Hwee's Obstetrics & Gynaecology

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Sources:

Hacker and Moore's Essentials of Obstetrics and Gynaecology 5th Edition
Oxford Handbook of Clinical Specialties 8th Edition
NUS Department of O&G Lecture Slides 2012/2013
KKH Lecture Slides 2012/2013
SGH A/Prof Tay Sun Kuie's Gynaecologic Oncology Lecture Slides

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ANTENATAL CARE

Introduction to Antenatal Care

- **Goals of Antenatal Care**
  - Detect maternal disease & ameliorate discomforts of pregnancy
  - Monitor & promote fetal well-being
  - Early & continued risk assessment to identify high-risk pregnancies
  - Prepare mother for labour

- **Overall Chronology of Routine Antenatal Care**
  - ***Pre-Conception Care***
    - Ideally, prenatal care should begin before pregnancy as modifiable maternal factors often have the greatest impact on the early events following conception
      - Implantation occurs 7 days after conception
      - Placental development then follows
      - Organogenesis occurs before 1st trimester ends
    - Hence by the time most pregnant women have their first antenatal visit, it is often too late to prevent certain birth defects or defective placental development
  - ***1st Trimester Antenatal Care***
    (4-weekly visits)
    - Confirm pregnancy & determine viability
    - Confirm gestational age & expected date of delivery with dating & viability scan (6-11 weeks)
    - Comprehensive history & physical examination
    - Routine antenatal screening blood tests
    - Identification of high-risk pregnancies (from above)
    - Preliminary maternal counseling
    - Management of maternal well-being
    - Offer 1st trimester prenatal screening
  - ***2nd Trimester Antenatal Care***
    (4-weekly visits)
    - Clinical fetal monitoring
    - Continued maternal counseling
    - Continued management of maternal well-being
    - Offer 2nd trimester prenatal screening (*in the event that patient presents only in the 2nd trimester*)
    - Detect possible problems with pregnancy with fetal screening (anomaly) ultrasound scan (20-22 weeks):
      - *Fetal anomalies*
      - *Abnormal placentation*
      - *Multiple pregnancies*
      - *Uterine abnormalities, pelvic tumours*
      - *Uterine blood flow waveform assessment*
  - ***3rd Trimester Antenatal Care***
    (2-weekly visits up till 35 weeks; weekly thereafter)
    - Clinical fetal monitoring
    - Continued maternal counseling
    - Continued management of maternal well-being
    - Assess fetal growth & well-being with fetal ultrasound growth scan (32 weeks):
      - *Growth parameters*
      - *Amniotic fluid index*
      - *Doppler assessment*
      - *± Cardiotocography*
    - Preparation for labour, delivery & puerperium
    - Close fetal well-being supervision for post-date gestations (from 40 weeks)

1st Trimester Antenatal Care

Confirmation of Pregnancy & Viability

Regardless of reason for initial presentation, a formal diagnosis of pregnancy followed by a determination of its viability are essential before progressing on to the other aspects of antenatal assessment or care

- **Symptoms of Pregnancy**
  - Amenorrhea (*commonest presentation*)
  - Urinary frequency
    - Note that acute urinary retention may occur at times with a growing gravid uterus especially in the context of a retroverted uterus
  - Breast engorgement &/or tenderness
  - Nausea/vomiting
  - Easy fatigability

- **Signs of Pregnancy**
  - ***Presumptive signs of pregnancy*** (skin, mucous membrane)
    - Dark discolouration of the vulva & vaginal walls (**Chadwick sign**)
    - Pigmentation of the skin & abdominal striae
      - **Linea nigra** (*pigmented midline running from umbilicus to pubic region*)
      - **Chloasma aka melasma** (*facial skin pigmentation, commonly under the eyes & over the nose bridge*)
  - ***Probable signs of pregnancy*** (uterus)
    - Globular uterus (as early uterine enlargement tends to occur in the anteroposterior diameter)
    - Disproportionate enlargement of 1 cornua of the uterus due to asymmetrical implantation of the ovum (**Piskacek sign**)
    - Palpable/compressible junction between the uterine corpus & cervix due to softening of the uterine consistency (**Hegar sign**)
    - Softening of the cervix
  - ***Positive signs of pregnancy***
    - Detection of fetal heartbeat
      - May be detected as early as 9 weeks with modern Doppler techniques, but usually only detected by <u>12 weeks</u> transabdominally as that is when the uterus becomes clinically palpable through the abdominal wall
      - Fetal heart tones can usually be detected with a stethoscope by <u>16-20 weeks</u>
    - Recognition of fetal movements
      - Primigravida usually by 18-20 weeks
      - Multiparous usually by 15-17 weeks

Linea nigra

Chloasma aka melasma

- **Investigations for Confirmation of Pregnancy**
  - ***Pregnancy test***
    - Detects human chorionic gonadotropin (hCG) in either the serum or urine, using the First International Reference Preparation (1st IRP)
    - Maternal serum hCG levels in early pregnancy:
      - 1st secreted ~7days after conception
      - Doubles every 2.2 days for the first 30 days
      - Reaches ~100IU/L by the time of the expected menses
    - Pregnancy test result interpretation (for serum hCG):
      - hCG < 5IU/L = negative
      - hCG >25IU/L = positive
      - hCG 6-24IU/L = equivocal, retest in 2 days (*hence most women presenting at the time of the 1st missed period would give a positive pregnancy test if they are truly pregnant*)
    - Possible false-positives:
      - Ectopic pregnancy
      - Molar pregnancy
      - hCG-secreting tumour
  - ***Transvaginal ultrasound***
    - Useful for excluding ectopic pregnancy & determining viability of the gestation:

Normal Ultrasound Findings in Early Gestation		
Gestational age	***U/S Finding***	***Mean hCG level***
5 weeks	Gestational sac	1500IU/L
6 weeks	Fetal pole	5200IU/L
7 weeks	Fetal cardiac motion	17500IU/L

    - Indications of probable embryonic demise (i.e. non-viable pregnancy):
      - Presence of gestational sac of 8mm without a demonstrable yolk sac
      - Presence of gestational sac of 16mm without a demonstrable embryo
      - Crown-rump length >5mm without any demonstrable fetal cardiac motion

Confirmation of Gestational Age & Expected Date of Delivery (EDD)

Gestational age confirmation is of paramount importance at the first antenatal visit as multiple decisions & assessments made at subsequent antenatal visits will depend on it

- **Determination via Menstrual History (Naegele's Rule)**
  - Expected date of delivery:

    Last menstrual period (LMP) + 9 months & 7 days
    Note: LMP = 1st day of last menses
  - Gestational age is approximated by number of weeks of amenorrhea (i.e. from LMP till present)
  - Assumptions of Naegele's Rule:
    - Assumes a 28-day menstrual cycle with ovulation occurring on day 14
    - EDD calculated corresponds to 40 weeks gestation
  - Hence inaccurate if cycles are not 28-day long or cycles are irregular
    - Can modify if cycles are not 28 days long (*works on the basis that luteal phase is usually a constant of 14 days whereas follicular phase is the main factor accounting for variability in cycle lengths between women*):
      - If cycles <28 days, subtract the difference from the calculated EDD
      - If cycles are >28 days, add the difference to the calculated EDD
    - Even then, probably still inaccurate (even with regular 28-day cycles, calculated dates still wrong in ~15% of cases)

- **Determination via Dating Ultrasound Scan**
  (*most accurate estimations of gestational age are obtained via 1st trimester ultrasound dating scans, hence recommended routinely for patients presenting early enough; for patients presenting later, other ultrasound parameters can still be used, but with significantly less accuracy*)
  - 1st trimester dating ultrasound scan estimates gestational age using **crown-rump length** measurement
    - Usually done between 6-11 weeks
    - Accuracy of dating up to ±3-4 days
  - 2nd trimester ultrasound scan estimates gestational age using multiple measurements:
    - Biparietal diameter, head & abdominal circumference, femur length
    - Accuracy of dating up to ±1-2 weeks

The First Antenatal Visit

Alongside confirmation of pregnancy, determining viability & confirmation of gestational age & EDD, a whole host of other history, physical examinations & investigations are essential at the first antenatal visit to establish a comprehensive maternal profile, which allows stratification of pregnancy risk which will determine whether the mother will be managed routinely or in a high-risk pregnancy clinic

- **Important History to Elicit**
  - ***Obstetric history***
    - Gynae code (*age/number of years married/number of previous pregnancies/number of children*)
    - Menstrual history (*last menstrual period, age of menarche, length of periods, regularity of periods, any menorrhagia*)
    - Details of each previous pregnancy:
      - *Gestational age at birth*
      - *Mode of delivery*
      - *Perinatal complications & events*
      - *Antenatal issues & problems (any obstetric condition diagnosed? any interventions or treatment administered?)*
    - Check pap smear status (*last one done when? results?*)
  - ***Past medical & surgical history***
    - Any past medical conditions (*chronic hypertension, diabetes mellitus, heart disease, anemia etc*)
    - Any past surgeries (*previous caesarian section, uterine surgery etc*)
    - Drug history (*current active medications, drug allergies*)
  - ***Family history***
    - Any family history of medical conditions (*e.g. first degree relatives with diabetes mellitus, thromboembolic disease*)
    - Any family history of obstetric conditions (*e.g. maternal history of pre-eclampsia*)
  - ***Social history***
    - Smoking, alcohol & recreational drug use
    - Occupation, financial issues
    - Get a profile of the spouse as well

- **Physical Examination on the 1st Antenatal Visit**
  - ***General examination***
    - Obtain a baseline height, weight & blood pressure
    - Look for pallor & edema
    - Do targeted systemic examinations:
      - Oral cavity, thyroid
      - Breast (*anticipate breastfeeding difficulties e.g. due to inverted nipples*)
      - Heart, lung
      - Fundoscopy if hypertensive/diabetic
  - ***Abdominal examination***
    - Inspect for cutaneous signs of pregnancy (*linea nigra, striae gravidarum*) & surgical scars
    - Palpate abdomen (*gravid uterus usually not palpable until ~12 weeks gestation*)
  - ***Pelvic examination***
    - Baseline assessment of the external genitalia, vaginal walls & cervix

- **Routine 1st Trimester Screening (Baseline Investigations)**
  - Full blood count
    - Assess baseline haemoglobin levels
    - Preliminary screen for thalassemia (*see "Anemia in Pregnancy for more details"*)
  - Blood group & antibodies
    - To assess need for management of possible rhesus alloimmunization
  - Hepatitis B screening (*test for HBsAg*)
  - HIV screening
  - Syphilis screening (*using VDRL*)
  - Urine protein & glucose
    - Assess baseline absence/presence to guide interpretation of results from every other subsequent antenatal visit

Other Routine 1st Trimester Care Issues

- **Manage Common Maternal Ailments** *(see below)*

- **1st Trimester Counseling**
  - Nutrition (*standard eat well & healthily advice; increase caloric intake by about 300kcal; avoid raw meats to prevent toxoplasmosis infection; give folic acid supplementation 5mg/day if not already on it*)
  - Lifestyle adjustments (*can continue to work; can engage in mild exercise, avoiding strenuous physical activity or activities with a significant risk of falls*)
  - Travel advice (*avoid long-haul flights*)
  - Coital advice (*can continue to engage in coitus; one thing to avoid is stimulation of the nipples as it induces a surge in serum oxytocin levels*)

- **Offer 1st Trimester Prenatal Screening** *(see below)*

- **Complications in 1st Trimester**
  - Ectopic pregnancy
  - Miscarriage (*occurs in 10-15% of all pregnancies*)
  - Hyperemesis gravidarum

2nd Trimester Antenatal Care

Clinical Fetal Monitoring

Beginning from the 2nd trimester, the gravid uterus becomes palpable through the abdomen, which allows for various parameters & characteristics to be assessed for at each antenatal visit; pointers here apply not only to 2nd trimester care but to any antenatal visit following the initial first (booking) antenatal visit

- **Routine Antenatal History Taking**
  - Enquire about general well-being & any symptoms since the previous visit
  - Ask about ***fetal movements***
    - Can consider starting patient on fetal movement chart from 30 weeks onwards, utilizing **Cardiff "count to ten" method** (*count 10 fetal movements beginning from a specific time each day; report if the fetus takes longer than usual to achieve the 10 movements, or if there are fewer than 10 movements in 12 hours*)
    - Fetal movements in theory help monitor fetal well-being, decrease in which may signal fetal compromise
    - Not proved by randomized controlled trials to reduce perinatal morbidity & mortality however

- **Routine Antenatal Physical Examination**
  - ***General examination***
    - Obtain current weight & blood pressure
  - ***Abdominal examination***
    - Can inspect for visible fetal movements
    - Measure **symphysial fundal height** (SFH), which can in turn help determine:
      - Appropriateness of size for gestational age (*another clinical method of gauging fetal growth as a surrogate measure of fetal well-being; not proven by randomized controlled trials to reduce perinatal morbidity & mortality however*):

        Gestational age (weeks) = SFH (cm) ± 2-3cm

      - Clinical estimation of fetal weight using **Johnson formula** (*not routinely done anymore*):

        Birth weight (g) = [SFH (cm) – 13] x 155
    - Palpate gravid uterus to determine (*usually only after 28 weeks, i.e. 3rd trimester onwards*):
      - Number of fetuses (*singleton or multiple?*)
      - Fetal orientation (*lie, presentation, back*)
      - Liquor volume
      - Degree of engagement
    - Auscultate fetal heart (*best heard over anterior shoulder of the fetus, using stethoscope or DopTone*)

- **Routine Antenatal Investigations**
  - Urine protein & glucose
  - Consider testing for diabetes mellitus with oral glucose tolerance test (OGTT) in patients with risk factors (*if done, usually performed between 24-28 weeks*):
    - Previous gestational diabetes mellitus
    - Body mass index >30
    - Personal history of chronic hypertension
    - Previous baby with birth weight >4.5kg
    - Previous malformed or stillborn child
    - 1st degree relative with diabetes mellitus

2nd Trimester Screening (Anomaly) Scan

Usually done between 20-22 weeks; ~2% of fetuses have malformations

- **Recognition of Fetal Anomalies**
  - Importance of detecting fetal anomalies:
    - Certain abnormalities not compatible with life (*option of termination of pregnancy)*
    - Certain abnormalities are associated with an underlying chromosomal abnormality (*e.g. if AVSD detected, high likelihood of Down's syndrome*)
    - Advance anticipation of need for perinatal &/or multidisciplinary care
  - Anomaly ultrasound scan is better at detecting externally impinging structural abnormalities than internal ones:
    - External: *anencephaly, spina bifida*
    - Internal: *structural heart defects, diaphragmatic hernia*
  - Can also detect "soft signs" of underlying abnormalities (markers of aneuploidy):
    - Nuchal thickening: *trisomy 21*
    - Choroid plexus cysts: *trisomies 18 & 21*
    - Echogenic bowel: *trisomy 21 & cystic fibrosis*
  - Overall sensitivity ~60-70%, hence a negative scan does not effectively exclude the presence of fetal anomalies
  - Prenatal diagnostic test (*see below*) to detect possible chromosomal abnormality offered if:
    - Major fetal anomaly detected (*cleft lip, congenital heart disease, exomphalos etc*)
    - ≥2 markers of aneuploidy detected

- **Detection of Other Abnormalities**
  - ***Detect low-lying placenta***
    - Present in ~28% of pregnancies at 24 weeks
    - With lower uterine segment development, only ~3% remaining at term (*placenta praevia*)
  - ***Diagnosis of multiple pregnancies***
  - ***Detection of uterine abnormalities or pelvic tumours***
  - ***Uterine artery waveform assessment***
    - Can be used to predict risk of developing pre-eclampsia, intrauterine growth restriction (IUGR) & placental abruption
    - Features increasing risk include:
      - High **pulsatility index** ([peak systolic flow – end-diastolic flow]/mean flow) which is a surrogate measure of vascular resistance
      - **Early diastolic notch** in the waveform (*only bilateral uterine artery notching is significant*)
    - Aspirin 75mg/day can be offered if uterine artery waveform abnormalities found to improve outcome

Other Routine 2nd Trimester Care Issues

- **Manage Common Maternal Ailments** *(see below)*

- **2nd Trimester Counseling**
  - As per 1st trimester, plus:
  - Breastfeeding advice
  - Antenatal classes

- **Offer 2nd Trimester Prenatal Screening** *(see below)*
  - This is in the case where the patient's first antenatal visit occurs after the 1st trimester & hence no longer eligible for the 1st trimester prenatal screening

3rd Trimester Antenatal Care

Clinical Fetal Monitoring

As per described for 2nd trimester care, except with increased frequency of follow-up visits; a few additional things to note on antenatal visits in the 3rd trimester are stated below

- **Additional Considerations at 36 Weeks**
  - Pelvic assessment on top of usual abdominal examination (*used to be for performing clinical pelvimetry to detect possible cephalopelvic disproportion; not routinely done anymore*)
  - Consider reviewing haemoglobin levels
    - In anticipation of blood loss during delivery
    - Safe options of managing iron-deficiency anemia such as iron pills take time to bring up Hb, hence review should be done early enough ahead of EDD
  - Consider high vaginal swab (HVS) to test for Group B *Streptococcus* (GBS) colonization
    - If positive, offer intrapartum antibiotic prophylaxis (usually IV penicillin or ampicillin)

- **Management of Post-Date Pregnancy**
  (*post-date pregnancy = >40 weeks; post-term = ≥42 weeks*)
  - Weekly monitoring of:
    - Amniotic fluid index (to assess liquor volume)
    - Umbilical artery Doppler assessment
    - Cardiotocography

Other Routine 3rd Trimester Care Issues

- **Manage Common Maternal Ailments** *(see below)*

- **3rd Trimester Counseling**
  - As per 2nd trimester, plus:
  - Counsel patient with regards to delivery:
    - Timing & mode of delivery
    - How to recognize onset of labour & what to do when labour begins (*come to A&E, will be sent to labour ward*)
    - Labour process & choice of anesthesia
    - Reinforce benefits of breastfeeding

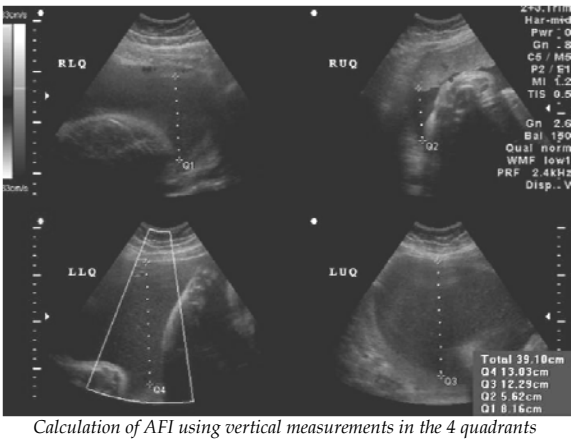
- **Complications in 3rd Trimester**
  - Antepartum hemorrhage
  - Pregnancy-induced hypertension, pre-eclampsia
  - Gestational diabetes mellitus

3rd Trimester Growth Scan

Usually done at around 32 weeks; sonographic parameters assessed are (i) growth parameters (ii) amniotic fluid index (iii) Doppler assessment; additionally, a cardiotocogram may also be done; application of these 4 parameters extend beyond the 3rd trimester growth scan, being used in various obstetric scenarios such as routine monitoring of high-risk pregnancies or acute assessment of fetal well-being in obstetric emergencies (e.g. pre-eclampsia)

- **Growth Parameters**
  - Fetal measurements (used to estimate fetal weight):
    - Biparietal diameter (BPD)
    - Head circumference
    - Abdominal circumference
    - Femoral length
    - Head:abdominal ratio (*calculated from head & abdominal circumference*)
  - Possible growth assessment results:
    - Appropriate for gestational age
    - **Large for gestational age (LGA)** = >90th percentile
    - **Small for gestational age (SGA)** = <10th percentile
  - Evaluation of SGA detected on growth scan:
    - First step is to reconsider if dates are correct
      - Check how gestational age was determined in the first place (*1st trimester dating scans are the most reliable compared to 2nd trimester dating scans or calculations based on LMP*)
      - If LMP was used to calculate, check patient's menstrual history (*if irregular, non-28 day cycle, makes it even less reliable*)
    - If dates are reliable (i.e. fetus is truly SGA), consider the 3 possibilities of SGA:
      (i) ***Constitutional*** (*20%, normal healthy fetuses who are small because their parents & siblings also tend to be on the small side*)
      (ii) ***Intrinsically small fetuses*** (*40%, usually due to 1st trimester intrauterine insult such as chromosomal abnormalities, intrauterine infections or exposure to teratogens*)
      (iii) ***Growth-restricted fetuses*** (*40%, usually due to mid & late trimester uteroplacental insufficiency due to conditions such as pre-eclampsia, chronic placental abruption, maternal thrombophilia etc*)
    - Determining pattern of intrauterine growth restriction (IUGR) can help assess the likely cause:
      - **Symmetrical IUGR** = head & abdominal circumference both at the same low centile (*likely to be constitutional or intrinsically small fetuses*)
      - **Asymmetrical IUGR** = head circumference relatively normal with abdominal circumference at low centile (*likely to be growth-restricted fetuses; occurs due to preferential redistribution of blood to fetal head when uteroplacental insufficiency sets in*)
  - Evaluation of LGA detected on growth scan:
    - First step is to check if dates are correct, as above
    - If dates are reliable (i.e. fetus is truly LGA), consider the 3 possibilities of LGA:
      (i) Constitutional
      (ii) Fetal syndromes
      (iii) Gestational diabetes mellitus (*consider an OGTT to test for it*)

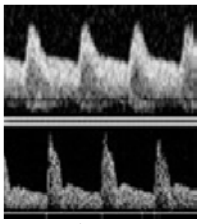
- **Amniotic Fluid Index (AFI)**
  - Assesses liquor volume
  - AFI = sum of the linear measurements (in cm) of the largest amniotic fluid pockets noted on ultrasound inspection of each of the 4 quadrants of the gestational sac
    - 4 quadrants of abdomen divided based on umbilicus
    - Transducer placed vertically in each quadrant, perpendicular to the floor
    - Largest vertical pool of liquor seen in each quadrant is measured & summed to give AFI
  - Interpretation of AFI:
    - **Oligohydramnios** = AFI < 8; *suggests fetal compromise & placental insufficiency (preferential redistribution of fetal blood to head reduces renal perfusion, hence lowering glomerular filtration & fetal urine production)*
    - **Polyhydramnios** = AFI > 18; *may indicate fetal anomaly (e.g. GIT malformation causing decreased fetal ingestion of amniotic fluid) or poor control in a diabetic pregnancy (fetal hyperglycemia causing osmotic diuresis)*

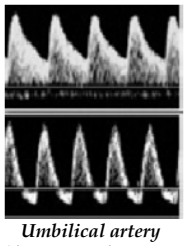


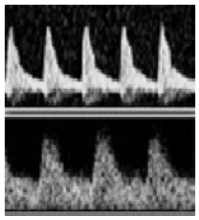
Calculation of AFI using vertical measurements in the 4 quadrants

- **Doppler Assessment**
  (*assesses placental sufficiency, useful in high-risk pregnancies; note that Doppler assessment is the only measure in antenatal monitoring of fetal growth & well-being that has been proven by meta-analysis to reduce perinatal morbidity & mortality*)

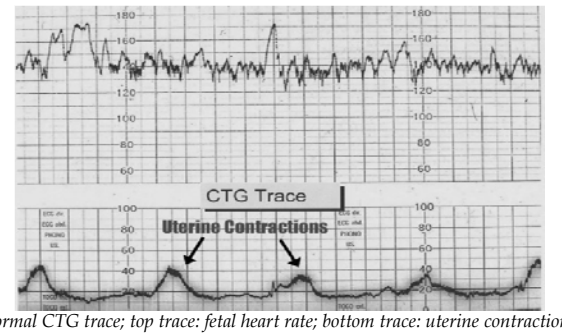
Vessel Assessed	*Indicator of Placental Insufficiency*
Uterine artery	High pulsatility index, early-diastolic notch
Umbilical artery	Absent or reverse end-diastolic waveform
Middle cerebral artery	Increased end-diastolic flow velocity (*due to preferential shunting of blood to the head in placental insufficiency*)
Ductus venosus	Reverse 'a' wave
Umbilical vein	Venous double pulsation


Uterine artery
Above: normal
Below: early-diastolic notch

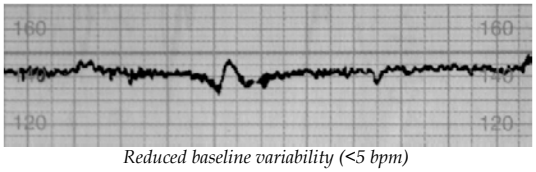

Umbilical artery
Above: normal
Below: reverse end-diastolic waveform

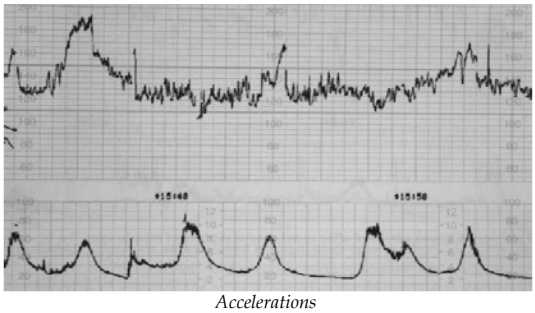

Middle cerebral artery
Above: normal
Below: increased end-diastolic flow velocity

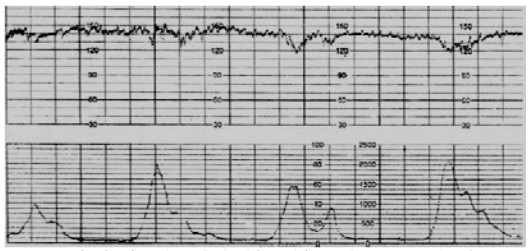
- **Cardiotocography**
  (*assesses fetal well-being, useful in high-risk pregnancies & fetal monitoring during labour*)
  - Assessment of fetal heart rate patterns with concomitant monitoring of uterine contractions
    - Fetal heart rate can be monitored transabdominally using external transducers <u>or</u> internally using fetal scalp electrodes (*applicable only during intrapartum monitoring*)
    - Uterine contractions can be monitored transabdominally using external transducers <u>or</u> internally using a transcervical placement of a plastic catheter (*applicable only during intrapartum monitoring*)
  - Interpretation of fetal heart rate patterns (*4 main parameters monitored*):
    - ***Baseline heart rate***
      - <u>Normal</u>: *110-160 beats per minute*
      - <u>Baseline tachycardia</u>: *maternal fever, β-agonist use, chorioamnionitis, acute/subacute fetal hypoxia, fetal tachyarrhythmias (in which case FHR > 200bpm)*
      - <u>Baseline bradycardia</u>: *fetal heart block, cord compression (late sign), fetal hypoxia (late sign)*
    - ***Baseline variability***
      - <u>Normal</u>: *amplitude >5 beats per minute*
      - <u>Loss of baseline variability</u> (i.e. flat trace): *acute/subacute fetal hypoxia, preterm infant who is asleep, drugs (benzodiazepines, morphine, phenothiazine), chorioamnionitis*
    - ***Accelerations***
      - <u>Normal</u>: *≥2 accelerations of amplitude ≥15 beats per minute (each lasting >15 seconds) over a 20 minute period (indicates intact fetal sympathetic activity)*
    - ***Decelerations***
      (*usually indicates fetal compromise; can be categorized into various subtypes if temporal relationship between FHR & uterine contractions is observed*)
      - <u>Early decelerations</u>: *only form of deceleration which can be considered normal; deceleration corresponds to simultaneous uterine contraction; can be observed during labour following engagement of the fetal head; due to* ***head compression*** *by uterine contractions, causing increased intracranial pressure which elicits vagally-mediated reflex bradycardia*
      - <u>Late decelerations</u>: *deceleration occurs following uterine contraction; indicates* ***uteroplacental insufficiency****; due to decreased placental perfusion during uterine contractions, which in a background of underlying uteroplacental insufficiency exacerbates fetal hypoxia, resulting in preferential shunting of fetal circulation to the head via vasoconstriction of systemic vessels, in turn increases systemic arterial pressure which elicits vagally-mediated reflex slowing of fetal heart rate*
      - <u>Variable decelerations</u>: *decelerations with variable time of onset & form (classically "M" shaped or described as "shouldering"), may be non-repetitive; due to* ***cord compression***
  - Format for reporting a CTG (DR BRaVADO):
    - <u>**D**</u>etermine <u>**R**</u>isk
    - <u>**B**</u>aseline <u>**Ra**</u>te
    - <u>**V**</u>ariability
    - <u>**A**</u>ccelerations
    - <u>**D**</u>ecelerations
    - <u>**O**</u>verall plan

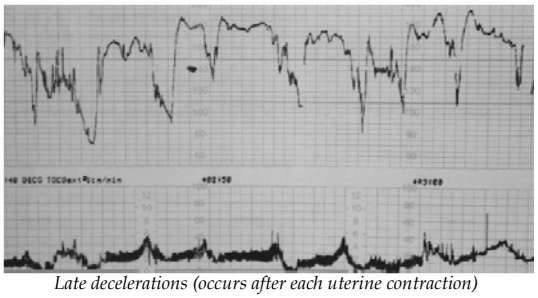


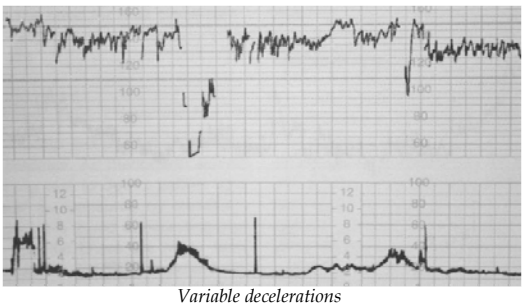
Normal CTG trace; top trace: fetal heart rate; bottom trace: uterine contractions


Reduced baseline variability (<5 bpm)


Accelerations


Early decelerations (coincides with uterine contractions)


Late decelerations (occurs after each uterine contraction)


Variable decelerations

Prenatal Screening & Diagnosis

Involves screening tests to assess the risk of genetic diseases in the fetus as well as follow-up diagnostic procedures to confirm it where the risk is assessed to be high

Prenatal Screening

Prenatal screening here mainly covers the standard screening tests for chromosomal disorders (specifically trisomies 13, 18 & 21) routinely offered to pregnant women during antenatal care; screening for other genetic conditions (e.g. thalassemia) are not discussed here

- **1st Trimester Screen For Chromosomal Abnormalities**
  (*note: detection rates & false positive rates reported here are with respect to the detection of trisomy 21 specifically*)
  - ***Maternal age***
    - Table charting gestational age of fetus against maternal age depicting risk of Down's syndrome
    - Ballpark risk figures of Down's syndrome at birth:
      - Maternal age of 35 years → 1:350
      - Maternal age of 40 years → 1:100
    - Risk based on maternal age (background risk) is further augmented if there is a history of previous chromosomal abnormalities:
      - Previous trisomy 13, 18 or 21 → background risk + 0.75%
      - Previous 45XO, 47XXY/XXX or triploidy → no increase to background risk
    - Detection rate = 30%, false positive rate = 5%
  - ***Nuchal translucency (NT)***
    - Ultrasound measurement of subcutaneous space between fetal skin & cervical spine in the mid-sagittal view
    - Risk is calculated with respect to maternal age
    - Detection rate = 80%, false positive rate = 5%
  - ***Combined test***
    - NT + pregnancy-associated plasma protein A (PAPPA) + β-hCG (w.r.t. maternal age)
    - Detection rate = 90%, false positive rate = 5%
    - Best screening test offered locally, hence the one routinely recommended for all patients eligible for it

- **2nd Trimester Screen For Chromosomal Abnormalities**
  - ***Triple test***
    - α-fetoprotein + β-hCG + estriol (w.r.t. maternal age)
    - Detection rate = 70%, false positive rate = 5%
    - Not as good as combined test, but the only alternative that can be offered to patients presenting in the 2nd trimester
  - ***Quadruple test***
    - α-fetoprotein + β-hCG + estriol + inhibin A (w.r.t. maternal age)
    - Detection rate = 81%, false positive rate = 5%
    - Better than triple test, but not offered locally as assay for inhibin A is not available locally

Prenatal Diagnostic Tests

3 main modalities: (i) CVS (ii) amniocentesis (iii) fetal blood sampling; Definitive diagnostic tests to detect fetal genetic conditions; Usually as a follow up to screening tests (not only chromosomal but others such as thalassemia screening) where risk of fetal condition is determined to be high (>1:300); there are several other uses for these procedures as delineated below

- **Chorionic Villus Sampling (CVS)**
  - Ultrasound-guided sampling of chorionic villi, can be performed transabdominally or transcervically
    - Tissue culture yields cytogenetic results in 6-8 days
    - Direct visualization of dividing villi cells allows for detection of chromosomal abnormalities in 3 days
  - Can be performed from 10 weeks onwards
    - Hence advantage over amniocentesis is that it can be performed earlier
  - Utility of test:
    - Karyotype for chromosomal abnormalities
    - Identify single gene mutations (*e.g. thalassemia*)
  - Complications:
    - Fetal loss rate = 1%
    - Culture failure rate = 0.5% (*i.e. no results can be determined after procedure is performed*)
    - Mosaicism rate = 1% (*i.e. >1 cell population which differ in genetic makeup present in chorionic villi, resulting in sampling error; however, the presence of mosaicism is almost always detectable during analysis of the sample, hence the main implication of this is that a follow-up amniocentesis may be required for definite diagnosis*)
    - Transplacental hemorrhage (*hence need to give anti-D to rhesus-negative mothers after procedure*)

- **Amniocentesis**
  - Ultrasound-guided aspiration of amniotic fluid sample using a 22G needle transabdominally
    - Amniocytes in sample are cultured, requiring 1-2 weeks before final chromosomal analysis is possible
    - Fluorescent in-situ hybridization (FISH) can be used using chromosome-specific probes (e.g. for trisomy 13, 18 & 21) can give preliminary results in 3 days
    - Amniotic fluid itself can be tested for various substances depending on the indication for the test
  - Can be performed from 16 weeks onwards
  - Utility of test:
    - Karyotype for chromosomal abnormalities
    - Identify single gene mutations (*e.g. thalassemia*)
    - Test for perinatal infections:
      - *Detect **intrauterine infections** (TORCH, VZV, parvovirus B19) if maternal exposure has occurred with ultrasonographic features suggestive of fetal infection (fetal hydrops, echogenic bowel, ventriculomegaly, intracranial calcification)*
      - *Analysis of amniotic fluid to diagnosis **preterm chorioamnionitis** (gram stain, white cell count, glucose level, culture)*
    - Biochemical tests for fetal structural abnormalities:
      - ***AFP**: elevated levels in neural tube (e.g. spina bifida) & ventral abdominal wall defects (e.g. gastrochisis, omphalocele)*
      - ***Acetylcholinesterase**: presence indicates open neural tube defect*
    - Test for fetal pulmonary maturity:
      - *Test for amniotic phospholipids to calculate **lecithin:sphingomyelin (L/S) ratio**; L/S ratio >2 is associated with low risk for respiratory distress in the neonate (not done anymore with advent of routine corticosteroid injections in threatened preterms to mature fetal lungs)*
    - Therapeutic amniocentesis for:
      - ***Polyhydramnios***
      - ***Twin-twin transfusion syndrome** (uses serial amniocentesis to remove excessive amniotic fluid from sac of recipient twin)*
  - Complications:
    - Fetal loss rate = 0.5%
    - Culture failure rate = 0.5%
    - Mosaicism rate = almost zero
    - Transplacental hemorrhage (*hence need to give anti-D to rhesus-negative mothers after procedure*)

- **Fetal Blood Sampling**
  - Ultrasound-guided percutaneous sampling of fetal blood; various sources of fetal blood possible (*umbilical vein aka cordocentesis, intrahepatic blood sampling, cardiocentesis*):
    - Fetal leukocytes are cultured, requiring as little as 3 days for chromosomal analysis results
    - Hence main indication is for rapid karyotyping (*as fetal leukocytes can be cultured more rapidly than amniocytes*)
  - Can be performed from 20-23 weeks onwards
  - Utility of test:
    - Karyotype for chromosomal abnormalities
    - Identify single gene mutations (*e.g. thalassemia*)
    - Assessment of fetal anemia (*historically in the setting of rhesus isoimmunization; not necessary anymore with the advent of middle cerebral artery Doppler as an effective indicator of fetal anemia*)
    - Therapeutic in-utero blood transfusion (*e.g. for parvovirus B19 infection, Bart's hydrops*)
  - Complications:
    - Fetal loss rate = 2-5%
    - Cord hematoma, hemorrhage

Maternal Ailments in Pregnancy

- **Nausea & Vomiting**
  - Occurs in up to 70% of pregnancies, usually worst during the 1st trimester
  - Non-pharmacological management:
    - Eat small, frequent meals
    - Avoid greasy & spicy food
    - Acupressure using sea-sickness arm bands
  - Pharmacological management:
    - Vitamin B6 (pyridoxine)
    - Antihistamines

- **Hyperemesis Gravidarum**
  - Severe persistent vomiting + significant weight loss (>5% of pre-pregnancy weight) + ketosis
    - Usually affects primips
    - Postulated to be due to high levels of hCG, hence can also be seen in special conditions associated with high maternal hCG levels (hence need to exclude):
      - Molar pregnancy
      - Multiple gestation
  - Management:
    - Exclude secondary causes of severe vomiting (*e.g. pre-eclampsia, pyelonephritis etc*)
    - Ensure adequate hydration & correction of hyponatremia & hypokalemia that may result (*admit for IV fluids if necessary*)
    - Consider giving thiamine to prevent Wernicke's encephalopathy
    - Consider venous thromboembolism prophylaxis
    - Symptomatic treatment:
      - 1st line: antihistamines (e.g. cyclizine)
      - 2nd line: corticosteroids

- **Heartburn**
  - Occurs in about 2/3 of pregnancies
  - Due to progesterone's effect on smooth muscle relaxation, hence lowering lower esophageal sphincter tone, predisposing to gastroesophageal reflux
  - Non-pharmacological management:
    - Eat small, frequent meals
    - Avoid greasy & spicy food
    - Avoid recumbent position immediately after meals
    - Raise head of bed while sleeping
  - Pharmacological management:
    - Antacids

- **Constipation**
  - Due to progesterone's effect on smooth muscle relaxation, decreasing colonic motility
  - Non-pharmacological management:
    - Dietary modification (increase fibre & water intake)
  - Pharmacological management:
    - Stool softeners in combination with bulk laxatives

- **Hemorrhoids & Varicosities**
  - Due to increased venous pressure with the gravid uterus compressing pelvic veins
  - Management:
    - Increased rest with elevation of legs
    - Avoid constipation

- **Leg Cramps**
  - Experienced by almost 50% of all pregnant women, particularly at night & in the later half of pregnancy
  - Management:
    - Massage & stretching exercises
    - Calcium & sodium chloride may help

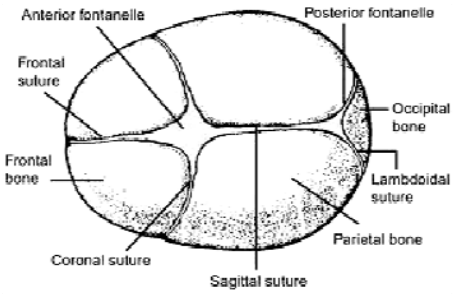
- **Back Aches**
  - Management:
    - Avoid excessive weight gain during pregnancy
    - Exercise
    - Analgesia (e.g. paracetamol)

Anatomic Considerations in Labour

Fetal Head Anatomy

The head is the largest & least compressible part of the fetus, hence it is the most important part from an obstetric viewpoint regardless of whether the presentation is cephalic or breech

- **Fetal Head Structure**
  - Fetal skull comprises the base & the vault (cranium)
    - Base of skull comprises large, ossified, firmly united & non-compressible bones to protect the brainstem
    - Cranium comprises occipital bone posteriorly, 2 parietal bones bilaterally & 2 frontal & temporal bones anteriorly; these bones are thin, weakly ossified, compressible & interconnected only by membrane at birth, hence able to overlap under external pressure to change the shape of the cranium to conform to the maternal pelvis (**moulding**)
  - **Sutures** refer to the membrane-occupied space between the cranial bones:
    - Frontal suture: *lies between the frontal bones, extending from the glabella to the bregma*
    - Coronal suture: *extends laterally from the bregma, separating the frontal & parietal bones*
    - Sagittal suture: *lies between the parietal bones, extending from the bregma to the lambda*
    - Lambdoid suture: *extends laterally from the lambda, separating the parietal & occipital bones*
  - **Fontanelles** refer to the membrane-filled spaces at the points where the sutures intersect:
    - Anterior fontanelle (**bregma**): *diamond-shaped space found at the intersection of the frontal, coronal & sagittal sutures; measures about 2x3cm; closes after birth at about 18 months of age*
    - Posterior fontanelle (**lambda**): *Y-shaped space found at the intersection of the sagittal & lambdoid sutures; much smaller than the bregma; closes after birth at about 6-8 weeks of age*

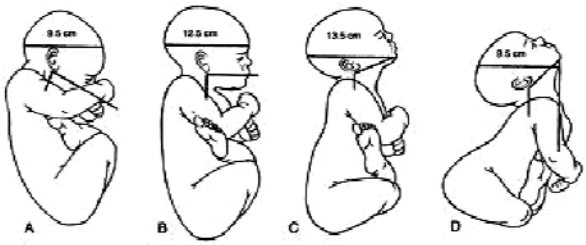


- **Landmarks**
  (*important landmarks of the fetal skull often used in the naming of diameters & fetal positioning during labour*)
  - Chin (mentum): *anterior prominence of the mandible*
  - Glabella: *elevated area between the orbital ridges*
  - Brow (sinciput): *area between the glabella inferiorly & the bregma superiorly*
  - Anterior fontanelle (bregma)
  - Vertex: *area between the fontanelles, bounded laterally by the parietal eminences*
  - Posterior fontanelle (lambda)
  - Occiput: *area posteroinferior to the lambda & lambdoid sutures*

- **Diameters of the Fetal Head**
  - Anteroposterior diameters
    (*relevant when fetus is exiting the pelvic outlet*)

Diameter	*Length*	*Presentation*
Suboccipitobregmatic	9.5cm	Cephalic (well flexed)
Occipitofrontal	11-12.5cm	Cephalic (deflexed)
Supraoccipitomental (aka Mentovertical)	13.5cm	Brow
Submentobregmatic	9.5cm	Face

  - Transverse diameters
    (*relevant when fetus is entering the pelvic inlet*)
    - Biparietal (9.5cm): *largest transverse diameter*
    - Bitemporal (8cm): *smallest transverse diameter*



A: suboccipitobregmatic, B: occipitofrontal, C: mentovertical, D: submentobregmatic

Maternal Pelvic Anatomy

- **Bony Pelvis**
  - Bony pelvis comprises 4 bones:
    - Sacrum: *comprises 5 fused sacral vertebrae, with the anterior-superior edge of S1 (the promontory) protruding slightly into the pelvic cavity; the sacrum has a concave anterior surface; it articulates with the ilium at its upper segment, with the coccyx at its lower segment & with the sacrospinous & sacrotuberous ligaments laterally*
    - Coccyx: *comprises 3-5 fused rudimentary vertebrae; articulates with the sacrum at the sacrococcygeal joint*
    - Innominate bone (x2): *comprises the ilium, ischium & pubis which fuse at puberty following the ossification of the tri-radiate cartilage*
  - The pelvis is anatomically divided into the false pelvis superiorly & the true pelvis inferiorly by the linea terminalis:
    - False pelvis: *bounded by lumbar vertebrae posteriorly, iliac fossae bilaterally, abdominal wall anteriorly*
    - True pelvis: *bounded by sacrum & coccyx posteriorly, ischium & pubis laterally & anteriorly; essentially a bony canal with relatively immobile internal borders*

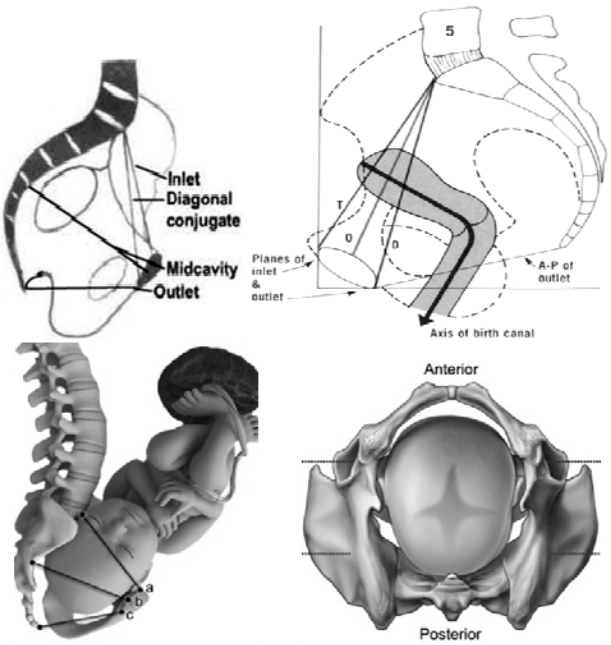
- **Pelvic Planes**
  - The true pelvis is divided into 4 **pelvic planes** for descriptive purposes, each constituting a flat surface extending across the pelvis at a different level:

Pelvic Plane	*Boundaries*		
	Anterior	*Lateral*	*Posterior*
Pelvic inlet	Superior edge of pubic symphysis	Linea terminalis	Sacral promontory
Zone of cavity	Posterior surface of midpoint of pubis	Upper part of the obturator foramina	S2/S3
Mid-pelvis	Posterior surface of lower edge of pubis	Ischial spines	S4/S5
Pelvic outlet	Subpubic arch	Sacrotuberous ligaments	Sacrococcygeal joint

    - Pelvic inlet: *uppermost plane; fetus in labour is said to be "engaged" when the largest diameter of the presenting part crosses this plane; fetus enters pelvis through this during labour in the* <u>*transverse position*</u>
    - Zone of cavity: *the plane of greatest diameter; the fetal head begins internal rotation into the anteroposterior position in this plane during labour*
    - Mid-pelvis: *the plane of least diameter; most arrests of descent during labour occur at this level*
    - Pelvic outlet: *lowermost plane; fetus exits the birth canal & is born through this plane during labour in the* <u>*anteroposterior position*</u>
  - Each plane in turn has a set of **pelvic diameters** which describes measurements made at the level of the plane in different directions (*not very important nowadays since clinical pelvimetry is no longer performed*); understanding the differences in at least the AP & transverse diameters at each plane however helps appreciation of the occurrence of rotation during labour:

Pelvic Plane	*Anteroposterior Diameter*	*Transverse Diameter*
Pelvic inlet	11.5cm	13.5cm
Zone of cavity	12.5cm	13.5cm
Mid-pelvis	12.5cm	12.5cm
Pelvic outlet	13.5cm	11.5cm

