Objectives

- Appreciate the clinical relevance and consequences of common infections of the female genital tract
- Understand the pathology of HPV-related diseases in the female genital tract
- Describe common non-neoplastic and benign neoplastic conditions affecting the uterine corpus and endometrium
- Understand the pathogenesis and risk factors of endometrial hyperplasia and carcinoma
- Appreciate the variety of neoplasms that may arise in the ovaries: epithelial tumours, germ cell tumours, sex cord-stromal tumours
- Understand normal placental anatomy, the various disorders that may arise in pregnancy and gestational trophoblastic diseases

Outline

I. **Normal Development of the Female Genital Tract**
II. **Infections**
    a. **Lower genital tract**
    b. **Pelvic inflammatory disease**
III. **Vulva**
    a. **Bartholin cyst**
    b. **Non-neoplastic epithelial lesions:** *Lichen sclerosus, squamous cell hyperplasia*
    c. **Benign exophytic lesions:** *Condyloma acuminatum, fibroepithelial polyp, squamous papilloma*
    d. **Squamous neoplastic lesions:** *Vulvar intraepithelial neoplasia and carcinoma*
    e. **Glandular neoplastic lesions:** *Papillary hidradenoma, Extramammary Paget's disease*
IV. **Vagina**
    a. **Developmental anomalies**
    b. **Neoplasms**
V. **Uterine Cervix**
    a. **Inflammation**
    b. **Endocervical polyps**
    c. **Premalignant and malignant neoplasms:** Squamous intraepithelial lesions (SIL), Cervical *Carcinoma*
VI. **Uterine Corpus and Endometrium**
    a. **Abnormal uterine bleeding:** *Anovulatory cycle, Inadequate luteal phase*
    b. **Inflammatory disorders:** *Acute and chronic endometritis*
    c. **Endometriosis and adenomyosis**
    d. **Endometrial polyps**
    e. **Endometrial hyperplasia**
    f. **Endometrial carcinoma**
    g. **Malignant mixed Mullerian tumour**

     h.   **Endometrial stromal tumours:** *Adenosarcomas, Benign stromal nodules, Endometrial Stromal Sarcoma*

     i.   **Myometrial tumours:** *Leiomyomas, Leiomyosarcoma*

VII.   Fallopian tubes

VIII.   Ovaries

     a.   **Non-neoplastic and functional cysts:** *Cystic follicles, polycystic ovarian syndrome etc.*

     b.   **Neoplasms:** *Epithelial tumours, Germ cell tumours, Sex cord-stromal tumours*

IX.   Gestational and Placental Disorders

     a.   **Normal placental anatomy**

     b.   **Disorders of early pregnancy:** *Spontaneous abortion, Ectopic pregnancy*

     c.   **Disorders of late pregnancy:** *Abnormalities of placental implantation, Placental Infections, Preeclampsia and eclampsia, Twin placentas*

     d.   **Gestational Trophoblastic Disease:** *Hydatidiform mole, Choriocarcinoma etc.*

References

Kumar V, Abbas A, Aster J. *Robbins & Cotran Pathologic Basis of Disease*. 9th ed.
Kurman R.J. Carcangiu M.L., Herrington C.S., Young R.H. (Eds.): *WHO Classification of Tumours of Female Reproductive Organs* (4th edition). IARC: Lyon 2014

Note: Pathweb Study Notes are based on the key topics covered in the lectures in the Yong Loo Lin School of Medicine, as well as additional topics covered in major texts. For more comprehensive discussion on specific pathology topics, readers are advised to refer to the recommended texts in your respective courses.

I. NORMAL DEVELOPMENT OF THE FEMALE GENITAL TRACT

Normal development of the female genital tract (FGT) is a series of events involving primordial germ cells, Mullerian (paramesonephric ducts), wolffian (mesonephric) ducts and urogenital sinus. The epithelial lining of the female genital tract and ovarian surface share a common origin from coelomic epithelium (mesothelium).

Germ cells	**Wk 4**: Arise in wall of yolk sac **Wk 5-6**: migrate into urogenital ridge and induce proliferation of the mesodermal epithelium	Gives rise to **Ovary** (epithelium and stroma)
Mullerian ducts	**Wk 6**: forms through invagination and fusion of the coelomic lining epithelium. Ducts grow caudally into pelvis, where they swing medially to fuse with the urogenital sinus	Unfused upper portions mature into **Fallopian tubes;** Fused lower portion forms **Uterus, Cervix and Upper Vagina**
Urogenital sinus	Develops when cloaca is subdivided by the urorectal septum	Forms **Lower Vagina** and vestibule of **External Genitalia**
Mesonephric ducts	Normally regress in the female	Remnants may persist → **epithelial inclusions** adjacent to ovaries, tubes, uterus, or form **Gartner duct cysts** in cervix/vagina

II. INFECTIONS

Many infections of the FGT are sexually transmitted. **Complications** include female infertility, preterm deliveries (e.g. *Ureaplasma, Mycoplasma*), or increased risk for cervical, vaginal and vulvar cancers

Herpes Simplex Virus **(HSV)**	
Lower genital tract: cervix>> vagina>>vulva *Sexual transmission* *Perinatal transmission*	- Common; ~1/3 are symptomatic (lesions +/- systemic symptoms e.g. fever, malaise, tender LNs) - Lesions develop 3-7 days post-transmission: red **papules** → **vesicles** → **ulcers** - **Latent infection** is established during the acute infection in the regional lumbosacral nerve ganglia – any subsequent decrease in immune status can trigger virus reactivation - **Microscopy**: HSV cytopathic changes (**multinucleation**, nuclear **molding** and **margination of chromatin** with ground-glass appearance of nuclear viral inclusions)
Molluscum Contagiosum **(Poxvirus)**	
Lower genital tract *Direct contact / shared articles* *Sexual transmission*	- Common in young children (2-12yo): trunk, arms, legs; or adults: genitals, lower abdomen, buttocks, inner thighs - Skin / mucosal lesions: **pearly dome-shaped papules with dimpled center** - **Microscopy**: intracytoplasmic eosinophilic viral inclusions
Fungal infections (e.g. *Candida*)	
Lower genital tract *Candidiasis* **not** *considered an STD*	- Extremely common; in fact, yeast are part of many women's normal vaginal microflora. Development of symptomatic candidiasis is typically a **result of disturbance in the patient's vaginal microbial ecosystem** e.g. DM, pregnancy - **Microscopy**: pseudospores or filamentous fungal hyphae
Trichomonas vaginalis	
Lower genital tract *Sexual transmission*	- Asymptomatic or yellow, frothy vaginal discharge, dysuria etc. - Characteristic colposcopic appearance: '**Strawberry cervix'** - **Microscopy**: Large flagellated ovoid protozoa

Gardnerella vaginalis	
Lower genital tract	- Main cause of **bacterial vaginosis; implicated in premature labour** - Thin green-gray 'fishy' vagina discharge - **Microscopy**: superficial and intermediate squamous cells covered with a shaggy coating of coccobacilli
Pelvic inflammatory disease (PID) e.g. *Neisseria gonorrhoeae, Chlamydia*	
Lower and upper genital tract	- Infection that begins in the vulva / vagina and spread upwards to involve rest of the FGT, resulting in pelvic pain, adnexal tenderness, fever and vaginal discharge - Acute complications: **peritonitis, bacteraemia** - Chronic complications: **infertility, ectopic pregnancy, pelvic pain, intestinal obstruction** - **Microscopy**: acute inflammation of involved mucosal surfaces, acute suppurative salpingitis, salpingo-oophoritis, tubo-ovarian abscesses, pyosalpinx. With time, can progress to chronic salpingitis (scarring and fusion of the plicae) or hydrosalpinx

III. VULVA

May be affected by inflammatory diseases, skin cysts and tumours that affect skin elsewhere, as well as more specific vulvar disorders.

Bartholin cyst: result from obstruction of the duct by inflammatory process. Bartholin gland infection (adenitis) may result in abscess.

