before surgery.
Outcomes: Control of uterine bleeding at week 13 was the primary outcome. Secondary outcomes included bleeding pattern, amenorrhea, changes in fibroid/uterine volume, and global pain score.
Patients: 307 premenopausal women with symptomatic fibroids and excessive uterine bleeding were randomly assigned to oral ulipristal acetate (5 mg or 10 mg) or intramuscular injections of leuprolide acetate.
Results: Control of bleeding at week 13 was not significantly different between the treatment groups. All three treatments reduced uterine volume, although this decrease was significantly greater in the leuprolide group (47% reduction) than in the ulipristal groups (20-22%). 40% of the leuprolide group reported moderate-to-severe hot flashes, but only 11% (5 mg) and 10% (10 mg) of the ulipristal groups did.
Conclusions: Oral ulipristal acetate (5 mg or 10 mg) is noninferior to intramuscular leuprolide acetate for control of uterine bleeding due to fibroids, and it had a better side-effect profile.

Contraception

- see Family Medicine, FM20

Table 7. Classification of Contraceptive Methods

Type	Effectiveness (Perfect Use, Typical Use)
Physiological	
Withdrawal/coitus interruptus	77%
Rhythm method/calendar/mucus/symptothermal	98%, 76%
Lactational amenorrhea	98% (first 6 mo postpartum)
Chance – no method used	10%
Abstinence of all sexual activity	100%
Barrier Methods	
Condom alone	98%, 85%
Spermicide alone	82%, 71%
Sponge – Parous	80%, 68%
– Nulliparous	91%, 84%
Diaphragm with spermicide	94%, 84%
Female condom	95%, 79%
Cervical cap – Parous	74%, 68%
– Nulliparous	91%, 84%

Counselling the Adolescent about Contraception
More than 90% of adolescent pregnancies are unintended, and ~50% of all pregnancies occur within the first 6 mo of initiating sexual activity; in addition, 85% of sexually active women become pregnant within 1 yr if no contraception is used and even some of the least effective contraceptive methods markedly decrease the risk of pregnancy

Table 7. Classification of Contraceptive Methods (continued)

Type	Effectiveness (perfect use, typical use)
Hormonal	
OCP	99.7%, 92%
Nuva Ring®	99.7%, 92%
Transdermal (Ortho Evra®)	99.7%, 92%
Depo-Provera®	99.7%, 97%
Progestin-only pill (Micronor®)	90-99%
Mirena® IUS	99.9%
Jaydess ® IUS	99.9%
Copper IUD	99.3%
Surgical	
Tubal ligation	99.65%
Vasectomy	99.9%
Emergency Postcoital Contraception (EPC)	
Yuzpe® method	98% (within 24 h), decreases by 30% at 72 h
"Plan B" levonorgestrel only	98% (within 24 h), decreases by 70% at 72 h
Postcoital IUD	99.9%

Effectiveness: percentage of women reporting no pregnancy after 1 yr of use

Hormonal Methods

Combined Oral Contraceptive Pills

- most contain low dose ethinyl estradiol (20-35 μg) plus progestin (norethinedrone, norgestrel, levonorgestrel, desogestrel, norgestimate, drospirenone)
- failure rate (0.3% to 8%) depending on compliance
- monophasic or triphasic formulations (varying amount of progestin throughout cycle)

Transdermal (Ortho Evra®)

- continuous release of 6 mg norelgestromin and 0.60 mg ethinyl estradiol into bloodstream
- applied to lower abdomen, back, upper arm, buttocks, NOT breast
- worn for 3 consecutive weeks (changed every wk) with 1 wk off to allow for menstruation
- as effective as OCP in preventing pregnancy (>99% with perfect use)
- may be less effective in women >90 kg
- may not be covered by drug plans

Contraceptive Ring (Nuva Ring®)

- thin flexible plastic ring; releases etonogestrel 120 μg/d and estradiol 15 μg/d
- works for 3 wk then removed for 1 wk to allow for menstruation
- as effective as OCP in preventing pregnancy (98%)
- avoids first pass effect
- side effects: vaginal infections/irritation, vaginal discharge
- may have better cycle control; i.e. decreased breakthrough bleeding

Starting Hormonal Contraceptives

- thorough history and physical exam, including blood pressure and breast exam
- can start at any time during cycle but ideal if within 5 d of LMP
- follow-up visit 6 wk after hormonal contraceptives prescribed
- pelvic exam not required as STI screening can be done by urine and pap smear screening does not start until >21 yr

Oral Contraceptives and the Risk of Venous Thromboembolism: An Update (2010)
J Obstet Gyn Canada 2010;32:1192-1197
Rates of Venous Thromboembolism
(VTE: DVT and PE) expressed in women/yr

Non-users of reproductive age	4-5/10,000
OCP users*	9-10/10,000
Pregnancy	29/10,000
Immediate post-partum	300-400/10,000

*Risk is highest in the first months of use and in medication switch.
Effect of Ethinyl Estradiol Dose
ALL OCPs with ≤35 μg ethinyl estradiol carry a lower risk of VTE compared with oral contraceptives with 50 μg.
Effect of Progestin Type
Drospirenone: third generation progestin, e.g. Yasmin® and Yaz®
Levonorgestrel: second generation progestin, e.g. Alesse®
Two high quality research studies found comparable VTE rates with drospirenone-containing OCPs and other approved products.
1. Dinger et al., *Contraception* 2007;75:344-354
2. Seeger et al., *Obstet Gynecol* 2007;110:587-593
Two reports with significant methodological flaws found increased VTE risk. Results and conclusions may have been distorted by residual confounding.
1. Lidegaard et al., *BMJ* 2009;339:b2890
2. Van Hylckama Vlieg et al., *BMJ* 2009;339:b2921
Conclusion
- Occurrence of serious risks, such as VTE, is rare with all contemporary OCPs.
- Individualized risk assessment is mandatory.
- For most healthy women of reproductive age, the benefits of OCPs will outweigh the risks.

Thrombotic Stroke and Myocardial Infarction with Hormonal Contraception
NEJM 2012;366:2257-2266
Study: 15 yr Danish historical cohort study. Non-pregnant women 15-49 yr of age with no history of cardiovascular disease or cancer.
Results: Total of 1,626,158 women, thrombotic stroke rate 21.4/100,000 person yr, MI rate 10.1/100,000 person yr. Oral contraceptives with ethinyl estradiol at a dose of 30-40 μg according to progestin type and risk of thrombotic stroke and MI (RR [CI]): norethindrone 2.2 (1.5-3.2) and 2.3 (1.3-3.9); levonorgestrel 1.7 (1.4-2.0) and 2.0 (1.6-2.5); norgestimate 1.5 (1.2-1.9) and 1.3 (0.9-1.9); desogestrel 2.2 (1.8-2.7) and 2.1 (1.5-2.8); gestodene 1.8 (1.6-2.0) and 1.9 (1.6-2.3); and drospirenone 1.6 (1.2-2.2) and 1.7 (1.0-2.6). With ethinyl estradiol at a dose of 20 μg, risks according to progestin type were: desogestrel 1.5 (1.3-1.9) and 1.6 (1.1-2.1); gestodene 1.7 (1.4-2.1) and 1.2 (0.8-1.9) and drospirenone 0.9 (0.2-3.5) and 0.0.
Conclusions: Although the absolute risk of thrombotic stroke and MI with hormonal contraception is low, it is increased by a factor of 0.9-1.7 with oral contraceptives that contain ethinyl estradiol at a dose of 20 μg and by a factor of 1.3-2.3 with ethinyl estradiol doses of 30-40 μg, with relatively small differences in risk according to progestin type.

Risk of Non-Fatal Venous Thromboembolism in Women Using Oral Contraceptives Containing Drospirenone Compared with Women Using Oral Contraceptives Containing Levonorgestrel: A Case-Control Study Using United States Claims Data
BMJ 2011;342:d2151
Study: Nested case-control and cohort study.
Patients: Women aged 15-44 yr receiving oral contraceptives.
Intervention: Drospirenone-containing contraceptive vs. levonorgestrel-containing contraceptive.
Outcome: Non-fatal venous thromboembolism.
Results: Women receiving drospirenone-containing oral contraceptives were two times as likely to develop non-fatal VTE compared to women receiving levonorgestrel-containing contraceptives (age adjusted incidence rate ratio was 2.8).

Table 8. Combined Estrogen and Progestin Contraceptive Methods

Mechanism of Action	Advantages	Side Effects	Contraindications
• Ovulatory suppression through inhibition of LH and FSH • Decidualization of endometrium • Thickening of cervical mucus resulting in decreased sperm penetration	• Highly effective • Reversible • Cycle regulation • Decreased dysmenorrhea and menorrhagia (less anemia) • Decreased benign breast disease and ovarian cyst development • Decreased risk of ovarian and endometrial cancer • Increased cervical mucus which may lower risk of STIs • Decreased PMS symptoms • Improved acne • Osteoporosis protection (possibly)	**Estrogen-related** • Nausea • Breast changes (tenderness, enlargement) • Fluid retention/bloating/edema • Weight gain (rare) • Migraine, headaches • Thromboembolic events • Liver adenoma (rare) • Breakthrough bleeding (low estradiol levels) **Progestin-related** • Amenorrhea/breakthrough bleeding • Headaches • Breast tenderness • Increased appetite • Decreased libido • Mood changes • HTN • Acne/oily skin* • Hirsutism* * Androgenic side effects may be minimized by prescribing formulations containing desogestrel, norgestimate, drospirenone, or cyproterone acetate	**Absolute** • Known/suspected pregnancy • Undiagnosed abnormal vaginal bleeding • Prior thromboembolic events, thromboembolic disorders (Factor V Leiden mutation; protein C or S, or antithrombin III deficiency), active thrombophlebitis • Cerebrovascular or coronary artery disease • Estrogen-dependent tumours (breast, uterus) • Impaired liver function associated with acute liver disease • Congenital hypertriglyceridemia • Smoker age >35 yr • Migraines with focal neurological symptoms (excluding aura) • Uncontrolled HTN **Relative** • Migraines (non-focal with aura <1 h) • DM complicated by vascular disease • SLE • Controlled HTN • Hyperlipidemia • Sickle cell anemia • Gallbladder disease **Drug Interactions/Risks** • Rifampin, phenobarbital, phenytoin, griseofulvin, primidone, and St. John's wort can decrease efficacy, requiring use of back-up method • No evidence of fetal abnormalities if conceived on OCP • No evidence that OCP is harmful to nursing infant but may decrease milk production; not recommended until 6 wk postpartum, ideally until 3 mo postpartum

Reference: World Health Organization Guidelines for Oral Contraceptive Pill Use

Table 9. Selected Examples of OCPs

Type	Active Compounds (estriol and progestin derivative)	Advantages	Disadvantages
Alesse®	• 20 µg ethinyl estradiol and 0.5 mg levonorgestrel	• Low dose (20 µg) OCP • Can improve acne and help regulate menstrual cycles	• Low-dose pills can often result in breakthrough bleeding • If this persists for longer than 3 mo, patient should be switched to an OCP with higher estrogen content
Tri-cyclen®	• 35 µg ethinyl estradiol and 0.180/0.215/0.250 mg norgestimate • Triphasic oral contraceptive (graduated levels of progesterone)	• Low androgenic activity can help with acne	• Triphasic OCPs should not be used continuously (unlike monophasic formulations), although should be used continuously for 1 pack
Yasmin® and Yaz®	• Yasmin®: 30 µg ethinyl estradiol + 3 mg drospirenone (a new progestin) • Yaz®: 20 µg ethinyl estradiol + 3 mg drospirenone – 24/4-d pill (4 d pill free interval) • Drospirenone has antimineralocorticoid activity and antiandrogenic effects	• Decreased perception of cyclic weight gain/bloating • Fewer PMS symptoms • Improved acne	• Hyperkalemia (rare, contraindicated in renal and adrenal insufficiency) • Check potassium if patient also on ACEI, ARB, K^+-sparing diuretic, heparin • Continue use of spironolactone

Irregular breakthrough bleeding often occurs in the first few months after starting OCP; usually resolves after three cycles

Missed Combined OCPs

Miss 1 pill in <24 h
- Take 1 pill ASAP, and the next pill at the usual time

Miss ≥1 pill in a row in first wk
- Take 1 pill ASAP, and continue taking one pill daily until the end of the pack
- Use back-up contraception for 7 d; EPC may be necessary

Miss <3 pills in 2nd or 3rd wk of cycle
- Take 1 pill ASAP, and continue taking one pill daily until the end of the pack
- Do not take placebo (28-d packs) or do not take a hormone free interval (21-d packs)
- Start the next pack immediately after finishing the previous one
- No need for back-up contraception

Miss ≥3 pills during the 2nd or 3rd wk
- Take 1 pill ASAP, and continue taking one pill daily until the end of the pack
- Don't take placebo (28-d packs) or do not take a hormone free interval (21-d packs)
- Start the next pack immediately after finishing the previous one
- Use back-up contraception for 7 d; EPC may be necessary

SOGC Committee Opinion on Missed Hormonal Contraceptives: New Recommendations. *JOGC* 2008;30:1050-1062. http://www.sogc.org/guidelines/documents/gui219ECO0811.pdf

PROGESTIN-ONLY METHOD

Table 10. Progestin Only Contraceptive Methods

Indications	Mechanism of Action	Side Effects	Contraindications
• Suitable for postpartum women (does not affect breast milk supply) • Women with contraindications to combined OCP (e.g. thromboembolic or myocardial disease) • Women intolerant of estrogenic side effects of combined OCPs	• Progestin prevents LH surge • Thickening of cervical mucus • Decrease tubal motility • Endometrial decidualization • Ovulation suppression – oral progestins (not IM) do not consistently suppress compared to combined OCPs	• Irregular menstrual bleeding • Weight gain • Headache • Breast tenderness • Mood changes • Functional ovarian cysts • Acne/oily skin • Hirsutism	**Absolute** • None

Selected Examples of Progestin-Only Methods

Progestin-Only Pill ("minipill")

- Micronor® 0.35 mg norethindrone
- taken daily at same time of day to ensure reliable effect; no pill free interval
- higher failure rate (1.1-13% with typical use, 0.51% with perfect use) than other hormonal methods
- ovulation inhibited in 60% of women; most have regular cycles (but may cause oligo/amenorrhea)
- highly effective if also post-partum breastfeeding, or if >35 yr

Depo-Provera®

- injectable depot medroxyprogesterone acetate
- dose 150 mg IM q12-14wk (convenient dosing)
- initiate within 5 d of beginning of normal menses, immediately postpartum in breastfeeding and non-breastfeeding women
- irregular spotting progresses to complete amenorrhea in 70% of women (after 1-2 yr of use)
- highly effective 99%; failure rate 0.3%
- side effect: decreased bone density (may be reversible)
- disadvantage: restoration of fertility may take up to 1-2 yr

Intrauterine Device

Table 11. IUS/IUD Contraceptive Methods

Mechanism of Action	Side Effects	Contraindications

• **Copper-Containing IUD (Nova-T®):** mild foreign body reaction in endometrium toxic to sperm and alters sperm motility
• **Progesterone-Releasing IUS (Mirena®, Jaydess®):** decidualization of endometrium and thickening of cervical mucus; minimal effect on ovulation
• Highly effective (95-99%); failure rate 0-1.2%
• Contraceptive effects last 5 yr
• Reversible, private, convenient
• May be used in women with contraindications to OCPs or wanting long-term contraception
	• **Both Copper and Progesterone IUD**
	  • Breakthrough bleeding
	  • Expulsion (5% in the 1st yr, greatest in 1st mo and in nulliparous women)
	  • Uterine wall perforation (1/1,000) on insertion
	  • If pregnancy occurs with an IUD, increased risk of ectopic
	  • Increased risk of PID (within first 10 d of insertion only)
	• **Copper IUD:** increased blood loss and duration of menses, dysmenorrhea
	• **Progesterone IUD:** bloating, headache
		Absolute
		• **Both Copper and Progesterone IUD**
		  • Known or suspected pregnancy
		  • Undiagnosed genital tract bleeding
		  • Acute or chronic PID
		  • Lifestyle risk for STIs*
		• **Copper IUD**
		  • Known allergy to copper
		  • Wilson's disease
		Relative
		• **Both Copper and Progesterone IUD**
		  • Valvular heart disease
		  • Past history of PID or ectopic pregnancy
		  • Presence of prosthesis
		  • Abnormalities of uterine cavity, intracavitary fibroids
		  • Cervical stenosis
		  • Immunnosuppressed individuals (e.g. HIV)
		• **Copper IUD:** severe dysmenorrhea or menorrhagia

*Cervical swabs for gonorrhea and chlamydia should be done prior to insertion

Missed Progestin-Only Pills >3 h
Use back-up contraceptive method for at least 48 h; continue to take remainder of pills as prescribed

Missed Depo-Provera

- If last injection given 13-14 wk prior: give next injection immediately
- if >14 wk prior, do β-hCG
  - If β-hCG is positive, give EPC and no injection
  - If β-hCG is negative, give next injection right away and:
    - Intercourse occurred in last 5 d: give EPC, use back-up contraception for 7 d Repeat β-hCG in 3 wk
    - Intercourse occurred >5 d ago but within the last 14 d: use back-up contraception for 7 d Repeat β-hCG in 3 wk
    - Intercourse occurred >14 d ago: use back-up contraception for 7 d
  - No evidence of fetal abnormalities if conceived on DMPA

SOGC Committee Opinion on Missed Hormonal Contraceptives: New Recommendations. *JOGC* 2008;30:1050-62. http://www.sogc.org/guidelines/documents/gui219EC00811.pdf

Steroidal Contraceptives and Bone Fractures in Women: Evidence from Observational Studies
Cochrane DB Syst Rev 2012;8:CD009849
Purpose: To review evidence from observational studies of hormonal contraceptive use and the risk of bone fracture.
Selection Criteria: Cohort and case-control studies of hormonal contraceptive use with fracture risk as the primary outcome.
Results: 7 case-control and 7 cohort studies. Overall, little evidence for an association between OPC use and fracture risk. One study reported increased fracture risk for ever-use of DMPA (OR 1.44, 95% CI 1.01-2.06) and the second also noted increased risk for any past use of DMPA (OR 1.17, 95% CI 1.07-1.29). One study reported reduced risk for ever-use of hormonal IUD (OR 0.75, 95% CI 0.64-0.87).
Conclusion: Observational studies do not indicate an overall association between OCP use and fracture risk. DMPA users may have an increased fracture risk.

Continuous or Extended Cycle vs. Cyclic Use of Combined Oral Contraceptives for Contraception
Cochrane DB Syst Rev 2005;3:CD004695
Background: The efficacy and side effects of cyclic administration vs. extended use (longer periods of active pills and/or shorter periods placebo) or continuous use (uninterrupted active pill administration) of combination oral contraceptives (COC) are unclear.
Study: Systematic review of randomized clinical trials comparing continuous or extended vs. cyclic COC administration.
Findings: Eight RCTs met inclusion criteria.

- No difference in efficacy of pregnancy prevention.
- No difference in compliance with dosing schedules.
- Extended cycle use lowered prevalence of menstrual symptoms (e.g. headaches, pain, fatigue).
- No difference in bleeding patterns, but continuous use may improve over time.

Depot Medroxyprogesterone Acetate and Bone Effects
ACOG Committee Opinion 415, 2008
Obstet Gynecol 2008;112:727-730

- The effect of DMPA on BMD should neither prevent practitioners from prescribing DMPA nor limit its use to 2 consecutive yr.
- The greatest loss of BMD occurs in the first 1-2 yr of DMPA use.
- Contraceptive implants and intrauterine devices that do not affect BMD should be considered as first-line for adolescents.
- Inform patients about benefits and the potential risks of DMPA, and encourage daily exercise, calcium and vitamin D intake.
- Routine BMD monitoring is not recommended for DMPA users.

Emergency Postcoital Contraception

Table 12. Emergency Contraceptive Methods

Method	Mechanism of Action	Side Effects	Contraindications
HORMONAL			
Yuzpe Method • Used within 72 h of unprotected intercourse; limited evidence of benefit up to 5 d • Ovral® 2 tablets then repeat in 12 h (ethinyl estradiol 100 μg/levonorgestrel 500 μg) • Can substitute with any OCP as long as same dose of estrogen used • 2% overall risk of pregnancy • Efficacy decreased with time (e.g. less effective at 72 h than 24 h)	• Unknown; theories include: ▪ Suppresses ovulation or causes deficient luteal phase ▪ Alters endometrium to prevent implantation ▪ Affects sperm/ova transport	• Nausea (due to estrogen; treat with Gravol®) • Irregular spotting	• Pre-existing pregnancy (although not teratogenic) • Caution in women with contraindications to OCP (although NO absolute contraindications)
"Plan B" • Consists of levonorgestrel 750 μg q12h for 2 doses (can also take 2 doses together); taken within 72 h of intercourse • Greater efficacy (75-95% if used within 24 h) and better side effect profile than Yuzpe method but efficacy decreases with time; 1st line if >24 h • No estrogen thus very few contraindications/side effects (less nausea) • Less effective in overweight individuals (>75 kg less effective, >80 kg not recommended)	• Same as above	• Same as above	• Same as above
Ulipristal • 30 mg PO within 5 d	• Selective Progesterone Receptor Modulator (SPERM) with primarily antiprogestin activity: • may delay ovulation by up to 5 d	• Headache, hot flashes, constipation, vertigo, endometrial thickening	• Same as above
NON-HORMONAL			
Postcoital IUD (Copper) • Insert up to 7 d postcoitus • Prevents implantation • 1% failure rate • Can use for short duration in higher risk individuals • Mirena® IUS cannot be used as EPC	• See Table 11	• See Table 11	• See Table 11

Follow-up
- 3-4 wk post treatment to confirm efficacy (confirmed by spontaneous menses or pregnancy test)
- contraception counseling

Any OCP can be used as EPC; 100 μg ethinyl estradiol PO q12h x 2 doses
- Levonorgestrel emergency contraception regimens are more effective and cause fewer side effects than the Yuzpe regimen
- Levonorgestrel emergency contraception single dose (1.5 mg) and the 2-dose levonorgestrel regimen (0.75 mg 12 h apart) have similar efficacy with no difference in side effects

SOGC Clinical Practice Guidelines: Emergency Contraception. *JOGC* 2012;34:870-878. http://www.sogc.org/guidelines/documents/gui280CPG1209E_000.pdf

Termination of Pregnancy

Definition
- active termination of a pregnancy before fetal viability (usually <500 g or <20 wk GA)

Indications
- inability to carry a pregnancy to term due to medical or social reasons (including patient preference)

Management
- medical
  - <9 wk: methotrexate + misoprostol
  - >12 wk: prostaglandins (intra- or extra-amniotically or IM) or misoprostol
- surgical
  - <12 wk: dilatation + vacuum aspiration ± curettage
  - >12 wk: dilatation and evacuation, early induction of labour
  - common complications: pain or discomfort
  - less common complications: hemorrhage, perforation of uterus, laceration of cervix, risk of infertility, infection/endometritis, Asherman's syndrome (adhesions within the endometrial cavity causing amenorrhea/infertility), retained products of conception
- counselling
  - supportive and counselling services
  - future contraception and family planning services
  - ensure follow-up

CMA Policy (1988)
"Induced abortion should be uniformly available to all women in Canada" and "there should be no delay in the provision of abortion services"

Terminations are generally done until the stage of viability (~23.5 wk), although this varies depending on the provider

Pregnancy-Related Complications

Spontaneous Abortions

- see *Termination of Pregnancy*, for therapeutic abortions

Table 13. Classification of Spontaneous Abortions

Type	History	Clinical	Management (± Rhogam®)
Threatened	Vaginal bleeding ± cramping	Cervix closed and soft	Watch and wait <5% go on to abort
Inevitable	Increasing bleeding and cramps ± rupture of membranes	Cervix closed until products start to expel, then external os opens	a) Watch and wait b) Misoprostol 400-800 μg PO/PV c) D&C ± oxytocin
Incomplete	Extremely heavy bleeding and cramps ± passage of tissue noticed	Cervix open	a) Watch and wait b) Misoprostol 400-800 μg PO/PV c) D&C ± oxytocin
Complete	Bleeding and complete passage of sac and placenta	Cervix closed, bleeding stopped	No D&C – expectant management
Missed	No bleeding (fetal death *in utero*)	Cervix closed	a) Watch and wait b) Misoprostol 400-800 μg PO/PV c) D&C ± oxytocin
Recurrent	≥3 consecutive spontaneous abortions		Evaluate mechanical, genetic, environmental, and other risk factors
Septic	Contents of uterus infected – infrequent		D&C IV broad spectrum antibiotics

Etiology of Recurrent Pregnancy Loss

MAKE ME

Type	History
Mechanical	Uterine anomalies • Congenital (septate uterus) • Leiomyoma • Endometrial polyps • Intrauterine adhesions
Autoimmune	Immunologic Factors • Antiphospholipid syndrome (blood tests: lupus anticoagulant, anti-cardiolipin Ab, anti-β2 glycoprotein-I)
Karyotype	• Aneuploidy • Chromosomal rearrangements • Check both parents • Young mother, ≥3 miscarriages, FHx miscarriage/stillbirth/ malformation
Endocrine	Poorly controlled disease • Thyroid (associated with high antibody/hormone levels) • DM (secondary to hyperglycemia, maternal vascular disease) • PCOS
Maternal Infection	No infectious agent has been proven to cause recurrent pregnancy loss, though some cause sporadic loss (*Listeria*, toxoplasmosis, CMV, HSV)
Environment	Obesity, smoking, alcohol use, and caffeine consumption may contribute
Other	Prothrombotic conditions (i.e. thrombophilia)

Ectopic Pregnancy

Definition

- embryo implants outside of the endometrial cavity

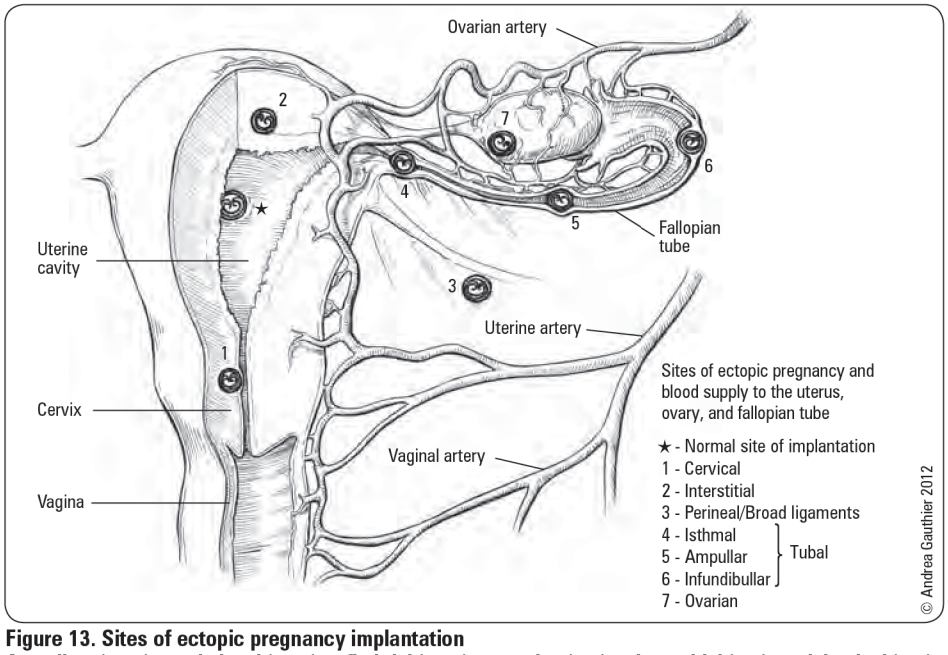


Figure 13. Sites of ectopic pregnancy implantation
Ampullary (70%) >> isthmal (12%) > fimbrial (11%) > ovarian (3%) > interstitial (2%) > abdominal (1%)

Epidemiology

- 1/100 pregnancies
- fourth leading cause of maternal mortality, leading cause of death in first trimester
- increase in incidence over the last 3 decades
- three commonest locations for ectopic pregnancy: ampullary (70%), isthmic (12%), fimbrial (11%)

Etiology

- 50% due to damage of fallopian tube cilia following PID
- intrinsic abnormality of the fertilized ovum
- conception late in cycle
- transmigration of fertilized ovum to contralateral tube

DDx of Lower Abdominal Pain
- Urinary tract: UTI, kidney stones
- GI: diverticulitis, appendicitis
- Gyne: endometriosis, PID, fibroid (degenerating, infarcted, torsion), ovarian torsion, ovarian neoplasm, ovarian cyst, pregnancy-related

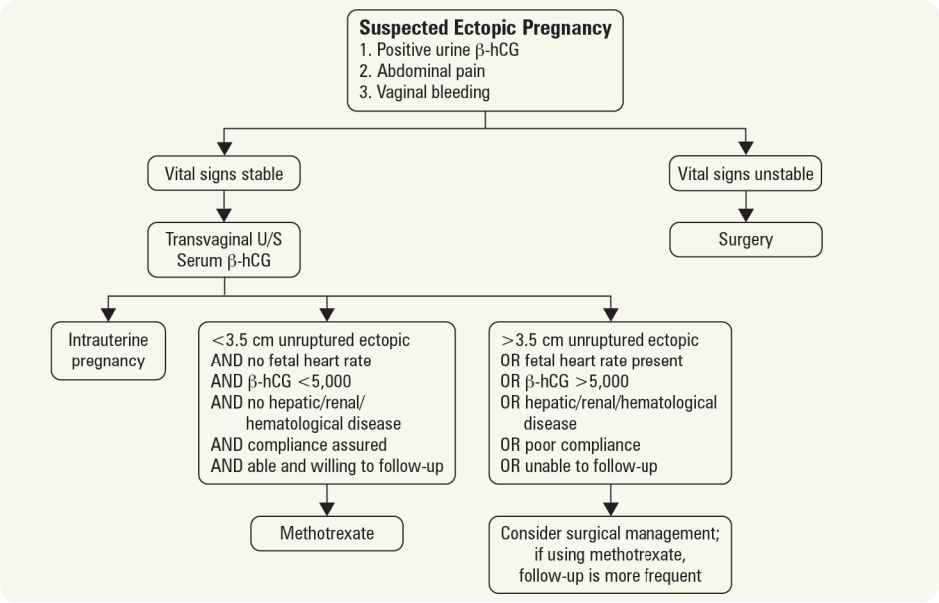


Figure 14. Algorithm for suspected ectopic pregnancy

Clinical Features of Ectopic Pregnancy

4Ts and 1S
Temperature >38°C (20%)
Tenderness: abdominal (90%) ± rebound (45%)
Tenderness on bimanual examination, cervical motion tenderness
Tissue: palpable adnexal mass (50%) (half have contralateral mass due to lutein cyst)
Signs of pregnancy (e.g. Chadwick's sign, Hegar's sign)

Risk Factors

- previous ectopic pregnancy
- gynecologic
  - current IUD use – increased risk of ectopic if pregnancy occurs
  - history of PID (especially infection with *C. trachomatis*), salpingitis
  - infertility
- infertility treatment (IVF pregnancies following ovulation induction [7% ectopic rate])
- previous procedures
  - any surgery on fallopian tube (for previous ectopic, tubal ligation, etc.)
  - abdominal surgery for ruptured appendix, etc.
- smoking
- structural
  - uterine leiomyomas
  - adhesions
  - abnormal uterine anatomy (e.g. T-shaped uterus)

More than half of patients with ectopic pregnancy have no risk factors

If Ectopic Pregnancy Ruptures
- Acute abdomen with increasing pain
- Abdominal distention
- Shock

Investigations

- serial β-hCG levels; normal doubling time with intrauterine pregnancy is 1.6-2.4 d in early pregnancy
  - rise of <20% of β-hCG is 100% predictive of a non-viable pregnancy
  - prolonged doubling time, plateau, or decreasing levels before 8 wk implies nonviable gestation but does not provide information on location of implantation
  - 85% of ectopic pregnancies demonstrate abnormal β-hCG doubling
- ultrasound
  - U/S is only definitive if fetal cardiac activity is detected in the tube or uterus
  - specific finding on transvaginal U/S is a tubal ring
- laparoscopy (sometimes used for definitive diagnosis)

Treatment

- goals of treatment: conservative (preserve tube if possible), maintain hemodynamic stability
- surgical = laparoscopy
  - linear salpingostomy an option if tube salvageable
  - salpingectomy if tube damaged or ectopic is ipsilateral recurrence
  - 15% risk of persistent trophoblast; must monitor β-hCG titres weekly until they reach non-detectable levels
  - consider Rhogam® if Rh negative
  - may require laparotomy if patient is unstable, extensive abdominal surgical history, etc.
- medical = methotrexate (for indications see Figure 4)
  - use 50 mg/m^2 body surface area; given in a single IM dose
  - this is 1/5 to 1/6 chemotherapy dose, therefore minimal side effects (reversible hepatic dysfunction, diarrhea, gastritis, dermatitis)

Management of Abortions
- Always rule out an ectopic
- Always check Rh; if negative, give Rhogam®
- Always ensure patient is hemodynamically stable

- follow β-hCG levels weekly until β-hCG is non-detectable
  - plateau or rising levels suggest persisting trophoblastic tissue (requires further treatment)
- 82-95% success rate, but up to 25% will require a second dose
- tubal patency following methotrexate treatment approaches 80%

Prognosis
- 9% of maternal deaths during pregnancy
- 40-60% of patients will become pregnant again after surgery
- 10-20% will have subsequent ectopic pregnancy

Interventions for Tubal Ectopic Pregnancy
Cochrane DB Syst Rev 2007;1:CD000324
Study: Cochrane Review of randomized controlled trials comparing treatments in women with tubal ectopic pregnancy.
Patients: Women with a diagnosis of tubal ectopic pregnancy.
Intervention: Surgery (salpingectomy/salpingostomy by open surgery or by laparoscopy), medical treatment, and expectant management.
Main Outcome: Primary treatment success, defined as an uneventful decline in serum β-hCG to undetectable levels by the initial treatment.
Results: Intramuscular MTX therapy and salpingostomy yielded similar treatment success rates (82-95% for MTX therapy vs. 80-92% for salpingostomy).

Infertility

Epidemiology
- 10-15% of couples
- must investigate both members of the couple

Infertility: inability to conceive or carry to term a pregnancy after one year of regular, unprotected intercourse

Primary infertility: infertility in the context of no prior pregnancies

Secondary infertility: infertility in the context of a prior conception

Generally, 75% of couples achieve pregnancy within 6 mo, 85% within 1 yr, 90% within 2 yr

Female Factors

Etiology
- ovulatory dysfunction (15-20%)
  - hypothalamic (hypothalamic amenorrhea)
    - stress, poor nutrition, excessive exercise (even with presence of menstruation)
  - pituitary (prolactinoma, hypopituitarism)
    - PCOS
  - ovarian
    - premature ovarian failure
    - luteal phase defect (poor follicle production, premature corpus luteum failure, failed uterine lining response to progesterone), poorly understood
  - systemic diseases (thyroid, Cushing's syndrome, renal/hepatic failure)
  - congenital (Turner's syndrome, gonadal dysgenesis or gonadotropin deficiency)
- outflow tract abnormality (15-20%)
  - tubal factors (20-30%)
    - PID
    - adhesions (previous surgery, peritonitis, endometriosis)
    - ligation/occlusion (e.g. previous ectopic pregnancy)
  - uterine factors (<5%)
    - congenital anomalies, bicornuate uterus, septate uterus, prenatal DES exposure
    - intrauterine adhesions (e.g. Asherman's syndrome)
    - infection (endometritis, pelvic TB)
    - fibroids/polyps (particularly intrauterine)
    - endometrial ablation
  - cervical factors (5%)
    - hostile or acidic cervical mucus
    - anti-sperm antibodies
    - structural defects (cone biopsies, laser or cryotherapy)
- endometriosis (15-30%)
- multiple factors (30%)
- unknown factors (10-15%)

Requirements for Conception
- Ovary
- Tube
- Cervix
- Endometrium
- Sperm

Investigations
- ovulatory
  - day 3: FSH, LH, TSH, prolactin ± DHEA, free testosterone (if hirsute) add estradiol for proper FSH interpretation
  - day 21-23: serum progesterone to confirm ovulation
  - initiate basal body temperature monitoring (biphasic pattern)
  - postcoital test: evaluate mucus for clarity, pH, spinnbarkeit/fibrosity (rarely done)
- tubal factors
  - HSG (can be therapeutic – opens fallopian tube)
  - SHG (can be therapeutic; likely less – opens fallopian tube)
  - laparoscopy with dye insufflation (or tubal dye test)
- peritoneal/uterine factors
  - HSG/SHG, hysteroscopy
- other
  - karyotype

When Should Investigations Begin?
- <35 yr: after 1 yr of regular unprotected intercourse
- 35-40 yr: after >6 mo
- >40 yr: immediately
- Earlier if
  - History of PID
  - History of infertility in previous relationship
  - Prior pelvic surgery
  - Chemotherapy/radiation in either partner
  - Recurrent pregnancy loss
  - Moderate-severe endometriosis

Controversial and Evolving Ethical Issues
- Infertility demands non-judgmental discussion
- Ethical issues surrounding therapeutic donor insemination in same sex couples, surrogacy, donor gametes, and other advanced reproductive technologies are still evolving and remain controversial
- If the doctor finds that certain treatment options lie outside of their moral boundaries, the infertile couple should be referred to another physician

Treatment

- education: timing of intercourse in relation to ovulation (from 2 d prior to 2 d following presumed ovulation), every other day
- medical
  - ovulation induction
    - clomiphene citrate (Clomid®): estrogen antagonist that causes a perceived decreased estrogen state, resulting in increased pituitary gonadotropins; causes increased FSH and LH, leading to ovulation induction (works much better if anovulatory)
    - followed by β-hCG for stimulation of ovum release
  - may add
    - bromocriptine (dopamine agonist) if elevated prolactin
    - dexamethasone for hyperandrogenism (adult onset congenital adrenal hyperplasia)
    - metformin (for PCOS)
    - luteal phase progesterone supplementation for luteal phase defect (mechanism not completely understood)
    - ASA (81 mg PO OD) for women with a history of recurrent spontaneous abortions
    - (for antiphospholipid antibody syndrome)
    - thyroid replacement to keep TSH < 2.5
- surgical/procedural
  - tubuloplasty
  - lysis of adhesions
  - artificial insemination: intracervical insemination (ICI), intrauterine insemination (IUI), intrauterine tuboperitoneal insemination (IUTPI), intratubal insemination (ITI)
  - sperm washing
  - IVF (*in vitro* fertilization)
  - IFT (intrafallopian transfer)
  - GIFT* (gamete intrafallopian transfer): immediate transfer with sperm after oocyte retrieval
  - ZIFT* (zygote intrafallopian transfer): transfer after 24 h culture of oocyte and sperm
  - TET* (tubal embryo transfer): transfer after >24 h culture
  - ICSI (intracytoplasmic sperm injection)
  - IVM (*in vitro* maturation)
  - ± oocyte or sperm donors
  - ± pre-genetic screening for single gene defects in karyotype of zygote
  - **Not performed in Canada*

Livebirth After Uterus Transplantation
Lancet 2015;385:607-16.
Purpose: Treatment for absolute uterine infertility. Eleven previous human uterus transplantations performed but all unsuccessful in producing livebirths.
Patient/Method: 35 yr old woman with congenital absence of uterus (Rokitansky syndrome) underwent transplantation of uterus donated from a living 61 yr old P2 woman. Implantation was performed using in vitro fertilization generated embryo derived from the recipient and her partner.
Results: Recipient and donor had uneventful postoperative recoveries. The recipient initiated menstruation 43 d after transplantation and her menstrual cycle remained regular, ranging from 26-36 d. Embryo transfer was performed 1 yr after transplantation, resulting in intrauterine pregnancy. The recipient was then treated with triple immunosuppressive therapy (tacrolimus, azathioprine, and corticosteroids), which was continued throughout her pregnancy. The patient experienced one episode of mild rejection during her pregnancy, which was treated with corticosteroids. Fetal growth parameters and doppler studies were normal throughout her pregnancy. The patient was admitted at 31 + 5 wk for pre-eclampsia and a caesarean section was performed owing to abnormal fetal tracings. A male baby with normal birth weight (1775g) and APGAR scores was born.
Conclusions: Successful proof-of-concept uterus transplantation as treatment for uterine factor infertility using live uterus donation from a postmenopausal donor.