    - AP diameter increases while transverse diameter decreases with descent of the fetal head through the true pelvis during labour
    - The AP diameters of the fetal head are greater than that of the greatest transverse diameter of the fetal head, which will result in the alignment of the AP diameter of the fetal head with the larger of the 2 diameters of the true pelvis along the descent at any point in time
    - Hence the fetal head enters the pelvic inlet in the <u>transverse</u> position (*AP diameter of fetal head aligned with transverse diameter of pelvic inlet*), rotates internally as it descends, & eventually exits the pelvic outlet in the <u>anteroposterior</u> position (*AP diameter of fetal head aligned with AP diameter of pelvic outlet*)



- **Pelvic Shapes**
  (*4 types of pelvises described based on the general bony architecture*)

Feature	*Pelvis Type*			
	Gynecoid	*Android*	*Anthropoid*	*Platypelloid*
Inlet	Round	Triangular	Oval; AP > transverse	Oval; AP < transverse
Side walls	Straight	Convergent	Straight	Straight or divergent
Ischial spines	Average	Prominent	Close to each other	Far apart from each other
Sacrospinous notches	Large	Long & narrow	Small	Long & small
Sacrum	Well-curved	Shallow curve	Posterior inclination	Posterior inclination, flat
Subpubic arch	Wide (90°)	Narrow	Narrow, outwardly shaped	Wide

  - ***Gynecoid pelvis***
    - Classical female type of pelvis (50% of women)
    - Overall cylindrical shape that is spacious throughout
    - Fetal head tends to rotate into the <u>occipitoanterior</u> position during descent
  - ***Android pelvis***
    - Typical male type of pelvis (<30% of women)
    - Funneling effect down the pelvis
    - Fetal head tends to rotate into the <u>occipitoposterior</u> position to conform to the narrow anterior pelvis; <u>arrest of descent</u> is common at the mid-pelvis
  - ***Anthropoid pelvis***
    - Resembles that of anthropoid apes (20% of women)
    - Fetus enters pelvic inlet in the anteroposterior position instead of the typical transverse position (usually occipitoposterior as there is more space in the posterior pelvis)
  - ***Platypelloid pelvis***
    - A flattened gynecoid pelvis (3% of women)

Anatomic Terminology Relating to Labour

- **Lie** = relation of the long axis of the fetus to the long axis of the mother
  - Longitudinal lie
  - Transverse lie

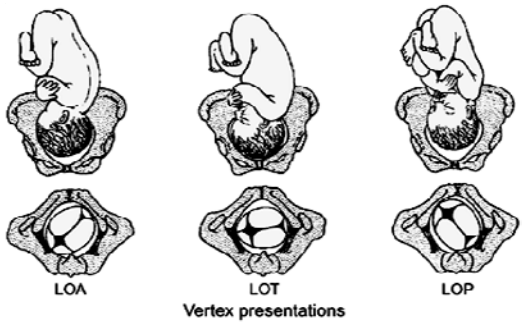
- **Presentation** = designation of the fetal part over the pelvic inlet
  - Cephalic/vertex presentation
  - Breech presentation (buttocks)
  - Transverse/shoulder presentation
  - Compound (multiple parts)
  - Face presentation
  - Brow presentation

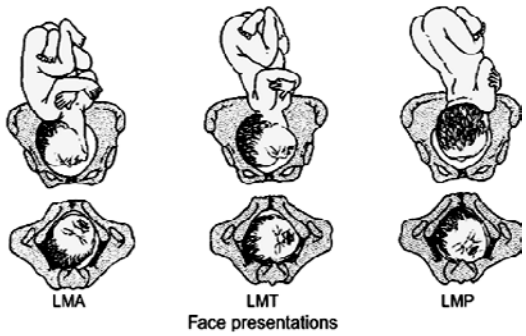
Longitudinal lie Vertex presentation | Longitudinal lie Breech presentation | Transverse lie shoulder presentation

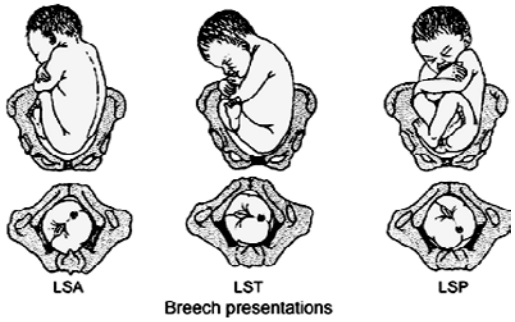
- **Attitude** = posture assumed by the fetus
  - Flexion
  - Extension (associated with larger presenting diameters & malpositions)

- **Position** = relation of an arbitrarily chosen potion of the presenting part (the **denominator**) to the maternal pelvis
  - For cephalic presentations, denominator is occiput
    - ***Occipitoanterior*** = occiput of fetal head facing the front of the maternal pelvis (*hence in lithotomy position during labour, fetus is delivered facing the floor*)
    - ***Occipitoposterior*** = occiput of fetal head facing the back of the maternal pelvis (*hence in lithotomy position during labour, fetus is delivered facing the ceiling*)
    - ***Occipitotransverse*** = occiput of fetal head facing the side of the maternal pelvis

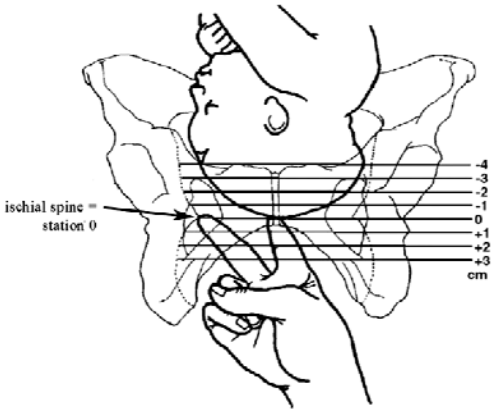
    Note: right & left can be put in front of the above descriptors to further specify if the occiput is slightly deflected to the right/left (for OA & OP)
  - For face or brow presentations, denominator is mentum
    - ***Mentoanterior*** = mentum of fetal head facing the front of the maternal pelvis (*hence in lithotomy position during labour, fetus is delivered facing the ceiling*)
    - ***Mentoposterior*** = occiput of fetal head facing the back of the maternal pelvis (*hence in lithotomy position during labour, fetus is delivered facing the floor – cannot actually occur in reality due to reasons specified later*)
  - For breech presentations, denominator is sacrum
    - ***Sacroanterior***
    - ***Sacroposterior***



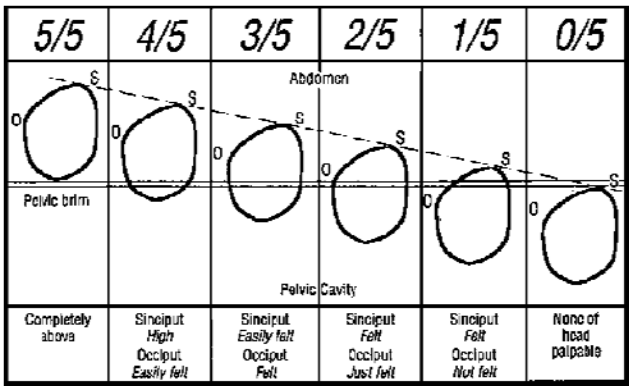




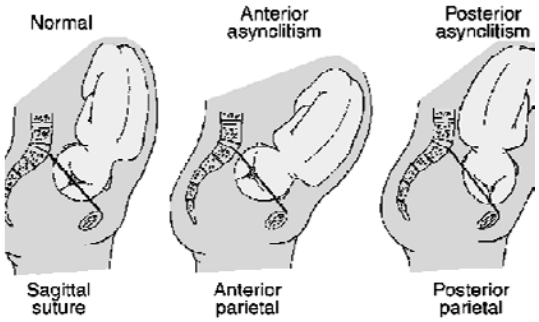
- **Station** = relation (in cm) of the bones of the presenting part to the level of the ischial spines during labour; used to denote fetal descent during labour
  - Station of 0 at level of ischial spines
  - Station of -5 at level of pelvic inlet
  - Station of +2 to +3 at level of perineal floor



- **Engagement** = descent of the largest diameter of the presenting part (that is lying in the anteroposterior diameter of the pelvic inlet) past the pelvic inlet
  - Depends on presentation:
    - For cephalic presentations, occurs when the ***biparietal*** diameter crosses the pelvic inlet
    - For breech presentations, occurs when the ***bi-ischial*** diameter crosses the pelvic inlet
  - Clinically assessed via abdominal palpation & using the **method of "fifths" palpable** (*engagement said to have occurred when only 2/5s palpable or less*):



- **Synclitism vs Asynclitism**
  - During engagement, in the context of a normal descent of the fetal head through the pelvic inlet in a transverse position (hence with the biparietal diameter in line with the AP diameter of the pelvic inlet):
    - If the biparietal diameter is parallel to the pelvic inlet plane (*hence sagittal suture runs midway between the anterior & posterior halves of the pelvic inlet plane*), the head position is considered to be **synclitic**
    - Otherwise, the head position is considered to be **asynclitic** (*usually deflected such that the sagittal sutures lie closer to the sacrum than the pubic symphysis*)
  - Relevance of this lies in that the presenting diameter is smaller in an asynclitic position than a synclitic position (which is essentially the biparietal diameter); hence asynclitism present helps permit a larger head to enter the pelvis than would be possible in a synclitic position

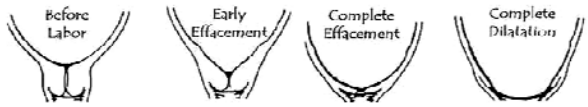


Normal Labour

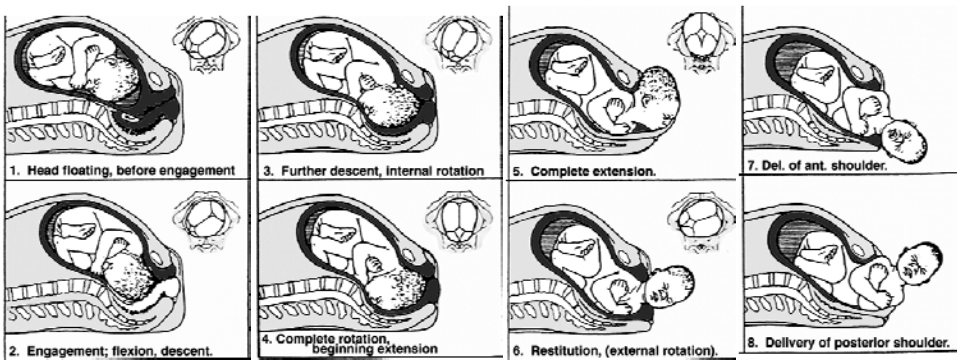
Overview of Normal Labour

- **Definition of Labour**
  - **Labour** = presence of contractions of sufficient frequency, strength & duration to cause cervical effacement & dilatation
    - **Cervical effacement** = the shortening of the length of the cervix (from ~3-4cm normally until it is completely indistinguishable from the uterine wall) at the onset of labour; occurs with concomitant softening of the cervix due to increased water content & collagen lysis
    - **Cervical dilatation** = the widening of the cervical os; progresses from closed → 3-4cm (*roughly coincides with complete cervical effacement, marks the onset of active phase of 1st stage of labour*) → 10cm (*complete cervical dilatation, marks the beginning of 2nd stage of labour*)
    - **Show** = small amount of blood-tinged mucous passed per vaginally (*due to release of the mucous plug normally occupying the endocervical canal when cervical effacement & dilatation occur*)
  - Diagnosis of labour
    - Patient presents with:
      - Regular painful contractions
      - ± Show
      - ± Leaking liquor (*may be reported as a sudden gush of fluid per-vaginally; ask for colour & presence of foul-smelling odour*)
    - Vaginal examination reveals:
      - Cervical effacement & dilatation
      - ± Pooling of liquor in the fornices
  - Differential diagnoses of labour
    - **Braxton-Hicks contractions**
      - Sporadic contractions which usually begin in the last 4-8 weeks of pregnancy, typically of mild intensity
      - *Differentiation from true labour*: no cervical changes
    - **Antepartum hemorrhage**
      - *Differentiation from true labour*: no cervical changes, no contractions
    - **Abruptio placentae**
      - Usually presents with acute onset of sudden abdominal pain ± per-vaginal bleed; palpation reveals a woody-hard uterus
      - *Differentiation from true labour*: no cervical changes, pain is usually constant rather than intermittent as for contractions
    - **Premature rupture of membranes (PROM)**
      - Usually present with a sudden gush of fluid per-vaginally
      - *Differentiation from true labour*: no cervical changes, no contractions

- **Stages of Labour**
  - ***1st stage of labour***
    - Begins with the onset of true labour, ends with the complete dilatation of the cervix
    - Further subdivided into 2 phases:
      - Latent phase (*initial cervical effacement & dilatation, variable duration – 6-18 hours in primiparous, 2-10 hours in multiparous – ends when cervical dilatation is 3-4cm*)
      - Active phase (*cervix is fully effaced, cervical dilatation continues to progress at a rate of 1cm/hour; if progress is slower than this, assessment for abnormal labour progress is performed*)
  - ***2nd stage of labour***
    - Begins with the complete dilatation of the cervix, ends with the delivery of the fetus
    - Lasts 30 minutes to 3 hours in primiparous, 5-30 minutes in multiparous
  - ***3rd stage of labour***
    - Begins with the delivery of the fetus, ends with delivery of the placenta, cord & membranes
    - Lasts 0-30 minutes in both primi- multiparous



- **Fetal Events During Labour**
  (*events here are for cephalic presentations; events occurring during other presentations will be discussed in "Malpresentations" below*)
  - ***Engagement***
    - Passage of the greatest diameter of the presenting part through the pelvic inlet (*see above*)
    - Assessed clinically via abdominal palpation using the **method of "fifths" palpable** (engagement occurs when only two-fifths palpable)
    - May occur before or after rupture of the membranes takes place during labour (*if engagement does not happen before rupture of membranes however, there is a risk of cord prolapse as the gush of liquor carries the cord out through the vagina with it; this risk is especially significant for non-cephalic presentations which doesn't have the large head to tamponade the flow of liquor following rupture of membranes*)
  - ***Descent***
    - Progress of presenting part through the birth canal brought about by the force of uterine contractions, maternal bearing down (Valsalva maneuver) & gravity (if mother is standing up)
    - Clinically assessed via periodic vaginal examination to determine the **station** of the presenting part
    - Fetal head changes during descent:
      - **Moulding** (*overriding of fetal cranial bones due to external pressure; helps head conform to birth canal*)
      - **Caput succedaneum** (*localized edematous swelling of the scalp superficial to the cranial periosteum due to pressure of the cervix on the head*)
  - ***Flexion***
    - Partial flexion is normally present even before labour due to the resting muscle tone of the fetus
    - During descent, resistance from the cervix, pelvic walls & pelvic floor cause further flexion of the fetal cervical spine, bringing the chin closer to the chest
    - Effect on the presenting part:
      - For occipitoanterior position, this changes the presenting diameter from occipitofrontal (*deflexed*) to suboccipitobregmatic (*well-flexed*) which has a smaller diameter
      - For occipitoposterior position, complete flexion may not occur (*as natural tilt of the maternal pelvis counteracts flexion with the natural tendency to extend at the cervical spine as the fetal head descends*), resulting in a larger presenting diameter which can contribute to longer labour
  - ***Rotation (internal rotation)***
    - Rotation of the fetal head within the pelvic cavity as it descends against the pelvic floor muscles
    - Usually rotates the fetal head from the original transverse position (*for it to pass through the pelvic inlet*) to an eventual anteroposterior position (*either occipitoanterior or occipitoposterior*)
  - ***Extension***
    - As the fetal head continues descent, it has to exit via extension (*as the vaginal outlet is directed up & forward*)
      - **Crowning** occurs when the largest diameter of the fetal head is encircled by the vulvar ring (*clinically defined when head retraction no longer occurs in between uterine contractions*)
      - An episiotomy may be made at this stage to aid in reducing perineal resistance
    - Birth of the fetal head depend on the position:
      - *Occipitoanterior*: head is born via rapid extension as the occiput, brow, nose, mouth & chin (in succession) pass over the perineum
      - *Occipitoposterior*: head is born via a combination of flexion & extension; at the time of crowning, the pelvic floor promotes further flexion, with the brow & occiput born as the fetal chin approaches the chest; subsequently, the occiput falls back & the nose, mouth & chin are born via extension
  - ***Restitution (external rotation)***
    - Following birth of the head, the head rotates back to its original position at the point of engagement to align itself with the fetal back & shoulders
    - Further rotation of the fetal head may occur (in accordance with the shoulders) as the fetal shoulders undergo internal rotation to align themselves anteroposteriorly within the pelvis
  - ***Expulsion***
    - Following birth of the fetal head, the shoulders are born with the anterior shoulder delivered under the pubic symphysis & the posterior shoulder delivered over perineal body; rest of the fetus then delivered



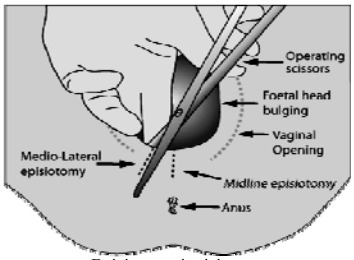
Management of Normal Labour

- **Basic Principles in Management of Normal Labour**
  - ***Siting of care***
    - There is no evidence to suggest that childbirth in a hospital (with obstetricians in attendance) improves perinatal outcomes as compared to childbirth at home (with midwives in attendance) for normal labour
    - Either way, a one-to-one trained care-to-mother ratio is recommended
    - In Singapore, most births usually occur in hospitals
  - ***Monitoring of progress***
    - A variety of methods for monitoring are employed to monitor the progress of labour as well as fetal & maternal well-being throughout the process
    - Findings are plotted on a **partogram**
    - If thresholds for abnormal labour progress are reached, interventions are introduced for labour augmentation (*see below*)
  - ***Terminology for interventions pertaining to labour***
    - **Induction of labour** = intervention to promote the onset of labour when it has not occurred
    - **Augmentation of labour** = intervention to speed up the progress of labour when labour has already been established
    - **Stimulation of labour** = intervention to promote the onset of labour when rupture of membranes have occurred (in which case it is termed pre-labour rupture of membranes)
  - ***Miscellaneous issues***
    - Analgesia provided as requested
    - Regular bladder emptying is encouraged to avoid over-distension of the bladder for prolonged periods of time as labour progresses
    - Perineal shaving not recommended (*shown to increase rates of colonization with gram negative bacteria*)
    - Bowel preparation with enemas not recommended
    - Keep nil-by-mouth in case of the need for emergency caesarean with general anaesthesia

- **Management of the 1st Stage**
  - ***Parameters monitored (recorded on a partogram)***
    - Vaginal examination every 4 hours to:
      - Assess cervical effacement
      - Assess cervical dilatation (*once 3-4cm, i.e. active phase has begun, should expect 1cm/hour dilation subsequently*)
      - Assess amniotic fluid colour (*if membranes have already ruptured*)
      - Assess station of presenting part
      - For cephalic presentations, presence of caput & moulding should also be noted
    - Abdominal examination every 30 minutes to:
      - Assess uterine contractions via palpation (*frequency of about 4 in 10 minutes is appropriate; at higher rates, uterus contracts inefficiently, causing poor labour progress & also increases the risk of fetal hypoxia as fetus has less time in between contractions to recover*)
      - Assess engagement of fetal head
    - Maternal well-being:
      - Blood pressure (every 4 hours)
      - Pulse rate (every 30 minutes)
      - Pain score
    - Fetal well-being assessment depends on technique:
      - Intermittent auscultation (*fetal heart rate assessed every 15 minutes for 1st stage*)
      - Cardiotocography (*continuous monitoring of fetal heart rate, usually done in Singapore*)
  - ***Maternal position***
    - Mother may ambulate
    - If in bed, lateral recumbent position is encouraged to ensure perfusion of the uteroplacental unit
  - ***Management***
    - IV fluids (IV line also provides route of administration of drugs for augmentation of labour if subsequently required)
    - Adequate analgesia
    - Baseline investigations (sent off at presentation after diagnosis of labour is made):
      - Full blood count (*check haemoglobin level*)
      - Group & cross match (*in case of the need for transfusion with excessive peripartum blood loss*)
      - Urine analysis (*check for presence of protein & glucose*)
      - Maternal blood group, rhesus type & antibody screen (*if not already known, as it determines need for maternal anti-D administration post-partum*)
      - Hepatitis B & HIV status (*if not already known, as they affect post-natal management of the child*)
      - High vaginal swab for Group B *Streptococcus* colonization (*if not already known, as it affects decision to give intrapartum antibiotics to prevent neonatal sepsis*)

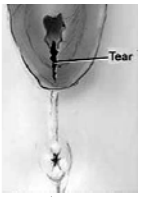
- **Management of the 2nd Stage**
  - ***Parameters monitored***
    - Fetal descent
      - Can be monitored by using fetal head station vaginally (every 30 minutes) & number of fifths palpable abdominally
      - Moulding & excessive caput formation can affect the accuracy of the assessment of fetal head station, hence the importance of also considering number of fifths palpable abdominally especially in difficult labours
    - Fetal well-being assessment depends on technique:
      - Intermittent auscultation (*fetal heart rate assessed every 5 minutes for 2nd stage of labour*)
      - Cardiotocography (*continuous monitoring of fetal heart rate, usually done in Singapore*)
  - ***Maternal position***
    - Mother can assume any position she prefers:
      - Upright or lateral positions are associated with a reduction in pain & assisted deliveries but with an increase in tears & blood loss >500ml
    - Mother should be encouraged to push/bear down once they have got a pressure sensation/urge to push (*usually occurs once cervix is fully dilated with the onset of the 2nd stage of labour*)
      - Maternal pushing efforts should be synced with the occurrence of uterine contractions
      - Note that the sensation to push may be decreased with the use of epidurals, hence the need for encouragement by the healthcare staff in attendance to push with contractions
  - ***Management***
    - **Episiotomy**
      - Done when crowning occurs to decrease perineal resistance to birth
      - 2 main types: **mediolateral** (*cut from 6 o' clock position obliquely left or right 45 degrees*) & **midline/median** (*cut from 6 o' clock position down towards direction of anus*)
      - Controversial; liberal use vs restrictive use
      - Pros of episiotomies: *creates a controlled perineal tear which is easier to repair*
      - Cons of episiotomies: *higher incidence of 3rd degree tears, creation of a tear larger than required*
    - Delivery of fetal head using **Ritgen maneuver** (*applies to the typical occipitoanterior position*)
      - Right hand draped with a towel exerts upward pressure through the perineal body onto the fetal supraorbital ridges (& subsequently chin) to facilitate extension
      - Left hand counteracts by exerting downward pressure on the fetal occiput to prevent overtly rapid extension of the fetal head
    - Delivery of rest of fetus
      - Mother is told to give only small pushes or just pant once the head has been delivered
      - Anterior shoulder is delivered via gentle downward traction on the externally rotated fetal head
      - Posterior shoulder is delivered via elevation of the fetal head
      - Rest of fetal body delivered via gentle traction on the shoulders
    - Cord clamping
      - Umbilical cord is usually clamped & cut within 15-20 seconds
      - Prolonged holding of the newborn below the level of the maternal introitus with a patent cord will promote infusion of the newborn with blood from the placenta (*can contribute to neonatal hyperbilirubinemia; may be used therapeutically for premature babies to decrease need for respiratory support post-natally*)
      - Cord blood sample taken for *G6PD & TSH ± umbilical artery pH for high-risk cases*
    - Initial management of neonate
      - APGAR score, resuscitate where needed
      - Examine for birth injuries
      - Vitamin K where indicated (*premature, complicated &/or instrumental delivery*)

Ritgen maneuver

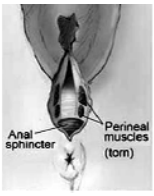


Episiotomy incisions

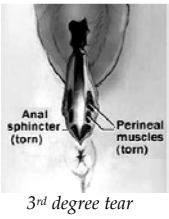
- **Management of the 3rd Stage**
  - ***Repair of perineal tears (including episiotomy if made)***
    - Classification of perineal tears
      - 1st degree = involves vaginal epithelium or perineal skin only (*doesn't need repair*)
      - 2nd degree = involves perineal muscles
      - 3rd degree = laceration involving the anal sphincter (*3a: <50% of the external anal sphincter, 3b: >50% of the external anal sphincter, 3c: involves internal anal sphincter*)
      - 4th degree: involves rectal mucosa
    - Episiotomy repair
      - Pre-repair to-do: *take informed consent, sterilize & drape, VE to assess for other tears, PR to assess for anal mucosal involvement, ensure adequate analgesia*
      - Repair is done using Vicryl rapid sutures
      - 1st repair done beginning from ~0.5cm above the apex of the vaginal incision (*to ensure that any retracted incised vessel is caught within the repair*), done with a continuous interlocking stitch until the mucocutaneous junction is reached
      - 2nd repair done involves apposition of perineal muscles with interrupted or continuous stitches
      - 3rd repair done involves repair of perineal skin using a subcuticular stitch or interrupted stitches
      - If anal sphincter torn, repair using PDS sutures
      - Post-repair to-do: *ensure no more bleeding, PR again to see if any suture went too deep through the anal mucosa, dispose of equipment appropriate, observe patient's pad chart thereafter*
  - ***Delivery of the placenta***
    - Separation of the placenta generally occurs 2-10 minutes after the end of the 2nd stage of labour
    - **Signs of placental separation**:
      - Cord elongation outside the vagina
      - Fresh short gush of blood
      - Uterus becomes smaller, firm & globular
    - Active management of placental delivery:
      - Controlled cord traction (*with abdominal massage of the uterus to stimulate contraction*)
      - IM syntometrine administration (*ergometrine + oxytocin, helps decrease blood loss*)



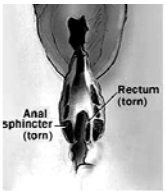
1st degree tear



2nd degree tear

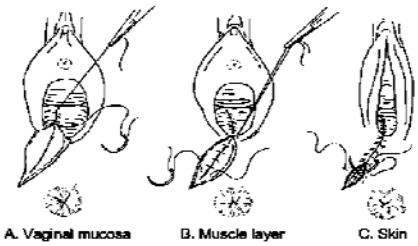


3rd degree tear



4th degree tear

Mediolateral incision



Mediolateral episiotomy repair

- **Pain Relief Options in Labour**
  - ***Non-pharmacological measures***:
    - Acupuncture
    - Hypnosis
    - Back massage
    - Transcutaneous electrical nerve stimulation (TENS)
  - ***Inhalational analgesia***
    - Entonox (1:1 mixture of O_2 & NO_2)
    - Short acting, works for as long as the patient inhales
    - Side-effects: nausea & vomiting, giddiness
  - ***Parenteral narcotics***
    - Pethidine, morphine, fentanyl
    - Easy to administer
    - Side effects: nausea & vomiting, neonatal respiratory depression (*especially if used within 1-3 hours of delivery; reverse by administrating naloxone to neonate*)
  - ***Local infiltrations***
    - Perineal/pudendal nerve blocks
    - Useful when performing episiotomy, repairs & instrumental deliveries
  - ***Epidural analgesia/anaesthesia***
    - Bupivacaine, 16-20 gauge needle, injected into epidural space at L2-L5
    - Very good pain relief, useful for both vaginal & caesarian deliveries
    - However, associated with increased risk for instrumental delivery (*due to decreased maternal sensation of urge to push during 2nd stage of labour*) & slight risk of headaches (<1%)
  - ***Spinal analgesia/anaesthesia***
    - Bupivacaine/lignocaine, 24-27 gauge needle, injected into subarachnoid space at L2-L5)
    - Easy & fast when compared to epidural, mainly employed for caesarian deliveries
    - However, limited time span of use (2 hours) & higher risk (1-2%) of post-dural puncture headache (*a severe positional headache*)

Fetal Surveillance & Intervention

This section gives a more in-depth discussion on the aspect on fetal surveillance during labour which has been briefly mentioned earlier in the management of the different stages of labour as well as the strategies for intervention when fetal distress is detected

- **Techniques for Fetal Surveillance During Labour**
  - ***Intermittent auscultation***
    - Manual auscultation of fetal heart rate using a stethoscope or DopTone at regular intervals:
      - Every 15 minutes for 1st stage of labour
      - Every 5 minutes in 2nd stage of labour
    - Not routinely done in Singapore
  - ***Cardiotocography***
    (*refer to "Cardiotocography" in the chapter on "Antenatal Care" for more details on interpretation of CTG patterns*)
    - Continuous monitoring of fetal heart rate using external transducers (*or where applicable, internally monitored using fetal scalp electrodes*) with simultaneous monitoring of uterine contractions
      - Indications for use of fetal scalp electrode monitoring: *multiple gestations, obese mother*
    - Useful for assessing both fetal well-being as well as frequency & amplitude of uterine contractions
    - Good negative predictive value (*i.e. if CTG is reassuring, fetus is most likely well*) but poor positive predictive value (*i.e. if CTG is pathological, fetus may often still be well*)
  - ***Fetal blood sampling***
    - Can be done from fetal scalp (*during 2nd stage of* labour) or umbilical artery (*after fetus is delivered*)
    - Done to assess fetal blood pH to detect fetal acidosis, which has a good accuracy for predicting neonatal outcome (*sensitivity 90%, specificity 92%*)
      - Umbilical artery blood pH <7.0 is associated with cerebral palsy
    - Indicated when fetal distress is suspected during labour (*non-reassuring CTG, meconium staining*)
    - Technique for fetal scalp blood sampling:
      - *Amnioscope is placed transvaginally against scalp*
      - *Cotton swabs are used to remove cervical mucus, before silicone grease is applied to the scalp to facilitate blood bead formation*
      - *2x2mm lancet is used to make a stab incision on the fetal scalp, before aspirating a drop of blood into a long heparinized capillary tube*
    - Complications of fetal scalp blood sampling:
      - Scalp abscess

- **Fetal Distress**
  - ***Implications of fetal distress:***
    - Fetal distress fundamentally signifies fetal hypoxia
    - Prolonged or repeated fetal hypoxia will result in fetal acidosis, which can result in perinatal fetal morbidity & mortality
  - ***Causes of fetal distress (both during labour & before)***:
    - Maternal conditions
      - Maternal hypertension, pre-eclampsia
      - Maternal hypotension, obstetric shock
      - Severe maternal anemia
      - Maternal cardiac & respiratory disease
      - Maternal seizures (*both eclamptic & otherwise*)
    - Uteroplacental conditions
      - Uterine tetany/hyperstimulation
      - Placental abruption
      - Post-mature placenta (>*42 weeks gestation*)
    - Umbilical cord conditions
      - Vasa praevia
      - Umbilical cord compression
      - Umbilical cord prolapse
      - Umbilical cord hematoma (*e.g. iatrogenic after cordocentesis*)
    - Fetal conditions
      - Fetal anemia
      - Intrauterine infections
      - Donor twin in twin-twin transfusion
  - ***Signs of fetal distress:***
    - Changes in fetal heart rate pattern on CTG:
      - Earliest sign is decelerations (*variable decels typical for cord compression, late decels typical for uteroplacental insufficiency*)
      - Baseline tachycardia sets in next as compensatory response to prolonged fetal hypoxia to improve circulation
      - Loss of baseline variability follows with further hypoxia due to blunted autonomic function with prolonged brain hypoxia
      - Baseline bradycardia is a late sign
    - Meconium passage
    - Fetal acidosis (detected on fetal blood sampling)

- **Strategies for Intervention**
  - ***Managing non-reassuring fetus status on CTG in labour***
    - Give 100% oxygen via face mask to mother
    - Change maternal position to left recumbent position
      - *Helps relieve fetal compression of umbilical cord in variable decelerations*
      - *Helps relieve gravid uterus compression of vena cava & aorta in late decelerations*
    - Assess maternal vitals to exclude correctable causes of poor uteroplacental perfusion (*e.g. maternal hypotension as a side effect of epidural anesthesia*)
    - Vaginal examination to exclude cord prolapse (*if diagnosed, see "Obstetric Emergencies"*)
    - Discontinue oxytocin infusion if present (*be it for induction or augmentation of labour initially*)
    - Consider administering IV tocolytic (*e.g. terbutaline 0.25mg or magnesium sulphate 2.0g*)
    - If abnormal CTG pattern persists, consider fetal scalp blood sampling:
      - pH ≥7.25 = observe, repeat blood sampling
      - pH ≤7.20 = consider immediate delivery
    - Consider **amnioinfusion** if in 2nd stage (*replacement of amniotic fluid with normal saline infused through a transcervical intrauterine pressure catheter*)
    - Consider assisted (instrumental) delivery if in 2nd stage & fetal station permits
    - Last resort: emergency caesarian delivery
  - ***Managing meconium passage in labour***
    - As above to manage/exclude poor uteroplacental perfusion
    - Amnioinfusion may be considered for its dilutional effect (*reported to reduce incidence of meconium-related fetal respiratory complications*)
    - After successful delivery, nasal suction of newborn should be avoided to prevent reflex gasping which may drive meconium further into lungs
    - Neonatal resuscitation of meconium aspiration requires swift intubation, endotracheal suction of meconium from airways & assisted ventilation (*do not bag & mask as per normal neonatal resuscitation protocol as this would drive meconium further down the respiratory tree*)

Induction of Labour

Induction of labour refers specifically to the intentional triggering of the onset of true labour in a pregnant woman who is not already in established labour & has not had her membranes ruptured yet

- **Indications for Induction of Labour**
  - ***Maternal indications***
    - Intrauterine fetal death (IUFD)
    - Polyhydramnios
    - Social reasons ("horoscope induction")
  - ***Fetal indications***
    - Evidence of fetal compromise
    - Intrauterine growth restriction (IUGR)
    - Oligohydramnios
    - Post-date pregnancy (*especially after 41 weeks*)
    - Maternal diabetes mellitus (*both pre-existing & GDM*)
    - Fetal abnormalities requiring earlier delivery
  - ***Indications pertaining to both mother & fetus***
    - Hypertensive disorders, pre-eclampsia
    - Placental abruption
    - Medical disorders (*e.g. SLE, chronic renal disease*)
    - Premature rupture of membranes (PROM)
    - Chorioamnionitis

- **Contraindications to Induction of Labour**
  - ***Maternal contraindications***
    - Contracted pelvis (*assumed cephalopelvic disproportion*)
    - Prior uterine surgery
    - Previous caesarian delivery (*risk of uterine rupture*)
  - ***Fetal contraindications***
    - Preterm fetus without lung maturity
    - Acute fetal distress
    - Malpresentation (*breech, transverse*)
    - Placenta praevia major
    - Vasa praevia

- **Principles of Induction of Labour**
  - ***Two main types of labour induction:***
    - Surgical induction of labour
      - Involves amniotomy/artificial rupture of membranes (ARM) (*stimulates endogenous prostaglandin production*) used in conjunction with IV oxytocin infusion
      - Used only if modified Bishop's score is favourable
    - Medical induction of labour
      - Involves use of vaginal prostaglandins (*pessary preparations of PGE1 analogues like misoprostol aka Cytotec; PGE2 analogues like dinoprostone aka Prostin*)
      - Usually used if modified Bishop's score is unfavourable (*helps with cervical "priming"*)
      - A disadvantage is that this method is not very titratable (*vs oxytocin infusion for surgical induction which can be titrated*)
  - ***Success of induction of labour depends on:***
    - Gestational age (*the closer to EDD, the better*)
    - Parity (*previous normal vaginal delivery better*)
    - State of cervix/cervical "ripeness"
  - ***Scoring system for assessment of cervical ripeness:***

Modified Bishop's Score (Cervical Score)			
Parameter	***0***	***1***	***2***
Cervical dilatation	0cm	1-2cm	3-4cm
Cervical length (effacement)	>2cm	1-2cm	<1cm
Cervical direction	Posterior	Axial	Anterior
Cervical consistency	Firm	Medium	Soft
Station of presenting part	-3	-2	-1
Score of >5 is favourable, surgical induction can be done *If score ≤5, medical induction is used instead*			

- **Induction of Labour in Special Circumstances**
  - ***Previous caesarian section***
    - Previous CS is a relative contraindication, but where vaginal delivery is desired by mother & indications for induction of labour is present, still possible
    - If modified Bishop's score is favourable, surgical induction of labour can be carried out
    - Cervical priming with prostaglandin analogues associated with a higher risk of uterine rupture with previous CS
  - ***Twin pregnancy***
    - Possible only if the 1st twin is in cephalic presentation

- **Risks & Complications of Induction of Labour**
  - Iatrogenic prematurity (*dates may be inaccurate*)
  - Failed induction/abnormal labour progress
    - Higher rates of need for assisted (instrumental) delivery & caesarian delivery for induced labours vs spontaneous labours
  - ***Risks & complications of amniotomy:***
    - Umbilical cord prolapse
    - Chorioamnionitis
  - ***Risks & complications of oxytocin infusion:***
    - Uterine hyperstimulation (*especially if >7 contractions every 10 minutes resulting in fetal hypoxia*)
    - Uterine rupture (*especially if previous caesarian section*)
    - Water intoxication (*especially if oxytocin infusion is prolonged, as oxytocin has anti-diuretic physiological effect, leading to hyponatremia*)
    - Uterine atony post-partum (*hence higher risk of post-partum hemorrhage*)

Abnormal Labour Progress

Approach to Poor Labour Progress

- **Types of Poor Labour Progress**
  - ***Primary dysfunctional labour***
    - Considered when labour progresses at a rate slower than expected
      - 1st stage: *prolonged latent or active phase of labour*
      - 2nd stage: *prolonged descent*
    - Suspect when:
      - 1st stage (latent phase): *>20 hours (nulliparous) or >14 hours (multiparous)*
      - 1st stage (active phase): *<0.5-1cm/hour of cervical dilatation after 3-4cm dilatation has been attained*
      - 2nd stage: *<1cm/hour (nulliparous) or <2cm/hour (multiparous) of presenting part descent* <u>*or*</u> *>2 hours in nullip (>3 hours if regional anesthesia used) or >1 hour in multip (>2 hours if regional anesthesia used)*
    - Usually a problem of poor uterine contractility
  - ***Secondary arrest of labour***
    - Considered when labour progresses normally at an expected rate initially before abruptly stopping or slows down very significantly
      - 1st stage: *arrest of dilatation*
      - 2nd stage: *arrest of descent*
    - Suspect when:
      - 1st stage: *when cervical dilatation rate falls significantly or ceases to dilate*
      - 2nd stage: *when fetal station ceases to progress*
      - Large caput succedaneum
      - Excessive moulding
      - Edematous cervix & vulva
    - Usually due to cephalopelvic disproportion

- **Assessing Poor Labour Progress – The 3 "Ps"**
  (*when dealing with poor labour progress, fall back on the 3 "Ps" to evaluate the possible etiology*)
  - ***Power***
    - Poor uterine contractility (*normally has frequency of 4 times in 10 minutes & amplitude of >50mmHg*)
    - Accounts of 90% of poor labour progress
    - Risk factors: *older age, obesity, primips*
  - ***Passage***
    - Inadequate maternal pelvic anatomy/dimensions to accommodate passage of fetus
  - ***Passenger***
    - Big baby (macrosomia, leading to **shoulder dystocia**, defined as difficult delivery of the shoulders)
    - Abnormal baby (large abdomen, hydrocephalus)
    - Malpositions
      - Persistent occipitotransverse position
      - Persistent occipitoposterior position
    - Malpresentations
      - Brow presentations
      - Face presentations
      - Transverse/shoulder presentations

- **Management of Poor Labour Progress**
  - ***Management of prolonged latent phase (of 1st stage)***
    - Give analgesia
      - Pain increases sympathetic activity which decreases uterine smooth muscle contractility (mediated via β2-adrenergic receptors)
  - ***Management of prolonged active phase (of 1st stage)***
    - Artificial rupture of membranes (ARM, amniotomy)
      - If rupture of membranes has not occurred
      - Works by stimulating endogenous release of prostaglandins by encouraging application of presenting part to the cervix
    - Augmentation with IV oxytocin (syntocin)
      - 1st-line management
      - Risks: *uterine hyperstimulation, uterine rupture*
      - *Common mistake: note that syntometrine & prostaglandins are* <u>*not*</u> *used in the augmentation of labour; syntometrine is only used after delivery of the fetus as part of managing the 3rd stage to reduce blood loss; prostaglandins are only used in the induction of labour*
    - Caesarian section
      - 2nd line management
      - Done if adequate uterine activity has been achieved for at least 2-4 hours without improvement in rate of cervical dilatation (*presumed cephalopelvic disproportion present*)
  - ***Management of prolonged descent (2nd stage)***
    - Augmentation with IV oxytocin (syntocin)
      - Used if uterine contractility is inadequate
    - Assisted delivery (*see "Assisted Delivery"*)
      - Used if uterine contractility is adequate
  - ***Management of arrested labour***
    (*depends on underlying etiology*)
    - Cephalopelvic disproportion
      - Absolute indication for caesarian section
    - Shoulder dystocia
      (*see "Obstetric Emergencies"*)
    - Malpositions
      - Persistent occipitotransverse position (*arrest of descent usually occurs at the level of the mid-pelvis; managed by manual rotation or midforceps rotation using a Kielland forceps*)
      - Persistent occipitoposterior position (*course of labour in OT positions usually normal except for tendency to be prolonged; can consider vacuum extraction ± mediolateral episiotomy*)
    - Malpresentations (*see below*)

- **Complications of Abnormal Labour Progress**
  - ***Obstructed (neglected) labour***
    - Occurs when arrested labour progresses without medical intervention
    - Maternal consequences:
      - Maternal tachycardia
      - Edematous cervical lips
      - Distended lower segment
      - Inadequate uterine relaxation
      - Haematuria (*prolonged bladder compression leading to bladder wall necrosis; long term sequelae: vesico-vaginal fistula*)
    - Fetal consequences:
      - Significant caput & excessive moulding
      - Fetal hypoxia
  - ***Uterine rupture***
  - **Erb's palsy**
    - Specifically in the setting of shoulder dystocia
    - Upper brachial plexus injury due to excessive fetal neck lateral flexion to the contralateral side
    - Erb's palsy on the <u>anterior shoulder</u> is often due to excessive traction by the delivery attendant
    - Erb's palsy on the <u>posterior shoulder</u> is most likely caused by abnormalities of the sacral promontory applying on the brachial plexus before delivery

Malpresentation

Refers to any presentation other than cephalic (vertex)

- **Breech Presentation**
  - ***Breech presentation*** = fetal buttocks or feet present into the maternal pelvis
    - Incidence is 1 in 25 deliveries (4%)
    - About 25% of all fetuses before 28 weeks gestation are in breech presentation, but eventually rotates to assume a vertex presentation as they grow & occupy more of the uterus (*hence breech isn't much of an issue except in the context of preterm labour or persistent breech presentation after 34 weeks gestation*)
  - ***Etiologies & associations:***
    - Prematurity (major predisposing factor)
    - Multiple gestation
    - Fetal structural abnormality (e.g. hydrocephalus)
    - Placenta praevia
    - Polyhydramnios
    - Uterine abnormalities (e.g. bicornuate uterus)
    - Contracted maternal pelvis
    - Pelvic tumours obstructing birth canal
  - ***Classification of breech presentations:***
    - Frank breech – 65% (*thighs flexed, knees extended*)
    - Complete breech – 25% (*thighs & knees flexed*)
    - Footling (incomplete) breech – 10% (*one or both thighs extended with one or both knees/feet lying below the level of the buttocks*)

Frank breech

Complete breech

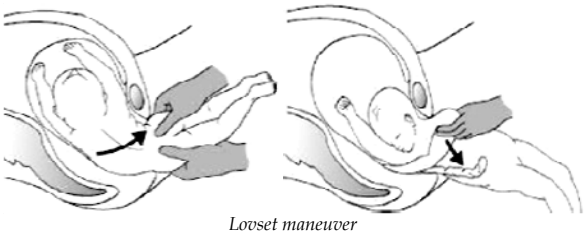
(Single) Footling breech

  - ***Issues pertaining to breech deliveries:***
    - High risk of cord prolapse
    - Risk of head entrapment (*when fetal body passes through a relatively undilated cervix with the head trapped subsequently; especially so an issue with very preterm babies with a larger head-to-body ratio*)
    - Birth trauma (*e.g. Erb's palsy*)
    - Perinatal mortality 2.5% vs 1.2-1.6% for non-breech
  - ***Diagnosis of breech presentations:***
    - Can be made antenatally by abdominal palpation & ultrasound scan
  - ***Management of breech presentations:***
    - Consider excluding fetal & uterine abnormalities
      - If breech presentation after 34 weeks
      - Look out for any Müllerian abnormalities, uterine fibroids or fetal structural abnormalities
    - **External cephalic version** (ECV)
      - Done at 37 weeks of gestation (*in case of need for emergency caesarian if complications arise*)
      - Under ultrasound guidance by an experienced obstetrician, extra-uterine manipulation is done to convert the breech fetus to a cephalic one; tocolytics helps facilitate procedure; CTG done before & after procedure; anti-D Ig given after procedure where indicated
      - Complications: *abruptio, cord compression, premature rupture of membranes (with cord prolapse), uterine rupture, fetomaternal hemorrhage*
      - Hence needs to be done in a hospital with the facilities for emergency caesarian with the patient prepped for the operation if needed (*nil-by-mouth, establish IV access*)
      - Immediate success rate = 35-76%
      - Contraindications to ECV: *evidence of placental insufficiency, placenta praevia, hypertension, IUGR, oligohydramnios, history of previous uterine surgery*

    - Caesarian section
      - Where ECV is not an option (*contraindicated or patient's refusal to do it*), caesarian section is the current standard of care for the delivery of breeches
      - **Term breech trial** (year 2000) demonstrated significant reduction in perinatal morbidity & mortality when elective caesarian was performed for breeches instead of normal vaginal delivery (1.6% vs 5.0%, $p<0.0001$)
    - Assisted breech delivery
      - Assisted vaginal delivery of breeches may still be performed in certain situations (*no facilities for caesarian, mother's wish to deliver vaginally, delivery of a breech 2nd twin*)
      - Fetus is allowed to descend naturally until the level of the umbilicus is reached
      - In frank breeches, delivery of the feet can be facilitated by the use of **Pinard maneuver** – *pressure on the popliteal fossa of the fetal lower limb to cause flexion of the knee, thereby bringing the foot down to the level of the vagina*

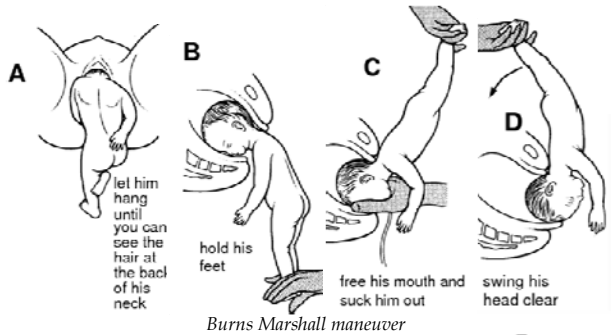
Pinard maneuver

- The delivery attendant's hands grasped on the fetal pelvis (*to avoid injury to abdominal viscera*), gentle traction is employed until the scapulae appear at the introitus
- The shoulders are then delivered by sweeping each arm in turn across the fetal chest; however, if the arms are stretched above the head (nuchal arms), may need to employ **Lovset maneuver**:

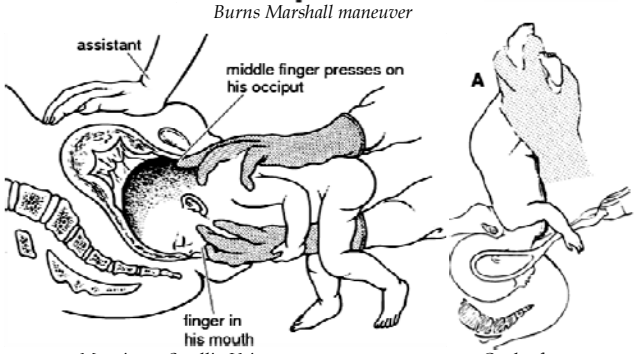


Lovset maneuver

- Delivery of the fetal head can proceed in 3 ways: (i) **Burns Marshall maneuver –** *hang fetus from the introitus until the hair at the back of his head can be seen, then grasp both legs & rotate the body of the fetus through an arc to bring him towards the mother's abdomen* (ii) **Mauriceau-Smellie-Veit maneuver –** *one hand is placed into the vagina with the palm facing the fetal face, with the index & ring fingers applying pressure on the fetal maxilla & middle finger in the fetal mouth (or alternatively on the fetal chin) to produce downward flexion of the neck; other hand is placed over the back of the fetal skull to provide flexion at the base of the skull* (iii) **Outlet forceps –** *books describe a special Piper forceps for this purpose; locally, a Wrigley forceps is used*

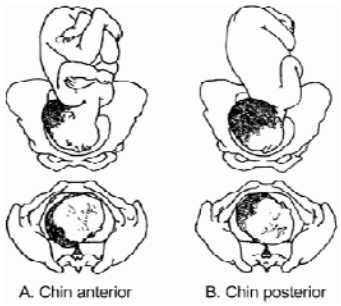


Burns Marshall maneuver



Mauriceau-Smellie-Veit maneuver *Outlet forceps*

- **Face Presentation**
  - ***Face presentation*** = fetal face (*between the chin & orbits*) is the presenting part as a result of hyperextension of the fetal neck
    - Incidence is about 1 in 500 deliveries
    - Presenting diameter is submentobregmatic (*9.5cm, similar to suboccipitobregmatic in typical occipitoanterior cephalic presentations*)
  - ***Etiology & associations:***
    - In most cases, no underlying cause is found
    - Extreme prematurity
    - High maternal parity
    - Polyhydramnios
    - Placenta praevia
    - Fetal goitre (*causes fetal neck extension*)
    - Anencephaly (*anencephalic fetuses present uniformly face-first, hence need to exclude this if face presentation is suspected*)
  - ***Issues pertaining to face presentations:***
    - Possible cause of abnormal labour progress
    - Fetal face injuries during birth
    - Perineal trauma during birth
    - Perinatal morbidity & mortality similar to that for cephalic presentations
  - ***Diagnosis of face presentations:***
    - Usually diagnosed intra-partum when the soft tissues of the fetal mouth & nose are noted adjacent to the malar bones & orbital ridges on vaginal examination
    - 60% are mentoanterior, 25% mentoposterior, 15% mentotransverse at the time of diagnosis
  - ***Management of face presentations:***
    - <u>Vaginal delivery</u>
      - Viable option for mentoanterior (*as fetal chin can rotate under pubic symphysis with fetal neck flexion, allowing vaginal delivery to occur*)
      - Can be assisted with low forceps (but not vacuum) if required
      - Mentoposterior positions cannot deliver vaginally due to inability for further neck extension to allow delivery to be completed; mentotransverse positions usually experience arrest of descent as well
      - However, about 50% of mentoposterior & mentotransverse spontaneously rotate to mentoanterior after a significant period of maternal pushing, hence can manage expectantly initially
      - Use of oxytocin for augmentation of labour controversial
    - <u>Caesarian section</u>
      - Reserved for persistent mentoposterior & mentotransverse positions which do not spontaneously rotate to mentoanterior

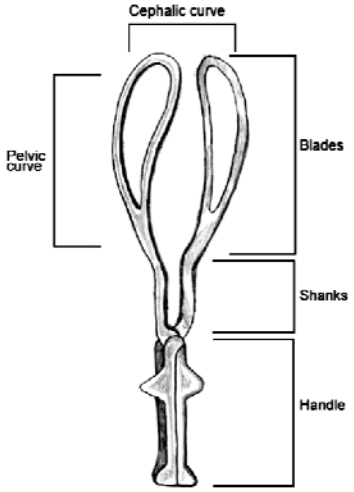


- **Brow Presentation**
  - ***Brow presentation*** = fetal brow (*between orbits & bregma*) is the presenting part as a result of extension of the fetal neck midway between hyperextension (*face presentation*) & flexion (*cephalic presentation*)
    - Incidence is 1 in 1400 deliveries
    - Presenting diameter is mentovertical (*13.5cm, the largest anteroposterior diameter of the fetal head possible*)
  - ***Etiologies & associations:***
    - Similar to those for face presentations
  - ***Issues pertaining to brow presentations:***
    - Possible cause of abnormal labour progress
    - Perinatal morbidity & mortality similar to that for cephalic presentations
  - ***Diagnosis of brow presentations:***
    - Head does not engage due to large presenting diameter, possibly with a sulcus that is palpable between the fetal occiput & back
    - On vaginal examination, anterior fontanelle & supraorbital ridges may be felt
    - Diagnosis often made late in labour
  - ***Management of brow presentations:***
    - Expectant treatment
      - May be indicated as the brow presentation is an unstable one (*50-70% will convert to a face or cephalic presentation*)
    - Caesarian section
      - Indicated for a persistent brow presentation

- **Transverse Lie – Shoulder & Compound Presentations**
  - ***Compound presentation*** = fetal extremity (*usually the hand*) prolapses alongside the presenting part (*the head*) & both parts enter the maternal pelvis at the same time; if the complete extremity prolapses = ***shoulder presentation***
    - Incidence is 1 in 700 deliveries
    - Spontaneous version occurs in 80-85% of cases
  - ***Etiologies & associations:***
    - Prematurity
    - Multiple pregnancy
    - Polyhydramnios
    - Placental praevia
    - Multiparity
    - Uterine abnormalities (e.g. arcuate/septate uterus)
  - ***Issues pertaining to transverse lie:***
    - High risk of cord prolapse
  - ***Diagnosis of transverse lie:***
    - Antenatally, uterus is felt to be ovoid in shape wider at the sides, with an empty lower pole & the fetal head felt in one flank
    - Symphysial fundal height less than expected
    - Confirmed with ultrasound
  - ***Management of transverse lie:***
    - External cephalic version
      - Admission at 37 weeks gestation for ECV may be attempted, followed by stabilizing induction of labour & controlled amniotomy
    - Caesarian section
      - Indicated for persistent malpresentation

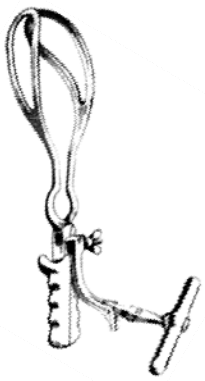
Assisted (Instrumental) Delivery

- **Forceps Delivery**
  - ***Obstetric forceps*** = instruments designed to provide traction & rotation of the fetal head when the expulsive efforts of the mother are insufficient to accomplish safe deliver of the fetus
  - ***Parts of a forceps:***



    - **Cephalic curve** = the curve on the inner aspect of the blades (*giving the blades a "cupped" surface*) to fit the fetal head
    - **Pelvic curve** = the curve along the lower margin of the blade (*hence when you put a locked forceps flat on a table the tips of the blades curve upwards*) to fit the birth canal
  - ***Types of forceps:***
    (*many different types; 3 main ones used locally described here*)
    - **Wrigley forceps**
      - *Has pelvic & cephalic curves*
      - *Used for outlet (lift-out) forceps procedures*
    - **Neville-Barnes forceps**
      - *Classic/standard forceps*
      - *Has pelvic & cephalic curves*
      - *Has a detachable attachment for better traction*
    - **Kielland forceps**
      - *Reduced pelvic curve, hence suitable for rotation*
      - *Sliding lock mechanism which allows adjustment of the blades even after both blades are locked, allowing for accommodating asynclitic presentations*
      - *Not routinely used nowadays (need training, high risk of birth trauma)*

Wrigley forceps


Neville-Barnes forceps

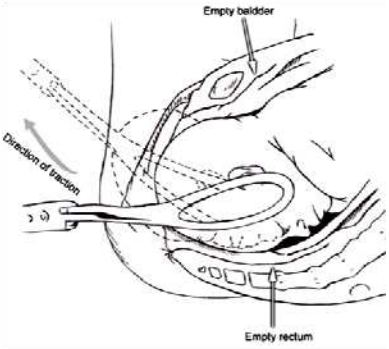
Kielland forceps

- ***Types of forceps operations:***
  - Outlet forceps ("lift-out") = *scalp is visible at introitus without separating the labia, fetal head at perineum, fetal skull at pelvic floor, sagittal suture is anteroposterior & rotation of fetal head* <45 *degrees*
  - Low forceps = *leading part of fetal skull is at station +2cm or more*
  - Mid forceps = *fetal head is engaged but leading point of skull is above station +2cm*
- ***Indications for forceps delivery:***
  - Prolonged 2nd stage of labour
  - Suspected immediate/impending fetal compromise
  - To stabilize aftercoming head during breech delivery
  - To shorten 2nd stage of labour for maternal benefit:
    - Maternal conditions (*hypertension, cardiac disorders, pulmonary disease*) in which strenuous pushing in 2nd stage of labour is hazardous
- ***Prerequisites for forceps delivery:***
  - Cervix must be fully dilated
  - Membranes must be ruptured
  - Fetal head must be engaged into the pelvis
  - Clinical assessment performed to determine level of presenting part, exact position of head, estimation of fetal size & adequacy of maternal pelvis
  - Bladder must be emptied
  - Adequate anesthesia:
    - Local infiltration (*e.g. pudendal nerve block*) for outlet forceps
    - Regional anesthesia for other procedures
- ***Forceps technique:***
  - Forceps blades are inserted sequentially into the vagina such that the sagittal suture of the fetal head is directly between & perpendicular to the shanks
  - Left blade is inserted before the right (*as the locking mechanism is such that the shank of the right blade needs to be above the left blade*)
  - Guiding toe of the blade along the natural pelvic curve of the birth canal helps avoid damage to maternal tissues
  - Forceps are locked &, timed in sync with contractions, traction is applied
  - **Pajot maneuver**: direction of pull should be parallel to the axis of the birth canal at that level, such that typically there is a downward traction initially, followed by an ever-increasing upward traction as delivery of the fetal head occurs
  - Episiotomy may be done when the crowning occurs
  - If progress of fetal head is not obtained with appropriate traction (i.e. failed forceps), procedure is abandoned in favour of a caesarian delivery
- ***Forceps complications:***
  - Failure rate = 7%
  - Maternal: *birth canal injuries (higher risk than with vacuum extraction)*
  - Fetal: *facial bruising, injury to CN7 & brachial plexus*

Introducing left blade

Introducing right blade

Forceps blades locked



Applying traction in sync with contractions

Episiotomy

- **Vacuum Extraction**
  - ***Vacuum extractor*** = instrument which uses a suction cup that is applied to the fetal head
  - ***Types of vacuum extractors:***

Kiwi cup

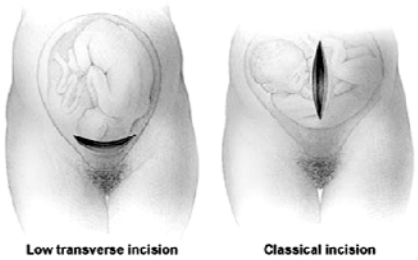
Ventouse (silc cup)

  - ***Indications for vacuum extraction:***
    - Largely similar to those for forceps delivery (*in fact, vacuum extraction is usually preferred due to relative ease of use*) except in the following cases where forceps use is indicated over vacuum extraction:
      - Preterm delivery (*preterm head & scalp more prone to injury from suction cup*)
      - Certain malpresentations (*breech, face*)
  - ***Prerequisites for vacuum extraction:***
    - Same as those for forceps delivery
    - Must be cephalic presentation
  - ***Vacuum extraction technique:***
    - Suction cup is placed with its edge 3cm posterior to the anterior fontanelle squarely over the sagittal suture to maintain flexion of the fetal head
      - *For occipitoanterior position, this involves placing the cup right onto the presenting part*
      - *For occipitoposterior position, this requires sliding the cup along the back of the fetal head as far as possible to place it (hence only kiwi cup can be used)*
    - Suction is created:
      - *For kiwi cup, hand pump attached is pumped until the pressure indicator reaches the green zone*
      - *For ventouse, foot pump is usually attached*
    - Traction is provided in sync with contractions parallel to the axis of the birth canal (*as for forceps*)
    - Detachment of the cup from the fetal head = **pop-off**
    - If progress of fetal head is not obtained with appropriate traction of if 2 pop-offs occur, procedure is abandoned in favour of a caesarian delivery
  - ***Vacuum extraction complications:***
    - Failure rate = 12%
    - Maternal: *birth canal injuries (less risk than with forceps)*
    - Fetal: *chignon, cephalohematoma, subgaleal hematoma, fetal retinal hemorrhages (overall more fetal morbidity than with forceps)*

Caesarian Delivery

- **Indications for Caesarian Delivery**
  - Abnormal labour progress
  - Malpresentation
    - Breech presentation (*not absolute indication, but standard of care as support by term breech trial*)
    - Persistent brow presentation
    - Persistent mentoposterior or mentotransverse face presentation
    - Persistent transverse lie
  - Repeat caesarian
    - Not absolute indication for previous lower segment caesarian section (LSCS)
    - Recommended for previous classical CS
  - Fetal distress
  - Previous full-thickness non-transverse incision through the myometrium
    - E.g. myomectomy for fibroids
    - Due to high risk of uterine rupture with NVD
  - Placenta praevia
    - Placenta praevia major is an absolute indication (*placenta blocking cervical os*)
    - Placenta praevia minor is a relative indication (*normal vaginal delivery still possible is edge of placenta is at least 2cm away from cervical os)*

- **Types of Caesarian Deliveries**
  - ***Classical caesarian section***
    - Vertical incision made in the upper segment of the uterus through the myometrium of the uterus
      - *Note that this refers only to the uterine incision; skin incision could still be a transverse suprapubic (pfannenstiel) incision*
    - Indications:
      - Preterm breech (*lower segment undeveloped*)
      - Transverse back-down fetal position (*as no fetal part to grasp after performing an LSCS*)
      - Poor access to lower segment due to fibroids or adhesions
      - Some cases of anterior placenta praevia with high risk of massive hemorrhage if an LSCS is done instead
      - Planned caesarian hysterectomy
    - Implications of a classical caesarian section:
      - Higher risk of post-partum hemorrhage, infections & thromboembolism (*vs NVD*)
      - Risk of uterine rupture in future pregnancies (4-7%; increased if induction of labour)
      - Hence patients with classical caesarian section are destined to have repeat caesarian deliveries for all subsequent pregnancies
  - ***Lower segment caesarian section (LSCS)***
    - Transverse incision (*Joel Cohen incision*)made in the lower uterine segment after establishing a bladder flap
    - Indications:
      - As per for indications for caesarian deliveries other than the circumstances in which classical caesarian is indicated
    - Implications of a LSCS:
      - Higher risk of post-partum hemorrhage, infections & thromboembolism (*vs normal vaginal delivery*)
      - Risk of uterine rupture in future pregnancies (<1%; increased if induction of labour)
      - Increased incidence of placenta praevia & placenta accreta



- **Complications & Risks of Caesarian Delivery**
  - ***Intra-operative risks:***
    - Anesthesia risk
    - Bleeding requiring transfusion or even hysterectomy
    - Injury to bladder, bowel, ureters
    - Amniotic fluid embolism
  - ***Post-operative risks:***
    - Post-partum hemorrhage
    - Infection (*wound, endometritis, other infections*)
    - Longer hospital stay & recovery (vs NVD)
  - ***Long-term complications:***
    - Post-operative adhesions (*future pelvic surgeries or repeat CS may be more difficult & complicated*)
    - Uterine rupture (*in future pregnancies*)
    - Increased risk of placentation problems in future pregnancies (*placenta accreta, placenta praevia*)

- **Pre-Operative Management for Caesarian Deliveries**
  - Take informed consent from mother for procedure
  - Establish large bore IV access, catheterize bladder
  - ***Pre-operative bloods & investigations:***
    - Take bloods for FBC, PT/PTT, GXM (4-6 units of blood), urea/creatinine
    - Consider ECG & chest x-ray
  - ***Measures to decrease risk of aspiration pneumonia in pregnancy if GA is used*** (**Mendelson syndrome**):
    - For elective CS: *nil-by-mouth + H2-antagonists (e.g. ranitidine to neutralize gastric contents)*
    - For emergency CS: *sodium citrate (for immediate neutralization of gastric contents) + metoclopramide (promote gastric emptying)*
    - Intubation: *cricoid pressure, cuffed endotracheal tube, rapid-sequence induction, pre-extubation gastric emptying*
  - ***Thromboprophylaxis***
    - Low-risk: *early mobilization, hydration*
    - Moderate-risk: *IV heparin + TED stockings*
    - High-risk: *IV heparin continued till 5-days post-op + TED stockings*
  - ***Antibiotic prophylaxis***
    - IV cefazolin, given after fetus is delivered & cord is clamped (*to prevent crossing over of drug*)
    - Reduces incidence of wound infection, endometritis & urinary tract infection post-op

- **Vaginal Birth After Caesarian (VBAC)**
  - A trial of labour offered to women in subsequent pregnancies if one or two previous LSCSs were performed, with the uterine incision not extending into the cervix or upper uterine segment
  - Benefits of VBAC vs repeat caesarian section:
    - Shorter hospital stay & recovery period
    - Lower rates of neonatal RDS
    - Successful VBAC increases likelihood of future successful VBACs
  - Overall success rate of VBAC ~70%

Obstetric Emergencies

Emergency situations which require immediate intervention to avoid maternal &/or fetal demise

Shoulder Dystocia

A delivery requiring additional obstetric maneuvers to release the shoulders after gentle downward traction has failed

- **Risk Factors for Shoulder Dystocia**
  - ***Past pregnancy factors:***
    - Previous delivery complicated by shoulder dystocia
    - Previous macrosomic baby
  - ***Maternal factors:***
    - Short maternal stature
    - Maternal obesity
  - ***Current antenatal factors:***
    - Maternal diabetes
    - Postdates pregnancy
    - Fetal macrosomia
    - High pregnancy weight & weight gain
  - *Note: despite these theoretical risk factors, a large number of shoulder dystocias still occur in patients without risk factors*

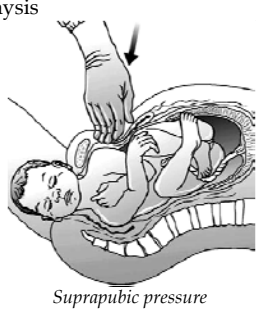
- **Diagnosis of Shoulder Dystocia**
  - Diagnosis is made <u>clinically</u> intra-partum with the observation of the following signs:
    - Abnormal labour progress
      - Prolonged or arrest of labour at 1st or 2nd stage
      - Need for oxytocin augmentation of labour
      - Need for assisted instrumental delivery
    - Head-bobbing in 2nd stage of labour (*significant head retractions occurring in between uterine contractions*)
    - **Turtle-necking** (*following delivery of fetal head, fetal head retracts back against the maternal perineum, causing fetal cheeks to bulge, resembling a turtle retracting its head back into its shell*)
    - Poor restitution following delivery of the fetal head

- **Complications of Shoulder Dystocia**
  - ***Maternal complications:***
    - Uterine rupture
    - Perineal tears & anal sphincter damage
    - Post-partum hemorrhage
    - Symphysial separation
  - ***Fetal complications:***
    - Brachial plexus injuries (Erb's palsy)
    - Clavicular & humeral fractures
    - Birth asphyxia, fetal acidosis, hypoxic brain injury
      - Fetal cord pH drops at 0.4 per minute once shoulder dystocia is established
      - Studies have shown that cord pH < 7.0 is highly associated with cerebral palsy
      - Hence, assuming an average cord pH of 7.2 at the time of shoulder dystocia establishment, there is only a short window period of 5 minutes to get the fetus delivered to avoid long-term hypoxic brain injury sequelae

- **Intrapartum Management of Shoulder Dystocia (HELPERR)**
  - <u>**H**</u>elp
    - Call for immediate help (*senior obstetrician, neonatologist, operating theatre, anesthetist, midwives*)
    - Ideally need at least 4 assistants for managing shoulder dystocia
    - Get someone to continually watch the time & regularly report the amount of time elapsed since shoulder dystocia was diagnosed
      - Very narrow window period for intervention to maximize fetal outcomes
      - Time is of the essence when deciding to escalate interventions
  - <u>**E**</u>valuate for need for episiotomy
    - This is typically done at the point before "enter vagina", primarily to allow easier entry of hands into the vagina to perform the maneuvers described
    - Note that an episiotomy does <u>not</u> intrinsically help shoulder dystocia because shoulder dystocia involves a bony obstruction while episiotomies only relieve soft tissue obstructions
  - <u>**L**</u>egs up
    - **McRobert maneuver**
      - Get patient into knee-chest position (*hyperflexion of both hips*) using the help of 2 assistants, each holding up 1 lower limb
      - Reduces lumbar lordosis & the angle between the lumbar spine & the sacrum
      - Does not change the pelvic inlet diameter, but rather, rotates the pubic symphysis more cephalad such that the plane of the pelvic inlet becomes more perpendicular to the direction of maternal expulsive efforts, which helps delivery of the shoulders

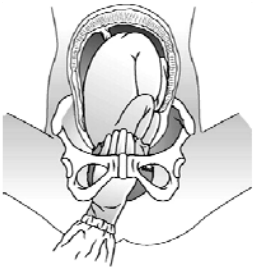
McRobert maneuver

  - <u>**P**</u>ressure (suprapubic)
    - Get an assistant to apply suprapubic pressure (*using 2 hands in a CPR-like position*), ideally directed in an oblique manner such that the pressure is applied onto the posterior aspect of the fetus' anterior shoulder
    - Helps dislodge the anterior shoulder from the pubic symphysis



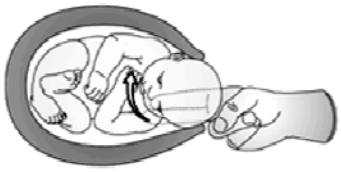
Suprapubic pressure

- Enter vagina (to attempt the following maneuvers)
  - **Rubin II maneuver**
    - Use 2 fingers to locate & press on the posterior aspect of the anterior shoulder
    - Apply a rotational force to turn the fetus to an oblique diameter to help deliver the anterior shoulder
  - **Woods corkscrew maneuver**
    - Using both hands, place one on the posterior aspect of the anterior shoulder & the other on the anterior aspect of the posterior shoulder
    - Apply pressure with both hands to rotate fetus
  - **Reverse Woods corkscrew maneuver**
    - Using both hands, place one on the anterior aspect of the anterior shoulder & the other on the posterior aspect of the posterior shoulder
    - Apply pressure with both hands to rotate fetus



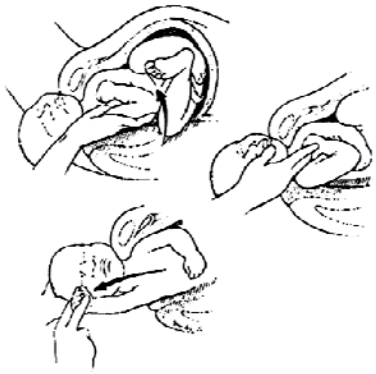
Woods corkscrew maneuver

Rubin II maneuver



Reverse Woods corkscrew maneuver

- Remove posterior arm
  - Use your hand corresponding to the direction of the fetal back (*right hand if fetal back facing maternal right, left hand if fetal back facing maternal left*)
  - Grasp the posterior arm of the fetus & move it into a flexed position at the elbow
  - Sweep the posterior arm across the fetal chest to deliver it, thereby helping reduce the shoulder diameter by 20% to help deliver the anterior shoulder



Remove posterior arm

- Roll patient over (**Gaskin maneuver**)
  - Roll patient over onto all fours
  - Uses gravity & an increased sacral hollow to help with delivery of the shoulders

Gaskin maneuver

- If everything above fails, may need to resort to the following heroic measures:
  - **Fracture fetal clavicles**
    - Intentional fracture of the fetal clavicles to decrease the diameter of the shoulders
  - **Zanavelli maneuver**
    - Manual replacement of fetal head into the vagina by steady upward pressure (*reverse restitution, manually flex fetal head*)
    - Send for emergency caesarian section
  - **Symphysiotomy**
    - Not performed locally due to significant maternal morbidity & easy accessibility to caesarian section following Zanavelli maneuver as a last resort
    - Stiff silicon catheter placed into mother's bladder to allow palpation of the urethra using a hand placed in the vagina
    - Urethra is manually deflected away from the midline before a scalpel is used to incise the pubic symphysis
    - Creates an iatrogenic open-book fracture of the pelvis, resulting in an increased pelvic inlet diameter to allow the delivery of the fetal shoulders

- **Postpartum Management of Shoulder Dystocia**
  - ***Management of mother:***
    - Inspect for perineal tears & repair them
    - Anticipate & manage post-partum hemorrhage
  - ***Management of fetus:***
    - Resuscitate accordingly
    - Assess for fetal injuries (Erb's palsy, fractures etc)
    - Test cord pH
  - ***Record the following clearly in notes:***
    - Direction fetal head faced after restitution
      - Determines which shoulder was anterior & which was posterior
      - Important medicolegal implications as only brachial plexus injuries of the anterior shoulder are considered iatrogenic, whereas posterior shoulder brachial plexus injuries are usually attributed to excessive traction resulting from impaction against the sacral promontory occurring naturally
    - Time of delivery of head & body respectively
    - Baby APGAR score
    - Umbilical cord blood acid-base measurement

Cord Prolapse

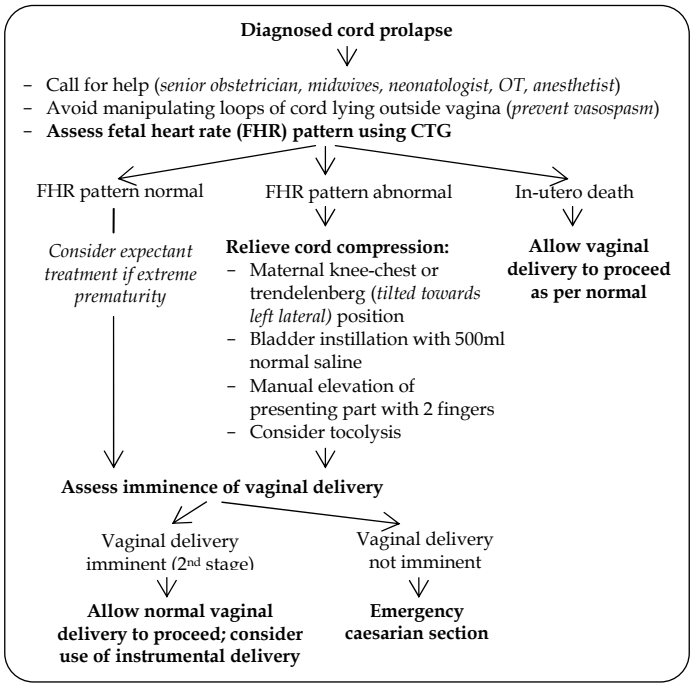
Descent of the umbilical cord through the cervix alongside (occult) or past the presenting part (overt) in the presence of ruptured membranes; occurs in approximately 0.2% of all births

- **Risk Factors for Cord Prolapse**
  - ***Fetal factors:***
    - Small fetus (low birth weight, prematurity)
    - Unengaged fetal presenting part
    - Malpresentation (breech, transverse lie)
    - Second twin
  - ***Uterine factors:***
    - Multiparity
    - Polyhydramnios
  - ***Placental & umbilical cord factors:***
    - Long umbilical cord
    - Placenta praevia
  - ***Procedure-related risk factors:***
    - Artificial rupture of membranes
    - Vaginal fetal manipulation in the presence of ruptured membranes
    - External cephalic version (*if rupture of membranes occurs during procedure*)

- **Diagnosis of Cord Prolapse**
  - ***When to suspect cord prolapse:***
    - Fetal heart rate pattern abnormalities detected on CTG (*e.g. variable decelerations, bradycardia*), especially if such changes occur soon after ROM
  - ***Diagnosis of cord prolapse:***
    - Vaginal examination (*either speculum or digital whichever is applicable depending on the stage of labour*) to detect presence of umbilical cord alongside or ahead of the presenting part

- **Complications of Cord Prolapse**
  - Birth asphyxia, fetal acidosis, hypoxic brain injury (*due to cord compression between presenting part & bony pelvic inlet*)

- **Management of Cord Prolapse**



Amniotic Fluid Embolism

Obstetric emergency resulting from entry of fetal cells into maternal circulation, leading to sudden maternal &/or fetal deterioration

- **Risk Factors for Amniotic Fluid Embolism**
  - Medical induction of labour (*especially in the presence of uterine tetany; doubles risk, but absolute excess risk is low*)
  - Invasive obstetric procedures:
    - Amniocentesis
    - Termination of pregnancy
    - Caesarian section

- **Diagnosis of Amniotic Fluid Embolism**
  - ***Symptoms:***
    - Shortness of breath
    - Chest pain
    - Altered mental state (*light-headedness, restlessness, distress, panic*)
    - Nausea & vomiting
    - Frank maternal collapse
  - ***Signs:***
    - Cardiovascular instability (*hypotension, cardiac arrest*)
    - Hypoxia (*dyspnea, cyanosis, respiratory arrest*)
    - Signs of coagulopathy
    - Seizures
  - ***Supportive investigations:***
    - ECG, chest x-ray
    - FBC, DIVC screen, group & cross match
    - Other investigations depending on differentials

- **Complications of Amniotic Fluid Embolism**
  - Maternal morbidity, multi-organ failure & mortality
  - Fetal morbidity & mortality

- **Management of Amniotic Fluid Embolism**
  - Initial management is as per for an undifferentiated obstetric shock/maternal collapse:
    - ABCs, resuscitation with oxygen & fluids
    - Inotropic support & vasopressors
    - Ventilatory support
    - Close (invasive) monitoring (*central venous line, arterial line, pulmonary wedge catheter, urinary catheter*)
    - Treat coagulopathy (*whole blood, packed cells, fresh frozen plasma, cryoprecipitate*)
  - No specific treatment for amniotic fluid embolism is validated (*supportive treatment + transfusion is mainstay*)

Puerperium

The puerperium is defined as the 6-week period following delivery during which various changes that occurred during pregnancy revert to the non-pregnant state

Normal Puerperal Changes & Monitoring

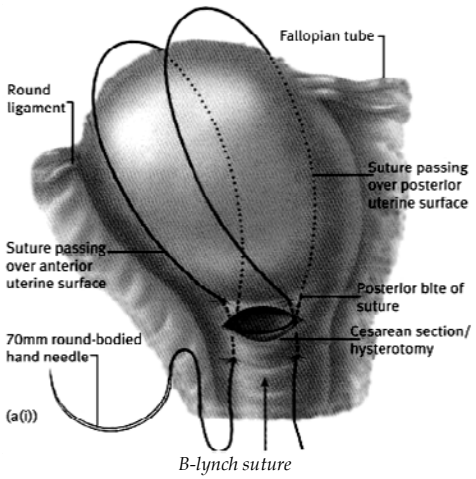
- **Puerperal Anatomical & Physiological Changes**
  - ***Involution of the uterus***
    - After delivery of the placenta, the uterus is approximately a 20-week size (level of umbilicus); subsequent reduction in size occurs at a rate of 1 finger breadth/day such that it cannot be palpable through the abdomen anymore after 2 weeks
    - Uterine weight decreases from 1kg at delivery to 200-300g at 3 weeks post-delivery
    - By the end of the puerperium, the uterus is only slightly larger than before pregnancy
  - ***Cervical changes***
    - Cervix regains firmness by the 3rd day
    - Internal os closes within 3 days, while the external os closes within 3 weeks
  - ***Vagina & perineal changes***
    - After delivery: vaginal wall is initially swollen, bluish & pouting; perineal edema present
    - Pelvic floor gradually regains former tone by 6 weeks (*may never return to the pre-pregnant state*)
    - **Kegel exercises** (intermittent tightening of the perineal muscles) can help
  - ***Lochia*** *(per-vaginal discharge of endometrial slough with red & white blood cells)*
    - Lochia rubra (red): *for first 3 days*
    - Lochia serosa (yellow): *transition from red to white over a 10-day period (sloughing of eschar at placental site at day 7-14 post-delivery may cause transient PV bleeding)*
    - Lochia alba (white): *discharged up to 6 weeks*
  - ***Cardiovascular changes***
    - Marked increased in peripheral resistance immediately after delivery due to removal of the low-pressure uteroplacental shunt
    - Cardiac output & plasma volume gradually returns to normal over the first 2 weeks, resulting in dieresis & marked weight loss
  - ***Return of menstruation & ovulation***
    - Without breastfeeding, menses returns by 6-8 weeks
    - With exclusive breastfeeding, lactational amenorrhea may occur up to 6 months, following which menstrual flow returns (*by 36 weeks post-delivery*)

- **Management & Assessment in Early Puerperium**
  - ***Regular monitoring of maternal parameters***
    - Temperature (*to detect puerperal sepsis*)
    - Blood pressure (*to detect concealed PPH*)
  - ***Regular physical examination***
    - Breasts (*look out for complications of breastfeeding such as mastitis & breast abscess*)
    - Fundal height (*to detect possible retained products of conception suggested by failure of uterine involution*)
    - Lochia (*check normal progression of lochia changes; persistent lochia rubra suggests retained products of conception; foul-smelling lochia suggests endometritis*)
    - Lower limbs (*check for signs of DVT*)
    - Assess for urinary function (*may have self-limiting overflow incontinence for ~24 hours after epidural use*)
  - ***Patient education, support & counseling***
    - Teach Kegel exercises to help regain pelvic floor tone
    - Support breastfeeding (*counsel patient appropriately to support them through the initial establishment of breastfeeding which is often the toughest*)
    - Contraception (*talk to patient about when they intend to have the next child, if at all; educate on contraceptive options to promote good family planning*)
  - ***Other miscellaneous issues:***
    - Anti-D (*within 72 hours of delivery where indicated*)
    - Check rubella status (*if previously unknown, so that vaccine can be administered before next pregnancy*)
    - Check relevant parameters at 6 weeks post-delivery for retrospective diagnosis:
      - Oral glucose tolerance test (*gestational diabetes should have resolved; if not, patient is determined to have diabetes mellitus*)
      - Blood pressure & urine protein (*pre-eclampsia should have resolved; if not, patient is determined to have chronic hypertension*)

Puerperal Complications

- **Common Puerperal Problems**
  - ***Perineal injury***
    - Perineal tears & episiotomies would still be painful in the immediate post-partum period
    - Infection may occur (*note that episiotomy wound infections are actually quite uncommon, possibly due to the high vascularity in the area which promotes good wound healing & immune defense against infection*)
    - Management: exclude wound site infection, give analgesia, rubber ring for sitting on
  - ***Bladder function***
    - Voluntary bladder emptying may be difficult in the first 24 hours, especially if epidural was used; requiring catheterization
    - Urinary incontinence (usually stress incontinence) may occur due to excessive pelvic floor stretch during labour; usually resolves by a few weeks, helped by Kegel exercises
    - More rarely, urinary fistulas may form (*e.g. between bladder & vagina*) as a complication of anterior vaginal wall injuries or obstructed labour, resulting in complete incontinence; requires surgical repair
  - ***Bowel function***
    - Constipation may persist for a short while; stool softeners are useful
    - Hemorrhoids may appear for the 1st time after labour or become more painful if already present previously
  - ***Mastitis***
    - May be due to failure to express milk from one part of the breast; can be further complicated by infection with *Staphylococcus aureus* & breast abscess formation
    - Management: ensure all milk is expressed, use of cold compress, flucloxacillin (*for S. aureus infection*), incision & drainage (*for breast abscess*)
  - ***Backache***
    - May persist after delivery, affects 25% of women
    - Pain may be considerable & last for several months
  - ***Postnatal blues***
    - Usually occurs on days 3-5, when 50-70% of women become temporarily sad & emotional
    - About 10% develop postnatal depression which can present anytime within the 1st year after delivery
    - Postulated to be due to hormonal changes, reaction to excitement of childbirth & doubts by the mother about her ability to care for the child
    - Management: counsel mother

- **Post-Partum Hemorrhage (PPH)**
  - ***Classification of PPH:***
    - Primary PPH = *loss of >500ml (>1000ml if caesarian) of blood within the first 24 hours after delivery*
    - Secondary PPH = *abnormal bleeding after 24 hours post-delivery up until 6 weeks*
  - ***Causes of PPH***
    - Typical causes of primary PPH:
      - Uterine atony (*accounts for 80% of cases; increased risk in conditions where excessive uterine stretch/contraction occurred – multiple gestation, polyhrdramnios, use of oxytocin for induction/augmentation of labour – use of halothane anesthesia, uterine fibroids & placental abruption*)
      - Retained products of conception (RPOC)
      - Low placental implantation (*as lower uterine segment contracts less well than the rest of the uterus, hence less able to constrict spiral arteries following placental separation*)
      - Genital tract injury (*may be concealed e.g. poor repair of perineal tears, forming a hematoma which is exquisitely painful; patient can exsanguinate as bleed continues tracking into ischiorectal fossae*)
      - Uterine inversion, uterine rupture
      - Coagulopathy (*may be pre-existing or due to complications such as placental abruption or amniotic fluid embolism*)
    - Typical causes of secondary PPH:
      - Poor epithelialization of placental site (*accounts for 80% of cases*)
      - Retained products of conception
      - Endometritis
  - ***Management of PPH & obstetric shock***
    - Initial management:
      - Resuscitate patient if necessary
      - Establish intravenous access & catheterize
      - Monitor patient's vitals closely
      - Group & cross match blood + FBC + PT/PTT if not already done before delivery
      - Palpate uterus (*detect uterine atony*)
      - Speculum examination (*exclude genital tract injuries, uterine inversion & pelvic hematoma; open os suggests RPOC*)
    - If <u>uterine atony</u> is determined to be the cause:
      - Massage uterus through abdomen
      - Administer uterotonic agents; options include:
      (i) IV oxytocin infusion 40-80U in 1L saline
      (ii) IM ergonovine maleate or methylergonovine 0.2mg (*ergot drugs may precipitate myocardial infarction & stroke; contraindicated in pre-eclampsia, severe hypertension, severe heart disease & familial hypercholesterolemia*)
      (iii) Per rectal misoprostol
      (iv) IM carboprost aka **Hemabate** 0.25mg every 15min up to max of 3 doses (*PGF2a analogue; can also be given straight into the myometrium which has a much faster onset of action: 4min vs 20min*)
      - If pharmacological measures fail, tamponade bleed using bimanual compression <u>or</u> uterine packing <u>or</u> balloon catheter (*e.g. Sengstaken-Blackmore tube or obstetric-specific* **Bakri balloon**) <u>or</u> external pressure on abdominal aorta
      - Uterine artery embolization (*enlist help of interventional radiology*) can be considered
      - Surgical measures as a last resort include use of **B-lynch suture** (*preferable option as it preserves fertility*) <u>or</u> stepwise arterial ligation (*uterine, ovarian, internal iliac*) <u>or</u> hysterectomy
    - If <u>retained products of conception</u> is the cause:
      - Always check completeness of placenta after 3rd stage of labour to ensure all cotyledons are present
      - If delivery of placenta cannot occur via the normal way, manual removal under general anesthesia may be required
    - If <u>genital tract injuries</u> is the cause:
      - Always ensure 1st suture in repair of vaginal lacerations is placed well above apex of tear to ensure any retracted vessel is caught
      - Repair any tears seen
      - Hematomas require urgent surgical management (*evacuation of clots, ligation of bleeding vessel, bilateral hypogastric artery ligation*)
    - If <u>uterine inversion</u> is the cause:
      - Usually a result of uncontrolled cord traction in the 3rd stage of labour; patient quickly goes into shock as profound vasovagal response causes systemic vasodilation which promotes heavy bleeding & extravasation of fluid
      - After stabilizing patient, attempt to replace uterus by placing a cupped hand around the fundus & elevating it in the long axis of the vagina
      - If unsuccessful, further attempt made after use of nitroglycerin general anesthesia to relax the uterine muscle
      - Once replaced, oxytocin administered to contract the uterus before removing the intrauterine hand
      - Rarely, if uterus cannot be replaced from below, surgery required (*vertical incision down cervix to incise the constriction ring to allow replacement of the fundus before suturing the cervical incision*)
    - If <u>coagulopathy</u> is the cause:
      - Correct coagulopathy with relevant transfusions
      - Amniotic fluid embolus often requires intensive supportive measures (*e.g. CPR, mechanical ventilation, inotropes etc*)
    - Managing <u>poor epithelialization</u> of placental site:
      - Ergometrine + antibiotics
      - Curettage necessary if bleeding persists



B-lynch suture

- **Puerperal Sepsis**
  - ***Puerperal pyrexia*** = temperate of ≥38°C during the first 14 days after delivery
  - ***Etiology of puerperal sepsis***
    - Usually due to anaerobic *Streptococci* which normally inhabit the vagina (*Peptostreptococcus, Peptococcus etc*)
    - Other common organisms include *Bacteroides fragilis, Escherichia coli & enterococci*
    - Ascending infections initially infect the placental bed & endometrium (*endometritis*), before spreading into the fallopian tubes & parametrium (*parametritis*)
  - ***Clinical features of puerperal sepsis***
    - Classically presents with fever on the postpartum day 2 or 3 with increasing uterine tenderness
    - Lochia may be foul-smelling; cessation of lochial flow may suggest occlusion of cervical os by slough material which itself predisposes to endometritis
    - Complicated cases with parametritis & pelvic peritonitis may had added features of fluctuating temperature, chills & rigors
  - ***Differential diagnoses for puerperal pyrexia***
    - Atelectasis
      - Usually presents with day 1 fever (*hence fevers on the 1st day post partum are usually managed expectantly without investigations or interventions*)
      - Self-resolving
    - Wound site infection
      - Usually first presents on day 2 or 3
      - Exclude by inspecting wound
    - Urinary tract infection
      - Usually presents after day 2
      - Ask for symptoms of flank pain, hematuria & lower urinary tract symptoms
      - Consider urine analysis & culture to exclude
    - Pneumonia
      - May be nosocomial or aspiration (*especially if general anesthesia was used for caesarian delivery*)
      - Ask for symptoms of pleuritic chest pain, productive cough & shortness of breath
      - Examine lungs
      - Consider chest x-ray to exclude
    - Mastitis
      - Examine breasts to exclude
    - Pelvic thrombophlebitis (non-infective)
      - Usually presents on days 7-10 with a persistent spiking fever
      - Managed using low molecular weight heparin
    - Thromboembolism (*see below*)
  - ***Management of puerperal sepsis***
    - History & thorough physical examination to exclude aforementioned causes
    - Aerobic & anaerobic cultures to be sent before administration of antibiotics:
      - Blood sample
      - Endocervical & uterine cavity samples
      - Urine sample
    - Start IV broad spectrum antibiotics:
      - Ampicillin or cephalosporin + aminoglycoside
      - Clindamycin can be considered as well (*in penicillin allergy or cases with Bacteroides fragilis*)
    - Pelvic abscess suspected if it does not respond to treatment:
      - Confirm with pelvic ultrasound or CT scan
      - Requires surgical drainage

- **Thromboembolism**
  - ***Risk factors:***
    - Maternal (*obesity, >35 years old*)
    - Caesarian delivery
  - ***Clinical features:***
    - Deep vein thrombosis: *low-grade fever, tachycardia, painful swollen calf*
    - Pulmonary embolism: *dyspnea, pleuritic chest pain, tachycardia*
  - ***Management of thromboembolism:***
    - Confirm diagnosis:
      - Doppler ultrasound of lower limbs to confirm diagnosis of DVT
      - CT pulmonary angiogram or ventilation-perfusion scan to confirm diagnosis of PE
    - Definitive treatment with IV heparin
  - ***Prevention of thromboembolism:***
    - Encourage early ambulation after delivery
    - Ensure adequate hydration
    - Use of thromboembolic deterrent (TED) stockings ± intermittent pneumatic calf compression

- **Postnatal Psychosis**
  - Affects 1-3/1000 women
  - Clinical features:
    - Usually begins abruptly at days 5-15 initially with confusion, anxiety, restlessness & sadness
    - Followed by rapid development of delusions & hallucinations (*e.g. baby died or deformed*) with deepening melancholy
  - Management:
    - Manage inpatient, preferably with baby also admitted with patient
    - Use of 1 or more drugs from the antidepressant, mood stabilizing or neuroleptic groups of drugs

Breastfeeding

- **Recommendations on Breastfeeding**
  - It is the obligation of every healthcare professional to encourage & support exclusive breastfeeding
  - Current recommendations:
    - Exclusive breastfeeding for 6 months
    - Continued breastfeeding (with introduction of solid feeds starting from 6 months) up till 1-2 years of age
    - If mother is willing, can breastfeed well beyond 2 years of age by all means

- **Benefits of Breastfeeding**
  - ***Maternal benefits*** – decreased risk of:
    - Type 2 diabetes mellitus by 12% for each year of breastfeeding
    - Ovarian cancer by 21%
    - Breast cancer by 28% in those whose lifetime duration of breastfeeding was 12 months or longer
  - ***Baby benefits*** – decreased risk of:
    - Acute otitis media
    - Nonspecific gastroenteritis
    - Severe lower respiratory tract infections
    - Atopic dermatitis, asthma
    - Obesity
    - Type 1 & 2 diabetes mellitus
    - Childhood leukemia
    - Sudden infant death syndrome
    - Necrotizing enterocolitis
  - ***Benefits to both mother & baby:***
    - Promotes mother-baby bonding

- **Breast Milk Content**
  - ***Anti-bacterial & anti-viral properties***
    - Secretory IgA
    - Bifidus factor (support growth of probiotic *Lactobacillus bifidus* in infant gut)
    - Lysozymes, lactoferrin (binds iron)
    - Interferons, macrophages & lymphocytes
  - ***Nutritional properties***
    - High whey:casein ratio
    - Lipid quality promotes digestibility & absorption
    - High lactose content with a small amount of oligosaccharides which act as prebiotics
    - Hypoallergenic
    - Lower mineral content (more suited to immature capacity of infants for renal excretion)
    - Calcium:phosphate ratio of 2:1 (promotes gut absorption of calcium)
    - Iron (high bioavailability)
    - Vitamins (rich in vitamins A C E, low in D K; all breastfeeding mothers need K supplementation, D supplementation if child does not get sun exposure, B supplementation if mother is vegetarian)

- **Correct Breastfeeding Technique**
  - ***Mother's position:*** any comfortable position
  - ***Baby's position:***
    - Baby held close to mother's body
    - Infant faces breast with head & body in straight line
    - Upper lip opposite nipple
    - Baby can reach breast easily
    - Move baby to breast, not breast to baby
  - ***Preparing for latch:***
    - Stimulate rooting reflex with nipple
    - Wait for baby to open mouth wide
    - Baby's bottom lip touches base of areola
    - Help baby take sufficient areola into mouth
  - ***Correct latch (CLAMS)***
    - **C**hin touching lip
    - Bottom **L**ip curling back
    - **A**reola more visible above top than below bottom lip
    - **M**outh wide open with a big mouthful of breast
    - **S**ucking pattern change from short sucks to long deep sucks with pauses