Lichen sclerosus: major non-neoplastic cause of leukoplakia (white plaques or macules that may coalesce, resembling parchment/porcelain). Most common in postmenopausal women, possibly related to an autoimmune process. Not premalignant but increases risk of squamous cell carcinoma of vulva.

Squamous cell hyperplasia (aka lichen simplex chronicus): also presents as leukoplakia; non-specific condition resulting from rubbing or scratching of the skin to relieve pruritus. Not premalignant.

Benign exophytic lesions

- **Condyloma acuminatum**: Benign genital wart caused by low oncogenic risk HPV (usu. type 6 and 11). Usually multifocal, may involve vulva, perineal, perianal regions, vagina and rarely cervix. Histology: characteristic viral cytopathic changes (koilocytic atypia)
- **Fibroepithelial polyp** (aka skin tag)
- **Squamous papilloma:** Benign exophytic proliferation covered by non-keratinised squamous epithelium

Squamous neoplastic lesions: Vulvar intraepithelial neoplasia (VIN) and vulvar carcinoma

(1) Vulvar carcinomas are uncommon; Squamous cell carcinoma is the most common histologic type
(2) 2 groups based on etiology, pathogenesis and histologic features:
  1. **Basaloid and warty carcinomas (30%)**: high risk HPV infection (usu HPV16). Younger age. Precursor: **classic vulvar intraepithelial neoplasia (VIN).** Risk factors same as those for cervical squamous intraepithelial lesions (CIN) which is also HPV related.
  Histology: Classic VIN appears similar to CIN. Basaloid carcinoma comprises nests and cords of small basaloid cells that lack maturation and resemble the basal layer of the normal

epithelium. Warty carcinoma displays exophytic papillary architecture and prominent koilocytic atypia.

2. **Keratinising squamous cell carcinomas (70%)**: unrelated to HPV infection. Older women. Precursor: **differentiated VIN / VIN simplex.** Occurs most often in women with long-standing lichen sclerosus or squamous cell hyperplasia, possibly due to chronic epithelial irritation facilitating acquisition of driver mutations in oncogenes and tumour suppressors. **Histology:** Differentiated VIN shows marked atypia of the basal layer and normal-appearing differentiation of the more superficial squamous cells. Invasive keratinizing squamous cell carcinoma comprises nests and tongues of malignant squamous epithelium with prominent keratin pearls.

- Risk of cancer development in VIN depends on duration and extent of disease, and immune status of patient. Once invasive cancer develops, the risk of metastatic spread depends on tumour size, depth of invasion and presence of lymphovascular invasion.

Glandular neoplastic lesions: Vulva contains modified apocrine sweat glands like the breast, and therefore may be involved by tumours with counterparts in the breast

Papillary hidradenoma: sharply circumscribed nodule usually on the labia majora or interlabial folds +/- ulceration. Histology: identical to intraductal papilloma of the breast.

Extramammary Paget disease: similar to Paget disease of the breast in clinical presentation - pruritic red crusted area usually on the labia majora. However, unlike Paget disease of the nipple, vulvar Paget is typically **not** associated with underlying cancer. In the rare cases when invasion occurs, prognosis is poor. Histology: intraepithelial proliferation of malignant cells with abundant pale cytoplasm.

IV. VAGINA

Developmental anomalies: include septate/double vagina and Gartner duct cysts.

Neoplasms: Primary tumours are rare.

- Most of the benign tumours of the vagina occur in reproductive age women and include stromal tumours (stromal polyps).
- The most common malignant tumour is **carcinoma spreading from the cervix**, followed by **primary squamous cell carcinoma of the vagina**. **Clear cell carcinoma** of the vagina has been reported in young women whose mothers were treated with diethylstilbestrol (DES, used to prevent threatened abortions in 1940-60s) and developed vaginal adenosis. Infants may develop **embryonal rhadomyosarcoma**, a rare malignant mesenchymal tumour with skeletal muscle differentiation that tends to grow as rounded polypoid masses with a 'grape-like' appearance (sarcoma botryoides).

V. UTERINE CERVIX

Consists of **ectocervix** (covered by squamous epithelium that is continuous with vaginal wall) and **endocervical canal** (lined by columnar mucinous epithelium). The position of the squamocolumnar

junction (aka "**transformation zone [TZ]**") is variable and changes with age and hormonal influence. Squamous metaplasia refers to the replacement of glandular epithelium by advancing squamous epithelium. Immature squamous metaplastic epithelial cells in the TZ are most susceptible to HPV infection, and hence this is where cervical precursor lesions and cancers develop.

Inflammation: Some degree of cervical inflammation (acute and chronic cervicitis) may be found in virtually all women (as a result in altered vaginal microenvironment through varies activities/events), and is usually of little clinical consequence. However, infections by gonococci, chlamydiae, mycoplasmas and HSV may produce significant inflammation and are important to identify due to their association with upper genital tract disease, complications during pregnancy and sexual transmission.

Endocervical polyps: Benign growths that may cause of irregular vaginal 'spotting' or bleeding

Premalignant and malignant neoplasms: Squamous intraepithelial lesions (SIL) and Cervical Carcinoma

- Death rate from cervical cancer has greatly declined due to 1. Effectiveness of cervical screening (Pap test) in detecting precursor lesions and low-stage curable cancers 2. Slow progression from precursor lesions to invasive carcinoma (over years) 3. Accessibility of the cervix to Pap testing and visual exam (colposcopy). Pap test is a cytologic examination of cells sampled from the TZ of the cervix via a brush or spatula and stained with the Papanicoloaou method. HPV DNA can also be tested in the cervical scape, which has a higher sensitivity but lower specificity than the Pap test (particularly in women < 30 yo)
- **Pathogenesis**: HPV of high oncogenic risk (**high-risk HPV**) are the most important factor: most commonly HPV 16 (accounts for 60% of cervical cancer cases) and 18 (10%), although there are ~15 types. High risk HPV is also implicated in squamous cell carcinomas in other sites e.g. penis, tonsils.
    - Genital HPV infections are common and mostly asymptomatic and transient, being eliminated by the immune response over months-2 years (high-risk HPV last longer than low-risk HPV). **Persistent infection** increases the risk of development of cervical precursor lesions and subsequent carcinoma.
    - HPV infects **immature basal cells** of the squamous epithelium in areas of epithelial damage or **immature metaplastic squamous cells** at the squamocolumnar junction. The cervix, with its relatively large area of immature squamous metaplastic epithelium, is thus more vulnerable to HPV infection than vulvar skin which is covered by mature squamous cells.
    - However, HPV viral replication occurs in **maturing squamous cells**. These more mature cells which are usually arrested in the G1 phase of the cell cycle continue to actively progress through the cell cycle when infected with HPV
    - HPV uses the host cell DNA synthesis machinery to replicate its own genome, with production of **viral proteins E6 and E7**. E7 binds the hypophosphorylated (active) form of RB and promotes its degradation, and also binds and inhibits cyclin-dependent kinase inhibitors p21 and p27. This enhances cell cycle progression and impairs DNA damage repair. E6 binds to and promotes degradation of tumour-suppressor protein p53, and also upregulates telomerase expression, leading to cellular immortalization. **Overall, there is increased**

proliferation of cells prone to acquired additional mutations that may lead to cancer development. E7 and E6 of low-risk HPVs have lower or no affinity with RB and p53.