Male Factors

- see Urology, U34

Etiology

- varicocele (>40%)
- idiopathic (>20%)
- obstruction (~15%)
- cryptorchidism (~8%)
- immunologic (~3%)

Investigations

- semen analysis and culture
- postcoital (Huhner) test: rarely done

Normal Semen Analysis (WHO lower reference limits)
- Must be obtained after 2-7 d of abstinence
  - Volume 1.5 cc
  - Count 15 million/cc
  - Vitality 58% live
  - Motility 32% progressive, 40% total (progressive + non-progressive)
  - Morphology 4.0% normal

Polycystic Ovarian Syndrome

- also called chronic ovarian androgenism

Etiology

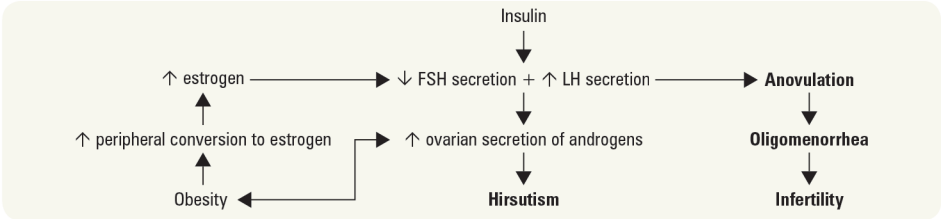


Figure 15. Pathophysiology of polycystic ovarian syndrome

Polycystic Ovarian Syndrome – HAIR-AN
Hirsutism, Hyper**A**ndrogenism, **I**nfertility, Insulin **R**esistance, **A**canthosis **N**igricans

Diagnosis
- Rotterdam diagnostic criteria: 2 of 3 required
  - oligomenorrhea/irregular menses for 6 mo
  - hyperandrogenism
    - clinical evidence - hirsutism or male pattern alopecia or
    - biochemical evidence - raised free testosterone
  - polycystic ovaries on U/S

Clinical Features
- average age 15-35 yr at presentation
- in adolescents, wait at least 1-2 yr to make diagnosis
- abnormal/irregular uterine bleeding, hirsutism, infertility, obesity, virilization
- insulin resistance occurs in both lean and obese patients
- acanthosis nigricans: browning of skin folds in intertriginous zones (indicative of insulin resistance)
- family history of DM

Investigations
- goal of investigations is to identify hyperandrogenism or chronic anovulation; and rule out specific pituitary or adrenal disease as the cause
- laboratory
  - prolactin, 17-hydroxyprogesterone, free testosterone, DHEA-S, TSH, free T_4, androstenedione, SHBG
  - LH:FSH >2:1; LH is chronically high with FSH mid-range or low (low sensitivity and specificity)
  - increased DHEA-S, androstenedione and free testosterone (most sensitive), decreased SHBG
- transvaginal or transabdominal U/S: polycystic-appearing ovaries ("string of pearls" – 12 or more small follicles 2-9 mm, or increased ovarian volume)
- tests for insulin resistance or glucose tolerance
  - fasting glucose:insulin ratio <4.5 is consistent with insulin resistance (U.S. units)
  - 75 g OGTT yearly (particularly if obese)
- laparoscopy
  - not required for diagnosis
  - most common to see white, smooth, sclerotic ovaries with a thick capsule; multiple follicular cysts in various stages of atresia; hyperplastic theca and stroma
- rule out other causes of abnormal bleeding

Treatment
- **cycle control**
  - lifestyle modification (decrease BMI, increase exercise) to decrease peripheral estrone formation
  - OCP monthly or cyclic Provera® to prevent endometrial hyperplasia due to unopposed estrogen
  - oral hypoglycemic (e.g. metformin) if type 2 diabetic or if trying to become pregnant
  - tranexamic acid (Cyklokapron®) for menorrhagia only
- **infertility**
  - medical induction of ovulation: clomiphene citrate, human menopausal gonadotropins (HMG [Pergonal®]), LHRH, recombinant FSH, and metformin
    - metformin may be used alone or in conjuction with clomiphene citrate for ovulation induction
  - ovarian drilling (perforate the stroma), wedge resection of the ovary
  - bromocriptine (if hyperprolactinemia)
- **hirsutism**
  - any OCP can be used
    - Diane 35® (cyproterone acetate): antiandrogenic
    - Yasmin® (drospirenone and ethinyl estradiol): spironolactone analogue (inhibits steroid receptors)
  - mechanical removal of hair
  - finasteride (5-α reductase inhibitor)
  - flutamide (androgen reuptake inhibitor)
  - spironolactone: androgen receptor inhibitor

PCOS may be Confused with
- Late onset congenital adrenal hyperplasia (21-hydroxylase deficiency)
- Cushing's syndrome
- Ovarian and adrenal neoplasms
- Hyperprolactinemia
- Hypothyroidism

Clinical Signs of Endocrine Imbalance
- Menstrual disorder/amenorrhea (80%)
- Infertility (74%)
- Hirsutism (69%)
- Obesity (49%)
- Impaired glucose tolerance (35%)
- DM (10%)

Long-Term Health Consequences
- Hyperlipidemia
- Adult-onset DM
- Endometrial hyperplasia
- Infertility
- Obesity
- Sleep apnea

Use of Metformin in Polycystic Ovary Syndrome: A Meta-Analysis
Obstet Gynecol 2008;111(4):959-68.
Study: This meta-analysis of 17 RCTs assessed the efficacy of metformin or metformin in combination with clomiphene citrate in women with PCOS who were seeking pregnancy.
Main Outcomes: Ovulation, pregnancy, and live birth. Patients: 1,639 patients with PCOS were followed up for up to 12 mo.
Results: Compared to placebo, metformin increased the odds of ovulation (OR 2.94, 95% CI 1.43-6.02). However, when used alone, metformin did not significantly increase the odds of achieving pregnancy (OR 1.56, 95% CI 0.74-3.33). When compared to clomiphene alone, the combination of metformin and clomiphene increased the likelihood of ovulation (OR 4.39, 95% CI 1.94-9.96) and pregnancy (OR 2.67, 95% CI 1.45-4.94). The effect of combination therapy was most prominent in clomiphene-resistant and obese women with PCOS. Furthermore, the combination therapy had a higher likelihood of having a live birth compared to clomiphene alone, but this did not reach significance (OR 1.74, 95% CI 0.79-3.86).
Conclusions: Metformin increases the likelihood of ovulation. When used together with clomiphene, metformin increases the likelihood of both ovulation and pregnancy, especially in clomiphene-resistant and obese women.

Diagnostic Criteria for Polycystic Ovary Syndrome: Pitfalls and Controversies
JOGC 2008;8:671-679
At present, there is no clear-cut definition of biochemical hyperandrogenemia, particularly since there is dependence on poor laboratory standards for measuring androgens in women. Clinical signs of hyperandrogenism are ill-defined in women with PCOS, and diagnosis of both hirsutism and polycystic ovarian morphology remains subjective. There is also the inappropriate tendency to assign ovulatory status solely on basis of menstrual cycle history or poorly timed endocrine measurements. Therefore it is important as clinicians to recognize the multi-factorial and complex nature of PCOS and place this in the context of our present diagnostic limitations.

Gynecological Infections

Physiologic Discharge

- clear, white, flocculent, odourless discharge; pH 3.8-4.2
- smear contains epithelial cells, *Lactobacilli*
- increases with increased estrogen states: pregnancy, OCP, mid-cycle, PCOS, or premenarchal
- if increased in perimenopausal/postmenopausal woman, consider investigation for other effects of excess estrogen (e.g. endometrial cancer)

Vulvovaginitis

PREPUBERTAL VULVOVAGINITIS

- clinical features
  - irritation, pruritus
  - discharge
  - vulvar erythema
  - vaginal bleeding (specifically due to Group A *Streptococci* and *Shigella*)
- differential diagnosis
  - non-specific vulvovaginitis (25-75%)
  - infections (respiratory, enteric, systemic, sexually acquired)
  - foreign body (toilet paper most common)
  - *Candida* (if using diapers)
  - pinworms
  - polyps, tumour (ovarian malignancy)
  - vulvar skin disease (lichen sclerosis, condyloma acuminata)
  - trauma (accidental straddle injury, sexual abuse)
  - psychosomatic vaginal complaints (specific to vaginal discharge)
  - endocrine abnormalities (specific to vaginal bleeding)
  - blood dyscrasia (specific to vaginal bleeding)
- etiology
  - infectious
    - poor hygiene, proximity of vagina to anus
    - recent infection (respiratory, enteric, systemic)
    - STI: investigate sexual abuse
  - non-specific
    - lack of protective hair and labial fat pads
    - lack of estrogenization
    - susceptible to chemicals, soaps (bubble baths), medications, and clothing
    - enuresis
- investigations
  - vaginal swab for culture (specifically state that it is a pre-pubertal specimen), pH, wet-mount, and KOH smear in adults only
- treatment
  - enhanced hygiene and local measures (handwashing, white cotton underwear, no nylon tights, no tight fitting clothes, no sleeper pajamas, sitz baths, avoid bubble baths, use mild detergent, eliminate fabric softener, avoid prolonged exposure to wet bathing suits, urination with legs spread apart)
  - A&D® dermatological ointment (vitamin A/D) to protect vulvar skin
  - infectious: treat with antibiotics for organism identified

Vulvovaginitis
Vulvar and vaginal inflammation

Prepubertal and Adolescent Gynecological Infections: Legal Aspects of Confidentiality
- Clinicians who treat adolescents must be aware of federal, state, and provincial laws related to adolescent consent and confidentiality
- They must be aware of guidelines governing funding sources for particular services and be familiar with the consent and confidentiality policies of the facility in which they practice

There is no high quality evidence showing a link between vulvovaginal candidiasis and hygienic habits or wearing tight or synthetic clothing

Table 14. Other Common Causes of Vulvovaginitis in Prepubertal Girls

	Pinworms	Lichen Sclerosis	Foreign Body
Diagnosis	Cellophane tape test	Area of white patches and thinning of skin	
Treatment	Empirical treatment with mebendazole	Topical steroid creams	Irrigation of vagina with saline, may require local anesthesia or an exam under anesthesia

Most common gynecological problem in prepubertal girls is non-specific vulvovaginitis, not yeast

POSTMENOPAUSAL VAGINITIS/ATROPHIC VAGINITIS

- clinical features
  - dyspareunia
  - postcoital spotting
  - mild pruritus
- investigations
  - atrophy is usually a visual diagnosis: thinning of tissues, erythema, petechiae, bleeding points, dryness on speculum exam
  - rule out malignancy: especially endometrial cancer
- treatment
  - local estrogen replacement (ideal): Premarin® cream, VagiFem® tablets, or Estring®
  - oral or transdermal hormone replacement therapy (if treatment for systemic symptoms is desired)
  - good hygiene

INFECTIOUS VULVOVAGINITIS

Table 15. Infectious Vulvovaginitis

	Candidiasis (Moniliasis)	Bacterial Vaginosis (BV)	Trichomoniasis
Organisms	*Candida albicans* (90%) *Candida glabrata* (<5%) *Candida tropicalis* (<5%)	*Gardnerella vaginalis* *Mycoplasma hominis* Anaerobes: *Prevotella, Mobiluncus, Bacteroides*	*Trichomonas vaginalis* (flagellated protozoan)
Pathophysiology or Transmission	Predisposing factors include: • Immunosuppressed host (DM, AIDS, etc.) • Recent antibiotic use • Increased estrogen levels (e.g. pregnancy, OCP)	Replacement of vaginal *Lactobacillus* with organisms above	Sexual transmission
Discharge	Whitish, "cottage cheese," minimal	Grey, thin, diffuse	Yellow-green, malodorous, diffuse, frothy
Other	• 20% asymptomatic	• 50-75% asymptomatic	• 25% asymptomatic
Signs/Symptoms	• Intense pruritus • Swollen, inflamed genitals • Vulvar burning, dysuria, dyspareunia	• Fishy odour, especially after coitus • Absence of vulvar/vaginal irritation	• Petechiae on vagina and cervix • Occasionally irritated tender vulva • Dysuria, frequency
pH	≤4.5	≥4.5	≥4.5
Saline Wetmount	KOH wetmount reveals hyphae and spores	• >20% clue cells = squamous epithelial cells dotted with coccobacilli (*Gardnerella*) • Paucity of WBC • Paucity of *Lactobacilli* • Positive whiff test: fishy odour with addition of KOH to slide (due to formation of amines)	• Motile flagellated organisms • Many WBC • Inflammatory cells (PMNs)

Treatment	• Clotrimazole, butoconazole, miconazole, terconazole suppositories, and/or creams for 1, 3, or 7 d treatments
	• Treatment in pregnancy is usually topical
	• Fluconazole 150 mg PO in single dose (can be used in pregnancy)
		• No treatment if non-pregnant and asymptomatic, unless scheduled for pelvic surgery or procedure
		• Oral
		  • Metronidazole 500 mg PO bid x 7 d
		• Topical
		  • Metronidazole gel 0.75% x 5 d OD (may be used in pregnancy)
		  • Clindamycin 2% 5 g intravaginally at bedtime for 7 d
		• Probiotics (lactobacillus sp.): oral or topical alone or as adjuvant
			• Treat even if asymptomatic
			• Metronidazole 2 g PO single dose or 500 mg bid x 7 d (alternative)
			• Symptomatic pregnant women should be treated with 2 g metronidazole once

Other	• Prophylaxis for recurrent infection includes boric acid, vaginal suppositories, luteal phase fluconazole • Routine treatment of partner(s) not recommended (not sexually transmitted)	• Associated with recurrent preterm labour, preterm birth, and postpartum endometritis • Need to warn patients on metronidazole not to consume alcohol (disulfiram-like action) • Routine treatment of partner(s) not recommended (not sexually transmitted)	• Warnings accompanying metronidazole use • Treat partner(s)

Sexually Transmitted Infections

• see Family Medicine, FM45

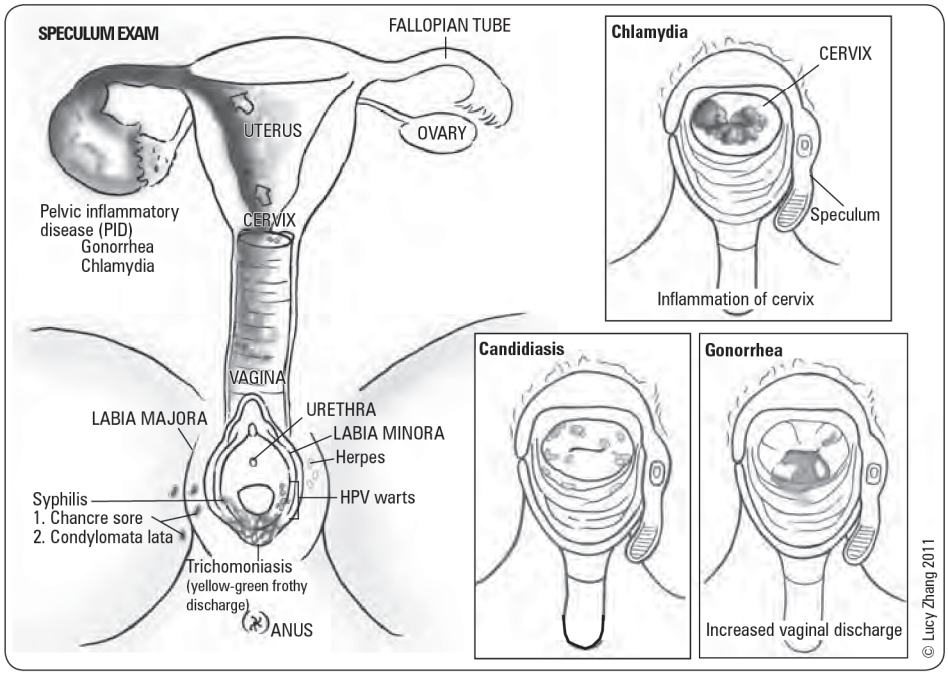


Figure 16. Speculum exam

CDC Notifiable Diseases
- Chancroid
- Chlamydia
- Gonorrhea
- Hepatitis A, B, C
- HIV
- Syphilis

Risk Factors for STIs
- History of previous STI
- Contact with infected person
- Sexually active individual <25 yr
- Multiple partners
- New partner in last 3 mo
- Lack of barrier protection use
- Street involvement (homelessness, drug use)

TRICHOMONIASIS
- see *Infectious Vulvovaginitis*, Table 15, GY27

CHLAMYDIA

Etiology
- *Chlamydia trachomatis*

Epidemiology
- most common bacterial STI in Canada
- often associated with *N. gonorrhoeae*

Clinical Features
- asymptomatic (80% of women)
- muco-purulent endocervical discharge
- urethral syndrome: dysuria, frequency, pyuria, no bacteria on culture
- pelvic pain
- postcoital bleeding or intermenstrual bleeding (particularly if on OCP and prior history of good cycle control)
- symptomatic sexual partner

Investigations
- cervical culture or nucleic acid amplification test
- obligate intracellular parasite: tissue culture is the definitive standard
- urine and vaginal tests now available, which are equally or more effective than cervical culture

STI Testing
- Vaginal swab
  - Tests for bacterial vaginosis, trichomoniasis, candida
- Cervical swab
  - Tests for gonorrhea and chlamydia

Treatment
- doxycycline 100 mg PO bid for 7 d or azithromycin 1 g PO in a single dose (may use in pregnancy)
- also treat gonorrhea because of high rate of co-infection
- treat partners
- reportable disease
- test of cure for chlamydia required in pregnancy (cure rates lower in pregnant patients) → retest 3-4 wk after initiation of therapy

Screening
- high risk groups
- during pregnancy
- with initiation of OCP (independent risk factor)

Complications
- acute salpingitis, PID
- Fitz-Hugh-Curtis syndrome (liver capsule inflammation)
- reactive arthritis (male predominance, HLA-B27 associated), conjunctivitis, urethritis
- infertility: tubal obstruction from low grade salpingitis
- ectopic pregnancy
- chronic pelvic pain
- perinatal infection: conjunctivitis, pneumonia

GONORRHEA

Etiology
- *Neisseria gonorrhoeae*
- symptoms and risk factors same as with chlamydia

Investigations
- Gram stain shows Gram-negative intracellular diplococci
- cervical, rectal, and throat culture (if clinically indicated)

Test of cure for *C. trachomatis* and *N. gonorrhoeae* is not routinely indicated
Repeat testing if symptomatic, if compliance with treatment is uncertain, or if pregnant

Treatment
- single dose of ceftriaxone 250 mg IM plus azithromycin 1 g PO
- if pregnant: above regimen or 2 g spectinomycin IM plus azithromycin 1 g PO (avoid quinolones)
- also treat chlamydia, because of high rate of co-infection
- treat partners
- reportable disease
- screening as with chlamydia

HUMAN PAPILLOMAVIRUS

Etiology
- most common viral STI in Canada
- >200 subtypes, of which >30 are genital subtypes
- HPV types 6 and 11 are classically associated with anogenital warts/condylomata acuminata
- HPV types 16 and 18 are the most oncogenic (classically associated with cervical HSIL)
- types 16, 18, 31, 33, 35, 36, 45 (and others) associated with increased incidence of cervical and vulvar intraepithelial hyperplasia and carcinoma

Clinical Features
- latent infection
  - no visible lesions, asymptomatic
  - only detected by DNA hybridization tests
- subclinical infection
  - visible lesion found during colposcopy or on Pap test
- clinical infection
  - visible wart-like lesion without magnification
  - hyperkeratotic, verrucous or flat, macular lesions
  - vulvar edema

Investigations
- cytology (see *Cervical Screening Pap Test*, GY44)
  - koilocytosis: nuclear enlargement and atypia with perinuclear halo
- biopsy of lesions at colposcopy
- detection of HPV DNA subtype using nucleic acid probes (not routinely done but can be done in presence of abnormal Pap test to guide treatment)

Treatment
- patient administered
  - podofilox 0.5% solution or gel bid x 3 d in a row (4 d off) then repeat x 4 wk
  - imiquimod (Aldara®) 5% cream 3x/wk qhs x 16 wk
- provider administered
  - cryotherapy with liquid nitrogen: repeat q1-2wk
  - podophyllin resin in tincture of benzoin: weekly
  - trichloroacetic acid (TCA) or bichloroacetic acid weekly (80-90%); safe in pregnancy
  - surgical removal/laser
  - intralesional interferon

Prevention
- vaccination: Gardasil®, Cervarix® see Table 25, GY46
- condoms may not fully protect (areas not covered, must be used every time throughout entire sexual act)

HERPES SIMPLEX VIRUS OF VULVA

Etiology
- 90% are HSV-2, 10% are HSV-1

Clinical Features
- may be asymptomatic
- initial symptoms: present 2-21 d following contact
- prodromal symptoms: tingling, burning, pruritus
- multiple, painful, shallow ulcerations with small vesicles appear 7-10 d after initial infection (absent in many infected persons); lesions are infectious
- inguinal lymphadenopathy, malaise, and fever often with first infection
- dysuria and urinary retention if urethral mucosa affected
- recurrent infections: less severe, less frequent and shorter in duration (especially with HSV-1)

Investigations
- viral culture preferred in patients with ulcer present, however decreased sensitivity as lesions heal
- cytologic smear (Tzanck smear)
  - multinucleated giant cells, acidophilic intranuclear inclusion bodies
- type specific serologic tests for antibodies to HSV-1 and HSV-2 (not available routinely in Canada)
- HSV DNA PCR

Genital Warts During Pregnancy
- Condyloma tend to get larger in pregnancy and should be treated early (consider excision)
- C-section only if obstruction of birth canal or risk of extensive bleeding
- Do not use imiquimod, podophyllin, or podofilox

Human Rights in Health Equity: Cervical Cancer and HPV Vaccines
Am J Law Med 2009;35:365-387
- While cervical cancer rates have drastically fallen in developed countries due to effective prevention and treatment, socially disadvantaged women within these countries remain disproportionately more likely to develop and die of cervical cancer.
- In most developing countries cervical cancer rates have risen or remained unchanged.
- Must recognize that cervical cancer disparities between race groups, urban and rural residence, and high and low socioeconomic status are attributed to disparate screening and vaccination coverage.
- Programs are implemented without sufficient attention to conditions that render screening less effective or inaccessible to disadvantaged social groups including: lack of information, undervaluing of preventive care, opportunistic delivery in limited health care settings, sexual health stigma, and related privacy concerns.

A 9-Valent HPV Vaccine Against Infection and Intraepithelial Neoplasia in Women
NEJM 2015;372:711-23.
Purpose: To determine the efficacy and immunogenicity of the qHPV (types 6, 11, 16, 18) vs. 9vHPV (five additional types 31, 33, 45, 52, 58) vaccines.
Method: International randomized, double-blinded phase 2B-3 study of 9vHPV vaccine in 14,215 women between ages of 16-26. Participants were randomized to the 9vHPV vaccine group or the qHPV vaccine group and each received a series of three IM injections (day 1, 2 and 6 months). Swabs of labial, vulvar, perineal, perianal, endocervical, and ectocervical tissue was obtained and used for HPV DNA testing/Pap smear.
Results: Rate of high-grade cervical, vulvar, or vaginal disease was 14.0 per 1,000 person-years in both vaccine groups. The rate of high-grade cervical, vulvar, or vaginal disease related to HPV-31, 33, 45, 52, and 58 was 0.1 per 1,000 person-years in the 9vHPV group and 1.6 per 1,000 person-years in the qHPV group (95% CI = 80.9-99.8). Antibody responses to HPV-6, 11, 16, and 18 were not significantly different between the two vaccine groups although adverse events related to injection sites were more common in the 9vHPV group.
Conclusions: The 9vHPV vaccine was non-inferior to qHPV vaccine in preventing infection and disease related to HPV-6, 11, 16, and 18 and also covered additional oncogenic types HPV-31, 33, 45, 52, and 58 in a susceptible population.

Treatment
- first episode
  - acyclovir 200 mg PO five times daily x 5-10 d, or famciclovir 250 mg PO tid x 7-10 5 d, or valacyclovir 1 g PO bid x 10 d
- recurrent episode
  - acyclovir 200 mg PO five times daily x 5 d, or famciclovir 125 mg PO bid x 5 d, or valacyclovir 500 mg PO bid OR 1 g PO OD x 3 d
- daily suppressive therapy
  - consider if more than 6 recurrences per yr or one every 2 mo
  - acyclovir 400 mg PO bid, or famciclovir 250 mg bid, or valacyclovir 0.5-1 g PO OD
- severe disease
- consider IV therapy: acyclovir 55 mg/kg IV over 60 min q8h
- education regarding transmission
- avoid contact from onset of prodrome until lesions have cleared
- use barrier contraception

HSV Infections During Pregnancy
- Antiviral suppression of women with first episode or history of HSV infections from 36 wk GA onward
- C-section should be performed on women who have active genital lesions at time of delivery
- Treatment: acyclovir 400 mg PO tid

SYPHILIS

Etiology
- *Treponema pallidum*

Classifications
- primary syphilis
  - 3-4 wk after exposure
  - painless chancre on vulva, vagina, or cervix
  - painless inguinal lymphadenopathy
  - serological tests usually negative, local infection only
- secondary syphilis (can resolve spontaneously)
  - 2-6 mo after initial infection
  - nonspecific symptoms: malaise, anorexia, headache, diffuse lymphadenopathy
  - generalized maculopapular rash: palms, soles, trunk, limbs
  - condylomata lata: anogenital, broad-based fleshy grey lesions
  - serological tests usually positive
- latent syphilis
  - no clinical manifestations; detected by serology only
- tertiary syphilis
  - may involve any organ system
  - neurological: tabes dorsalis, general paresis
  - cardiovascular: aortic aneurysm, dilated aortic root
  - vulvar gumma: nodules that enlarge, ulcerate and become necrotic (rare)
- congenital syphilis
  - may cause fetal anomalies, stillbirths, or neonatal death

Epidemiology of Genital Ulcers

HSV	70-80%
1° Syphilis	5%
Chancroid (*Haemophilus ducreyi*)	<1%

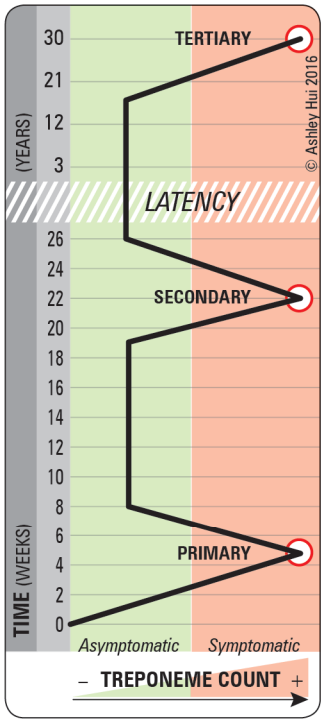


Figure 17. Natural history of syphilis infection

Investigations
- aspiration of ulcer serum or node
- darkfield microscopy (most sensitive and specific diagnostic test for syphilis)
  - spirochetes
- non-treponemal screening tests (VDRL, RPR); nonreactive after treatment, can be positive with other conditions
- specific anti-treponemal antibody tests (FTA-ABS, MHA-TP, TP-PA)
  - confirmatory tests; remain reactive for life (even after adequate treatment)

Treatment
- treatment of primary, secondary, latent syphilis of <1 yr duration
  - benzathine penicillin G 2.4 million units IM single dose
  - treat partners, reportable disease
- treatment of latent syphilis of >1 yr duration
  - benzathine penicillin G 2.4 million units IM q1wk x 3 wk
- treatment of neurosyphilis
  - IV aqueous penicillin G 3-4 million units IM q4h x 10-14 d
- screening
  - high risk groups
  - in pregnancy (see Obstetrics, Table *Infections During Pregnancy*, OB30)

Complications
- if untreated, 1/3 will experience late complications

HIV
- see Infectious Diseases, ID28

Bartholinitis/Bartholin Gland Abscess

Etiology
- often anaerobic and polymicrobial
- *U. urealyticum, N. gonorrhoeae, C. trachomatis, E. coli, P. mirabilis, Streptococcus* spp., *S. aureus* (rare)
- blockage of duct

Clinical Features
- unilateral swelling and pain in inferior lateral opening of vagina
- sitting and walking may become difficult and/or painful

Treatment
- sitz baths, warm compresses
- antibiotics: cephalexin x 1 wk
- incision and drainage using local anesthesia with placement of Word catheter (10 French latex catheter) for 2-3 wk
- marsupialization under general anesthetic – more definitive treatment
- rarely treated by removing gland

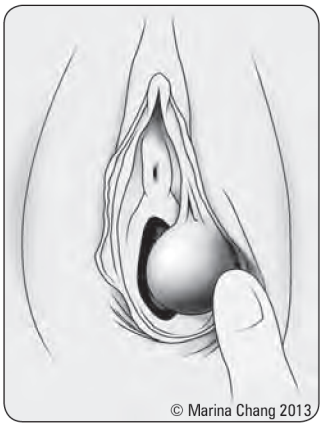


Figure 18. Bartholin's gland abscess

Pelvic Inflammatory Disease

- up to 20% of all gynecology-related hospital admissions

PID accounts for up to 20% of all gynecological hospital admissions

Etiology
- causative organisms (in order of frequency)
  - *C. trachomatis*
  - *N. gonorrhoeae*
  - gonorrhea and chlamydia often co-exist
  - endogenous flora: anaerobic, aerobic, or both
    - *E. coli, Staphylococcus, Streptococcus, Enterococcus, Bacteroides, Peptostreptococcus, H. influenzae, G. vaginalis*
    - cause of recurrent PID
    - associated with instrumentation
  - *Actinomyces israelii* (Gram-positive, non acid-fast anaerobe)
    - 1-4% of PID cases associated with IUDs
  - others (TB, Gram-negatives, CMV, *U. urealyticum*, etc.)

PID
Inflammation of the upper genital tract (above cervix) including endometrium, fallopian tubes, ovaries, pelvic peritoneum, ± contiguous structures

Risk Factors
- age <30 yr
- risk factors as for chlamydia and gonorrhea
- vaginal douching
- IUD (within first 10 d after insertion)
- invasive gynecologic procedures (D&C, endometrial biopsy)

PID Diagnosis
Must have
- Lower abdominal pain

Plus one of
- Cervical motion tenderness
- Adnexal tenderness

Plus one or more of
- High risk partner
- Temperature >38°C
- Mucopurulent cervical discharge
- Positive culture for *N. gonorrhoeae, C. trachomatis, E. coli*, or other vaginal flora
- Cul-de-sac fluid, pelvic abscess or inflammatory mass on U/S or bimanual
- Leukocytosis
- Elevated ESR or CRP (not commonly used)

Clinical Presentation
- up to 2/3 asymptomatic: many subtle or mild symptoms
- common
  - fever >38.3°C
  - lower abdominal pain and tenderness
  - abnormal discharge: cervical or vaginal
- uncommon
  - N/V
  - dysuria
  - AUB
- chronic disease (often due to chlamydia)
  - constant pelvic pain
  - dyspareunia
  - palpable mass
  - very difficult to treat, may require surgery

Investigations

- blood work
  - β-hCG (must rule out ectopic pregnancy), CBC, blood cultures if suspect septicemia
- urine R&M
- speculum exam, bimanual exam
  - vaginal swab for Gram stain, C&S
  - cervical cultures for *N. gonorrhoeae, C. trachomatis*
  - endometrial biopsy will give definitive diagnosis (rarely done)
- ultrasound
  - may be normal
  - free fluid in cul-de-sac
  - pelvic or tubo-ovarian abscess
  - hydrosalpinx (dilated fallopian tube)
- laparoscopy (gold standard)
  - for definitive diagnosis: may miss subtle inflammation of tubes or endometritis

Treatment

- must treat with polymicrobial coverage
- inpatient if
  - moderate to severe illness
  - atypical infection
  - adnexal mass, tubo-ovarian or pelvic abscess
  - unable to tolerate oral antibiotics or failed oral therapy
  - immunocompromised
  - pregnant
  - adolescent – first episode
  - surgical emergency cannot be excluded (e.g. ovarian torsion)
  - PID is secondary to instrumentation
  - recommended treatment
    - cefoxitin 2 g IV q6h (no longer available in U.S.A.) + doxycycline 100 mg IV/PO q12h or clindamycin 900 mg IV q8h + gentamicin 2 mg/kg IV/IM loading dose then gentamicin 1.5 mg/kg IV q8h maintenance dose
    - continue IV antibiotics for 24 h after symptoms have improved then doxycycline 100 mg PO bid to complete 14 d
    - percutaneous drainage of abscess under U/S guidance
    - when no response to treatment, laparoscopic drainage
    - if failure, treatment is surgical (salpingectomy, TAH/BSO)
- outpatient if
  - typical findings
  - mild to moderate illness
  - oral antibiotics tolerated
  - compliance ensured
  - follow-up within 48-72 h (to ensure symptoms not worsening)
  - recommended treatment
    - ceftriaxone 250 mg IM x 1 + doxycycline 100 mg PO bid x 14 d or cefoxitin 2 g IM x 1 + probenecid 1 g PO + doxycyline 100 mg PO bid ± metronidazole 500 mg PO bid x 14 d
    - ofloxacin 400 mg PO bid x 14 d or levofloxacin 500 mg PO OD x 14 d ± metronidazole 500 mg PO bid x 14 d
    - consider removing IUD after a minimum of 24 h of treatment
    - reportable disease
    - treat partners
    - consider re-testing for *C. trachomatis* and *N. gonorrhoeae* 4-6 wk after treatment if documented infection

Alternative PID Treatments
For patients with contraindications to treatment with cephalosporins or quinolones, recent evidence suggests that a short course of azithromycin at a dose of either 250 mg PO daily for 1 wk or 1 g PO weekly for 2 wk combined with metronidazole is effective in achieving a clinical cure for acute PID

Source: Update to the *Canadian Guidelines on Sexually Transmitted Infections*. January 2010

Treat PID with **FOXY DOXY**
(cefoxitin + doxycycline)

Complications of Untreated PID

- chronic pelvic pain
- abscess, peritonitis
- adhesion formation
- ectopic pregnancy
- infertility
  - 1 episode of PID → 13% infertility
  - 2 episodes of PID → 36% infertility
- bacteremia
- septic arthritis, endocarditis

PID Complications

I FACE PID
Infertility
Fitz-Hugh-Curtis syndrome
Abscesses
Chronic pelvic pain
Ectopic pregnancy
Peritonitis
Intestinal obstruction
Disseminated infection (sepsis, endocarditis, arthritis, meningitis)

Toxic Shock Syndrome

- see Infectious Diseases, ID23

Risk Factors
- tampon use
- diaphragm, cervical cap, or sponge use (prolonged use, i.e. >24 h)
- wound infections
- post-partum infections
- early recognition and treatment of syndrome is imperative as incorrect diagnosis can be fatal

Clinical Presentation
- sudden high fever
- sore throat, headache, diarrhea
- erythroderma
- signs of multisystem organ failure
- refractory hypotension
- exfoliation of palmar and plantar surfaces of the hands and feet 1-2 wk after onset of illness

Toxic Shock Syndrome
Multiple organ system failure due to *S. aureus* exotoxin (rare condition)

Treatment
- remove potential sources of infection (foreign objects and wound debris)
- debride necrotic tissues
- adequate hydration
- penicillinase-resistant antibiotics, e.g. cloxacillin
- steroid use controversial but if started within 72 h, may reduce severity of symptoms and duration of fever

Surgical Infections

Post-Operative Infections in Gynecological Surgery
- pelvic cellulitis
  - common post hysterectomy, affects vaginal vault
  - erythema, induration, tenderness, discharge involving vaginal cuff
  - treat if fever and leukocytosis with broad spectrum antibiotics, i.e. clindamycin and gentamicin
  - drain if excessive purulence or large mass
  - can result in intra-abdominal and pelvic abscess
- see General Surgery, *Post-Operative Fever*, GS7

Sexual Abuse

- see Family Medicine, FM27, Emergency Medicine, ER27

Sexuality and Sexual Dysfunction

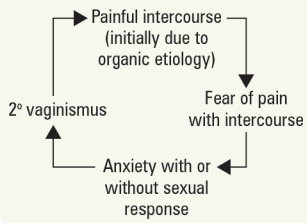
SEXUAL RESPONSE
1. desire: energy that allows an individual to initiate or respond to sexual stimulation
2. arousal: physical and emotional stimulation leading to breast and genital vasodilation and clitoral engorgement
3. orgasm: physical and emotional stimulation is maximized, allowing the individual to relinquish their sense of control
4. resolution: most of the congestion and tension resolves within seconds, complete resolution may take up to 60 min

SEXUAL DYSFUNCTION

Etiology
- psychological or emotional: depression, abuse
- hormonal: menopause
- neurologic dysfunction: spinal cord injury
- vascular insufficiency: DM
- drug side effects: β-blockers
- trauma: episiotomy

Classification
- lack of desire (60-70% of women)
- lack of arousal
- anorgasmia (5-10%)
  - primary anorgasmia: never before achieved orgasm under any circumstances
  - secondary anorgasmia: was able to achieve orgasms before but now unable to
- dyspareunia (3-6%): painful intercourse, superficial or deep
  - vaginismus (15%)
  - vulvodynia
  - vaginal atrophy
  - vulvar vestibulitis: associated with history of frequent yeast infections
  - PID

Dyspareunia Cycle



Treatment
- lack of desire: assess factors, rule out organic causes, relationship therapy, sensate focus exercises
- anorgasmia: self-exploration/pleasuring, relationship therapy if needed, bridging techniques (different sexual positions, clitoral stimulation during intercourse)
- dyspareunia
  - Kegel and reverse Kegel exercises
  - dilator treatment
  - comfort with self-exam
  - psychotherapy, other behavioural techniques
  - female on top position: allows for control of speed and duration
  - vestibulitis: remove local irritants, change in contraceptive methods, dietary changes (increased citrate, decreased oxalate), and vestibulectomy (rare)
  - vulvodynia: local moisturization, cold compresses, systemic nerve blocking therapy (amitriptyline, gabapentin), topical anesthetics, estrogen cream
  - pain clinic

Kegel Exercises
Regular contraction and relaxation to strengthen pelvic floor muscles

Reverse Kegel Exercises
1 s contraction then 5 s of relaxation

Menopause

- see Family Medicine, FM42

Definitions
- lack of menses for 1 yr
- types of menopause
  - physiological; average age 51 yr (follicular atresia)
  - premature ovarian failure; before age 40 (autoimmune disorder, infection, Turner's syndrome)
  - iatrogenic (surgical/radiation/chemotherapy)