- **Measures to Support Breastfeeding**
  - Give adequate patient education & counseling (*should be done both antenatally & continued post-delivery*)
  - Address common concerns of breastfeeding mothers:
    - Concerns about child not getting enough milk (*may be due to perception of too little milk expressed or because child seems to be hungry all the time*)
      - Tell mother that so long as child is happy, growing well & has adequate urine & bowel output, child is definitely getting enough
      - In fact, breastfeeding may help prevent overfeeding babies because babies feed as much as they want to each time, without mothers feeling a need to finish feeding a whole bottle in the case of formula feeding
    - Maternal fatigue
      - Tell mother to get support at home to help out with household chores etc so that she can concentrate on breastfeeding the baby & resting
      - Alternatively, can express breast milk & get someone else to help bottle feed at times
  - Ask about breastfeeding at every subsequent postnatal visit & continue encouraging/counseling/educating

Contraception Post-Delivery

- **Conception After Delivery**
  - Contraception is not required in the 21 days after childbirth (*earliest that ovulation can occur is day 27 after delivery in the absence of breastfeeding*)
  - Subsequently, contraception should be employed if pregnancy in the short-term is not desired

- **Options for Post-Delivery Contraception**
  - ***Lactational amenorrhea***
    - Useful only if exclusive breastfeeding & complete amenorrhea is present, up to 6 months post-delivery
    - Not reliable after 6 months
    - Barrier contraception should still be encouraged as an added precaution
  - ***Intrauterine devices (IUD)***
    - Useful option
    - Levonorgestrel-releasing IUD (Mirena) especially useful if patient also has history of menorrhagia
    - Should only be inserted 2-3 weeks after delivery (*earlier insertion has higher incidence of spontaneous expulsion of IUD*)
  - ***Progestogen-only pill (POP)***
  - ***Etonogestrel implant (Implanon)***
  - ***Injectable progesterone contraceptives***
  - ***Post-partum sterilization (PPS)***
    - Interval tubal ligation (*done 2-3 weeks after delivery*) recommended as failure rates are higher for immediate ligation after delivery (*due to swollen tubes which are less easily occluded*)
    - Exception is when elective caesarian is done, during which concomitant tubal ligation can be done so as to combined both procedures in one setting
    - Remember that vasectomy is also an option
  - ***Combined oral contraceptives (COCs)***
    - The only contraception method which interferes with breastfeeding (*hence not recommended for breastfeeding mothers*)

Preterm Labour

Defined as the occurrence of regular painful contractions associated with cervical changes between the gestational ages of 24 (after onset of viability) & 36+6 weeks (before term) inclusive

- **Epidemiology & Associations**
  - ***Leading cause of fetal morbidity & mortality***
  - ***Incidence of preterm delivery:***
    - 6% of all singleton pregnancies
    - 46% of all twin pregnancies
    - 79% of all triplet or higher order pregnancies
  - ***Risk factors for preterm delivery:***
    - Low socioeconomic status, single mothers, stress
    - Smoking & alcohol
    - Extremes of reproductive age (<20 or >35 years)
    - Untreated genital tract infections:
      - B*acterial vaginosis*
      - *Trichomoniasis*
      - *Chlamydial infection*
      - *Gonorrhea*
    - Previous preterm labour:
      - 1 previous → RR 3.9
      - 2 previous → RR 6.5
    - Previous spontaneous abortions:
      - Any 2nd trimester spontaneous abortion
      - Repeated 1st trimester spontaneous abortions

- **Causes of Preterm Delivery**
  - 40% unknown (spontaneous preterm labour)
  - 25% due to elective preterm delivery
  - 10% due to multiple gestations
  - 25% due to other causes:
    - Preterm premature rupture of membranes (PPROM)
    - Pregnancy-associated hypertension
    - Structural abnormalities of the reproductive tract (cervical incompetence, uterine anomalies)
    - Antepartum hemorrhage
    - Intrauterine growth restriction
    - Polyhydramnios
    - Urinary tract infections

- **Pathophysiology of Preterm Labour**
  - ***Infection-cervical pathway:***
    - Genital tract infections have been shown to be an independent risk factor for preterm labour:
      - Treating bacterial vaginosis decreases incidence of preterm labour
      - Treating women in preterm labour with antibiotics significantly prolongs the time from onset of treatment to delivery compared to that in patients without antibiotic treatment
    - Vaginal & cervical infections have also been shown to be associated with progressive changes in cervical length, which is in turn related to preterm labour with the following relative risks:
      - Cervical length 3.5cm (50th centile) → RR 2.4
      - Cervical length 2.5cm (10th centile) → RR 6.2
  - ***Placental-vascular pathway:***
    - Process of implantation occurring early in pregnancy involves important changes at the placental-decidual-myometrial interface:
      - Immunological switch from TH_1 immunity to TH_2 immunity; prevents embryo rejection
      - Trophoblastic invasion of the spiral arteries in both the decidual & myometrial portions to establish dilated vascular channels with low resistance
    - Disruptions to these early changes play a pathophysiological role in poor fetal growth (itself an important cause of preterm delivery, both spontaneous & elective) & pre-eclampsia
  - ***Stress-strain pathway:***
    - Stress response increases release of cortisol & catecholamines:
      - Cortisol initiates early corticotrophin-releasing hormone (CRH) gene expression in the fetus which results in elevated CRH levels known to initiate labour at term
      - Catecholamines affects perfusion of the uteroplacental unit & induces uterine contractions (norepinephrine specifically)
    - Sources of maternal stress:
      - Emotional/work stress
      - Poor nutrition
  - ***Uterine stretch pathway:***
    - Involved in normal initiation of labour with increased uterine stretch with fetal growth
    - Excessive uterine stretch before term may predispose to labour initiation, seen in several conditions:
      - Multiple gestations
      - Polyhydramnios

- **Complications of Preterm Labour**
  - ***Intrapartum complications:***
    - Fetal distress (*fetal acidosis, asphyxia, meconium*)
    - Cord prolapse following rupture of membranes
    - Malpresentation (*higher incidence of breech in preterm labour, in which case cervical entrapment of the aftercoming fetal head can occur as the head is proportionally larger than the body before term*)
  - ***Post-partum complications:***
    - Respiratory distress syndrome
    - Periventricular leukomalacia (PVL) & intraventricular hemorrhage (IVH) with subsequent risk of cerebral palsy
    - Necrotizing enterocolitis
    - Hyperbilirubinemia
    - Hypoglycemia, hypothermia, hypomagnesemia
    - Patent ductus arteriosis

- **Diagnosis of Preterm Labour**
  - Similar to the diagnosis of labour at term, just that it is diagnosed before term (37 weeks):
    - Regular painful contractions (usually ≥4 in 20 min)
    - Cervical changes (effacement, dilatation)
    - ± bloody show, leaking liquor

- **Adjuncts for Diagnosis of Preterm Labour**
  - **Actim partus**
    - Rapid screening test to determine the likelihood of patient going into preterm labour
    - Test detects phosphorylated insulin-like growth factor binding protein-1 (phIGFBP-1) which is a major protein found in the decidua, which is detectable when the decidua & chorion begin to separate following cervical maturity
    - Not present in semen or urine, hence highly accurate
    - Test procedure:
      - Sterile cotton swab used to sample cervical os
      - Swab is then placed into the specimen extraction solution & swirled vigorously for 10s
      - Yellow front of the dipstick is then placed into the specimen extraction solution & held there until the liquid front reaches the result area
      - Negative (confirmed in 5min) = 1 blue line
      - Positive (as soon as it appears) = 2 blue lines
      - Best used to rule out preterm labour (*negative predictive value 99%; i.e. if results negative, patient is extremely unlikely to go into preterm labour in the next 7 days*)
  - ***Other biochemical tests:***
    - Fetal fibronectin (fFN)
    - Corticotrophin releasing hormone (CRH)
    - Salivary estriol
    - Metalloproteinases (MMP)
    - Interleukins (e.g. IL-6)
  - ***Sonographic measurement of cervical changes***
    - Most commonly used parameter is **cervical length**
      - Usual threshold used: 25mm
    - Methods of measuring cervical length:
      - Transvaginal ultrasound (*provides most reliable and consistent results*)
      - Translabial/transperineal (*cervical length may be unmeasurable in up to 20% of cases*)
      - Transabdominal (*unmeasurable in up to 40-50% of cases; requires a full bladder which falsely increases cervical length*)
    - Applications of sonographic cervical length:
      - Diagnosis of preterm labour
      - Prognostic tool for cerclage cases
      - Screening tool for risk of preterm labour in high-risk pregnancies: r*isk of preterm labour before 32 weeks is 78% if 5mm, 4% if 15mm, 1.1% if 25mm*

- **Management of Preterm Labour**
  - ***Initial management:***
    - Admit mother to labour ward
    - Vaginal examination to determine:
      (*provided membranes <u>not</u> ruptured & no other contraindications to VE such as placenta praevia*)
      - Cervical effacement & dilatation
      - Nature of presenting part & station
    - Rest mother in lateral decubitus position
    - Monitor maternal vitals
    - CTG monitoring of fetus
  - ***Initial investigations:***
    - Routine bloods: *FBC, GXM, PT/PTT, renal panel*
    - Urine FEME & culture (*detect urinary tract infection*)
    - High vaginal swab for microscopic examination & culture
    - Vaginal swab for group B streptococcus
    - Ultrasound: *estimate fetal weight, confirm presentation, detect possible etiology (e.g. multiple gestation, polyhydramnios, uterine anomalies)*

→ *in 20-50% of cases, contractions cease spontaneously with initial management (bed rest, hydration, treat underlying infections); further management needs to be instituted for cases likely to persist to delivery*

  - ***Subsequent management:***
    - **<u>Antibiotic prophylaxis:</u>**
      - Advocated by several studies due to association of preterm labour with subclinical chorioamnionitis (but <u>not</u> locally practiced)
      - Helps prolong interval to eventual delivery & possibly prevents progression of a subclinical infection to clinical amnionitis
      - Options: *ampicillin &/or erythromycin; clindamycin is an alternative for penicillin allergy*

    - **<u>Consider tocolysis:</u>**
      (*see "PPROM below for more details*)
      - Tocolysis in preterm labour is controversial (*association with subclinical infection suggests that attempts to prolong gestation may result in progression of infection; furthermore, studies have failed to show the efficacy of tocolysis at decreasing preterm births on the whole*)
      - Tocolysis however still has a role for certain purposes: *prolong gestation sufficiently to allow corticosteroids to work maximally or allow in-utero transfer of fetus to a tertiary hospital*
      - Options: *nifedipine (aka Adalat), atosiban (oxytocin receptor antagonist), salbutamol, terbutaline, GTN patch, magnesium sulphate, indomethacin)*
      - Contraindications to tocolysis: *chorioamnionitis, fetal death or lethal abnormalities, maternal or fetal condition requiring immediate delivery (severe pre-eclampsia, abruptio, IUGR), severe hemorrhage from placenta praevia*
      - Tocolysis unlikely to be successful in cases with infection, ruptured membranes or significantly dilated cervix (>4cm)

- **Corticosteroids for fetal lung maturation:**
  - Antenatal corticosteroid therapy for fetal lung maturity achieves several benefits: *decreased fetal mortality, incidence of respiratory distress syndrome (↓ RDS by 40-50%), intraventricular hemorrhage & necrotizing enterocolitis*
  - Indicated for gestational ages of 24-34 weeks (*between 34 & 36+6 weeks, benefits are still present but number needed to treat is much higher than before 34 weeks, hence not recommended on grounds of overall healthcare economic feasibility; however, in many cases, steroids are still given for gestational ages within this range anyway*)
  - Dosing regimens: *IM dexamethasone 6mg x 4 doses 12 hours apart or IM betamethasone 12mg x 2 doses 24 hours apart (SGH is the only hospital in Singapore to use this regime; studies have shown it to be associated with lower incidence of necrotizing enterocolitis than dexamethasone)*
  - Optimal benefit begins 24 hours after initiation of the 1st dose, lasting for 7 days, but significant benefits still accrue even before 24 hours (*hence steroids should still be given even if labour is expected to occur within <24 hours*)

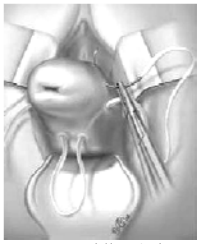
– ***Delivery of the preterm infant:***
- For vertex presentations:
  - Vaginal delivery is preferred regardless of gestational age, provided fetal acidosis & trauma are avoided
  - Use of outlet forceps & episiotomy to shorten the 2nd stage of labour are advocated
  - Some reports recommend caesarian delivery of very-low-birth-weight fetuses (<1500g)
- For breech presentations:
  - High incidence in preterm deliveries (*23% fetuses are breech at 28 weeks gestation*)
  - Significant risk of cord prolapse & cervical entrapment of aftercoming head
  - However, no landmark studies to date have evaluated the definite benefit of caesarian delivery of breech preterms (*term breech trial studies breech deliveries of babies at term*)
  - Caesarian delivery improves neonatal outcome for very-low-birth-weight breech fetuses (<1500g)

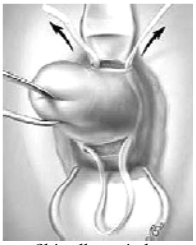
- **Prevention of Preterm Labour In Subsequent Pregnancies**

– ***Progesterone therapy***
- Can be offered to women with previous spontaneous preterm delivery at <34 weeks gestation
- Shown to decrease risk of preterm delivery in subsequent pregnancies
- Start at 16-20 weeks gestation & continue through to 36 weeks gestation
- Options:
  - IM 17-hydroxyprogesterone weekly
  - Vaginal progesterone pessary daily

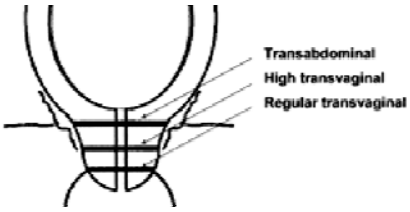
– ***Screening for infections***
- Bacterial vaginosis, candidiasis, trichomoniasis, asymptomatic bacteriuria
- Treat as appropriate if detected

– ***Cervical cerclage***
- Offered in cases of cervical incompetence
- Types of cervical cerclage:
  - Primary cerclage (*in cases where history is suggestive of cervical incompetence; offered electively in 2nd trimester*)
  - Secondary cerclage (*in cases where history is unclear for cervical incompetence; serial ultrasound cervical length monitoring; cerclage offered when significant shortening is detected*)
  - Tertiary/emergency cerclage (*in cases where cervical dilatation ≥2cm occurs in the absence of regular painful uterine contractions, where membranes may be bulging or prolapsing through cervical opening*)
- Surgical options for cervical cerclage:
  - **McDonald's stitch**: *a transvaginal procedure entailing placement of a monofilament pursestring suture near the cervicovaginal junction*
  - **Shirodkar stitch**: *a transvaginal procedure entailing incision through the vaginal mucosa, dissection of the bladder & rectum off the cervix, placement of the cerclage as close to the internal os as possible, before replacing the vaginal mucosa over the knot*
  - **Transabdominal cervicoisthmic cerclage**: *performed through an abdominal incision, involving dissection of the bladder from the lower uterine segment, after which a stitch at the isthmus is placed*


McDonald's stitch


Shirodkar stitch

Transabdominal cerclage



Premature Rupture of Membranes

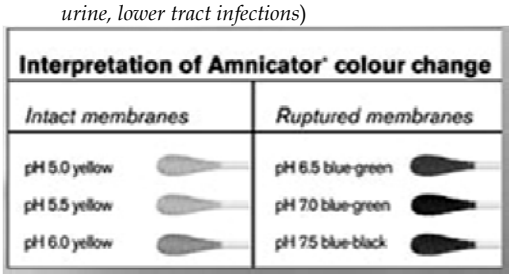
PROM; also known as prelabour rupture of membranes; defined as the spontaneous rupture of membranes (amniorrhexis) before the onset of labour; note that "premature" in PROM is a misnomer in that it does not denote prematurity; preterm premature rupture of membranes (PPROM) refers to the subset of PROM occurring before term (before 37 weeks gestation)

- **Epidemiology & Associations**
  - PPROM affects 2% of all pregnancies
  - PROM is seen in 8% of all term pregnancies
  - Associations/risk factors:
    - Vaginal & cervical infections
    - Abnormal membrane physiology
    - Cervical incompetence
    - Nutritional deficiencies

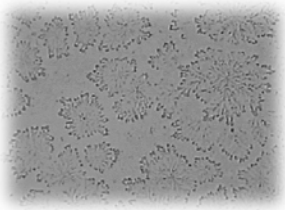
- **Complications of PROM & PPROM**
  - ***Complications of PPROM***
    - Oligohydramnios, with sequelae of pulmonary hypoplasia & positional skeletal deformities (*e.g. talipes equinovarus*) if it occurs early (<24 weeks)
    - Infection (*loss of membranes & amniotic fluid as natural barrier; predisposes to chorioamnionitis & fetal infections*)
    - Preterm labour
    - Cord prolapse (*especially in PPROM as fetus is usually much smaller & more likely to not be in cephalic presentation at the time of rupture of membranes*)
  - ***Complications of PROM***
    - Cord prolapse
    - Infection (*more so with prolonged rupture of membranes at term: >18 hours*)
    - Placental abruption (*especially in cases with pre-existing polyhydramnios; resulting from rapid decompression of the amniotic cavity*)

- **Diagnosis of PROM & PPROM**
  (*diagnosis for both is similar, just that PPROM is the diagnosis made if PROM occurs before term*)
  - ***History for suspected PROM:***
    - Nature of per vaginal fluid discharge (*sudden unprovoked gush is typical for PROM; dribbling may suggest urine leakage*)
    - Duration of per vaginal fluid discharge
    - Characteristics of discharge: colour, odour, any presence of blood (*foul smelling fluid suggests chorioamnionitis; dark green fluid suggests meconium*)
    - Other associated symptoms:
      - Any pain or contractions (*PROM is usually painless; constant lower abdominal pain may be present in chorioamnionitis; intermittent regular crampy pain may suggest preterm labour*)
      - Any other vaginal discharge (*infection*)
      - Any fever (*infection*)
    - Fetal movements (*assess for fetal well being; may be compromised if infection, cord prolapse &/or abruption complicates the PROM*)
  - ***Physical examination for suspected PROM:***
    - General examination:
      - Assess patient's vitals
      - General condition (*well? toxic looking?*)
    - Abdominal examination:
      - Inspect for fetal movements
      - Symphysial fundal height (*may be small for dates if significant liquor loss has occurred*)
      - Palpate uterus for tenderness/irritability
      - Assess fetal lie, presentation & engagement
      - Assess liquor volume (*fetal parts become more easily palpable in significant liquor losses*)
    - **<u>Sterile</u>** speculum examination:
      - Visualize cervical os (*closed unless preterm labour supervenes*)
      - Rule out cord prolapse
      - Look for pool of liquor in the posterior fornix (*test if it is truly amniotic fluid using tests below*)
      - Ask patient to cough (*spurt of liquor from cervical os is diagnostic of PROM if present*)
    - Vaginal examination is <u>contraindicated</u> to prevent infection & stimulation of preterm labour in the case of PPROM; only done in certain circumstances:
      - Regular painful contractions present (*suspect preterm labour, need VE to assess cervical changes*)
      - Non-reassuring CTG status (*to rule out occult cord prolapse not visible on speculum examination*)

- ***Investigations for confirmation of PROM:***
  - Tests to confirm amniotic fluid:
    - **Nitrazine paper** or **Amnicator test** (*detects pH changes; normal vaginal pH is acidic; turns dark blue/black when it contacts amniotic fluid due to alkaline pH; false positive rate of 17%: blood, semen, urine, lower tract infections*)



    - Examine for **ferning** using microscopy (*place sample of fluid on microscopic slide, air-dry it then examine it for ferning pattern which is diagnostic of amniotic fluid*)



Ferning pattern of amniotic fluid under microscopy

    - **Actim PROM** (*dipstick test detecting insulin-like growth factor binding protein-1 IGFBP-1 present in amniotic fluid; highly sensitive – able to detect as little as 0.5µl – & specific – no false positives with semen, urine or blood; test procedure is similar to that for Actim Partus, just that vaginal fluid is sampled instead of the cervical os*)

Actim PROM dipstick

After vaginal fluid is sampled with swab & swirled into the specimen extraction solution, the yellow portion of this dipstick (left-most region) is dipped into the solution; the fluid front progresses from left to right & eventually reaches the results area where either 1 or 2 blue lines will appear (2 blue lines indicating a positive result for PROM in this picture)

  - Ultrasound to assess liquor volume:
    - Decreased liquor volume/AFI supports diagnosis of PROM
    - Amount of liquor present also has prognostic value in determining outcomes of pregnancy

- **Other Initial Investigations for PROM & PPROM**
  - Routine blood tests:
    - Full blood count, PT/PTT, GXM
    - Urea/electrolytes
    - CRP (*monitor for signs of infection*)
  - Tests for infection:
    - Urine FEME & culture (*for UTI*)
    - Amniotic fluid microscopy & culture (*for underlying infections*)
    - Vaginal swab (*for underlying infections & group B streptococcus carriage*)

- **Management of PROM (i.e. 37 weeks gestation onwards)**
  - Active management of PROM is associated with decreased maternal infective morbidity without increasing rates of caesarian section or operative vaginal deliveries
  - However, up to 24 hours of expectant management of PROM can be done based on the clinician's discretion if the following criteria are met:
    - Fixed cephalic presentation
    - Group B *Streptococcus* negative
    - No signs of infection (*uterine tenderness, fever, maternal tachycardia*)
    - Reassuring CTG status
    - No history of digital vaginal examination or cervical suture in place
    - 4-hourly monitoring of maternal parameters
  - ***Expectant management of PROM:***
    - Admit patient
    - Regular monitoring of parameters:
      - Maternal temperature & vitals
      - Pad chart
      - CTG for fetal monitoring
    - Consider prophylactic antibiotics:
      - Penicillin G for GBS-positive cases
      - Erythromycin prophylaxis given 12 hours after onset of PROM
    - Await spontaneous labour onset:
      - Follows PROM within 24 hours in 70%
      - Follows PROM within 48 hours in 85%
      - Follows PROM within 96 hours in 95%
  - ***Induction (stimulation) of labour in PROM:***
    (*technically speaking, promoting the onset of labour after membranes have already ruptured without the spontaneous onset of labour is termed "stimulation of labour", but most people would refer to it as induction anyway*)
    - Indicated after 24 hours of expectant management of PROM without spontaneous labour onset <u>or</u> earlier based on clinician's discretion
      - Risk of maternal and neonatal infection increases significantly 24 hours after PROM
    - Options for induction of labour in PROM:
      - Prostin vaginal pessary (*associated with higher rates of chorioamnionitis & neonatal infections when used in PROM*)
      - Oral misoprostol
      - IV oxytocin infusion (*may not be feasible if the cervix is extremely unfavourable at the time of induction of labour*)

- **Management of PPROM**
  (*essentially involves concomitant management of both the issues of premature rupture of membranes and possibility of preterm delivery*)
  - ***Admit & monitor patient closely:***
    - Establish large bore IV access for blood taking & IV fluids where required
    - Maternal vitals, pad chart
    - CTG daily for fetal monitoring
    - PPROM charting:
      - FBC every other day
      - CRP every other day
      - Ultrasound every other day for liquor volume
      - High vaginal swab for culture once a week
    - Complete rest in bed + thromboprophylaxis
  - ***Empirical antibiotics:***
    - Erythromycin 250mg orally 6-hourly x 10 days
      - Given as prophylactic antibiotics for all PPROM patients
      - Shown to decrease risk of chorioamnionitis (RR 0.57), prolong time to delivery & decrease risk of neonatal infection (RR 0.68)
      - Recommended over previous use of Augmentin (*ORACLE trial demonstrated increased risk of necrotizing enterocolitis vs placebo with use of Augmentin especially in very premature neonates <32 weeks gestation*)
    - Penicillin G 5mu loading dose, 2.5mu every 4-hourly
      - Given in addition to erythromycin in cases of Group B *Streptococcus* carriage
  - ***Consider tocolysis:***
    - Routine tocolysis for patients with PPROM without uterine activity is <u>not</u> recommended (*no proven decrease in preterm delivery or improvement in perinatal outcomes demonstrated*)
    - Tocolysis should be reserved for patients with PPROM & uterine activity in these situations:
      - Antenatal corticosteroids
      - In-utero transfer to a tertiary hospital
    - Options for tocolysis:

Nifedipine (Adalat) (PO loading dose 10mg q 15-30min x 4 up to 40mg/h; maintenance dose up to 20mg/6h)	– Calcium channel blocker – Effective & cheap tocolytic agent – **First-line** tocolytic agent – Side effects: *headache, flushing, hypotension, tachycardia*
Atosiban (IV)	– Oxytocin receptor blocker – Approved for use in Europe; not in USA – Expensive, not routinely used in Singapore
Salbutamol (IV)	– β-agonist – Side effects: *maternal tachycardia & palpitations, fluid overload, pulmonary edema, hypokalemia, tachyphylaxis (requiring increasing doses of salbutamol to remain effective)*
Terbutaline (IV or SQ)	– β-agonist – Quick & short-acting; for short requirements
Nitroglycerin (GTN) (transdermal patch)	– Smooth muscle relaxant via production of nitrous oxide
Magnesium sulphate (IV)	– Competes with calcium for cellular entry at the time of depolarization – Side effects: *warmth & flushing shortly after administration, respiratory depression, cardiac arrhythmias; accumulates in renal impairment*
Indomethacin (PO 25mg TDS or PR 100mg)	– Cyclo-oxygenase inhibitor which blocks synthesis of prostaglandins – Side effects limited if restricted to use not exceeding 48-72 hours – Side effects: *oligohydramnios, closure of ductus arteriosus leading to pulmonary hypertension & cardiac failure in the fetus*

  - ***Corticosteroids for fetal lung maturation:***
    - Same considerations, options & administration regimen as that for preterm labour
  - ***Watch out for & treat chorioamnionitis:***
    - Monitor for signs of chorioamnionitis 12-hourly:
      - Maternal pyrexia (>37.8°C)
      - Maternal tachycardia
      - Uterine tenderness
      - Offensive vaginal discharge
      - Fetal tachycardia on CTG monitoring
      - Maternal leukocytosis
    - Treatment of clinical chorioamnionitis:
      - Empirical: *rocephine + flagyl* while awaiting culture & sensitivity results to be back
  - ***Delivery in PPROM:***
    - Indications for delivery at any point in time: *clinical chorioamnionitis, fetal distress*
    - Otherwise, delivery planned at 34 weeks gestation (*i.e. for borderline PPROM cases presenting at 34 weeks to 36+6 weeks gestation, can manage as per for term PROM, with the additional consideration of inducing labour after fetal lung maturation with corticosteroids*)
    - Mode of delivery determined by presentation & progress of labour

Intrauterine Growth Restriction

Refers to the situation where a fetus is unable to achieve its genetically-determined potential for physical growth

- **Causes of IUGR**
  - ***Maternal causes***:
    - Maternal hypertension
    - Cyanotic heart disease & chronic pulmonary disease
    - Thrombophilia, SLE, antiphospholipid syndrome
    - Maternal smoking, alcoholism, drugs, malnutrition
  - ***Placental causes***:
    - Maternal conditions causing placental insufficiency (chronic hypertension, chronic renal disease, pregnancy-induced hypertension)
    - Placental &/or cord abnormalities
  - ***Fetal causes***:
    - Chromosomal anomalies, congenital syndromes
    - Intrauterine infections
    - Multiple gestation

- **Clinical Features of IUGR**
  - IUGR is usually defined as an estimated fetal weight (or neonatal weight) at or below the 10th percentile for gestational age
  - IUGR can further be subtyped based on the distribution of the growth restriction:
    - **Symmetrical IUGR** = both head & abdominal circumferences are at or below the 10th percentile for gestational age
      - Usually due to intrauterine insults in the 1st trimester (*chromosomal anomalies, congenital syndromes, early intrauterine infections*)
    - **Asymmetrical IUGR** = abdominal circumference is at or below the 10th percentile for gestational age with sparing of head circumference
      - Usually due to insults at a later stage of pregnancy resulting in uteroplacental insufficiency (*e.g. pre-eclampsia*)
      - Asymmetry of head vs truncal growth is due to preferential shunting of blood flow to the head in uteroplacental insufficiency

- **Diagnosis of IUGR**
  - ***History & physical examination***
    - Comprehensive history-taking & physical examination at the booking visit may highlight characteristics indicative of a pregnancy at-risk of IUGR
      - Maternal past medical history (*hypertension, cyanotic heart disease, chronic lung disease, SLE*)
      - Past obstetric history (*past IUGR, pre-eclampsia*)
      - Maternal alcohol, tobacco & drug use
    - Serial uterine symphysial fundal height (SFH) measurements made at each routine antenatal visit serves as primary screening tool for IUGR
      - If SFH lags >2-3cm behind a well-established gestational age of the pregnancy, further sonographic assessment may be indicated
  - ***Ultrasound assessment***
    - Fetal measurements
      - Parameters used: *biparietal diameter (BPD), head circumference, abdominal circumference, head-to-abdominal circumference ratio, femoral length, estimated fetal weight*
      - In **symmetrical IUGR**, both head & abdominal circumferences will be at or below 10th percentile, with a normal head-to-abdominal circumference ratio
      - In **asymmetrical IUGR**, head circumference will remain normal while abdominal circumference will be at or below 10th percentile, with a high head-to-abdominal circumference ratio
      - In both cases, estimated fetal weight would be at or below 10th percentile for gestational age
    - Ultrasound Doppler
      - Uterine artery Doppler: *bilateral notching predicts higher risk of developing IUGR*
      - Umbilical artery Doppler: *absent or reversed diastolic waveform indicates uteroplacental insufficiency*
      - Middle cerebral artery Doppler: *increased end-diastolic flow velocity indicates preferential shunting of blood to the fetal head (as seen in asymmetrical IUGR)*
    - Amniotic fluid volume
      - IUGR may be accompanied by abnormalities in amniotic fluid volume depending on the underlying etiology (*e.g. oligohydramnios in uteroplacental insufficiency, polyhydramnios in congenital abnormalities with congenital GI tract atresia*)

- **Management of IUGR**
  - ***Pre-conception management***
    (*applies to women with pre-existing risk factors for IUGR*)
    - Lifestyle medications (*improve nutrition, quit smoking, drinking & drug use*)
    - Low-dose aspirin for antiphospholipid syndrome
    - Low-dose heparin ± low-dose aspirin for hereditary thrombophilias
  - ***Antepartum management***
    (*once a fetus has been identified to have IUGR*)
    - Lifestyle modifications
    - Close follow-up & monitoring of fetal well-being
    - Eventual objective is to expedite delivery of the fetus before occurrence of fetal compromise but after fetal lung maturation has been achieved
  - ***Delivery of IUGR fetuses***
    - Close monitoring during labour due to lower capacity of IUGR infants to tolerate asphyxia
    - Management issues following delivery:
      - Examination to look for congenital anomalies
      - Higher incidence of hypoglycemia, hypothermia & respiratory distress requiring close monitoring & prompt management

- **Prognosis of IUGR**
  - Depends on the underlying etiology
    - Chromosomal abnormalities & early intrauterine infections may have poorer prognoses
    - IUGR also confers a greater risk on future development of adult-onset disease such as hypertension, diabetes mellitus & atherosclerosis in the IUGR infant

Post-Term Pregnancy

Defined as a pregnancy persisting to 42 weeks or beyond from the onset of the last menstrual period

- **Relevant Terminology**
  - Preterm = *before 37 weeks (i.e. up to 36+6 weeks)*
  - Term = *37 to 41+6 weeks*
  - Post-dates = *after estimated date of delivery (EDD, 40 weeks)*
  - Post-term = *42 weeks and after*

- **Causes of Post-Term Pregnancy**
  - Idiopathic (most cases)
  - Anencephaly
  - Placental sulfatase deficiency
  - Extra-uterine pregnancy

- **Complications of Post-Term Pregnancy**
  - ***Post-maturity (dysmaturity) syndrome***
    - Seen in 20-30% of post-term pregnancies
    - Results from aging and infarction of the placenta with resultant placental insufficiency
    - Physical features of dysmaturity syndrome:
      - Meconium staining of umbilical cord, fetal membranes, skin & nails
      - Loss of subcutaneous fat
      - Long fingernails, abundant hair
      - Dry, peeling skin
    - Associated with an increased risk of intrauterine fetal demise & stillbirths
  - ***Macrosomia***
    - Seen in a proportion of the remaining post-term fetuses not affected by dysmaturity syndrome
    - Defined as a birth weight of >4000g
    - Complications of macrosomia:
      - Shoulder dystocia
      - Birth trauma
      - Increased incidence of caesarian delivery

- **Management of Post-Term Pregnancy**
  - Begin close follow-up & screening (weekly) in post-date pregnancies (i.e. after 40 weeks gestational age):
    - Amniotic fluid volume
    - Umbilical arterial Doppler flow
    - Fetal heart rate tracing (CTG)
  - Indications for induction of labour:
    - Any evidence of uteroplacental insufficiency (*oligohydramnios, absent or reversed umbilical arterial Doppler flow, non-reassuring fetal CTG status*)
    - Clinician's discretion (*locally, many clinicians would opt to induce labour once 41 weeks gestation is reached without spontaneous onset of labour*)

Intrauterine Fetal Demise

Fetal death occurring after 20 weeks gestation but before onset of labour; fetal death occurring before gestational age of viability (ranges from 20-24 weeks depending on which country you're in) is termed a miscarriage

- **Causes of IUFD**
  - Idiopathic (up to 50% of cases)
  - ***Maternal conditions***
    - Hypertensive diseases of pregnancy
    - Diabetes mellitus
    - Hereditary thrombophilias
    - Antiphospholipid syndrome
  - ***Uteroplacental conditions***
    - Fetomaternal hemorrhage
    - Umbilical cord accidents
  - ***Fetal conditions***
    - Congenital anomalies
    - Intrauterine infections
    - Erythroblastosis fetalis (rhesus isoimmunization)

- **Diagnosis of IUFD**
  - ***Clinical suspicion:***
    - Mother reports absence of fetal movements
    - Uterus is small for date
    - Fetal heart tone not heard with DopTone
    - *Note: after IUFD, placenta may continue to produce hCG, hence a positive pregnancy test does <u>not</u> exclude IUFD*
  - ***Diagnostic confirmation by ultrasound:***
    - Absence of fetal cardiac activity
    - Lack of fetal movement

- **Management of IUFD**
  - ***Watchful expectancy:***
    - About 80% of patients with IUFD will experience spontaneous onset of labour within 2-3 weeks of fetal demise
    - Problems with approach of watchful waiting:
      - Patient's personal feeling of guilt & loss
      - Risk of chorioamnionitis
      - Risk of disseminated intravascular coagulation (10% risk if dead fetus is retained for >5 weeks)
    - Monitoring for coagulopathy:
      - Indicated for as long as expectant management is carried out in IUFD
      - Weekly platelet count, PT, aPTT, d-dimer, fibrinogen levels
  - ***Induction of labour:***
    - Similar regime as for medical induction of labour in normal pregnancies (*vaginal pessary of prostaglandin analogues such as misoprostol or dinoprostone*)
  - ***Follow-up after IUFD:***
    - Investigate for possible cause of IUFD:
      - Investigation for intrauterine infections (TORCH, parvovirus B19, *Listeria* etc)
      - Testing for maternal antiphospholipid antibodies ± hereditary thrombophilias
      - Consider fetal autopsy & fetal chromosomal studies
      - **Kleihauer-Betke test** to detect fetomaternal hemorrhage
    - Psychological/emotional support for parents
    - Subsequent pregnancies should be managed as high-risk cases

HYPERTENSIVE DISORDERS OF PREGNANCY

Overview

- **Definition of Hypertension in Pregnancy**
  - Systolic blood pressure ≥140mHg &/or Diastolic blood pressure ≥90mmHg
    - At least 2 blood pressure measurements should fulfill this criteria, taken at least 4-6 hours apart

- **Classification of Hypertensive Disorders of Pregnancy**
  - ***Chronic hypertension***
    - Criteria (any of the following):
      (i) Known hypertension before pregnancy
      (ii) Development of hypertension during pregnancy <u>before</u> 20 weeks gestation
      (iii) Development of hypertension during pregnancy after 20 weeks gestation, with persistence beyond 12 weeks post-partum
    - Causes of chronic hypertension:
      - Essential hypertension (most cases)
      - Secondary hypertension (*renal, endocrine, aortic coarcation etc*)
  - ***Preeclampsia***
    - Criteria (all of the following):
      (i) Development of hypertension during pregnancy <u>after</u> 20 weeks gestation
      (ii) Development of new-onset proteinuria (≥0.3g/24 hour urine collection) during pregnancy after 20 weeks gestation
    - Subtypes of preeclampsia:
      - Mild preeclampsia
      - Severe preeclampsia
      - HELLP syndrome (hemolysis, elevated liver enzymes, low platelets)
  - ***Eclampsia***
    - Criteria (all of the following):
      (i) Criteria for preeclampsia met
      (ii) Presence of generalized tonic-clonic seizures which cannot be attributed to other causes
  - ***Chronic hypertension with superimposed preeclampsia***
    - Criteria (any of the following):
      (i) Known hypertension before pregnancy, with development of proteinuria (≥0.3g/24 hour urine collection) during pregnancy after 20 weeks gestation
      (ii) Known hypertension & proteinuria before pregnancy, with significant increases in blood pressure &/or proteinuria during pregnancy (*not a definite diagnosis per se, needs to be evaluated at the clinician's discretion in accordance with other warning signs & symptoms of preeclampsia*)
    - Carries a worse prognosis than either chronic hypertension or preeclampsia does alone
  - ***Gestational (transient) hypertension***
    - Criteria (all of the following):
      (i) Development of hypertension during pregnancy after 20 weeks gestation <u>or</u> within 48-72hours after delivery
      (ii) No development of proteinuria
      (iii) Resolution of hypertension by 12 weeks post-partum
    - Difficult to differentiate from early-stage preeclampsia; a diagnosis made in retrospect

Preeclampsia & Eclampsia

- **Etiology & Associations**
  - "Disease of theories" – has multiple proposed etiologies
    - Genetic, immunologic, hormonal, environmental
  - Risk factors for developing preeclampsia:
    - Primigravidity
    - Primipaternity (*i.e. in a woman who has had a previous pregnancy, the first pregnancy she has with a new male partner thereafter is at greater risk of preeclampsia*)
    - Mothers >35 years old
    - History of pregnancy-induced hypertension (*either personally or patient's mother*)
    - Pre-existing maternal conditions (*renal disease, chronic hypertension, diabetes mellitus, obesity, autoimmune*)
    - Multiple gestation
    - Molar pregnancy (****note: in molar pregnancies, especially complete moles, may present with atypical early-onset pre-eclampsia, i.e. before 20 weeks gestation*)
    - Smoking is <u>protective</u> against preeclampsia
  - Complications 5-7% of all pregnancies

- **Pathophysiology of Preeclampsia**
  - ***Pathogenesis of preeclampsia:***
    - Multifactorial initial etiology (?immunogenetic) results in inadequate trophoblastic invasion
      - Cytotrophoblasts normally invades the uterine spiral arteries to establish a low-resistance uteroplacental circulation
      - Failure to do so results in subsequent impairment of uteroplacental perfusion
    - Placental ischemia then results in oxidative stress & production of toxins which enters the circulation:
      - Widespread inflammation
      - Endothelial injury & dysfunction, leading to altered permeability & vasospasm
      - Inappropriate activation of coagulation system
    - Net effect of the above processes results in:
      - Widespread vasoconstriction resulting in systemic hypertension & ischemic damage in various vascular beds
      - Extravasation of fluid from intravascular space
      - Intravascular coagulation with progressive consumptive coagulopathy
  - ***Pathology of preeclampsia:***
    - Lack of decidualization of myometrial segments of the spiral arteries
      - Normally, invasion of the spiral arteries by trophoblastic tissue results in the replacement of the muscular & elastic layers of the spiral arteries by fibrinoid & fibrous tissue, resulting in large, tortuous & low-resistance channels that extend through the myometrium
      - In preeclampsia, such changes are mostly limited to the decidual segments of the vessels
      - As such, the myometrial segments of the vessels may have a 60% reduction in diameter compared to that in a normal placenta
    - Glomerular capillary endotheliosis
      - Marked swelling of the glomerular capillary endothelium with deposits of fibrinoid material in & beneath the endothelial cells
    - Ischemia, hemorrhage & necrosis in multiple organs

- **Clinical Features**
  - ***Maternal manifestations:***
    - Weight gain & edema
      - One of the earliest signs of preeclampsia
      - Due to extravasation of fluid secondary to increased capillary permeability
      - May also manifest as increased hematocrit due to hemoconcentration
      - While preeclamptic patients have an increase in total body fluid volume, they are relatively intravascularly volume-depleted due to the extravasation of fluid
    - Systemic hypertension
      - Due to widespread vasoconstriction
      - Diastolic pressure is particularly affected as it more closely reflects a rise in peripheral vascular resistance
    - Renal impairment
      - Glomerular arteriolar vasoconstriction results in decreased glomerular filtration rate, manifesting as oliguria or even anuria
      - Altered glomerular capillary permeability results in proteinuria
    - Coagulopathy
      - Due to thrombocytopenia most commonly
      - Disseminated intravascular coagulation may occur as well, especially in the context of placental abruption complicating preeclampsia
    - Liver impairment
      - Systemic vasoconstriction results in ischemic damage to the liver, with resultant focal hemorrhages & infarctions
      - May present as right upper quadrant or epigastric pain
      - In rare instances, hepatic rupture may occur
    - Neurological impairment
      - Visual field disturbances
      - New-onset headache
      - Hyperreflexia, clonus
      - Seizures (*in which case it becomes eclampsia*)
    - Cardiopulmonary impairment
      - Pulmonary edema
  - ***Fetoplacental manifestations:***
    - Intrauterine growth restriction (*usually asymmetrical*)
    - Intrauterine fetal demise
    - Oligohydramnios
    - Abruptio placentae

- **Grades of Severity in Preeclampsia**
  - ***Mild preeclampsia***
    - Does not fulfill criteria for severe preeclampsia
  - ***Severe preeclampsia***
    (*any of the following present makes it severe preeclampsia*)
    - Severe hypertension (≥160/110mmHg)
    - Heavy proteinuria (≥3g/24 hour urine collection)
    - Oliguria (<500ml/24 hour)
    - Cerebral &/or visual disturbances
    - Pulmonary edema or cyanosis
    - Epigastric or right upper quadrant pain
    - Impaired liver function (elevated liver enzymes)
    - Thrombocytopenia
    - Fetal growth restriction
  - ***HELLP syndrome***
    - A variant of severe preeclampsia with particularly high morbidity & mortality
    - Entails a combination of hemolysis, elevated liver enzymes & low platelets

- **Important History & Physical Examination in Preeclampsia**
  - ***History:***
    - Age, P_G_
    - Presenting complaints
      - Weight gain, edema
      - Headache, blurred vision
      - Epigastric/right upper quadrant pain
      - Shortness of breath
      - Oliguria
      - Hemorrhagic manifestations
      - Per-vaginal bleed (*abruption*)
      - Fetal movements (*assess fetal well being*)
    - Antenatal history
      - Routine blood pressure & urine dipstick
      - Results of ultrasound scans so far (*fetal growth, any abnormalities noted*)
    - Past obstetric history
      - Previous pregnancy-induced hypertension
      - Previous preeclampsia
    - Past medical history
      - Pre-existing hypertension, diabetes mellitus
      - Chronic renal disease, autoimmune disease
    - Family history
      - Preeclampsia in patient's mother
  - ***Physical examination:***
    - General examination
      - Vitals (BP, HR, RR, SpO_2)
      - Weight (note trend if available)
      - Pallor, petechiae, edema
    - Chest examination
      - Lungs (crepitations in pulmonary edema)
    - Abdominal examination
      Epigastric or right upper quadrant tenderness
    - Neurological examination
      - Hyperreflexia, clonus
      - Visual field testing
    - Obstetric examination
      - Symphysial fundal height (small for dates?)
      - Palpate for fetal lie & presentation (*important to note if emergent induction of labour is required*)
      - Palpate for uterine tenderness (*if tender & "woody-hard", may indicate abruption*)
      - Estimate liquor volume (*fetal parts very well felt in oligohydramnios*)
      - DopTone for fetal heart sounds

- **Investigations**
  - ***Maternal hematological investigations***
    - Full blood count
      - Anemia (*due to hemolysis in HELLP syndrome*)
      - Thrombocytopenia
    - Renal panel + serum uric acid
      - Raised serum creatinine & urea
      - Raised serum uric acid levels is the earliest change in renal impairment in preeclampsia
    - 24-hour urinary total protein
      - Needed for formal diagnosis of preeclampsia
      - May indicate severe preeclampsia if heavy proteinuria is present
    - Liver function test
      - Raised AST & ALT levels
      - Unconjugated hyperbilirubinemia (*hemolysis*)
    - Coagulation profile
      - PT & aPTT ± d-dimers & fibrinogen (for DIVC)
  - ***Fetal ultrasound***
    - Estimated fetal weight, fetal lie & presentation, liquor volume, umbilical artery Doppler flow

- **Management of Preeclampsia**
  (*the only definitive treatment for preeclampsia is delivery of the fetus; as such, the decision on when to deliver needs to take into account maximizing gestational age for fetal growth & pulmonary maturity alongside managing the maternal effects of preeclampsia*)

  – ***Admission for further work-up & monitoring***
    - All newly-diagnosed preeclamptic patients need to be admitted
    - Perform relevant investigations to determine severity of preeclampsia (*mild vs severe*)
    - Put patient on preeclampsia charting:
      - BP, HR, weight, edema
      - Urinary protein
      - Input & output
      - Fetal movement, fetal heart rate
    - Consider the 3 main aspects of pre-delivery management of preeclampsia:
      (i) Blood pressure control
      (ii) Fluid management
      (iii) Seizure prophylaxis & management

  (i) Blood pressure control
    - Antihypertensive agents:
      - Labetalol
      - Hydralazine
      - Nifedipine (Adalat)
      - Methyldopa
    - Choice of agent & administration route depends on clinical evaluation of severity of preeclampsia:
      - Mild preeclampsia: *oral methyldopa, nifedipine or labetalol*
      - Severe preeclampsia with blood pressure ≥160/110mmHg: *IV labetalol or hydralazine (beware precipitous drop in BP especially with hydralazine which may worsen placental perfusion; ensure fluid preloading & close fetal CTG monitoring)*