- **Integration of the viral DNA** into the host cell genome increases risk of malignant transformation, due to the increased expression of E6 and E7, and potential dysregulation of oncogenes such as *MYC* near sites of viral insertion. In contrast, viral DNA is extrachromosomal (episomal) in precursor lesions or condylomata.
- **HPV alone is insufficient to cause cancer**; other factors e.g. exposure to co-carcinogens and host immune status determine whether an HPV infection regresses or persists and eventually progresses to cancer

- **Risk factors**: Early age at first intercourse, multiple sexual partners, male partner with multiple previous sexual partners, increased parity, presence of high-risk HPV, genital infections, smoking, oral contraceptives
- Vaccination against high-risk HPVs is now recommended for cervical cancer prevention, but as it does not protect against all high-risk HPC types, patients should still go for cervical cancer screening

Cervical intraepithelial neoplasia (CIN) / Squamous intraepithelial lesion (SIL)

- **Low-grade SIL (LSIL)**: refers to lesions with only koilocytic atypia or mild dysplasia (CIN1)
  - 10 times more common than HSIL. >80% a/w high-risk HPV, mostly HPV-16.
  - Associated with a productive HPV infection in which there is high level of viral replication and only mild alterations in the growth of host cells
  - Most regress; 10% progress to HSIL. **Does not progress directly to invasive carcinoma**
  - Can be followed-up +/- local ablation
  - **Histology**: Koilocytic atypia = nuclear hyperchromasia and irregularity +/- multinucleation with perinuclear haloes. Immature cell layer (expanded from its normal basal layer) is confined to lower 1/3 of the squamous epithelium
- **High-grade SIL (HSIL)**: refers to lesions of moderate dysplasia (CIN2) or severe dysplasia (CIN3)
  - Majority develop from LSIL; 20% are de-novo. 100% a/w high-risk HPV, mostly HPV-16
  - Progressive deregulation of the cell cycle by HPV results in increased cellular proliferation, decreased or arrested epithelial maturation and a lower rate or viral replication
  - Considered **high risk for progression to carcinoma** (~10% progress to ca within 2-10 yrs)
  - Treated with cervical conization (superficial excision)
  - **Histology**: Immature cell layer (expanded from its normal basal layer) involves the upper 2/3 of the squamous epithelium. The disturbed growth regulation also leads to overexpression of p16, a CDK inhibitor, and increased mitotic activity (e.g. via a proliferation marker Ki-67) which can be detected on immunohistochemistry

Cervical carcinoma

- ~80% are **squamous cell carcinoma** (keratinizing or non-keratinising); 15% are **adenocarcinoma** (precursor = adenocarcinoma in-situ); remaining 5% are adenosquamous and neuroendocrine carcinomas
- All these tumour types are caused by high-risk HPVs

- **Clinical features**: More than half are detected in women who did not participate in regular screening. **Prognosis**: Depends on stage of cancer at diagnosis, and to some degree, histologic subtype (small cell neuroendocrine carcinoma have a very poor prognosis). Advanced cervical carcinoma spreads by (i) direct extension to contiguous tissues, including paracervical soft tissue, bladder, ureters, rectum and vagina (ii) lymphovascular invasion to lymph nodes and (iii) distant metastases. Most patients with advanced cervical cancer die of complications from local tumour invasion e.g. ureteral obstruction rather than distant metastases. **Treatment**: Early invasive carcinomas (microinvasive carcinomas) can be treated by cervical cone excision; most other invasive carcinomas require hysterectomy with LN dissection +/- radiation and chemotherapy

VI. UTERINE CORPUS AND ENDOMETRIUM

The endometrium undergoes dynamic physiologic and morphologic changes during the menstrual cycle in response to sex steroid hormones produced in the ovary, which is itself regulated by the hypothalamus-pituitary axis

Endometrial histology in the menstrual cycle	
Menses	Shedding of the superficial portion of the endometrium (*functionalis*) due to dissolution of the corpus luteum and drop in progesterone levels: Glandular and stromal breakdown
Proliferative phase	Rapid growth of glands and stroma arising from the deeper portion of the endometrium (*basalis*) due to estrogen stimulation: tubular glands lined by tall pseudostratified columnar cells with mitotic activity within a compact cellular endometrial stroma
Ovulation	Cessation of endometrial proliferation and start of glandular differentiation in response to progesterone secreted by the ovarian corpus luteum
Secretory phase	Secretory vacuoles (subnuclear in early phase, supranuclear in late phase) in the glandular epithelium, with increasing dilatation and tortuosity / serration of the glands. Increasing stromal oedema; later phase shows pre-decidual change (stromal cell hypertrophy and eosinophilia)

Abnormal uterine bleeding

Causes include specific pathologic conditions e.g. infections (chronic endometritis), anatomic lesions (endometrial polyps, submucosal leiomyomas, endometrial neoplasms), or hormonal disturbances resulting in dysfunctional uterine bleeding (uterine bleeding that lacks any underlying structural abnormality e.g. anovulatory cycle, inadequate luteal phase).

- **Anovulatory cycle** (failure to ovulate): Most frequent cause of dysfunctional bleeding. Most common at menarche and perimenopausal period, and other conditions causing hormonal imbalance e.g. endocrine disorders (thyroid, adrenal, pituitary), polycystic ovaries, generalized metabolic disturbances e.g. obesity, malnutrition. Results in excessive endometrial stimulation by estrogens unopposed by progesterone, which usually resolve with a subsequent ovulatory cycle. Repeated anovulation may result in heavy bleeding or endometrial hyperplasia. **Histology**: proliferative endometrium with mild architectural disorder (e.g. cystic dilatation)
- **Inadequate luteal phase:** due to inadequate progesterone production during post-ovulatory period. **Histology**: secretory endometrium with features lagging behind those expected for the date

Inflammatory disorders

Acute endometritis: uncommon; limited to bacterial infections that arise after delivery, abortion or miscarriage e.g. retained products of conception (POC)

Chronic endometritis: occurs in association with chronic pelvic inflammatory disease (PID), retained POC, intrauterine contraceptive devices or tuberculosis (from military spread or tuberculous salpingitis). 15% have no apparent cause. Diagnosis requires histologic identification of plasma cells in the stroma. The responsible organism may not be detected by culture, but antibiotic therapy still indicated to prevent other complications e.g. salpingitis

Endometriosis and Adenomyosis

- **Endometriosis:** presence of "ectopic" endometrial tissue (endometrial stroma +/- glands) at a site outside of the uterus e.g. ovaries, uterine ligaments, rectovaginal septum, bowel and appendix, laparotomy scars). **Adenomyosis:** related condition - endometrial tissue within the myometrium (uterus is usually diffusely enlarged with a trabeculated cut surface)
- **Pathogenesis**: Several proposed theories – *(1) Regurgitation theory*: endometrial tissue implants at ectopic sites via retrograde flow of menstrual endometrium; *(2) Benign metastases theory*: endometrial tissue can "spread" to distant sites e.g. bone, lung, via lymphovascular spread; *(3) metaplastic theory*: endometrium arises directly from coelomic epithelium (mesothelium of the abdopelvis) due to shared origin (see 'I. Normal Development'). Mesonephric remnants may also undergo endometrial differentiation; (4) *extrauterine stem/progenitor cell theory*: stem/progenitor cells from the bone marrow differentiate into endometrial tissue
- **Clinical features**: Affects ~10% of women of reproductive age. Endometriotic lesions bleed in response to both extrinsic cyclic (ovarian) and intrinsic hormonal stimulation. Can present with infertility, dysmenorrhea (painful menses), pelvic pain, intestinal symptoms (due to involvement of bowel wall). Also associated with endometrioid and clear cell ovarian cancers
- **Gross**: Nodules with red-blue to yellow-brown appearance on or just beneath the mucosal/serosal surfaces at sites of involvement. When extensive, organizing haemorrhage and cause extensive fibrous adhesions between organs. Ovaries can have large cystic masses filled with haemorrhagic brown fluid (endometriotic 'chocolate' cysts).
- **Histology**: Endometrial stroma +/- glands +/- haemosiderin. **Atypical endometriosis** (likely precursor to endometriosis-related ovarian carcinomas) can have cytologic epithelial atypia and/or architectural atypia (glandular crowding) resembling complex atypical endometrial hyperplasia

Endometrial polyps: usually sessile exophytic endometrial mass(es) projecting in the uterine cavity. May be asymptomatic or cause abnormal bleeding if they ulcerate or undergo necrosis. Polyps are responsive to estrogen but show little/no response to progesterone. A/w tamoxifen (used in breast cancer due to its anti-estrogenic effects in the breast, but has weak pro-estrogenic effects in the endometrium). Adenocarcinoma can rarely arise within endometrial polyps