Menopause
Occurrence of last spontaneous menstrual period, resulting from loss of ovarian function (loss of oocyte response to gonadotropins)

"Being in menopause"
Lack of menses for 1 yr

Perimenopause
Period of time surrounding menopause (2-8 yr preceding + 1 yr after last menses) characterized by fluctuating hormone levels, irregular menstrual cycles, and symptom onset

Clinical Features
- associated with estrogen deficiency
  - vasomotor instability (tends to dissipate with time)
    - hot flushes/flashes, night sweats, sleep disturbances, formication, nausea, palpitations
  - urogenital atrophy involving vagina, urethra, bladder
    - dyspareunia, pruritus, vaginal dryness, bleeding, urinary frequency, urgency, incontinence
  - skeletal
    - osteoporosis, joint and muscle pain, back pain
  - skin and soft tissue
    - decreased breast size, skin thinning/loss of elasticity
  - psychological
    - mood disturbance, irritability, fatigue, decreased libido, memory loss

- 85% of women experience hot flashes
- 20-30% seek medical attention
- 10% are unable to work

Investigations
- increased levels of FSH (>35 IU/L) on day 3 of cycle (if still cycling) and LH (FSH>LH)
- FSH level not always predictive due to monthly variation; use absence of menses for 1 yr to diagnose
- decreased levels of estradiol (later)

Menopause Pathophysiology

Degenerating theca cells fail to react to endogenous gonadotropins (FSH, LH)
↓
Less estrogen is produced
↓
Decreased negative feedback on hypothalamic-pituitary-adrenal axis
↓
Increased FSH and LH
↓
Stromal cells continue to produce androgens as a result of increased LH stimulation

Treatment
- goal is for individual symptom management
  - vasomotor instability
    - HRT (first line), SSRIs, venlafaxine, gabapentin, propranolol, clonidine
    - acupuncture
  - vaginal atrophy
    - local estrogen: cream (Premarin®), vaginal suppository (VagiFem®), ring (Estring®)
    - lubricants (Replens®)
  - urogenital health
    - lifestyle changes (weight loss, bladder re-training), local estrogen replacement, surgery

- osteoporosis
  - 1,000-1,500 mg calcium OD, 800-1,000 IU vitamin D, weight-bearing exercise, smoking cessation
  - bisphosphonates (e.g. alendronate)
  - selective estrogen receptor modifiers (SERMs): raloxifene (Evista®) – mimics estrogen effects on bone, avoids estrogen-like action on breast and uterine cancer; does not help hot flashes
  - HRT: second-line treatment (unless for vasomotor instability as well)
- decreased libido
  - vaginal lubrication, counseling, androgen replacement (testosterone cream or the oral form Andriol®)
- cardiovascular disease
  - management of cardiovascular risk factors
- mood and memory
  - antidepressants (first line), HRT (augments effect)
- alternative choices (not evidence-based, safety not established)
  - black cohosh, phytoestrogens, St. John's wort, gingko biloba, valerian, evening primrose oil, ginseng, Don Quai

- Osteoporosis is the single most important health hazard associated with menopause
- Cardiovascular disease is the leading cause of death post-menopause

- Increased risk of breast cancer (RR 1.3) is associated with estrogen+progesterone HRT, but not with estrogen-only HRT
- All women taking HRT should have periodic surveillance and counseling regarding its benefits and risks

Hormone Replacement Therapy

- see Family Medicine, FM42
- primary indication is treatment of menopausal symptoms (vasomotor instability)
- keep doses low (e.g. 0.3 mg Premarin®) and duration of treatment short (<5 yr)

HRT Components

- estrogen
  - oral or transdermal (e.g. patch, gel)
  - transdermal preferred for women with hypertriglyceridemia or impaired hepatic function, smokers, and women who suffer from headaches associated with oral HRT
  - low-dose (preferred dose: 0.3 mg Premarin®/25 μg Estradot® patch, can increase if necessary)
- progestin
  - given in combination with estrogen for women with an intact uterus to prevent development of endometrial hyperplasia/cancer

Table 16. Examples of HRT Regimens

HRT Regimen	Estrogen Dose	Progestin Dose	Notes
Unopposed Estrogen	CEE 0.625 mg PO OD	None	If no intact uterus
Standard-dose	CEE 0.625 mg PO OD	MPA 2.5 mg PO OD, or micronized progesterone 100 mg PO OD	Withdrawal bleeding may occur in a spotty, unpredictable manner Usually abates after 6-8 mo due to endometrial atrophy Once patient has become amenorrheic on HRT, significant subsequent bleeding episodes require evaluation (endometrial biopsy)
Standard-dose Cyclic	CEE 0.625 mg PO OD	MPA 5-10 mg PO days 1-14 only, or micronized progesterone 200 mg PO OD days 1-14 only	Bleeding occurs monthly after day 14 of progestin (can continue for years) PMS-like symptoms (breast tenderness, fluid retention, headache, nausea) are more prominent with cyclic HRT
Pulsatile	CEE 0.625 mg PO OD	MPA low-dose	3 d on, 3 d off
Transdermal	Estroderm®-Estradiol 0.05 mg/d or 0.1 mg/d Estalis®-Estradiol 140 μg/d or 250 μg/d	Estroderm®-MPA 2.5 mg PO OD Estalis®-NEA 50 μg/d	Use patch twice weekly Can use oral progestins (Estroderm®) Combined patches available (Estalis®)
Topical	Estrace® 2-4 g/d x 1-2 wk, 1 g/d maintenance Premarin® 0.5-2 g/d for 21 d then off 7 d for vaginal atrophy, 0.5 g/d for 21 d then off 7 d or twice/wk for dyspareunia Estragyn® 2-4 g/d	Crinone® 4% or 8% (45 or 90 mg applicator)	If simultaneously taking oral estrogen tablet, may need to adjust dosing If intact uterus, also take progesterone

CEE = conjugated equine estrogen (e.g. Premarin®); MPA = medroxyprogesterone acetate (e.g. Provera®); NEA = norethindrone acetate
Consider lower dose regimens, PREMPRO® 0.45/1.5 (Premarin® 0.45 mg and Provera® 1.5 mg); Estrace® (topical 17β-estradiol) = 0.1 mg active ingredient/g; Premarin® (topical CEE) = 0.625 mg active ingredient/g; Estragyn® (topical estrone) = 1 mg active ingredient/g

Side Effects of HRT
- abnormal uterine bleeding
- mastodynia – breast tenderness
- edema, bloating, heartburn, nausea
- mood changes (progesterone)
- can be worse in progesterone phase of combined therapy

Contraindications to HRT
- absolute
  - acute liver disease
  - undiagnosed vaginal bleeding
  - known or suspected uterine cancer/breast cancer
  - acute vascular thrombosis or history of severe thrombophlebitis or thromboembolic disease
  - cardiovascular disease
- relative
  - pre-existing uncontrolled HTN
  - uterine fibroids and endometriosis
  - familial hyperlipidemias
  - migraine headaches
  - family history of estrogen-dependent cancer
  - chronic thrombophlebitis
  - DM (with vascular disease)
  - gallbladder disease, hypertriglyceridemia, impaired liver function (consider transdermal estrogen)
  - fibrocystic disease of the breasts

Absolute Contraindications to HRT

ABCD
Acute liver disease
Undiagnosed vaginal **B**leeding
Cancer (breast/uterine), **C**ardiovascular disease
DVT (thromboembolic disease)

WOMEN'S HEALTH INITIATIVE (launched in 1991)
- two non-randomized studies investigating health risks and benefits of HRT in healthy postmenopausal women 50-79 yr old
  - continuous combined HRT (CEE 0.625 mg + MPA 2.5 mg OD) in 16,608 women with an intact uterus
  - estrogen-alone (CEE 0.625 mg) in 10,739 women with a previous hysterectomy
- both arms of the trial were stopped early because of evidence of increased risk of breast cancer, stroke, PE, and CHD in the combined HRT arm, and increased risk of stroke with no CHD benefits in the estrogen-alone arm
- the apparent increase in CHD was in disagreement with results of previous observational trial
- results of the WHI study have since been challenged and revision of how CHD was diagnosed led to loss of statistical significance of the results
- benefits and risks reported as number of cases per 10,000 women each year

Table 17. HRT Benefits vs. Risks

Benefits	Risks
Vasomotor Symptoms: less frequent and severe with use of either combined or estrogen-alone HRT	**Stroke:** 8 additional cases with combined HRT, and 12 additional cases for estrogen alone (WHI)
Osteoporosis: 5 fewer cases of hip fractures and 47 fewer cases of all fractures with combined HRT; 6 fewer cases of hip fractures with estrogen alone	**DVT/PE**: 18 additional cases with combined HRT, and 9 additional cases for estrogen-alone (WHI)
Colon Cancer: 6 fewer cases with combined HRT (WHI) One additional case with estrogen-alone	**CHD**: 7 additional MIs with combined HRT (WHI); secondary analysis suggests greater absolute risk for women aged >70 yr and for women who start HRT >10 yr post-menopause
	Breast Cancer: 8 additional cases with combined HRT (WHI) Risk only increased after >5 yr of combined HRT use; no increased risk for estrogen-alone
	Dementia and Mild Cognitive Impairment: 50% greater risk of developing dementia in women taking estrogen-alone after age 65; risk is greater for women taking combined HRT; risk of developing dementia was reduced for women taking HRT before age 65

Long-Term Hormone Therapy for Perimenopausal and Postmenopausal Women
Cochrane DB Syst Rev 2012;7:CD004143
Purpose: To determine the effect of long-term HRT on mortality, cardiovascular outcomes, cancer, gallbladder disease, fractures, cognition, and QOL in perimenopausal and postmenopausal women, during HRT use, and after cessation of HRT.
Results: 23 studies with 42,380 women included. 70% of the data from the WHI (1998) and HERS (1998). None of the studies focused on perimenopausal women. Combined continuous HRT: increased risk of coronary event after 1 yr (absolute risk 18/1,000, 95% CI 3-7), venous thromboembolism after 1 yr (AR 7/1,000, 95% CI 4-11), stroke after 3 yr (AR 18/1,000, 95% CI 14-23), breast cancer after 5.6 yr (AR 23/1,000, 95% CI 19-29), gallbladder disease after 5.6 yr (AR 27/1,000, 95% CI 21-34), and death from lung cancer after 5.6 yr use (AR 9/1,000, 95% CI 6-13). Estrogen only HRT: increased risk of venous thromboembolism after 1-2 yr use (AR 5/1,000, 95% CI 2-10; after 7 yr AR 21/1,000, 95% CI 16-28), stroke after 7 yr (AR 32/1,000, 95% CI 25-40), and gallbladder disease after 7 yr use (AR 45/1,000, 95% CI 36-57) and did not significantly affect the risk of breast cancer. Women >65 yr of age taking combined HRT had a statistically significant increase in the incidence of dementia after 4 yr use (AR 18/1,000, 95% CI 11-30). Women taking HRT had a decreased risk of fractures with combined HRT after 5.6 yr (AR 86/1,000, 95% CI 79-84) and 7.1 yr of estrogen only HRT (AR 102/1,000, 95% CI 91-112).
Conclusions: HRT is not indicated for primary or secondary prevention of cardiovascular disease or dementia. Although HRT is considered effective for the prevention of postmenopausal osteoporosis, it is generally recommended as an option only for women at significant risk, for whom non-estrogen therapies are unsuitable.

Urogynecology

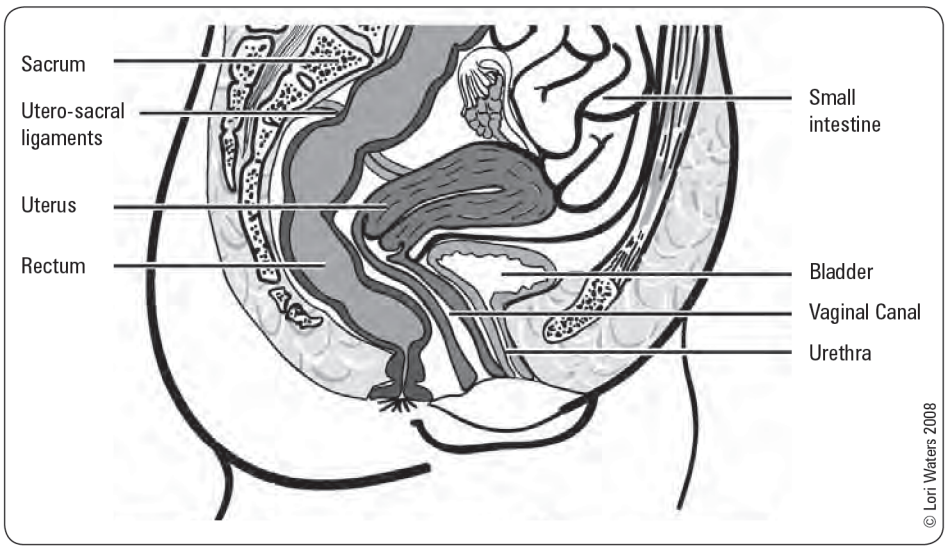


Figure 19. Pelvic anatomy

Pelvic Relaxation/Prolapse

Etiology

- relaxation, weakness, or defect in the cardinal and uterosacral ligaments which normally maintain the uterus in an anteflexed position and prevent it from descending through the urogenital diaphragm (i.e. levator ani muscles)
- related to
  - vaginal childbirth
  - aging
  - decreased estrogen (post-menopause)
  - following pelvic surgery
  - increased intra-abdominal pressure (obesity, chronic cough, constipation, ascites, heavy lifting)
  - congenital (rarely)
  - ethnicity (Caucasian women > Asian or African women)
  - collagen disorders

Grading of Pelvic Organ Prolapse

- 0 = no descent during straining
- 1 = distal portion of prolapse >1 cm above level of hymen
- 2 = distal portion of prolapse ≤1 cm above or below level of hymen
- 3 = distal portion of prolapse >1 cm below level of hymen but without complete vaginal eversion
- 4 = complete eversion of total length of lower genital tract
- **Procidentia:** failure of genital supports and complete protrusion of uterus through the vagina

GENERAL CONSERVATIVE TREATMENT

(for pelvic relaxation/prolapse and urinary incontinence)

- Kegel exercises
- local vaginal estrogen therapy
- vaginal pessary (intravaginal suspension disc)

Pelvic Relaxation/Prolapse
Protrusion of pelvic organs into or out of the vagina

Table 18. Pelvic Prolapse

Type	Clinical Features	Treatment
Cystocele (protrusion of bladder into the anterior vaginal wall)	• Frequency, urgency, nocturia • Stress incontinence • Incomplete bladder emptying ± associated increased incidence of urinary tract infections – may lead to renal impairment	• See above • Anterior colporrhaphy ("anterior repair") • Consider additional/alternative surgical procedure if documented urinary stress incontinence
Enterocele (prolapse of small bowel in upper posterior vaginal wall)		• Similar to hernia repair • Contents reduced, neck of peritoneal sac ligated, uterosacral ligaments, and levator ani muscles approximated
Rectocele (protrusion of rectum into posterior vaginal wall)	• Straining/digitation to evacuate stool • Constipation	• See above • Also laxatives and stool softeners • Posterior colporrhaphy ("posterior repair"), plication of endopelvic fascia and perineal muscles approximated in midline to support rectum and perineum (can result in dyspareunia)

The only **true** hernia of the pelvis is an ENTEROCELE because peritoneum herniates with the small bowel

Table 18. Pelvic Prolapse (continued)

Type	Clinical Features	Treatment

Uterine Prolapse (protrusion of cervix and uterus into vagina)	• Groin/back pain (stretching of uterosacral ligaments)
	• Feeling of heaviness/pressure in the pelvis
	  • Worse with standing, lifting
	  • Worse at the end of the day
	  • Relieved by lying down
	• Ulceration/bleeding (particularly if hypoestrogenic)
	• ± urinary incontinence
		• See above
		• Vaginal hysterectomy ± surgical prevention of vault prolapse
		• Consider additional surgical procedures if urinary incontinence, cystocele, rectocele, and/or enterocele are present

Vault Prolapse (protrusion of apex of vaginal vault into vagina, post-hysterectomy)		• See above • Sacralcolpopexy (vaginal vault suspension), sacrospinous fixation, or uterosacral ligament suspension

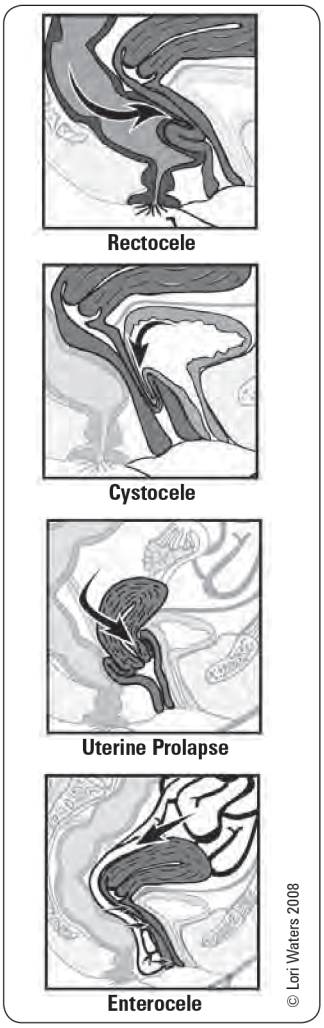


Figure 20. Rectocele, cystocele, uterine prolapse, enterocele

Urinary Incontinence

• see Urology, U5

STRESS INCONTINENCE

Definition
• involuntary loss of urine with increased intra-abdominal pressure (coughing, laughing, sneezing, walking, running)

Risk Factors for Stress Incontinence in Women
• pelvic prolapse
• pelvic surgery
• vaginal delivery
• hypoestrogenic state (post-menopause)
• age
• smoking
• neurological/pulmonary disease

Treatment
• see *General Conservative Treatment*, GY37
• surgical
  ▪ tension-free vaginal tape (TVT), tension-free obturator tape (TOT), prosthetic/fascial slings or retropubic bladder suspension (Burch or Marshall-Marchetti-Krantz procedures)

URGE INCONTINENCE

Definition
• urine loss associated with an abrupt, sudden urge to void
• "overactive bladder"
• diagnosed based on symptoms

Etiology
• idiopathic (90%)
• detrusor muscle overactivity ("detrusor instability")

Associated Symptoms
• frequency, urgency, nocturia, leakage

Treatment
• behaviour modification (reduce caffeine/liquid, smoking cessation, regular voiding schedule)
• Kegel exercises
• medications
  ▪ anticholinergics: oxybutinin (Ditropan®), tolterodine (Detrol®), solifenacin (VESIcare®)
  ▪ tricyclic antidepressants: imipramine

Urge Incontinence
Urine loss associated with an abrupt, sudden urge to void

Rule Out Neurological Causes of Urge Incontinence
• MS
• Herniated disc
• DM

Gynecological Oncology

Uterus

ENDOMETRIAL CARCINOMA

Epidemiology

- most common gynecological malignancy in North America (40%); 4th most common cancer in women
- 2-3% of women develop endometrial carcinoma during lifetime
- mean age is 60 yr
- majority are diagnosed in early stage due to detection of symptoms
- 85-90% 5 yr survival for stage I disease
- 70-80% overall 5 yr survival for all stages

Incidence of Malignant Gynecological Lesions in North America
endometrium > ovary > cervix > vulva > vagina > fallopian tube

Risk Factors

- Type I: excess estrogen (estrogen unopposed by progesterone)
  - obesity
  - PCOS
  - unbalanced HRT (balanced HRT is protective)
  - nulliparity
  - late menopause
  - estrogen-producing ovarian tumours (e.g. granulosa cell tumours)
  - HNPCC (hereditary non-polyposis colorectal cancer)/Lynch II syndrome
  - tamoxifen
- Type II: not estrogen-related
  - possibly tamoxifen

Risk Factors for Endometrial Cancer

COLD NUT
Cancer (ovarian, breast, colon)
Obesity
Late menopause
Diabetes mellitus

Nulliparity
Unopposed estrogen: PCOS, anovulation, HRT
Tamoxifen: chronic use

Classification and Clinical Features

- Type I (well-differentiated endometrioid adenocarcinoma) ~80% of cases
  - postmenopausal bleeding in majority, abnormal uterine bleeding in majority of affected pre-menopausal women (menorrhagia, intermenstrual bleeding)
- Type II (serous, clear cell carcinoma, grade 3 endometrioid, undifferentiated, carcinosarcoma) ~15% of cases
  - may not present with bleeding in early stage, more likely to present with advanced stage disease with symptoms like ovarian cancer (i.e. bloating, bowel dysfunction, pelvic pressure)

Postmenopausal bleeding = endometrial cancer until proven otherwise (95% present with vaginal bleeding)

Investigations

- endometrial sampling
  - office endometrial biopsy
  - D&C ± hysteroscopy
- ± pelvic ultrasound (in women where adequate endometrial sampling not feasible without invasive methods)
  - not acceptable as alternative to pelvic exam or endometrial sampling to rule out cancer

An endometrial thickness of 5 mm or more is considered abnormal in a postmenopausal woman with vaginal bleeding

Table 19. FIGO Staging of Endometrial Cancer (2009)

Stage	Description	Stage	Description
I	**Confined to corpus**	IIIC	Metastasis to pelvic ± para-aortic LNs
IA	No or less than half myometrial invasion	IIIC1	Positive pelvic LN
IB	Invades through ≥½ of myometrium	IIIC2	Positive para-aortic LN ± positive pelvic LNs
II	**Tumour invades cervical stroma, but does not extend beyond uterus***	**IV**	**Invasion of bladder ± bowel mucosa ± distant metastases**
		IVA	Invasion of bladder ± bowel mucosa
III	**Local and/or regional spread of the tumour**	IVB	Distant mets, including intra-abdominal mets ± inguinal LNs
IIIA	Invasion of serosa, corpus uteri ± adnexae		
IIIB	Vaginal ± parametrial involvement		

FIGO: International Federation of Gynecology and Obstetrics
*Note: endocervical glandular involvement is now considered as Stage I (previously Stage II)

Prognostic Factors
Most important is FIGO stage
Other Prognostic Factors:
- Age
- Grade
- Histologic subtype
- Depth of myometrial invasion
- Presence of lymphovascular space involvement (LVSI)
- Hormone receptor status

Spread

- direct extension is most common
- lymphatic spread to pelvic and para-aortic nodes
- transtubal dissemination to peritoneal cavity
- hematogenous spread (usually to lungs, liver)

Treatment

- surgical: hysterectomy/bilateral salpingo-oophorectomy (BSO) and pelvic washings ± pelvic and para-aortic node dissection ± omentectomy
  - goals: diagnosis, staging, treatment, defining optimal adjuvant treatment
  - laparoscopic approach associated with improved quality of life (optimal for most patients)

Complications of Therapy
- Surgical site infection
- Lymphedema
- Radiation fibrosis
- Cystitis
- Proctitis

- adjuvant radiotherapy (for improved local control in patients at risk for local recurrence) and adjuvant chemotherapy (in patients at risk for distant recurrence or with metastatic disease): based on presence of poor prognostic factors in definitive pathology
- chemotherapy: often used for recurrent disease (especially if high grade or aggressive histology)
- hormonal therapy: progestins can be used for recurrent disease (especially if low grade)

Uterine Sarcoma – Symptoms

BAD-P
Bleeding
Abdominal distention
Foul smelling vaginal **D**ischarge
Pelvic Pressure

A rapidly enlarging uterus, especially in a postmenopausal woman, should prompt consideration of leiomyosarcoma

UTERINE SARCOMA

- rare; 2-6% of all uterine malignancies
- arise from stromal components (endometrial stroma, mesenchymal or myometrial tissues)
- behave more aggressively and are associated with worse prognosis than endometrial carcinoma; 5-yr survival is 35%
- vaginal bleeding is most common presenting symptom

Table 20. Summary of Uterine Sarcoma Subtypes and Features

Type	Epidemiology	Features	Diagnosis	Treatment
PURE TYPE				
1. Leiomyosarcoma	• Accounts for 40% • Average age of presentation is 55 yr but may present in pre-menopause • Often coexists with benign leiomyomata (fibroids) • 50% arise within a fibroid ("sarcomatous degeneration")	• Histologic distinction from leiomyoma 1. Increased mitotic count (>10 mitoses/10 high power fields) 2. Tumour necrosis 3. Cellular atypia • Rapidly enlarging fibroids in a pre-menopausal woman • Enlarging fibroids in a postmenopausal woman	• Often post-operatively after uterus removed for presumed fibroids • Staging using FIGO 2009 staging for leiomyosarcomas	• Hysterectomy/BSO usually • No routine pelvic lymphadenectomy • Adjuvant chemotherapy may be used if tumour has spread beyond uterus, for palliation • Radiation therapy does not improve local control or survival • Poor outcomes overall, even for early stage disease
2. Endometrial Stromal Sarcoma (ESS)	• Accounts for 10-15% • Usually presents in perimenopausal or postmenopausal women with abnormal uterine bleeding	• Abnormal uterine bleeding • Good prognosis	• Diagnosed by histology of endometrial biopsy or D&C • Staging using FIGO 2009 staging for ECC and adenosarcoma	• Hysterectomy/BSO (remove ovaries as ovarian hormones may stimulate growth) • No routine pelvic lymphadenectomy • Adjuvant therapy based on stage and histologic features (hormones and/or radiation) • Hormonal therapy (progestins) may be used for metastatic disease
3. Undifferentiated Sarcoma	• Accounts for 5-10%	• Severe nuclear pleomorphism, high mitotic activity, tumour cell necrosis, and lack smooth mucle or endometrial stromal differentiation • Poor prognosis	• Often found incidentally post-operatively for abnormal bleeding	• Treatment primarily surgical • Radiation and/or chemotherapy for advanced diseased or unresectable disease
MIXED TYPE				
4. Adenosarcoma	• The rarest of the uterine sarcoma • Mixed tumour of low malignant potential	• Present with abnormal vaginal bleeding • Polypoid mass in uterine cavity	• Mixture of benign epithelium with malignant low-grade sarcoma • Often found incidentally at time of hysterectomy for PMB	• Treatment is surgical with TAH/BSO
RECLASSIFIED				
5. Carcinosarcoma	• Most common (43%) • Recently reclassified as high grade endometrioid carcinoma with associated metaplasia of the mesenchyme, rather than arising separately from stroma • Surgical staging using FIGO 2009 staging for endometrial cancer	• Both epithelial and stromal malignant elements present • Tend to form bulky polypoid masses that often fill uterine cavity and extend into or through the endocervical canal – often have extrauterine disease at presentation	• Diagnosed by histology of endometrial biopsy or D&C	• Usually treated as "high grade endometrial carcinoma" since behaviour and treatment similar (i.e. surgical staging and resection of any gross metastatic disease, adjuvant chemotherapy and radiation)

Table 21. FIGO Staging of Uterine Sarcoma (2009)

Stage	Description	Stage	Description
I	**Tumour limited to uterus**	**III**	
IA	<5 cm	IIIA	Tumour invades abdominal tissues, one site
IB	>5 cm	IIIB	Metastasis to pelvic and/or para-aortic lymph nodes
		IIIC	Tumour invades bladder and/or rectum
II	**Tumour extends beyond uterus**	**IV**	
IIA	To the pelvis, adnexal involvement	IVA	Tumour invades bladder and/or rectum
IIB	To extra-uterine pelvic tissue	IVB	Distant metastasis

Ovary

BENIGN OVARIAN TUMOURS

- see Table 22
- many are asymptomatic
- usually enlarge slowly, if at all
- may rupture or undergo torsion, causing pain
  - pain associated with torsion of an adnexal mass usually originates in the iliac fossa and radiates to the flank
- peritoneal irritation may result from an infarcted tumour – rare

Ovaries are like GEMS

Germ-cell
Epithelial
Metastatic
Sex cord stromal

MALIGNANT OVARIAN TUMOURS

- see Table 22

Epidemiology

- lifetime risk 1.4% (1/70)
- in women >50 yr, more than 50% of ovarian tumours are malignant
- causes more deaths in North America than all other gynecologic malignancies combined
- 4th leading cause of cancer death in women
- 65% epithelial; 35% non-epithelial
- 5-10% of epithelial ovarian cancers are related to hereditary predisposition

Most (70%) epithelial ovarian cancers present at stage III disease

Risk Factors (for epithelial ovarian cancers)

- excess estrogen
  - nulliparity
  - early menarche/late menopause
- age
- family history of breast, colon, endometrial, ovarian cancer
- race: Caucasian

Protective Factors (for epithelial ovarian cancers)

- OCP: likely due to ovulation suppression (significant reduction in risk even after 1 yr of use)
- pregnancy/breastfeeding
- salpingectomy (prophylactic)
- hysterectomy (without removal of ovaries)
- BSO (prophylactic surgery performed for this reason in high risk women – i.e. BRCA mutation carriers)

Risk/Protective Factors for Epithelial Ovarian Cancer

NO CHILD
Nulliparity
OCP, breastfeeding, tubal ligation, hysterectomy (protective)
Caucasian
Family **H**istory
Increasing age (>40 yr)
Late menopause
Delayed child-bearing

Screening

- no effective method of mass screening
- routine CA-125 level measurements or U/S not recommended
  - high false positive rates
- controversial in high risk groups: transvaginal U/S and CA-125, starting age 30 (no consensus on interval)
  - familial ovarian cancer (>1 first degree relative affected, BRCA-1 mutation)
  - other cancers (e.g. endometrial, breast, colon)
  - BRCA-1 or BRCA-2 mutation: may recommend prophylactic bilateral oophorectomy after age 35 or when child-bearing is completed

Ovarian Tumour Markers

- Epithelial cell – CA-125
- Stromal
  - Granulosa cell – inhibin
  - Sertoli-Leydig – androgens
- Germ cell
  - Dysgerminoma – LDH
  - Yolk sac – AFP
- Choriocarcinoma – β-hCG
- Immature Teratoma – none
- Embryonal cell – AFP + β-hCG

Clinical Features

- most women with epithelial ovarian cancer present with advanced stage disease since often "asymptomatic" until disseminated disease (symptoms with early stage disease are vague and non-specific)
- when present, symptoms may include
  - abdominal symptoms (nausea, bloating, dyspepsia, anorexia, early satiety)
  - symptoms of mass effect
    - increased abdominal girth – from ascites or tumour itself
    - urinary frequency
    - constipation
  - postmenopausal bleeding; irregular menses if pre-menopausal (rare)

Diagnosis of ovarian tumours requires surgical pathology

Any adnexal mass in postmenopausal women should be considered malignant until proven otherwise

Low Malignant Potential (also called "Borderline") Tumours

- pregnancy, OCP, and breastfeeding are protective factors
- ~15% of all epithelial ovarian tumours
- tumour cells display malignant characteristics histologically, but no invasion is identified
- able to metastasize, but not commonly
- treated primarily with surgery (BSO/omental biopsy ± hysterectomy)
  - NO proven benefit of chemotherapy
- generally slow growing, excellent prognosis
  - 5 yr survival >99%
  - recurrences tend to occur late, may be associated with low grade serous carcinoma

Omental Cake: a term for ascites plus a fixed upper abdominal and pelvic mass; almost always signifies ovarian cancer

Malignant Ovarian Tumour Prognosis

5 Year Survival	
Stage I	75-95%
Stage II	60-75%
Stage III	23-41%
Stage IV	11%

Table 22. Ovarian Tumours

Type	Description	Presentation	Ultrasound/Cytology	Treatment
FUNCTIONAL TUMOURS (all benign)				
Follicular Cyst	Follicle fails to rupture during ovulation	Usually asymptomatic May rupture, bleed, tort, infarct causing pain ± signs of peritoneal irritation	4-8 cm mass, unilocular, lined with granulosa cells	Symptomatic or suspicious masses warrant surgical exploration Otherwise if <6 cm, wait 6 wk then re-examine as cyst usually regresses with next cycle OCP (ovarian suppression) – will prevent development of new cysts Treatment usually laparoscopic (cystectomy vs. oophorectomy, based on fertility choice)
Lutein Cyst	Corpus luteum fails to regress after 14 d, becoming cystic or hemorrhagic	More likely to cause pain than follicular cyst May delay onset of next period	Larger (10-15 cm) and firmer than follicular cysts	Same as for follicular cysts
Theca-Lutein Cyst	Due to atretic follicles stimulated by abnormal β-hCG levels	Associated with molar pregnancy, ovulation induction with clomiphene		Conservative Cyst will regress as β-hCG levels fall
Endometrioma	See *Endometriosis*, GY13			
Polycystic Ovaries	See *Polycystic Ovarian Syndrome*, GY25			
BENIGN GERM-CELL TUMOURS				
Benign Cystic Teratoma (dermoid)	Single most common ovarian germ cell neoplasm Elements of all 3 cell lines; contains dermal appendages (sweat and sebaceous glands, hair follicles, teeth)	May rupture, twist, infarct 20% bilateral 20% occur outside of reproductive yr	Smooth-walled, mobile, unilocular Ultrasound may show calcification which is pathognomonic	Treatment usually laparoscopic cystectomy; may recur
MALIGNANT GERM-CELL TUMOURS				
General Information	Rapidly growing, 2-3% of all ovarian cancers	Usually children and young women (<30 yr)		Surgical resection (often conservative unilateral salpingo-oophorectomy ± nodes) ± chemotherapy
Dysgerminoma	Produces LDH	10% bilateral		Usually very responsive to chemotherapy, therefore complete resection is not necessary for cure
Immature Teratoma	No tumour marker identified			
Gonadoblastoma				
EPITHELIAL OVARIAN TUMOURS (malignant or borderline)				
General Information	Derived from mesothelial cells lining peritoneal cavity Classified based on histologic type 80-85% of all ovarian neoplasms (includes malignant)		Varies depending on subtype	**Borderline** Cystectomy vs. unilateral salpingo-oophorectomy **Malignant** 1. Early stage (stage I): Hysterectomy/BSO/staging (omentectomy, peritoneal biopsies, washings, pelvic and para-aortic lymphadenectomy) 2. Advanced stage: Upfront cytoreductive (debulking) followed by adjuvant chemotherapy consisting of IV carboplatic/paclitaxel vs. intraperitoneal chemotherapy (stage III) neoadjuvant chemotherapy with IV carboplatin/paclitaxel, followed by delayed debulking with further adjuvant IV chemotherapy
Serous	Most common ovarian tumour 50% of all ovarian cancers 75% of epithelial tumours 70% benign	20-30% bilateral	Lining similar to fallopian tube epithelium Often multilocular Histologically contain Psamomma bodies (calcified concentric concretions)	
EPITHELIAL OVARIAN TUMOURS (malignant or borderline)				
Mucinous	20% of epithelial tumours 85% benign	Rarely complicated by *Pseudomyxoma peritoneii:* implants seed abdominal cavity and produce large quantities of mucin	Resembles endocervical epithelium Often multilocular May reach enormous size	Poor response to chemotherapy If mucinous, remove appendix as well to rule out possible source of primary disease

Table 22. Ovarian Tumours (continued)

Type	Description	Presentation	Ultrasound/Cytology	Treatment
SEX CORD STROMAL OVARIAN TUMOURS				
General Information				Surgical resection of tumour Chemotherapy may be used for unresectable metastatic disease
Fibroma/Thecoma (benign)	From mature fibroblasts in ovarian stroma	Non-functioning Occasionally associated with Meig's syndrome (benign ovarian tumour and ascites and pleural effusion)	Firm, smooth rounded tumour with interlacing fibrocytes	
Granulosa-Theca Cell Tumours (benign or malignant)	Can be associated with endometrial cancer Inhibin is tumour marker	Estrogen-producing → feminizing effects (precocious puberty, menorrhagia, postmenopausal bleeding)	Histologic hallmark of cancer is small groups of cells known as Call-Exner bodies	
Sertoli-Leydig Cell Tumour (benign or malignant)	Can measure elevated androgens as tumour markers	Androgen-producing → virilizing effects (hirsutism, deep voice, recession of front hairline)		
METASTATIC OVARIAN TUMOURS				
From GI Tract, Breast, Endometrium, Lymphoma	4-8% of ovarian malignancies Krukenberg tumour – metastatic ovarian tumour (usually GI tract, commonly stomach or colon, breast) with "signet-ring" cells			

Investigation of Suspicious Ovarian Mass

- women with suspected ovarian cancer based on history, physical, or investigations should be referred to a gynecologic oncologist
  - bimanual examination
    - solid, irregular, or fixed pelvic mass is suggestive of ovarian cancer
  - RMI (Risk of Malignancy Index) is best tool available to assess likelihood of ovarian malignancy and need for pre-operative gynecologic oncology referral (see sidebar, GY44)
- blood work: CA-125 for baseline, CBC, liver function tests, electrolytes, creatinine
- radiology
  - bone scan or PET scan not indicated
  - transvaginal ultrasound best to visualize ovaries
  - CT scan abdomen and pelvis to look for metastatic disease
- try to rule out other primary source if suspected, based on
  - occult blood per rectum: endoscopy ± barium enema
  - gastric symptoms, gastroscopy ± upper GI series
  - abnormal vaginal bleeding, endometrial biopsy to rule out concurrent endometrial cancer, colposcopy ± ECC to rule out cervical cancer if abnormal cervix
  - breast lesion identified or risk factors present: mammogram

Table 23. FIGO Staging for Primary Carcinoma of the Ovary (Surgical Staging) (2009)

Stage	Description
I	**Growth limited to the ovaries**
IA	1 ovary, no ascites, no tumour on external surface, capsule intact
IB	2 ovaries, no ascites, no tumour on external surface, capsule intact
IC	1 or 2 ovaries with any of the following: capsule ruptured, tumour on ovarian surface, or malignant cells in ascites
II	**Growth involving one or both ovaries with pelvic extension**
IIA	Extension ± metatases to uterus/tubes
IIB	Extension to other pelvic structures
IIC	II A/B with malignant cells in ascites or positive peritoneal washings
III	**Tumour involving one or both ovaries with peritoneal implants outside the pelvis and/or positive retroperitoneal or inguinal nodes; superficial liver mets is Stage III**
IIIA	Microscopic peritoneal metastasis beyond pelvis, LNs negative
IIIB	Macroscopic peritoneal metastasis beyond pelvis <2 cm, LNs negative
IIIC	Implant >2 cm and/or retroperitoneal or inguinal nodes
IV	**Distant metastasis beyond peritoneal cavity**

FIGO = International Federation of Gynecology and Obstetrics

Effects of Screening on Ovarian Cancer Mortality: The Prostate, Lung, Colorectal, and Ovarian Cancer Screening Randomized Controlled Trial
JAMA 2011;305:2295-2303
Objective: To evaluate the effect of screening for ovarian cancer with CA-125 and transvaginal ultrasound on mortality in the prostate, lung, colorectal, and ovarian (PLCO) cancer screening trial.
Participants: 78,216 women aged 55-74 yr.
Study Groups: Intervention group – annual screening with CA-125 for 6 yr, transvaginal ultrasound for 4 yr; control group – no CA-125 or transvaginal ultrasound screening, received usual medical care.
Follow-up: Maximum 13 yr (median, 12.4 yr).
Outcome Measures: Mortality from ovarian cancer, including primary fallopian tube cancers. Secondary outcomes included ovarian cancer incidence and complications associated with screening, examinations, and diagnostic procedures.
Results: Of those diagnosed with ovarian cancer in the intervention and usual care group, the mortality was 3.1% and 2.6% respectively. 15% of women undergoing diagnostic evaluation following a false positive screening test suffered a complication of the procedure.
Conclusions: Simultaneous screening with CA-125 and transvaginal ultrasound compared with usual care did not reduce ovarian cancer mortality. Diagnostic evaluation following a false positive screening test was associated with complications.