  (ii) Fluid management
    - Fluid replacement to treat intravascular depletion in preeclampsia as well as to minimize risk of precipitous drop in blood pressure following administration of antihypertensive agents
    - Precautions to avoid iatrogenic pulmonary edema:
      - Auscultate to ensure clear lungs
      - Chart input & output, consider urinary catheterization to accurately chart output
      - Consider invasive monitoring where deemed necessary (*CVP, pulmonary artery wedge pressure*)
    - Fluid replacement regime:
      - Start with 1L Hartman solution (500ml over 30min followed by 500ml over 4h)
      - If urine output is satisfactory (>30ml/h), infuse another 1L Hartman solution over 12h
      - If urine output remains inadequate (<30ml/h), proceed with judicious volume loading ± diuretics; consider invasive monitoring

  (iii) Seizure prophylaxis & management
    - Agent of choice = IV magnesium sulphate
      - Validated by the **Magpie trial** (Magnesium Sulphate for Prophylaxis of Eclampsia)
      - Shown to reduce recurrent seizures (50% reduction), reduce maternal mortality & morbidity, as well as to improve neonatal outcome
      - Superior to valium & phenytoin
    - Indications for magnesium sulphate treatment:
      - Severe preeclampsia
      - Signs & symptoms of imminent eclampsia (*hyperreflexia, clonus, severe headaches*)
      - Eclampsia (*in which case $MgSO_4$ is as treatment*)
    - **Pritchard Regime** for $MgSO_4$ administration:
      - Intramuscular regimen: *4g IV loading dose followed immediately by 10g IM, then 5g IM every 4 hours in alternating buttocks*
      - Intravenous regimen: *4g IV loading dose, followed by maintenance infusion of 1-2g/h by a controlled infusion pump*
    - Monitoring for $MgSO_4$ toxicity:
      - Narrow therapeutic range (2-4mmol/L)
      - Progressive symptoms & signs of increasing serum magnesium levels: *loss of patellar reflexes, warmth & flushing, somnolence, slurring of speech, paralysis & respiratory difficulties, cardiac arrest*
      - Hence patient needs to be regularly assessed for tendon reflexes, pulse oximetry & urine output (*as magnesium is renally excreted*)
      - Resuscitation equipment + calcium gluconate *(antidote for magnesium toxicity; IV 10ml of a 10% solution*) should be on standby

  – ***Delivery***
    - Remains the only cure for preeclampsia
    - Timing of delivery is dictated by the clinical state of the mother & fetus (but maternal interests are of paramount importance)
    - Concept of "temporizing management"
      - Symptomatic management of mother to "buy time" for fetal pulmonary maturity & growth
      - Administer corticosteroid where indicated to accelerate fetal pulmonary maturation
      - Plan for induction of labour at 34 weeks gestation if no overriding indication for induction occurs prior to that
    - Indications for emergent induction of labour:
      - Severe preeclampsia with maternal complications refractory to medical management (*refractory hypotension, pulmonary edema, oliguria, HELLP, impending eclampsia*)
      - Severe IUGR, signs of fetal compromise, suspected placental abruption

- **Management of Eclampsia**
  (*eclampsia is a true obstetric emergency*)
  - ***Initial resuscitation & stabilization***
    - Airway, breathing, circulation
      - Position patient in left lateral position
      - Clear & protect airway
      - Supplemental oxygen by face mask
      - Establish large bore IV access
    - Place patient on close monitoring (*BP, HR, pulse oximetry, ECG, urinary catheter*)
    - Consider & exclude other possible causes of seizures
      - Pre-existing epilepsy
      - Hypertensive encephalopathy
      - Metabolic derangements (*hypoglycemia, hyponatremia*)
      - Intracranial hemorrhage or infection
  - ***Pharmacologic stabilization***
    - Seizure management with magnesium sulphate:
      - Loading dose of ~~6g~~ 4 g, 1g/h for 24 h IV (*higher than that used for seizure prophylaxis in preeclampsia*) followed by maintenance infusion of 2g/h
      - Monitor tendon reflexes, pulse oximetry & urine output
      - May consider adding on diazepam for refractory seizures (*monitor for respiratory depression & be prepared to intubate*)
    - Blood pressure control:
      - IV labetalol or hydralazine
      - Ensure adequate fluid preloading & watch for precipitous drop in BP
  - ***Delivery***
    - Delivery should only be attempted after stabilization of maternal condition as induction of labour or caesarian section during the acute phase may aggravate the course of the disease
    - Expedite delivery once maternal condition is stabilized, preferable by the vaginal route

- **Sequelae & Outcome of Preeclampsia**
  - ***Post-natal follow-up of preeclamptic patient:***
    - Monitor for resolution of hypertension & proteinuria
    - Persistence beyond 12 weeks postpartum necessitates physician referral for further investigations
  - ***Prognosis (maternal):***
    - Mild preeclampsia has no long-term maternal sequelae
    - Severe preeclampsia increases risk of:
      - Cardiovascular disease in later life
      - Recurrent preeclampsia risk (up to 40%)
  - ***Prognosis (fetal):***
    - Depends on impact of preeclampsia on fetal growth
    - If IUGR occurred, child may be at increased risk of adult-onset diseases (*hypertension, diabetes etc*)

Chronic Hypertension in Pregnancy

- **Main Goals of Management**
  - Control hypertension
  - Detect development of superimposed preeclampsia
  - Detect IUGR in fetus

- **Baseline Evaluation**
  - Review records to determine cause of hypertension (*essential hypertension vs secondary hypertension*)
    - If no prior evaluations done, may consider investigations to rule out some of the more common endocrine, renal or cardiovascular causes
  - Other baseline investigations are similar to that for normal pregnancies
    - Baseline blood pressure & presence of proteinuria especially important to aid detection of development of superimposed preeclampsia later on
    - Additional baseline assessment of end-organ changes from chronic hypertension:
      - Fundoscopy for hypertensive retinopathy
      - Renal panel
      - ECG for hypertensive heart disease

- **Pharmacological Management of Hypertension**
  - ***Principles of antihypertensive use in pregnancy:***
    - Use safest possible antihypertensive at lowest possible dose
    - Keep blood pressure at about 130/80mmHg to 140/90mmHg
      - Little evidence that lowering blood pressure too much benefits the pregnancy
      - Lowering blood pressure too much may compromise uteroplacental perfusion & result in fetal compromise
      - In many cases, blood pressures will decrease to normal in the 2nd trimester, during which antihypertensives can be taken off
  - ***Antihypertensive options:***
    - Methyldopa (*safest antihypertensive in pregnancy*)
    - Nifedipine
    - Labetalol
  - ***Antihypertensives <u>not</u> recommended in pregnancy:***
    - ACE-inhibitors & angiotensin II receptor blockers (*to be avoided in all stages of pregnancy due to potential fetal toxicity*)
    - Beta-blockers (*to be used with caution as it can result in fetal growth restriction*)
    - Diuretics

- **Antenatal Care**
  - Consider early & serial ultrasound monitoring
    - To detect signs of IUGR early
  - Monitor routine BP & urine dipstick closely
    - Significant increase in blood pressure &/or worsening of pre-existing proteinuria are likely signs of superimposed preeclampsia (15-25% incidence)

OBSTETRIC HEMORRHAGE

Overview of Obstetric Hemorrhage

- **Types of Obstetric Hemorrhage**
  - ***Bleeding in early pregnancy***
    - Bleeding in pregnancy before 24 weeks gestation
      - No minimum bleeding volume required
    - Differential diagnosis:
      - Miscarriage (spontaneous abortion)
      - Ectopic pregnancy
      - Gestational trophoblastic disease (*refer to "Gynaecologic Oncology"*)
      - Lower genital tract pathology
  - ***Antepartum hemorrhage (APH)***
    - Bleeding in pregnancy at or after 24 weeks gestation (i.e. after gestational age of viability)
      - No minimum bleeding volume required
      - Underlying etiological agents may be similar to that for miscarriage, but clinical distinction is made because fetus is considered salvageable after 24 weeks gestation
    - Differential diagnosis:
      - Placenta praevia
      - Abruptio placentae
      - Vasa praevia
      - Lower genital tract pathology (*cervicitis, cervical polyps, cervical cancer etc*)
      - Systemic coagulopathy
      - (Preterm) labour
  - ***Postpartum hemorrhage (PPH)***
    - Bleeding after delivery
      - Primary PPH = *loss of >500ml (or >1000ml if caesarian delivery) of blood within the 1st 24 hours post-partum*
      - Secondary PPH = *abnormal bleeding after 24 hours postpartum up until 6 weeks*

    (*Refer to "Labour & Puerperium"*)

Bleeding in Early Pregnancy

Miscarriage (Spontaneous Abortion)

Defined as fetal loss between the time of conception & the time of fetal viability (at 24 weeks gestation); may alternatively also include cases with expulsion of a fetus or embryo weighing ≤500g; fetal loss after the time of fetal viability (of 24 weeks) is termed intrauterine fetal demise (IUFD; see "Obstetric Complications")

- **Epidemiology of Miscarriages**
  - Miscarriage occurs in approximately 10-20% of all clinically-recognizable pregnancies
    - Many conceptions may never reach clinical recognition (e.g. biochemical pregnancies)
    - **Biochemical pregnancy** = presence of hCG in maternal serum 7-10 days post-ovulation in whom menstruation occurs as expected; indicative of conception that occurred but subsequently lost without prolongation of the menstrual cycle
    - If one were to consider both clinically-recognized pregnancies & biochemical pregnancies, total miscarriage rate would be even higher (*some studies suggest over 50%, mostly occurring within the 14 days following conception*)
- **Causes of Miscarriages**
  - ***Fetal abnormalities***
    - Most common cause of miscarriages (>50%)
    - Often due to chromosomal abnormalities (*trisomy, monosomy, triploidy etc*)
    - Usually sporadic (*occurring by chance in the particular conceptus*), but may occasionally be due to chromosomal aberrations in one or both parents:
      - Germline mosaicism
      - Balanced (Robertsonian) translocations
  - ***Local maternal factors***
    - Congenital uterine abnormalities
      - Septate uterus, bicornuate uterus etc
    - Acquired uterine abnormalities
      - Submucous fibroids
      - Endometrial polyps
      - Intrauterine adhesions (synechiae)
      - Asherman's syndrome (*obliteration of most of the uterine cavity with extensive synechiae*)
    - Cervical incompetence
      - May be congenital or acquired (*e.g. after cone biopsy of cervix*)
      - Tends to present with 2nd trimester abortions
  - ***General maternal factors***
    - Advance maternal age
      - If a live fetus is demonstrated with ultrasound at 8 weeks gestation, <2% will abort spontaneously if the mother is <30 years old, but risk increases to >10% if >40 years old & up to 50% at 45 years old
      - Probably due to increased incidence of chromosomally abnormal conceptus in older mothers
    - Maternal medical conditions
      - Diabetes mellitus
      - Hypothyroidism, hyperthyroidism
      - Chronic renal disease
      - Systemic lupus erythematosus
      - Antiphospholipid syndrome
    - Maternal infections
      - TORCH infections (toxoplasmosis, rubella, cytomegalovirus, herpes simplex virus)
      - *Mycoplasma*, *Ureaplasma* infections
      - *Listeria, Brucella,* syphilis
    - Maternal substance use
      - Alcohol, smoking, drug abuse
    - Immunological factors
      - Abnormal alloimmune response resulting in failure to accept the fetus for the duration of a normal pregnancy

- **Types & Clinical Features of Miscarriages**

  - ***Threatened miscarriage/abortion***
    - Salient features: *PV bleed without any impending fetal loss, fetus remains viable*
    - History findings:
      - Per-vaginal bleed (*usually small amount*)
      - With or without abdominal pain
      - Symptoms of pregnancy (*e.g. nausea*) present
    - Physical examination findings:
      - Uterus is appropriate for dates
      - Cervical os closed
    - Investigation findings:
      - Ultrasound reveals a viable (*fetal cardiac activity present*) intrauterine pregnancy

  - ***Inevitable miscarriage/abortion***
    - Salient features: *PV bleed with open cervical os with no loss of fetus yet; will invariably lead on to an incomplete or complete abortion with fetal loss*
    - History findings:
      - Per-vaginal bleed (*usually large amount*)
      - Abdominal pain likely to be present
    - Physical examination findings:
      - May have signs of acute blood loss (*pallor, tachycardia, hypotension*)
      - Uterus is appropriate for dates
      - Cervical os open without products of conception seen at cervical os
    - Investigations findings:
      - Ultrasound reveals an intrauterine pregnancy which may or may not be viable

  - ***Incomplete miscarriage/abortion***
    - Salient features: *PV bleed with fetal loss in progress*
    - History findings:
      - Per-vaginal bleed (*usually large amount*)
      - Abdominal pain likely to be present
    - Physical examination findings:
      - May have signs of acute blood loss (*pallor, tachycardia, hypotension*)
      - Uterus may be smaller than expected for dates
      - Cervical os open with products of conception seen at the cervical os
    - Investigations findings:
      - Ultrasound reveals non-viable (*absent fetal cardiac* activity) intrauterine pregnancy, thick endometrial lining & retained products of conception within uterus & at the cervical os (*note that ultrasound is <u>not</u> required to diagnose an incomplete abortion; pelvic examination would suffice*)

  - ***Complete miscarriage/abortion***
    - Salient features: *PV bleed with completed process of fetal loss; uterus reverts back to pre-pregnant conditions*
    - History findings:
      - Per-vaginal bleed (*history of "gush of blood" possibly with greyish tissues passed together with it; bleeding usually of small amount at the time of presentation*)
      - Abdominal pain would have been experienced during prior "gush of blood", may not be present at the time of presentation
      - Symptoms of pregnancy (*e.g. nausea*) absent
    - Physical examination findings:
      - Uterus smaller than expected for dates
      - Cervical os closed
    - Investigations findings:
      - Ultrasound reveals an empty uterus with normal endometrial lining

  - ***Missed miscarriage/abortion***
    - Salient features: *fetal death or failure of development of fetal tissue to start with, with no extrusion of products of conception*
    - History findings:
      - Per-vaginal bleed is usually absent
      - Abdominal pain is usually absent
      - Pregnancy symptoms may be absent or less intense (*placenta can still produce hCG*)
    - Physical examination findings:
      - Uterus smaller than expected for dates
      - Cervical os closed
    - Investigations findings:
      - Ultrasound reveals a non-viable (*absent fetal cardiac activity despite a crown-rump length of >7mm*) intrauterine pregnancy
      - In the case of an **anembryonic pregnancy** (*aka* **blighted ovum**, *where conception occurs with the development of a gestational sac with no subsequent normal development of an embryo*), ultrasound would reveal a gestational sac >25mm in size but with no fetal pole
      - Note that pregnancy test at this point can still be positive as placenta can continue to produce hCG even after fetal death

  - ***Septic miscarriage/abortion***
    - Salient findings: *similar to an incomplete abortion but complicated by infection*
    - History findings:
      - Per-vaginal bleed ± discharge
      - Abdominal pain usually present
      - May have prior history of instrumentation of uterus (*e.g. amniocentesis*)
    - Physical examination findings:
      - Uterus may be smaller than expected for dates
      - Cervical os open with products of conception seen at cervical os
      - Cervical motion tenderness
      - Adnexal tenderness
    - Investigations findings:
      - Ultrasound reveals non-viable (*absent fetal cardiac* activity) intrauterine pregnancy, thick endometrial lining & retained products of conception within uterus & at the cervical os

  - ***Recurrent miscarriage/abortion***
    - Salient features: *defined as ≥3 consecutive miscarriages*

- **Management of Miscarriages**

  - ***Management of threatened miscarriage***
    - Reassure patient & continue routine antenatal follow-up visits
    - Consider progesterone therapy (*some evidence that it reduces the risk of miscarriage & preterm labour*)

  - ***Management of inevitable, incomplete & septic miscarriages***
    - Stabilize & resuscitate patient
      - Airway, breathing, circulation
      - Establish IV access & start fluid infusion
      - Draw bloods for preliminary investigations (*full blood count, group & cross match*)
      - Start empirical IV antibiotics in cases of septic miscarriage
    - Remove any products of conception at cervical os
      - Use sponge forceps (*can be done even if the primary care setting before considering need to send patient to a hospital*)
      - In certain cases, cervical os may close following removal of products of conception at cervical os (*if no POC is left*), with subsequent cessation of per-vaginal bleeding
    - Arrange for evacuation of uterus
      - Surgical evacuation via vacuum aspiration after cervical priming with 400µg misoprostol PV 3 hours prior (*indicated if patient is bleeding profusely, septic or requires tissue for analysis such as in the context of recurrent miscarriage*)
      - Medical evacuation via misoprostol (+ *mifepristone if available*) PV (*indicated if patient is unfit for anaesthesia or has retained fetal parts >14 weeks gestation in size which may render surgical evacuation unsafe*)
    - Other general management considerations:
      - Anti-D immunoglobulin if rhesus negative
      - Psychological support & counselling
      - Follow-up to convey findings of pathological report (*if tissue sample was obtained & sent*) & reassure about chances of future reproductive success where appropriate

  - ***Management of complete miscarriage***
    - No specific treatment required if patient is stable
    - Other general management considerations:
      - Anti-D immunoglobulin if rhesus negative
      - Psychological support & counselling

  - ***Management of missed miscarriage***
    - If in doubt of diagnosis (*e.g. very early on in the pregnancy where the case is borderline for the thresholds used to diagnose a non-viable* pregnancy), repeat ultrasound scan after 7-14 days
    - Arrange for evacuation of uterus (*similar considerations as for inevitable/incomplete abortion*)
    - Expectant management is an option if patient is stable & non-febrile:
      - Patient may subsequently spontaneously expel dead fetus & products of conception or reabsorb trophoblastic tissue with no bleeding
      - Need to arrange close follow-up visits (*risk of DIVC in mother with retained dead fetus*)
      - Tell patient to return immediately if excessive bleeding or fever develops
    - Other general management considerations:
      - Anti-D immunoglobulin if rhesus negative
      - Psychological support & counselling
      - Follow-up to convey findings of pathological report (*if tissue sample was obtained & sent*) & reassure about chances of future reproductive success where appropriate

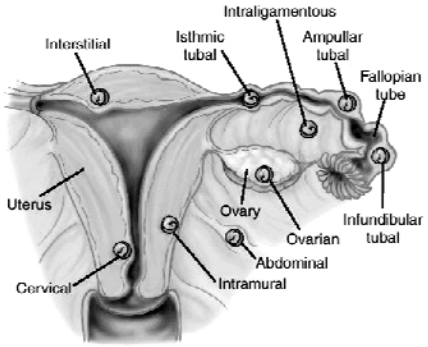
  - ***Management of recurrent miscarriage***
    - Offer investigations to determine possible cause(s):
      - Rule out maternal medical conditions (*diabetes mellitus, thyroid disease, renal disease, SLE*)
      - Rule out maternal infections
      - Rule out uterine & cervical abnormalities (*pelvic ultrasound, hysterography, hysteroscopy*)
    - Treat any causes identified appropriately:
      - Medical management of maternal conditions
      - Treat underlying infections
      - Surgical &/or hysteroscopic management of uterine abnormalities
      - Cervical cerclage for cervical incompetence (*see "Obstetric Complications"*)

Ectopic Pregnancy

Gestation that implants outside the endometrial cavity; estimated to occur in 1 in every 80 spontaneously conceived pregnancies

- **Etiology & Associations**
  - Risk factors for ectopic pregnancy:
    - History of tubal inflammation
      - Pelvic inflammatory disease
      - Endometriosis
    - History of tubal surgery
      - Previous tubal reconstructive surgery
      - Previous tubal sterilization in past 1-2 years (especially if cauterization was used)
    - Use of intrauterine contraceptive devices (*if a pregnancy occurs while an IUCD is in place, higher risk of ectopic pregnancy; but given that IUCD vastly decreases the chance of a pregnancy, the overall rate of ectopic pregnancy with an IUCD vs without is still lower*)
    - Use of assisted reproductive technologies
      - Associated with a higher risk for development of **heterotropic implantation** (*simultaneous intrauterine pregnancy & ectopic pregnancy*)
    - Previous ectopic pregnancy
      - Risk of recurrence after 1 previous = 15%
      - Risk of recurrence after 2 previous = 30%
    - Subfertility due to tubal factors
    - Smoking (relative risk of 1.26)

- **Sites of Ectopic Pregnancy**



  - ***Extra-uterine sites***
    - Tubal (98%)
      - Isthmic (12%)
      - Ampullary (75-80%)
      - Infundibular & fimbrial (6-11%)
    - Ovarian (0.5%)
    - Abdominal & intraligamentous (0.1%)
  - ***Intra-uterine sites***
    - Cervical (0.4%)
    - Cornual/interstitial (1%)

- **Natural History of Tubal Ectopic Pregnancy**
  - Tubal rupture
  - Tubal abortion into peritoneal cavity
  - Spontaneous resolution/resorption of pregnancy

- **Clinical Features of Ectopic Pregnancy**
  - ***History:***
    - Classical triad of symptoms in ectopic pregnancy: *prior missed menses + PV bleed + lower abdominal pain*
      - PV bleed can originate from bleeding from a tubal ectopic pregnancy or from shed endometrial lining due to insufficient pregnancy hormones provided by an ectopic pregnancy to support the endometrium
    - May have additional features of an acute abdomen (*diffuse abdominal pain, ipsilateral shoulder pain from phrenic nerve irritation due to blood in the upper abdomen, dizziness from acute blood loss*) in the setting of a ruptured ectopic pregnancy
    - Enquire about risk factors for ectopic pregnancies
  - ***Physical examination:***
    - General examination:
      - Assess vitals for signs of hypovolemia & acute blood loss
    - Abdominal examination:
      - Assess for tenderness
      - Guarding & rebound tenderness if ruptured
    - Pelvic examination:
      - Per-vaginal bleeding
      - Cervical motion tenderness
      - Tender adnexal mass
      - Slightly enlarged, globular uterus

- **Differential Diagnosis:**
  - ***Gynaecologic differentials:***
    - Threatened, inevitable or incomplete abortion
    - Ruptured corpus luteal cyst
    - Adnexal accidents (e.g. ovarian cyst torsion)
    - Acute pelvic inflammatory disease
    - Red degeneration of fibroid (*not uncommonly seen in pregnancy with pre-existing fibroids of significant size*)
  - ***Non-gynaecologic differentials:***
    - Acute appendicitis, diverticulitis
    - Pyelonephritis, ureteric colic
    - Acute pancreatitis
    - Perforated peptic ulcer

- **Diagnosis & Evaluation**
  - ***Diagnose pregnancy:***
    - Urine pregnancy test
    - Serum hCG quantification
      - Helps to (i) diagnose pregnancy (ii) aid in management algorithm in the event that pelvic ultrasound is non-diagnostic (see below)
    - Pelvic ultrasound
      - Empty uterus + free fluid in the pouch of Douglas coupled with a positive urine pregnancy test is diagnostic
      - May occasionally be able to visualize a non-ruptured tubal ectopic pregnancy as a "**double ring sign**"
      - Visualization of intrauterine pregnancy does <u>not</u> rule out possibility of concomitant ectopic pregnancy (heterotropic implantation)
  - ***Investigations to aid management:***
    - Investigations to rule out differentials
    - Full blood count, PT, aPTT, group & cross match

- **Management of Ectopic Pregnancy**

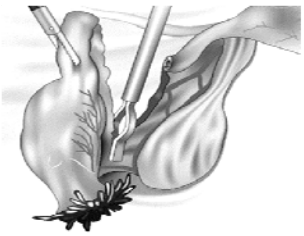
  - ***Management of a ruptured ectopic pregnancy***
    - Ruptured ectopic pregnancy would present with a clinical acute abdomen
    - Initial resuscitation, stabilization & investigations:
      - ABCs
      - Large bore IV access, infuse fluids
      - Take essential bloods (FBC, PT aPTT, GXM), do urine pregnancy test ± pelvic ultrasound
    - Emergent surgical intervention
      - Emergency laparotomy usually indicated with a clinical picture of an acute abdomen
      - In stable cases, an exploratory laparoscopy first may be appropriate to determine etiology
      - Procedure of choice in ruptured ectopic is usually salpingectomy

  - ***Management of a non-ruptured ectopic pregnancy***
    (*various management options available for a confirmed ectopic pregnancy in a non-emergency setting*)

    Medical Management
    - Using methotrexate IM 50mg/m^2 in divided doses (*usually half the dose in each buttock*)
    - Patient returns on days 4 & 7 for repeat hCG measurements:
      - If hCG falls ≥15% between days 4 & 7, continue follow up on a weekly interval to ensure ≥15% fall every 7 days until hCG titres are undetectable (*may take 1-3 months*)
      - If hCG titres plateau or fall too slowly (<15% every 7 days), give another dose of MTX
      - If patient becomes more symptomatic or if hCG titres rise (*failure rate 15-25%*), surgical treatment is indicated
      - Patient to avoid foods & vitamins containing folic acid, NSAIDs & alcohol during treatment period; offer effective contraception for at least 3 months after treatment to allow wash out (*methotrexate is teratogenic*)
    - Advantages of medical treatment:
      - Avoids surgical risks
      - Preserves future fertility
    - Criteria to meet for methotrexate treatment:
      (i) hCG levels <5000IU/L
      (ii) Ultrasound reveals absence of yolk sac & fetus, adnexal mass ≤3.5cm in its greatest diameter, no free fluid in the pouch of Douglas
      (iii) Good understanding & compliance
      (iv) Hemodynamically stable
      (v) No contraindications to methotrexate (*breastfeeding, immunodeficiency, peptic ulcer disease, active pulmonary disease, renal or hepatic insufficiency, coexisting viable intrauterine pregnancy, allergy to methotrexate*)
    - Side-effects of methotrexate therapy:
      - Pain within 1st week of receiving treatment due to tubal abortion or tubal distension from hematoma formation (*common; can be controlled with paracetamol*)
      - Conjunctivitis, dermatitis, alopecia
      - Stomatitis, gastritis, enteritis
      - Pneumonitis
      - Elevated liver enzymes
      - Bone marrow suppression

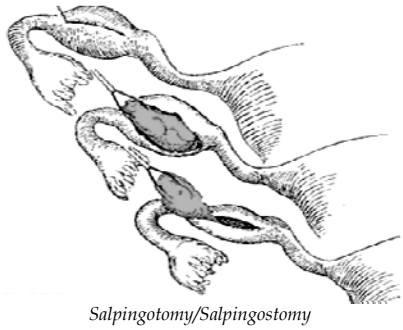
    Surgical Management
    - Surgical approaches:
      - Laparotomy (*indicated in patients who are hemodynamically unstable as rapid access to the bleeding site is critical*)
      - Laparoscopy (*gold standard for hemodynamically stable patients with advantages of less postop pain, shorter postop length of stay & quicker recovery*)
    - Surgical options:
      - **Salpingectomy** = *removal of entire fallopian tube*
      - **Partial salpingectomy** = *removal of a portion of the fallopian tube; remnants of the tube may be reapproximated in the future*
      - **Salpingotomy** = *operative identification of ectopic pregnancy site in tube → injection of vasoconstrictive agents → incision made parallel to the axis of the tube along its antimesenteric border over the site of implantation → gentle removal of products of conception using hydrodissection → primary closure of incision*
      - **Salpingostomy** = *similar procedure as salpingotomy, except that incision is left open at the end of the procedure*
      - **Salpingocentesis** = *at the time of laparoscopy, injection of methotrexate, prostaglandins or hyperosmolar glucose into the amniotic sac of the ectopic pregnancy; currently still experimental*
    - Factors affecting choice of surgical option:
      - 10-20% risk of residual trophoblastic tissue with salpingotomy or salpingostomy (*need to repeat hCG titres 3-7 days postop to confirm decline in hCG; if it fails to decline appropriately, methotrexate therapy can be started*)
      - Trend towards higher risk of recurrence of ectopic pregnancy in salpingotomy vs salpingectomy with no significant different in rates of subsequent intrauterine pregnancy (*hence in the presence of a normal healthy contralateral fallopian tube, no evidence that salpingotomy should be used in preference to salpingectomy*)
      - Partial salpingectomy reserved for cases where implantation is at the mid-ampullary portion with a possibility of ≥6cm of function tube left after resection

    Expectant Management
    - A possible option in a select group of patients:
      - hCG ≤200mIU/mL
      - Hemodynamically stable
      - No signs of impending or ongoing rupture (*e.g. persistent abdominal pain or >300ml free peritoneal fluid outside the pelvic cavity*)
      - Compliant to follow-up
    - Risk of rupture with hCG <1000mIU/mL is 20%
    - Requires close follow-up monitoring of hCG
      - Every 48 hours initially to confirm declining trend in hCG
      - Weekly thereafter until hCG titre becomes undetectable
      - If hCG levels plateau, offer methotrexate
      - If hCG levels rise or patient becomes more symptomatic, surgical intervention indicated



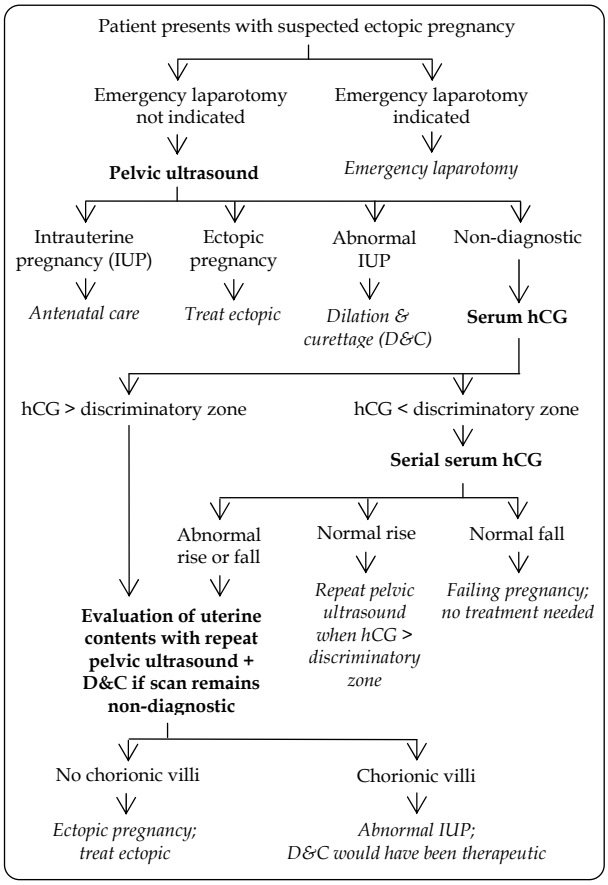
Salpingectomy

Partial Salpingectomy



Salpingotomy/Salpingostomy

– ***Management if initial investigations are non-diagnostic***
  - Use of serum hCG levels to guide further management
  - Dynamics of serum hCG during pregnancy:
    - Rapidly dividing fertilized egg begins to produce hCG, but communication with maternal circulation to allow detection of hCG begins with implantation
    - Normally in the 1st trimester, hCG levels increase exponentially, with a doubling time varying from 1.2 days shortly after implantation to 3.5 days at 2 months amenorrhea
    - Most pregnancies demonstrate doubling time of 48 hours in the first few weeks of pregnancy, with the slowest rise being 53% within 2 days accepted as being normal
    - Also, following spontaneous loss of a normal pregnancy, the minimal decline in hCG levels is 21-35% within 2 days
    - Also, there exists the idea of a **discriminatory zone**, defined as the hCG titre at which an intrauterine sac should be reliably seen with transvaginal ultrasonography in a normal pregnancy (*this value differs between institutions; locally taken as 1500IU/L*)
  - As such, the following situations would suggest an ectopic pregnancy <u>or</u> abnormal intrauterine pregnancy (i.e. molar pregnancy):
    - Rise in hCG <53% in 2 days
    - Fall in hCG <20% in 2 days
    - hCG level >1500IU/L with <u>no</u> intrauterine gestational sac seen on transvaginal ultrasound
  - Differentiation between ectopic & abnormal intrauterine pregnancy would require evaluation of uterine contents to look for presence of chorionic villi (*via repeat ultrasound + dilation & curettage if ultrasound remains non-diagnostic*)



- **Outcomes & Sequelae of Ectopic Pregnancy**
  – Patients with ectopic pregnancy have:
    - Decreased fertility
      - No difference however between patients managed expectantly vs patients managed via surgical management
    - Increased risk of subsequent ectopic pregnancy
      - 15% after 1 previous ectopic pregnancy
      - 30% after 2 previous ectopic pregnancies
  – Hence proper counselling on risks of future ectopic pregnancies is indicated after an episode of ectopic pregnancy

Antepartum Hemorrhage

Per-vaginal bleeding occurring during pregnancy from the time of fetal viability (24 weeks gestation) to before delivery

Approach to Antepartum Hemorrhage

- **History**
  - ***Characterize per-vaginal bleed:***
    - Onset, duration, number of episodes, amount
    - Any precipitating factor(s)
      - *Blunt abdominal trauma → abruptio*
      - *Rupture of membranes → abruptio or vasa praevia*
  - ***Associated symptoms:***
    - Pain vs painless
      - *Abruptio usually painful*
      - *Placenta praevia & vasa praevia usually painless*
    - Uterine contractions
      - *Abruptio placentae usually associated with strong uterine contractions*
      - *Placenta praevia & vasa praevia usually not associated with uterine contractions*
      - *Regular uterine contractions may indicate onset of (preterm) labour*
    - Fetal movements
  - ***Antenatal history:***
    - Results of investigations & scans done so far
      - *Placental &/or umbilical cord abnormalities noted (e.g. low-lying placenta, aberrant cord insertion)*
      - *Any preeclampsia (increases risk of abruptio)*
    - Use of assisted reproductive technologies
      - *Increased risk of placenta praevia*
      - *Increased risk of vasa praevia (multiple gestations)*
  - ***Obstetric history:***
    - Any previous antepartum hemorrhage & diagnosis
    - Any previous caesarian section or uterine surgery
      - *Increased risk of placenta praevia*
  - ***Past medical, surgical, social history***
    - Any known lower genital tract pathology
      - *Cervicitis, cervical polyps, cervical cancer etc*
      - *Last Pap smear & results*
    - Any pre-existing hypertension or thrombophilia
      - *Increased risk of abruptio*
    - Any known coagulopathy
    - Smoking & drug use
      - *Increased risk of placenta praevia & abruptio*

- **Physical Examination**
  - ***General examination:***
    - Maternal vitals (BP, HR, RR, SpO_2)
    - Assess for pallor & signs of coagulopathy
  - ***Obstetric examination:***
    - Palpate for tenderness (*abdominal &/or uterine*), uterine consistency (*woody hard uterus in abruption*) & fetal lie + presentation
    - DopTone to look for fetal heartbeat
  - ***Pelvic examination:***
    (*done only <u>after</u> ultrasound is performed to rule out placenta praevia in which case a pelvic examination is contraindicated*)
    - Rule out lower genital tract pathology
    - Assess for cervical dilatation/effacement (*indicates preterm delivery which can occur as a result of other causes of antepartum hemorrhage as well*)

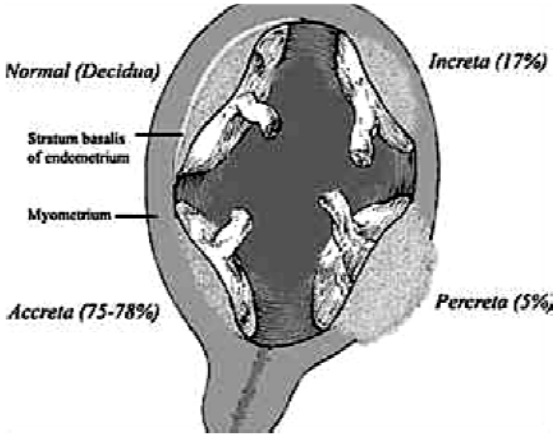
- **Investigations**
  - Pelvic ultrasound
    - Helps clinch diagnosis in certain cases
      - *Placenta praevia*
      - *Retroplacental hematoma may be seen in abruptio*
      - *Vasa praevia may be visualized*
    - Assesses for signs of fetal compromise
      - *IUGR, oligohydramnios, absent or reversed end-diastolic umbilical arterial Doppler flow*
    - Assess fetal lie & presentation to guide mode of delivery
  - Hematological investigations:
    - Full blood count
    - PT, aPTT ± DIVC screen (*fibrinogen, d-dimers*)
    - Group & cross-match (4-6 units of blood)
  - Fetal cardiotocography

- **Principles of Management**
  - ***Initial resuscitation & investigations:***
    - ABCs, establish IV access
    - Establish close monitoring of maternal parameters & fetal CTG
    - Investigate accordingly to determine cause(s) of antepartum hemorrhage
  - ***Decide between expectant vs emergent management:***
    - Balance to be struck between maternal well-being & fetal maturity
  - ***Mode of delivery:***
    - Vaginal delivery general preferred unless clear indications for caesarian are present (*e.g. placenta praevia, previous classical caesarian, rapid bleed control*)
  - ***Other general considerations:***
    - Anti-D immunoglobulin for rhesus negative mother
    - Post-partum hemorrhage management (*conditions leading to antepartum hemorrhage can predispose to post-partum hemorrhage*)

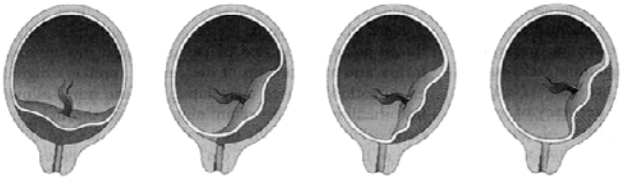
Placenta Praevia

The most common type of abnormal placentation (incidence 0.5%); defined as a placenta that is partially or completely located in the lower uterine segment (hence lies over or proximate to the internal cervical os)

- **Etiology & Associations**
  - ***Risk factors for placenta praevia:***
    - Maternal factors:
      - Advanced maternal age
      - Multiparity
      - Smoking or cocaine use
    - Previous procedure which may have resulted in uterine scar tissue &/or endometrial damage:
      - Previous caesarian delivery
      - Previous intrauterine surgical procedures
      - Previous abortion
    - Prior placenta praevia (*4-8% subsequent risk*)
    - Multiple gestation
    - Use of assisted reproductive technologies
  - ***May be associated with other forms of abnormal placental implantation such as placenta accreta:***
    - Abnormal attachment of placenta through the uterine myometrium as a result of defective decidual formation:
      - Decidua basalis is the decidual layer (endometrium lining) directly beneath the site of implantation, which gives rise to the basal plate of the placenta
      - As implantation progresses, trophoblastic giant cells invade the decidua basalis extensively, establishing the placenta
      - Where the invading trophoblastic tissue meets the decidua basalis normally appears a zone of fibrinoid degeneration (**Nitabuch's layer**)
      - Absence of the Nitabuch's layer is seen in placenta accreta, as the trophoblastic invasion extends beyond the decidual layer into the uterine myometrium
    - Types of placenta accreta:
      - **Placenta accreta** = *abnormal attachment of placenta to myometrium is superficial*
      - **Placenta increta** = *abnormal attachment of placenta to myometrium extends into myometrium partially*
      - **Placenta percreta** = *abnormal attachment of placenta to myometrium extends through the whole myometrium to the serosal surface*



- **Classification of Placenta Praevia**
  - ***Complete placenta praevia (praevia major)***
    - Placenta covers internal cervical os completely
    - **Central placenta praevia** is a subtype in which the internal cervical os is approximately equidistant between the anterior & posterior edges of the placenta (*20-30% of complete placenta praevia*)
  - ***Partial placenta praevia (praevia major)***
    - Placenta covers internal cervical os partially
  - ***Marginal placenta praevia***
    - Placental edge is adjacent to/at the edge of the internal cervical os without covering it
  - ***Low-lying placenta (praevia minor)***
    - Placenta is partially or completely in the lower uterine segment, with the placental edge >0cm but <2cm away from the internal cervical os
    - Low-lying placenta is also used to describe a placenta found to be in the lower portion of the uterus (*including those partially or completely covering the internal cervical os*) in the 2nd trimester
      - By definition, lower uterine segment only develops in the 3rd trimester, hence strictly put, a placenta praevia cannot be diagnosed until the 3rd trimester
      - Most low-lying placentas discovered in the 2nd trimester eventually 'migrate' superiorly due to growth & development of the lower uterine segment in the 3rd trimester such that at term, they are in normal position
      - A minority of low-lying placentas discovered in 2nd trimester however persists to become placenta praevia in the 3rd trimester (*especially those already found to be covering the internal os*)



Complete *Partial* *Marginal* *Low-lying*

- **Complications of Placenta Praevia**
  - ***Maternal complications:***
    - Uncontrolled hemorrhage
      - Antenatally
      - Postpartum (*as lower uterine segment does not contract well following delivery, hence placentation in the lower uterine segment increases risk of PPH; risk is further heightened if there is a concomitant placenta accreta associated with the praevia*)
    - Abruptio placentae
    - Disseminated intravascular coagulation (*especially with heavy bleeding & abruptio placentae*)
  - ***Fetal complications:***
    - Fetal malpresentation (*due to mass effect & distortion of the lower uterine segment*)
    - Preterm delivery
    - Premature rupture of membranes
    - IUGR, IUFD

- **Diagnosis of Placenta Praevia**
  - ***Clinical presentation:***
    - Per-vaginal bleeding
      - Painless in majority of cases (70-80%); associated with contractions in remaining cases
      - 1st episode of bleed occurs prior to 30 weeks gestation in one-third, between 30 & 36 weeks in one-third, & after 36 weeks in most of the remaining patients
      - 10% reach term without any PV bleed episode
  - ***Investigations:***
    - Ultrasound
      - Confirms placental site, establishing firm diagnosis of placenta praevia (*should ideally precede digital vaginal examination in cases of antepartum hemorrhage to exclude placenta praevia because inadvertent palpation of the placenta in placenta praevia can lead to severe hemorrhage*)
      - Transabdominal ultrasound is 1st-line; transvaginal ultrasound used if diagnosis remains uncertain after transabdominal scan

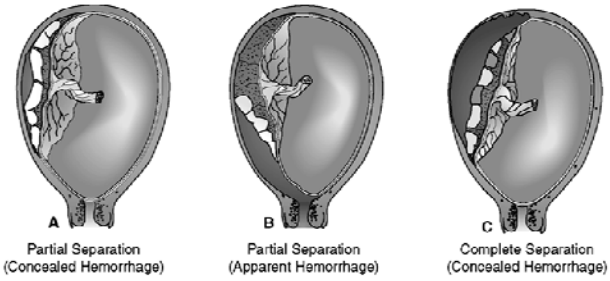
- **Management of Placenta Praevia**
  - ***Initial resuscitation & assessment:***
    - Assess ABCs
    - Establish large bore IV access & begin fluid infusion
    - Put patient on close monitoring:
      - BP, HR, RR, SpO_2
      - Catheterize for urine output
    - Initial investigations:
      - FBC, PT, aPTT, GXM (4-6 units of blood)
      - Urgent ultrasound (*confirm diagnosis, confirm exact placental location, assess for fetal well-being, determine fetal lie & position*)
      - Fetal CTG
    - Decide on expectant vs emergent management depending on:
      - Maternal status (*maternal compromise, e.g. uncontrolled bleeding, is indication for emergent management*)
      - Fetal status (*fetal compromise, e.g. non-reassuring CTG status, is indication for emergent management*)
      - Gestational age (*low threshold for emergent management if already past 34 weeks gestation*)
      - Presence of concomitant conditions (*concomitant preterm labour, PROM, abruptio etc would require additional relevant management plans as indicated*)
  - ***Expectant management:***
    - Hospitalize patient & manage conservatively:
      - Regular maternal parameters monitoring (*vitals, FBC, pad chart*)
      - Regular fetal CTG assessment
      - Corticosteroids to accelerate fetal pulmonary maturation (*in case of precipitous bleed*)
    - Consider discharge & outpatient management if patient is stable, no longer bleeding & compliant with follow-up
      - Educate on condition prior to discharge
      - Tell patient to return immediately if further episodes occur
      - Advise to avoid sexual intercourse
    - Plan for elective delivery at term (37-38 weeks):
      - Usually via caesarian unless placental margin is >2cm from internal os (*in which case vaginal delivery can be considered*)
      - May require classical caesarian instead of LSCS (*e.g. in anterior placenta praevia where placenta is directly under the site of the incision made for a LSCS*)
      - Low threshold for immediate delivery once >34 weeks gestation if patient has further episodes of PV bleed
  - ***Emergent management:***
    - Stabilize patient
    - Expedite delivery (*usually via caesarian section as for elective delivery mentioned above*)
  - ***Other general considerations (for both expectant & emergent management plans):***
    - Give anti-D immunoglobulin after each episode of PV bleed antenatally if mother is rhesus-negative
    - Manage post-partum hemorrhage following delivery
      - Higher risk of PPH in placenta praevia (*refer to "Labour & Puerperium"*)

Abruptio Placentae

Retroplacental bleeding (i.e. bleeding occurring at the decidual-placental interface) resulting in placental separation (specifically separation of the decidua from the basal plate); occurs in 1 in 120 pregnancies (0.4-1.3%)

- **Etiology & Associations**
  - ***Risk factors for abruptio placentae:***
    - Maternal risk factors:
      - Maternal medical conditions (*hypertension, thrombophilias*)
      - Maternal tobacco & cocaine use
      - Uterine abnormalities (*bicornuate uterus, large submucous fibroids*)
    - Pregnancy-related factors:
      - Previous abruptio placentae (*5-15% risk after 1, 20-25% risk after 2 previous abruptions*)
      - Preeclampsia in the current pregnancy
      - Rupture of membranes (*PROM, iatrogenic in context of surgical induction of labour*)
      - Intrauterine infections
      - Short umbilical cord
    - Mechanical factors:
      - Maternal abdominal trauma
      - Rapid decompression of amniotic sac (*e.g. rupture of membranes in the setting of polyhydramnios*)

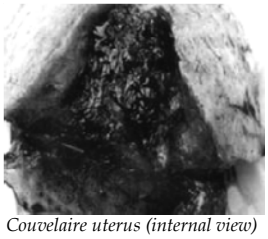
- **Pathophysiology of Abruptio Placentae**
  - Initiating event is usually the rupture of a maternal vessel in the decidua basalis (*rarely due to bleeding from a fetal-placental vessel rupture*):
    - Results in hemorrhage into the decidua basalis
    - Splits the decidua, separating a thin layer of decidua with its placental attachment from the basal plate
    - Depending on the extent of continued hemorrhage, the bleed may continue to dissect through the placental-decidual interface
    - Detached portion of placenta becomes non-functional
    - If retroplacental hemorrhage dissects downwards towards the cervix, an external (revealed) hemorrhage results (*vs a concealed hemorrhage if the retroplacental hematoma does not reach the cervix*)
  - Initial bleed from maternal vessels in the decidua basalis could be caused by various factors:
    - Mechanical (*trauma, rapid uterine decompression*)
      - Causes shearing of the inelastic placenta
    - Vasoconstrictive (*smoking, cocaine*)
      - Causes local areas of ischemia, reflex vasodilatation & disruption of vascular integrity
    - Abnormal placentation (*uterine abnormalities*)
      - Causes inadequate placentation & decidualization which may predispose to vascular disruption with relatively minor mechanical forces
  - Severity of clinical consequences depend on source of retroplacental bleed:
    - Arterial bleed (*usually in central area of placenta*)
      - Rapid development of potentially life-threatening clinical manifestations (*acute onset of maternal hemodynamic instability & fetal compromise*)
    - Venous bleed (*usually in periphery of placenta*)
      - More likely to present with clinical manifestations which occur over time (*light intermittent PV bleed, oligohydramnios, IUGR*)
  - Thrombin plays a key role in clinical consequences of abruptio placentae:
    - Decidual bleeding results in production of thrombin via various pathways (*directly induction of tissue factor release from injured decidual cells which initiates cascade to activate thrombin; hypoxia-induced production of VEGF which in turn induces aberrant production of tissue factor & thereafter, thrombin*)
    - Thrombin in turn causes:
      - Direct uterotonic effect inducing uterine contractions
      - Enhanced expression of matrix metalloproteinases
      - Induced expression of inflammatory cytokines (IL-8) leading to tissue necrosis
    - Hence thrombin production results in further vascular disruption & tissue damage, initiating a vicious cycle, often leading to initiation of labour & rupture of membranes
    - Furthermore, large amounts of activated thrombin entering maternal circulation can induce widespread activation of the coagulation cascade, leading to maternal DIVC