Endometrial hyperplasia

- Increased proliferation of endometrial glands relative to stroma, resulting in increased gland:stroma ratio. Important cause of abnormal bleeding and frequent precursor to endometrial endometrioid carcinoma (both share specific acquired genetic alterations linked to oncogenesis e.g. inactivation of *PTEN* tumour suppressor gene, an important negative regulator of the PI3K/AKT growth-regulatory pathway, is seen in >20% of hyperplasias and 30-80% of endometrial carcinomas).
- **Pathogenesis**: Prolonged estrogenic stimulation of the endometrium, which can be due to **anovulation** (e.g. in polycystic ovarian syndrome, menopause), **increased endogenous estrogen production** (e.g. obesity where there is peripheral conversion of androgens to estrogens, functioning ovarian granulomas cell tumours or ovarian cortical stromal hyperplasia), or **exogenous estrogen** (e.g. estrogen replacement therapy)
- **Histology**: Increased gland:stroma ratio +/- nuclear atypia (**hyperplasia without atypia vs atypical hyperplasia / endometrial intraepithelial neoplasia**). The features of atypical hyperplasia can overlap with well-differentiated endometrioid carcinoma

Endometrial carcinoma

- Most common invasive carcinoma of the female genital tract
- **Pathogenesis**: broadly classified into type I and II based on clinicopathologic studies and molecular analyses

Type I (~80%, 55-65 yo)	Type II (~15%, 65-75 yo)
Mostly **endometrioid carcinomas** (tumours that mimic proliferative endometrial glands), mostly low-grade. Poorer differentiated tumours have more solid growth pattern (excludes areas of squamous differentiation).	Poorly differentiated (high grade) carcinomas, most commonly **serous carcinomas,** less commonly clear cell carcinoma, malignant mixed Mullerian tumour. Serous carcinomas classically have a papillary growth pattern with marked cytologic atypia.
Setting / precursor: **Endometrial hyperplasia** A/w unopposed estrogen stimulation, obesity, diabetes, hypertension	Setting: **Endometrial atrophy.** Precursor – **serous endometrial intraepithelial carcinoma (SEIC)**
A/w gene mutations that increase signaling through the **PI3K/AKT pathway** e.g. *PTEN* tumour suppressor gene, *PIK3CA* oncogene, activating *KRAS* mutations, Loss of function mutations in *ARID1A.* Other genetic pathways include defects in **DNA mismatch repair genes** (both sporadic and patients with HNPCC. *TP53* loss-of-functions mutations only in poorly diff carcinoma (~50%)	A/w *TP53* **mutations** (>90% of serous carcinomas, 75% of SEIC); also *PIK3CA*. Serous carcinoma presumably begins as a surface epithelial neoplasm that extends into adjacent gland structures and later invades endometrial stroma.
Spread generally occurs by myometrial invasion, then direct extension to adjacent structures / organs. Late stages include LN spread and distant metastases. Indolent; Prognosis generally better	High propensity to exfoliate, travel through fallopian tubes and implant on peritoneal surfaces like their ovarian counterparts (intraperitoneal spread) Aggressive; Prognosis poorer

- **Clinical features**: Peak incidence in postmenopausal women. Usually presents with irregular / postmenopausal vaginal bleeding. Prognosis depends on clinical stage at diagnosis, histologic grade and subtype. Stage 1 endometrioid carcinoma (grade 1 or 2) has ~90% 5-yr survival with surgery alone or in combination with radiation therapy. Serous carcinoma has propensity for extrauterine spread even when apparently confined to endometrium / surface epithelium; the overall 5-yr

survival is 18-27%, with recurrence rate as high as 80% even when confined to uterus. Patients may be treated with chemotherapy due to the aggressive nature of serous carcinoma, even in the absence of detectable extrauterine spread

Malignant Mixed Mullerian Tumours (MMMT) (aka Carcinosarcomas): Endometrial adenocarcinomas with a malignant mesenchymal component, which can resemble uterine mesenchymal elements (stromal sarcoma, leiomyosarcoma) or heterologous elements (rhabdomyosarcoma, chondrosarcoma). Studies suggest that the most of these tumours are **carcinomas with sarcomatous differentiation**, as mutations found in MMMTs tend to involve the same genes that are mutated in endometrial carcinoma e.g. *PTEN*, *TP53*, *PIK3CA*. MMMTs tend to be bulky and polypoid, occur in post-menopausal women and present with bleeding. Prognosis is poor, and worse for tumours with heterologous mesenchymal components. Metastases usually only contain the epithelial components.

Endometrial stromal tumours (<5% of endometrial cancers)

Adenosarcomas: Malignant stromal tumour admixed with benign but abnormally shaped glands. Often large broad-based endometrial polypoid growths in 30-40 yo women. Low-grade malignancy.

Pure stromal neoplasms: includes **Benign stromal nodules** (well-circumscribed tumours) and **Endometrial stromal sarcomas** (infiltrative tumours - low grade ESS are a/w *JAZF1* gene translocation; high grade ESS show marked atypia and a/w other gene fusions). About half of stromal sarcomas (both low and high grade) recur, with possible late distant metastases.

Myometrial tumours

Leiomyomas: Commonly called fibroids. Benign smooth muscle neoplasm that is possibly the most common tumour in females, most often multiple. *MED12* mutations have recently been identified in ~70% of uterine leiomyomas.

- **Clinical features**: Patients can be asymptomatic, or present with abnormal bleeding (especially if submucosal), urinary frequency (from bladder compression), pain from infarction of large or pedunculated tumours, and impaired fertility (due to distortion of the uterine cavity). Complications include increased risk of spontaneous abortion, fetal malpresentation and post-partum haemorrhage. Malignant transformation, if it occurs at all, is extremely rare.
- **Gross**: sharply circumscribed, discrete, found, firm gray-white tumours that vary in size, mostly within the myometrium (rarely uterine ligaments, cervix) and can be submucosal (just beneath the endometrium), intramural or subserosal. Cut surface has a classic bulging whorled pattern. Can have haemorrhage (especially in pregnancy and progestin therapy)
- **Histology**: interlacing bundles of smooth muscle cells with 'cigar-shaped' nuclei and abundant eosinophilic fibrillary cytoplasm. Several variants exist, including Cellular leiomyoma, leiomyoma with bizarre nuclei (symplastic leiomyoma), benign metastasizing leiomyoma

Leiomyosarcomas: Uncommon malignant tumours. Thought to arise from myometrium or endometrial stromal precursor cells rather than leiomyomas. Leiomyosarcomas have complex karyotypes, although a subset also have *MED12* mutations.

- **Clinical features:** Peak incidence at 40-60 yo. Tumours often recur following surgery, and >50% eventually have distant metastases or dissemination throughout the abdominal cavity
- **Gross:** either bulky fleshy masses that invade the uterine wall, or polypoid masses that project into the uterine cavity.
- **Histology:** Distinction from leiomyoma is based on (1) nuclear atypia, (2) mitotic index, and (3) tumour cell necrosis.

VII. FALLOPIAN TUBES

- Most commonly affected by **infections / inflammatory conditions** (e.g. **suppurative salpingitis** caused by pyogenic organisms, most commonly *Gonococcus* and *Chlamydiae*; **tuberculous salpingitis**). Other conditions include **ectopic (tubal) pregnancy**, **endometriosis, paratubal cysts** or **hydatids of Morgagni** (small cysts lined by tubal-type epithelium, presumed to arise in remnants of the Mullerian duct).
- Tumours of the fallopian tube are uncommon. Benign tumours include **adenomatoid tumours** (mesothelial origin). Malignant tumours include **adenocarcinoma**, with recent studies suggesting that at least a subset of serous ovarian cancers actually arise from the fallopian tube epithelium.