Incorporation of Bevacizumab in the Primary Treatment of Ovarian Cancer
NEJM 2011;365:2473-2483
Purpose: To evaluate the effect of bevacizumab addition to standard front-line therapy for epithelial ovarian cancer.
Study: Double-blind, placebo-controlled phase 3 trial with patients with newly diagnosed stage III (incompletely resectable) or stage IV epithelial ovarian cancer who had undergone debulking surgery to receive one of three treatments. All three treatments included chemotherapy with intravenous paclitaxel plus carboplatin. Patients received chemotherapy with placebo, bevacizumab-initiation treatment (cycles 2-6 of 22 cycles) or bevacizumab-throughout (cycles 2-22).
Results: 1,873 participants. The median progression-free survival was 10.3 mo in the control group, 11.2 mo in the bevacizumab-initiation group, and 14.1 mo in the bevacizumab-throughout group. The rate of hypertension requiring medical therapy was higher in the bevacizumab-initiation group (16.5%) and bevacizumab-throughout group (22.9%) than in the control group (7.2%) as well as gastrointestinal wall disruption (2.8%, 2.6%, 1.2%, respectively).
Conclusions: The use of bevacizumab during and up to 10 mo after carboplatin and paclitaxel chemotherapy prolongs the median progression-free survival by about 4 mo in patients with advanced epithelial ovarian cancer.

Cervix

BENIGN CERVICAL LESIONS

- Nabothian cyst/inclusion cyst
  - no treatment required
- endocervical polyps
  - treatment is polypectomy (office procedure)

MALIGNANT CERVICAL LESIONS

Epidemiology

- majority are SCC (95%); adenocarcinomas increasing (5%); rare subtypes include small cell, adenosquamous
- 8,000 deaths annually in North America
- annual Pap test reduces a woman's chance of dying from cervical cancer from 0.4% to 0.05%
- average age at presentation: 52 yr old

Etiology

- at birth, vagina is lined with squamous epithelium; columnar epithelium lines only the endocervix and the central area of the ectocervix (original squamocolumnar junction)
- during puberty, estrogen stimulates eversion of a single columnar layer (ectopy), thus exposing it to the acidic pH of the vagina, leading to metaplasia (change of exposed epithelium from squamous to columnar)
  - a new squamocolumnar junction forms as a result
- the transformation zone (TZ) is the area located between the original and the current squamocolumnar junction
- the majority of dysplasias and cancers arise in the TZ of the cervix
- must have active metaplasia in presence of inducing agent (HPV) to get dysplasia
- dysplasia → carcinoma *in situ* (CIS) → invasion
- slow process (~10 yr on average)
- growth is by local extension
- metastasis occurs late

Risk Factors

- HPV infection
  - see *Sexually Transmitted Infections*, GY28
  - high risk of neoplasia associated with types 16, 18
  - low risk of neoplasia associated with types 6, 11
  - >99% of cervical cancers contain one of the high risk HPV types
- high risk behaviours (risk factors for HPV infection)
  - multiple partners
  - other STIs (HSV, trichomonas)
  - early age at first intercourse
  - high risk male partner
- smoking
- poor screening uptake is the most important risk factor for cervical cancer in Canada
- at-risk groups include
  - immigrant Canadians
  - First Nations Canadians
  - geographically isolated Canadians
  - sex-trade workers
  - low socioeconomic status

Cervical Cancer Screening Guidelines (Pap Test)

- see Family Medicine, FM4

Clinical Features

- SCC: exophytic, fungating tumour
- adenocarcinoma: endophytic, with barrel-shaped cervix
- early
  - asymptomatic
  - discharge: initially watery, becoming brown or red
  - postcoital bleeding
- late
  - 80-90% present with bleeding: either postcoital, postmenopausal or irregular bleeding
  - pelvic or back pain (extension of tumour to pelvic walls)
  - bladder/bowel symptoms
- signs
  - friable, raised, reddened, or ulcerated area visible on cervix

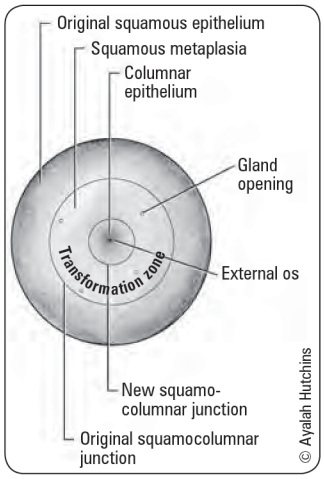


Figure 21. The cervix

A Risk of Malignancy Incorporating CA125, Ultrasound, and Menopausal Status for the Accurate Pre-Operative Diagnosis of Ovarian Cancer
BJOG 1990;97:922-929

RMI = U x M x CA-125

Ultrasound Findings (1 pt for each)
- Multilocular cyst
- Evidence of solid areas
- Evidence of metastases
- Presence of ascites
- Bilateral lesions

U = 1 (for U/S scores of 0 or 1)
U = 4 (for U/S scores of 2-5)

Menopausal Status
- Postmenopausal: M = 4
- Premenopausal: M = 1

Absolute Value of CA-125 Serum Level
- For RMI > 200: Gynecologic oncology referral is recommended

Cervical cancer is most prevalent in developing countries and therefore is the only gynecologic cancer that uses clinical staging; this facilitates consistent international staging with countries that do not have technologies, such as CT and MRI

The Bethesda Classification System is based on cytological results of a Pap test that permits the examination of cells but not tissue structure. Cervical intraepithelial neoplasia (CIN) or cervical carcinoma is a histological diagnosis, requiring a tissue sample via biopsy of suspicious lesions seen during colposcopy

With development of hypertension early in pregnancy (i.e. <20 wk), think gestational trophoblastic disease

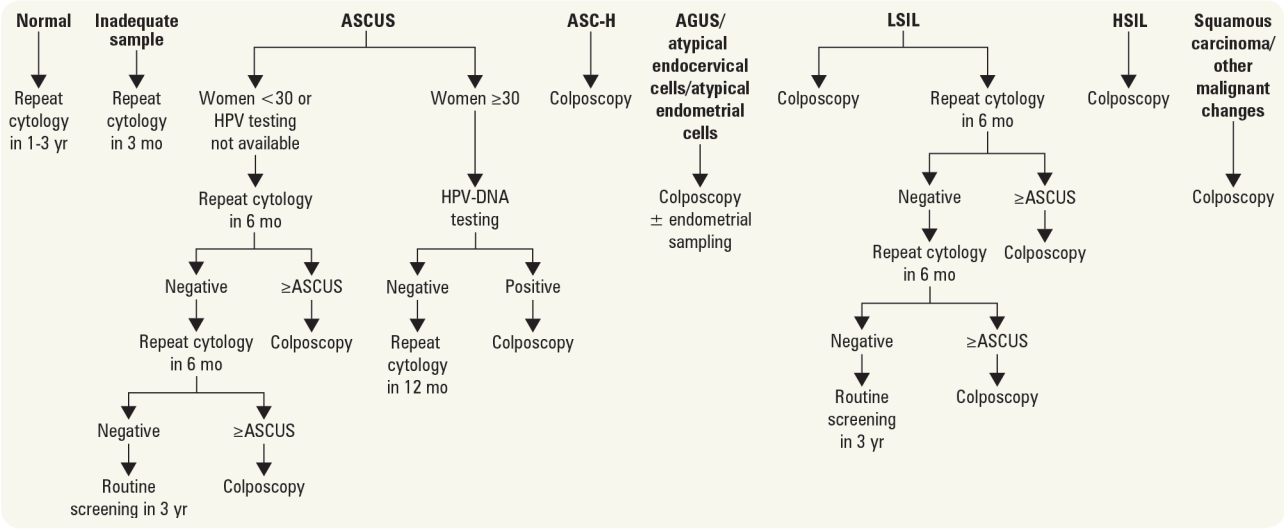


Figure 22. Decision making chart for Pap test (not applicable for adolescents)

Adapted from: Ontario Cervical Screening Practice Guidelines. May 2012. Cervical screening guidelines unique to each province

Diagnosis

- apply acetic acid and identify acetowhite lesions, punctation, mosaicism, and abnormal blood vessels to guide cervical biopsy
- endocervical curettage (ECC) if entire lesion is not visible or no lesion visible
- diagnostic excision (LEEP) if
  - lesion extends into endocervical canal
  - positive ECC
  - discrepancy between Pap test results and colposcopy
  - microinvasive carcinoma
- consider cold knife conization (in OR) if glandular abnormality suspected based on cytology or colposcopic findings due to concern for margin interpretation
- tests permitted for FIGO clinical staging include: physical exam (including EUA), cervical biopsy (including cone biopsy), proctoscopy/cystoscopy, IVP, ultrasound liver/kidneys, CXR, LFTs
- MRI and/or CT and/or PET scan often done to facilitate planning of radiation therapy, results do not influence clinical stage

Table 24. FIGO Staging Classification of Cervical Cancer (Clinical Staging) (2009)

Stage	Description
I	**Confined to cervix**
IA	Microinvasive (diagnosed only by microscopy)
IA_1	Stromal invasion not >3 mm deep, not >7 mm wide
IA_2	3-5 mm deep; not >7 mm wide
IB	Clinically visible lesion confined to cervix, or microscopic lesion >IA
IB_1	Clinically visible lesion ≤4 mm in greatest dimension
IB_2	Clinically visible lesion >4 mm in greatest dimension
II	**Beyond uterus but not to the pelvic wall or lower 1/3 of vagina**
IIA	No obvious parametrial involvement
IIA_1	Clinically visible lesion ≤4 mm in greatest dimension
IIA_2	Clinically visible lesion >4 mm in greatest dimension
IIB	Obvious parametrial involvement
III	**Extends to pelvic wall, and/or involves lower 1/3 of vagina and/or causes hydronephrosis or non-functioning kidney**
IIIA	Involves lower 1/3 vagina but no extension into pelvic side wall
IIIB	Extension into pelvic side wall and/or hydronephrosis or non-functioning kidney
IV	**Carcinoma has extended beyond true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum**
IVA	Spread of the growth to adjacent organs
IVB	Distant metastases

Causes of Elevated CA-125

- Age influences reliability of test as a tumour marker
- 50% sensitivity in early stage ovarian cancer (poor) – therefore not good for screening

Malignant

- Gyne: ovary, uterus
- Non-Gyne: pancreas, stomach, colon, rectum

Non-Malignant

- Gyne: benign ovarian neoplasm, endometriosis, pregnancy, fibroids, PID
- Non-Gyne: cirrhosis, pancreatitis, renal failure

CA-125 is indicated for monitoring response to treatment

Cervical Cancer Prognosis

5-yr Survival	
Stage 0	99%
Stage I	75%
Stage II	55%
Stage III	30%
Stage IV	7%
Overall	50-60%

Treatment: Prevention and Management

Prevention: HPV Vaccine

- two vaccines currently approved (Gardasil®, Cervarix®)

Table 25. Comparison of Two Vaccines against Human Papillomavirus (HPV)

	Gardasil®	Cervarix®
Viral strains covered	6, 11, 16, 18	16, 18
Route of administration	IM	IM
Schedule of dosing	0, 2, 6 mo	0, 1, 6 mo
Side effects	Local: redness, pain, swelling General: headache, low grade fever, GI upset	Local: redness, pain, swelling General: headache, low grade fever, GI upset
Approved age	Females age 9-45, males age 9-26	Females age 10-25
Contraindications	Pregnant women and women who are nursing (limited data)	

*Gardasil-9 also covers types 31, 33, 45, 52, and 58; also used to prevent genital warts

- should be administered before onset of sexual activity (i.e. before exposure to virus) for optimal benefit of vaccination
- may be given at the same time as hepatitis B or other vaccines using a different injection site
- not for treatment of active infections
- most women will not be infected with all four types of the virus at the same time, therefore vaccine is still indicated for sexually active females or those with a history of previous HPV infection or HPV-related disease
- conception should be avoided until 30 d after last dose of vaccination

Efficacy of Human Papillomavirus (HPV)-16/18 AS04-Adjuvanted Vaccine Against Cervical Infection and Precancer Caused by Oncogenic HPV Types (PATRICIA): Final Analysis of a Double-Blind, Randomized Study in Young Women
Lancet 2009;374:301-314
Study: Phase III double-blind, controlled RCT.
Patients: 18,644 women aged 15-25.
Selected Outcomes: Development of HPV-16/18 associated CIN II+ was the primary outcome. Secondary to this were persistence of infections with HPV-16, HPV-18, or other oncogenic HPV types.
Selected Results: Efficacy against development of HPV-16/18 associated CIN II+ was 98.1% ($p<0.0001$). High levels of cross-protection were observed for persistent infection with HPV-31 and HPV-45 and HPV-31 or HPV-45 associated CIN II+.
Conclusions: The HPV-16/18 AS04-adjuvanted vaccine protected against HPV-16/18 associated CIN II+ lesions and lesions associated with HPV-31, HPV-33, and HPV-45.

Table 26. Management of Patients Abnormal Cervical Histology and Cervical Cancer

	Management
CIN I	• Preferred option for biopsy-proven CIN I is observation • Repeat assessment and cytology in 12 mo • Management according to cytology results If after HSIL or AGC • Cytology and histology should be reviewed • If discrepancy remains, excisional biopsy may be considered
CIN II and CIN III	Women ≥25 yr • CIN II or III should be treated • Excisional procedures preferred for CIN III • Those with positive margins should have follow-up with colposcopy and directed biopsies and/or endocervical curettage • Treatment for recurrent CIN II or III should be by excision Women <25 yr • Pathologist should be asked to clarify whether lesion is CIN II or CIN III • CIN II: observe with colposcopy at 6-mo intervals for up to 24 mo before treatment considered • CIN III: should be treated During pregnancy: • CIN II or III suspected or diagnosed during pregnancy, repeat colposcopy and treatment delayed until 8-12 wk after delivery
Stage IA_1 (no LVSI)	• Trachelectomy (removal of only the cervix) if future fertility desired (and lesion ≤2 cm) • Simple hysterectomy if future fertility is not desired
Stage IA_2, IB_1	• Typically treated with radical hysterectomy and pelvic lymphadenectomy (sentinel nodes under study) • Equal cure rates may be obtained with primary radiation therapy; advantage of surgery: may accurately stage and grade and more targeted adjuvant therapy • Advantage is that ovaries can be spared if pre-menopausal • For fertility preservation, may have radical trachelectomy (removal of cervix and parametria) and nodes instead of radical hysterectomy for early-stage disease • Concurrent chemoradiation therapy if adverse high risk prognostic factors on radical surgical specimen, such as: positive pelvic lymph nodes, positive parametria, and/or positive margins
Stages IB_2 (>4 cm), II, III, IV	• Primary chemoradiation therapy • PET/CT to grade: evaluate pelvic and para-aortic nodes • For positive nodes on PET: primary chemoradiation with extended field RT • Hysterectomy generally not suggested following primary treatment with curative intent

Abnormal Pap Tests in Pregnancy

- incidence: 1/2,200
- Pap test at all initial prenatal visits
- if abnormal Pap or suspicious lesion, refer to colposcopy
- if diagnostic conization required, should be deferred until second trimester (T2) to minimize risk of pregnancy loss
- if invasive cancer ruled out, management of dysplasia deferred until completion of pregnancy (may deliver vaginally)
- if invasive cancer present, management depends on prognostic factors, degree of fetal maturity, and patient wishes
  - general recommendations in T1: consider pregnancy termination, management with either radical surgery (hysterectomy vs. trachelectomy if desires future fertility), or concurrent chemoradiation therapy
  - recommendations in T2/T3: delay of therapy until viable fetus and C/S for delivery with concurrent radical surgery or subsequent concurrent chemoradiation therapy

Vulva

BENIGN VULVAR LESIONS

Non-Neoplastic Disorders of Vulvar Epithelium
- biopsy is necessary to make diagnosis and/or rule out malignancy
- hyperplastic dystrophy (squamous cell hyperplasia)
  - surface thickened and hyperkeratotic
  - pruritus most common symptom
  - typically postmenopausal women
  - treatment: 1% fluorinated corticosteroid ointment bid for 6 wk
- lichen sclerosis
  - subepithelial fat becomes diminished; labia become thin, atrophic, with membrane-like epithelium and labial fusion
  - pruritus, dyspareunia, burning
  - 'figure of 8' distribution
  - most common in postmenopausal women but can occur at any age
  - treatment: ultrapotent topical steroid 0.05% clobetasol x 2-4 wk then taper down, can consider long term suppression twice a week
- mixed dystrophy (lichen sclerosis with epithelial hyperplasia)
  - hyperkeratotic areas with areas of thin, shiny epithelium
  - treatment: fluorinated corticosteroid ointment

Tumours
- papillary hidradenoma, nevus, fibroma, hemangioma

MALIGNANT VULVAR LESIONS

Epidemiology
- 5% of genital tract malignancies
- 90% SCC; remainder melanomas, basal cell carcinoma, Paget's disease, Bartholin's gland carcinoma
  - Type I disease: HPV-related (50-70%)
    - more likely in younger women
    - 90% of VIN contain HPV DNA (usually types 16, 18)
  - Type II disease: not HPV-related, associated with current or previous vulvar dystrophy
    - usually postmenopausal women

Risk Factors
- HPV infection
- VIN: precancerous change which presents as multicentric white or pigmented plaques on vulva (may only be visible at colposcopy)
  - progression to cancer rarely occurs with appropriate management
  - treatment: local excision (i.e. superficial vulvectomy ± split thickness skin grafting to cover defects if required) vs. ablative therapy (i.e. laser, cauterization) vs. local immunotherapy (imiquimod)

Clinical Features
- many patients asymptomatic at diagnosis (many also deny or minimize symptoms)
- most lesions occur on the labia majora, followed by the labia minora (less commonly on the clitoris or perineum)
- localized pruritus or lesion most common
- less common: raised red, white or pigmented plaque, ulcer, bleeding, discharge, pain, dysuria
- patterns of spread
  - local
  - groin lymph nodes (usually inguinal → pelvic nodes)
  - hematogenous

Investigations
- ± colposcopy
- ALWAYS biopsy any suspicious lesion

Any suspicious lesion of the vulva should be biopsied

Prognosis
- depends on stage – particularly nodal involvement (single most important predictor followed by tumour size)
- lesions >4 cm associated with poorer prognosis
- overall 5 yr survival rate: 79%

Vagina

BENIGN VAGINAL LESIONS

- inclusion cysts
  - cysts form at site of abnormal healing of laceration (e.g. episiotomy)
  - no treatment required
- endometriosis
  - dark lesions that tend to bleed at time of menses
  - treatment: excision
- Gartner's duct cysts
  - remnants of Wolffian duct, seen along side of cervix
  - treatment: conservative unless symptomatic
- urethral diverticulum
  - can lead to recurrent urethral infection, dyspareunia
  - treatment: surgical correction if symptomatic

MALIGNANT VAGINAL LESIONS

Epidemiology

- primary carcinomas of the vagina represent 2-3% of malignant neoplasms of the female genital tract
- 80-90% are SCC
- more than 50% diagnosed between 70-90 yr old

Risk Factors

- associated with HPV infection (analogous to cervical cancer)
- increased incidence in patients with prior history of cervical and vulvar cancer

Investigations

- cytology
  - significant false negative rate for existing malignancy (i.e. if gross lesion present, biopsy!)
- colposcopy
- Schiller test (normal squamous epithelium takes up Lugol's iodine)
- biopsy, partial vaginectomy (wide local excision for diagnosis)
- rule out disease on cervix, vulva, or anus (most vaginal cancers are actually metastatic from one of these sites)
- staging

Clinical Features

Table 27. Clinical Features of Malignant Vaginal Lesions

Type	Clinical Features
Vaginal Intra-Epithelial Neoplasia (VAIN)	Grades: analogous to cervical dysplasia
Squamous Cell Carcinoma (SCC)	Most common site is upper 1/3 of posterior wall of vagina Asymptomatic Painless discharge and bleeding Vaginal discharge (often foul-smelling) Vaginal bleeding especially during/post-coitus Urinary and/or rectal symptom 2° to compression
Adenocarcinoma	Most are metastatic, usually from cervix, endometrium, ovary, or colon Most primaries are clear cell adenocarcinomas 2 types: non-DES and DES syndrome

Fallopian Tube

- least common site for carcinoma of female reproductive system (0.3%)
- usually serous epithelial carcinoma
- recently considered to be origin of serous ovarian cancer
- more common in fifth and sixth decade

Clinical Features

- classic triad present in minority of cases, but very specific
  - watery discharge (most specific) = "hydrops tubae profluens"
  - vaginal bleeding or discharge in 50% of patients
  - crampy lower abdominal/pelvic pain
- most patients present with a pelvic mass (see *Ovarian Tumours*, GY41 for guidelines regarding diagnosis/investigation)

Treatment

- as for malignant epithelial ovarian tumours

Gestational Trophoblastic Disease/Neoplasia

- refers to a spectrum of proliferative abnormalities of the trophoblast

Epidemiology
- 1/1,000 pregnancies
- marked geographic variation – as high as 1/125 in Taiwan
- 80% benign, 15% locally invasive, 5% metastatic
- cure rate >95%

HYDATIDIFORM MOLE (Benign GTD)

Complete Mole
- most common type of hydatidiform mole
- diffuse trophoblastic hyperplasia, hydropic swelling of chorionic villi, no fetal tissues, or membranes present
- 46XX or 46XY, chromosomes completely of paternal origin (90%)
- 2 sperm fertilize empty egg or 1 sperm with reduplication
- 15-20% risk of progression to malignant sequelae
- risk factors
  - geographic (South East Asia most common)
  - others (maternal age >40 yr, β-carotene deficiency, vitamin A deficiency) – not proven
- clinical features
- often present during apparent pregnancy with abnormal symptoms/findings
  - vaginal bleeding (97%)
  - excessive uterine size for LMP (51%)
  - theca-lutein cysts >6 cm (50%)
  - preeclampsia (27%)
  - hyperemesis gravidarum (26%)
  - hyperthyroidism (7%)
  - β-hCG >100,000 IU/L
  - no fetal heart beat detected

With development of hypertension early in pregnancy (i.e. <20 wk), think gestational trophoblastic disease

Partial (or Incomplete) Mole
- focal trophoblastic hyperplasia and hydropic villi are associated with fetus or fetal parts
- often triploid (XXY, XYY, XXX) with chromosome complement from both parents
  - usually related to single ovum fertilized by two sperm
- low risk of progression to malignant sequelae (<4%)
- associated with fetus, which may be growth-restricted, and/or have multiple congenital malformations
- clinical features
  - typically present similar to threatened/spontaneous/missed abortion
  - pathological diagnosis often made after D&C

Investigations
- quantitative β-hCG levels (tumour marker) abnormally high for gestational age
- U/S findings
  - if complete: no fetus (classic "snow storm" due to swelling of villi)
  - if partial: molar degeneration of placenta ± fetal anomalies, multiple echogenic regions corresponding to hydropic villi, and focal intrauterine hemorrhage
- CXR (may show metastatic lesions)
- features of molar pregnancies at high risk of developing persistent GTN post-evacuation
  - local uterine invasion as high as 31%
  - β-hCG >100,000 IU/L
  - excessive uterine size
  - prominent theca-lutein cysts

Treatment
- suction D&C with sharp curettage and oxytocin
- Rhogam® if Rh negative
- consider hysterectomy (if patient no longer desires fertility)
- prophylactic chemotherapy of no proven benefit
- chemotherapy for GTN if develops after evacuation

Follow-Up
- contraception required to avoid pregnancy during entire follow-up period
- serial β-hCGs (as tumour marker) every week until negative x 3 (usually takes several wk), then monthly for 6-12 mo prior to trying to conceive again
- increase or plateau of β-hCG indicates GTN → patient needs chemotherapy

GTN (MALIGNANT GTD)

Invasive Mole or Persistent GTN
- diagnosis made by rising or plateau in β-hCG, development of metastases following treatment of documented molar pregnancy
- histology: molar tissue from D&C
- metastases are rare (4%)

Choriocarcinoma
- often present with symptoms from metastases
- highly anaplastic, highly vascular
- no chorionic villi, elements of syncytiotrophoblast and cytotrophoblast
- may follow molar pregnancy, abortion, ectopic, or normal pregnancy

Placental-site Trophoblastic Tumour
- rare aggressive form of GTN
- abnormal growth of intermediate trophoblastic cells
- low β-hCG, production of human placental lactogen (hPL), relatively insensitive to chemotherapy

CLASSIFICATION of GTN
- non-metastatic
  - ~15% of patients after molar evacuation
  - may present with abnormal bleeding
  - all have rising or plateau of β-hCG
  - negative metastases on staging investigations
- metastatic
  - 4% patients after treatment of complete molar pregnancy
  - metastasis more common with choriocarcinoma which tends toward early vascular invasion and widespread dissemination
  - if signs or symptoms suggest hematogenous spread, do not biopsy (they bleed)
    - lungs (80%): cough, hemoptysis, CXR lesion(s)
    - vagina (30%): vaginal bleeding, "blue lesions" on speculum exam
    - pelvis (20%): rectal bleeding (if invades bowel), U/S lesion(s)
    - liver (10%): elevated LFTs, U/S or CT findings
    - brain (10%): headaches, dizziness, seizure (symptoms of space-occupying lesion), CT/MRI findings
  - highly vascular tumour → bleeding → anemia
  - all have rising or plateau of β-hCG
  - classification of metastatic GTN
    - divided into good prognosis and bad prognosis
    - features of bad prognosis
      - long duration (>4 mo from antecedent pregnancy)
      - high pre-treatment β-hCG titre: >100,000 IU/24 h urine or >40,000 IU/L of blood
      - brain or liver metastases
      - prior chemotherapy
      - metastatic disease following term pregnancy
    - good prognosis characterized by the absence of each of these features

Lungs are #1 site for malignant GTN metastases; when pelvic exam and chest x-ray are negative, metastases are uncommon

Investigations – For Staging
- blood work: CBC, electrolytes, creatinine, β-hCG, TSH, LFTs
- imaging: CXR, U/S pelvis, CT abdo/pelvis, CT brain
- if suspect brain metastasis but CT brain negative, consider lumbar puncture for CSF β-hCG
- ratio of plasma β-hCG:CSF β-hCG <60 indicates metastases

Table 28. FIGO Staging and Management of Malignant GTN

Stage	Findings	Management
I	Disease confined to uterine corpus	Single agent chemotherapy for low risk disease (WHO score ≤6) 1st line: pulsed – actinomycin D (Act-D) IV q2wk Alternatives: MTX-based regimen 20% of patients need to switch to alternate single-agent regimen due to failure of β-hCG to return to normal Combination chemotherapy (EMA-CO: etoposide, MTX, ACT-D, cyclophosphamide, vincristine) if high risk (WHO score ≥7) or if resistant to single agent chemotherapy Can consider hysterectomy if fertility not desired or placental-site trophoblastic tumour
II	Metastatic disease to genital structures	As above
III	Metastatic disease to lungs with or without genital tract involvement	As above
IV	Distant metastatic sites including brain, liver, kidney, GI tract	Usually high risk (EMA-CO) with surgical resection of sites of disease Persistence/resistance to chemotherapy Consider radiation for brain mets

Table 29. WHO Prognostic Score for GTD (2011)

	Score			
Prognostic Factor	**0**	**1**	**2**	**4**
Maternal Age	>40	40		
AP	Mole	Abortion	Term	
Interval (end of AP to chemotherapy in months)	<4	4-6	7-13	>13
HCG IU/1	<103	103-104	104-105	>105
Number of Metastases	0	1-4	5-8	>8
Site of Metastases	Lung	Spleen, kidney	GI tract	Brain, liver
Largest Tumour Mass		3-5 cm	>5 cm	
Prior Chemotherapy			Single drug	Two drug

Follow-up (for GTN)

- contraception for all stages to avoid pregnancy during entire follow-up period
- stage I, II, III
  - weekly β-hCG until 3 consecutive normal results
  - then monthly x 12 mo
- stage IV
  - weekly β-hCG until 3 consecutive normal results
  - then monthly x 24 mo

GTN Diagnosis

- β-hCG plateau: <10% drop in β-hCG over four values in 3 wk (e.g. days 1, 7, 14, and 21) OR
- β-hCG rise >20% in any two values over two wk or longer (e.g. measure at days 1, 7, 14) OR
- β-hCG persistently elevated >6 mo OR
- Metastases on workup

Common Medications

Table 30. Common Medications

Drug Name (Brand Name)	Action	Dosing Schedule	Indications	Side Effects (S/E), Contraindications (C/I), Drug Interactions (D/I)
acyclovir (Zovirax®)	Antiviral; inhibits DNA synthesis and viral replication	**First Episode:** 400 mg PO tid x 7-10 d **Recurrence:** 400 mg PO tid x 5 d	Genital herpes	**S/E**: headache, GI upset **D/I**: zidovudine, probenecid
bromocriptine (Parlodel®)	Dopaminomimetic Agonist at D_2R Antagonist at D_1R Acts directly on anterior pituitary cells to inhibit synthesis and release of prolactin	**Initial:** 1.25-2.5 mg PO qhs with food **Then:** increase by 2.5 mg every 2-7 d as needed until optimal therapeutic response **Usual Range:** 1.5-15 mg OD For IVF: **Initial:** 1.25 mg/d PO between days 4-6 of follicular phase **Then:** 2.5 mg/d until 3 d after onset menstruation	Galactorrhea + amenorrhea 2° to hyperprolactinemia Prolactin-dependent menstrual disorders and infertility Prolactin-secreting adenomas (microadenomas, prior to surgery of macroadenomas) IVF	**S/E**: N/V, headache, postural hypotension, somnolence **C/I**: uncontrolled HTN, pregnancy-induced HTN, CAD, breastfeeding **D/I**: domperidone, macrolides, octreotide
clomiphene citrate (Clomid®)	Increases output of pituitary gonadotropins which induces ovulation	50 mg OD x 5 d Try 100 mg or 160 mg OD if ineffective 3 courses = adequate trial	Patients with persistent ovulatory dysfunction (e.g. amenorrhea, PCOS) who desire pregnancy	**S/E**: Common – hot flashes, abdominal discomfort, exaggerated cyclic ovarian enlargement, accentuation of Mittelschmerz Rare – ovarian hyperstimulation syndrome, multiple pregnancy, visual blurring, birth defects **C/I**: pregnancy, liver disease, hormone-dependent tumours, ovarian cyst, undiagnosed vaginal bleeding
clotrimazole (Canesten®)	Antifungal; disrupt fungal cell membrane	**Tablet**: 100 mg/d intravaginally x 7 d or 200 mg/d x 3 d or 500 mg x 1 dose **Cream** (1 or 2%): 1 applicator intravaginally qhs x 3-7 d **Topical**: apply bid x 7 d	Vulvovaginal candidiasis	**S/E**: vulvar/vaginal burning
danazol (Cyclomen® – CAN) (Danocrine® – US)	Synthetic steroid that inhibits pituitary gonadotropin output and ovarian steroid synthesis Has mild androgenic properties	200-800 mg in 2-3 divided doses Used for 3-6 mo Biannual hepatic U/S required if >6 mo use	Endometriosis 1° menorrhagia/DUB	**S/E**: weight gain, acne, mild hirsutism, hepatic dysfunction **C/I**: pregnancy, undiagnosed vaginal bleeding, breastfeeding, severely impaired renal/hepatic/cardiac function, porphyria, genital neoplasia, thromboembolic disease **D/I**: warfarin, carbamazepine, cyclosporine, tacrolimus, anti-hypertensives

Table 30. Common Medications (continued)

Drug Name (Brand Name)	Action	Dosing Schedule	Indications	Side Effects (S/E), Contraindications (C/I), Drug Interactions (D/I)
doxycycline	Tetracycline derivative; inhibit protein synthesis	100 mg PO bid x ≥7 d	Chlamydia, gonococcal infection, syphilis	**S/E**: GI upset, hepatotoxicity **C/I**: pregnancy, severe hepatic dysfunction **D/I**: warfarin, digoxin
fluconazole (Diflucan®)	Antifungal; disrupt fungal cell membrane	150 mg PO x 1 dose	Vulvovaginal candidiasis unresponsive to clotrimazole	**S/E**: headache, rash, N/V, abdominal pain, diarrhea **D/I**: terfenadine, cisapride, astemizole, hydrochlorothiazide, phenytoin, warfarin, rifampin
leuprolide (Lupron®)	Synthetic GnRH analog Induces reversible hypoestrogenic state	3.75 mg IM q1mo or 11.25 mg IM q3mo Usually ≤6 mo, check bone density if >6 mo Retreatment with Lupron® alone not recommended because of effects on bone density	Endometriosis Leiomyomata DUB Precocious puberty	**S/E**: hot flashes, sweats, headache, vaginitis, reduction in bone density, acne, GI upset **C/I**: pregnancy, undiagnosed vaginal bleeding, breastfeeding
menotropin (Pergonal®)	Human gonadotropin with FSH and LH effects; induce ovulation and stimulate ovarian follicle development	75-150 U of FSH and LH IM OD x 7-12 d, then 10,000 U hCG one day after last dose	Infertility	**S/E**: bloating, irritation at injection site, abdominal/pelvic pain, headache, N/V, multiple pregnancy **C/I:** primary ovarian failure, intracranial lesion (e.g. pituitary tumour), uncontrolled thyroid/adrenal dysfunction, ovarian cyst (not PCOS), pregnancy, undiagnosed uterine bleeding
metronidazole (Flagyl®)	Bactericidal; forms toxic metabolites which damage bacterial DNA	2 g PO x 1 dose or 500 mg PO bid x 7 d	Bacterial vaginosis, trichomonas vaginitis	**S/E**: headache, dizziness, N/V, diarrhea, disulfiram-like reaction (flushing, tachycardia, N/V) **C/I**: pregnancy (1st trimester) **D/I**: cisapride, warfarin, cimetidine, lithium, alcohol, amiodarone, milk thistle, carbamazepine
oxybutinin (Ditropan®)	Anticholinergic – relaxes bladder smooth muscle, inhibits involuntary detrusor contraction	5 or 10 mg/d PO May increase doses by 5 mg weekly to a max of 30 mg/d	Overactive bladder (urge incontinence)	**S/E**: dry mouth/eyes, constipation, palpitations, urinary retention, dizziness, headache **C/I**: glaucoma, GI ileus, severe colitis, obstructive uropathy, use with caution if impaired hepatic/renal function
tolterodine (Detrol®)	Anticholinergic	1-2 mg PO bid	Overactive bladder (urge incontinence)	**S/E**: anaphylaxis, psychosis, tachycardia, dry mouth/eyes, headache, constipation, urinary retention, chest pain, abdominal pain **C/I**: glaucoma, gastric/urinary retention, use with caution if impaired hepatic/renal function
tranexamic acid (Cyklokapron®)	Anti-fibrinolytic, reversibly inhibits plasminogen activation	1-1.5 g tid-qid for first 4 d of cycle Max 4 g/d Ophthalmic check if used for several wk	Menorrhagia	**S/E**: N/V, diarrhea, dizziness, rare cases of thrombosis, abdominal pain, MSK pain **C/I**: thromboembolic disease, acquired disturbances of colour vision, subarachnoid hemorrhage, age <15 yr
ulipristal acetate (Fibristal®)	Selective progesterone receptor modulator (SPRM)	5 mg PO OD for max 3 mo; first tablet taken anytime during first 7 days of menstruation	Leiomyoma (pre-operative)	**S/E:** headache, hot flushes, constipation, vertigo, endometrial thickening **C/I:** pregnancy, undiagnosed vaginal bleeding, any gyne cancer
urofollitropin (Metrodin®)	FSH	75 U/d SC x 7-12d	Ovulation induction in PCOS	**S/E**: ovarian enlargement or cysts, edema and pain at injection site, arterial thromboembolism, fever, abdominal pain, headache, multiple pregnancy **C/I**: primary ovarian failure, intracranial lesion (e.g. pituitary tumour), uncontrolled thyroid/adrenal dysfunction, ovarian cyst (not PCOS), pregnancy, abnormal uterine bleeding
combined oral contraceptive pill (OCP)	Ovulatory suppression by inhibiting LH and FSH Decidualization of endometrium Thickening of cervical mucus to prevent sperm penetration		Contraception Disorders of menstruation	See Tables 8-12
intrauterine device (IUD) copper IUD (Nova-T®) progesterone-releasing IUD (Mirena®, Jaydess®)	**Copper IUD**: mild foreign body reaction in endometrium which is toxic to sperm and alters sperm motility **Progesterone-releasing IUD**: decidualization of endometrium and thickening of cervical mucus, may suppress ovulation	Contraceptive effects last 5 yr	Same as above	See Table 8-12

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U Urology

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Acronyms

β-hCG	beta-human chorionic gonadotropin
ABx	antibiotics
AFP	alpha-fetoprotein
ART	assisted reproductive technologies
AUA	American Urology Association
BCG	Bacillus Calmette-Guérin
BPH	benign prostatic hyperplasia
CAH	congenital adrenal hyperplasia
CaP	prostatic carcinoma
CBI	continuous bladder irrigation
CFU	colony-forming unit
CHF	congestive heart failure
CIC	clean intermittent catheterization
CIS	carcinoma *in situ*
CMG	cystometrogram
CPPS	chronic pelvic pain syndrome
CTU	CT urography
CUA	Canadian Urological Association
CVA	costovertebral angle
d/c	discharge
DHT	dihydrotestosterone
DMSA	dimercaptosuccinic acid
DRE	digital rectal exam
DSD	detrusor sphincter dyssynergia
EBRT	external beam radiation therapy
ED	erectile dysfunction
EPS	expressed prostatic secretions
ESWL	extracorporeal shockwave lithotripsy
FNA	fine needle aspiration
GA	general anesthesia
GAG	glycosaminoglycan
HIFU	high-intensity focused ultrasound
HPF	high power field
HPTA	hypothalamic-pituitary-testicular axis
ICSI	intracytoplasmic sperm injection
IFN-α	interferon-alpha
IL-2	interleukin-2
IPSS	International Prostate Symptom Score
ISD	intrinsic sphincter deficiency
IUI	intrauterine insemination
IVF	*in vitro* fertilization
IVP	intravenous pyelogram
KUB	kidneys, ureters, bladder
LFT	liver function test
LMN	lower motor neuron
LUTS	lower urinary tract symptoms
MAG3	mercaptoacetyltriglycine
MET	medical expulsive therapy
MS	multiple sclerosis
NSGCT	non-seminomatous germ cell tumour
PCKD	polycystic kidney disease
PCNL	percutaneous nephrolithotomy
PDE	phosphodiesterase
PID	pelvic inflammatory disease
PMC	pontine micturition centre
POD	post-obstructive diuresis
PSA	prostate specific antigen
PUV	posterior urethral valve
PVD	peripheral vascular disease
PVR	post-void residual
QOL	quality of life
RCC	renal cell carcinoma
RFA	radio-frequency ablation
RP	radical prostatectomy
RPLND	retroperitoneal lymph node dissection
RTA	renal tubular acidosis
RUG	retrograde urethrogram
SA	semen analysis
SCC	squamous cell carcinoma
SUI	stress urinary incontinence
TMP/SMX	trimethoprim/sulfamethoxazole
TRUS	transrectal ultrasound
TUIP	transurethral incision of the prostate
TUNA	transurethral needle ablation
TURBT	transurethral resection of bladder tumour
TURP	transurethral resection of the prostate
U/A	urinalysis
U/O	urine output
U/S	ultrasound
UCC	urothelial cell carcinoma
UMN	upper motor neuron
UPJ	ureteropelvic junction
URS	ureteroscopy
UTI	urinary tract infection
UVJ	ureterovesicular junction
VB1	voided bladder, initial (urethra)
VB2	voided bladder, midstream (bladder)
VB3	voided bladder, post-massage/ digital rectal exam
VCUG	voiding cystourethrogram
VIU	visual internal urethrotomy
VUR	vesicoureteral reflux