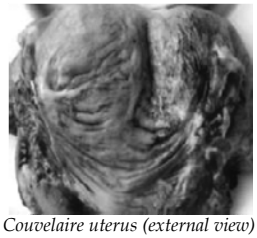


- **Complications of Abruptio Placentae**
  - ***Maternal consequences:***
    - Excessive maternal hemorrhage (*may lead to permanent end-organ damage e.g. Sheehan's syndrome*)
    - Disseminated intravascular coagulation
  - ***Fetal consequences:***
    - IUGR, IUFD
    - Preterm labour, PROM

- **Diagnosis of Abruptio Placentae**
  - ***Clinical presentation:***
    - Patient usually presents with:
      - Acute onset of PV bleed (*unless concealed abruption occurs*)
      - Mild to moderate abdominal &/or back pain
      - Uterine contractions
    - Physical examination findings:
      - Signs of acute hemorrhage (*pallor, tachycardia, hypotension*)
      - Abdominal tenderness
      - "Woody-hard" uterus (*classically described*)
  - ***Investigations:***
    - Ultrasound
      - Identification of retroplacental hematoma is the classical ultrasound finding confirming presence of placental abruption
      - Other suggestive findings: *subchorionic fluid collections, echogenic debris in amniotic fluid, thickened placenta which shimmers with maternal movement (***"Jello sign"***)*
      - Sensitivity for diagnosis of abruption is only 25-50% (*i.e. if negative, does not confidently rule out presence of placental abruption*)
      - Hence need to correlate with clinical findings & assessment of maternal & fetal well-being to decide on management plan in many cases

- **Management of Abruptio Placentae**
  - ***Initial resuscitation & investigations:***
    - Assess ABCs
    - Establish large bore IV access & begin fluid infusion
    - Put patient on close monitoring:
      - BP, HR, RR, SpO_2
      - Catheterize for urine output
    - Initial investigations:
      - FBC, PT, aPTT, GXM (4-6 units of blood)
      - Consider DIVC screen
      - Urgent ultrasound (*confirm diagnosis, confirm exact placental location to exclude concomitant placenta praevia, assess for fetal well-being, determine fetal lie & position*)
      - Fetal CTG
    - Decide on management options based on:
      - Maternal status (*maternal compromise, e.g. uncontrolled bleeding or DIVC, is indication for emergent management*)
      - Fetal status (*fetal compromise, e.g. non-reassuring CTG status, is indication for emergent management; fetus being alive vs dead also changes management considerations*)
      - Gestational age (*low threshold for emergent management if already past 34 weeks gestation*)
      - Presence of concomitant conditions (*concomitant preterm labour, PROM, placenta praevia etc would require additional relevant management plans as indicated*)
  - ***Expectant management:***
    - Usually reserved for minor abruptions with stable maternal & fetal condition before 34 weeks gestation
    - Hospitalize patient & manage conservatively:
      - Regular maternal parameters monitoring (*vitals, FBC, pad chart*)
      - Regular fetal CTG assessment
      - Corticosteroids to accelerate fetal pulmonary maturation (*in case of precipitous bleed*)
    - Plan for elective delivery at term (37-38 weeks):
      - Via vaginal route unless indications for caesarian delivery is present (*e.g. concomitant placenta praevia, rapid control of heavy bleed*)
      - Low threshold for immediate delivery if >34 weeks gestation in cases of recurrent bleed or worsening of maternal &/or fetal condition
  - ***Emergent management:***
    - Indicated if:
      - Maternal &/or fetal compromise requiring immediate delivery
      - Fetal demise (*in which case there is no need to weigh benefits of immediate delivery against risks of neonatal prematurity*)
    - Correct coagulopathy prior to delivery:
      - Many experts recommend that operative intervention should not begin until coagulopathy is corrected, which is desirable but not always possible
      - Monitor coagulation status & treat DIVC with necessary transfusions (*packed cells, platelets, fresh frozen plasma, cryoprecipitate etc*) to achieve:
        (i) platelet count ≥ 50000
        (ii) fibrinogen ≥ 100mg/dL
        (iii) PT & aPTT < 1.5x control
        (iv) hematocrit ≥ 25-30%
    - Mode of delivery:
      - Vaginal delivery is generally preferable (*as patient is usually contracting vigorously in abruptio, an amniotomy may be all that is required to expedite delivery ± oxytocin augmentation*)
      - Caesarian delivery is indicated if (i) rapid control of bleeding required (ii) obstetric contraindications to vaginal birth (*e.g. concomitant placenta praevia, previous classical caesarian, certain malpresentations*)
  - ***Other general considerations (for both expectant & emergent management plans):***
    - Give anti-D immunoglobulin if mother is rhesus-negative
    - Manage post-partum hemorrhage following delivery; higher risk of PPH especially if:
      - **Couvelaire uterus** (*blood extravasated into myometrium which renders uterus atonic*), which has a higher incidence of requiring a post-partum hysterectomy
      - DIVC complicating abruption
      (*refer to "Labour & Puerperium"*)

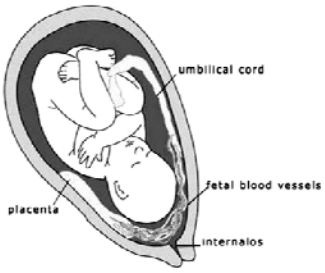

Couvelaire uterus (internal view)


Couvelaire uterus (external view)

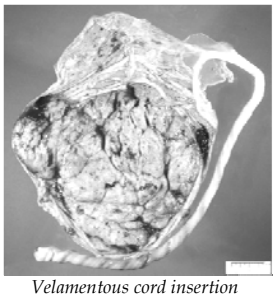
Vasa Praevia

A unique condition which may arise in cases of velamentous insertion of the cord involving passage of unprotected umbilical vessels over the internal cervical os

- **Pathophysiology of Vasa Praevia**
  - **Velamentous cord insertion** = insertion of vessels of the umbilical cord between the amnion & chorion at a point away from the placental site (*i.e. the vessels will have a segment which courses between the amnion & chorion before reaching the placenta*)
    - Occurs in 1% of singleton pregnancies, 10% in twin pregnancies & 50% in triplets
    - In itself increases the risk of vessel rupture, resulting in fetal hemorrhage
  - **Vasa praevia** = velamentous cord insertion with the unprotected umbilical vessels coursing over the internal cervical os
    - Occurs in 1 in 5000 pregnancies
    - Accentuates risk of vessel rupture compared to velamentous cord insertion without vasa praevia
    - 50% perinatal fetal mortality rate (75% if membranes rupture)
      - Note that unlike other causes of antepartum hemorrhage in which blood loss is <u>maternal</u> in origin, bleeding from vasa praevia is <u>fetal</u> in origin



Vasa praevia


Velamentous cord insertion

- **Diagnosis of Vasa Praevia**
  - ***Clinical presentation:***
    - Painless per-vaginal bleeding (*patient is otherwise very well as it involves fetal rather than maternal exsanguination*)
    - May present for the first time following rupture of membranes which ruptures the vessels crossing the internal cervical os
  - ***Investigations:***
    - Ultrasound can possibly diagnose via visualization of umbilical vessels crossing internal cervical os (*especially with Doppler flow*)

- **Management of Vasa Praevia**
  - Immediate delivery via caesarian section indicated if antepartum hemorrhage is suspected to be from vasa praevia

Endocrine Disorders

Diabetes Mellitus in Pregnancy

- **Definitions & Terminology**
  - ***Pre-existing diabetes mellitus***
    - Existing type 1 or type 2 diabetes mellitus in an individual prior to pregnancy
  - ***Gestational diabetes mellitus (GDM)***
    - Glucose intolerance with onset during pregnancy & eventual resolution within 6 weeks post-partum

- **Pathophysiology of Diabetes Mellitus in Pregnancy**
  - Gestational diabetes mellitus occurs due to hormonal alterations in pregnancy:
    - Production of human placental lactogen, progesterone, prolactin & cortisol
    - Results in increased peripheral insulin resistance
  - Maternal hyperglycemia results in fetal hyperglycemia (*as glucose crosses the placental barrier easily*) & thereafter, secondary fetal hyperinsulinism
  - Fetal hyperglycemia has various fetal effects:
    - Teratogenic during embryogenesis (*hence pre-existing DM is associated with birth defects while GDM is not*)
    - Fetal osmotic diuresis & polyuria, leading to polyhydramnios
  - Fetal hyperinsulinism has various fetal effects:
    - Fetal overgrowth, leading to macrosomia
    - Neonatal hypoglycemia following delivery
  - Vascular complications of pre-existing DM can further augment the effect of DM on pregnancy due to increased risk of uteroplacental insufficiency, resulting in:
    - Early pregnancy loss
    - Increased risk of pre-eclampsia
    - Intrauterine growth restriction
    - Oligohydramnios

- **Clinical Features**
  - ***Maternal risks:***
    - In cases of pre-existing DM:
      - Accelerated retinopathy & nephropathy
      - Increased risk of diabetic ketoacidosis
      - Increased risk of preeclampsia
      - Increased risk of infections (*e.g. UTI*)
      - Hypoglycemia (*due to overly tight control*)
    - In cases of gestational DM:
      - Perineal trauma during birth secondary to fetal macrosomia
      - Hypoglycemia (*due to overly tight control*)
  - ***Fetal risks:***
    - In cases of pre-existing DM:
      - Early pregnancy loss (*miscarriage, may be a cause of recurrent miscarriages*)
      - Congenital defects (*cardiac, neural tube, caudal regression syndrome – very rare but very unique to pre-existing DM in pregnancy*)
      - Intrauterine growth restriction
      - Oligohydramnios
      - Intrauterine fetal demise (*especially in the setting of poor DM control*)
      - Neonatal hypoglycemia, hypocalcemia, hypomagnesemia, hyperbilirubinemia & respiratory distress syndrome
    - In cases of gestational DM:
      - Polyhydramnios (*with its attendant risks of preterm labour, PROM, cord prolapse*)
      - Macrosomia (*with its attendant risks of birth trauma, shoulder dystocia*)
      - Intrauterine fetal demise (*especially in the setting of poor DM control*)
      - Neonatal hypoglycemia, hypocalcemia, hypomagnesemia, hyperbilirubinemia & respiratory distress syndrome

- **Screening & Diagnosis**
  - ***Screening for diabetes mellitus during pregnancy:***
    - Pre-existing DM:
      - History & previous investigations done are reviewed at booking visit to identify known pre-existing DM cases
      - Urine dipstick test at booking visit may reveal glycosuria in an undiagnosed pre-existing DM, prompting further testing for diagnosis
    - Gestational DM:
      - Universal screening vs targeted screening (*Singapore practices targeted screening based on risk factors for GDM*)
      - Risk factors for GDM:
        - → Advance maternal age (>35 years old)
        - → Maternal obesity
        - → 1st-degree relative with DM
        - → Obstetric history (*previous GDM, fetal macrosomia, stillbirth, fetal anomaly or polyhydramnios*)
      - Women with any risk factors identified will undergo diagnostic oral glucose tolerance test (75g 2-hour OGTT) at 28 weeks gestation (*or earlier where clinically indicated; e.g. persistent glycosuria detected in early antenatal visits*)
  - ***Diagnosis of diabetes mellitus during pregnancy:***
    - Pre-existing DM:
      - Fasting blood glucose ≥7.0mmol/L
      - Random blood glucose ≥11.1mmol/L
      - 75g 2-hour OGTT ≥ 11.1mmol/L
      - ****DM diagnosis needs (i) 2 positive tests on 2 different occasions if patient is asymptomatic or (ii) 1 positive test if patient is symptomatic or (iii) first presentation with a diabetic emergency (e.g. DKA)*
    - Gestational DM:
      - Fasting blood glucose ≥7.0mmol/L
      - Random blood glucose ≥11.1mmol/L
      - 75g 2-hour OGTT ≥ 7.8mmol/L
      - ****in pregnancy, impaired oral glucose tolerance (OGTT ≥7.8mmol/L is regarded as GDM)*
    - Note that if a patient presents for booking visit late, it may be difficult to determine if a positive test for DM indicates undiagnosed pre-existing or gestational DM; possible differentiating factors include:
      - Presence of vascular complications of DM (*retinopathy, nephropathy, neuropathy etc*) is suggestive of pre-existing DM
      - Fetal anomalies, IUGR & oligohydramnios are suggestive of pre-existing DM
      - Polyhydramnios & fetal macrosomia are suggestive of GDM

- **Antenatal Management**
  - ***Principles of antenatal management of DM in pregnancy:***
    - DM renders a pregnancy a high-risk pregnancy
      - Needs to be followed-up antenatally in a high-risk clinic/joint clinic with endocrinology
      - Multidisciplinary management (*obstetrician, endocrinologists, diabetic nurse clinician, dietician*)
      - Monitoring for fetal abnormalities & IUGR
    - Pre-existing DM requires baseline tests for assessing complications:
      - Renal panel (*assess renal function*)
      - Ophthalmology review (*assess retinopathy*)
      - Neurological testing (*assess neuropathy*)
      - Cardiac testing (*ECG, echocardiogram*)
    - Tight blood sugar control is required to decrease incidence of congenital anomalies & perinatal morbidity & mortality
    - Regular blood sugar monitoring to determine level of glycemic control, which influences:
      - Treatment option (diet alone or + insulin)
      - Planned delivery date
    - Delivery is planned at different gestational ages depending on the degree of glycemic control during pregnancy in order to achieve a balance between maximizing gestational age of fetus & minimizing risk of antenatal obstetric complications
  - ***Blood sugar control:***
    - Dietary control
      - Remains the cornerstone
      - Caloric control (*1800kcal/day or 30kcal/kg/day*)
      - + moderate intensity exercise
      - Insulin is added on top of dietary control if DM is not adequately controlled with diet alone
    - Insulin
      - Most commonly used dosing regime is the **basal-bolus regime** (4 injections daily)
      - 1 injection of intermediate-acting insulin before bedtime (10pm) + 1 injection of short-acting insulin before each of the 3 main meals
    - Oral hypoglycemic agents
      - Not conventionally used in DM treatment during pregnancy due to concerns of teratogenicity
      - Metformin has recently been used however in certain instances, but still not routine
  - ***Blood sugar monitoring:***
    - Home blood sugar monitoring:
      - 7-point blood sugar profile (*once before & once after each of the 3 main meals + once before bedtime/10pm*)
      - Ideal pre-meal level: 4.5-5.5mmol/L
      - Ideal post-meal level: 5.5-6.6mmol/L
      - 7-point BSP done daily initially, can be reduced to weekly BSP if well-controlled
    - Clinic HbA1c monitoring:
      - Test at baseline when DM is diagnosed & thereafter at 3-monthly intervals
      - Ideal HbA1c: ≤6.0%
  - ***Antenatal fetal monitoring:***
    - For pre-existing DM:
      - Early fetal anomaly scan (16-18 weeks)
      - Detailed fetal anomaly scan at 20-22 weeks as per for normal pregnancies
      - Serial growth scans after 28 weeks
    - For gestational DM:
      - Detailed fetal anomaly scan at 20-22 weeks as per for normal pregnancies
      - Serial growth scans after 28 weeks
  - ***Planned delivery:***
    - Gestational age at which delivery is planned depends on type of treatment & adequacy of control:
      - Well-controlled on diet alone → *allow to go up to EDD (40 weeks)*
      - Poorly-controlled on diet alone → *indication for adding on insulin, after which adequacy of controlled reassessed to determine planned delivery date*
      - Well controlled on diet + insulin → *38 weeks*
      - Poorly-controlled on diet + insulin → *may require earlier delivery, based on severity, but generally always after 34 weeks*
    - Mode of delivery is preferably vaginal in the absence of contraindications

- **Intrapartum Management**
  - ***Tight blood sugar control***
    - Establish insulin infusion using sliding scale (*starting at 1unit/hour*) + dextrose drip
    - Hourly assessment of blood sugar level to guide insulin infusion titration:
      - BSL <4mmol/L → stop insulin infusion
      - BSL 4-7mmol/L → continue insulin 1U/hour
      - BSL >7mmol/L → up insulin to 2U/hour
  - ***If elective LSCS is arranged:***
    - Arrange as 1st case of the day (*to avoid prolonged pre-op fasting which increases risk of hypoglycemia*)

- **Postnatal Management**
  - ***Blood sugar management:***
    (*insulin requirements drop drastically following delivery of the placenta as this source of the hormonal antagonists of insulin activity is removed*)
    - Pre-existing DM previously on insulin:
      - Revert to previous insulin regime
    - Pre-existing DM previously on oral hypoglycemic:
      - Consider continuing on lower doses of subcutaneous insulin for time the being (*as oral hypoglycemic agents cross into breast milk & can cause neonatal hypoglycemia in breastfeeding mothers*)
    - Gestational DM:
      - Frequently able to stop insulin immediately
  - ***Gestational DM follow-up:***
    - Perform OGTT at 6 weeks post partum to ensure that results revert back to normal
    - Counsel patients with GDM regarding risk of long-term metabolic sequelae (*30% of GDM patients develop diabetes mellitus subsequently; should maintain healthy diet & exercise level to minimize risk*)
  - ***Other general considerations:***
    - Give contraception advice
    - For pre-existing DM, advise to return early for assessment & adequate control of blood sugar when planning the next child in order to optimize pregnancy outcomes

Thyroid Disorders in Pregnancy

- **Thyroid Physiology in Pregnancy**
  - ***Maternal thyroid function:***
    - Increase in glomerular filtration rate results in increase in renal iodine excretion, with plasma inorganic iodine levels nearly halved
      - Goitre from iodine insufficiency unlikely so long as plasma inorganic levels >0.08μg/dL
      - Inorganic iodine supplementation up to 250μg/day is sufficient to prevent goitre formation during pregnancy
    - Pregnancy increases hepatic production of serum proteins which bind circulating thyroid hormone (*albumin, thyroid-binding globulin*)
      - Total T3 & T4 levels may be increased during pregnancy despite euthyroidism
      - Free T4 levels remain normal
  - ***Fetal thyroid function:***
    - Fetal thyroid gland does not contain organic iodine before 10 weeks gestation
    - Able to produce iodothyronines & T4 by weeks 11-12
    - Able to concentrate iodine by weeks 12-14
  - ***Placental barrier in thyroid physiology:***
    - Placenta allows free transfer of iodide, TRH & thyroid stimulating antibodies, limited transfer of T4 & no transfer of TSH
      - Transfer of maternal T4 to fetal circulation is vital in the 1st trimester while fetal thyroid function is absent for proper neural development
      - Transfer of maternal TRH to fetal circulation has minimal effect due to low levels present in maternal systemic circulation
      - Transfers of maternal thyroid stimulating antibodies can cause fetal thyrotoxicosis
    - Thyroid drugs with smaller molecular weights (*propylthiouracil, methimazole*) can also cross the placenta, causing fetal hypothyroidism

- **Hypothyroidism in Pregnancy**
  - ***Etiology & associations:***
    - Incidence of neonatal congenital hypothyroidism = 1 in 4000
    - Causes of congenital hypothyroidism:
      - Insufficient maternal iodine ingestion
      - Maternal goitrogen ingestion
      - Thyroid dysgenesis/agenesis
      - Inborn-errors of metabolism pertaining to thyroid hormones (dyshormonogenesis)
  - ***Clinical features:***
    - Maternal features:
      - Similar to hypothyroidism in normal patients
    - Fetal features:
      - Increased risk of miscarriage, preeclampsia, intrauterine fetal demise, low birth weight & lower intelligence
      - Fetal hypothyroidism affecting neural development in the 1st trimester can result in cretinism
  - ***Diagnosis & evaluation:***
    - Thyroid function test (TSH, free T4)
  - ***Management:***
    - Thyroxine replacement

- **Hyperthyroidism in Pregnancy**
  - ***Etiology & associations:***
    - Incidence of maternal thyrotoxicosis = 1 in 500
    - Causes of maternal hyperthyroidism:
      - Graves disease (*most common, even though most cases of Graves experience transient remission during pregnancy, postulated to be due to the increased immunological tolerance in pregnancy*)
      - Toxic multinodular goitre
      - Hydatidiform mole (*as hCG, which is produced in high levels, is structurally analogous to TSH*)
  - ***Clinical features:***
    - Maternal features:
      - Signs & symptoms of a hyperdynamic circulation (*may be difficult to differentiate from the normal changes that occur in pregnancy*)
      - Signs & symptoms supporting diagnosis of hyperthyroidism vs normal pregnancy changes: *thyroid eye signs, weight loss, heat intolerance*
      - Thyroid storm is the major maternal risk of hyperthyroidism in pregnancy with >25% mortality; may be precipitated by: *infection, labour, caesarian delivery or non-compliance with thyroid medications*
    - Fetal features:
      - Increased risk of preterm labour, IUGR, preeclampsia & intrauterine fetal demise
      - 1% of maternal Graves results in neonatal thyrotoxicosis due to transplacental transfer of thyroid stimulating antibodies (*transient & lasts for <2-3 months but associated with mortality rate of 16%*); may be suspected by persistent fetal tachycardia & visualization of fetal goitre on ultrasound
  - ***Diagnosis & evaluation:***
    - Thyroid function test (*TSH, free T4, thyroid stimulating antibody*)
  - ***Management:***
    - Antithyroid medications:
      - Thioamides remains mainstay of treatment
      - Drugs: *propylthiouracil, carbimazole, methimazole*
      - No conclusive evidence that they result in fetal anomalies & cretinism, although 1-5% of fetus exposed in-utero may develop a goitre
      - PTU is minimally excreted in breastmilk, hence can be safely continued in the postpartum period in breastfeeding mothers
    - Radioactive iodine is <u>contraindicated</u> in pregnancy
    - Surgical treatment:
      - Reserved for cases refractory to medical treatment, preferably performed in the 2nd trimester as per for most elective surgeries during pregnancy

Cardiovascular Disorders

Heart Disease in Pregnancy

- **Cardiovascular Physiology in Pregnancy**
  - ***Circulatory changes:***
    - Both plasma volume & red blood cell count increases during pregnancy, with a disproportionately higher increase in plasma volume
      - Results in hemodilution & physiological anemia of pregnancy
      - Results in increased cardiac output which places greater strain on the heart
    - Blood pressure generally decreases during the early half of pregnancy
      - Diastolic pressure decreases more than systolic (due to decrease in systemic resistance)
      - Blood pressure begins increasing in the 2nd trimester & progresses back to normal towards term
  - ***Mechanical effects of the gravid uterus:***
    - **Supine hypotensive syndrome**
      - Gravid uterus compresses iliac veins & inferior vena cava, especially when patient is in supine position
      - Causes decrease in venous return which may in turn result in decreased cardiac output & maternal hypotension
    - Pelvic vein compression
      - Gravid uterus compresses pelvic veins
      - Results in venous stasis & impaired venous drainage of pelvic structures & lower limbs
      - May manifest as lower limb edema, varicose veins, hemorrhoids
      - Predisposes to venous thromboembolism
    - **Poseiro effect**
      - Gravid uterus compresses abdominal aorta & its branches, especially when patient is in supine position
      - Typically occurs during late pregnancy if at all
      - Can result in compromised uteroplacental perfusion & subsequent fetal distress

- **Risks of Heart Disease in Pregnancy**
  - ***Maternal risks:***
    - Decompensation of existing heart disease
      - Stenotic valvular lesions do not tolerate decrease in afterload well due to an impaired ability to increase cardiac output adequately, resulting in congestive cardiac failure, cardiac arrhythmias (*e.g. atrial fibrillation*) & pulmonary edema
      - Pulmonary hypertension may also decompensate with the increase in intravascular volume during pregnancy
      - Shunt reversals may also be precipitated by the drop in left-sided afterload (Eisenmenger)
    - Peripartum cardiomyopathy
    - Infective endocarditis
  - ***Fetal risks:***
    - Early pregnancy loss, intrauterine fetal demise
    - Intrauterine growth restriction

- **Risk Stratification of Heart Disease in Pregnancy**
  - ***New York Heart Association (NYHA) classification:***
    - NYHA class specifications:
      - Class I = *no signs or symptoms of cardiac decompensation*
      - Class II = *No symptoms at rest, minor limitation of physical activity*
      - Class III = *No symptoms at rest, marked limitation of physical activity*
      - Class IV = *Symptoms present at rest*
    - In general:
      - Class I & II are low risk
      - Class III & IV are high risk
  - ***Other factors augmenting risk:***
    - Type of valve defect (*stenotic worse than regurgitant*)
    - Presence of pulmonary hypertension
    - Poor left-ventricular ejection fraction (<40%)
    - Marfan's syndrome
    - Presence of prosthetic valves
    - History of cardiac event or arrhythmia

- **Management of Heart Disease in Pregnancy**
  - ***Prenatal management:***
    - Ideally, patients should be assessed & worked up thoroughly & counseled on the risks of pregnancy before conception
  - ***Antenatal management:***
    - Multidisciplinary management (*including cardiologist*) with frequent antenatal visits ± admissions
    - General measures:
      - Avoid excessive weight gain & edema (*low salt diet, regular left-lateral decubitus position for >1 hour each day to promote venous return from lower extremities & subsequent diuresis*)
      - Avoid strenuous activity
      - Avoid anemia
    - Pharmacological management:
      - Loop diuretics ± β-blockers if sodium restriction is inadequate in preventing excessive fluid retention
      - Patients requiring anticoagulation should be on full anticoagulation using heparin, with warfarin reinstituted post-partum
  - ***Intrapartum management:***
    - Vaginal delivery is preferable unless indications for caesarian delivery are present
    - General considerations:
      - Patient should be placed in left lateral position to minimize compression of major vessels by the gravid uterus
      - Adequate analgesia should be ensured to minimize excessive strain on cardiac function brought on by pain
      - Pushing should be avoided in the 2nd stage of labour (*consider assisted vaginal delivery*)
      - Ergometrine should be <u>avoided</u> in the 3rd stage of labour due to its side effect of raised BP
      - Antibiotic prophylaxis is <u>not</u> indicated for delivery alone, but should be given if patient is high-risk (*prosthetic valves, unrepaired or incompletely repaired congenital heart defects*) & bacteremia is suspected (*e.g. chorioamnionitis*)
    - Acute decompensation of heart failure:
      - Managed as a medical emergency
      - Medical therapy instituted (*oxygen, morphine, vasodilators [nitroglycerin, hydralazine], inotropic support [dopamine, dobutamine]*)

Anemia in Pregnancy

- **Relevance of Anemia in Pregnancy**
  - Physiological anemia occurs during pregnancy due to hemodilution from greater increase in plasma volume than in red blood cell mass
    - Normal Hb levels during pregnancy ~ 12-16g/dL
    - Lower levels (<11g/dL) suggests an underlying pathological cause of anemia requiring work-up
  - Untreated anemia can have adverse pregnancy outcomes:
    - Maternal risks:
      - High-output cardiac failure
    - Fetal risks:
      - Uteroplacental insufficiency, leading to IUGR, intrauterine fetal demise, preterm labour etc
  - Maternal anemia may be due to a hereditary cause, with implications for the fetus
    - Locally, thalassemia is of the greatest relevance

- **Screening for Anemia**
  - ***Booking visit:***
    - Baseline FBC is performed as a basic screening tool for previously undetected anemia
    - If anemia is detected, further investigations are required to determine the cause of the anemia & to determine if there is undiagnosed thalassemia in the mother (*has implications for genetic testing; see below*)
  - ***During episodes of antepartum hemorrhage:***
    - FBC done at presentation to screen for anemia as a possible complication of antepartum hemorrhage
  - ***Peripartum:***
    - FBC can be done to screen for anemia, especially in cases where blood loss is expected to be excessive (*caesarian deliveries, maternal anticoagulation, placenta praevia, placental abruption etc*)

- **Thalassemia Work-up**
  (*if anemia is picked up at booking visit, thalassemia work-up is indicated to determine risk of thalassemia in the child*)
  - ***Maternal blood investigations:***
    - Full blood count (*Hb, MCV*)
      - Can use **Mentzer index** (MCV/RBC count) to help differentiate between iron-deficiency anemia & thalassemia (*<13 suggests thalassemia*)
    - Iron panel (*iron, ferritin, transferrin, TIBC*)
    - Peripheral blood film
      - Microcytic hypochromic RBCs, target cells (*these findings are seen in thal but are not specific*)
      - HbH inclusion bodies (*seen using Brilliant Cresyl Blue stain*) are indicative of α-thal
    - Hb electrophoresis
      - Much higher yield for β-thal (*decreased HbA, increased HbA2 & HbF*)
    - Genetic testing
      - Definitive diagnosis can be made
  - ***Paternal screening:***
    - Indicated if mother is found to have thalassemia to determine if father has thalassemia as well (*affects risk of fetus having serious forms of thalassemia such as thal-major, HbH disease or Barts hydrops*)
  - ***Prenatal diagnosis:***
    - Decision to perform prenatal diagnosis depends on:
      - Calculated risk based on results from maternal & paternal screening for thalassemia
      - Whether knowledge makes a difference to the couple (*decision to abort or make plans in advance*)
    - Options: chorionic villus sampling, amniocentesis

- **Management of Anemia**
  - ***Management of anemia in pregnancy is etiology-specific***
    - Remember that anemia is <u>not</u> a diagnosis in itself, & an underlying cause has to be sought
  - ***Options for management of iron-deficiency anemia:***
    - Haematinics (oral supplementation)
      - Iron gluconate (Sangobion), iron fumarate
      - 1st-line option for prophylaxis against anemia & for treatment of mild, stable cases
      - Side-effect: *constipation, black stools*
    - Parenteral iron
      - IV iron dextrin, IM iron sorbitol
      - Quicker onset of therapeutic action than oral iron, doesn't require patient compliance
      - Reserved for more serious cases of anemia requiring more urgent normalization of hemoglobin levels (*e.g. planned caesarian soon*)
      - Side-effect: *pain, skin discolouration, anaphylaxis*
    - Blood transfusion
      - Last-resort for serious cases requiring normalization of hemoglobin levels quickly (*Hb<7g/dL, symptomatic anemia etc*)

Venous Thromboembolism in Pregnancy

- **Superficial Thrombophlebitis**
  - ***Clinical features:***
    - Usually seen in patients with varicose veins, obesity &/or limited physical activity
    - Usually affects the calf area:
      - Swelling, erythema, warmth, tenderness
      - Palpable cord
  - ***Management:***
    - Symptomatic (*bed rest, pain medications*)
    - Wear support hose to prevent recurrences

- **Deep Vein Thrombosis & Pulmonary Embolism**
  - ***Clinical features:***
    - Some cases may be asymptomatic
    - Symptomatic presentations:
      - DVT: dull ache, tightness, pain; **Homans' sign** (*pain on passive dorsiflexion of the ankle*)
      - PE: SOB, cough, chest pain, tachycardia
  - ***Diagnosis & evaluation:***
    - Deep vein thrombosis:
      - Compression ultrasonography with Doppler flow studies is primary investigation of choice
      - MRI may be considered in cases where iliac vein thrombosis is suspected
    - Pulmonary embolism:
      - Baseline investigations (*chest x-ray, ECG*)
      - Diagnostic investigations (*CTPA, ventilation-perfusion scan, pulmonary angiography*)
  - ***Management:***
    - Anticoagulation using unfractionated heparin or low molecular weight heparin
      - Continued until at least 6 weeks post-partum
      - Monitor aPTT if heparin is used; no monitoring required for LMWH (*factor Xa is used for monitoring but not practical*)
      - Side-effects: *heparin-induced thrombocytopenia (monitor platelet count), osteoporosis (consider calcium & vitamin D)*
    - Switch to warfarin if need for long-term anticoagulation is determined post-partum
    - Consider prophylactic anticoagulation (*with UFH or LMWH*) in future pregnancies

Autoimmune Disorders

- **Rheumatoid Arthritis**
  - ***Effect of pregnancy on RA:***
    - RA usually improves during pregnancy
  - ***Effect of RA on pregnancy:***
    - No significant effects on both mother & fetus
    - Some medications for RA have teratogenic effects
  - ***Transplacental transfer of antibodies:***
    - None

- **Idiopathic Thrombocytopenic Purpura**
  - ***Effect of pregnancy on ITP:***
    - No significant effect
  - ***Effect of ITP on pregnancy:***
    - Increases risk of maternal antepartum, intrapartum & postpartum hemorrhage
      - Treatment not initiated unless plt <40000
      - Options: *steroids, IVIG, splenectomy*
    - Neonatal thrombocytopenia may occur, leading to neonatal intracranial hemorrhage in rare cases
      - Monitor neonatal platelet counts
  - ***Transplacental transfer of antibodies:***
    - Anti-platelet antibodies

- **Graves' Disease**
  - ***Effect of pregnancy on Graves' disease:***
    - Graves' disease usually improves during pregnancy
    - May experience postpartum exacerbation
  - ***Effect of Graves' disease on pregnancy:***
    - If thyrotoxicosis is not well-controlled, may have increased risk of preterm labour, IUGR, preeclampsia, intrauterine fetal demise
    - 1% risk of neonatal thyrotoxicosis
  - ***Transplacental transfer of antibodies:***
    - Thyroid stimulating immunoglobulins

- **Myasthenia Gravis**
  - ***Effect of pregnancy on myasthenia gravis:***
    - Pregnancy has variable effects on myasthenia gravis
    - Moderate exacerbation postpartum
  - ***Effect of myasthenia gravis on pregnancy:***
    - May have transient neonatal myasthenia
  - ***Transplacental transfer of antibodies:***
    - Acetylcholine receptor antibodies

- **Systemic Lupus Erythematosus**
  - ***Effect of pregnancy on SLE:***
    - 1/3 improves, 1/3 same, 1/3 worsens in pregnancy
  - ***Effect of SLE on pregnancy:***
    - Increased risk of miscarriage, preterm labour, IUGR, preeclampsia, intrauterine fetal demise
    - 10% risk of neonatal lupus (*skin lesions, hematologic manifestations, congenital heart block, endomyocardial fibrosis*)
  - ***Transplacental transfer of antibodies:***
    - Anti-Ro (SS-A)
    - Anti-La (SS-B)

Seizure Disorders

- **Effect of Pregnancy on Seizure Disorders**
  - Pregnancy itself does not usually alter seizure frequency
  - Pregnancy-related factors may affect plasma levels of antiepileptic drugs (AED), resulting in breakthrough seizures & increased seizure frequency:
    - Nausea & vomiting affecting GI absorption of AED
    - Increased intravascular volume resulting in larger volume of distribution of AED
    - Induction of hepatic enzymes metabolizing AED
    - Increased glomerular filtration rate increasing renal excretion of AED

- **Risks of Seizures in Pregnancy**
  - ***Obstetric events & complications (due to seizures):***
    - Preeclampsia
    - Abruptio placentae
    - IUGR or intrauterine fetal demise
  - ***Fetal congenital anomalies (due to AED use):***
    - Neural tube defects are especially associated with AED use in pregnancy; requires higher-dose folic acid supplementation than normal pregnancies
    - Overall risk for major malformations with AED use in pregnancy is 4-6% (*higher than women without epilepsy & women with epilepsy not on AED*)

- **Management of Seizure Disorders in Pregnancy**
  - ***Anti-epileptic drug treatment:***
    - If no seizure activity for ≥2 years, can consider stopping AED before conception
    - For patients requiring AED maintenance:
      - Stick with existing AED if it has been effective
      - Aim for monotherapy with lowest possible dose needed
      - No ideal AED as all are teratogenic to varying extents (*but valproate is especially teratogenic & should be avoided where possible*)
      - Should be maintained throughout pregnancy, intrapartum & postpartum
  - ***Supplementation:***
    - Folic acid supplementation
      - Indicated for use of all AEDs
      - To minimize risk of neural tube defects
      - Dosage: *1mg/day if on most AEDs; 4mg/day if on carbamazepine or valproate*
    - Vitamin K supplementation
      - Indicated for use of enzyme-inducing AEDs (*carbamazepine, phenytoin, phenobarbitone, topiramate, oxcarbazepine*)
      - Dosage: *10mg/day in the last month of pregnancy*
    - Vitamin D supplementation
      - Indicated for use of AEDs which interfere with intestinal absorption of calcium (*phenytoin, phenobarbitone, primidone*)
      - Begin taking from 34 weeks gestation
  - ***Status epilepticus management:***
    - Resuscitate & stabilize
    - IV diazepam or lorazepam ± phenytoin infusion ± phenobarbitone
    - Check plasma AED levels
    - Monitoring fetal well-being
    - Admit patient

Infectious Diseases in Pregnancy

Human Immunodeficiency Virus (HIV)

- **Etiology & Transmission**
  - ***Caused by the human immunodeficiency virus (HIV)***
    - Retrovirus, RNA genome
    - Infects & replicates within T4 helper lymphocytes, macrophages & other cells in the hematopoietic system & central nervous system
    - Viral antigens:
      - Surface proteins gp120, gp41
      - Core proteins p24, p18
  - ***Transmission:***
    - Sexual contact, blood
    - Vertical transmission:
      - Risk of transmission is 20-30%
      - 50% of transmission occurs peripartum
      - Antenatal transmission risk may theoretically be increased by invasive procedures (*e.g. amniocentesis*) but exact risk is unknown
      - Postpartum transmission by breastfeeding has risk of 10-20%

- **Clinical Features**
  - ***Maternal features:***
    - Chronic progressive course of disease after infection
      - Seroconversion usually occurs 3-14 weeks after exposure, but may take up to 6 months; this phase is marked by a mononucleosis-like syndrome (*flu, cervical lymphadenopathy, rash*)
      - An asymptomatic period then follows, during which T-cell count gradually drops
      - Eventually, more generalized symptoms set in (*generalized lymphadenopathy, constitutional symptoms*)
      - Opportunistic infections gradually set in
      - Average duration interval from initial infection to full-blown AIDS is 10 years in untreated cases
    - Pregnancy does not affect the course of HIV
    - HIV in pregnancy increases the risk of infections during pregnancy
  - ***Fetal features:***
    - HIV has no significant antenatal effects
    - Disease progression in children after birth is much faster than in adults
      - 50% develop full blown AIDS within 1st year of life, 80% by 3rd year of life
      - Average survival time for diagnosis = 3 years

- **Diagnosis & Evaluation**
  - ***Screening for HIV in pregnancy:***
    - Offered to all women presenting at booking visit
  - ***Diagnostic tests for maternal infection:***
    - Enzyme-linked immunosorbent assay (ELISA)
      - Detects HIV antibodies or p24 antigen
      - 93-99% sensitive; 99% specific
    - Western blot
      - Detects HIV core & surface antigens
      - 99% sensitive, 98.5 specific
    - HIV PCR, HIV tissue culture

- **Management**
  - ***Antiretroviral therapy:***
    - Antenatal antiretroviral therapy shown to decrease the rates of vertical transmission significantly:
      - Pediatric AIDs Clinical Trial 079 in 1994 demonstrated that use of zidovudine to mother antenatally & to infant for 6 weeks postpartum reduced maternal transmission of HIV from 25.5% to 8.3%
      - More potent antiretroviral therapies currently have been shown to reduce risk to 1-2%
    - Principles of antiretroviral therapy in pregnancy:
      - Multiple agents to minimize risk of resistance
      - All regimes should include zidovudine unless it is contraindicated
    - Classes of antiretroviral drugs:
      - Nucleoside reverse transcriptase inhibitors (NRTIs): *zidovudine, lamivudine*
      - Non-nucleoside reverse transcriptase inhibitors (NNRTIs): *efavirenz, nevirapine*
      - Protease inhibitors (PIs): *saquinavir, indinavir, lopinavir, ritonavir*
    - Monitoring while on antiretroviral drugs:
      - NRTIs & NNRTIs: *liver enzymes, renal function*
      - PIs: *OGTT at 28 weeks to screen for GDM*
      - Monitor maternal plasma HIV RNA concentration to determine effectiveness of treatment (target <1000 copies/mm)
  - ***Antibiotic prophylaxis:***
    - Offered when mother is significantly immunocompromised (CD4 T-cell <200/µL)
    - Organisms to target include:
      - Pneumocystis carinii
      - Mycobacterium avium complex
  - ***Intrapartum management:***
    - Mode of delivery:
      - Offer elective caesarian at 38 weeks if maternal plasma HIV RNA >1000 copies/mm
      - Offer normal vaginal delivery if maternal plasma HIV RNA <1000 copies/mm (*transmission risk is very low, 1-2%)*
    - Avoid intrapartum measures which increase the risk of HIV transmission to the fetus:
      - Artificial rupture of membranes
      - Fetal scalp electrodes
      - Fetal scalp blood sampling
      - Assisted vaginal delivery
      - Episiotomy
    - For vaginal delivery, once membranes have ruptured, augment with oxytocin to reduce the interval between membrane rupture & delivery
  - ***Postpartum management:***
    - Neonate should continue to receive antiretroviral treatment for the first few weeks of life
    - Avoid breastfeeding to mitigate transmission risk
    - Confirmation of HIV status in neonate:
      - Done using Western blot, PCR or culture (*serological methods not accurate initially due to false positive results from maternal antibodies*)
      - At least 2 positive results using 2 different tests should be obtained before confirming neonatal HIV infection
      - At least 2 negative results, at least 1 done after 6 months of life, should be obtained to predict absence of neonatal HIV infection (*confirmation is by demonstrating absence of HIV antibodies at 15 months of age*)

Rubella (German Measles)

- **Etiology & Transmission**
  - ***Caused by the Rubella virus:***
    - Togavirus, RNA genome
  - ***Transmission:***
    - Respiratory route
    - Vertical transmission:
      - Risk of congenital rubella syndrome is primarily dependent on the time of pregnancy during which maternal infection occurs
      - 80% risk if infection occurred in the 1st trimester, drops to 30-50% thereafter
      - Congenital rubella syndrome rarely occurs if infection occurs after 20 weeks gestation

- **Clinical Features**
  - ***Maternal features:***
    - Incubation period of 14-21 days
    - Prodromal flu-like illness
    - Maculopapular rash
  - ***Fetal features:***
    - Fetus may be entirely unaffected by rubella
    - Affected fetuses manifest the congenital rubella syndrome to varying extents:
      - Symmetrical IUGR
      - Congenital deafness
      - Cataracts, retinopathy, microphthalmia
      - PDA, pulmonary artery hypoplasia
      - Hepatosplenomegaly
      - Microcephaly, panencephalitis, intra-cranial calcifications
      - Thrombocytopenic purpura (*classical blueberry muffin rash*)

- **Diagnosis & Evaluation**
  - ***Screening for rubella in pregnancy:***
    - Rubella screening is not routinely performed locally (*as rubella vaccination as part of MMR is part of the national immunization schedule*)
    - For patients unsure of immune status (*e.g. foreign*), can offer to test for rubella IgG antibodies to determine immune status at booking visit
  - ***Diagnostic tests for maternal infection:***
    - Serologic testing:
      - Demonstrate presence of rubella IgM antibody
      - Demonstrate 4-fold rise in paired titres of rubella antibodies taken 2 weeks apart
    - Culture & isolation

- **Management**
  - ***No specific treatment for rubella available:***
    - Rubella in the adult (*in the mother in this case*) is usually a transient illness without significant complications or long-term sequelae
  - ***Rubella immunization***
    - Offered to non-immune mother post-partum (*live-attenuated viral vaccine, hence cannot be given during pregnancy*)

Cytomegalovirus (CMV)

- **Etiology & Transmission**
  - ***Caused by cytomegalovirus***
    - Herpesvirus family (HHV5), DNA genome
    - Extremely prevalent within the population
  - ***Transmission:***
    - Blood, sexual contact, urine, saliva
    - Vertical transmission:
      - May be transmitted transplacentally or at delivery via direct contact
      - 40-50% transmission rate if mother has an acute infection during pregnancy
      - 0.15-1% transmission rate if mother has a reactivation of CMV infection during pregnancy

- **Clinical Features**
  - ***Maternal features:***
    - Commonly asymptomatic
    - Symptomatic presentation resembles a mononucleosis-like illness
    - Virus usually establishes latency after acute infection & may reactivate years later
  - ***Fetal features:***
    - May be symptomatic at birth (10-15%)
      - Non-immune hydrops
      - Symmetrical IUGR
      - Chorioretinitis
      - Hepatosplenomegaly
      - Microcephaly, cerebral calcifications, hydrocephalus
    - May only manifest features later in life (80-90%)
      - Visual impairment
      - Progressive hearing loss
      - Delayed psychomotor development
      - Mental retardation

- **Diagnosis & Evaluation**
  - ***Screening for CMV in pregnancy:***
    - Not routinely performed
  - ***Diagnostic tests for maternal infection:***
    - Serologic testing:
      - Demonstrate CMV IgM antibody (*peaks at 3-6 months after infection, resolves by 1-2 years; prolonged elevation of IgM levels makes delineation of timing of infection difficult*)
    - Culture (*from urine or other bodily secretions*)
  - ***Diagnostic tests for fetal infection:***
    - Ultrasound
      - Look for associated fetal anomalies
    - CMV PCR
      - Done on amniocentesis sample
      - Offered if ultrasound is inconclusive & definitive diagnosis is desired (*affects choice of management option*)

- **Management**
  - ***If ultrasound shows signs of fetal abnormalities or CMV PCR for CMV is positive:***
    - Can offer hyperimmune anti-CMV globulin
    - Advise patient on option of termination of pregnancy

Varicella-Zoster Virus (VZV)

- **Etiology & Transmission**
  - ***Caused by varicella-zoster virus***
    - Herpesvirus family (HHV3), DNA genome
    - Acute infection causes varicella (chickenpox) whereas reactivation causes zoster (shingles)
      - Zoster does not pose significant risks to mother or child, hence will not be discussed
  - ***Transmission:***
    - Direct contact with vesicular fluid, respiratory route
    - Vertical transmission:
      - Transplacental transmission of varicella results in one of two possible fetal/neonatal outcomes if at all: (i) congenital varicella syndrome (ii) neonatal varicella
      - Risk of congenital varicella syndrome if:
        <13 weeks gestation = 0.4%
        13-20 gestation weeks = 2%
        >20 weeks gestation = extremely rare