VIII. OVARIES

Non-neoplastic and functional cysts

Cystic follicles: very common, often multiple. Originate from unruptured graafian follicles / follicles that ruptured and immediately sealed. Follicle cysts are >2 cm in size. Histology shows inner granulosa lining cells and outer theca cells, that may undergo pronounced luteinization (hyperthecosis) which may be associated with increased estrogen production and endometrial abnormalities.

Luteal cysts (corpora lutea): present in normal ovaries of women of reproductive age. Lined by a rim of bright yellow tissue containing luteinized granulosa cells.

Polycystic ovarian syndrome (PCOS): ~6-10% of reproductive age women worldwide. **Complex endocrine disorder** characterized by hyperandrogenism, menstrual abnormalities, polycystic ovaries (numerous cystic follicles/follicle cysts that enlarge the ovaries), chronic anovulation and decreased fertility, and a/w obesity, type 2 diabetes (insulin resistance) and premature atherosclerosis. Due to the increase in free serum estrone levels, patients are at risk for endometrial hyperplasia and carcinoma. Note: polycystic ovaries alone is not specific and can be seen in 20-30% of all women.

Stromal hyperthecosis (cortical stroma hyperplasia): disorder of ovarian stroma most often in post-menopausal women but may overlap with PCOS in younger women. Characterised by (bilateral) uniform ovarian enlargement (up to 7 cm) with homogenous white-tan appearance. Histology shows

hypercellular stroma and luteinized stromal cells. Can be mimicked by **theca lutein hyperplasia of pregnancy**, a physiologic condition in response to pregnancy hormones.

Neoplasms

Can be grouped according to their origin from each of the 3 main ovarian cell types: 1. **Mullerian epithelium**, 2. **germ cells** and 3. **sex cord-stromal cells**. 80% are benign, most in young women (20-45 yo). Borderline tumours occur at slightly older ages, and malignant tumours in older women (45-65 yo). Most ovarian cancers have spread beyond the ovary at the time of diagnosis and thus account for a disproportionate number of deaths from cancer of the female genital tract. **Metastases to the ovary** are mostly from primary Mullerian origin (e.g. uterus, fallopian tube, contralateral ovary), or breast and gastrointestinal tract (Krukenberg tumour is the classic metastatic GI cancer causing bilateral ovarian metastatses composed of signet-ring cancer cells, usually from the stomach).

(1) Epithelial tumours
Accounts for most primary ovarian neoplasms. Classification is based on histologic type of epithelium (**serous, mucinous, endometrioid, clear cell, transitional cell**) and their degree of proliferation (**benign, borderline, malignant**). The benign tumours may be further subclassified based on the presence of cystic and fibrous components (**cystadenoma**, **cystadenofibroma**, **adenofibroma**). Ovarian carcinomas may be broadly categorized into **Type I** (low-grade tumours, often arise in a/w borderline tumours or endometriosis e.g. low-grade serous, endometrioid and mucinous tumours) and **Type II** (mostly high-grade serous carcinoma that arise from serous intraepithelial carcinoma).
Clinical presentation: Similar in all ovarian carcinomas, mostly lower abdominal pain and abdominal enlargement, also gastrointestinal symptoms, urinary frequency, pelvic pressure etc. Malignant lesions also tend to cause progressive weakness, weight loss and cachexia. If there is breach of the ovarian capsule and seeding of the peritoneal cavity, massive ascites may be seen. Metastasis may occur to the opposite ovary, regional lymph nodes, distant sites e.g. liver, lung etc. **Prognosis**: Most women with ovarian carcinoma present with high stage disease, resulting in relatively poor 5- and 10-year survival rates. CA-125 serum marker is used in patients with known disease to monitor disease recurrence / progression.

Serous Tumours (~50% of ovarian epithelial tumours, and 40% of all ovarian cancers)
- 70% are benign / borderline (~20-45 yo), and 30% are malignant (older women unless familial)
- **Pathogenesis**: Not well-established, but **nulliparity**, **family history** and **heritable mutations** (*BRCA1 and 2*) are important in development of serous carcinomas. Women 40-59 yo who have taken **oral contraceptives** or undergone **tubal ligation** have reduced risk. Serous ovarian carcinoma is divided into 2 major groups based on their degree of nuclear atypia and differing mutational profiles, and correlates with patient survival:
    1. **Low-grade serous carcinoma:** may arise in a/w **serous borderline tumours**.
       KRAS, *BRAF* or *ERBB2* oncogene mutations, and wild-type *TP53*.
    2. **High-grade serous carcinoma:** may arise from in-situ lesions in the fallopian tube fimbriae (**serous tubal intraepithelial carcinoma** [STIC]) or **serous inclusion cysts** within the ovary.

(Women at high-risk for ovarian carcinoma thus now undergo salpingo-oophorectomy and not just oophorectomy).

TP53 mutations, and lack *KRAS/BRAF* mutations. Almost all ovarian carcinomas arising in women with *BRCA1/2* mutations are HGSC with *TP53* mutations, although interestingly, *BRCA1/2* mutations are rare in sporadic HGSC.

- **Clinical features**: Both low and high grade serous carcinomas have propensity to spread to peritoneal surfaces and omentum (especially if there is ovarian surface involvement), and are commonly a/w ascites. However, low grade carcinomas, even after spread outside ovary, often progress slowly, in contrast to high grade tumours which are aggressive and a/w rapid clinical deterioration. Prognosis therefore depends on stage as well pathologic classification of the tumour. Borderline tumours may also involve the peritoneal surfaces as non-invasive or invasive implants. Because of their protracted course, borderline tumours may recur after many years

- **Gross**: Frequently bilateral (~66% of serous carcinomas). Multicystic lesion in which there are intracystic papillary epithelial proliferations or as a mass projecting from the ovarian surface. Benign tumours usually have a smooth wall with no epithelial thickening or small papillary projections; borderline tumours have increased numbers of papillary projections; malignant tumours tend to have large solid or papillary areas and fixation/nodularity of the capsule. Both borderline and malignant tumours may involve the ovarian capsular surface.

- **Histology**: **Benign cysts** are lined by tubal-type epithelium / columnar ciliated cells. **Serous borderline tumours** show increased complexity of the stromal papillae with nuclear stratification and atypia. It can grow in a delicate micropapillary pattern, thought to be the precursor to low-grade serous carcinoma. **High grade serous carcinomas** have more complex growth patterns and widespread infiltration / invasion or frank effacement of the underlying stroma, with marked nuclear atypia, atypical mitoses and multinucleation. **STIC** comprises cells morphologically identical to high grade serous carcinoma but lacks invasion. Psammomatous (concentric) calcifications are characteristic of serous tumours but not specific.

Mucinous tumours (~20-25% of all ovarian neoplasms, and 3% of all ovarian cancers)
- Mostly benign/borderline tumours, in middle adult life
- **Pathogenesis**: *KRAS* proto-oncogene mutation seen in 58% of benign mucinous cystadenomas, 75-86% of mucinous borderline tumours and 85% of mucinous carcinomas. The other mutations that collaborate with *KRAS* mutation are still largely unknown
- **Clinical features**: 10 year survival is generally good, except for those that have spread beyond the ovary (usually fatal); bilateral presentation of mucinous tumours or associated pseudomyxoma peritonei (extensive mucinous ascites, cystic epithelial implants on peritoneal surfaces and adhesions) is however uncommon and metastatic mucinous adenocarcinoma (e.g. from appendix/GIT) should be excluded
- **Gross**: Rarely (5%) bilateral, and seldom involves ovarian surface. Tend to be large multiloculated cystic masses filled with sticky gelatinous fluid rich in glycoproteins
- **Histology**: **Benign mucinous tumours** are lined by tall columnar cells with apical cytoplasmic mucin – mostly gastric/intestinal-type differentiation, and less commonly endocervical-type differentiation.