Basic Anatomy Review

- recall that the anatomical position of the penis is erect; therefore, the anatomical ventral side of the penis appears to be the dorsal side of the flaccid penis

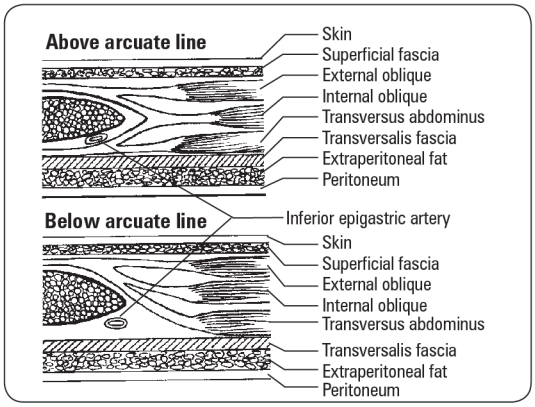


Figure 1. Midline cross-section of abdominal wall

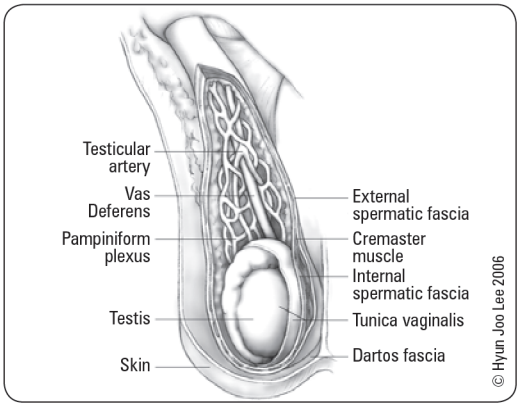


Figure 2. Anatomy of scrotum

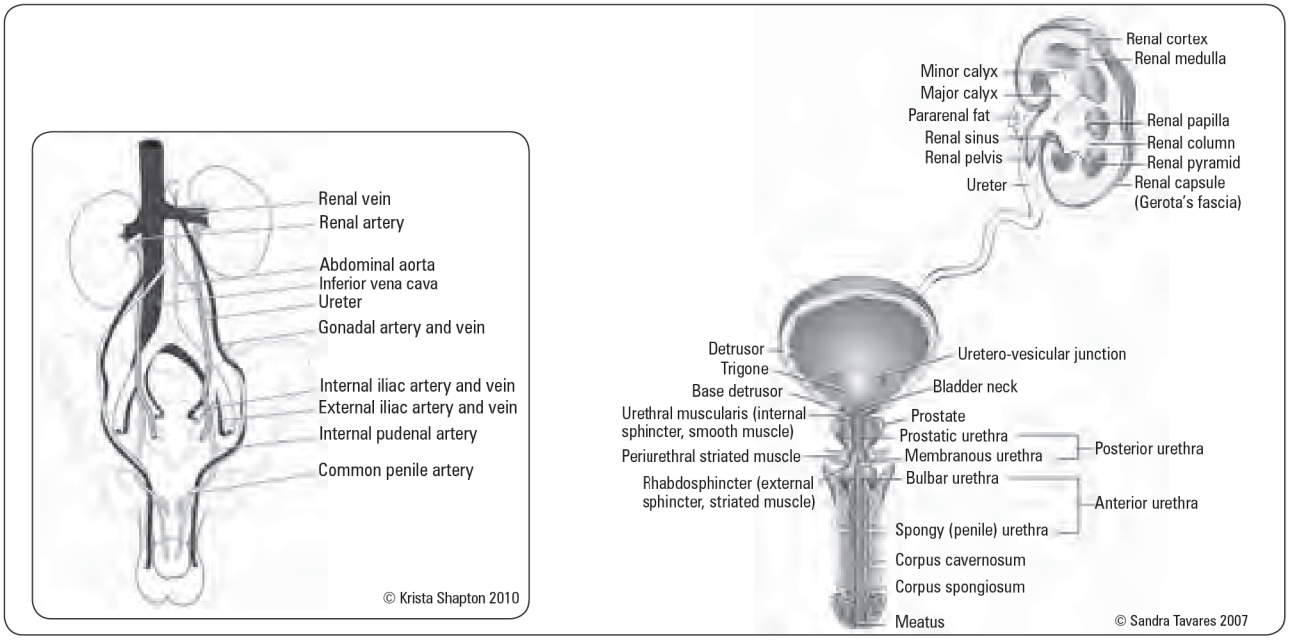


Figure 3. Essential male genitourinary tract anatomy

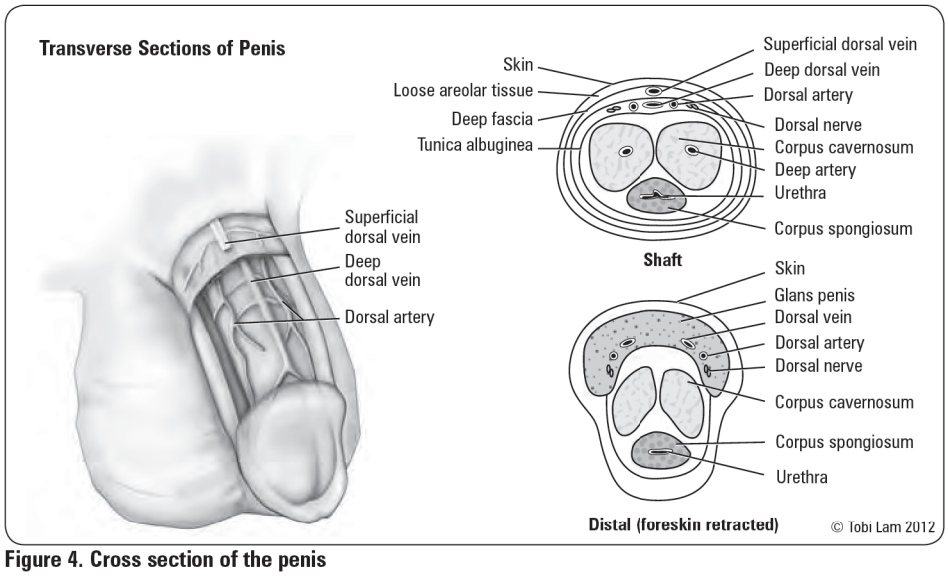


Figure 4. Cross section of the penis

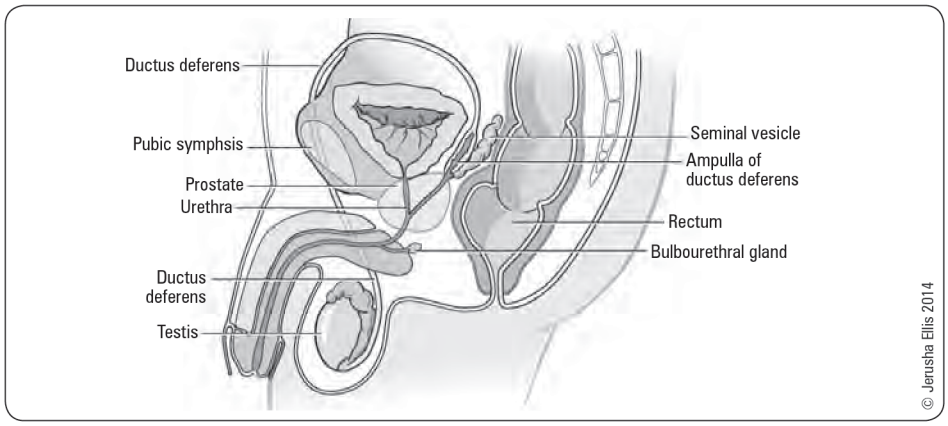


Figure 5. Median sagittal section of the male pelvis and perineum

Urologic History

- follow the OPQRSTUVW approach
  - note that pain may not be limited to the genital region (e.g. lower abdomen, CVA)
- inquire about risk factors: past urologic disease (e.g. UTI, stones, STI, cancers, anatomic abnormalities, family Hx, medications, lifestyle factors, trauma, previous surgical procedures)
- urinary habits
  - frequency of voiding, quality of urine, volume of voids, incontinence, nocturia
  - specific urinary symptoms include
    - storage symptoms: frequency, nocturia, urgency
    - voiding symptoms: straining, hesitancy, dysuria, intermittency, post-void dribbling, reduced stream, feeling of incomplete voiding
    - hematuria: part of stream during which bleeding occurs, blood clots
    - incontinence: rushing to washroom (urge); leakage with coughing, sneezing, laughing (stress); constant dribbling (overflow)
- sexual function
  - scrotal mass: see *Scrotal Mass*, U29
  - ED: see *Erectile Dysfunction*, U30
  - infertility: see *Infertility*, U34
- risk factors
  - past urologic disease (e.g. UTI, stones, cancers, STI), anatomic abnormalities, trauma, previous surgical procedures, medications, family Hx, lifestyle factors
- associated symptoms
  - N/V
  - bowel dysfunction
- constitutional symptoms
  - fever, chills, unintentional weight loss, night sweats, fatigue, malaise

Always ask about sexual function on history. Change in erectile function can be one of the first symptoms that there is concomitant vascular disease. If there is new onset ED, consider screening for DM and CAD risk factors

Hematuria (Blood in the Urine)

Macroscopic (Gross) Hematuria

Definition
- blood in the urine that can be seen with the naked eye

Classification
- see Nephrology, NP20

Etiology

Table 1. Etiology by Age Group

Age (yr)	Etiology	
0-20	UTI, glomerulonephritis, congenital abnormalities	
20-40	UTI, stones, bladder tumour	
40-60	Male: bladder tumour, stones, UTI	Female: UTI, stones, bladder tumour
>60	Male: BPH, bladder tumour, UTI, RCC	Female: bladder tumour, UTI, RCC

Table 2. Etiology by Type

Pseudohematuria	Infectious/ Inflammatory	Malignancy	Benign	Structural	Hematologic
Vaginal bleeding Dyes (beets, rhodamine B in candy and juices) Hemoglobin (hemolytic anemia) Myoglobin (rhabdomyolysis) Drugs (rifampin, phenazopyridine, phenytoin) Porphyria Laxatives (phenolphthalein)	Pyelonephritis Cystitis Urethritis Glomerulonephritis Interstitial nephritis Tuberculosis	RCC (mainly in adult population) UCC Wilms' tumour (mainly in pediatric population) Leukemia	BPH Polyps Exercise-induced	Stones Trauma Foreign body Urethral stricture Polycystic kidneys Arteriovenous malformation Infarct	Anticoagulants Coagulation defects Sickle cell disease Thromboembolism

Gross, painless hematuria in adults is bladder cancer until proven otherwise

Common Urologic Causes of Hematuria can be Classified as:

TICS
Trauma/**T**umour/**T**oxins
Infection/**I**nflammatory
Calculi/**C**ysts
Surgery/**S**ickle cell and other hematological causes

History
- inquire about timing of hematuria in urinary stream
  - initial: anterior urethra
  - terminal: bladder neck and prostatic urethra
  - total: bladder and/or above

Investigations
- CBC (rule out anemia, leukocytosis), electrolytes, Cr, BUN, INR, PTT
- urine studies
  - U/A, C&S, cytology
- imaging
  - CT (with contrast) has largely replaced IVP to investigate upper tracts
    - consider contraindications to contrast: allergy, renal insufficiency
    - U/S alone is not sufficient
  - cystoscopy to investigate lower tract (possible retrograde pyelogram)

Upper Tract Imaging Options

CT Urography (CTU): Optimal test for renal parenchyma, calculi, and infections. Involves exposure to radiation and IV contrast. Assess kidney function, allergies prior to use of contrast

U/S: Superior to IVP for evaluation of renal parenchyma and renal cysts. Limited sensitivity for UCC and small renal masses. U/S alone is not sufficient for upper tract imaging

Intravenous Pyelogram (IVP): Traditional option but rarely used (replaced by CTU). Reasonable sensitivity for UCC, but poor sensitivity for RCC

Acute Management of Severe Bladder Hemorrhage
- manual irrigation via catheter with normal saline to remove clots
- CBI using large (22-26 Fr) 3-way Foley to help prevent clot formation
- cystoscopy if active bleeding
  - identify resectable tumours
  - coagulate obvious sites of bleeding
- refractory bleeding
  - intravesical agents
    - continuous intravesical irrigation with 1% aluminum potassium sulfate solution as needed
    - intravesical instillation of 1% silver nitrate solution
    - intravesical instillation of 1-4% formalin (requires GA and pre-procedure cystogram to rule out reflux)
  - embolization or ligation of iliac arteries
  - cystectomy and diversion (rarely performed)

Microscopic Hematuria

Definition
- blood in the urine that is not visible to the naked eye
- >3 RBCs/HPF on urinalysis of at least two separate samples

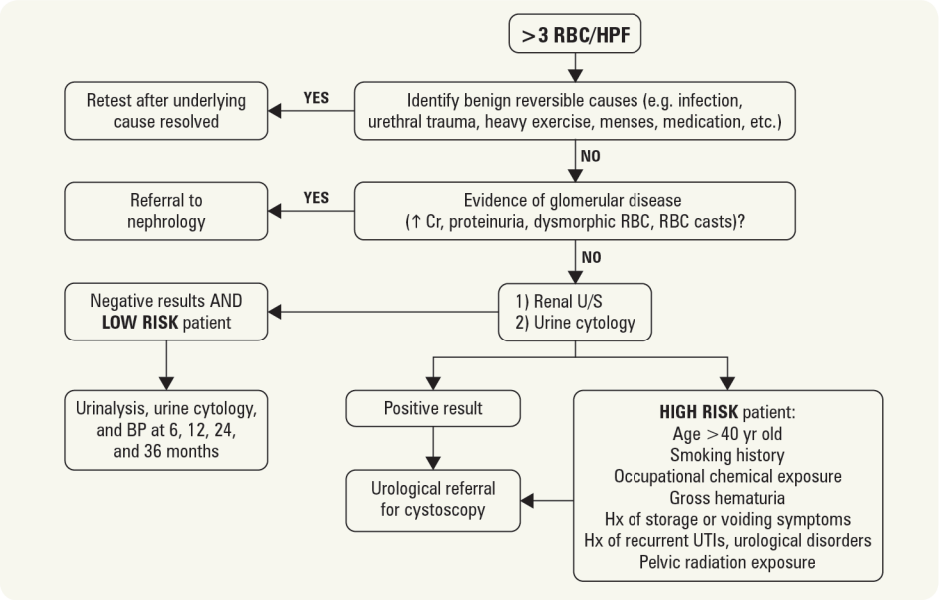


Figure 6. Workup of asymptomatic microscopic hematuria
Based on CUA Guidelines. Alternatively, the AUA recommends cystoscopy and CT urogram for all patients with confirmed microscopic hematuria; follow-up for negative workup is urinalysis yearly for two years, with repeat anatomic evaluation if microscopic hematuria persists

Lower Urinary Tract Dysfunction

- see Gynecology, GY37 for relevant female topics

Voiding

- two phases of lower urinary tract function
  1. storage phase (bladder filling and urine storage)
     - accommodation and compliance
     - no involuntary contraction
  2. voiding phase (bladder emptying)
     - coordinated detrusor contraction
     - synchronous relaxation of outlet sphincters
     - no anatomic obstruction
- voiding dysfunction can therefore be classified as
  - failure to store: due to bladder or outlet
  - failure to void: due to bladder or outlet
- three types of symptoms
  - storage (formerly known as irritative)
  - voiding (formerly known as obstructive)
  - post-voiding

Urinary Incontinence

Definition
- involuntary leakage of urine

Etiology
- urgency incontinence
  - detrusor overactivity
    - CNS lesion, inflammation/infection (cystitis, stone, tumour), bladder neck obstruction (tumour, stone), BPH, idiopathic

Lower Urinary Tract Symptoms (LUTS)

Storage (FUND)
Frequency
Urgency
Nocturia
Dysuria

Voiding (SHED)
Stream changes
Hesitancy
Incomplete **E**mptying
Dribbling

  - decreased compliance of bladder wall (inability to store urine)
    - CNS lesion, fibrosis
    - sphincter/urethral problem
- stress urinary incontinence (SUI)
  - common in women; seen in men after prostate cancer treatment or pelvic operations
  - urethral hypermobility
    - weakened pelvic floor and musculofascial urethral and vaginal supporting mechanisms allows bladder neck and urethra to descend with increased intra-abdominal pressure
    - urethra is pulled open by greater motion of posterior wall of outlet relative to anterior wall
    - associated with childbirth, pelvic surgery, aging, levator muscle weakness, obesity
  - intrinsic sphincter deficiency (ISD): weakness of the urethra and associated smooth and striated muscle elements
    - pelvic surgery, neurologic problem, aging and hypoestrogen state
  - ISD and urethral hypermobility can co-exist
- mixed incontinence
  - combination of stress and urgency incontinence
- overflow incontinence
  - is a term sometimes used to describe urinary incontinence as a complication of urinary retention; for causes of urinary retention see Table 4
  - use of the term should be accompanied by the associated pathophysiology (e.g. BPH with overflow incontinence)

Causes of Reversible Urinary Incontinence

DIAPERS
Delirium
Inflammation/**I**nfection
Atrophic vaginitis/urethritis
Pharmaceuticals/**P**sychological
Excess U/O
Restricted mobility/**R**etention
Stool impaction

Epidemiology
- variable prevalence in women: 25-45%
- F:M = 2:1
- more frequent in the elderly, affecting 5-15% of those living in the community and 50% of nursing home residents

Table 3. Urinary Incontinence: Types and Treatments

Type	Urgency	Stress	Mixed
Definition	Involuntary leakage of urine preceded by a strong, sudden urge to void	Involuntary leakage of urine with sudden increases in intra-abdominal pressure	Urinary leakage associated with urgency and increased intra-abdominal pressure
Etiology	Bladder (detrusor overactivity)	Urethra/sphincter weakness, post-partum pelvic musculature weakness	Combination of bladder and sphincter issues
Diagnosis	Hx Urodynamics	Hx Urodynamics Stress test (have patient bear down/cough)	Hx Urodynamics Stress test
Therapy	Lifestyle changes (fluid alterations, diet, etc.) Bladder habit training Anticholinergics β3 agonist Neuromodulation Botulinum toxin A	Weight loss Kegel exercises Bulking agents Surgery (slings, tension-free vaginal tape, transobturator tape, artificial sphincters)	Combination of management of urge and stress incontinence

Urgency is the symptom of a strong need to void; it is not necessarily associated with incontinence

Urinary Retention

Table 4. Etiology of Urinary Retention

Outflow Obstruction	Bladder Innervation	Pharmacologic	Infection
• Bladder neck or urethra: calculus, clot, foreign body, neoplasm, neurological (DSD) • Prostate: BPH, prostate cancer • Urethra: stricture, phimosis, traumatic disruption • Miscellaneous: constipation, pelvic mass	• Intracranial: CVA, tumour, Parkinson's, cerebral palsy • Spinal cord: injury, disc herniation, MS • DM • Post-abdominal or pelvic surgery	• Anticholinergics • Narcotics • Antihypertensives (ganglionic blockers, methyldopa) • OTC cold medications containing ephedrine or pseudoephedrine • Antihistamines • Psychosomatic substances (e.g. ecstasy)	• GU: UTI, prostatitis, abscess, genital herpes • Infected foreign body • Varicella zoster

Acute vs. Chronic Retention

Acute retention is a medical emergency characterized by suprapubic pain and anuria with normal bladder volume and architecture

Chronic retention can be painless with greatly increased bladder volume and detrusor hypertrophy followed by atony (late)

If a trauma patient is unable to void, has blood at urethral meatus, a scrotal hematoma, or a high riding prostate, there is urethral injury until proven otherwise so catheterization is CONTRAINDICATED unless performed by urology staff or resident

Clinical Features
- suprapubic pain
- palpable and/or percussible bladder (suprapubic)
- possible purulent/bloody meatal discharge
- increased size of prostate or reduced anal sphincter tone on DRE
- neurological: presence of abnormal or absent deep tendon reflexes, reduced "anal wink", saddle anesthesia

Investigations
- CBC, electrolytes, Cr, BUN, U/A and urine C&S, U/S, cystoscopy, urodynamic studies, PVR

Patients with ascites may have a falsely elevated PVR measured by bladder scan

Treatment
- treat underlying cause
- catheterization
  - acute retention
    - immediate catheterization to relieve retention; leave Foley in to drain bladder; follow-up to determine cause; closely monitor fluid status and electrolytes (risk of POD)
  - chronic retention
    - intermittent catheterization by patient may be used; definitive treatment depends on etiology
- suprapubic tube placement
- for post-operative patients with retention:
  - encourage ambulation
  - α-blockers to relax bladder neck outlet
  - may need catheterization
  - definitive treatment will depend on etiology

Benign Prostatic Hyperplasia

Definition
- periurethral hyperplasia of stroma and epithelium in prostatic transition zone
- prostatic smooth muscle cells play a role in addition to hyperplasia

Etiology
- etiology unknown
  - DHT required (converted from testosterone by 5-α reductase)
  - possible role of impaired apoptosis, estrogens, other growth factors
  - genetic: increased risk in 1st degree relatives and twin studies

Epidemiology
- age-related, extremely common (50% of 50 yr olds, 80% of 80 yr olds)
- 25% of men will require treatment

Clinical Features
- result from outlet obstruction and compensatory changes in detrusor function
- voiding and storage symptoms
- DRE
  - prostate is smooth, rubbery, and symmetrically enlarged
- complications
  - retention
  - overflow incontinence
  - hydronephrosis
  - renal insufficiency
  - infection
  - gross hematuria
  - bladder stones

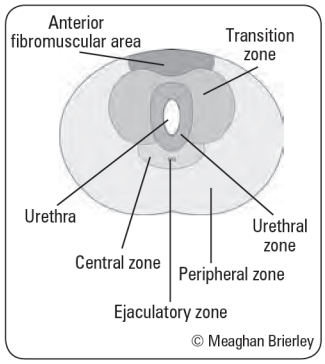


Figure 7. Cross-section of prostate

Prostate size does not correlate well with symptoms in BPH

Approximate Prostate Sizes
- 20 cc – chestnut
- 25 cc – plum
- 50 cc – lemon
- 75 cc – orange
- 100 cc – grapefruit

Investigations
- Hx, assessing LUTS and impact on QOL
  - may include self-administered questionnaires (IPSS or AUA symptom index for severity, progression, and treatment response)
- P/E, including DRE
- U/A to exclude UTI
- Cr to assess renal function
- renal U/S to assess for hydronephrosis
- PSA to rule out malignancy (see *Prostate Cancer Screening*, U25)
- uroflowmetry to measure flow rate (optional)
- PVR (optional)
- consider cystoscopy or transrectal ultrasound prior to potential surgical management to evaluate outlet and prostate volume
- biopsy if suspicious for malignancy, i.e. elevated PSA or abnormal DRE

AUA BPH Symptom Score

FUNWISE
Frequency
Urgency
Nocturia
Weak stream
Intermittency
Straining
Emptying, incomplete feeling of

Each symptom graded out of 5
0-7: Mildly symptomatic
8-19: Moderately symptomatic
20-35: Severely symptomatic

Note: dysuria not included in score but is commonly associated with BPH

Treatment

Table 5. Treatment of BPH

	Conservative	Medical	Surgical	Minimally Invasive Surgical Therapies
When to use	Asymptomatic patients	Moderate to severe symptoms that are distressing for patient	Significant symptom burden, acute urinary retention, refractory hematuria, recurrent infections	Patients who wish to avoid or may not tolerate surgery
Options	• Watchful waiting: 50% of patients improve spontaneously • Lifestyle modifications (e.g. evening fluid restriction, planned voiding)	• α-adrenergic antagonists: reduce stromal smooth muscle tone • 5-α reductase inhibitor: block conversion of testosterone to DHT; act to reduce prostate size • Combination is synergistic • Anti-cholinergic agents (for storage LUTS, without elevated PVR)	• TURP (see U42) • Laser ablation • TUIP (prostate <30 g) • Open prostatectomy	• Microwave therapy • TUNA • Prostatic stent (not commonly used)

Men with planned cataract surgery should avoid starting α-adrenergic antagonists until after their surgery due to the risk of intraoperative floppy iris syndrome

BPH Surgery
Absolute Indication
- Renal failure with obstructive uropathy
- Refractory urinary retention

Relative Indications
- Recurrent UTIs
- Recurrent hematuria refractory to medical treatment
- Renal insufficiency (rule out other causes)
- Bladder stones

Finasteride for Benign Prostatic Hyperplasia
Cochrane DB Syst Rev 2010;10:CD006015
Purpose: To examine the effectiveness and safety of finasteride versus placebo or other active controls for the treatment of urinary tract symptoms.
Summary of Findings:
1. Finasteride improved urinary symptoms more than placebo in trails >1 yr duration and significantly lowered the risk of BPH progression.
2. Compared with α-blockers, finasteride was less effective than either doxazosin or terazosin, but equally as effective as tamsulosin.
3. Symptom improvement with finasteride + doxazosin is equal to doxazosin alone.
4. Finasteride treatment resulted in an increased risk of ejaculation disorder, impotence and lowered libido compared with placebo.
5. Compared with doxazosin and terazosin, finasteride had a lower risk of asthenia, dizziness, and postural hypotension.

Microwave Thermotherapy for Benign Prostatic Hyperplasia
Cochrane DB Syst Rev 2012;9:CD004135
Purpose: To evaluate the efficacy and safety of microwave thermotherapy for the treatment of benign prostatic obstruction.
Selection Criteria: RCTs evaluating transurethral microwave therapy (TUMT) for men with symptomatic BPH with multiple comparison groups.
Results: 15 studies, 1,585 patients, mean age 66.8 yr, 3-60 mo duration. Mean urinary symptom scores decreased by 65% with TUMT and 77% with TURP. The pooled mean peak urinary flow increased by 70% with TUMT and 119% with TURP. Compared with TURP, TUMT was associated with decreased risks for retrograde ejaculation, treatment for strictures, hematuria, blood transfusions and transurethral resection syndrome, but increased risk for dysuria, urinary retention and retreatment for BPH symptoms.
Conclusions: Overall, microwave thermotherapy techniques are effective alternatives to TURP and α-blockers for treating symptomatic BPH, although less effective than TURP in improving symptom score and urinary flow.

Urethral Stricture

Definition
- decrease in urethral calibre due to scar formation in urethra (may also involve corpus spongiosum)
- M>F

Etiology
- congenital
  - failure of normal canalization (i.e. posterior urethral valves)
- trauma
  - instrumentation/catheterization (most common)
  - external trauma (e.g. burns, straddle injury)
  - foreign body
- infection
  - long-term indwelling catheter
  - STI (gonococcal or chlamydial disease)
- inflammation
  - balanitis xerotica obliterans (BXO; lichen sclerosis or chronic progressive sclerosing dermatosis of the male genitalia) causing meatal and urethral stenosis

Clinical Features
- voiding symptoms
- urinary retention
- hydronephrosis
- related infections: recurrent UTI, secondary prostatitis/epididymitis

Investigations
- laboratory findings
  - flow rates <10 mL/s (normal ~20 mL/s) on uroflowmetry
  - urine culture usually negative, but U/A may show pyuria
- radiologic findings
  - RUG and VCUG will demonstrate location
- cystoscopy

Treatment
- urethral dilatation
  - temporarily increases lumen size by breaking up scar tissue
  - healing will often reform scar tissue, recurrence of stricture
- visual internal urethrotomy (VIU)
  - endoscopically incise stricture
  - equal success rates to dilation with mid bulbar strictures <2 cm
  - high rate of recurrence (30-80%), avoid in younger patients
- open surgical reconstruction
  - complete stricture excision with anastomosis, ± urethroplasty depending on location and size of stricture

Neurogenic Bladder

Definition

- malfunctioning urinary bladder due to deficiency in some aspect of its innervation

Neurophysiology

Table 6. Efferent Sympathetic, Parasympathetic, and Somatic Nerve Supply

Nerve Fibres	Nerve Roots	Neurotransmitter/Receptor	Target
Sympathetic	T10-L2	NA/Adrenergic	Trigone, internal sphincter, proximal urethra (α) Bladder body (β)
Somatic (Pudendal)	S2-4	ACh/Nicotinic	External sphincter
Parasympathetic	S2-4	ACh/Muscarinic (M2, M3)	Detrusor

Nerve roots in micturition:
"S2-3-4 keeps the urine off the floor"

- stretch receptors in the bladder wall relay information to PMC and activate micturition reflex (normally inhibited by cortical input)
  - micturition
    - stimulation of parasympathetic neurons (bladder contraction)
    - inhibition of sympathetic and somatic neurons (internal and external sphincter relaxation, respectively)
  - urine storage
    - opposite of micturition
- voluntary action of external sphincter (pudendal nerve roots S2-S4) can inhibit urge to urinate
- cerebellum, basal ganglia, thalamus, and hypothalamus all have input at PMC in the brainstem

Classification of Neurologic Voiding Dysfunction

"Spinal shock", initially manifests as atonic bladder

- neuropathic detrusor overactivity (formerly termed detrusor hyperreflexia)
  - lesion above PMC (e.g. stroke, tumour, MS, Parkinson's disease)
  - loss of voluntary inhibition of voiding
  - intact pathway inferior to PMC maintains coordination of bladder and sphincter
- detrusor sphincter dyssynergia (DSD)
  - suprasacral lesion of spinal cord (e.g. trauma, MS, arteriovenous malformation, transverse myelitis)
  - loss of coordination between detrusor and sphincter (detrusor contracts on closed sphincter and vice versa)
  - component of detrusor overactivity as well
- detrusor atony/areflexia
  - lesion of sacral cord or peripheral efferents (e.g. trauma, DM, disc herniation, MS, congenital spinal cord abnormality, post abdominoperineal resection)
  - flaccid bladder which fails to contract
  - may progress to poorly compliant bladder with high pressures
- peripheral autonomic neuropathy
  - deficient bladder sensation → increasing residual urine → decompensation (e.g. DM, neurosyphilis, herpes zoster)
- muscular lesion
  - can involve detrusor, smooth/striated sphincter

Neuro-Urologic Evaluation

- Hx and P/E (urologic and general neurologic)
- U/A, renal profile
- imaging
  - IVP (less used), U/S to rule out hydronephrosis and stones
- cystoscopy
- urodynamic studies
  - uroflowmetry to assess flow rate, pattern
  - filling CMG to assess capacity, compliance, detrusor overactivity
  - voiding CMG (pressure-flow study) to assess bladder contractility and extent of bladder outflow obstruction
  - video study to visualize bladder/bladder neck/urethra during CMG using x-ray contrast
  - EMG ascertains presence of coordinated or uncoordinated voiding, allows accurate diagnosis of DSD

Treatment

- goals of treatment
  - prevent renal failure
  - prevent infections
  - achieve social continence

- clean intermittent catheterization (CIC)
- treatment options depend on status of bladder and urethra
  - bladder hyperactivity → anticholinergic medications to relax bladder (see *Urinary Incontinence*, U5)
    - if refractory
      - botulinum toxin injections into bladder wall
      - occasionally augmentation cystoplasty (enlarging bladder volume and improving compliance by grafting section of detubularized bowel onto the bladder)
      - occasionally urinary diversion (ileal conduit or continent diversion) in severe cases if bladder management unsuccessful
  - flaccid bladder → CIC

Dysuria

Definition
- painful urination

Etiology

Table 7. Differential Diagnosis of Dysuria

Infectious	Cystitis, urethritis, prostatitis, epididymitis/orchitis (if associated with lower tract inflammation), cervicitis, vulvovaginitis, perineal inflammation/infection, TB, vestibulitis
Neoplasm	Kidney, bladder, prostate, penis, vagina/vulva, BPH
Calculi	Bladder stone, urethral stone, ureteral stone
Inflammatory	Seronegative arthropathies (reactive arthritis: arthritis, uveitis, urethritis), drug side effects, autoimmune disorders, chronic pelvic pain syndrome (CPPS), interstitial cystitis
Hormonal	Endometriosis, hypoestrogenism
Trauma	Catheter insertion, post-coital cystitis (honeymoon cystitis)
Psychogenic	Somatization disorder, depression, stress/anxiety disorder
Other	Contact sensitivity, foreign body, radiation/chemical cystitis, diverticulum

Investigations
- focused Hx and P/E to determine cause (fever, d/c, conjunctivitis, CVA tenderness, back/joint pain)
  - any d/c (urethral, vaginal, cervical) should be sent for gonococcus/chlamydia testing; wet mount if vaginal d/c
  - U/A and urine C&S
  - if suspect infection, may start empiric ABx treatment (see Table 8, U11)
  - ± imaging of urinary tract (tumour, stones)

Hydronephrosis

Definition
- dilation of the renal pelvis and calyces caused by the impairment in antegrade urine flow

Etiology
- mechanical
  - congenital: see *Congenital Abnormalities*, U35
  - acquired
    - intrinsic: trauma, inflammation and bleeding, calculi, urologic neoplasms, BPH, urethral stricture, phimosis, previous urological surgery
    - extrinsic: trauma, neoplasms (uterine fibroid; colorectal, uterine, and cervical malignancies; lymphoma), aortic aneurysm, pregnancy (gravid uterus)
- functional
  - neuropathic: neurogenic bladder, diabetic neuropathy, spinal cord disease
  - pharmacologic: anticholinergics, α-adrenergic agonists
  - hormonal: pregnancy (progesterone decreases ureteral tone)

Investigations
- focused Hx, inquiring about pain (flank, lower abdomen, testes, labia), U/O, medication use, pregnancy, trauma, fever, Hx of UTIs, calculi, and PID and urological surgery

- CBC, electrolytes, Cr, BUN, U/A, C&S
- imaging studies (U/S is >90% sensitive and specific)
  - MAG3 diuretic renogram: evaluates differential renal function and demonstrates if functional obstruction exists

Treatment
- hydronephrosis can be physiologic
- treatment should be guided at improving symptoms, treating infections, or improving renal function
- urgent treatment may require percutaneous nephrostomy tube or ureteral stenting to relieve pressure

Post-Obstructive Diuresis

Definition
- polyuria resulting from relief of severe chronic obstruction
- >3 L/24 h or >200 cc/h over each of two consecutive hours

Pathophysiology
- **physiologic POD** secondary to excretion of retained urea, Na^+, and H_2O (high osmotic load) after relief of obstruction
  - self-limiting; usually resolves in 48 h with PO fluids but may persist to pathologic POD
- **pathologic POD** is a Na^+-wasting nephropathy secondary to impaired concentrating ability of the renal tubules due to
  - decreased reabsorption of NaCl in the thick ascending limb and urea in the collecting tubule
  - increased medullary blood flow (solute washout)
  - increased flow and solute concentration in the distal nephrons

Management
- admit patient and closely monitor hemodynamic status and electrolytes (Na^+ and K^+ q6-12h and replace prn; follow Cr and BUN to baseline)
- monitor U/O q2h and ensure total fluid intake <U/O by replacing every 1 mL U/O with 0.5 mL 1/2 NS IV (PO fluids if physiologic POD)
- avoid glucose-containing fluid replacement (iatrogenic diuresis)

Overactive Bladder

Definition
- a symptom complex that includes urinary urgency with or without urgency incontinence, urinary frequency (voiding >8 times in a 24 hr period), and nocturia (awakening two or more times at night to void)

Etiology
- etiology unknown
- symptoms usually associated with involuntary contractions of the detrusor muscle. The overactivity of the muscle could be neurogenic, myogenic or idiopathic

Epidemiology
- F:M= 1:1
- prevalence increases with age. 42% in males 75 years old or older; 31% in females 75 years old or older

Diagnosis
- the diagnostic process should document symptoms and signs that define overactive bladder and exclude other disorders that could cause of the patient's symptoms
- minimal requirements for the process consist of
  - focused history including past genitourinary disorders and conditions outlined in Table 8, questionnaires of LUTS for women and diaries of urination frequency, volume and pattern
  - P/E including genitourinary, pelvic and rectal examination
  - urinalysis to rule out hematuria and infection
- in some patients, the following investigations could be considered
  - bladder scan for residual urine in patients with risk factors of urinary retention
  - cystoscopy to rule out recurrent infections, carcinoma in situ and other intravesical abnormalities
    - urodynamics to rule out obstruction in older men

Treatment

- non-pharmacological: behaviour therapies such as bladder training, bladder control strategies, pelvic floor muscle training, fluid management, and avoidance of caffeine
- pharmacological
  - anti-muscarinics such as oxybutinin hydrochloride, tolterodine, solifenacin, fesoterodine, or trospium
  - β3-adrenoceptor agonist such as mirabegron
- refractory patients may be treated with
  - neuromuscular-junction inhibition such as botulinum toxin bladder injection
- other interventional procedures include
  - posterior tibial nerve stimulation (not used commonly in Canada)
  - sacral neuromodulation

Table 8. Conditions that could contribute to symptoms of Overactive Bladder

Lower urinary tract conditions	UTI, obstruction, impaired bladder contractility
Neurological conditions	Stroke, MS, dementia, diabetic neuropathy
Systemic diseases	CHF, sleep disorders (primarily nocturia)
Functional and behavioral	Excessive caffeine and alcohol, constipation, impaired mobility
Medication	Diuretics, anticholinergic agents, narcotics, calcium-channel blocker, cholinesterase inhibitors

Infectious and Inflammatory Diseases

Table 8. Antibiotic Treatment of Urological Infections

Condition	Drug	Duration
Urethritis	Non-Gonococcal	
	azithromycin (1 g PO)	x 1
	OR	
	doxycycline (100 mg PO bid)	7 d
	Gonococcal	
	ceftriaxone (250 mg IM) AND treat for *Chlamydia trachomatis*	x 1
Simple, Uncomplicated UTI	TMP-SMX (160 mg/800 mg PO bid)	3 d
	OR	
	nitrofurantoin (100 mg PO bid)	5 d
Complicated UTI (see *Classification*, U13 for features)	ciprofloxacin (1 g PO daily OR 400 mg IV q12h)	up to 2-3 wk
	OR	
	ampicillin (1 g IV q6h) + gentamicin (1 mg/kg IV q8h)	up to 2-3 wk
	OR	
	ceftriaxone (1-2 g IV q24h)	up to 2-3 wk
Recurrent/Chronic Cystitis	rophylactic treatment	
	Continuous: TMP-SMX (40 mg/200 mg PO qd OR 3x/wk)	6-12 mo
	OR	
	nitrofurantoin (50-100 mg PO qd)	6-12 mo
	Post-Coital: TMP-SMX (40 mg/200 mg-80 mg/400 mg)	within 2 h of coitus
	OR	
	nitrofurantoin (50-100 mg PO qd)	within 2 h of coitus
Acute Prostatitis	ciprofloxacin (500-750 mg PO bid)	2-4 wk
	OR	
	TMP-SMX (160 mg/800 mg PO bid)	4 wk
	OR	
	IV therapy with gentamicin and ampicillin, penicillin with β-lactamase inhibitor, 3rd gen cephalosporin, OR a fluoroquinolone	4 wk total (IV and oral step-down)
Chronic Prostatitis	ciprofloxacin (500 mg PO bid)	4-6 wk
Epididymitis/Orchitis	<35 yr	
	ceftriaxone (200 mg IM)	x 1
	AND	
	doxycycline (100 mg PO bid)	10 d
	≥35 yr	
	ofloxacin (300 mg PO bid)	10 d
Acute Uncomplicated Pyelonephritis	ciprofloxacin (500 mg PO bid)	7 d
	± ceftriaxone (1 g IV) OR ciprofloxacin (400 mg IV)	x 1
	OR	
	IV therapy with a fluoroquinolone, gentamicin and ampicillin, extended spectrum cephalosporin, extended spectrum penicillin, OR a carbapenem	14 d total (IV and oral step-down)