- **Clinical Features**
  - ***Maternal features:***
    - Incubation period of 10-21 days
    - Primary feature of varicella is a systemic rash:
      - Polymorphous in nature (*maculopapular → vesicular → crusted*), with rashes of different stages seen at the same time
      - Usually affects the trunk > extremities
    - Complications of varicella (*more commonly seen in adults than children*)
      - Encephalitis, aseptic meningitis
      - Pneumonitis (*complicates 16% of cases, with a mortality rate of up to 40%*)
  - ***Fetal features:***
    - Congenital varicella syndrome
      - Symmetrical IUGR
      - Limb hypoplasia
      - Cutaneous scars
      - Chorioretinitis, cataracts
      - Cortical atrophy, microcephaly
    - Neonatal varicella
      - Mild illness if maternal infection occurred 5 to 21 days prior to delivery (*transplacental transfer of maternal antibodies would have occurred, which confers effective protection for the neonate*)
      - Fulminant varicella infection if maternal infection occurred between 5 days prior to delivery & 2 days after delivery (*transplacental transfer of maternal antibodies would not have occurred*)

- **Diagnosis & Evaluation**
  - ***Diagnostic tests for maternal infection:***
    - Serologic testing:
      - Demonstrate VZV IgM antibody
      - Demonstrate rise in paired VZV IgG titres taken 2 weeks apart
    - Culture (*from vesicular fluid*)

- **Management**
  - ***Management of mother:***
    - Symptomatic management in uncomplicated cases
    - Chest x-ray should be done to rule out varicella Pneumonitis (*if suspected, need admission for close monitoring& antiviral therapy*)
  - ***Management of fetus/neonate:***
    - Decision to treat depends on:
      - Immunity of mother after exposure (*if immune status unknown, offer IgG testing; if mother has acute varicella, confirms lack of immunity*)
      - Time of exposure/infection
    - Immune mother with exposure at any time:
      - No treatment required
    - Non-immune mother with exposure/infection occurring between 13 & 20 weeks gestation:
      - Offer IV VZIG to patient (*best given within 6 days of exposure*)
      - Role of antiviral treatment is not established
      - Can do serial ultrasounds to monitor for signs of fetal anomaly (*but no reliable method of prenatal diagnosis for congenital varicella syndrome is currently available*) & counsel on option of termination of pregnancy where indicated
    - Non-immune mother with exposure/infection occurring before 13 weeks <u>or</u> after 20 weeks:
      - Counsel mother on the extremely small risk of the fetus being affected
      - IV VZIG can still be offered to patient if patient still decides to have it
    - Non-immune mother with exposure/infection occurring between 5 & 21 days prior to delivery:
      - Counsel mother that neonate is immune due to transplacental transfer of maternal antibodies, hence no need for treatment
    - Non-immune mother with exposure/infection occurring between 5 days prior to delivery & 2 days after delivery:
      - Administer IV VZIG to neonate
      - Place neonate in contact isolation

Herpes Simplex Virus (HSV)

- **Etiology & Transmission**
  - ***Caused by herpes simplex virus***
    - Herpesvirus family (HHV1 & 2), DNA genome
    - 2 serotypes (HSV-1 & HSV-2)
  - ***Transmission:***
    - Intimate mucocutaneous contact
    - Vertical transmission:
      - No congenital syndrome due to vertical transmission of herpes described
      - Neonatal herpes can occur due to intrauterine (5%), peripartum (85%) or postnatal (10%) transmission

- **Clinical Features**
  - ***Maternal features:***
    - Primary genital herpes
    - Recurrent genital herpes
      See "Reproductive Tract Infections"
  - ***Fetal features:***
    - Maternal primary genital herpes is associated with an increased risk of miscarriage, IUGR & preterm labour (*minimal risk for recurrent genital herpes*)
    - Neonatal herpes
      - Especially high risk if active genital herpetic lesions (*either primary or recurrent*) are present during normal vaginal delivery
      - Symptoms usually present on day 2-3 of life
      - 3 main manifestations:
        (i) Disseminated disease
        (ii) CNS disease with encephalitis
        (iii) Skin, eye or mouth infection with localized involvement
      - Even with treatment, 30-50% of disseminated disease die; 2/3 of survivors have long-term neurologic sequelae (*microcephaly, mental retardation, seizures, microphthalmos*)

- **Management**
  - ***Antenatal treatment:***
    - Antenatal prophylactic antiviral therapy (*acyclovir, valacyclovir*) from 36 weeks gestation until delivery
      - Decreases asymptomatic shedding of virus
      - Decreases herpes outbreak at delivery
      - Decreases need for caesarian delivery
    - For patients with active genital herpetic lesions at the time of labour, should be delivered via caesarian section
  - ***Treatment of neonates with suspected neonatal herpes:***
    - IV acyclovir

Hepatitis B Virus (HBV)

- **Etiology & Transmission**
  - ***Caused by hepatitis B virus***
    - Hepadnavirus, DNA genome
  - ***Transmission:***
    - Blood, sexual contact
    - Vertical transmission:
      - Mostly occurs peripartum (*hence effectiveness of postpartum passive & active immunization of neonate remains very high*)

- **Clinical Features**
  - ***Maternal features:***
    - Chronic asymptomatic carrier state
    - Chronic hepatitis B
    - Hepatitis B cirrhosis
  - ***Fetal features:***
    - Effects on pregnancy depends on maternal condition:
      - Chronic carriage has no effect on pregnancy
      - Chronic hepatitis B is associated with an increased risk of preterm labour, low birth weight & neonatal death
      - Hepatitis B cirrhosis carries very poor prognosis for both mother & pregnancy
    - Acute hepatitis B at birth
      - 10% risk if mother is only HBsAg+; 70-90% risk if mother if HBsAg+ & HBeAg+
      - Acute hepatitis B in the neonate may be fulminant & lethal
    - Chronic asymptomatic carriage
      - Can occur without clinical acute infection or following acute hepatitis B at birth
      - Much higher risk of chronic carriage in vertical transmission as compared to adults who are infected by hepatitis B virus

- **Diagnosis & Evaluation**
  - ***Screening for hepatitis B in pregnancy:***
    - Offered to all women at booking visit
      - Test for HBsAg & anti-HBS antibody

- **Management**
  - ***For non-immune & uninfected mother:***
    - Offer vaccination (*vaccine is safe for use in pregnancy*)
  - ***For chronic infection in mother:***
    - Perform liver function tests & complete hepatitis panel (including HBeAg level determination)
    - Following delivery, administer hepatitis B immunization to neonate:
      - Passive immunization (HBIG)
      - Active immunization (hepatitis B vaccine at 0, 1 & 6 months)
    - Test for hepatitis B immune status of child at 9 months:
      - If immune, no further action
      - If not immune but not carrier, readminister full dose of vaccination (0, 1 & 6 months)
      - If not immune but carrier, refer for long-term follow-up with gastroenterology

Group B Streptococcus (GBS)

- **Etiology & Transmission**
  - ***Caused by group B streptococcus***
    - Gram positive cocci, β-hemolytic streptococcus
    - Considered part of the normal flora of humans
      - Gastrointestinal tract is the major reservoir
      - Can also be found in vagina, cervix, throat, skin, urethra & urine of healthy individuals
  - ***Transmission:***
    - Faecal contamination or sexual transmission from a colonized partner
    - Vertical transmission:
      - Occurs during delivery in women with GBS colonization in the lower reproductive tract
      - In absence of preventive efforts, 50% of neonates born to GBS-colonized mothers will develop GBS carriage as well, of which 2% will develop invasive disease (*see below*)

- **Clinical Features**
  - ***Maternal features:***
    - Typically asymptomatic
    - Colonization can be episodic/intermittent in nature, hence early & mid trimester cultures are inaccurate predictors of GBS carriage at term
  - ***Fetal features:***
    - GBS is the most common cause of early-onset (<72 hours postpartum) neonatal sepsis:
      - Neonatal sepsis
      - Neonatal meningitis
      - Neonatal pneumonia

- **Diagnosis & Evaluation**
  - Screening for GBS colonization in pregnancy:
    - Done using vaginal swab & culture
    - Screening for GBS carriage can be offered near term (35-37 weeks gestation)

- **Management**
  - ***Intrapartum antibiotic prophylaxis (IAP)***
    - IV antibiotic (penicillin or ampicillin) given during intrapartum period for cases with positive GBS carriage diagnosed or high risk cases
    - High risk cases:
      - Preterm labour
      - Prolonged rupture of membranes (>18 hours)
      - Maternal intrapartum fever (>38.0°C)
      - Previous child with invasive GBS disease
      - GBS bacteriuria in this current pregnancy
    - IAP is <u>not</u> indicated if:
      - Planned caesarian delivery without ruptured membranes
      - Risk factors present but GBS culture negative

Syphilis

- **Etiology & Transmission**
  - ***Caused by Treponema pallidum***
    - Spirochaete bacteria
  - ***Transmission:***
    - Sexually-transmitted infection
    - Vertical transmission
      - Occurs transplacentally at any gestational age
      - Risk of transmission is 50-80%

- **Clinical Features**
  - ***Maternal features:***
    - Primary syphilis
    - Secondary syphilis
    - Tertiary syphilis
      (*see "Reproductive Tract Infections"*)
  - ***Fetal features:***
    - Early congenital syphilis (*presents at birth*)
      - Nonimmune hydrops
      - Hepatosplenomegaly, hepatitis
      - Profound anemia, thrombocytopenia
      - Skin lesions
      - Osteitis, periostitis
      - Pneumonia
      - 50% perinatal mortality rate
    - Late congenital syphilis (*presents after 1-2 years*)
      - Hutchinson's teeth, mulberry molars
      - Sabre shins
      - Saddle nose deformity
      - Interstitial keratitis
      - Eighth nerve deafness
      - Failure to thrive

- **Diagnosis & Evaluation**
  - ***Screening for syphilis in pregnancy:***
    - Offered to all women at booking visit
    - 1st-line screening test would be a non-treponemal specific test (e.g. VDRL)
      - Has a false-positive rate of 0.5-14%
      - Hence diagnostic treponemal specific test is performed if screening test is positive
  - ***Diagnostic investigations for maternal infection:***
    - Non-treponemal specific tests:
      - Venereal disease research laboratory (VDRL)
      - Rapid plasma regain (RPR)
    - Treponemal-specific tests:
      - Fluorescent treponemal antibody absorption test (FTA-Abs)

- **Management**
  - ***Antibiotic treatment:***
    - Penicillin G is treatment of choice
      - 2.4 million units IM single dose for primary, secondary or latent syphilis of <12 months duration
      - Cases with >12 months duration require weekly IM penicillin G for 3 weeks
      - Neurosyphilis requires admission for prolonged IV penicillin therapy
    - Monitoring for effectiveness of treatment:
      - Monthly VDRL or RPR titres to observe a downward trend which would indicate successful treatment
      - FTA-Abs will remain positive for life after infection & hence cannot be used to monitor response to treatment

Toxoplasmosis

- **Etiology & Transmission**
  - ***Caused by Toxoplasma gondii***
    - Protozoa
  - ***Transmission:***
    - Ingestion of uncooked meat, drinking contaminated water, exposure to contaminated cat faeces, blood transfusion containing tachyzoites (rarely)
    - Vertical transmission:
      - Risk of vertical transmission increases with increasing gestational age:
        - 1st trimester risk = 15%
        - 2nd trimester risk = 25%
        - 3rd trimester risk = 65%
      - However, severity of fetal infection decreases with increasing gestational age (*congenital defects rarely seen if infected after 20 weeks*)

- **Clinical Features**
  - ***Maternal features:***
    - Most infections are asymptomatic
    - Symptomatic cases present as an infectious mononucleosis-like illness
  - ***Fetal features:***
    - Early congenital toxoplasmosis (*presents at birth*)
      - Chorioretinitis, microphthalmia
      - Hydrocephalus, cerebral calcifications, microcephaly
      - Delayed mental development, convulsions
      - Rash, lymphadenopathy
      - Anemia
      - Pneumonia
    - Late congenital toxoplasmosis (*presents later on*)
      - Visual impairment
      - Hearing loss
      - Delayed psychomotor development
      - Seizure disorders
      - Spasticity, palsies
      - Mental retardation

- **Diagnosis & Evaluation**
  - ***Screening for toxoplasmosis in pregnancy:***
    - Not routinely performed locally
  - ***Diagnostic investigations for maternal infection:***
    - Serologic tests:
      - Demonstrate toxoplasma IgM
  - ***Diagnostic investigations for fetal infection:***
    - Toxoplasma PCR
      - Done using amniocentesis sample
      - Offered to women with a confirmed diagnosis of primary toxoplasmosis at 18-20 weeks gestation

- **Management**
  - ***Treatment of toxoplasmosis:***
    - Toxoplasmosis is usually a self-limiting illness in adults, hence primary indication for treatment is to reduce fetal infection risk
    - Drug options:
      - Spiramycin (*given to diagnosed maternal infections without confirmed fetal infection*)
      - Pyrimethamine + sulphadiazine + folinic acid (*given in cases of confirmed fetal infection*)
    - Treatment of infected infants for 1st year of life is also recommended as many infected infants may appear asymptomatic at birth but develop morbidity later

Benign Conditions of the Vulva

Congenital Anomalies of the Vulva

- **Ambiguous Genitalia**
  - ***Possible presentations of ambiguous genitalia:***
    - Clitoromegaly; bifid clitoris
    - Midline fusion of the labioscrotal folds
  - ***Causes of ambiguous genitalia in females:***
    - **Genetic mosaicism**

      - Genetic mosaicism, with 2 or more cell populations present in an individual with different genetic make-up, specifically with respect to the sex chromosomes in this context
      - Commonly 45XO/46XY
      - Results in varying degrees of virilization & Müllerian development
      - Gonads are dysgenetic & should be located & surgically removed prophylactically due to significant risk of eventual neoplastic transformation (*gonadoblastoma, dysgerminoma*)
    - **Partial androgen insensitivity syndrome**

      - An incomplete form of the androgen insensitivity syndrome, in which a genotypic male (46XY) is phenotypically female due to a genetic deficiency (usually X-linked recessive) in the androgen receptors
      - In the complete form, testes are usually undescended, the external genitalia is phenotypically normal female due to lack of testosterone effect & no internal genitalia is present (*Müllerian inhibiting factor secreted normally causing Müllerian duct involution; lack of testosterone effect causes Wolffian duct involution*)
      - In the partial form, varying degrees of responsiveness to testosterone results in incomplete virilization of the external genitalia
      - In either case, testes should be located & removed due to significant risk of malignant transformation in undescended testes
    - **Congenital adrenal hyperplasia (CAH)**

      - A group of autosomal recessive disorders involving enzyme deficiencies in the production of steroidal hormones (*cortisol & aldosterone*)
      - Most common: *21-hydroxylase*
      - Others: *11β-hydroxylase, 17a-hydroxylase, aldosterone synthetase, 20,22-desmolase*
      - Different mutations in the same gene can result in a spectrum of phenotypes – clinically unapparent, mild form which only presents in adolescence or adulthood (*late-onset CAH*) or severe disease that results in adrenal insufficiency in infancy
      - Enzyme deficiencies can cause build-up of upstream intermediate precursors of cortisol &/or aldosterone which then get shunted towards the production of adrenal androgens
      - Hyperandrogenism in turn causes virilization of the external genitalia (*severe forms present at birth; mild forms may cause signs & symptoms of virilization in adolescence & adulthood*)
    - **Androgen-producing tumour; exogenous androgen**

Lumps & Bumps of the Vulva

- **Fox-Fordyce Disease**
  - Series of pruritic, raised, yellowish retention cysts; often inflamed; resulting from keratin-plugged apocrine glands
  - Can occur in the labia, mons or axilla
- **Galactocele**
  - Milk-containing cysts which can form anywhere along the milk line which extends from the axilla to the vulva
  - Usually seen in pregnant & post-partum women
- **Vulvar Varicosity**
  - Dilated vulvar veins; can enlarge & become clinically apparent (e.g. in pregnancy)
  - Causes discomfort & carries risk of rupture or thrombosis
- **Urethral Caruncle**
  - Small fleshy red painful growths at distal edge of urethra
  - Seen in extremes of age:
    - Children: *spontaneous prolapse of urethral epithelium*
    - Post-menopausal women: *due to hypoestrogenic vaginal epithelium contracting; everts urethral epithelium*
- **Vulvar Vestibulitis (Vulvar Adenitis)**
  - Multiple small (1-4mm) erythematous dots in the vestibule which are exceedingly tender when touched
  - Due to non-infectious inflammation of the minor vestibular glands
  - Clinically: severe introital dyspareunia & vulvar pain
  - Management options:
    - Topical estrogen cream
    - Topical corticosteroids
    - Surgical excision of affected glandular area
- **Other Common Cutaneous Lumps & Bumps**
  - Sebaceous cyst, lipoma, fibroma, neurofibroma

Traumatic Lesions of the Vulva

- **Blunt Trauma to the Vulva**
  - Commonly results from saddle injuries, motor vehicle accidents or sexual assault
  - Results in vulvar bruising, lacerations or hematomas
  - Hematomas should be monitored closely & managed with surgical exploration & drainage (*as blood loss can be extensive, tracking deep into large potential spaces such as the ischiorectal fossae*)
- **Female Genital Mutilation (Female Circumcision)**
  - Continues to be a common practice in certain countries
  - WHO classification of female genital mutilation (2008):
    - Type I: *partial or total removal of the clitoris &/or prepuce (clitoridectomy)*
    - Type II: *partial or total removal of the clitoris & labia minora, with or without excision of the labia majora*
    - Type III: *narrowing of the vaginal orifice with creation of a covering seal by cutting & appositioning the labia minora &/or the labia majora, with or without excision of the clitoris (infibulation)*
    - Type IV: *all other harmful procedures to the female genitalia for nonmedical purposes*

Epithelial Conditions of the Vulva

- **Lichen Simplex Chronicus**
  - Squamous cell hyperplasia which results from a prolonged itch-scratch cycle
  - Clinically: *pruritus & pain; examination reveals a white or reddish, thickened, leathery & raised surface*
  - Histologically: *thick keratin layer (hyperkeratosis) with deepened rete ridges & a dense infiltrate of chronic inflammatory cells in the superficial dermis*
  - Treatment:
    - Moderate-strength steroid ointments
    - Anti-pruritic agents

- **Lichen Sclerosis**
  - Idiopathic epithelial condition more commonly presenting in the elderly; can involve any body part, but usually found on the vulva of the menopausal woman
  - Clinically: *intense pruritus, burning pain & dyspareunia; examination reveals skin that is thin, inelastic, white & crinkled (tissue paper appearance)*
  - Histologically: *thin epithelium with loss of rete ridges & inflammatory cells lining the basement membrane*
  - Long-term sequelae if left untreated:
    - Labia minora lost, labia majora flattened, introitus severely constricted, clitoris inverted & trapped
    - Development of vulvar intraepithelial neoplasia (VIN) & eventual vulvar cancer
  - Treatment:
    - Potent topical steroids (0.05% clobetasol)
    - Topical emollients

- **Vulvar Involvement in Other Systemic Disorders**
  - ***Lichen planus***
    - Presents as purplish polygonal papules that may appear in erosive forms
    - May involve vulva, vagina & mouth (**vulvar-vaginal-gingival syndrome**)
  - ***Psoriasis***
    - Appears velvety on the vulva, often without the usual scaly patches seen in other affected areas
  - ***Pemphigus***
    - Autoimmune blistering condition that can involve the vulvovaginal & conjunctival areas
  - ***Behçet's disease***
    - Classically involves ulcers of the genitalia & oral cavity with superficial ocular lesions
  - ***Crohn disease***
    - Vulvar ulcers can occur as an extra-gastrointestinal manifestation of Crohn disease
    - Draining sinuses to the rectum may also occur

Benign Conditions of the Vagina

Congenital Anomalies of the Vagina

- **Canalization Defects of the Vagina**
  - ***Imperforate hymen***
    - Occurs at the site where the vaginal plate contacts the urogenital sinus
    - Presents with primary amenorrhea associated with cyclical pelvic pain (*due to menstrual blood pooling up proximal to the imperforate hymen*)
    - Hematocolpos results (*old blood within vagina*)
    - Treatment: **cruciate incision** of hymen
  - ***Transverse vaginal septum***
    - Similar anomaly as imperforate hymen
    - Usually found at the junction between the upper & middle thirds of the vagina
  - ***Vaginal atresia***
    - Represents a more substantial lack of canalization at either the cranial or caudal end of the vaginal plate
    - Cranially-placed vaginal atresia usually also have an absent cervix but with normal uterus & fallopian tubes present
  - ***Double vagina (longitudinal vaginal septum)***
    - Many variants:
      - Septum may be partially present at various levels in the upper & middle vagina or throughout
      - Septum may be midline or deviated to a side
      - Septum may deviate & attach to the lateral vaginal wall, creating a blind vaginal pouch
    - May be associated with duplication anomalies of the upper tract

- **Vaginal Agenesis**
  - Most extreme form of congenital vaginal anomalies
    - Total absence of the vagina except for the most distal portion that is embryologically derived from the urogenital sinus
  - May occur in isolation (rare) or in association with congenital absence of the uterus & underdevelopment of the fallopian tubes – Müllerian agenesis (**Rokitansky-Küster-Hauser syndrome**)

- **Adenosis of the Vaginal Wall**
  - Islands of columnar epithelium in the normal squamous epithelium of the vagina
  - Often in the upper third
  - One of many associations of **in-utero exposure to diethylstilbestrol (DES)**:
    - Vaginal adenosis
    - Structural anomalies of the cervix & vagina
      - Transverse vaginal septum
      - Cervical collar
      - Cockscomb (*raised ridge on anterior cervix*)
      - Cervical hypoplasia
    - Structural anomalies of the uterus
      - T-shaped uterus with small uterine cavity
    - Clear cell adenocarcinoma of the vagina

- **Gartner's Duct Cyst**
  - Most common dysontogenic cyst of the vagina (thick-walled soft cysts resulting from embryonic remnants)
  - Arises from remnant of the mesonephros (Wolffian duct)
  - 1-5cm in size, found in the anterolateral walls of the upper vagina & more laterally in the lower vagina

Lumps & Bumps of the Vagina

- **Urethral Diverticula**
  - Small (0.3-3cm) sac-like projections found in the anterior vagina along the course of the urethra
  - Clinically: *recurrent urinary tract infections, dysuria, dyspareunia, urinary dribbling*
  - Treatment:
    - Urethral dilation
    - Surgical excision

- **Vaginal Inclusion Cysts**
  - Common lesions resulting from the infolding of vaginal epithelium, usually located in the posterior or lateral wall of the lower third of the vagina
  - Most commonly associated with lacerations from childbirth or gynaecologic surgery

- **Bartholin's Cyst**
  - Cyst arising from the Bartholin's glands of the vagina
  - Clinical presentation:
    - Asymptomatic swelling seen in the posterolateral aspect of the introitus
    - If infected, may become a large painful inflammatory mass
  - Treatment:
    - Small asymptomatic cysts can be left alone
    - Large symptomatic non-infected cysts can be marsupialized
    - Infected cysts can be treated by inserted an inflatable bulb-tipped catheter (**Word catheter**) through a small stab incision into the mass & left in place for 4-6 weeks to form an epithelialized fistula tract which will remain open for drainage
    - In women >40 years old, careful examination of the base of the cyst needed to exclude an underlying Bartholin's gland carcinoma

- **Endometriosis**
  - Endometriotic deposits on the vagina (usually upper third) appear as steel-gray or black cysts that may bleed slightly at the time of menstruation

- **Pelvic Organ Prolapse**
  (*see "Urogynaecology" for more details*)
  - Anterior vaginal prolapse (cystocele)
  - Posterior vaginal prolapse (rectocele, enterocele)
  - Apical vaginal & uterine prolapse

Benign Conditions of the Cervix

Structural Conditions of the Cervix

- **Nabothian Cysts**
  - Common condition resulting from squamous metaplasia:
    - A layer of superficial squamous epithelium entraps an invagination of columnar cells beneath it
    - Underlying columnar cells continue to secrete mucus, hence a mucous retention cyst is formed

- **Cervical Ectropion (Cervical Erosion)**
  - ***Normal developmental changes in cervical appearance:***
    - At birth, the cervix comprises columnar epithelium (*lining the endocervical canal*) & squamous epithelium (*lining the ectocervix*)
    - At puberty, under the influence of estrogen, the endocervical canal undergoes a degree of eversion, exposing the lower part of the columnar epithelium
    - Acidification of the vagina at puberty → squamous metaplasia of the exposed columnar epithelium
    - Hence cervical ectropion represents an area of columnar epithelium that has yet to undergo squamous metaplasia
  - ***Clinical features:***
    - Increased vaginal secretions
    - Post-coital spotting/bleeding
  - ***Treatment:***
    - None needed once other etiologies (especially cervical neoplasia) ruled out with Pap smear

- **Cervical Polyps**
  - ***Types of cervical polyps:***
    - Endocervical polyps (*beefy red, arise from endocervical canal on a long pedunculated stalk*)
    - Ectocervical polyps (*less common, pale, arise from the ectocervix to form a broad-based protrusion*)
  - ***Clinical features:***
    - Asymptomatic
    - Symptomatic polyps: *menorrhagia, post-coital bleeding*
  - ***Management:***
    - Narrow based polyps: *twist polyp off its base*
    - Broad based polyps: *excised with electrocautery*
    - All specimens should be sent for histological examination to rule out cancer

Functional Conditions of the Cervix

- **Cervical Stenosis**
  - ***Causes of cervical stenosis:***
    - Trauma (*dilatation & curettage, LLETZ, cone biopsy*)
    - Hypoestrogenism (*menopause, prolonged DMPA*)
  - ***Clinical features & consequences:***
    - Hematometra (*as blood is unable to escape*)
    - Subfertility (*as sperm is unable to pass through cervix*)
    - Cervical dystocia (*difficult labour due to stenosed cervix*)

- **Cervical Incompetence**
  - ***Causes of cervical incompetence:***
    - Intrinsic (*poor ground substance in cervix*)
    - In-utero diethylstilbestrol exposure leading to cervical hypoplasia
    - Cervical surgery (*LLETZ, cone biopsy*)
  - ***Clinical features & consequences:***
    - Increased risk of early pregnancy loss
    - Increased risk of premature labour

Benign Conditions of the Uterine Corpus

Congenital Anomalies of the Uterus & Cervix

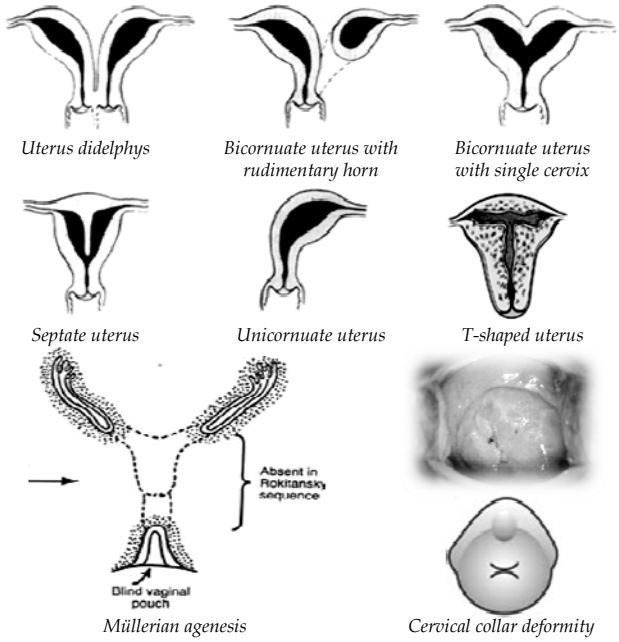
In the absence of Müllerian inhibiting factor without a Y chromosome, the Müllerian ducts develop; Müllerian ducts first appear at 6 weeks gestation lateral to the cranial pole of the Wolffian ducts & expand caudally; by 9-10 weeks, they fuse in the midline at the urogenital septum to form the uterovaginal primordium; subsequent dissolution of the septum leads to the development of a single uterus & cervix

- **Incomplete Fusion of the Müllerian Ducts**
  - ***Uterus didelphys***
    - Complete failure of fusion of Müllerian ducts
    - 2 separate uterine bodies, each with its own cervix & attached fallopian tube & vagina
  - ***Bicornuate uterus with rudimentary horn***
    - 2 cornua present, but fusion failure results in 1 of them remaining underdeveloped
  - ***Bicornuate uterus***
    - Single uterine cavity fused at the caudal end but incompletely fused at cranial end
    - May be with a single or double cervix

- **Incomplete Dissolution of Midline Fusion of the Ducts**
  - ***Septate uterus***
    - Complete fusion of Müllerian ducts but incomplete dissolution of the septum to a varying extent

- **Failure of Formation**
  - ***Unicornuate uterus***
    - Failure of formation & development of 1 of the 2 Müllerian ducts
  - ***Müllerian agenesis*** *(Rokitansky-Küster-Hauser syndrome)*
    - Failure of complete development of both Müllerian ducts, resulting in incomplete fallopian tube development with absent uterus, cervix & most of the vagina

- **Diethylstilbestrol (DES) Associated Anomalies**
  - ***T-shaped uterus***
  - ***Cervical collar deformity***



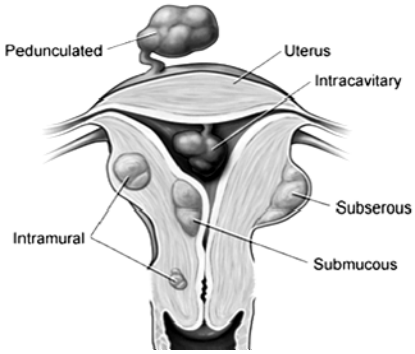
Uterus didelphys | *Bicornuate uterus with rudimentary horn* | *Bicornuate uterus with single cervix*

Septate uterus | *Unicornuate uterus* | *T-shaped uterus*

Müllerian agenesis | *Cervical collar deformity*

Uterine Leiomyoma (Fibroid)

- **Pathophysiology of Fibroids**
  - ***Pathology of fibroids:***
    - Benign proliferation of a single clone of smooth muscle cells within the myometrium of the uterus
    - Grossly: *spherical, well-circumscribed, white, firm lesions with a whorled appearance on cut surface*
    - Compressed smooth muscle cells on the tumour's periphery forms a pseudocapsule
    - Few blood vessels traverse the pseudocapsule, hence degenerative changes occur as the tumour enlarges:
      - Hyaline acellularity (*replacement of fibrous & smooth muscle tissues with hyaline tissue*)
      - Cystic degenerations (*breakdown of hyaline substance with further reduction in blood supply*)
      - Calcification of degenerated fibroids may occur (*particularly after menopause*)
      - Fatty degeneration (*uncommon*)
      - **Red degeneration** (*painful condition resulting from hemorrhage into the tumour, usually occurring during pregnancy*)
  - ***Hormonal influence on fibroids:***
    - Fibroids have increased numbers of estrogen & progesterone receptors compared to normal smooth muscle cells of the uterus:
      - Estrogen stimulates smooth muscle cell proliferation
      - Progesterone induces increased production of cellular proteins which interfere with apoptosis
    - Fibroid growth hence reflects hormonal changes in a woman's reproductive life:
      - Usually only appear after menarche
      - Ceases to enlarge & tends to decrease in size after menopause
      - Rapid increase in size may occur in pregnancy, & use of clomiphene, which may be complicated by red degeneration
  - ***Classification of fibroids by location:***
    - Intramural fibroids
    - Submucosal fibroids
      - Beneath the endometrial surface
      - If pedunculated, can abort through the endocervical canal, causing cramping pain
      - Distortion of endometrial surface may cause abnormal uterine bleeding
    - Subserosal fibroids
      - Beneath the serosal surface of the uterus
      - If pedunculated, can be complicated by torsion
    - Parasitic fibroids
      - Rare situation where a pedunculated subserosal fibroid attaches to the vascular supply of omentum or bowel mesentery & subsequently loses its uterine connection



- **Clinical Features**
  - ***Asymptomatic***
    - Most fibroids are asymptomatic
    - May be incidentally picked up on imaging
  - ***Mass effect***
    - Bloating, early satiety
    - Sense of heaviness in the lower abdomen
    - Dull back ache/pain
    - Urinary symptoms: *frequency; rarely if fibroid is big enough, may cause urinary retention & even hydronephrosis*
  - ***Abnormal uterine bleeding (AUB)***
    - Usually occurs in cases of submucosal & large intramural fibroids which distort the endometrium
    - Any abnormal uterine bleeding that results is usually heavy (menorrhagia) or prolonged, which may be accompanied by symptoms of anemia if prolonged
    - Irregularity of cycles & intermenstrual bleeding do <u>not</u> classically occur
    - *Note: bleeding cause by fibroids is dependent on the presence of menstruation, hence fibroids are <u>not</u> classically considered a cause of post-menopausal bleed*
  - ***Acute abdominal/pelvic pain***
    - Fibroids are usually <u>not</u> painful
    - Acute pain can arise from fibroids in certain uncommon situations:
      - Red degeneration (*usually during pregnancy*)
      - Torsion of pedunculated subserosal fibroid
  - ***Effects on fertility & pregnancy***
    - Negative effects usually due to submucosal or large intramural fibroids which distorts the uterine cavity:
      - Subfertility (*due to placentation challenges posed*)
      - Early pregnancy loss
      - Malpresentation (*fibroid mass in the lower uterus may hinder cephalic presentation*)

- **Physical Examination**
  - ***General examination***
    - Assess patient's vitals & look for pallor
    - Look for signs of malignancy (*uterine & ovarian malignancies are potential differentials*):
      - Supraclavicular lymphadenopathy
      - Pleural effusion
  - ***Abdominal examination***
    - Palpate for any abdominopelvic mass (*large fibroid resulting in a uterus bigger than a 12-week size may be palpable in the lower abdomen*)
    - Look for signs of malignancy (*uterine & ovarian malignancies are potential differentials*):
      - Hepatomegaly, ascites
  - ***Pelvic examination***
    - Speculum examination:
      - Visualize cervix & take a Pap smear to rule out cervical pathology
    - Digital vaginal examination:
      - Test for cervical excitation (*if present, may be indicative of PID with a tubo-ovarian abscess as a differential in this context*)
    - Bimanual palpation:
      - Assess uterine size & surface (*may be enlarged with bosselated protrusions if fibroids are intramural or subserosal*)
      - Assess mobility of any uterine or adnexal mass felt while simultaneously assessing whether cervix moves (*if both move together, mass is attached to uterus; if not, may still be a fibroid which is pedunculated*)

- **Investigations**
  (*investigations are usually tailored according to the presentation; being benign & usually asymptomatic, differentials for each presentation need to be ruled out first before it is appropriate to presume that any fibroid(s) found is responsible for the symptoms*)
  - ***Pelvic ultrasound***
    - Most useful modality for visualizing fibroid(s), determining their location & size
    - Also useful for diagnosing common differentials for a abdominopelvic or pelvic mass:
      - Adenomyosis/adenomyoma
      - Ovarian cysts/adnexal masses

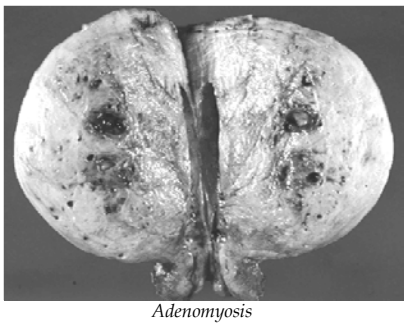
- **Management of Fibroids**
  (*incidentally detected asymptomatic fibroids do not need treatment; treatment of symptomatic fibroids should be tailored according to the presentation as well as the specific patient's context – e.g. desire for future fertility*)
  - ***Medical management of fibroids***
    - 1st line management for AUB due to fibroids
    - Options available:
      - Tranexamic acid (*anti-fibrinolytic*)
      - Mefenamic acid aka Ponstan (*NSAID*)
      - Hormonal (*combined oral contraceptive pill, progestin-only therapies like POPs or Mirena*)
      - GnRH agonists (*helps halt endometrial proliferation & can sometimes even reduce fibroid size; not routinely used due to high costs & deleterious effects on bone mineral density & vasomotor symptoms*)
  - ***Surgical management of fibroids***
    (*for failed medical treatment of AUB or for mass symptoms*)
    - **Myomectomy**
      - Surgical excision of fibroid
      - Can be done via laparoscopy, laparotomy or even hysteroscopy (*for submucosal fibroids*)
      - <u>Pros</u>: good option for patients desiring uterine preservation or desiring future fertility (*but if endometrial cavity is entered during the time of myomectomy, future deliveries need to be via elective caesarian due to significant risk of uterine rupture*)
      - <u>Cons</u>: fibroids can recur in myometrium
    - **Uterine artery embolization**
      - Interventional radiology procedure where uterine artery is accessed & embolized via a transcutaneous femoral approach
      - Occludes blood supply of fibroids, causing them to shrink by 40-60% in size (*uterus still receives sufficient blood supply from collaterals*)
      - <u>Pros</u>: good option for patients desiring uterine preservation or desiring future fertility
      - <u>Cons</u>: future pregnancies may be at higher risk
    - **Endometrial ablation**
      - Hysteroscopic procedure where endometrial lining is destroyed, thereby treating abnormal uterine bleeding (~70% effective)
      - Option for patients desiring uterine preservation but not fertility
    - **Hysterectomy**
      - Provides definitive treatment for fibroids (*no more abnormal uterine bleeding, no risk of recurrence of fibroids*)
      - Transvaginal or transabdominal can be done (*but latter needed if subtotal hysterectomy desired*)
      - Concomitant bilateral salpingo-oophorectomy can be offered for post-menopausal women (*negates risk for future development of ovarian CA*)

Endometrial Conditions

- **Endometrial Polyps**
  - Benign condition where polyps arising from the endometrium protrude into the uterine cavity
  - ***Clinical features:***
    - Asymptomatic
    - Abnormal uterine bleeding (*menorrhagia, prolonged menstruation*)
  - ***Investigations & management:***
    - Pelvic ultrasound (*visualizes endometrial polyps as a focal thickening of the endometrial stripe*)
    - Biopsy of polyp via endometrial sampling or dilatation & curettage (*may miss polyp though if they are too large to be aspirated through the sampling orifice or are flexible enough to fold out of the path of the curette*)
    - Hysteroscopy may be indicated to visualize the polyp & allow an excision of the polyp for histological assessment (*curative + allows exclusion of underlying malignancy*)

- **Endometrial Hyperplasia**
  - Overabundant growth & proliferation of the endometrium resulting from prolonged unopposed estrogen stimulation:
    - Extremes of reproductive age where anovulation is common (*initial post-menarche; peri-menopausal*)
    - Polycystic ovary syndrome (*chronic anovulation*)
    - Obesity (*increased extra-ovarian aromatization of circulating adrenal androstenedione into estrone*)
    - Granulosa-theca cell tumours (*estrogen-producing*)
    - Prolonged use of estrogen-only hormonal therapy
    - Chronic tamoxifen use (*selective estrogen modulator that is agonistic on endometrial tissue*)
  - ***Clinical features:***
    - Asymptomatic
    - Abnormal uterine bleeding (*menorrhagia, prolonged menstruation; any associated menstrual irregularity is usually due to the underlying cause*)
  - ***Investigations:***
    - Pelvic ultrasound
      - Used to measure the endometrial thickness
      - >5mm is considered suspicious for endometrial hyperplasia or even cancer (*most useful post-menopausally; pre-menopausally, it may be confounded by the time of the menstrual cycle the women was in at the time of ultrasound, hence biopsy is usually only indicated if woman is older*)
    - Endometrial biopsy
      - Can be done via endometrial sampling &/or dilatation & curettage ± hysteroscopy
      - Indicated as a follow-up to pelvic ultrasound finding suspicious of endometrial hyperplasia to rule out any underlying dysplasia or cancer (*see "Endometrial Cancer" for algorithm for endometrial evaluation*)
      - Possible results: *normal endometrium; simple hyperplasia; complex hyperplasia without atypia; complex hyperplasia with atypia; endometrial cancer*
  - ***Management of endometrial hyperplasia:***
    - Simple hyperplasia: *progestins (10d/month x3 months)*
    - Complex hyperplasia without atypia: *evaluate with D&C to rule out underlying malignancy; treat with progestins (daily for 3-6 months)*
    - Complex hyperplasia with atypia: *evaluate with D&C to rule out underlying malignancy; consider hysterectomy to negate future risk of malignancy*

- **Adenomyosis**
  - Condition defined by the extension of endometrial glands & stroma into the uterine musculature (myometrium) >2.5mm beneath the basalis layer of the endometrium
  - ***Pathology of adenomyosis:***
    - Grossly: *diffuse uterine enlargement (globular uterus) with accompanying thickened myometrium containing glandular irregularities with implants containing endometrial tissue*
    - Histologically: *normal endometrial glands & stroma extending into the myometrium*
    - In some cases, the adenomyosis may be more pronounced in a focal region of the myometrium, forming an **adenomyoma** (*resembling a fibroid*)
  - ***Clinical features:***
    - Abnormal uterine bleeding (*usually menorrhagia; should not cause post-menopausal bleeding as it usually regresses after menopause*)
    - Secondary dysmenorrhea (*usually severe*)
    - Deep-thrust dyspareunia (*especially during premenstrual period*)
    - Physical examination findings:
      - Diffusely enlarged uterus
      - Adenomyoma may cause asymmetrical enlargement of the uterus, making it difficult to differentiate from fibroids (*but significant feature of severe dysmenorrhea usually makes adenomyosis more likely as fibroids are classically painless*)
  - ***Investigations***
    - Pelvic ultrasound
      - Reveals a poorly defined endomyometrial junction with thickened myometrium featuring a heterogeneous echotexture
      - Adenomyomata may appear similar to fibroids on ultrasound
    - MRI pelvis
      - Greater sensitivity in definitive diagnosis of an adenomyomata
    - Endometrial biopsy
      - May be indicated in the setting of a clinical presentation of abnormal uterine bleeding in older women to rule out endometrial hyperplasia &/or cancer
  - ***Management of adenomyosis:***
    - Medical management:
      - Tranexamic acid (*anti-fibrinolytic*)
      - Mefenamic acid aka Ponstan (*NSAID; helps with both the bleeding & the dysmenorrhea*)
      - Hormonal (combined oral contraceptive pill, progestin-only therapies)
    - Surgical management:
      (*indicated when refractory to medical management*)
      - Endometrial ablation
      - Hysterectomy



Adenomyosis

- **Asherman Syndrome**
  - Condition in which the endometrium is denuded with the uterine cavity filled with adhesions (**synechiae**)
  - ***Causes of Asherman syndrome:***
    - Endometrial curettage (*especially in high-risk settings such as treatment of post-partum hemorrhage or septic abortion*)
    - Endometrial ablation (*endometrial denudation in this case is intended*)
  - ***Clinical features:***
    - Oligomenorrhea or amenorrhea
    - Subfertility

Endometriosis

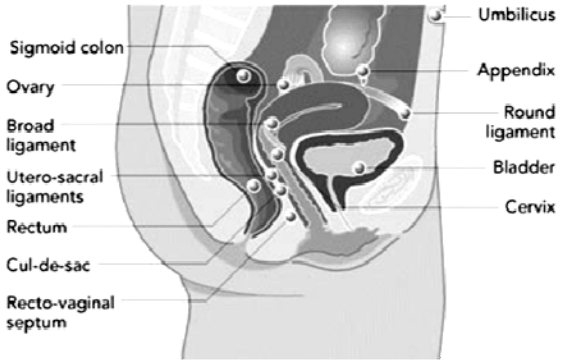
Benign condition in which endometrial glands & stroma are present outside the uterine cavity & walls

- **Epidemiology & Associations**
  - About 1 in 6 women have clinical endometriosis (*probably more have subclinical endometriosis which may be incidentally found on gynaecologic laparotomies*)
  - Proportion of endometriosis is higher in women with chronic gynaecologic conditions:
    - One third of women with chronic pelvic pain
    - Half of women with subfertility

- **Pathophysiology of Endometriosis**
  (*3 main hypotheses for its pathogenesis present*)
  - ***Retrograde menstruation theory (Sampson)***
    - Proposes that fragments of endometrial tissue is transported through the fallopian tubes at the time of menstruation which subsequently implant & grow on various intra-abdominal sites; hematogenous spread further accounts for deposits found in extra-abdominal sites
    - Features supporting this theory:
      - Endometriotic implants tends to be in gravity dependent sites in the pelvis (*e.g. pouch of Douglas*)
      - High prevalence of endometriosis in patients with congenital genital outflow tract obstructions (*e.g. transverse vaginal septum*)
      - Studies have demonstrated an association with uterotubal hypotonia (*possibly leading to lack of effective tubal opening occlusion during menstruation, allowing endometrial fragments to enter the tubes & be propagated into the peritoneal cavity*)
    - Further augmentations to this theory (*attempts to explain why endometriosis does <u>not</u> occur in every woman with retrograde menstruation*):
      - Differences in chemical & biologic pathways (*reduced apoptosis, altered cell polarization & adhesion, increased angiogenesis, altered oncogene expression*)
      - Differences in immunologic responses in the pelvis (*altered macrophage function, decreased T-killer cell & natural killer cell function*)
  - ***Müllerian metaplasia theory (Meyer)***
    - Proposes that metaplastic transformation of the peritoneal mesothelium into endometrium occurs under the influence of certain generally unidentified stimuli
  - ***Lymphatic spread theory (Halban)***
    - Proposes that endometrial tissues can be taken by lymphatics draining the uterus & subsequently transported to various pelvic & extra-pelvic sites

- **Developmental Stages of Endometriosis**
  - Vesicular stage
    - 1st stage, where endometriotic implant appears as a discrete vesicle
    - Mean age = 21.5 years
  - Red nodular stage
    - 2nd stage, where endometriotic implant appears red due to accumulation of hemosiderin from cycles of bleeding during menstruation
    - Mean age = 26.3 years
  - Blue nodular stage
    - 3rd stage, where endometriotic implant appears dusky & bluish due to old blood seen through a layer of fibrosis
    - Mean age = 29.5 years
  - Fibrotic stage
    - Final stage, where dense fibrosis predominates at site of original endometriotic implant
    - Mean age = 31.9 years

- **Sites of Occurrence of Endometriosis**



  - ***Ovarian involvement is the most common (2 in 3)***
    - Endometriotic implants initially on the mesothelial surface of the ovary
    - Subsequently invaginates into stroma of ovary facilitated by cyclical bleeding
    - Forms endometriotic cysts (chocolate cysts)
  - ***Peripheral sites not mentioned in above diagram:***
    - Laparotomy scars (*especially after caesarian delivery or myomectomy where the endometrial cavity is entered; probably due to seeding of endometrial tissue in the surgical incision*)
    - Distant sites (*e.g. lungs – can present with cyclical hemoptysis*)

- **Clinical Features of Endometriosis**
  - ***Asymptomatic***
  - ***Dysmenorrhea***
    - Initially cyclical, beginning 1-2 days before menstruation & lasting till the end of the menses (*due to intense inflammatory reaction induced by the premenstrual swelling & subsequent extravasation of blood & debris when endometriotic implants shed*)
    - Over time, chronic pelvic pain may predominate (*due to chronic inflammation established*), with exacerbations at the time of menstruation each month
  - ***Dyspareunia***
    - Usually deep-thrust dyspareunia, occurring when the uterosacral ligaments, pouch of Douglas & posterior vaginal fornix are involved
  - ***Dyschezia***
    - Pain occurring during defaecation
    - Occurs with uterosacral ligament, pouch of Douglas & rectosigmoid colon involvement
  - ***Other presentations:***
    - Cyclical bleeding from organ involved (*menstrual hematuria, hematochezia, hemoptysis etc*)
    - Subfertility (*due to distortion of pelvic structures from extensive fibrosis*)
    - Abnormal uterine bleeding (*e.g. menorrhagia*) does <u>not</u> usually occur in endometriosis as the bleeding from the ectopic endometrial tissue occurs in extra-uterine sites
  - ***Physical examination findings:***
    - Tender pelvic nodules
      - Uterosacral nodules
      - Pouch of Douglas nodules
      - Tender nodule/mulberry-like spot may be seen in the posterior fornix of the vagina
    - Adnexal mass, which may be fixed & tender (*due to endometriotic cyst/endometriomas of the ovary or endometrial implants on the other adnexal structures*)

- **Investigations**
  (*endometriosis is generally presumptively diagnosed on clinical grounds with a history & physical examination findings suggestive of it; any investigation performed is limited for its confirmation but should be done to rule out important differentials*)
  - ***Non-radiological investigations:***
    - Urine pregnancy test (*to rule out ectopic pregnancy*)
    - Serum CA-125 (*levels are usually raised in endometriosis, typically in the range of 50-100 U/ml; positive predictive value is poor however & hence should not be used for the diagnosis of endometriosis*)
  - ***Pelvic ultrasound***
    - Only diagnostic of endometriosis when an endometriotic cyst of the ovary is present
    - Useful for ruling out other pelvic differentials of endometriosis:
      - Ectopic pregnancy
      - Tubo-ovarian abscess in chronic PID
      - Hemorrhagic corpus luteum
      - Other ovarian cysts/masses

- **Classification System for Endometriosis**

THE AMERICAN FERTILITY SOCIETY
REVISED CLASSIFICATION OF ENDOMETRIOSIS

Patient's Name _____ Date _____

Stage I (Minimal) - 1-5
Stage II (Mild) - 6-15
Stage III (Moderate) - 16-40
Stage IV (Severe) - >40
Total _____

Laparoscopy _____ Laparotomy _____ Photography _____
Recommended Treatment _____
Prognosis _____

	ENDOMETRIOSIS	<1cm	1-5cm	>5cm
PERITONEUM	Superficial	1	2	4
	Deep	2	4	6
OVARY	R Superficial	1	2	4
	Deep	4	16	20
	L Superficial	1	2	4
	Deep	4	16	20

POSTERIOR CULDESAC OBLITERATION	Partial	Complete
	4	40

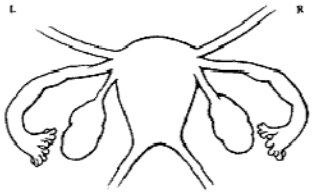
	ADHESIONS	<1/3 Enclosure	1/3-2/3 Enclosure	>2/3 Enclosure
OVARY	R Filmy	1	2	4
	Dense	4	8	16
	L Filmy	1	2	4
	Dense	4	8	16
TUBE	R Filmy	1	2	4
	Dense	4*	8*	16
	L Filmy	1	2	4
	Dense	4*	8*	16

*If the fimbriated end of the fallopian tube is completely enclosed, change the point assignment to 16.