Mucinous borderline tumours display epithelial stratification, tufting and/or papillary intraglandular growth. **Mucinous carcinomas** typically show confluent glandular growth ("expansile invasion")

Endometrioid tumours (~10-15% of all ovarian cancers)
- Benign/borderline tumours are uncommon
- **Pathogenesis**: ~15-20% of endometrioid carcinomas coexist with endometriosis (these tumours arise a decade earlier than those not a/w endometriosis); are also occasionally a/w areas of borderline tumour. Molecular changes show similarity to endometrial endometrioid carcinoma: *PTEN*, *PIK3CA*, *ARID1A* and *KRAS* mutations that increase PI3K/AKT pathway signaling, mismatch DNA repair gene mutations and *CTNNB1* mutations. *TP53* mutations are only common in poorly differentiated tumours.
- **Clinical features**: 5 year survival for stage 1 tumours is ~75%. 15-30% of ovarian endometrioid carcinomas occur concurrently with endometrial carcinoma, and likely arise independently rather than metastatic spread (due to relatively good prognosis in such cases)
- **Gross**: 40% bilateral (which usually implies extension of the neoplasm beyond the genital tract). Endometrioid carcinoma typically present with solid and cystic areas
- **Histology**: Usually low grade with tubular glands resembling benign or malignant endometrium

Clear cell carcinoma
- Benign and borderline clear cell tumours are rare, and clear cell carcinomas are uncommon
- **Pathogenesis**: May arise in a/w endometriosis or endometrioid carcinoma of the ovary, and also shares common genetic alterations (*PIK3CA*, *ARID1A*, *KRAS, PTEN* and *TP53*) with endometrioid carcinoma (although at different frequencies).
- **Clinical features**: 90% 5-yr survival when confined to ovaries, but poor outcome in advanced stages
- **Gross**: can be predominantly solid or cystic
- **Histology**: Large epithelial cells with abundant clear cytoplasm, which can be arranged in sheets or tubules (in solid neoplasms) or lining cystic spaces.

Transitional cell tumours (aka Brenner tumours; ~10% of ovarian epithelial tumours)
- Usually benign and unilateral; contains nests of neoplastic epithelial cells that resemble urothelium. Malignant Brenner tumours (considered low-grade (type I) carcinomas) have a benign Brenner tumour component, while transitional cell carcinomas (considered high grade (type II) carcinomas) do not show this benign component.

(2) Germ cell tumours

Constitutes 15-20% of all ovarian tumours. Most are benign cystic teratomas in women of reproductive age; others are mostly malignant in young women and children. Largely similar to germ cell tumours in the male testis.
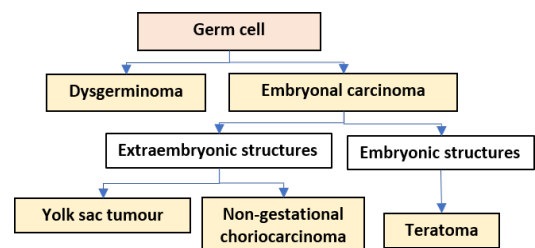
Teratomas
(i)   **Mature (Benign) Teratomas (dermoid cysts)**
Mostly cystic, bilateral in 10-15% of case, in young women during reproductive years. May be incidental or a/w paraneoplastic syndromes. ~1% may undergo malignant transformation, most commonly to squamous cell carcinoma. Genetic analyses indicate that the majority of teratomas arise from an ovum after the first meiotic divison.
Gross: Unilocular cysts containing hair and sebaceous material. Often a solid nodule within the wall which may contain teeth, bone or calcifications.
Microscopy: tissues derived from ectodermal, mesodermal and endodermal lineages e.g. stratified squamous epithelium with pilosebaceous units, glandular epithelium, cartilage, bone, neural tissue. Dermoid cysts may sometimes be incorporated within the wall of a mucinous cystadenoma.

(ii)   Immature (Malignant) Teratomas
Rare tumours that differ from benign teratomas in the presence of embryonal and immature fetal tissue (histologic grade is based on the proportion of tissue containing immature neuroepithelium). Mostly in prepubertal adolescents and young women (~18 yo). Rapid growth with frequent ovarian capsule involvement with local or distant spread. Stage I tumours which are low grade have excellent prognosis, while higher grade tumours confined to the ovary are generally treated with prophylactic chemotherapy.

(iii)   Monodermal Teratomas
Always unilateral. Most commonly **struma ovarii** (composed entirely of mature thyroid tissue which may be functional) and **carcinoid** (presumably arises from intestinal tissue found in teratomas; can also be functional and cause carcinoid syndrome even in the absence of hepatic metastases since ovarian veins are directly connected to systemic circulation. Ddx: Metastatic intestinal carcinoid, which is almost always bilateral). **Struma carcinoid** = combination of struma ovarii and carcinoid

Dysgerminoma (~2% of ovarian cancers, ~50% of malignant ovarian germ cell tumours)
- Ovarian counterpart of testicular seminoma. 75% occur in 10-30 yo.
- **Clinical features**: All dysgerminomas are malignant, but only ~1/3 are aggressive. Responsive to chemotherapy. Overall survival >80%
- **Gross**: 80-90% are unilateral. Solid yellow-white to gray-pink, soft and fleshy appearance
- **Microscopy**: Sheets or cords of large vesicular cells with clear cytoplasm, well-defined cell borders and centrally placed nuclei. Scant fibrous stroma containing mature lymphocytes +/- occasional granulomas.
- Immunohistochemical profile: OCT3/4+ CKIT+ (~1/3 have activating mutations in *KIT* gene – can be a therapeutic target)

Yolk Sac Tumour (aka endodermal sinus tumour)
- 2nd most common malignant tumour of germ cell origin
- Thought to be derived from malignant germ cells that are differentiating along the extraembryonic yolk sac lineage; tumour cells thus also secrete alpha-fetoprotein
- **Clinical features**: usually children or young women presenting with abdominal pain and a rapidly growing pelvic mass; usually unilateral. Survival >80% with combination chemotherapy

- **Histology**: characteristic histologic features = Schiller-Duval body (glomerulus-like structure composed of a central blood vessel enveloped by tumour cells within a space that is also lined by tumour cells), intracellular and extracellular hyaline droplets

Choriocarcinoma
- More commonly of placental origin; a germ cell origin can be confirmed only in prepubertal females because after this age, an origin from an ovarian ectopic pregnancy cannot be excluded. Most occur in combination with other germ cell tumours
- **Clinical features**: Secretes high levels of chorionic gonadotropins. Aggressive, would usually have metastasized hematogenously to lungs, liver, bone and other sites by the time of diagnosis. Unlike placental choriocarcinomas, ovarian choriocarcinomas are generally unresponsive to chemotherapy and are often fatal
- **Histology**: identical to placental choriocarcinoma

Other germ cell tumours
Includes **embryonal carcinoma** (similar to that arising in testes), **polyembryoma** (a malignant tumour containing so-called embryoid bodies), and **mixed germ cell tumours** (containing various combinations of dysgerminoma, teratoma, yolk sac tumour and choriocarcinoma).

(3) Sex cord-stromal tumours

Derived from ovarian stroma which is itself derived from sex cords of the embryonic gonad. All cell types from the undifferentiated gonadal mesenchyme (Sertoli and Leydig in males, granulosa and theca in females) can be found in the ovary. Their corresponding tumours can secrete androgens or estrogens, be masculinizing or feminizing, respectively.

Granulosa cell tumours (GCT) *(5% of all ovarian tumours)*
- 95% are adult granulosa cell tumours (distinction between adult and juvenile granulosa cell tumours based on age of patient as well as morphologic findings). *FOXL2* mutations seen in 97% of AGCT.
- **Clinical features**: Mostly in postmenopausal women. May secrete large amounts of estrogen (resulting in precocious puberty in prepubertal girls or associated with proliferative breast disease, endometrial hyperplasia and endometrial carcinoma in adult women). All GCTs have malignant potential but generally are indolent / behave like low-grade malignancies in which local recurrences (can be 10-20 years later) are amendable to surgical therapy.
- **Gross**: Usually unilateral. Can be microscopic foci to large, solid and cystic masses. Yellowish if they are hormonally active, due to intracellular lipids.
- **Histology:** Adult GCT are composed of cords, sheets or strands of small cuboidal to polygonal cells resembling granulosa cells of developing ovarian follicles. Variable histologic patterns. Call-Exner bodies are characteristic (small gland-like structures with central acidophilic material, resembling immature follicles). Can have a thecoma component.