Antibiotic therapy should always be based on local resistance patterns and adjusted according to culture and sensitivity results

Cystitis: Common Pathogens

KEEPS
K*lebsiella sp.*
E. *coli* (90%), other Gram-negatives
E*nterococci*
P*roteus mirabilis*, ***P****seudomonas*
S. *saprophyticus*

Acute uncomplicated pyelonephritis: suspected or confirmed enterococcus infection requires treatment with ampicillin

Urinary Tract Infection

- for UTIs during pregnancy, see Obstetrics, OB29

Definition
- symptoms suggestive of UTI + evidence of pyuria and bacteriuria on U/A or urine C&S
  - if asymptomatic + 100,000 CFU/mL = asymptomatic bacteriuria; only requires treatment in certain patients (e.g. pregnancy)

Classification
- uncomplicated: lower UTI in a setting of functionally and structurally normal urinary tract
- complicated: structural and/or functional abnormality, male patients, immunocompromised, diabetic, iatrogenic complication, pregnancy, pyelonephritis, catheter-associated
- recurrent: see *Recurrent/Chronic Cystitis*

Risk Factors
- stasis and obstruction
  - residual urine due to impaired urine flow e.g. PUVs, reflux, medication, BPH, urethral stricture, cystocele, neurogenic bladder
- foreign body
  - introduce pathogen or act as nidus of infection e.g. catheter, instrumentation
- decreased resistance to organisms
  - DM, malignancy, immunosuppression, spermicide use, estrogen depletion, antimicrobial use
- other factors
  - trauma, anatomic abnormalities, female, sexual activity, fecal incontinence

Prevention of UTIs
- Maintain good hydration (try cranberry juice)
- Wipe from front to back to avoid contamination of the urethra with feces from the rectum
- Avoid feminine hygiene sprays and scented douches
- Empty bladder immediately before and after intercourse

Clinical Features
- storage symptoms: frequency, urgency, dysuria
- voiding symptoms: hesitancy, post-void dribbling
- other: suprapubic pain, hematuria, foul-smelling urine
- pyelonephritis – if present: typically presents with more severe symptoms (e.g. fever/chills, CVA tenderness, flank pain)

Organisms
- typical organisms
- atypical organisms
  - tuberculosis (TB)
  - *Chlamydia trachomatis*
  - Mycoplasma (*Ureaplasma urealyticum*)
  - fungi (*Candida*)

Indications for Investigations
- pyelonephritis
- persistence of pyuria/symptoms following adequate antibiotic therapy
- severe infection with an increase in Cr
- recurrent/persistent infections
- atypical pathogens (urea splitting organisms)
- Hx of structural abnormalities/decreased flow

Investigations
- U/A, urine C&S
  - UA: leukocytes ± nitrites ± hematuria
  - C&S: midstream, catheterized, or suprapubic aspirate
- if hematuria present, retest post-treatment, if persistent need hematuria workup (see *Microscopic Hematuria*, U5)
- U/S, CT scan if indicated

Treatment
- see Table 8 for approach to ABx therapy
- if febrile, consider admission with IV therapy and rule out obstruction

Recurrent/Chronic Cystitis

Definition
- ≥3 UTIs/yr

Etiology
- bacterial reinfection (80%) vs. bacterial persistence (relapse)
  - **bacterial reinfection**
    - recurrence of infection with either 1) a different organism, 2) the same organism if cultured >2 wk following therapy, or 3) with any organism with an intermittent sterile culture
  - **bacterial persistence**
    - same organism cultured within 2 wk of sensitivity-based therapy

Investigations
- assess predisposing factors as described above
- investigations may include cystoscopy, U/S, CT

Treatment
- lifestyle changes (limit caffeine intake, increase fluid/H_2O intake)
- ABx: continuous vs. post-coital
- post-menopausal women: consider topical or systemic estrogen therapy
- no treatment for asymptomatic bacteriuria except in pregnant women or patients undergoing urinary tract instrumentation

Interstitial Cystitis (Painful Bladder or Bladder Pain Syndrome)

Definition
- bladder pain, chronic urgency and frequency without other reasonable causation

Classification
- non-ulcerative (more common)
- ulcerative

Etiology
- unknown
  - theories: increased epithelial permeability, autoimmune, neurogenic, defective GAG layer overlying mucosa
  - associations: severe allergies, IBS, fibromyalgia

Epidemiology
- prevalence: 20/100,000
- 90% of cases are in females
- mean age at onset is 40 yr (non-ulcerative tends to affect a younger to middle-aged population, while ulcerative tends to be seen in middle-aged to older)

Cystoscopic evaluation is not necessary to make a diagnosis

Clinical Features
- pain associated with the bladder
- glomerulations (submucosal petechiae) or Hunner's lesions (ulcers) on cystoscopic examination
- urinary urgency
- negative U/A, urine C&S, and urine cytology

Four Symptom Scores Exist to Evaluate and Monitor Patients with Interstitial Cystitis
- Interstitial Cystitis Symptom Index (ICSI)
- Interstitial Cystitis Problem Index (ICPI)
- Wisconsin Interstitial Cystitis (UW-IC) Scale
- Pain, Urgency and Frequency (PUF) Score

Differential Diagnosis
- UTI, vaginitis, bladder tumour
- radiation/chemical cystitis
- eosinophilic/TB cystitis
- bladder calculi

Treatment
- first-line: patient empowerment (diet, lifestyle, stress management), pain management
- second-line
  - oral: pentosan polysulfate sodium, amitriptyline, cimetidine, hydroxyzine
  - intravesical: dimethylsulfoxide (DMSO), heparin, lidocaine
- third-line: cystoscopy with bladder hydrodistention (traditionally diagnostic) under GA, treat Hunner's lesions if present
- other: neuromodulation, cyclosporine A, intradetrusor botulinum toxin
- surgery (last resort): augmentation cystoplasty, or urinary diversion ± cystectomy

Acute Pyelonephritis

Definition
- infection of the renal parenchyma with local and systemic manifestations
- clinical diagnosis of flank pain, fever and elevated WBC

Etiology
- ascending (usually GN bacilli) or hematogenous route (usually GP cocci)
- causative microorganisms
  - gram positives: *Enterococcus faecalis, S. aureus, S. saphrophyticus*
  - gram negatives: *E. coli* (most common), *Klebsiella, Proteus, Pseudomonas, Enterobacter*
- common underlying causes of pyelonephritis
  - stones, strictures, prostatic obstruction, vesicoureteric reflux, neurogenic bladder, catheters, DM, sickle-cell disease, PCKD, immunosuppression, post-renal transplant, instrumentation, pregnancy

Clinical Features
- rapid onset (<24 h)
- LUTS including frequency, urgency, hematuria; NOT dysuria unless concurrent cystitis
- fever, chills, nausea, vomiting, myalgia, malaise
- CVA tenderness or exquisite flank pain

Investigations
- U/A, urine C&S
- CBC and differential: leukocytosis, left shift
- imaging indicated if suspicious of complicated pyelonephritis or symptoms do not improve with 48-72 h of treatment
  - abdominal/pelvic U/S
  - CT
- nuclear medicine: DMSA scan can be used to help secure the diagnosis
  - a photopenic defect indicates active infection or scar; if normal alternative diagnoses should be considered

Treatment
- hemodynamically stable
  - outpatient oral ABx treatment ± single initial IV dose (see Table 9)
- severe or non-resolving
  - admit, hydrate, and treat with IV ABx (see Table 9)
- emphysematous pyelonephritis
  - percutaneous nephrostomy tube and antibiotics first line
  - consider early nephrectomy after IV ABx started and patient stabilized
- renal obstruction
  - admit for emergent stenting or percutaneous nephrostomy tube

Nitrofurantoin has poor tissue penetration and therefore is not used to treat pyelonephritis (requires post-renal uroconcentration)

Prostatitis/Prostatodynia

Epidemiology
- most common urologic diagnosis in men <50 yr
- prevalence 2-12%

Classification

Table 10. Comparison of the Three Types of Prostatitis

	Category I: Acute Bacterial Prostatitis	Category II: Chronic Bacterial Prostatitis	Category III: Chronic Pelvic Pain Syndrome (CPPS) (Abacterial)
Etiology	Ascending urethral infection with KEEPS (see U12 sidebar): 80% *E. coli* Often associated with outlet obstruction, recent cystoscopy, prostatic biopsy Most infections occur in the peripheral zone (see Figure 7, U7)	Recurrent exacerbations of acute prostatitis-like signs and symptoms Recurrent UTI with same organism	Divided into inflammatory (IIIA) and non-inflammatory (IIIB) Intraprostatic reflux of urine ± urethral hypertonia Multifactorial (immunological, neuropathic, neuroendocrine, psychosocial)
Clinical Features	Acute onset fever, chills, malaise Rectal, lower back, and perineal pain LUTS	Pelvic pain, storage LUTS, ejaculatory pain, post-ejaculatory pain	Pelvic pain, storage LUTS, ejaculatory pain, post-ejaculatory pain
Investigations	P/E: abdomen, external genitalia, perineum, prostate U/A Blood CBC, C&S Transrectal U/S if non-resolving/ suspect prostatic abscess	P/E: as per Category I + pelvic floor Urine C&S: 4-glass test VB1 (voided bladder): initial (urethra) VB2: midstream (bladder) EPS (expressed prostatic secretions): not usually performed VB3: post-massage/DRE	Same as per Category II NIH-CPSI score* Consider psychological assessment
Treatment	Supportive measures PO or IV ABx depending how sick (see Table 9) May consider catheterization in patients with severe obstructive LUTS or retention I&D of abscess if present	ABx (see Table 9) Consider addition of an α-blocker	Supportive measures Trial of ABx therapy if newly diagnosed Multimodal treatment strategy may include: α-blocker Anti-inflammatories Phytotherapy (quercetin, cernilton)

*NIH-CPSI: National Institute of Health Chronic Prostatitis Symptom Index

4-Glass Test: Prostatic source is suggested when colony counts in EPS and VB3 exceed those of VB1 and VB2 by 10x

It is not recommended to do a serum PSA during acute bacterial prostatitis

Prostatic massage may cause extreme tenderness and increased risk of inducing sepsis, abscess, or epididymo-orchitis

Epididymitis and Orchitis

Etiology
- common infectious causes
  - <35 yr: *N. gonorrhoeae* or *Chlamydia trachomatis*
  - ≥35 yr or penetrative anal intercourse: GI organisms (especially *E. coli*)
- other causes
  - mumps infection may involve orchitis, post-parotitis
  - TB
  - syphilis
  - granulomatous (autoimmune) in elderly men
  - amiodarone (involves only head of epididymis)
  - chemical: reflux of urine into ejaculatory ducts

Risk Factors
- UTI
- unprotected sexual contact
- instrumentation/catheterization
- increased pressure in prostatic urethra (straining, voiding, heavy lifting) may cause reflux of urine along vas deferens → sterile epididymitis
- immunocompromise

Clinical Features
- sudden onset scrotal pain and swelling ± radiation along cord to flank
- scrotal erythema and tenderness
- fever
- storage symptoms, purulent d/c
- reactive hydrocele

Prehn's Sign: pain may be relieved with elevation of testicles in epididymitis but not in testicular torsion (poor sensitivity, especially in children)

Investigations
- U/A, urine C&S
- ± urethral d/c: Gram stain/culture
- if diagnosis uncertain, must do
  - colour-flow Doppler U/S to rule out testicular torsion

If unsure between diagnoses of epididymitis and torsion, always go to OR

Remember: torsion >6 h has poor prognosis

Treatment
- rule out torsion (see *Investigations* Table 24, U29)
- see Table 9 for ABx therapy
- scrotal support, bed rest, ice, analgesia

Complications
- if severe → testicular atrophy
- 30% have persistent infertility problems

Inadequately treated acute epididymitis may lead to chronic epididymitis or epididymo-orchitis

Urethritis

Etiology
- infectious or inflammatory (e.g. reactive arthritis)

Reactive Arthritis (formerly known as Reiter's syndrome)
Urethritis, uveitis (or conjunctivitis), and arthritis
(can't pee, can't see, can't climb a tree)

Table 11. Infectious Urethritis: Gonococcal vs. Non-Gonococcal

	Gonococcal	Non-Gonococcal
Causative Organism	*Neisseria gonorrhoeae*	Usually *Chlamydia trachomatis*
Diagnosis	Hx of sexual contact, thick, profuse, yellow-grey purulent d/c, LUTS Gram stain (GN diplococci), urine PCR and/or culture from urethral specimen	Hx of sexual contact, mucoid whitish purulent d/c, ± storage LUTS Gram stain demonstrates >4 PMN/oil immersion field, no evidence of *N. gonorrhoeae*, urine PCR and/or culture from urethral specimen
Treatment	See Table 9	See Table 9

If culture negative or unresponsive to treatment consider: *Ureaplasma urealyticum, Mycoplasma genitalium, Trichimonas vaginalis*, HSV, or adenovirus

Stone Disease

Epidemiology
- prevalance of 2-3%
- M:F = 3:1
- peak incidence 30-50 yr of age
- recurrence rate: 10% at 1 yr, 50% at 5 yr, 60-80% lifetime

Risk Factors
- hereditary: RTA, Glucose-6-phosphate dehydrogenase deficiency, cystinuria, xanthinuria, oxaluria, etc.
- lifestyle: minimal fluid intake; excess vitamin C, oxalate, purines, calcium
- medications: loop diuretics (furosemide, bumetanide), acetazolamide, topiramate, and zonisamide
- medical conditions: UTI (with urea-splitting organisms: *Proteus, Pseudomonas, Providencia, Klebsiella, Mycoplasma, Serratia, S. aureus*), myeloproliferative disorders, IBD, gout, DM, hypercalcemia disorders (hyperparathyroidism, tumour lysis syndrome, sarcoidosis, histoplasmosis), obesity (BMI >30)

Key Points in Stone Hx
- Diet (especially FLUID INTAKE)
- Predisposing medical conditions
- Predisposing medications
- Previous episodes/investigations/treatments
- Family Hx (1st degree relative)

Clinical Features
- urinary obstruction → upstream distention → pain
  - flank pain from renal capsular distention (non-colicky)
  - severe waxing and waning pain radiating from flank to groin, testis, or tip of penis due to stretching of collecting system or ureter (ureteral colic)
- writhing, never comfortable, nausea, vomiting, hematuria (90% microscopic), diaphoresis, tachycardia, tachypnea
- occasionally symptoms of trigonal irritation (frequency, urgency)
- bladder stones result in: storage and voiding LUTS, terminal hematuria, suprapubic pain
- if fever, rule out concurrent pyelonephritis and/or obstruction

The four narrowest passage points for upper tract stones are:
- UPJ
- Pelvic brim
- Under vas deferens/broad ligament
- UVJ

Table 12. Differential Diagnosis of Renal Colic

GU	Abdominal	Neurological
• Pyelonephritis • Ureteral obstruction from other cause: UPJ obstruction, clot colic secondary to gross hematuria, sloughed papillae • Gynecological: ectopic pregnancy, torsion/rupture of ovarian cyst, PID	• AAA • Bowel ischemia • Pancreatitis • Other acute abdominal crisis	• Radiculitis (L1): herpes zoster, nerve root compression

Location of Stones
- calyx: may cause flank discomfort, persistent infection, persistent hematuria, or remain asymptomatic
- pelvis: tend to cause obstruction at UPJ, may cause persistent infection
- ureter: <5 mm diameter will pass spontaneously in 75% of patients

	Radiopaque	Radiolucent
KUB	Calcium Struvite Cystine	Uric acid Indinavir Atazanavir
CT	Calcium Struvite Cystine Uric acid	Indinavir Atazanavir

Stone Pathogenesis
- supersaturation of stone constituents (at appropriate temperature and pH)
- stasis, low flow, and low volume of urine (dehydration)
- crystal formation and stone nidus
- loss of inhibitory factors
  - citrate (forms soluble complex with calcium)
  - magnesium (forms soluble complex with oxalate)
  - pyrophosphate
  - Tamm-Horsfall glycoprotein

Approach to Renal Stones

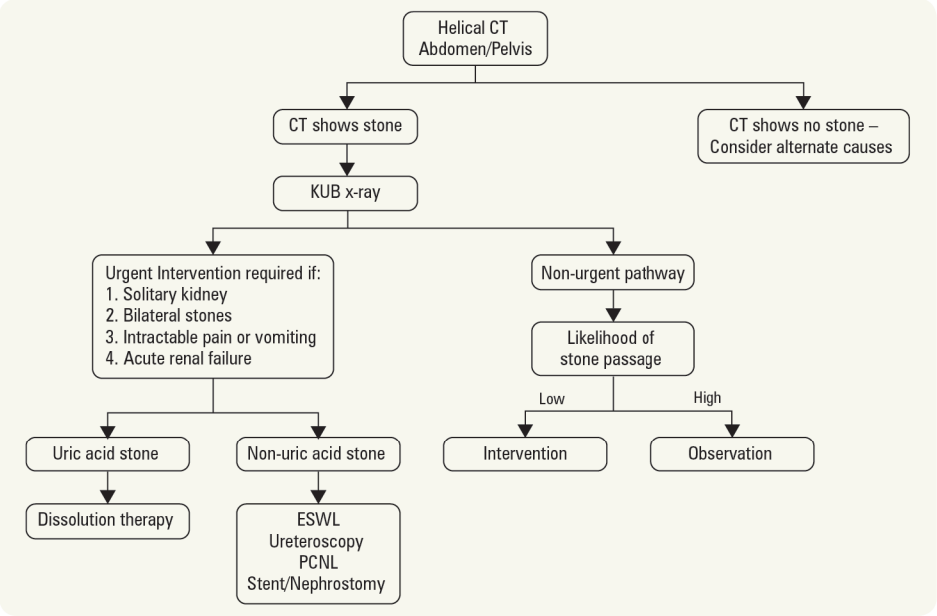


Figure 8. Approach to renal stone

Although hypercalciuria is a risk factor for stone formation, decreasing dietary calcium is NOT recommended to prevent stone formation. Low dietary calcium leads to increased GI oxalate absorption and higher urine levels of calcium oxalate

Stones and Infection
If septic, urgent decompression via ureteric stent or percutaneous nephrostomy is indicated. Definitive treatment of the stone should be delayed until the sepsis has cleared

Indications for PCNL
- Size >2 cm
- Staghorn
- UPJ obstruction
- Calyceal diverticulum
- Cystine stones (poorly fragmented with ESWL)
- Anatomical abnormalities
- Failure of less invasive modalities

Investigations

Table 13. Investigations for Renal Stones

	CBC, Uric Acid, U/A, Urine C&S	KUB x-ray	CT Scan	Abdominal Ultrasound	Cystoscopy	PTH, 24 h urine x 2 for volume, Cr, Ca^{2+}, Na^{+}, PO_4^{3-}, Mg^{2+}, oxalate, citrate, ± cystine
Who gets it?	Everyone	Most	First episode renal colic	Pediatric cases or those concerning for obstruction	± Those concerning for bladder stone	Recurrent Ca^{2+} stone formers ± pediatric cases
Why is it done?	May show signs of infection, ± sensitivities	90% of stones are radiopaque Good for follow-up	Distinguish radiolucent stone from soft tissue filling defect X-ray comparison	Identify and follow-up stone without radiation exposure Visualize hydronephrosis	Visualize bladder	Need to rule out metabolic cause for stones
Cautions	–	Do not mistake phleboliths for stones!	Radiation (especially if female of child bearing age) Must be a non-contrast scan	Not good at visualizing stones in ureter	–	–

Treatment – Acute

- medical
  - analgesic ± antiemetic
  - NSAIDs help lower intra-ureteral pressure
  - medical expulsion therapy (MET)
    - α-blockers: increase rate of spontaneous passage in distal ureteral stones
    - calcium channel blockers
  - ± Abx for bacteriuria
  - IV fluids if vomiting (note: IV fluids do NOT promote stone passage)
- interventional
  - required if obstruction endangers patient, e.g. sepsis, renal failure
  - first line: ureteric stent (via cystoscopy)
  - second line: image-guided percutaneous nephrostomy
- admit if necessary
  - *Indications for Admission to Hospital*

24 h urine collections must be done AFTER discontinuing stone preventing/promoting medications

Indications for Admission to Hospital
- Intractable pain
- Intractable vomiting
- Fever (suggests infection)
- Compromised renal function (including single kidney, bilateral obstructing stone)
- Pregnancy

Treatment – Elective

- medical
  - likely conservative if ureteral stone <10 mm or kidney stone <5 mm and no complications/symptoms well controlled
    - stones <5 mm especially likely to pass spontaneously
  - PO fluids to increase urine volume to >2 L/d (3-4 L if cystine) and MET
  - specific to stone type (see Table 14)
  - periodic imaging to monitor stone position and assess for hydronephrosis
  - progress to interventional stone removal methods if symptoms worsen or fail to improve (indicating stone passage)

Detailed metabolic studies are NOT recommended unless complex patient (recurrent stone formers, pregnancy, pediatrics, strong family Hx, underlying kidney or systemic disease, etc.)

- interventional
  - kidney
    - may stent prior to ESWL if stone is 1.5-2.5 cm
    - ESWL if stone <2 cm
    - PCNL if stone >2 cm
  - ureteral stones >10 mm
    - ESWL and URS are both first line treatment modalities for all locations
      - URS has significantly greater stone-free rates for stones at all locations in ureter, but also has higher complication rates (ureter perforation, stricture formation, etc.)
    - PCNL is second line treatment
    - laparoscopic or open stone removal (very rare)
  - bladder
    - transurethral stone removal or cystolitholapaxy
    - remove outflow obstruction (TURP or stricture dilatation)

Prevention

- dietary modification
  - increase fluid (>2 L/d), K^+ intake
  - reduce animal protein, oxalate, Na^+, sucrose, and fructose intake
  - avoid high-dose vitamin C supplements
- medications
  - thiazide diuretics for hypercalciuria
  - allopurinol for hyperuricosuria
  - potassium citrate for hypocitraturia, hyperuricosuria

Alpha-blockers as Medical Expulsive Therapy for Ureteral Stones
Cochrane DB Syst Rev 2014;4:CD008509
Purpose: To determine whether or not alpha blockers compared with other pharmacological treatments or placebo improve stone clearance rates and other clinically relevant outcomes in patients presenting with symptoms of stones less than 10mm confirmed by imaging.
Results/Conclusions: 32 RCTs, 5,864 participants. Although patients using alpha-blockers were more likely to experience adverse effects compared to standard therapy, stone-free rates were significantly higher in the alpha-blocker group (RR 1.48, 95% CI 1.33-1.64), expulsion time was 2.91 days shorter, and there was a reduction in the number of pain episodes (MD -0.48, 95% CI -0.94 to -0.01), the need for analgesic medication (MD -38.17, 95% CI -74.93 to -1.41), and hospitalization (RR 0.35, 95% CI 0.13-0.97). Alpha blockers should therefore be offered as a primary treatment modality for ureteral stones.

Consideration must be given to monitoring stone formers with periodic imaging (i.e. at year 1 and then q2-4yr based on likelihood of recurrence)

Table 14. Stone Classification

Type of Stone	Calcium (75-85%)	Uric Acid (5-10%)	Struvite (5-10%)	Cystine (1%)
Etiology	Hypercalciuria Hyperuricosuria (25% of patients with Ca^{2+} stones) Hyperoxaluria (<5% of patients) Hypocitraturia (12% of patients) Other causes: • Hypomagnesemia – associated with hyperoxaluria and hypocitraturia • High dietary Na^+ • Decreased urinary proteins • High urinary pH, low urine volume (e.g. GI water loss) • Hyperparathyroidism, obesity, gout, DM	Uric acid precipitates in low volume, acidic urine with a high uric acid concentration: • Hyperuricosuria alone • Low urinary pH, low urine volume (e.g. GI water loss) • Drugs (ASA, thiazides) • Diet (purine rich red meats) • Hyperuricosuria with hyperuricemia • Gout • High rate of cell turnover or cell death (leukemia, cytotoxic drugs)	Infection with urea-splitting organisms (*Proteus, Pseudomonas, Providencia, Klebsiella, Mycoplasma, Serratia, S. aureus*) results in alkaline urinary pH and precipitation of struvite (magnesium ammonium phosphate)	Autosomal recessive defect in small bowel mucosal absorption and renal tubular absorption of dibasic amino acids results in "COLA" in urine (cystine, ornithine, lysine, arginine)
Key Features	Radiopaque on KUB Reducing dietary Ca^{2+} is NOT an effective method of prevention/ treatment	Radiolucent on KUB Radiopaque on CT Acidic urine, pH <5.5 (NOT necessarily elevated urinary uric acid)	Perpetuates UTI because stone itself harbours organism Stone and all foreign bodies must be cleared to avoid recurrence Associated with staghorn calculi Positive urine dip and cultures Note: *E. coli* infection does not cause struvite stones M:F = 3:1, UTI more common in female	Aggressive stone disease seen in children and young adults Recurrent stone formation, family Hx Often staghorn calculi Faintly radiopaque on KUB Positive urine sodium nitroprusside test, urine chromatography for cystine
Treatment Medical if stone <5 mm and no complications Procedural/Surgical treatment if stone >5 mm or presence of complications (see U17 for treatment)	Fluids to increase urine volume to >2 L/d For calcium stones: cellulose phosphate, orthophosphate for absorptive causes Calcium oxalate: thiazides, ± potassium citrate, ± allopurinol Calcium struvite: ABx (stone must be removed to treat infection)	Increased fluid intake Alkalinization of urine to pH 6.5 to 7 (bicarbonate, potassium citrate) ± allopurinol	Complete stone clearance ABx for 6 wk Regular follow-up urine cultures	Increased fluid intake (3-4 L of urine/d) Alkalinize urine (bicarbonate, potassium citrate), Penicillamine/ α-MPG or Captopril (form complex with cystine) ESWL not effective

Urological Neoplasms

Approach to Renal Mass

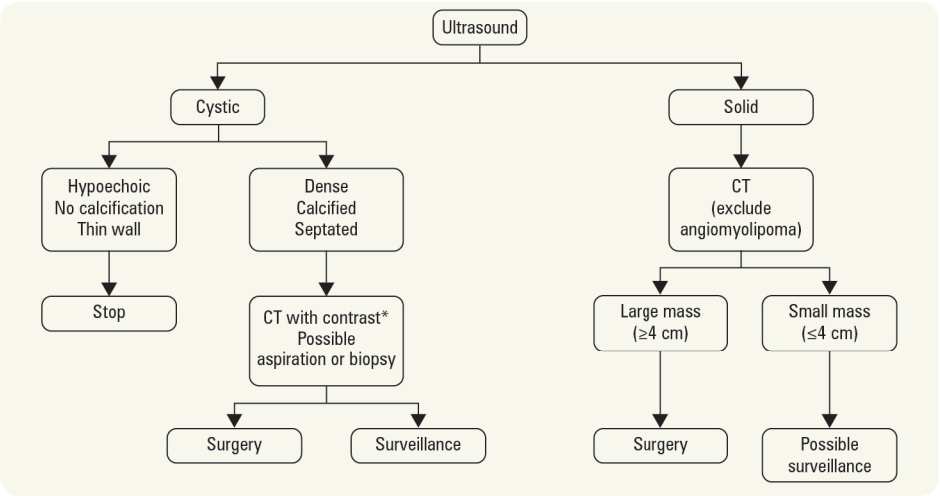


Figure 9. Workup of a renal mass
*Imaging modality may be different in cases of contrast allergy or elevated creatinine

There is controversy over optimal m[illegible]ement of small renal masses

Benign Renal Neoplasms

CYSTIC KIDNEY DISEASE

- **simple cysts**: usually solitary or unilateral
  - very common: up to 50% at age 50
  - usually incidental finding on abdominal imaging
  - **Bosniak Classification** is used to stratify for risk of malignancy based on cyst features from contrast CT
- **polycystic kidney disease**
  - autosomal recessive: multiple bilateral cysts, often leading to early renal failure in infants
  - autosomal dominant: progressive bilateral disease leading to HTN and renal failure, adult-onset
- **medullary sponge kidney**: cystic dilatation of the collecting ducts
  - usually benign course, but patients are predisposed to stone disease
- **von Hippel-Lindau syndrome**: multiple bilateral cysts or clear cell carincomas (50% incidence of RCC)
  - renal cysts, cerebellar, spinal and retinal hemangioblastomas, pancreatic and epididymal cysts, pheochromocytomas

Table 15. Bosniak Classification of Renal Cysts

Class	Description	Features	Risk of Malignancy	Management Plan
I	Simple cyst	Round, no septations, no calcifications, no solid component	Near zero	Follow-up usually not required
II	Simple cyst	A few thin septa, no true enhancement, well-marginated, uniform high attenuation, <3 cm	Minimal	Follow-up usually not required
IIF	Minimally complex cyst with extra features that require follow-up	Still well-marginated and non-enhancing, but now multiple thin septa or some thickening/ calcification of septa/wall, >3 cm	5-20%	Requires follow-up with imaging q6-12mo If the lesion evolves, may require surgical resection
III	Complex cyst	Thicker or more irregular walls with measurable enhancement	>50%	Requires surgical resection
IV	Clearly malignant	Class III + enhancing soft-tissue components	>90%	Requires surgical resection

Table 16. Benign Renal Masses

	Angiomyolipoma (Renal Hamartoma)	Renal Oncocytoma	Renal Adenoma
Epidemiology	<1% of adult renal tumours F>M 20% associated with tuberous sclerosis (especially if multiple, recurrent)	3-7% of renal tumours M>F Oncocytomas also found in adrenal, thyroid and parathyroid glands	Most common benign renal neoplasm M:F = 3:1 Incidence increases with age Found in 7-23% of all autopies
Characteristics	Clonal neoplasm consisting of blood vessels (angio-), smooth muscle (-myo-), and fat (-lipoma) May extend into regional lymphatics and other organs and become symptomatic	Spherical, capsulated with possible central scar Histologically organized aggregates of eosinophilic cells originating from intercalated cells of collecting duct	Small cortical lesions <1 cm Majority are solitary but can be multifocal
Diagnosis	Incidental finding on CT Negative attenuation (-20 HU) on CT is pathognomonic Rare presentation of hematuria, flank pain, and palpable mass (same as RCC)	Incidental finding on CT Difficult to distinguish from RCC on imaging – treated as RCC until proven otherwise Biopsy may be performed to rule out malignancy	Incidental finding on CT Rarely symptomatic Controversy as to whether this represents benign or pre-malignant neoplasm
Management	May consider surgical excision or embolization if symptomatic (pain, bleeding) or higher risk of bleeding (e.g. pregnancy) Potential role for mTOR inhibitors in unresectable/ metastatic disease Follow with serial U/S	Partial/radical nephrectomy for large masses HIFU or RFA for smaller masses	If mass >3 cm, likely not a benign adenoma; will require partial/radical nephrectomy due to increased likelihood of malignancy

Malignant Renal Neoplasms

RENAL CELL CARCINOMA

Etiology
- cause unknown
- originates from proximal convoluted tubule epithelial cells in clear cell subtype (most common)
- hereditary forms seen with von Hippel-Lindau syndrome and hereditary papillary renal carcinoma

Epidemiology
- 8th most common malignancy (accounts for 3% of all newly diagnosed cancers)
- 85% of primary malignant tumours in kidney
- M:F = 3:2
- peak incidence at 50-60 yr of age

Pathology
- histological subtypes: clear cell (75-85%), papillary (10-15%), chromophobic (5-10%), collecting duct
- sarcomatoid elements in any subtype is a poor prognostic factor

Risk Factors
- top 3 risk factors: smoking, HTN, obesity
- miscellaneous: horseshoe kidney, acquired renal cystic disease
- role of environmental exposures (aromatic hydrocarbons, etc.) remains an unproven risk factor for development of RCC

Clinical Features
- usually asymptomatic: frequently diagnosed incidentally by U/S or CT
- poor prognostic indicators: weight loss, weakness, anemia, bone pain
- classic "too late triad" found in 10-15%
  - gross hematuria 50%
  - flank pain <50%
  - palpable mass <30%
- was called the "internist's tumour" because of paraneoplastic symptomatology – now called the "radiologist's tumour" because of incidental diagnosis via imaging
- metastases: seen in 1/3rd of new cases; additional 20-40% will go on to develop metastases
  - bone, brain, lung and liver most common site
  - may invade renal veins and inferior vena cava lumen. This may result in ascites, hepatic dysfunction, right atrial tumour, and pulmonary emboli

Investigations
- routine labs for paraneoplastic syndromes (CBC, ESR, LFTs, extended electrolytes)
- U/A (60-75% have hematuria)
- renal U/S: solid vs. cystic lesion

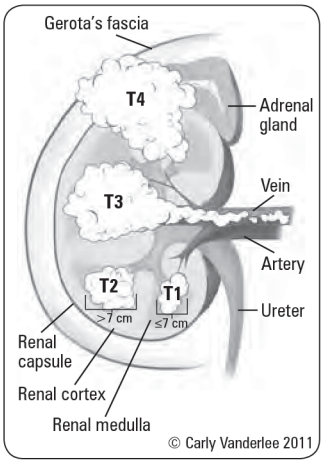


Figure 10. RCC staging

Role of environmental exposures (aromatic hydrocarbons, etc.) remains an unproven risk factor for development of RCC

RCC Systemic Effects: paraneoplastic syndromes (10-40% of patients)
- Hematopoietic disturbances: anemia, polycythemia, raised ESR
- Endocrinopathies: hypercalcemia (increased vitamin D hydroxylation), erythrocytosis (increased erythropoietin), HTN (increased renin), production of other hormones (prolactin, gonadotropins, TSH, insulin, and cortisol)
- Hepatic cell dysfunction or Stauffer syndrome: abnormal LFTs, decreased WBC count, fever, areas of hepatic necrosis; no evidence of metastases; reversible following removal of primary tumour
- Hemodynamic alterations: systolic HTN (due to AV shunting), peripheral edema (due to caval obstruction)

- contrast-enhanced CT: higher sensitivity than U/S for detection of renal masses and for staging purposes
- MRI: useful for evaluation of vascular extension
- renal biopsy: to confirm diagnosis if considering observation or other non-surgical therapy

Tumour may invade renal veins and inferior vena cava lumen. This may result in ascites, hepatic dysfunction, right atrial tumour, and pulmonary emboli

Staging
- involves CT, CXR, liver enzymes and LFTs, bone/head imaging (if symptoms dictate)

Table 17. 2010 TNM Classification of Renal Cell Carcinoma

T	N	M
T1: tumour <7 cm, confined to renal parenchyma **T1a**: <4 cm **T1b**: 4-7 cm **T2**: tumour >7 cm, confined to renal parenchyma **T2a**: tumour >7 cm but ≤10 cm in greatest dimension, limited to the kidney **T2b**: tumour >10 cm, limited to the kidney **T3**: tumour extends into major veins or perinephric tissues, but NOT into ipsilateral adrenal or beyond Gerota's fascia **T3a**: into renal vein or sinus fat **T3b**: into infradiaphragmatic IVC **T3c**: into supradiaphragmatic IVC **T4**: tumour extends beyond Gerota's fascia including extension into ipsilateral adrenal	**N0**: no regional nodes **N1**: metastasis to a single node, <2 cm **N2**: metastasis to a single node between 2-5 cm or multiple nodes <2 cm **N3**: node >5 cm	**M0**: no evidence of metastasis **M1**: presence of distant metastasis

Treatment
- surgical
  - radical nephrectomy: en bloc removal of kidney, tumour, ipsilateral adrenal gland (in upper pole tumours) and intact Gerota's capsule and paraaortic lymphadenectomy
  - partial nephrectomy (parenchyma-sparing): small tumour (roughly <4 cm) or solitary kidney/bilateral tumours
  - surgical removal of solitary metastasis may be considered
- ablative techniques (cryoablation, RFA)
- palliative radiation to painful bony lesions
- therapy for advanced stage
  - tyrosine kinase inhibitors for metastatic disease (e.g. sunitinib, sorafenib)
  - anti-angiogenesis/anti-VEGF (e.g. bevacizumab)
  - mTOR inhibitors (e.g. temsirolimus, everolimus)
  - high-dose IL-2 (high toxicity but able to induce long-term cure in 5-7% of patients)
  - IFN α: monotherapy has been largely replaced by molecularly targeted agents listed above

Sorafenib in Advanced Clear-Cell Renal Cell Carcinoma – TARGET Trial
NEJM 2007;356:125-134
Study: Phase III, double-blind RCT comparing multikinase inhibitor, sorafenib, with placebo in treatment of advanced clear-cell renal cell carcinoma.
Methods: Patients with clear cell renal cell carcinoma, resistant to standard therapy. The main intervention and outcome were sorafenib and overall survival, respectively.
Results: Progression-free survival in intervention group was 5.5 mo, compared with 2.8 mo in the placebo group. The survival improvement was associated with an increased number of adverse events.

Prognosis
- stage at diagnosis most important prognostic factor
  - T1: 90-100% 5 yr survival
  - T2-T3: 60% 5 yr survival
  - metastatic disease: <5% 10 yr survival

Axitinib vs. Sorafenib as Second-Line Treatment for Advanced Renal Cell Carcinoma: Overall Survival Analysis and Updated Results from a Randomized Phase 3 Trial
Lancet Oncol 2013;14:552-562
Study: Phase 3 trial of patients with clear cell metastatic renal cell carcinoma randomized to receive axitinib 5 mg twice daily (n=361) or sorafenib 400 mg twice daily (n=362).
Results: Median overall survival was 20.1 mo with axitinib (16.7 -23.4) and 19.2 monwith sorafenib (17.5-22.3) (HR 0.969, 95% CI 0.800-1.174). Median progression-free survival was 8.3 months with axitinib (6.7-9.2) and 5.7 mo with sorafenib (4.7-6.5) (HR 0.656, 95% CI 0.552-0.779).
Conclusions: Axitinib should be a second-line treatment option for patients with metastatic renal cell carcinoma.