Fibromas, Thecomas and Fibrothecomas *(4% of all ovarian tumours)*
- **Fibromas**: comprising fibroblasts; **Thecomas**: plump spindle cells with lipid droplets; **Fibrothecomas**: mixture of both cells

- **Clinical features**: Relatively common; fibromas are usually hormonally inactive while thecomas (or thecal-predominant fibrothecomas) may be hormonally active. Usually present as pelvic mass +/- pain. May be associated with ascites +/- hydrothorax (Meigs syndrome) or basal cell nevus syndrome. Mostly benign; rare fibrosarcomas exist.
- **Gross**: unilateral, solid encapsulated hard gray-white masses
- **Histology**: fibromas show well-differentiated fibroblasts with scant collagenous stroma

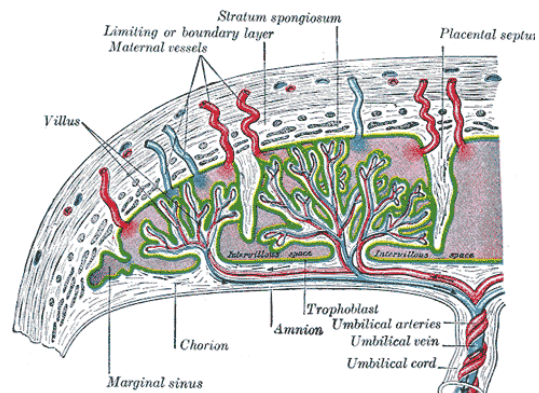### *Sertoli-Leydig Cell Tumours*
- **Clinical features**: often functional resulting in masculinization /defeminization (rarely estrogenic). All ages but mostly 10-30yo. >50% have *DICER1* mutations. <5% incidence of recurrence / metastasis
- **Gross**: unilateral, solid gray-golden brown cut surface
- **Histology**: well-differentiated tumours show tubules composed of Sertoli cells or Leydig cells interspersed with stroma. Poorly-differentiated tumours have a sarcomatous pattern with mostly absent Leydig cells and no well-formed tubules. Heterologous elements may be seen

Other Sex Cord-Stromal Tumours e.g. Hilus cell tumour, pregnancy luteoma, gonadoblastoma

IX. GESTATIONAL AND PLACENTAL DISORDERS

Normal placental anatomy

- Placenta is composed of chorionic plate, chorionic villi and decidua. Chorionic villi are composed of central stroma surrounded by an outer layer of syncytiotrophoblasts and an inner layer of cytotrophoblasts

Source: Henry Gray (1918) Anatomy of the Human Body, Plate 39

- Fetal blood enters through 2 umbilical arteries, branches into chorionic arteries and then capillaries within the chorionic villi, before returning through the umbilical vein. Maternal blood enters through the endometrial spiral arteries into the intervillous space, before flowing into the decidua and endometrial veins. The chorionic villi therefore provide a large contact area between the fetal and maternal circulations for gas and nutrient diffusion across the villous capillary endothelial cells and the thinned out syncytiotrophoblasts and cytotrophoblasts. Under normal circumstances, there is little or no mixing between fetal and maternal blood

Disorders of early pregnancy

Spontaneous abortion ('miscarriage')

- Pregnancy loss before 20 weeks of gestation; occurs in up to 40% of early pregnancies
- **Causes**: unknown in most individual instances. Known causes include **fetal chromosomal anomalies** (e.g. aneuploidy, polyploidy, translocations), **maternal endocrine factors** (e.g. luteal phase defect, poorly controlled diabetes, **physical defects of the uterus** (e.g. submucosal leiomyomas) that may

prevent or disrupt implantation, **systemic disorders affecting maternal vasculature** (e.g. hypertension, coagulopathies), and **infections** (e.g. Toxoplasma, Listeria, or viruses)

Ectopic pregnancy

- Implantation of the fetus in a site other than the normal intrauterine location (~90% of cases in the extrauterine fallopian tube; also ovary, abdominal cavity and intrauterine portion of the fallopian tube [cornual pregnancy]). ~2% of confirmed pregnancies
- **Risk factors**: 35-50% of cases have **prior pelvic inflammatory disease** (resulting in chronic salpingitis with intraluminal scarring). Other factors include **peritubal scarring / adhesions** (e.g. due to appendicitis, endometriosis, previous surgery), **intrauterine contraceptive device**
- **Clinical features**: Tubal pregnancies eventually **rupture** often with massive intraperitoneal haemorrhage, usually 6-8 weeks after the last menstrual period. **This is a medical emergency**. Patients present with moderate to severe abdominal pain and vaginal bleeding, and may rapidly develop haemorrhagic shock with signs of an acute abdomen. Less commonly, the tubal pregnancy may undergo spontaneous regression and resorption, or be extruded through the fimbriated end of the tube into the abdominal cavity (tubal abortion).
- **Gross**: In each abnormal location, the fertilized ovum develops as usual, forming placental tissue, amniotic sac and fetus. The host implantation site may develop decidual changes. For tubal pregnancies, usually appears as hematosalpinx (blood-filled fallopian tube) and should always be suspected when a tubal hematoma is present. With time, the growth of the gestational sac distends the fallopian tube causing wall thinning and rupture

Disorders of late pregnancy

Usually placental-related causes, and can be lethal to the fetus and mother.

Abnormalities of placental implantation

- **Placenta previa**: placenta implants in the lower uterine segment or cervix, often leading to serious 3rd trimester bleeding. If the placenta covers the internal cervical os, Cesarean section is necessary to avert placental rupture and fatal maternal haemorrhage during vaginal delivery
- **Placenta accreta**: partial or complete absence of the decidua, such that placental villous tissue adheres directly to the myometrium, leading to failure of placental separation at birth and severe potentially life-threatening postpartum bleeding. Risk factors: placenta previa, previous C-section
- **Abruptio placentae:** premature incomplete or complete separation of normally positioned placenta from uterine wall during pregnancy or before delivery (antepartum haemorrhage) – can result in concealed or revealed bleeding. If severe, can result in maternal shock and DIC, and fetal distress

Placental infections

Can occur via:
(1) **Ascending infection** through the birth canal: more common, usually bacterial. Localized infection of the membranes can cause premature rupture of membranes and preterm delivery. Amniotic fluid

may be cloudy with purulent exudate. Histologically, chorionamnion contains neutrophils (chorioamnionitis). Can also involve umbilical cord (funisitis) and chorionic villi (villitis)

(2) **Haematogenous (transplacental) infection**: classically the TORCH group (toxoplasmosis, others [syphilis, tuberculosis, listeriosis, hepatitis B], rubella, cytomegalovirus, herpes simplex)

Consequences include intrauterine growth retardation, low birth weight, premature delivery, congenital anormalies and deafness.