Carcinoma of the Renal Pelvis and Ureter

Etiology
- risk factors include
  - smoking
  - chemicals/dietary exposures (industrial dyes and solvents; aristolochic acid)
  - analgesic abuse (acetaminophen, ASA, and phenacetin)
  - Balkan nephropathy

Epidemiology
- rare: accounts for 5% of all urothelial cancers
- frequently multifocal, 2-5% are bilateral
- M:F = 3:1
- relative incidence: bladder:renal:ureter = 100:10:1

Radiotherapy With or Without Chemotherapy in Muscle-Invasive Bladder Cancer
NEJM 2012;366:1477-1488
Study: Phase 3 trial with random assignment of 360 patients with muscle-invasive bladder cancer to radiotherapy with or without chemotherapy.
Results: At 2 yr, rates of locoregional disease-free survival were 67% in the chemoradiotherapy group and 54% in the radiotherapy group (HR 0.68, 95% CI 0.48-0.96). Five year overall survival rates were 48% in the chemoradiotherapy group and 35% in the radiotherapy group (HR 0.82, 95% CI 0.63-1.09).
Conclusions: Chemotherapy with fluorouracil and mitomycin C in combination with radiotherapy improves locoregional control of bladder cancer compared to radiotherapy alone, with no significant increase in adverse events.

Pathology
- 85% are papillary urothelial cell carcinoma; others include SCC and adenocarcinoma
- UCC of ureter and renal pelvis are histologically similar to bladder UCC

Clinical Features
- gross/micrscopic hematuria
- flank pain
- storage or voiding symptoms (dysuria only if lower urinary tract involved)
- flank mass ± hydronephrosis (10-20%)

Investigations
- IVP/CT urogram
- cystoscopy and retrograde pelogram

Treatment
- radical nephroureterectomy with cuff of bladder
- distal ureterectomy for distal ureteral tumours
- emerging role for endoscopic laser ablation in patients with low grade disease, poor baseline renal health

Differential Diagnosis of Filling Defect
- Urothelial carcinoma (differentiate via cytology and CT scan)
- Uric acid stone (differentiate via cytology and CT scan)
- Blood clot
- Pyelitis cystica
- Papillary necrosis
- Fungus ball
- Gas bubble from gas producing organisms

Bladder Carcinoma

Etiology
- unknown, but environmental risk factors include
  - smoking (main factor – implicated in 60% of new cases)
  - aromatic amines: naphthylamines, benzidine, tryptophan, phenacetin metabolites
  - cyclophosphamide
  - prior Hx of radiation treatment to the pelvis
  - *Schistosoma hematobium* infection (associated with SCC)
  - chronic irritation: cystitis, chronic catheterization, bladder stones (associated with SCC)
  - aristolochic acid: associated with Balkan Nephropathy (renal failure, upper tract urothelial cancer) and Chinese Herbal Nephropathy

Epidemiology
- 2nd most common urological malignancy
- M:F = 3:1, more common among whites than blacks
- mean age at diagnosis is 65 yr

Pathology
- classification
  - UCC >90%
  - SCC 5-7%
  - adenocarcinoma 1%
  - others <1%
- stages and prognoses of urothelial carcinoma at diagnosis
  - non-muscle invasive (75%) → >80% overall survival
    - 15% of these will progress to invasive UCC
    - the majority of these patients will have recurrence
  - invasive (25%) → 50-60% 5 yr survival
    - 85% have no prior Hx of superficial UCC (i.e. *de novo*)
    - 50% have occult metastases at diagnosis, and most of these will develop overt clinical evidence of metastases within 1 yr – lymph nodes, lung, peritoneum, liver
- carcinoma *in situ* → flat, non-papillary erythematous lesion characterized by dysplasia confined to urothelium
  - more aggressive, worse prognosis
  - usually multifocal
  - may progress to invasive UCC

The "field defect" theory helps to explain why UCC has multiple lesions and has a high recurrence rate. The entire urothelium (pelvis to bladder) is bathed in carcinogens

Clinical Features
- asymptomatic (20%)
- hematuria (key symptom: 85-90% at the time of diagnosis)
- pain (50%) → location determined by size/extent of tumour (i.e. flank, suprapubic, perineal, abdominal, etc.)
- clot retention (17%)
- storage urinary symptoms → consider carcinoma *in situ*
- palpable mass on bimanual exam → likely muscle invasion
- obstruction of ureters → hydronephrosis and uremia (nausea, vomiting, and diarrhea)

The ENTIRE urinary tract must be evaluated in patients with hematuria unless there is clear evidence of glomerular bleeding (e.g. red cell casts, dysmorphic RBCs, etc.)

Investigations
- U/A, urine C&S, urine cytology
- U/S
- CT scan with contrast → look for filling defect
- cystoscopy with biopsy (gold standard)
- biopsy to establish diagnosis and to determine depth of penetration
- specific bladder tumour markers (e.g. NMP-22, BTA, Immunocyt, FDP)

Cystoscopy is the initial procedure of choice for the diagnosis and staging of urothelial malignancy

Unexplained hematuria in any individual >40 yr old must be investigated to rule out a malignancy

Grading
- low grade: <=10% invasive, 60% recur
- high grade: 50-80% are invasive or should progress to invasive over time

Tumour grade is the single most important prognostic factor for progression

Staging
- for invasive disease: CT or MRI, CXR, LFTs, extended electrolytes (Ca^{2+}, Mg^{1+}, PO_4^{3-}) (metastatic workup)

Table 18. 2010 TNM Classification of Bladder Carcinoma

T	N	M
TX: Primary tumour cannot be assessed	**NX:** Lymph nodes cannot be assessed	**M0:** No distant metastasis
T0: No evidence of primary tumour	**N0:** No lymph node metastasis	**M1:** Distant metastasis
Ta: Noninvasive papillary carcinoma	**N1:** Single regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac, or presacral lymph node)	
Tis: Carcinoma *in situ*: "flat tumour"	**N2:** Multiple regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac, or presacral lymph node metastasis)	
T1: Tumour invades subepithelial connective tissue	**N3:** Lymph node metastasis to the common iliac lymph nodes	
T2: Tumour invades muscularis propria		
pT2a: Tumour invades superficial muscularis propria (inner half)		
pT2b: Tumour invades deep muscularis propria (outer half)		
T3: Tumour invades perivesical tissue		
pT3a: Microscopically		
pT3b: Macroscopically (extravesical mass)		
T4: Tumour invades any of the following: prostatic stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall		
T4a: Tumour invades prostatic stroma, uterus, vagina		
T4b: Tumour invades pelvic wall, abdominal wall		

Neoadjuvant Chemotherapy plus Cystectomy Compared with Cystectomy Alone for Locally Advanced Bladder Cancer
NEJM 2003;349:859-866
Study: Randomized clinical trial.
Patients: 317 patients with transitional-cell carcinoma of the bladder (T2N0M0 to T4aN0M0).
Intervention: Randomized to undergo radical cystectomy or to receive three cycles of combined chemotherapy (methotrexate, vinblastine, doxorubicin, and cisplatin) followed by radical cystectomy.
Main Outcome: Survival. Secondary objective was to quantify down-staging of tumour following chemotherapy.
Results: At 5 yr after treatment initiation, 57% of the combination-therapy group vs. 43% of the cystectomy group were alive (p=0.06). In the combination-therapy group, 38% of the patients were pathologically free of cancer at the time of cystectomy vs. 15% of the cystectomy-only group at the time of surgery (p<0.001).
Conclusions: For locally advanced bladder carcinoma, neoadjuvant chemotherapy significantly reduces tumour volume and also improves survival.

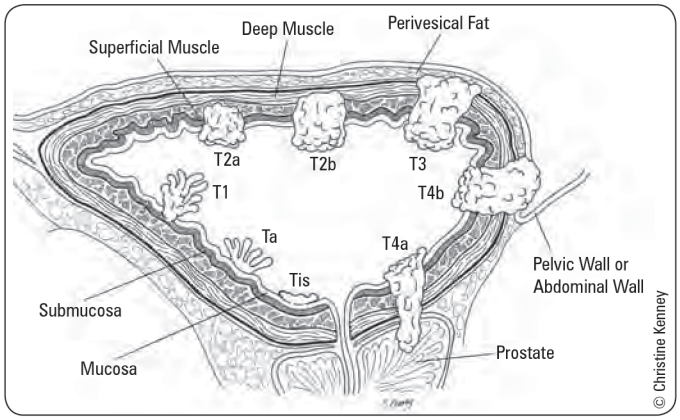


Figure 11. Urothelial carcinoma of bladder

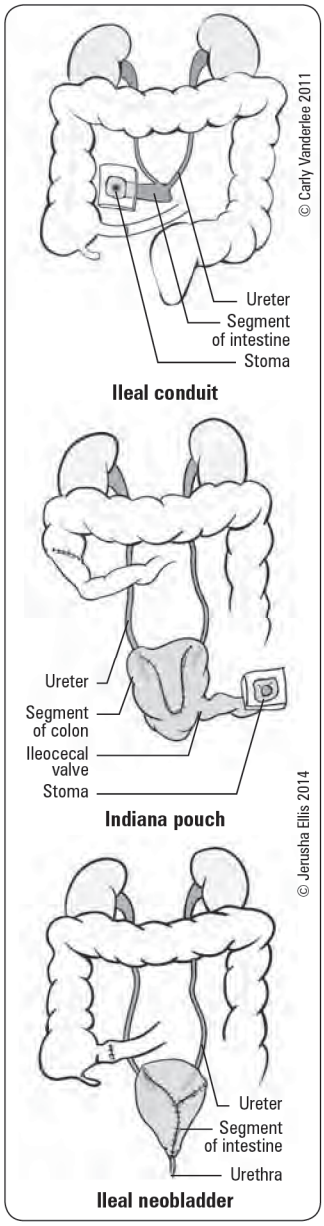


Figure 12. Ileal conduit, Indiana pouch, ileal neobladder

Treatment

- superficial (non-muscle invasive) disease: Tis, Ta, T1
  - low-grade disease
    - single dose mitomycin c within 24 hours of resection reduces recurrence rates
  - high-grade
    - TURBT ± intravesical chemo/immuno-therapy (e.g. BCG, mitomycin C) to decrease recurrence rate
    - maintenance with intravesical chemotherapy with BCG for 3 cycles every 3 mo, may be continued for 2-3 yr
- invasive disease: T2a, T2b, T3
  - radical cystectomy + pelvic lymphadenectomy with urinary diversion (e.g. ileal conduit, Indiana pouch, ileal neobladder) or TURBT + chemo-radiation (bladder sparing) for small tumours with non-obstructed ureters
  - neo-adjuvant chemotherapy prior to cystectomy may also be done
  - use of adjuvant chemotherapy after definitive local treatment is controversial
- advanced/metastatic disease: T4a, T4b, N+, M+
  - initial combination of systemic chemotherapy ± irradiation ± surgery

Prognosis

- depends on stage, grade, size, number of lesions, recurrence and presence of CIS
  - T1: 90% 5 yr survival
  - T2: 55% 5 yr survival
  - T3: 20% 5 yr survival
  - T4/N+/M+: <5% 5 yr survival

Prostate Cancer

Etiology

- not known
- risk factors
  - increased incidence in persons of African descent
  - high dietary fat = 2x risk

- family Hx
  - 1st degree relative = 2x risk
  - 1st and 2nd degree relatives = 9x risk

Epidemiology
- most prevalent cancer in males
- 3rd leading cause of male cancer deaths (following lung and colon)
- up to 50% risk of CaP at age 50
- lifetime risk of death from CaP is 3%
- 75% diagnosed between ages of 60 and 85; mean age at diagnosis is 72

Pathology
- adenocarcinoma
  - >95%, often multifocal
- urothelial carcinoma of the prostate (4.5%)
  - associated with UCC of bladder; does NOT follow TNM staging below; not hormone-responsive
- endometrial (rare)
  - carcinoma of the utricle

Anatomy (see Figure 7, U7)
- 60-70% of nodules arise in the peripheral zone
- 10-20% arise in the transition zone
- 5-10% arise in the central zone

Clinical Features
- usually asymptomatic
- most commonly detected by DRE, elevated PSA, or as an incidental finding on TURP
  - DRE: hard irregular nodule or diffuse dense induration involving one or both lobes
  - PSA: see *Prostate Cancer Screening*, U26
- locally advanced disease
  - storage and voiding symptoms, ED (all uncommon without spread)
- metastatic disease
  - bony metastases to axial skeleton common
  - visceral metastases are less common (liver, lung, and adrenal gland most common sites)
  - leg pain and edema with nodal metastases obstructing lymphatic and venous drainage

Methods of Spread
- local invasion
- lymphatic spread to regional nodes
  - obturator > iliac > presacral/para-aortic
- hematogenous dissemination occurs early

Investigations
- DRE
- PSA elevated in the majority of patients with CaP
- TRUS-guided needle biopsy
- bone scan may be omitted in untreated CaP with PSA <10 ng/mL
- CT scanning to assess metastases
- MRI: being investigated for possible role in detection, staging, MRI-guided biopsying and active surveillance

Table 19. 2010 TNM Classification of Prostate Carcinoma

T	N	M
T1: clinically undetectable tumour, normal DRE and TRUS **T1a**: tumour incidental histologic finding in <5% of tissue resected **T1b**: tumour incidental histologic finding in >5% of tissue resected **T1c**: tumour identified by needle biopsy (due to elevated PSA level) **T2**: palpable, confined to prostate **T2a**: tumour involving ≤ one half of one lobe **T2b**: tumour involving > one half of one lobe, but not both lobes **T2c**: tumour involving both lobes **T3**: tumour extends through prostate capsule **T3a**: extracapsular extension (unilateral or bilateral) **T3b**: tumour invading seminal vesicle(s) **T4**: tumour invades adjacent structures (besides seminal vesicles)	**NX**: regional lymph nodes were not assessed **N0**: no regional lymph node metastasis **N1**: spread to regional lymph nodes	**M0**: no distant metastasis **M**: distant metastasis **M1a**: nonregional lymph nodes **M1b**: bone(s) **M1c**: other site(s) with or without bone disease

Table 20. Prostate Cancer Mortality Risk

	Low Risk	Intermediate Risk (if any of following)	High Risk (if any of following)
PSA	<10	10-20	>20
Gleason Score	<7	7	8-10
Stage	pT1-2a	pT2b-T2c	pT3/4

Treatment
- T1/T2 (localized, low-risk)
  - if adequate life expectancy or no other significant comorbidities, consider active surveillance vs. definitive local treatment (RP, brachytherapy, or EBRT)
  - no difference in cure rate between definitive treatment modalities
  - in older population: watchful waiting + palliative treatment for symptomatic progression
- T1/T2 (intermediate or high-risk)
  - definitive therapy over active surveillance
- T3, T4
  - EBRT + androgen deprivation therapy or RP + adjuvant EBRT
- N >0 or M >0
  - requires hormonal therapy/palliative radiotherapy for metastases; may consider combined androgen blockade
  - bilateral orchiectomy – removes 90% of testosterone
  - GnRH agonists (e.g. leuprolide, goserelin)
  - GnRH antagonist (e.g. degarelix)
  - estrogens (e.g. diethylstilbestrol [DES])
  - antiandrogens (e.g. bicalutamide)
  - local irradiation of painful secondaries or half-body irradiation
- hormone-refractory prostate cancer
  - chemotherapy: docetaxel, cabazitaxel, sipuleucel-T

Table 21. Treatment Options for Localized Prostate Cancer

Modality	Population Considered	Limitations
Watchful Waiting	Short life expectancy (<5-10 yr); will likely only receive non-curative hormonal therapy if disease progresses	Disease progression
Active Surveillance (serial PSA, DRE, and biopsies)	Low grade disease, good follow-up; is still considering more curative treatment if disease progresses	Disease progression; decrease in QOL associated with serial testing; risks associated with biopsies; no optimal monitoring schedule has been defined to date
Brachytherapy	Low volume, low PSA (<10), low grade	ED (50%), long-term effectiveness not well-established
EBRT	Locally advanced disease, older patients	Radiation proctitis (5%), ED (50%), risk of rectal cancer
RP	Young patients (<75 yr), high-risk disease	Incontinence (10%), ED (30-50%)

*Other options include cryosurgery, HIFU, hormonal ablation

Radical Prostatectomy vs. Watchful Waiting in Early Prostate Cancer (Scandinavian Prostate Cancer Group Study)
NEJM 2011;364:1708-1717
Study: Randomized clinical trial comparing watchful waiting with radical prostatectomy for localized prostate cancer.
Methods: 695 men from 14 centres in Finland, Sweden, and Iceland with newly diagnosed, localized prostate cancer were included in this study.
Main Outcomes: Mortality, distant metastases, local progression.
Results: For men with low-risk prostate cancer (PSA<10, Gleason score<7), at 15 yr after treatment initiation, the relative risk of death due to prostate cancer in the radical prostatectomy group versus watchful waiting was 0.62 (p=0.01). The cumulative incidence of death from prostate cancer after radical prostatectomy was high as compared with other studies.
Conclusions: Radical prostatectomy was associated with reduced rate of death due to prostate cancer.

Radical Prostatectomy vs. Observation for Localized Prostate Cancer (Prostate Cancer Intervention vs. Observation Trial (PIVOT) Study Group)
NEJM 2012;367:203-213
Study: Randomized clinical trial comparing observation with radical prostatectomy for localized prostate cancer.
Methods: 731 men at 52 United States centres with localized prostate cancer participated.
Main Outcomes: Mortality, bone metastases, surgical morbidity.
Results: Radical prostatectomy did not reduce all-cause or prostate cancer mortality relative to observation (relative risk 0.60, p=0.09), through at least 12 yr of follow-up.
Conclusions: Observation is recommended for localized prostate cancer, especially in men with low PSA and low-risk disease.

Prognosis
- T1-T2: comparable to normal life expectancy
- T3-T4: 40-70% 10-yr survival
- N+ and/or M+: 4 % 5 yr survival
- prognostic factors: tumour stage, tumour grade, PSA value, PSA doubling time

Prostate Cancer Screening

Digital Rectal Exam
- should be included as part of initial screening
- suspicious findings: abnormal feeling, nodularity, focal lesion, discrete change in texture/fullness/symmetry

Prostate Specific Antigen
- glycoprotein produced by epithelial cells of prostate gland
- leaks into circulation in setting of disrupted glandular architecture
- value of <4 ng/mL traditionally considered as cut-off to differentiate normal from pathologic value, but no single justifiable cutpoint
- measured serum PSA is a combination of free (15%) and bound PSA (85%)
- PSA velocity, PSA density, and free:total PSA: all intended to increase sensitivity and specificity of serum PSA values
  - association of increased CaP rates with decreased free are total PSA, elevated PSA velocity and density

Causes of Increased PSA
BPH, prostatitis, prostatic ischemia/infarction, prostate biopsy/surgery, prostatic massage, acute urinary retention, urethral catheterization, cystoscopy, TRUS, strenuous exercise, perineal trauma, ejaculation, acute renal failure, coronary bypass graft, radiation therapy

PSA is specific to the PROSTATE, but NOT to prostate cancer

Screening Recommendations
- conflicting evidence regarding mortality reduction with PSA-based screening and debate regarding overdiagnosis/overtreatment

- Long-Term Care and United States Preventative Services Task Force all recommend against PSA testing as a population-wide screening tool
- however, serum PSA screening recommended in any man with >10 yr life-expectancy and any of the following
  - suspicious finding on DRE
  - moderate-severe LUTS
  - high risk individuals
  - investigating secondary carcinoma of unknown origin to rule out CaP as primary

Canadian Urological Association Guidelines (2011) re: CaP Screening
- harms and benefits of PSA testing must be explained to the patient and an informed, shared decision to test must be established
- initial screening should include both serum PSA and DRE
- all men should be offered screening at age 50 if >10 yr life-expectancy
- high-risk individuals (family Hx of CaP or African ancestry) should be offered screening at age 40 if >10 yr life-expectancy
- standard has been annual screening, but q2-4yr screening acceptable
- no strict cutpoint for when to biopsy. Decision to biopsy should be based on more than a single PSA value

*new guidelines under development, however, AUA guidelines recommend against universal routine PSA screening for CaP

Screening for Prostate Cancer
Cochrane DB Syst Rev 2013;1:CD004720
Background: Screening for prostate cancer has an unclear benefit for reducing prostate cancer-specific mortality and morbidity.
Study: Systematic review of randomized clinical trials of screening vs no screening. A total of 31 trials were retrieved for this review.
Results: A meta-analysis of 5 RCTs with 341,342 participants was done. Collectively, there was no significant reduction in prostate cancer-specific mortality within 10 yr of follow-up. Screening procedures and biopsies were commonly associated with bleeding, bruising, and short-term anxiety; subsequent over-diagnosis and overtreatment resulted in additional harms, some severe.
Conclusions: Men who have a life expectancy less than 10-15 yr should be informed that screening for prostate cancer is unlikely to be beneficial. Significant harms are associated with screening, over-diagnosis, and overtreatment.

Testicular Tumours

Etiology/Risk Factors
- cryptorchidism, atrophy, sex hormones, HIV infection, infertility, family Hx, past Hx of testicular cancer

Epidemiology
- rare, but most common solid malignancy in young males 15-34 yr
- any solid testicular mass or acute hydrocoele in young patient – must rule out malignancy
- slightly more common in right testis (corresponds with slightly higher incidence of right-sided cryptorchidism)
- 2-3% bilateral (simultaneously or successively)

Pathology
- primary
  - 1% of all malignancies in males
  - cryptorchidism has increased risk (10-40x) of malignancy
  - 95% are germ cell tumours (all are malignant)
    - seminoma (35%) → classic, anaplastic, spermatocytic
    - NSGCT → embryonal cell carcinoma (20%), teratoma (5%), choriocarcinoma (<1%), yolk sac (<<1%), mixed cell type (40%)
  - 5% are non-germ cell tumours (usually benign) → Leydig (testosterone, precocious puberty), Sertoli (gynecomastia, decreased libido)
- secondary
  - male >50 yr
  - usually lymphoma or metastases (e.g. lung, prostate, GI)

Clinical Features
- **painless** testicular enlargement (painful if intratesticular hemorrhage or infarction)
- dull, heavy ache in lower abdomen, anal area or scrotum
- associated hydrocele (10%)
- coincidental trauma (10%)
- infertility (rarely presenting complaint)
- gynecomastia due to secretory tumour effects
- supraclavicular and inguinal lymphadenopathy
- abdominal mass (retroperitoneal lymph node mets)

Methods of Spread
- local spread follows lymphatics
  - right → medial, paracaval, anterior and lateral nodes
  - left → left lateral and anterior paraaortic nodes
  - "cross-over" metastases from right to left are fairly common, but no reports from left to right
- hematogenous most commonly to lung, liver, bones, and kidney

Investigations
- diagnosis is established by pathological evaluation of specimen obtained by radical inguinal orchidectomy
- tumour markers (β-hCG, LDH, AFP)
  - β-hCG and AFP are positive in 85% of non-seminomatous tumours
  - elevated marker levels return to normal post-operatively if no metastasis
  - β-hCG positive in 7% of pure seminomas, AFP never elevated with seminoma
- testicular U/S (hypoechoic area within tunica albuginea = high suspicion of testicular cancer)
- evidence of testicular microlithiasis is not a risk factor for testicular cancer
- needle aspiration contraindicated

Testes and scrotum have different lymphatic drainage, therefore trans-scrotal approach for biopsy or orchiectomy should be avoided

Staging
- Clinical: CXR (lung mets), markers for staging (β-hCG, AFP, LDH), CT abdomen/pelvis (retroperitoneal lymphadenopathy)
  - Stage I: disease limited to testis, epididymis, or spermatic cord
  - Stage II: disease limited to the retroperitoneal nodes
  - Stage III: disease metastatic to supradiaphragmatic nodal or visceral sites

Table 22. 2010 TNM Classification of Testicular Carcinoma

T	N	M
Tis: intratubular germ cell neoplasia **T1**: limited to testis and epididymis without vascular/lymphatic invasion **T2**: limited to testis and epididymis with vascular/lymphatic invasion **T3**: invasion of the spermatic cord ± vascular/lymphatics **T4**: invasion of the scrotum ± vascular/lymphatics	**N** status: same as RCC	**M0**: no distant mets **M1**: distant mets **M1a**: nonregional lymph node(s) or pulmonary mets **M1b**: distant mets other than to regional lymph nodes and lung

Management
- orchiectomy through inguinal ligament for all stages
- consider sperm banking, testicular prosthesis
- adjuvant therapies

Orchiopexy
Surgical descent (orchiopexy) of undescended testis does not eliminate the risk of malignancy, but allows for earlier detection by self-examination and reduces the risk of infertility

Prognosis
- 99% cured with stage I and II disease
- 70-80% complete remission with advanced disease

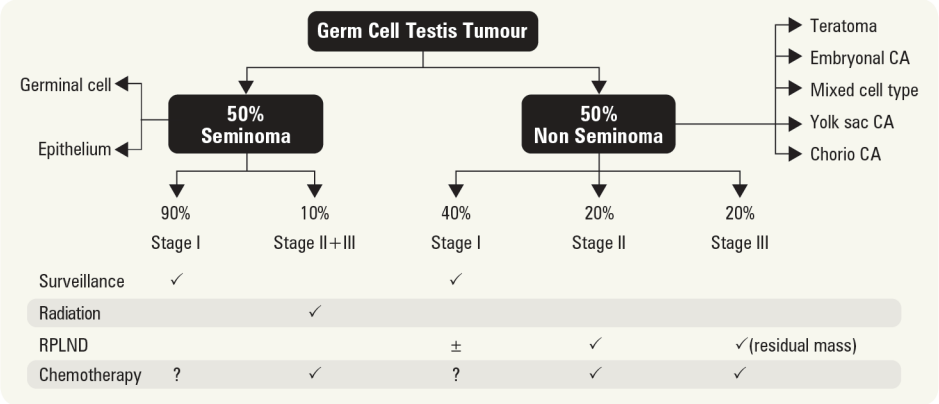


Figure 13. Adjuvant management of testicular cancer post-orchiectomy
Adapted from Dr. MAS Jewett

Penile Tumours

Epidemiology
- rare (<1% of cancer in males in U.S.)
- most common in 6th decade

Benign
- cyst, hemangioma, nevus, papilloma

Pre-Malignant
- balanitis xerotica obliterans, leukoplakia, Buschke-Lowenstein tumour (large condyloma)

Pre-invasive Cancer
- carcinoma *in situ*
  - Bowen's disease → crusted, red plaques on the shaft
  - erythroplasia of Queyrat → velvet red, ulcerated plaques on the glans
  - treatment options: local excision, laser, radiation, topical 5-fluorouracil

Malignant
- risk factors
  - chronic inflammatory disease
  - STI
  - phimosis
  - uncircumcised penis
- 2% of all urogenital cancers
- SCC (>95%), basal cell, melanoma, Paget's disease of the penis (extremely rare)
- definitive diagnosis requires full thickness biopsy of lesion
- lymphatic spread (superficial/deep inguinal nodes → iliac nodes) >> hematogenous

Treatment
- wide surgical excision with tumour-free margins (dependent on extent and area of penile involvement) ± lymphadenectomy
- consider less aggressive treatment modalities in CIS (cryotherapy, laser therapy, etc.) if available

Scrotal Mass

Table 23. Differentiating between Scrotal Masses

Condition	Pain	Palpation	Additional Findings
Torsion	+	Diffuse tenderness Horizontal lie of testicle	Absent cremaster reflex, negative Prehn's sign
Epididymitis (U16)	+	Epididymal tenderness	Present cremaster reflex, positive Prehn's sign
Orchitis (U16)	+	Diffuse tenderness	Present cremaster reflex, positive Prehn's sign
Hematocele	+	Diffuse tenderness	No transillumination
Hydrocele	–	Testis not separable from hydrocele, cord palpable	Transillumination, Hx of trauma
Spermatocele	–	Testis separable from spermatocele, cord palpable	Transillumination
Varicocele	–	Bag of worms	No transillumination, increases in size with Valsalva, decrease in size if supine
Indirect Inguinal	– (+ if strangulated)	Testis separable from hernia, cord not palpable, cough impulse may transmit, may be reducible	No transillumination
Tumour	– (+ if hemorrhagic)	Hard lump/nodule	
Generalized/ Dependant edema	–	Diffuse swelling	Often post-operative or immobilized, check for liver dysfunction
Idiopathic	–		

Varicocele Grading
- Grade 1: Palpable only with Valsalva manoeuvre
- Grade 2: Palpable without Valsalva
- Grade 3: Visible through scrotal skin

Suspect a Retroperitoneal Mass/ Process in a Patient with a Varicocele if
- Acute onset
- Right sided (isolated)
- Palpable abdominal mass
- Does not reduce while supine

Indications for Treatment of Varicocele
- Impaired sperm quality or quantity
- Pain or dull ache affecting QOL
- Affected testis fails to grow in adolescents
- Cosmetic indications (especially in adolescents)

Table 24. Benign Scrotal Masses

Type	Varicocele	Spermatocele	Hydrocele	Testicular Torsion	Inguinal Hernia
Definition	Dilatation and tortuosity of pampiniform plexus	A benign, sperm filled epididymal retention cyst	Collection of serous fluid that results from a defect or irritation in the tunica vaginalis	Twisting of the testicle causing venous occlusion and engorgement as well as arterial ischemia and infarction	Protrusion of abdominal contents through the inguinal canal into the scrotum
Etiology	15% of men Due to incompetent valves in the testicular veins 90% left sided	Multiple theories, including: Distal obstruction Aneurysmal dilations of the epididymis Agglutinated germ cells	Usually idiopathic Found in 5-10% testicular tumours Associated with trauma/ infection Communicating: patent processus vaginalis, changes size during day (peds) Non-communicating: non-patent processus vaginalis (adult)	Trauma Cryptorchidism "Bell clapper deformity" Many occur in sleep (50%) Necrosis of glands in 5-6 h	Indirect (through internal ring, often into scrotum): congenital Direct (through external ring, rarely into scrotum): abdominal muscle weakness
Hx/P/E	"Bag of worms" Often painless Pulsates with Valsalva	Non-tender, cystic mass Transilluminates	Non-tender, intrascrotal mass Cystic Transilluminates	Acute onset severe scrotal pain, swelling GI upsets cases Retracted and transverse testicle (horizontal lie) Negative Phren's sign Absent cremasteric reflex	A small bulge in the groin that may increase in size with Valsalva and disappear when lying down Can present as a swollen or enlarged scrotum Discomfort or sharp pain – especially when straining, lifting, or exercising
Investigations	P/E Valsava	P/E U/S to rule out tumour	U/S to rule out tumour	U/S with colour flow Doppler probe over testicular artery Decrease uptake on ^{99m}Tc-pertechnetate scintillation scan (doughnut sign)	Hx and P/E Invagination of the scrotum Valsalva
Treatment	Conservative Surgical ligation of testicular veins Percutaneous vein occlusion (balloon, sclerosing agents) Repair may improve sperm count/ motility 50-75%	Conservative Avoid needle aspiration as it can lead to infection, reaccumulation and spilling of irritating sperm within scrotum Excise if symptomatic	Conservative Needle drainage Surgical	**Emergency surgical exploration and bilateral orchiopexy** Orchiectomy if poor prognosis	Surgical repair

TORSION OF TESTICULAR APPENDIX
- twisting of testicular/epididymal vestigial appendix

Signs and Symptoms
- clinically similar to testicular torsion, but vertical lie and cremaster reflex preserved
- "blue dot sign"
  - blue infarcted appendage seen through scrotal skin (can usually be palpated as small, tender lump)

Treatment
- analgesia – most will subside over 5-7 d
- surgical exploration and excision if refractory pain

HEMATOCELE
- trauma with bleed into tunica vaginalis
- U/S helpful to exclude fracture of testis which requires surgical repair

Treatment
- ice packs, analgesics, surgical repair

Acute scrotal swelling/pain in young boys is torsion until proven otherwise

Transillumination refers to if light is able to transmit through tissue (i.e. due to excess fluid)

Differential of a Benign Scrotal Mass

HIS BITS
Hydrocele
Infection (epididymitis/orchitis)
Sperm (spermatocele)
Blood (hematocele)
Intestines (hernia)
Torsion
Some veins (varicocele)

Penile Complaints

Table 25. Penile Complaints

Type	Peyronie's Disease	Priapism	Paraphimosis	Phimosis	Premature Ejaculation
Definition	Benign curvature of penile shaft secondary to fibrous thickening of tunica albuginea	Prolonged erection lasting >4 h in the absence of sexual excitement/desire	Foreskin caught behind glans leading to edema → inability to reduce foreskin	Inability to retract foreskin over glans penis	Ejaculation prior to when one or both partners desire it, either before or soon after penetration
Etiology	Etiology unknown Trauma/repeated inflammation Familial predisposition Associated with DM, vascular disease, autoimmunity, Dupuytren's contracture, erectile dysfunction	50% idiopathic Ischemic (common) • Thromboembolic (sickle cell) Non-Ischemic • Trauma • Medications • Neurogenic	Iatrogenic (post cleaning/instrumentation) Trauma Infectious (balanitis, balanopsthitis)	Congential (90% natural separation by age 3) Balanitis Poor Hygiene	Psychological factors Primary: no period of acceptable control Secondary: symptoms after a period of control, not associated with general medical condition
Hx/P/E	Penile curvature/shortening Pain with erection Poor erection distal to plaque	Painful erection ± signs of necrosis	Painful, swollen glans penis, foreskin Constricting band proximal to corona Dysuria, decreased urinary stream in children	Limitation and pain when attempting to retract foreskin Balanoposthitis (infection of prepuce)	Ejaculatory latency ≥1 min Inability to control or delay ejaculation Psychological distress
Investigations	Hx and P/E	Hx and P/E Cavernosal blood gas analysis	Hx and P/E	Hx and P/E	Hx and P/E Testosterone levels if in conjunction with impotence
Treatment	Watchful waiting (spontaneous resolution in up to 50%) Intralesional or topical verapamil Incision/excision of plaque Shortening of less affected side ± penile prosthesis	Treat reversible causes High-flow: • Self-limited • Consider arterial embolization Low-flow: • Needle aspirated decompression • Phenylephrine intracorporeal injection q3-5min • Surgical shunt no response within 1 h	Manual pressure (with analgesia) Dorsal slit Circumcision (urgent or electively to prevent recurrence)	Proper hygiene Topical corticosterioids Dorsal slit Circumcision	rule out medical condition Address psychiatric concerns, counselling Medication: • SSRI or clomipramine • Topical lidocaine, prilocaine

Erectile Dysfunction

Definition
- consistent (>3 mo duration) or recurrent inability to obtain or maintain an adequate erection for satisfactory sexual performance

Physiology
- erection involves the coordination of psychologic, neurologic, hemodynamic, mechanical, and endocrine components
- nerves: sympathetic (T11-L2), parasympathetic (S2-4), somatic (dorsal penile/pudendal nerves [S2-4])

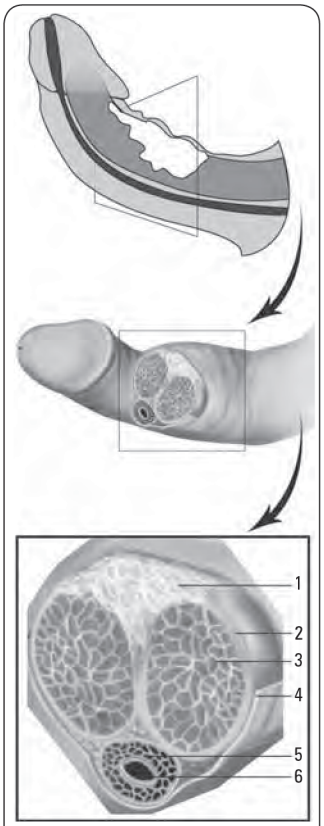
- erection ("POINT")
  - parasympathetics → release of nitric oxide (NO) → increased cGMP levels within corpora cavernosa leading to:
    1. arteriolar dilatation
    2. sinusoidal smooth muscle relaxation → increased arterial inflow and compression of penile venous drainage (decreased venous outflow)
- emission ("SHOOT")
  - sensory afferents from glans
  - secretions from prostate, seminal vesicles, and ejaculatory ducts enter prostatic urethra (sympathetics)
- ejaculation ("SHOOT")
  - bladder neck closure (sympathetic)
  - spasmodic contraction of bulbo-cavernosus and pelvic floor musculature (somatic)
- detumescence
  - sympathetic nerves, norepinephrine, endothelin-1 → arteriolar and sinusoidal constriction → penile flaccidity

Erections POINT AND SHOOT
parasympathetics = **point**; and
sympathetics/**s**omatics = **shoot**

Classification

Table 26. Classification of Erectile Dysfunction

	Psychogenic	Organic
Proportion	10%	90%
Onset	Sudden	Gradual
Frequency	Sporadic	All circumstances
Variation	With partner and circumstance	No
Age	Younger	Older
Organic Risk Factors (HTN, DM, dyslipidemia)	No organic risk factors	Risk factors present
Nocturnal/AM Erection	Present	Absent



1. Fibrous plaque
2. Tunica albuginea
3. Corpus cavernosum
4. Buck's fascia
5. Corpus spongiosum
6. Urethra

Figure 14. Peyronie's disease

Etiology ("IMPOTENCE")

- **I**atrogenic: pelvic surgery, pelvic radiation
- **M**echanical: Peyronie's, post-priapism
- **P**sychological: depression, stress, anxiety, PTSD, widower syndrome
- **O**cclusive vascular: arterial HTN, DM, smoking, hyperlipidemia, PVD, venous (impaired veno-occlusion)
- **T**rauma: penile/pelvic, bicycling
- **E**xtra factors: renal failure, cirrhosis, COPD, sleep apnea, malnutrition
- **N**eurogenic: CNS (e.g. Parkinson's, MS, spinal cord injury, Guillain-Barré, spina bifida, stroke), PNS (e.g. DM, peripheral neuropathy)
- **C**hemical: antihypertensives, sedatives, antidepressants, antipsychotics, anxiolytics, anticholingerics, antihistamines, anti-androgens (including 5-α reductase inhibitors), statins, GnRH agonists, illicit drugs
- **E**ndocrine: DM, hypogonadism, hyperprolactinemia, hypo/hyperthyroid

Diagnosis

- complete Hx (include sexual, medical, and psychosocial aspects)
- self-administered questionnaires (e.g. International Index of Erectile Function, Sexual Health Inventory for Men Questionnaire, ED Intensity Scale, ED Impact Scale)
- focused P/E, including vascular and neurologic examinations, secondary sexual characteristics
- lab investigations, dependent on clinical picture
  - risk factor evaluation: fasting blood glucose or HbA1c, cholesterol profile
  - optional: TSH, CBC, U/A, testosterone (free and total), prolactin, LH
- specialized testing including nocturnal penile tumescence monitoring usually unnecessary
- psychological/psychiatric assessment could be considered to rule out performance anxiety
- evaluation of penile vasculature only relevant with past history of trauma (i.e. pelvic fracture)

Penile vascular abnormalities may be a marker of risk for CV disease. Young men with vascular ED have 50x higher risk of having a CV event

Testosterone deficiency is an uncommon cause of ED

Treatment

- can often be managed by family doctor, see sidebar for when to refer
- must fully inform patient/partner of options, benefits and complications
- non-invasive
  - lifestyle changes (alcohol, smoking), psychological (sexual counseling and education)
  - change precipitating medications
  - treat underlying causes (DM, CVD, HTN, endocrinopathies)

When to Consider Referral

FAT PEN
Failed medical therapy
penile **A**natomic abnormality
pelvic/perineal **T**rauma
Psychogenic cause
Endocrinopathy
vascular/**N**eurologic assessment

- minimally invasive
  - oral medication (see *Common Medications*, U43)
    - sildenafil, tadalafil, vardenafil, avanafil: inhibits PDE-5 to increase intracavernosal cyclic GMP levels
      - all four have similar effectiveness, but tadalafil has certain advantages: earlier onset, longer half-life, no cyanopsia, can be taken on empty or full stomach (others better on empty stomach)
  - vacuum devices: draw blood into penis via negative pressure, then put ring at base of penis once erect
  - MUSE: male urethral suppository for erection – vasoactive substance (PGE1) capsule inserted into urethra
- invasive
  - intracavernous vasodilator injection/self-injection
    - triple therapy (papaverine, phentolamine, PGE1) or PGE1 alone
    - complications: priapism (overdose), thickening of tunica albuginea at site of repeated injections (Peyronie's plaque) and hematoma
- surgical
  - penile implant (last resort): malleable or inflatable
  - penile artery reconstruction (in young men with isolated vascular lesion – investigational)

PDE-5 inhibitors are contraindicated in patients on nitrates/nitroglycerin due to severe hypotension

Initial trial of MUSE® or intracavernosal injection should be done under medical supervision

Trauma

- see Emergency Medicine, ER41

Renal Trauma

Classification According to Severity
- minor
  - contusions and superficial lacerations/hematomas: 90% of all blunt traumas, surgical exploration seldom necessary
- major
  - laceration that extends into medulla and collecting system, major renal vascular injury, shattered kidney

Etiology
- 80% blunt (MVC, assaults, falls) vs. 20% penetrating (stab wounds and gunshots)

Clinical Features
- mechanism of injury raises suspicion
- can be hemodynamically unstable secondary to renal vascular injury and/or other sustained injuries: ABCs
- upper abdominal tenderness, flank tenderness, flank contusions, lower rib/vertebral transverse process fracture

Investigations
- U/A
  - hematuria: requires workup but degree does not correlate with the severity of injury
- imaging
  - CT (contrast, triphasic) if patient stable: look for renal laceration, extravasation of contrast, retroperitoneal hematoma, and associated intra-abdominal organ injury

Staging (does not necessarily correlate well with clinical status)
- I: contusion/hematoma
- II: <1 cm laceration without urinary extravasation
- III: >1 cm laceration without urinary extravasation
- IV: urinary extravasation
- V: shattered kidney or avulsion of pedicle

Treatment
- microscopic hematuria + isolated well-staged minor injuries → no hospitalization
- gross hematuria + contusion/minor lacerations → hospitalize, bedrest, repeat CT if bleeding persists
- surgical intervention/minimally invasive angiography and embolization
  - absolute indications
    - hemorrhage and hemodynamic instability

  - relative indications
    - non-viable tissue and major laceration
    - urinary extravasation
    - vascular injury
    - expanding or pulsating peri-renal mass
    - laparotomy for associated injury
- follow-up with U/S or CT before discharge, and at 6 wk

Complications
- HTN in 5% of renal trauma

Bladder Trauma

Classification
- contusions: no urinary extravasation, damage to mucosa or muscularis
- intraperitoneal ruptures: often involve the bladder dome
- extraperitoneal ruptures: involve anterior or lateral bladder wall in full bladder

Etiology
- blunt (MVC, falls, and crush injury) vs. penetrating trauma to lower abdomen, pelvis, or perineum
- blunt trauma is associated with pelvic fracture in 97% of cases

Clinical Features
- abdominal tenderness, distention, peritonitis, and inability to void
- can be hemodynamically unstable secondary to pelvic fracture, other sustained injuries: ABCs
- suprapubic pain

Investigations
- U/A: gross hematuria in 90%
- imaging (including CT cystogram and post-drainage films for extravasation)

Treatment
- penetrating trauma → surgical exploration
- contusion → urethral catheter until hematuria completely resolves
- extraperitoneal bladder perforations → typically non-operative with foley insertion, and follow with cystograms
  - surgery if: infected urine, rectal/vaginal perforation, bony spike into bladder, laparotomy for concurrent injury, bladder neck involvement, persistent urine leak and failed conservative management
- intraperitoneal rupture usually requires surgical repair and suprapubic catheterization

Complications
- complications of bladder injury itself are rare
- mortality is around 20%, and is usually due to associated injuries rather than bladder rupture

Urethral Injuries

Etiology
- posterior urethra
  - common site of injury is junction of membranous and prostatic urethra due to blunt trauma, MVCs, pelvic fracture
  - shearing force on fixed membranous and mobile prostatic urethra
- anterior urethra
  - straddle injury can crush bulbar urethra against pubic rami
- other causes
  - iatrogenic (instrumentation, prosthesis insertion), penile fracture, masturbation with urethral manipulation
- always look for associated bladder rupture

Clinical Features
- blood at urethral meatus
- high-riding prostate on DRE
- swelling and butterfly perineal hematoma
- penile and/or scrotal hematoma
- sensation of voiding without U/O
- distended bladder

Investigations
- must perform RUG or cystoscopy prior to catheterization

All patients with suspected urethral injury should undergo RUG

Treatment
- simple contusions
  - no treatment
- partial urethral disruption
  - very gentle attempt at catheterization by urologist
  - with no resistance to catheterization → Foley x 2-3 wk
  - with resistance to catheterization → suprapubic cystostomy or urethral catheter alignment in OR
- periodic flow rates/urethrograms to evaluate for stricture formation
- complete disruption
  - immediate repair if patient stable, delayed repair if unstable (suprapubic tube in interim)

Complications
- stricture

Infertility

Definition
- failure to conceive after one year of unprotected, properly timed intercourse
- incidence
  - 15% of all couples
  - ~ 35-40% female, 20% male, 25-30% combined problem

Female Factors

- see Gynecology, GY23

Male Factors

Male Reproduction
- hypothalamic-pituitary-testicular axis (HPTA)
  - pulsatile GnRH from hypothalamus acts on anterior pituitary stimulating release of LH and FSH
  - LH acts on Leydig (interstitial) cells → testosterone synthesis and secretion
  - FSH acts on Sertoli cells → structural and metabolic support to developing spermatogenic cells
  - FSH and testosterone support germ cells (responsible for spermatogenesis)
  - sperm route: epididymis → vas deferens → ejaculatory ducts → prostatic urethra

Etiology
- idiopathic (40-50% infertile males)
- testicular
  - varicocele (35-40% infertile males)
  - tumour
  - congenital (Klinefelter's triad: small, firm testes, gynecomastia, and azoospermia)
  - post-infectious (epididymo-orchitis, STIs, mumps)
  - uncorrected torsion
  - cryptorchidism (<5% of cases)
- obstructive
  - iatrogenic (surgery: see below)
  - infectious (gonorrhea, chlamydia)
  - trauma
  - congenital (absence of vas deferens, CF)
  - bilateral ejaculatory duct obstruction, epididymal obstructions
  - Kartagener's syndrome (autosomal recessive disorder causing defect in action of cilia)
- endocrine (see Endocrinology, E48)
- HPTA (2-3%) e.g. Kallmann's syndrome (congenital hypothalamic hypogonadism), excess prolactin, excess androgens, excess estrogens
- other
  - retrograde ejaculation secondary to surgery
  - medications
  - drugs: marijuana, cocaine, tobacco, alcohol
  - increased testicular temperature (sauna, hot baths, tight pants or underwear)
  - chronic disease: e.g. liver, renal
  - unexplained infertility

Male Infertility Factors

SPERM COUNT
Systemic factor/**S**moking
Psychological illness
Endocrinopathy
Retrograde ejaculation
Medications

Chronic disease
Obstructive
Unexplained
Narcotics
Testicular

History
- age of both partners
- medical: past illness, DM, trauma, CF, genetic syndromes, STIs, cryptorchidism
- surgical: vasectomy, herniorrhaphy, orchidopexy, prostate surgery
- fertility: pubertal onset, previous pregnancies, duration of infertility, treatments
- sexual: libido, erection/ejaculation, timing, frequency
- family Hx
- medications: cytotoxic agents, GnRH agonists, anabolic steroids, nitrofurantoin, cimetidine, sulfasalazine, spironolactone, α-blockers
- social Hx: alcohol, tobacco, cocaine, marijuana
- occupational exposures: radiation, heavy metals

Physical Exam
- general appearance: sexual development, gynecomastia, obesity
- scrotal exam: size, consistency, and nodularity of testicles; palpation of cord for presence of vas deferens; DRE; Valsalva for varicocele

Investigations
- semen analysis (SA) at least 2 specimens, collected 1-2 weeks apart
  - delivery to lab within 1 hour, 2-7 days of abstinence prior to collection
- hormonal evaluation
  - indicated with abnormal SA (rare to be abnormal with normal SA)
  - testosterone and FSH
  - serum LH and prolactin are measured if testosterone or FSH are abnormal
- genetic evaluation
  - chromosomal studies (Klinefelter's syndrome – XXY)
  - genetic studies (Y-chromosome microdeletion, CF gene mutation)
- immunologic studies (antisperm antibodies in ejaculate and blood)
- testicular biopsy
- scrotal U/S (varicocele, testicular size)
- vasography (assess patency of vas deferens)

Common Terminology on SA
- Teratospermia: Abnormal morphology
- Asthenospermia: Abnormal motility
- Oligospermia: Decreased sperm count
- Azoospermia: Absent sperm in semen
- Mixed types: i.e. oligoasthenospermia

Mutation of cystic fibrosis transmembrane conductance regulator (CFTR) gene is associated with congenital bilateral absence of vas deferens and epididymal cysts, even if patient manifests no symptoms of CF

Treatment
- assessment of partner
- lifestyle
  - regular exercise, healthy diet
  - eliminate alcohol, tobacco and illicit drugs
- medical
  - endocrine therapy (see Endocrinology, E49)
  - treat retrograde ejaculation
  - discontinue anti-sympathomimetic agents, may start α-adrenergic stimulation (phenylpropanolamine, pseudoephedrine, or ephedrine)
  - treat underlying infections
- surgical
  - varicocelectomy (if indicated)
  - vasovasostomy (vasectomy reversal) or epididymovasostomy
  - transurethral resection of blocked ejaculatory ducts
- assisted reproductive technologies (ART)
  - refer to infertility specialist
  - sperm washing + intrauterine insemination (IUI)
  - *in vitro* fertilization (IVF)
  - intracytoplasmic sperm injection (ICSI) after CF screening of patient and partner in patients with congenital bilateral absence of vas deferens

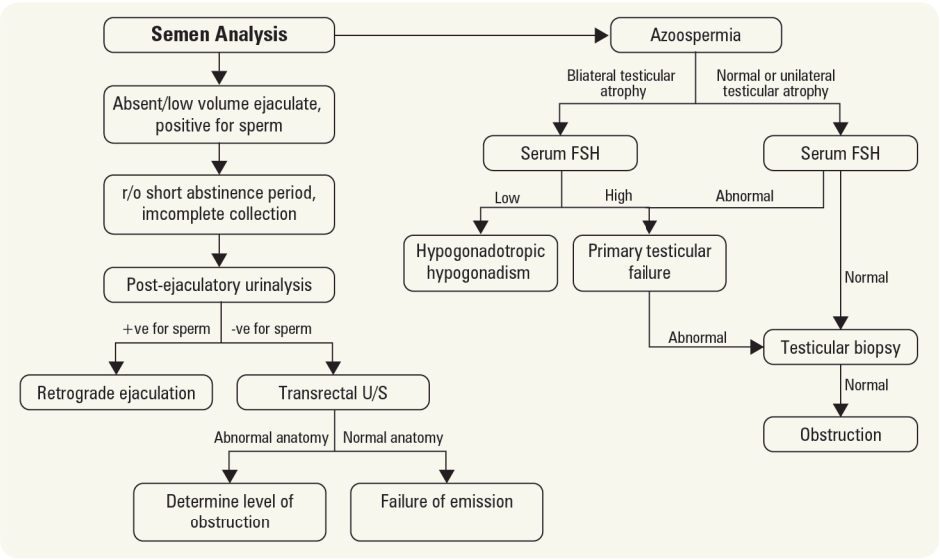


Figure 15. Infertility work up

WHO Guidelines
Normal Semen Values
- Volume: 2-5 mL
- Concentration: >15 million sperm/mL
- Morphology: 30% normal forms
- Motility: >40% adequate forward progression
- Liquefaction: complete in 20 min
- pH: 7.2-7.8
- WBC: <10/HPF or $<10^6$ WBC/mL semen

Pediatric Urology

Congenital Abnormalities

- not uncommon; 1/200 have congenital abnormalities of the GU tract
- six common presentations of congenital urological abnormalities

1. ANTENATAL HYDRONEPHROSIS

Majority of antenatal hydronephroses resolve during pregnancy or within the first year of life

Epidemiology
- 1-5% fetal U/S, detectable as early as first trimester
- most common urological consultation in perinatal period and one of most common U/S abnormalities of pregnancy

Differential Diagnosis
- UPJ or UVJ obstruction
- multi-cystic dysplastic kidney
- VUR
- PUVs (only in boys)
- duplication anomalies
- ureterocele
- ectopic ureter

Treatment
- antenatal *in utero* intervention rarely indicated unless evidence of PUVs with oligohydramnios

2. POSTERIOR URETHRAL VALVES

Epidemiology
- the most common congenital obstructive urethral lesion in male infants

Pathophysiology
- abnormal mucosal folds at the distal prostatic urethra causing varying degrees of obstruction

Clinical Presentation
- dependent on age
  - antenatal: bilateral hydronephrosis, distended bladder, oligohydramnios
  - neonatal (recognized at birth): palpable abdominal mass (distended bladder, hydronephrosis), ascites (transudation of retroperitoneal urine), respiratory distress (pulmonary hypoplasia from oligohydramnios), weak urinary stream
  - neonatal (not recognized at birth): within weeks present with urosepsis, dehydration, electrolyte abnormalities, failure to thrive

  - toddlers: UTIs or voiding dysfunction
  - school-aged boys: voiding dysfunction → urinary incontinence
- associated findings include renal dysplasia and secondary VUR

Investigations
- most commonly recognized on prenatal U/S → bilateral hydronephrosis, thickened bladder, dilated posterior urethra ("keyhole sign"), oligohydramnios in a male fetus
- VCUG → dilated and elongated posterior urethra, trabeculated bladder, VUR

Treatment
- immediate catheterization to relieve obstruction, followed by cystoscopic resection of PUV when baby is stable
- if resection of PUV is not possible, vesicostomy is indicated

3. URETEROPELVIC JUNCTION OBSTRUCTION

Etiology
- unclear: adynamic ureteral segment, stenosis, strictures, extrinsic compression, stenosis, strictures, aberrant blood vessels
- can rarely be secondary to tumour, stone, etc, in children

Epidemiology
- the most common congenital defect of the ureter
- M:F = 2:1
- up to 40% bilateral, which may be associated with worse prognosis

Clinical Presentation
- symptoms depend on severity and age at diagnosis (mostly asymptomatic finding on antenatal U/S)
  - infants: abdominal mass, urinary infection
  - children: pain, vomiting, failure to thrive
- some cases are diagnosed after puberty and into adulthood
  - in adolescents and adults, the symptoms may be triggered by episodes of increased diuresis, such as following alcohol ingestion (Dietl's crisis)

Investigations
- antenatal U/S most common, Doppler U/S (rare), IVP (rare), and renal scan ± furosemide

Treatment
- surgical correction (pyeloplasty), consider nephrectomy if <15% differential renal function

4. VESICOURETERAL REFLUX

Definition
- retrograde passage of urine from the bladder, through the UVJ, into the ureter

Classification
- primary reflux: incompetent or inadequate closure of UVJ
  - lateral ureteral insertion, short submucosal segment
- secondary reflux: abnormally high intravesical pressure resulting in failure of UVJ closure
  - often associated with anatomic (PUV) or functional (neuropathic) bladder obstruction

Epidemiology
- estimated ~1% of newborns, but not well known
- incidence and clinical relevance higher in children with febrile UTIs and prenatal hydronephrosis
- risk factors: race (white > black), female gender, age (<2 yr), genetic predisposition

Investigations
- focused Hx, particularly of voiding dysfunction (frequency, urgency, diurnal enuresis, constipation, encopresis)
  - also screen for signs of infection (UTI, pyelonephritis, urosepsis) and renal failure (uremia, HTN)
- initial evaluation of renal status, growth parameters, and blood pressure is warranted in any child with VUR due to high incidence of renal scarring
  - height, weight, blood pressure
  - Cr
  - U/A, C&S
  - renal U/S
  - DMSA renal scan if at high risk (greater sensitivity in detecting structural defects associated with dysplasia, renal scarring or pyelonephritis; entails radiation exposure)
  - family screening is controversial

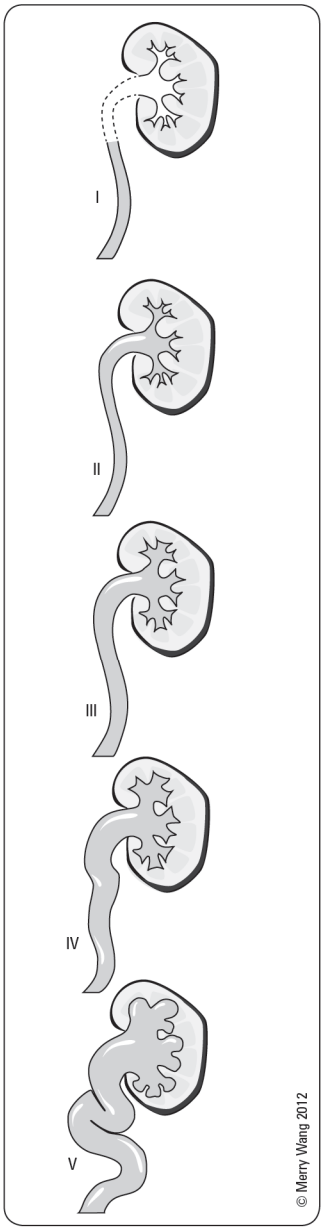


Figure 16. VUR grading
(based on cystogram)

Treatment
- spontaneous resolution in 60% of primary reflux
  - in lower grades (I-III), goal is to prevent infection or renal damage via medical treatment and monitoring
- medical treatment: daily ABx prophylaxis at half the treatment dose for acute infection (see Table 9 - TMP/SMX, trimethoprim, amoxicillin, or nitrofurantoin)
- surgical treatment: ureteral reimplantation ± ureteroplasty, or subureteral injection with bulking agents (Deflux® or Macroplastique®)
  - indications include failure of medical management, renal scarring (e.g. renal insufficiency, HTN), breakthrough UTIs, persistent high grade (IV or V) reflux

VUR Grading (based on cystogram)
- **Grade I:** ureters only fill
- **Grade II:** ureters and pelvis fill
- **Grade III:** ureters and pelvis fill with some dilatation
- **Grade IV:** ureters, pelvis, and calyces fill with significant dilatation
- **Grade V:** ureters, pelvis, and calyces fill with major dilatation and tortuosity

5. HYPOSPADIAS

Definition
- a condition in which the urethral meatus opens on the ventral side of the penis, proximal to the normal location in the glans penis
- depending on severity, may result in difficulty directing urinary stream, having intercourse or depositing sperm in vagina

Defer circumcision in patients with hypospadias

Epidemiology
- very common; 1/300 live male births
- distal hypospadias more common than proximal
- white >> black
- may be associated with ventral penile curvature, disorders of sexual differentiation, undescended testicles or inguinal hernia

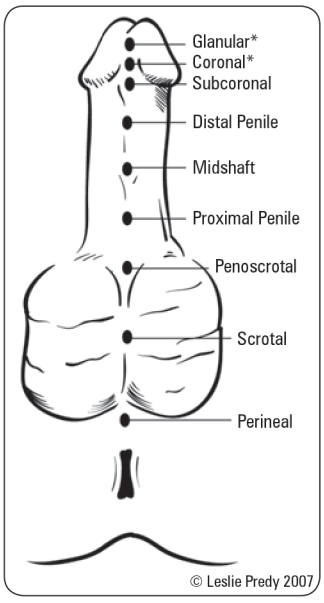


Figure 17. Classification of hypospadias (*account for 75%)

Treatment
- early surgical correction; optimal repair before 2 yr
- neonatal circumcision should be deferred because the foreskin may be utilized in the correction

6. EPISPADIAS-EXSTROPHY COMPLEX

Definition
- a spectrum of defects depending on the timing of the rupture of the cloacal membrane
  - bladder exstrophy: congenital absence of a portion of lower abdominal and anterior bladder wall, with exposure of the bladder lumen
  - cloacal exstrophy
    - exposed bladder and bowel with imperforate anus
    - associated with spina bifida in >50%
  - epispadias (least severe)
    - urethra opens on dorsal aspect of the penis, often associated with penile curvature

Etiology
- represents failure of closure of the cloacal membrane, resulting in the bladder and urethra opening directly through the abdominal wall

Epidemiology
- rare: incidence 1/30,000, M:F = 3:1 predominance
- high morbidity → multiple reconstructive surgeries, incontinence, infertility, reflux

Treatment
- surgical correction at birth
- later corrections for incontinence, VUR, and low bladder capacity may be needed

Nephroblastoma (Wilms' Tumour)

Etiology
- arises from abnormal proliferation of metanephric blastema

Epidemiology
- 5% of all childhood cancers, 5% bilateral
- most common primary malignant renal tumour of childhood
- average age of incidence is 3 yr

Clinical Features
- abdominal mass: large, firm, unilateral (80%)
- HTN (25%)
- flank tenderness
- microscopic hematuria
- nausea/vomiting

Treatment
- always investigate contralateral kidney and renal vein (for tumour thrombus)
- unilateral disease: radical nephrectomy ± radiation ± chemotherapy
- bilateral disease: nephron-sparing surgery following neoadjuvant chemotherapy

Prognosis
- 5 yr survival 80%

Cryptorchidism/Ectopic Testes

Definition
- abnormal location of testes somewhere along the normal path of descent (external inguinal ring > inguinal canal > abdominal)
- ectopic testis (testis found outside its normal path of descent) is most commonly located within a superficial pouch between the external oblique fascia and Scarpa's fascia (Denis Browne pouch)
- differential diagnosis:
  - retractile testes
  - atrophic testes
  - disorders of sexual differentiation (bilateral impalpable gonads)

Normal Testicular Development and Descent *in Utero*

2nd month: Testicle begins to form

4th month: Begins to take on its normal appearance and migrates from its origin at the kidney to the internal inguinal ring

7th month: The testis, surrounded in peritoneal covering, begins to descend through the internal ring, inguinal canal and external ring to terminate in the scrotum

Epidemiology
- 2.7% of full term newborns
- 0.7-0.8% at 1 yr

Treatment
- orchiopexy
- hormonal therapy not proven to be of benefit over standard surgical treatment

Prognosis
- reduction in fertility
  - untreated bilateral cryptorchidism: ~100% infertility
  - paternity rates: 53%, 90%, and 93% in formerly bilateral cryptorchid, formerly unilateral cryptorchid, and normal men, respectively
- increased malignancy risk
  - intraabdominal > inguinal
  - surgical correction facilitates testicular monitoring and may reduce malignancy risk
- increased risk of testicular torsion (reduced by surgical correction)

Disorders of Sexual Differentiation

Definition
- formerly known as intersex disorders
- abnormal genitalia for chromosomal sex due to the undermasculinization of males or the virilization of females
- considered a social emergency

Classification
1. 46 XY DSD
   - defect in testicular synthesis of androgens
   - androgen resistance in target tissues
   - palpable gonad
2. 46 XX DSD
   - most due to CAH (21-hydroxylase deficiency most common enzymatic defect) → shunt in steroid biosynthetic pathway leading to excess androgens
   - undiagnosed and untreated CAH can be associated with life-threatening electrolyte abnormalities in the newborn (salt-wasting CAH)
3. ovotesticular DSD
4. mixed gonadal dysgenesis (46 XY/45 XO most common karyotype)
   - presence of Y chromosome → partial testis determination to varying degrees

A phenotypic male newborn with bilateral non-palpable testicles should be considered 46XX with salt-wasting CAH and must undergo proper evaluation prior to discharge

Diagnosis
- thorough family Hx noting any consanguinity
- maternal Hx, especially medication/drug use during pregnancy (maternal hyperandrogenemia)
- P/E: palpable gonad (= chromosomal male), hyperpigmentation, evidence of dehydration, HTN, stretched phallus length, position of urethral meatus
- laboratory tests
  - plasma 17-OH-progesterone (after 36 h of life) → increased in 21-hydroxylase deficiency (CAH)
  - plasma 11-deoxycortisol → increased in 11-β-hydroxylase deficiency
  - basal adrenal steroid levels
  - serum testosterone and DHT pre- and post-hCG stimulation (2,000 IU/d for 4 d)
  - serum electrolytes
  - chromosomal evaluation including sex karyotype
- U/S of adrenals, gonads, uterus, and fallopian tubes
- endoscopy and genitography of urogenital sinus

Treatment
- steroid supplementation as indicated (e.g. CAH)
- sex assignment after extensive family consultation
  - must consider capacity for sexually functioning genitalia in adulthood, fertility potential, and psychological impact
- reconstruction of external genitalia between 6 and 12 mo
- long-term psychological guidance and support for both patient and family

Enuresis

- see Pediatrics, P9

Selected Urological Procedures

Bladder Catheterization

- catheter size measured by the French (Fr) scale – circumference in mm
- each 1 mm increase in diameter = approximately 3 Fr increase (standard size 16-18 Fr)
- should be removed as soon as possible to reduce the risk of UTI

Continuous Catheterization
- indications
  - accurate monitoring of U/O
  - relief of urinary retention due to medication, neurogenic bladder, or intravesical obstruction
  - temporary therapy for urinary incontinence
  - perineal wounds
  - clot prevention (24-28 Fr) for CBI
  - post-operative

Alternatives to Continuous Catheterization
- intermittent catheterization
  - PVR measurement
  - to obtain sterile diagnostic specimens for U/A, urine C&S
  - management of neurogenic bladder or chronic urinary retention
- condom catheter
- suprapubic catheter

Causes of Difficult Catheterizations and Treatment
- patient discomfort → use sufficient lubrication (± xylocaine)
- collapsing catheter → lubrication as above ± firmer or larger catheter (silastic catheter)
- meatal/urethral stricture → dilate with progressively larger catheters/balloon catheter
- BPH → use coudé catheter as angled tip can help navigate around enlarged prostate
- urethral disruption/obstruction → filiform and followers or suprapubic catheterization
- anxious patient → anxiolytic medication

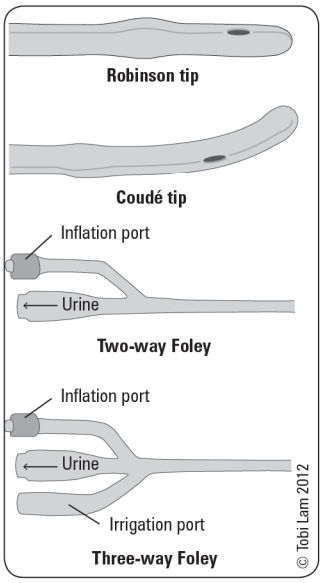


Figure 18. Transurethral (Foley) catheters

Complications of Catheterization
- infection: UTI
- meatal/urethral trauma

Contraindications
- urethral trauma: blood at the meatus of the urethra, scrotal hematoma, pelvic fracture, and/or high riding prostate

Circumcision

Definition
- removal of some or all of the foreskin from the penis

Epidemiology
- 30% worldwide
- frequency varies depending on geographic location, religious affiliation, socioeconomic classification

Medical Indications
- phimosis and recurrent paraphimosis
- recurrent UTIs (particularly in infants and in association with other urinary abnormalities)
- balanitis xerotica obliterans or other chronic inflammatory conditions

Contraindications
- unstable or sick infant
- congenital genital abnormalities (hypospadias)
- family Hx of bleeding disorders warrants laboratory investigation prior to circumcision

Complications
- bleeding
- infection
- penile entrapment, skin bridges
- fistula
- glans injury
- penile sensation deficits

Male Circumcision for Prevention of Heterosexual Acquisition of HIV in Men
Cochrane DB Syst Rev 2009;2:CD003362
Purpose: To evaluate the effectiveness and safety of male circumcision for preventing acquisition of HIV in heterosexual men.
Methods: The analyzed data is from three randomized controlled trials to assess the efficacy of male circumcision for preventing HIV acquisition in men in Africa.
Results: Medical male circumcision reduces the acquisition of HIV by heterosexual men (38%-66% over 24 mo).

Circumcision Status and Risk of HIV and Sexually Transmitted Infections among Men who have Sex with Men: A Meta-Analysis
JAMA 2008;300:1674-1684
Purpose: To describe the association between male circumcision and HIV infection and other sexually transmitted infections (STIs) among men who have sex with men (MSM).
Methods: Meta-analysis of 15 studies (n=53,567)
Results: The associations between circumcision and HIV-positive and STIs were not statistically significant. Male circumcision had a protective association with HIV in studies of MSM conducted before the introduction of highly active anti-retroviral therapy.
Conclusions: There is insufficient evidence to support that male circumcision protects against HIV infection or other STIs.

Cystoscopy

Objective
- endoscopic inspection of the lower urinary tract (urethra, prostate, bladder, and ureteral orifices), samples for cytology
- scopes can be flexible or rigid

Indications
- gross hematuria
- LUTS (storage or voiding)
- urethral and bladder neck strictures
- bladder stones
- bladder tumour surveillance
- evaluation of upper tracts with retrograde pyelography (ureteric stents, catheters)

Complications
- during procedure
  - bleeding
  - anesthetic-related
  - perforation (rare)
- post-procedure (short-term)
  - infections, e.g. epididymo-orchitis (rare)
  - urinary retention
- post-procedure (long-term)
  - stricture

Male Circumcision
Pediatrics 2012;130:e756-e785
Study: Guidelines by the American Academy of Pediatrics (AAP).
Recommendations: The American Academy of Pediatrics radically changed their position on male circumcision in 2012. The report from the AAP now states that the preventative health benefits outweigh the risks of the procedure and that the procedure is well-tolerated with adequate pain management and sterility. Stated benefits include the prevention of urinary tract infection, penile cancer, transmission of some sexually transmitted infections, including HIV. There is believed to be no effect on penile sexual function, sensitivity or sexual satisfaction. Acute complications are rare and more common if the procedure is done by an untrained provider.
Note: The Canadian Pediatric Society (CPS) has not yet updated their position on male circumcision since 1996, which stated that the CPS is opposed to routine circumcision. A new statement is expected soon.

Radical Prostatectomy

Objective
- the removal of the entire prostate and prostatic capsule via a lower midline abdominal incision, laparoscopically or robotically
  - internal iliac and obturator vessel lymph nodes may also be dissected and sent for pathology (dependent on risk: clinical stage, grade, PSA)
  - seminal vesicle vessels are also partially or completely removed

Indications
- treatment for localized prostate cancer

Complications
- immediate (intraoperative)
  - blood loss
  - rectal injury (extremely rare)
  - ureteral injury (extremely rare)
- perioperative
  - lymphocele formation
- late
  - moderate to severe urinary incontinence (3-10%)
  - mild urinary incontinence (20%)
  - ED (~50%, depending on whether one, both, or neither of the neurovascular bundles are involved in extracapsular extension of tumour)

Retropubic, Laparoscopic, and Robot-Assisted Radical Prostatectomy: A Critical Review of Outcomes Reported by High-Volume Centres
J Endourology 2010;24:2003-2015
Study: A systematic review to compare perioperative outcomes, positive surgical margin (PSM) rates, and functional outcomes in retropubic radical prostatectomy (RRP) laparoscopic RP (LRP) and robot-assisted radical prostatectomy (RARP).
Methods: Medline database was searched. Weighted means (based on number of participants in each study) were calculated for all outcomes.
Results: 58 articles were reviewed. LRP and RARP were associated with better perioperative outcomes compared to RRP. RRP, LRP, and RARP had similar post-operative complication rates ranging from 10.3-10.98%. RARP had a lower overall PSM rate than LRP, and RRP. RARP had the highest continence rate and mean potency rates.
Conclusion: In high-volume centers, RRP, LRP and RARP are safe options for treating patients with localized prostate cancer. LRP and RARP are associated with better perioperative outcomes and RARP showed lower PSM rates, higher potency and continence compared to RRP and LRP.

Transurethral Resection of the Prostate

Objective
- to partially resect the periurethral portion of the prostate (transition zone) to decrease symptoms of urinary tract obstruction
- accomplished via a transurethral (cystoscopic) approach using an electrocautery loop, irrigation (glycine), and illumination

Indications
- obstructive uropathy (large bladder diverticula, renal insufficiency)
- refractory urinary retention
- recurrent UTIs
- recurrent gross hematuria
- bladder stones
- intolerance/failure of medical therapy

Complications
- acute
  - intra- or extraperitoneal rupture of the bladder
  - rectal perforation
  - incontinence
  - incision of the ureteral orifice (with subsequent reflux or ureteral stricture)
  - hemorrhage
  - epididymitis
  - sepsis
  - transurethral resection syndrome (also called "post-TURP syndrome")
    - caused by absorption of a large volume of the hypotonic irrigation solution used, usually through perforated venous sinusoids, leading to a hypervolemic hyponatremic state
    - characterized by dilutional hyponatremia, confusion, nausea, vomiting, HTN, bradycardia, visual disturbances, CHF, and pulmonary edema
    - treat with diuresis and (if severe) hypertonic saline administration
- chronic
  - retrograde ejaculation (>75%)
  - ED (5-10% risk increases with increasing use of cautery)
  - incontinence (<1%)
  - urethral stricture
  - bladder neck contracture

Extracorporeal Shock Wave Lithotripsy

Objective
- to treat renal and ureteral calculi (proximal, middle or distal) which cannot pass through the urinary tract naturally
- shockwaves are generated and focused onto stone → fragmentation, allowing stone fragments to pass spontaneously and less painfully

Indications
- potential first-line therapy for renal and ureteral calculi <2.5 cm
- individuals with calculi in solitary kidney
- individuals with HTN, DM or renal insufficiency

*patient preference and wait-times play a large role in stone management

Contraindications
- acute UTI or urosepsis
- bleeding disorder or coagulopathy
- pregnancy
- obstruction distal to stone

Complications
- bacteriuria
- bacteremia
- post-procedure hematuria
- ureteric obstruction (by stone fragments)
- peri-nephric hematoma

A Comparison of Treatment Modalities for Renal Calculi Between 100 and 300 mm^2: Are Shockwave Lithotripsy, Ureteroscopy, and Percutaneous Nephrolithotomy Equivalent?
J Endourol 2011;25:481-485

Purpose: To describe the outcomes of a series of patients who underwent shockwave lithotripsy (SWL), ureteroscopy (URS) or percutaneous nephrolithotomy (PCNL).

Methods: Patients treated for intermediate-sized upper tract calculi (100-300 mm^2) at a single tertiary centre were included. Demographic and clinical data were collected from a prospectively maintained database.

Results: Of 137 patients, 38.7%, 29.9%, and 31.4% were treated with SWL, URS, and PCNL, respectively. Stone-free rate (95.3%) and single treatment success rate (95.3%) were highest for PCNL compared to SWL and URS ($p<0.001$). When allowing for up to two SWL treatments, success rates became equivalent for the three treatment groups ($p=0.66$). Auxiliary treatments were more frequent after SWL compared to URS and PCNL. Clavien grade complications did not differ between the three groups.

Conclusion: Up to two SWL treatments have equivalent success rate as compared to URS and PCNL. Hence, multiple SWL treatments may be a reasonable therapeutic option for patients who prefer SWL or who are not good candidates for alternative therapies.

Common Medications

Table 27. Erectile Dysfunction Medications

Drug	Class	Mechanism	Adverse Effects
sildenafil tadalafil vardenafil (PDE5s for use when some erection present)	Phosphodiesterase 5 inhibitor	Selective inhibition of PDE5 (enzyme which degrades cGMP) Leads to sinusoidal smooth muscle relaxation and erection	Severe hypotension (very rare) Contraindicated if Hx of priapism, or in conditions predisposing to priapism (leukemia, myelofibrosis, polycythemia, sickle cell disease) Contraindicated with nitrates
alprostadil (MUSE®), PGE_1 + phentolamine + papaverine mixture	Prostaglandin E_1	Activation of cAMP, relaxing sinusoidal smooth muscle Local release (capsule inserted into urethra)	Penile pain Presyncope
alprostadil, papaverine (intracavernosal injection) triple therapy also used: papaverine, phentolamine, PGE_1	See above	See above	Thickening of tunica albuginea at site of repeated injections (Peyronie's plaque) Painful erection Hematoma Contraindicated if Hx of priapism, or in conditions predisposing to priapism

Table 28. Benign Prostatic Hyperplasia Medications

Drug	Class	Mechanism	Adverse Effects
terazosin doxazosin tamsulosin alfuzosin silodosin	α_1 blockers α_{1A} selective	α-adrenergic antagonists reduce stromal smooth muscle tone Reduce dynamic component of bladder outlet obstruction	Presyncope Leg edema Retrograde ejaculation Headache Asthenia Nasal congestion
finasteride dutasteride	5-α reductase inhibitor	Blocks conversion of testosterone to DHT Reduces static component of bladder outlet obstruction Reduces prostatic volume	Sexual dysfunction PSA decreases

Table 29. Prostatic Carcinoma Medications (N>0, M>0)

Drug	Class	Mechanism	Adverse Effects
leuprolide, goserelin	GnRH agonist	Initially stimulates LH, increasing testosterone and causing "flare" (initially increases bone pain) Later causes low testosterone	Hot flashes Headache Decreased libido
*diethylstilbestrol (DES)	Estrogens	Inhibit LH and cytotoxic effect on tumour cells	Increased risk of cardiovascular events (no longer available commercially in North America)
*cyproterone acetate	Steroidal antiandrogen	Competes with DHT for intracellular receptors: 1. Prevent flare produced by GnRH agonist 2. Use for complete androgen blockade 3. May preserve potency	
flutamide, bicalutamide	Non-steroidal antiandrogen	As above	Hepatotoxic: AST/ALT monitoring
*ketoconazole, spironolactone	Steroidogenesis inhibitors	Blocks multiple enzymes in steroid pathway, including adrenal androgens	GI symptoms Hyperkalemia Gynecomastia

*Very rarely used

Table 30. Continence Agents and Overactive Bladder Medications

Drug	Class	Mechanism	Indication	Adverse Effects
oxybutynin	Antispasmotic	Inhibits action of ACh on smooth muscle Decreases frequency of uninhibited detrusor contraction Diminishes initial urge to void	Overactive bladder Urge incontinence + urgency + frequency	Dry mouth Blurred vision Constipation Supraventricular tachycardia
oxybutynin, tolterodine, trospium, solifenacin, darifenacin fesoterodine	Anticholinergic	Muscarinic receptor antagonist Selective for bladder Increases bladder volume Decreases detrusor pressure	Overactive bladder Urge incontinence + urgency + frequency	As above
mirabegron	β3 agonist	Beta sympathetic receptor blocker in the bladder; relaxes bladder during storage phase	Overactive bladder Urge incontinence + urgency + frequency	Blood pressure should be monitored
imipramine	Tricyclic antidepressant	Sympathomimetic effects: urinary sphincter contraction Anticholinergic effects: detrusor relaxation	Stress and urge incontinence	As above Weight gain Orthostatic hypotension Prolonged PR interval

Note: All anti-cholinergics are equally effective and long-acting formulations are better tolerated. Newer muscarinic M3 receptor specific agents (solifenacin, darifenacin) are equally efficacious as older drugs, however, RCTs based on head-to-head comparison to long acting formulations are lacking.

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