Preeclampsia and eclampsia (toxaemia of pregnancy)

- **Preeclampsia:** systemic syndrome characterized by widespread maternal endothelial dysfunction that presents during pregnancy with hypertension, edema and proteinuria (in contrast to gestational hypertension, where hypertension occurs during pregnancy but without proteinuria). **Eclampsia**: more severe form of preeclampsia with central nervous system involvement, including convulsions and eventual coma. ~10% of women with severe preeclampsia develop microangiopathic hemolytic anemia, elevated liver enzymes and low platelets (**HELLP syndrome**)
- **Pathogenesis**: Placenta plays a central role since the symptoms disappear rapidly after delivery of the placenta. The critical abnormalities are **diffuse endothelial dysfunction**, **vasoconstriction** (leading to hypertension), and **increased vascular permeability** (resulting in proteinuria and edema), most likely mediated by placenta-derived factor(s) released into the maternal circulation. The principal pathophysiologic aberrations appear to be the following:
    - **Abnormal placental vasculature**: precipitating events are abnormal trophoblastic implantation and a failure of physiologic remodeling of the maternal vessels (i.e. the conversion of decidual spiral arteries from small-caliber resistance vessels to large capacity uteroplacental vessels lacking a smooth muscle coat), which is required for adequate perfusion of the placental bed. Hence, this failure predisposes to placental ischaemia
    - **Endothelial dysfunction and imbalance of angiogenic and anti-angiogenic factors:** the theory is that the ischemic placenta releases factors (likely sFlt1 and endoglin) into the maternal circulation that cause an imbalance in angiogenic and anti-angiogenic factors leading to systemic maternal endothelial dysfunction
    - **Coagulation abnormalities:** preeclampsia is associated with a hypercoagulable state that may lead to the formation of thrombi in arterioles and capillaries throughout the body, but particularly in the liver, kidneys, brain and pituitary (likely related to the reduced endothelial production of PGI_2 and increased release of procoagulant factors)
- **Clinical features**: 3-5% of pregnant women, usually 3rd trimester (can be earlier in women with hydatidiform mole or pre-existing kidney disease, hypertension or coagulopathies) and primiparas (1st pregnancy). Typically insidious onset of hypertension and oedema, followed by proteinuria. Headaches and visual disturbances are indicative of severe preeclampsia, often requiring delivery. **Treatment**: depends on gestational age and disease severity. For term pregnancies, delivery is preferred regardless of disease severity. For preterm pregnancies, patients with mild disease can be managed expectantly. However, eclampsia or other complications are indications for delivery regardless of gestational age. Antihypertensive therapy does not affect the disease course or

improve outcomes. **Prognosis**: Proteinuria and hypertension usually disappear within 2 wks of delivery. Although in most instances preeclampsia has no lasting sequelae, there is 2x increase in long-term risk of vascular diseases of the heart nad brain, and ~20% of affected women develop hypertension and microalbuminuria within 7 years of the pregnancy

- **Gross/Histology**: Placenta shows changes that reflect malperfusion, ischemia and vascular injury e.g. placental infarcts, increased syncytial knots of the chorionic villi, retroplacental hematomas, abnormal decidual vessels with fibrinoid necrosis, acute atherosis, thrombi etc.

Twin placentas

- Twin pregnancies arise from fertilization of two ova (dizygotic) or from division of one fertilized ovum (monozygotic)
- There are 3 basic types of twin placentas: **diamnionic dichorionic** (DADC, which may be fused), **diamnionic monochorionic** (DAMC) and **monoamnionic monochorionic** (MAMC). Monochorionic placentas imply monozygotic (identical) twins, and the time at which splitting of the developing embryo occurs determines whether one or two amnions are present. Dichorionic plancetas can occur with either monozygotic or dizygotic twins.
- Monochorionic twin pregnancies may be complicated by **twin-twin transfusion syndrome**, whereby one twin may be underperfused and the other twin fluid overloaded if there are arteriovenous shunts connecting the circulations of the twins that preferentially increase blood flow to one twin at the expense of the other

Gestational trophoblastic disease

Encompasses a spectrum of tumours and tumour-like conditions characterized by proliferation of placental tissue

Hydatidiform mole

- Usually diagnosed during early pregnancy by pelvic ultrasound. Can develop at any age but risk is higher at the 2 ends of the reproductive life (i.e. teenagers and 40-50yo). More common in SE Asia vs US.
- **Complete:** 2.5% risk of subsequent choriocarcinoma and 15% risk of persistent/invasive mole. Genetic material is completely paternally derived as it results from fertilization of an egg that has lost its female chromosomes and duplication of the genetic material of one sperm (90% have a 46XX karyotype). Fetal tissues usually not identified as the embryo dies very early in development. **Clinical presentation**: usually present with spontaneous miscarriage or undergo curettage because of abnormal villous enlargement on ultrasound. HCG levels much higher than a normal pregnancy of similar gestational age. **Treatment**: curettage, with monitoring of HCG levels; if HCG remains elevated, may indicate persistent/ invasive moles. **Gross**: delicate friable mass of thin-walled translucent cystic grapelike structures consisting of swollen edematous (hydropic) villi. **Histology**: almost all villi are enlarged and hydropic with central cistern formation (cavitation), trophoblastic inclusions and circumferential abnormal trophoblastic hyperplastic proliferation. Absence of p57

nuclear immunostaining in cytotrophoblasts and villous stroma cells (p57 is encoded by the paternally imprinted and maternally expressed gene *CDKN1C*).

- **Partial:** not a/w choriocarcinoma. Increased risk of persistent molar disease. Result from fertilization of an egg with 2 sperm (mostly triploid karyotype e.g. 69XXY). Fetal tissues are typically present. **Clinical presentation and treatment**: largely similar to complete mole. **Gross**: hydropic change involving only some villi. Fetal tissue/gestational sac may be present. **Histology**: only a fraction of villi are enlarged and edematous, with less marked trophoblastic hyperplasia. Retained p57 nuclear staining in cytotrophoblasts and villous stroma cells.

- **Invasive:** a mole that penetrates or even perforates the uterine wall. Locally destructive and may invades parametrium, blood vessels and embolise to distant sites e.g. lungs, brain (although they do not grow there and eventually regress in those sites). **Clinical presentation**: vaginal bleeding, irregular uterine enlargement, persistently elevated serum HCG. **Treatment**: responds well to chemotherapy but may result in uterine rupture and necessitate hysterectomy. **Histology**: invasion of the myometrium by hydropic chorionic villi, a/w proliferation of cytotrophoblasts and syncytiotrophoblasts.

Choriocarcinoma

- Malignant neoplasm of trophoblastic cells derived from a previously normal or abnormal pregnancy (50% arise in complete hydatidiform moles, 25% in previous abortions, 22% in normal pregnancies and the rest in ectopic pregnancies). Rarely, a nongestational choriocarcinoma may develop from germ cells in the ovaries or mediastinum

- **Clinical features**: usually presents as irregular vaginal spotting of bloody brown fluid, which may appear in the course of normal pregnancy, after a miscarriage or after curettage (possibly months after). High risk for hematogenous spread, and often presents with widespread metastases (lung and vagina, brain, liver, bone and kidney). HCG levels usually higher than in hydatidiform moles. **Treatment**: depends on tumour stage. Usually evacuation of uterus contents and chemotherapy. Highly responsive to chemotherapy with nearly 100% remission (vs non-gestational chorioca).

- **Gross**: Soft fleshy yellow-white tumour with large pale areas of necrosis and extensive haemorrhage.

- **Histology**: no chorionic villi. Consists entirely of proliferation syncytiotrophoblasts and cytotrophoblasts, with numerous mitoses. Invades the underlying myometrium and possibly further, frequently penetrates blood vessels

Placental site trophoblastic tumour (<2% of gestational trophoblastic neoplasms)

- Neoplastic proliferation of extravillous implantation site-type intermediate trophoblasts, which are usually found in the implantation site in normal pregnancies and produce human placental lactogen. May follow a normal pregnancy (50%), spontaneous abortion or hydatidiform mole. **Clinical features**: Presents as a uterine mass a/w abnormal uterine bleeding/amenorrhoea and moderately elevated HCG. Excellent prognosis if localized disease; 10-15% women die of disseminated disease. **Histology**: malignant pleomorphic trophoblastic cells diffusely infiltrating the endomyometrium

Epithelioid trophoblastic tumour

- Neoplastic proliferation of chorionic-type intermediate trophoblasts. May follow normal pregnancy (67%), spontaneous abortion or hydatidiform mole. Similar presentation and prognosis as PSTT. **Histology**: nodular growth of nests/cords of moderately atypical trophoblastic cells associated with eosinophilic hyaline-like material, extensive geographic necrosis, mostly in cervix or lower uterine segment