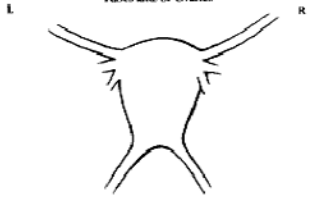
Additional Endometriosis: _____

Associated Pathology: _____

To Be Used with Normal Tubes and Ovaries

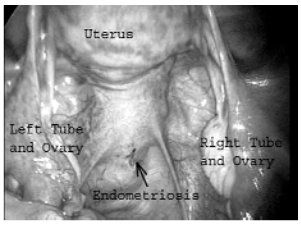


To Be Used with Abnormal Tubes and/or Ovaries



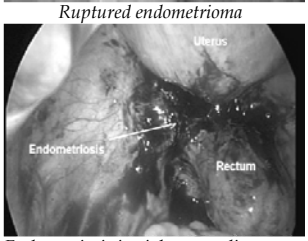
  - 4 stages (I to IV) of endometriosis based on sites involved & extent of visualized disease
  - However, there is poor clinical correlation between this staging system & the actual manifestation of endometriosis in the patient (*in terms of fertility & pain*), hence this staging system is not routinely used

- **Management of Endometriosis**
  - ***Basic principles in managing endometriosis:***
    - Choice of management options depends on:
      - Certainty of the diagnosis on clinical grounds
      - Severity of the symptoms
      - Extent of the disease
      - Patient's age & desire for future fertility
    - All three main approaches (*medical treatment alone, surgical treatment alone & medical + surgical treatment*) have been shown to be superior to placebo in treating endometriosis, with no difference in pain scores at 6 months between the three approaches
    - Hence choice of which method to employ depends largely on the treatment objectives & patient's unique circumstances:
      - Medical management generally 1st-line (*within which there are 1st & 2nd line agents to be tried*)
      - Surgical management indicated if symptoms refractory to medical treatment
      - Surgery (*fertility-preserving procedures specifically*) may also be beneficial if endometriosis is suspected to be a contributing factor to subfertility
  - ***Medical management of endometriosis:***
    - **NSAIDs (e.g. mefenamic acid aka Ponstan)**
      - 1st-line treatment alongside hormonal therapy options for relief of pain in endometriosis
    - **Hormonal therapy**
      - Oral contraceptives & low-dose progestins are useful 1st-line treatment for pain in endometriosis, helping induce a variable amount of regression in the disease (*curious feature of endometriosis in that it grows with cyclical physiologic hormonal exposure but tends to regress with continuous hormonal exposure, especially in higher doses*)
      - High dose progestins can be used as 2nd-line treatment as well
      - Mirena (Levonorgestrel-releasing intrauterine system) is also a good long-term option
    - **Danazol (17α-ethinyl testosterone)**
      - Derivative of ethisterone (a synthetically modified testosterone)
      - 1st drug specifically licensed in 1970s for the treatment of endometriosis; currently a 2nd-line option alongside GnRH agonists for treatment of endometriosis refractory to 1st-line therapy
      - Physiologically induces a 'pseudomenopause', suppressing menstruation & hence helping suppress the growth & symptoms of endometriosis as well
      - Side effects: *hirsutism, acne*
    - **GnRH agonist (+ estrogen add-back)**
      - Options: *leuprolide, goserelin*
      - 2nd-line treatment for endometriosis
      - Mechanism of action: *continuous steady levels of GnRH initially causes surge in gonadotropins ('flare effect'); subsequently leads to desensitization due to internalization of pituitary GnRH receptors, in turn resulting in decreased gonadotropin production, causing a temporary medically-induced menopausal state which relieves pain & brings about regression of endometriosis*
      - Side effects: *hot flushes, decreased bone mineral density, worsened lipid profile (+ very expensive)*
      - Low-dose estrogen & progestin add-back helps mitigate some of the side-effects, thereby permitting longer use of GnRH agonists
    - **Dienogest (Visanne)**
      - Orally-active semi-synthetic progestin; differs from conventional progestins in that it has anti-androgenic effects
      - Studies have shown that it is as effective as GnRH agonists for treating endometriosis, but without the hypoestrogenic side effects of GnRH agonists
      - Hence currently the 2nd-line treatment of choice (over Danazol & GnRH agonists)
      - Side effects (similar to those for most progestins except that it has no androgenic side-effects): *nausea, weight gain, increased blood pressure*
  - ***Surgical management of endometriosis:***
    - **Fertility-preserving surgery (ablative + excisional)**
      - Can be done via laparoscopy or laparotomy
      - Removal of all adhesions & destruction of all visible implants
      - Endometriomas >3cm should be excised (*occasionally, adhesions surrounded endometrioma may preclude feasible cystectomy, hence oophorectomy may be required*)
    - **Total hysterectomy + bilateral salpingo-oophorectomy (THBSO)**
      - Definitive surgical treatment for endometriosis, usually done in combination with concomitant ablative procedures of all visible implants & adhesions
      - Complications: *bowel & urinary system injury; abrupt menopausal effects if patient is pre-menopausal (severe hot flushes, loss of libido, decreased bone mineral density)*
      - Need for hormone replacement therapy with estrogen-only therapy if patient is pre-menopausal
      - There is still a 20% recurrence rate of endometriosis with this procedure, usually involving the bowel
    - ***Adjunctive medical therapy:***
      - Pre-operative medical therapy (e.g. with GnRH agonists) for 3-6 months can improve surgical success (*helps induce some regression of the disease to make surgical intervention easier*)
      - Post-operative long-term hormonal therapy (*e.g. Depo-Provera, continuous oral contraceptives, Mirena*) helps reduce risk of post-surgical recurrence of endometriosis



Ruptured endometrioma

Implant on uterosacral ligament



Endometriosis in right paracolic gutter

Benign Conditions of the Fallopian Tube

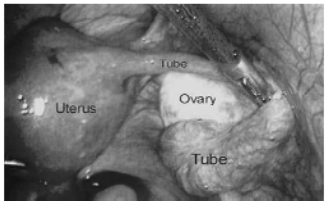
Congenital Anomalies of the Fallopian Tube

- **Sporadic Anomalies of the Fallopian Tubes**
  - Aplasia or atresia (*usually of the distal ampullary segment*)
  - Duplication (*complete duplication rare; distal duplication or accessory ostia relatively common*)

- **Diethylstilbestrol (DES) Associated Anomalies**
  - Shortened fallopian tubes
  - Distorted fallopian tubes
  - Clubbed fallopian tubes

Structural Conditions of the Fallopian Tube

- **Hydrosalpinx & Pyosalpinx**
  - Enlarged fallopian tube secondary to blockage of the fimbrial end of the tube due to tubal inflammation
    - Hydrosalpinx = fluid filled
    - Pyosalpinx = pus-filled
  - Sequelae of pelvic inflammatory disease; common causes:
    - *Chlamydia trachomatis*
    - *Neisseria gonorrheae*
  - **Actinomycosis** of the fallopian tubes:
    - Filamentous branched clubbed organism
    - Gram positive, non-acid fast
    - Associated with intrauterine device use (36%)



- **Salpingitis Isthmica Nodosa**
  - Idiopathic condition usually seen in young women
  - Diverticulae of the fallopian tube which communicate with the lumen results in nodular swellings of the tube
  - Bilateral in 80% of cases
  - Clinical consequences: *subfertility, ectopic pregnancy*

- **Benign Neoplasms of the Fallopian Tube**
  (*relatively rare compared to the other parts of the female genital tract*)
  - ***Tubal neoplasms***
    - Epithelial adenomas/polyps
    - Myomas
    - Angiomas
    - Inclusion cysts (from mesothelium)
  - ***Paratubal (paraovarian) neoplasms***
    - **Hydatids of Morgagni** (*paratubal cysts derived from remnants of the Müllerian duct*)
    - Neoplasms derived from Wolffian remnants

Benign Conditions of the Ovary

Congenital Anomalies of the Ovary

- **Non-Chromosomal-Related Anomalies**
  - Congenital duplication of ovaries
  - Congenital absence (agenesis) of ovaries
  - Ectopic ovaries
  - Ovotestis (*occurs when bipotentiality noted in embryological development progresses without the usual regression of one system*)

- **Chromosomal-Related Anomalies**
  - **Turner syndrome (45XO)**
    - Rudimentary streaked ovaries
    - Women with turner syndrome usually still progress through puberty & develop secondary sexual characteristics but subsequently enter menopause shortly thereafter

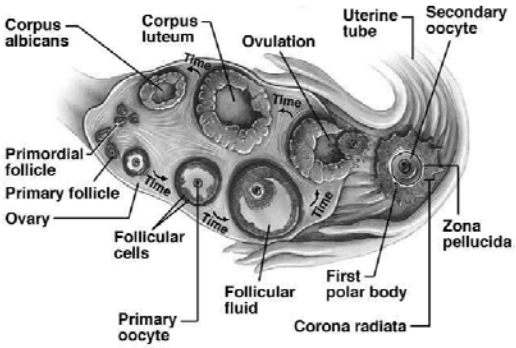
Benign Ovarian Cysts

- **Non-Neoplastic Ovarian Cysts**
  - ***Cysts of mesothelial origin***
    - Germinal inclusion cysts
      - *Formed by the invagination of ovarian surface mesothelium into the cortex or stroma of the ovary*
      - *Cystic enlargement occurs from accumulation of serous fluid secreted by the mesothelium*
      - *No association with epithelial ovarian cancer*
  - ***Cysts of follicular origin (functional cysts)***
    - Follicular cysts
      - *Develop from partially-developed follicles that undergo atresia*
      - *Mostly physiological; extremely common*
      - *Usually undergoes spontaneous regression*
    - Corpus luteal cysts
      - *Develops after corpus luteal hematoma is formed following ovulation*
      - *Lined by luteinized granulosa cells with a deeper layer of theca cells*
      - *Persistence leads to continued secretion of progesterone which clinically results in delayed menstruation*
      - *May rarely rupture; if it does, classically associated with massive intraperitoneal hemorrhage*
    - Theca lutein cysts
      - *Formed as a result of intensely luteinized theca interna cells occurring when the corpus luteum comes under the influence of high levels of hCG*
      - *Usually small, but may be large & multiple as well*
      - *Associated with multiple gestations, molar pregnancies & patients on gonadotropin treatment (ovarian hyperstimulation syndrome)*
    - Polycystic ovary syndrome
      - *Multiple eccentrically-placed follicular cysts within the ovary, as a result of chronic anovulation*
      - *See "Polycystic Ovary Syndrome"*
  - ***Cysts of inflammatory conditions***
    - Tubo-ovarian abscess
      - *Abscess resulting from pelvic inflammatory disease*
    - Endometriotic cysts (endometrioma; chocolate cysts)
      - *Ovarian cysts enclosing stale/old blood*
      - *Result from endometriotic implant on ovary (initially on surface; subsequently invaginates into stroma with repeated cyclical bleeding)*

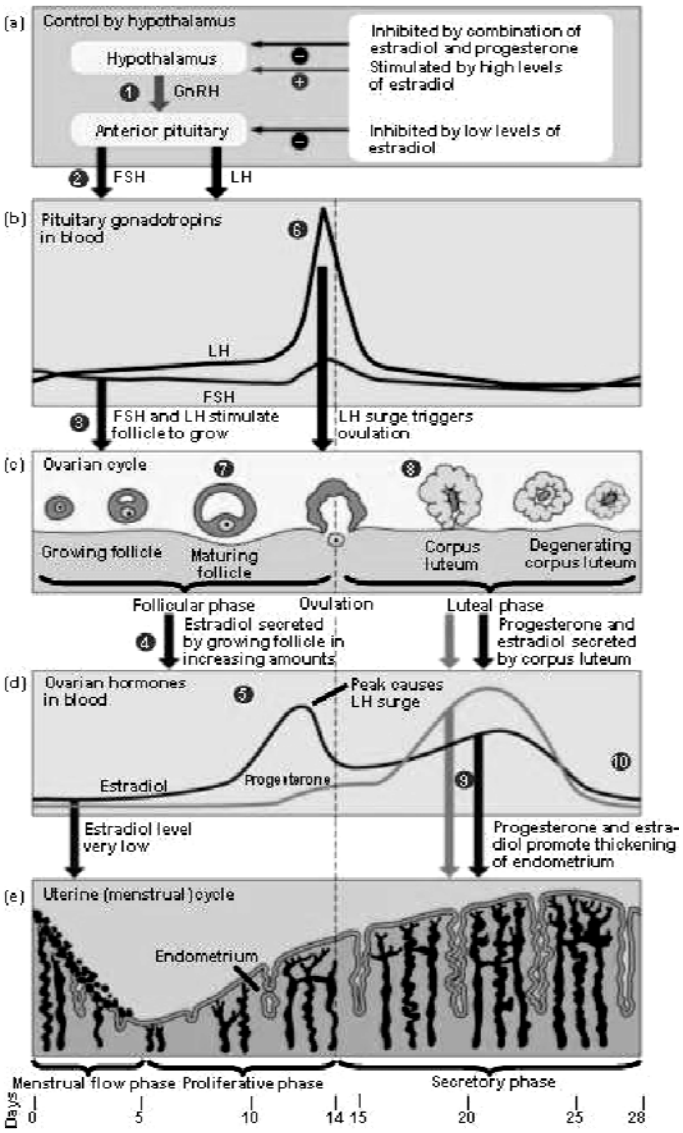
Normal Menstrual Cycle

- **Hypothalamic-Pituitary-Ovarian (HPO) Axis**
  - ***Hypothalamus***
    - **Gonadotropin-releasing hormone (GnRH)** is a decapeptide synthesized primarily within the arcuate nucleus
    - GnRH release from the hypothalamus occurs in a pulsatile manner throughout the menstrual cycle:
      - Increases from once every 90 min in the early follicular phase to once every 60-70 min in the immediate pre-ovulatory phase
      - Luteal phase pulse frequency is lower but with greater amplitude
    - Release of GnRH by the hypothalamus is influenced by various factors (both hormonal & from higher centres in the brain):
      - Stress, emotional factors
      - Nutritional status
      - Level of physical activity/exercise
    - GnRH is carried from the hypothalamus to the anterior pituitary via the hypophyseal venous plexus, where it acts on the gonadotrophs
  - ***Pituitary***
    - Anterior pituitary (adenohypophysis) comprises various cell populations, each producing a different anterior pituitary hormone
    - Gonadotrophs release 2 types of gonadotropins in response to GnRH from the hypothalamus:
      - **Follicle-stimulating hormone (FSH)**
      - **Luteinizing hormone (LH)**
      - *Note: the a-subunit of FSH, LH, thyroid-stimulating hormone (TSH) & human chorionic gonadotropin (hCG) is identical; each has its own distinct β-subunit*
    - Gonadotrophs physiologically respond to pulsatile GnRH release; if GnRH exposure is continuous instead, there would be a desensitization of gonadotrophs to GnRH via down-regulation of GnRH receptors
      - This effect is used therapeutically via exogenous GnRH administration in situations where it is desirable to shut down the endogenous ovarian hormonal cycle (*e.g. endometriosis, fibroids, precocious puberty etc*)
    - FSH effects on the ovary:
      - Recruit follicles at the beginning of each menstrual cycle, stimulating their growth & development
      - Induces aromatization of testosterone within granulosa cells to produce estrogen
    - LH effects on the ovary:
      - Induces testosterone production by theca cells which acts as the substrate for estrogen production by granulosa cells
      - Increases proteolytic enzymes & prostaglandin F2α production in the follicles which results in eventual rupture of the follicle at the point of ovulation (induced by a "**LH surge**")
      - Luteinizes the granulosa cells, resulting in the production of progesterone during the luteal phase of the menstrual cycle
  - ***Ovary***
    - Ovaries contain a finite number of follicles, each containing an oocyte, from birth:
      - At 8-10 weeks of fetal development, oocytes get surrounded by precursor granulosa cells which in turn are separated from the surrounding ovarian stroma by a basal lamina; this forms the **primordial follicles**
      - Between 20-24 weeks gestation, in response to gonadotropins & ovarian steroids with further fetal development, the granulosa cells become more cuboidal & the surrounding stromal cells become more prominent, forming **primary follicles**
      - With further proliferation of granulosa cells, a clear gelatinous material surrounds the oocyte, forming the **zona pellucida**; this forms the **secondary follicles**, which remain dormant in the ovary from birth until puberty
    - From the onset of puberty, with the beginning of each menstrual cycle, increasing FSH secretion from the anterior pituitary recruits a cohort of follicles for development:
      - Follicular growth & development occurs with increasing levels of estrogen & inhibin produced by the follicular cells
      - Inhibin elicits negative feedback on FSH secretion, limiting the FSH rise
      - With low FSH levels, only 1 follicle (**dominant follicle**) will be able to continue responding & developing as it has the highest number of FSH & LH receptors, aromatase enzyme & intrafollicular estrogen
      - Other hormonal factors involved in enhancing responsiveness of follicles to FSH include **insulin**, insulin-like growth factor-1 (IGF-1) & epidermal growth factor (EGF)
      - Remaining follicles of the recruited cohort undergo atresia induced by high local androgen levels (*these follicles can be 'rescued' from atresia via exogenous administration of gonadotropins, an effect used therapeutically in assisted reproductive techniques*)
    - Various structural changes occur in the dominant follicle as it continues to grow in the lead-up to ovulation:
      - Dominant follicle develops from a secondary follicle into a **graafian follicle** where the innermost 3-4 layers of rapidly multiplying granulosa cells become adherent to the oocyte (forms the **cumulus oophorus**) with concomitant formation of a fluid-filled antrum among the granulosa cells
      - Continued accumulation of antral fluid causes the central located oocyte to migrate eccentrically to the wall of the follicle; innermost layer of the cumulus oophorus become elongated & forms the **corona radiata**, which is released with the oocyte at the point of ovulation

- Following ovulation, the **corpus luteum** forms:
  - After ovulation, under the influence of LH, the granulosa cells of the ruptured follicle undergo luteinization
  - These luteinized cells then produce progesterone & estrogen
  - The corpus luteum is programmed to have a functional life span of 9-10 days, after which time it regresses & becomes an avascular scar known as **corpus albicans**



- **Menstrual Cycle**
  - *Menstrual phase*
    - 1st phase of the menstrual cycle, usually occurring from day 1 to day 5 of the menstrual cycle
    - Histological changes:
      - Disruption & disintegration of the endometrial glands & stroma (*functionalis layer sloughs while retaining the basalis layer of the endometrium*)
      - Leukocyte infiltration & red cell extravasation
    - Corresponds to the immediate period following the complete regression of the corpus luteum in the ovary which results in a drastic fall in serum ovarian hormone levels (estrogen & progesterone)
  - *Proliferative phase*
    - Follows the menstrual phase up to ovulation
    - Histological changes:
      - Endometrial proliferation under the influence of increasing serum estrogen levels
      - Cellular proliferation is accompanied by growth of the basal arteries (in the basalis layer) to form spiral arteries extending into the new developing functionalis layer
      - Resultant endometrial glands formed are straight with narrow lumens
  - *Secretory phase*
    - Follows ovulation with the change in the circulating ovarian hormone profile
    - Histological changes:
      - Progesterone secreted by the corpus luteum stimulates glandular cells to secrete glycogen, mucus & other substances
      - Glands also become tortuous with dilated lumens filled with the secreted substances
      - Stroma becomes edematous
      - Spiral arteries continue to extend into the functionalis layer & become convoluted
      - If implantation does not occur by day 23, the corpus luteum begins to regress, with the resultant decreasing ovarian hormonal levels inducing endometrial involution
      - In the immediate period before the menstrual phase, the spiral arteries undergo marked constriction, causing ischemia of the functionalis layer



- **Key Features of a Normal Menstrual Cycle**
  - *Length of menstrual cycle*
    - Defined as the interval between the 1st day of one menses to the 1st day of the next menses
    - Normal length = 21-35 days (28 days ± 1 week)
  - *Duration of menstruation*
    - Normal duration = 3-7 days
  - *Amount of menstrual bleeding*
    - Normal volume of menstrual bleeding = 20-80ml (*but difficult to quantify clinically*)
    - Usually heaviest on the first 1-3 days
    - Surrogate assessment of amount of menstrual bleed:
      - ≤4 pads a day
      - No excessive blood clots
      - No flooding
  - *Intermenstrual bleeding*
    - Small amount of intermenstrual bleeding can be physiological & normal (*sudden drop in estrogen levels following ovulation may result in some degree of endometrial sloughing*)
  - *Pain*
    - Some discomfort & cramps is normal during menses, & should not affect day-to-day activities

Amenorrhea & Oligomenorrhea

Amenorrhea = absence of menstruation
Primary amenorrhea = failure of occurrence of menarche before 16 years
Secondary amenorrhea = cessation of menses for ≥6 months
Oligomenorrhea = infrequent menstruation with >35 days length

Primary Amenorrhea

Defined as failure of occurrence of menarche before 16 years of age; however, work-up should be done earlier in girls with failure of occurrence of thelarche before 14 years of age or failure of occurrence of menarche within 2 years after thelarche

- **Causes of Primary Amenorrhea**
  - ***Hypothalamic pathology***
    - Constitutional delay of puberty
      - Delay in normal onset of puberty
      - Attributable to undefined hereditary factors (*history of delayed puberty in family members*)
      - Diagnosis of exclusion
    - Systemic stresses:
      - Significant weight loss (*e.g. anorexia nervosa*)
      - Excessive physical activity/exercise
      - Severe emotional distress
      - Chronic illness
    - Kallmann syndrome
      - Congenital syndrome due to failure of developmental neuronal migration
      - Clinically manifests as primary amenorrhea (*due to failure of GnRH secretion*) + anosmia or hyposmia (*no or impaired of sense of smell*)
    - Destructive lesions of the hypothalamus
      - Neoplasms/space-occupying lesions (*e.g. craniopharyngioma, which can compress on pituitary stalk*)
      - Previous encephalitis
  - ***Pituitary pathology***
    - Hyperprolactinemia
      - Pituitary adenoma
      - Primary hypothyroidism
      - Drugs
    - Destructive lesions of the pituitary
      - Neoplasms/space occupying lesions
  - ***Ovarian pathology***
    - Developmentally abnormal gonads
      - Pure gonadal dysgenesis (46XX & 46XY)
      - Pseudohermaphroditism (*androgen insensitivity syndrome, testicular regression syndrome, Leydig cell agenesis*)
      - Chromosomal defects affecting gonadal development (*Turner syndrome, mosaicism with or without Y chromosome*)
    - Enzymatic defects
      - Rare defects in enzymes involved in androgen & estrogen production
      - e.g. 17-hydroxylase deficiency (*results in lack of sex hormone production, with precursors shunted to aldosterone production, which may result in hypokalemia & secondary hypertension*)
  - ***Anatomic abnormalities of the reproductive tract***
    - Congenital obstructive reproductive tract anomalies
      - Imperforate hymen
      - Transverse vaginal septum
      - Cervical agenesis
    - Congenital uterine abnormalities
      - e.g. Müllerian agenesis (Rokitansky-Küster-Hauser syndrome)

- **Approach to Primary Amenorrhea**
  - ***History:***
    - Pubertal status: *any thelarche/pubarche yet? (e.g. hyperprolactinemia can present with primary amenorrhea despite thelarche & pubarche having occurred)*
    - Hypothalamic: *family history of delayed puberty, chronic illness, stress, exercise, diet, headache, visual field disturbance, sense of smell*
    - Pituitary: *headache, visual field disturbance, hypothyroid symptoms, drug use*
    - Ovarian: *usually asymptomatic*
    - Anatomic: *cyclical pelvic pain, bulge at introitus*
  - ***Physical examination:***
    - General: *pubertal assessment (Tanner staging), blood pressure, height/weight/nutritional status, dysmorphism*
    - Systemic: *sense of smell, visual fields, fundoscopy, thyroid examination, breast examination*
    - Pelvic examination: *inspect obstructive abnormalities; if vagina only rudimentarily present as a dimple, assess presence of uterus via rectal examination*
  - ***Investigations & work-up:***
    - **Amenorrhea panel** (*FSH, LH, E2, T, prolactin ± TSH*)
      - Low FSH, LH & E2 in hypothalamic & pituitary causes (*hypogonadotropic hypogonadism*)
      - High FSH & LH + low E2 in primary ovarian causes (*hypergonadotropic hypogonadism*)
      - Normal FSH, LH & E2 in anatomical causes (*however note that some ovarian causes may also be associated with reproductive tract anomalies*)
    - **Chromosomal & genetic studies**
      - Karyotype for chromosomal anomalies
      - Genetic testing for suspected genetic causes
    - **Pelvic ultrasound**
      - Assess uterine size (*onset of puberty is suggested by a uterine corpus:cervix ratio of ≥2:1*)
      - Detect structural abnormalities of the reproductive tract & presence of gonads
    - **Intravenous pyelogram**
      - Indicated in cases of reproductive tract abnormalities to rule out concomitant urinary tract structural abnormalities
    - **MRI brain**
      - Assess for hypothalamic & pituitary pathology

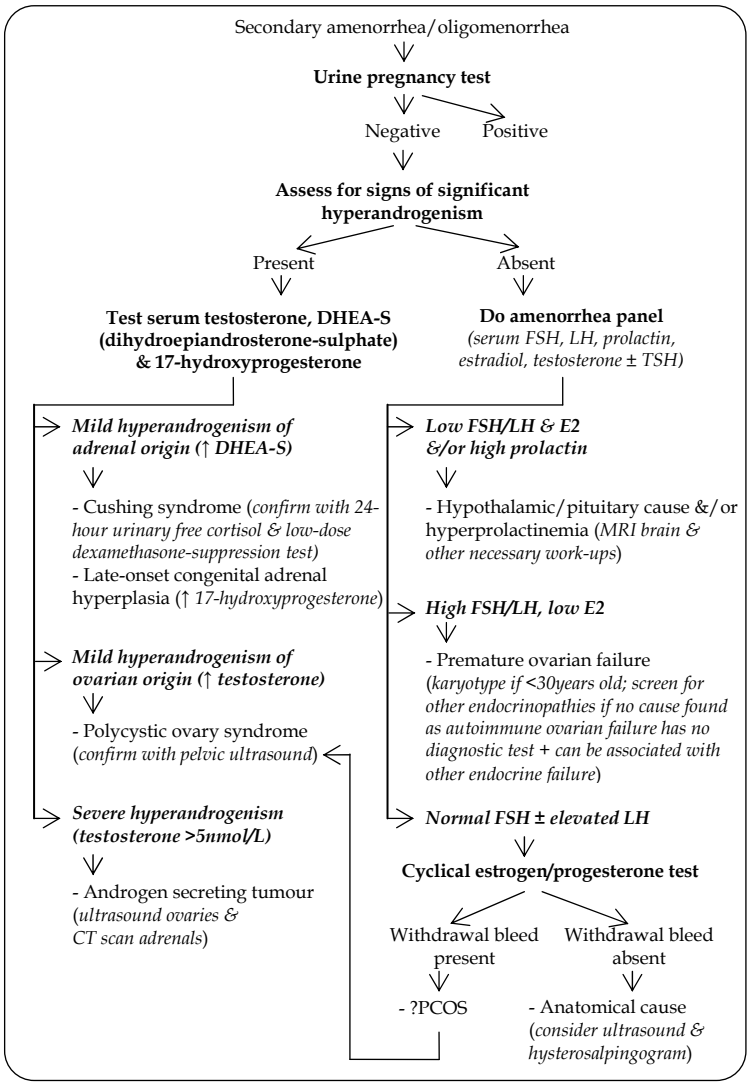
- **Management of Primary Amenorrhea**
  - ***Management of hypothalamic pathology:***
    - Reassurance & follow-up constitutional delay
    - Lifestyle modifications
    - Exogenous estrogen to induce breast development for untreatable hypogonadotropic causes
    - Surgical resection of tumours
  - ***Management of pituitary pathology:***
    - Dopamine agonists for hyperprolactinemia (*bromocriptine, cabergoline*)
    - Thyroxine replacement for hypothyroidism
    - Exogenous estrogen to induce breast development for untreatable hypogonadotropic causes
    - Surgical resection of tumours
  - ***Management of ovarian pathology:***
    - Exogenous estrogen to induce breast development for untreatable hypogonadism
    - Surgical removal of gonads if dysgenetic gonads diagnosed to prevent malignant transformation
  - ***Management of anatomical causes:***
    - Surgical treatment for obstructive causes (*e.g. cruciate incision for imperforate hymen*)
    - Neovagina creation (*Frank method of vagina dilation, McIndoe vaginoplasty*)

Secondary Amenorrhea/Oligomenorrhea

Secondary amenorrhea = cessation of menses for ≥6 months
Oligomenorrhea = infrequent menstruation with >35 days length

- **Causes of Secondary Amenorrhea/Oligomenorrhea** (*always rule out pregnancy first*)
  - ***Hypothalamic dysfunction (35%)***
    - Systemic stresses:
      - Significant weight loss (*e.g. anorexia nervosa*)
      - Excessive physical activity/exercise
      - Severe emotional distress
      - Chronic illness
    - Destructive lesions of the hypothalamus:
      - Neoplasms/space-occupying lesions (*e.g. craniopharyngioma, which can compress on pituitary stalk*)
      - Sarcoidosis
      - Previous encephalitis
  - ***Pituitary dysfunction (20%)***
    - Hyperprolactinemia (15%)
      - Pituitary adenoma
      - Drugs (*anti-psychotics, metoclopramide, butyrophenones & phenothiazines*)
      - Breast-feeding or breast stimulation
      - Primary hypothyroidism (*leads to secondary elevation of TRH which has stimulatory effect on prolactin secretion*)
      - Chronic renal failure (*decreased clearance of prolactin leading to its accumulation in serum*)
    - Destructive lesions of the pituitary (5%)
      - Neoplasms/space-occupying lesions
      - Sarcoidosis
      - Sheehan syndrome
      - Iatrogenic (*previous transphenoidal resection of pituitary tumours or cranial radiation)*
  - ***Ovarian dysfunction (40%)***
    - Premature ovarian failure
      - Dysgenetic gonads (*e.g. Turner's*)
      - Autoimmune premature ovarian failure
      - Infections (*e.g. mumps*)
      - Iatrogenic (*pelvic radiation, chemotherapy*)
    - Hyperandrogenic disorders
      - Ovarian disorders: *PCOS, HAIR-AN (hyperandrogenic insulin resistance & acanthosis nigricans) syndrome, virilizing tumours (arrhenoblastoma, lipid cell tumour)*
      - Adrenal disorders: *late-onset CAH, Cushing syndrome, androgen-secreting adrenal tumour*
  - ***Anatomic abnormalities of the reproductive tract (5%)***
    - Asherman syndrome (*past terminations of pregnancy, dilatation & curettage*)

- **Approach to Secondary Amenorrhea/Oligomenorrhea**
  - ***History:***
    - Hypothalamic: *chronic illness, stress, exercise, diet, headache, visual field disturbance*
    - Pituitary: *headache, visual field disturbance, hypothyroid symptoms, drug use, galactorrhea*
    - Ovarian: *perimenopausal vasomotor symptoms, hirsutism, virilizing changes, history of pelvic radiation or chemotherapy*
    - Anatomic: *any past TOPs or dilatation & curettage*
  - ***Physical examination:***
    - General: *body habitus/BMI, signs of virilization, cutaneous signs (acanthosis nigricans), secondary sexual characteristics, dysmorphism*
    - Systemic: *visual fields, fundoscopy, thyroid examination, breast examination, pelvic examination*
  - ***Investigations & work-up:***



- **Urine pregnancy test**
  - Always important to rule out pregnancy in women of reproductive age presenting with amenorrhea
- **Serum LH/FSH**
  - Low in states of decreased gonadotropin production (*hypothalamic & pituitary dysfunction*)
  - Very high FSH is suggestive of a menopausal state (*premature ovarian failure*)
  - Normal FSH is present in PCOS & anatomical causes of amenorrhea
  - Reversed LH:FSH ratio (normal is 1:1; ratios ≥3:1 may be present in PCOS
- **Serum prolactin & TSH**
  - Diagnoses hyperprolactinemia
  - Extremely high prolactin (>1000) is suggestive of a pituitary adenoma
  - High TSH suggests a primary hypothyroidism cause of hyperprolactinemia
- **Serum estradiol**
  - Low in hypothalamic/pituitary dysfunction & premature ovarian failure

- **Serum testosterone**
  - Elevated in PCOS
  - Very high testosterone (>5nmol/L) is suggestive of an androgen producing tumour
- **Serum dihydroepiandrosterone-sulphate (DHEA-S)**
  - Elevated in adrenal hyperandrogenic disorders (Cushing's, late onset CAH)
- **Serum 17-hydroxyprogesterone**
  - Elevated in late onset CAH
- **Cyclical estrogen/progesterone test**
  - Tests for withdrawal bleed which if present, indicates an normal responsive endometrial lining (*hence ruling out anatomical causes*)
- **Pelvic ultrasound**
  - Assess for possible ovarian tumours
  - Assess for PCOS
  - Assess for anatomical abnormalities
- **MRI brain**
  - Assess for hypothalamic & pituitary pathology
- **CT abdomen**
  - Assess for adrenal tumours

Reference Ranges for Amenorrhea Panel

Phase	*FSH (IU/L)*	*LH (IU/L)*	*Estradiol (pmol/L)*	*Testosterone (nmol/L)*	*Prolactin (mIU/L)*
Follicular	3.5-12.5	2.4-12.6	90-716	0.22-2.90	70-510
Ovulating	4.7-21.5	14.0-45.6	243-1509		
Luteal	1.7-7.7	1.0-11.4	147-958		
Menopause	25.8-134.8	7.7-58.5	<50-145		

- **Management of Secondary Amenorrhea/Oligomenorrhea**
  - ***Management of hypothalamic dysfunction:***
    - Lifestyle modifications (*improve nutrition, cut down on excessive exercise, psychosocial help*)
    - Combined oral contraceptives (*to help prevent osteoporosis & maintain normal breast & vagina tissue*)
    - Surgical resection of tumours
  - ***Management of pituitary dysfunction:***
    - Dopamine agonists for hyperprolactinemia (*bromocriptine, cabergoline*)
    - Thyroxine replacement for hypothyroidism
    - Combined oral contraceptives (*to help prevent osteoporosis & maintain normal breast & vagina tissue*)
    - Surgical resection of tumours
  - ***Management of premature ovarian failure:***
    - Hormonal replacement therapy (combined estrogen + progestin) to prevent osteoporosis
    - Surgical removal of gonads if dysgenetic gonads diagnosed to prevent risk of malignant transformation
  - ***Management of hyperandrogenism:***
    - Androgen blockers for hirsutism (*spironolactone, cyproterone acetate, flutamide*)
    - Progestin therapy for chronic anovulation – e.g. in PCOS – to protect against endometrial hyperplasia & endometrial cancer
    - Combined oral contraceptives (*to regulate menstrual cycle & suppress gonadotropin stimulation of excess ovarian androgen production in PCOS*)
    - Surgical resection of tumours
  - ***Management of anatomical causes:***
    - Hysteroscopic excision of synechiae for Asherman's

Polycystic Ovary Syndrome (PCOS)

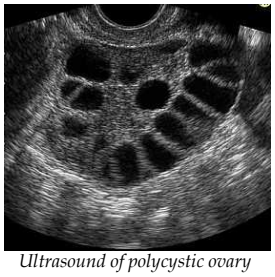
Syndrome of chronic anovulation/oligo-ovulation with clinical or laboratory evidence of hyperandrogenism after excluding any other underlying condition (a diagnosis of exclusion)

- **Epidemiology & Associations**
  - 6-10% of pre-menopausal women have some form of PCOS
  - ***Associations:***
    - Peripheral insulin resistance, hyperinsulinemia
    - Diabetes mellitus (type 2), obesity, dyslipidemia, hypertension (metabolic syndrome)
    - Hirsutism
  - **Stein-Leventhal syndrome** characterizes the subset of women with PCOS demonstrating all the combined features of obesity, hirsutism & polycystic ovaries

- **Pathophysiology of Polycystic Ovary Syndrome**
  - Exact etiology & pathogenesis in unknown; however, the following pathophysiological features are noted:
    - Hereditary component (*1st degree relative affected increases risk of PCOS*)
    - Peripheral insulin resistance
  - ***Hormonal changes in PCOS:***
    - Increased serum LH levels, which in turn promotes increased amount of ovarian androgen (*testosterone, androstenedione*) secretion
      - *High androgen levels induces atresia of ovarian follicles, interfering with normal follicular development leading up to ovulation*
      - *High androgen levels also results in increased peripheral aromatization of androgens into estrogen, resulting in tonically elevated estrogen levels which suppresses FSH secretion*
      - *Lack of normal estrogen rise results in lack of LH surge, with resultant anovulation*
    - Peripheral insulin resistance often found concomitantly results in secondary hyperinsulinemia
      - *High insulin levels stimulate further ovarian androgen production*
      - *High insulin levels combined with elevated androgens also suppresses hepatic secretion of sex-hormone binding proteins, resulting in an increased serum unbound fraction of androgens*

- **Clinical Consequences of Polycystic Ovary Syndrome**
  - ***Gynaecological consequences:***
    - Oligomenorrhea, amenorrhea
    - Increased risk of endometrial hyperplasia & cancer due to chronic anovulation leading to prolonged unopposed estrogenic stimulation of endometrium
    - Subfertility
    - Increased risk of GDM during pregnancy
  - ***Hyperandrogenic consequences:***
    - Hirsutism (*can be scored using Ferriman Gallwey score*)
    - Balding, oily skin, acne
  - ***Complications related to metabolic syndrome:***
    - Hypertension, diabetes mellitus, dyslipidemia
    - Atherosclerotic diseases
    - Obstructive sleep apnea

- **Rotterdam Criteria (2003) for the Diagnosis of PCOS**
  (*European Society of Human Reproduction & Embryology/American Society for Reproductive Medicine (ESHRE/ASRM) sponsored workshop on PCOS in 2003; requires ≥2 out of the following 3 criteria met + exclusion of other possible etiologies*)
  1. ***Evidence of oligo- &/or anovulation***
     - <8 menstrual cycles per year
  2. ***Evidence of hyperandrogenism***
     - Clinical evidence: **Ferriman Gallwey score** &/or
     - Biochemical evidence: serum total testosterone
  3. ***Evidence of polycystic ovaries***
     - Presence of ≥12 follicles 2-9mm in diameter &/or
     - Increased ovarian volume (>10ml)
     - *Note: only 1 ovary fitting this criteria is sufficient*
  - ***Following differentials should be ruled out:***
    - Late onset CAH
    - Androgen-secreting tumours
    - Cushing syndrome



Ultrasound of polycystic ovary

- **Other Adjunctive Investigations**
  - ***Amenorrhea panel:***
    - May be performed in the initial work-up for a presenting complain of oligo-/amenorrhea
    - Typical profile seen in PCOS:
      - Normal FSH ± ↑LH
      - Reversed LH:FSH ratio (~3:1)
      - Normal/slightly elevated estradiol
      - Elevated testosterone
      - Prolactin may be elevated
  - ***Hyperandrogenism panel:***
    - Elevated testosterone
    - Normal 17-hydroxyprogesterone (*rules out late onset congenital adrenal hyperplasia*)
  - ***24-hour urinary free cortisol & low dose dexamethasone suppression test***
    - Rules out Cushing syndrome
  - ***Radiological investigations:***
    - CT abdomen (*excludes androgen secreting tumour of the adrenals*)
  - ***Screening for co-morbidities:***
    - Test for diabetes with OGTT
    - Test fasting lipids to detect dyslipidemia
    - Measure blood pressure

- **Management of Polycystic Ovary Syndrome**
  - ***Conservative management:***
    - Lifestyle modifications (*exercise, dietary modifications, quit smoking*)
      - Can have dramatic effect on normalizing menstrual cycles & improving insulin resistance
  - ***Medical management:***
    - **Combined oral contraceptives**
      - Helps regulate menstrual cycle
      - Protects against unopposed estrogen stimulation of endometrium in long run
      - Has also been shown to suppress excess ovarian androgen production & increase hepatic synthesis of serum sex-hormone binding globulin
    - **Progestin therapy**
      - Used to induce withdrawal bleed every month
      - Useful in patients in whom exogenous estrogen is risky or contraindicated
      - Protects against unopposed estrogen stimulation of endometrium in long run
    - **Metformin**
      - Used to improve insulin sensitivity which can result in menstrual regularity & ovulatory function
      - Used as adjunctive treatment to clomiphene in women with PCOS trying to conceive
    - **Androgen blockers**
      - Spironolactone, cyproterone acetate, flutamide
      - Used to treat hirsutism
      - Pregnancy should be avoided due to teratogenic effects of these drugs
    - **Clomiphene**
      - Selective estrogen receptor modulator with antagonistic effect on pituitary estrogen receptors (*blocks negative feedback, hence stimulating gonadotropin release, which induces follicular development in the ovaries*)
      - 1st-line treatment for women with PCOS trying to conceive
      - Risks: *multiple pregnancies, epithelial ovarian cancers, ovarian hyperstimulation*
    - **Medical treatment of other co-morbidities** (*diabetes mellitus, hypertension, dyslipidemia*)
  - ***Surgical management:***
    - **Ovarian drilling**
      - Creation of holes in ovaries using laser or diathermy with the intent of reducing steroid hormone production
      - 2nd-line treatment for women with PCOS trying to conceive after failed clomiphene treatment
    - **Assisted reproductive techniques (IVF)**

Abnormal Uterine Bleeding

Uterine bleeding which is excessive in amount, duration &/or frequency occurring in reproductive years (i.e. pre-menopausal)

- **Types of Abnormal Uterine Bleeding (AUB)**
  - ***Menorrhagia***
    - Excessive (>80ml) &/or prolonged menses (>7 days) occurring at normal intervals (*i.e. regularity normal*
  - ***Polymenorrhea***
    - Abnormally frequent menses (length <21 days)
  - ***Metrorrhagia***
    - Irregular episodes of uterine bleeding of normal amount (*normal regularity completely disrupted*)
  - ***Metromenorrhagia***
    - Uterine bleeding that is excessive & irregular
  - ***Intermenstrual bleed (IMB)***
    - Scant bleeding occurring between 2 consecutive menses (*usually at ovulation, lasting 1-2days*)

- **Causes of Abnormal Uterine Bleeding**
  - ***Dysfunctional uterine bleeding***
    - Abnormal uterine bleeding for which no organic cause is found (*diagnosis of exclusion*)
    - 2 main types:
      - **Ovulatory DUB**: *corpus luteal deficiency with resultant insufficiency of progesterone secretion during luteal phase, causing shortened menstrual cycles & pre-menstrual spotting*
      - **Anovulatory DUB**: *failure of achieving ovulation with no resultant corpus luteum or progesterone secretion, hence unopposed estrogen continues stimulating endometrial proliferation; however, lack of progesterone which is required for inducing adequate vascular growth to support further endometrial growth results in eventual breakdown & sloughing of endometrium; this sloughing tends to be heavy, prolonged & irregular due to the thickened endometrial lining & lack of clear hormonal events to induce a thorough sloughing (unlike in normal cycles where regression of corpus luteum results in a sharp fall in hormones)*
    - Anovulatory DUB is most commonly seen in extremes of reproductive life:
      - Post-menarche: *HPO-axis may not be fully sensitized & functional initially*
      - Pre-menopausal: *diminishing population of follicles left in the ovaries*
  - ***Pregnancy complications:***
    - Miscarriage (*threatened, incomplete, complete*)
    - Ectopic pregnancy, molar pregnancy
  - ***Pelvic pathology:***
    - Uterine fibroids
    - Adenomyosis
    - Endometrial pathology (*polyps, hyperplasia, cancer*)
    - Cervical pathology (*polyps, cancer)*
    - Lower tract neoplasms
    - Infection (*endometritis, cervicitis, lower tract infection*)
    - Trauma/lacerations
  - ***Systemic causes:***
    - Coagulopathy/blood dyscrasias
    - Thyroid disease (*usually hypothyroidism*)
    - Liver disease (*may cause coagulopathy & increased levels of serum estrogen due to decreased metabolism*)
  - ***Iatrogenic causes:***
    - Anti-platelets & anti-coagulants
    - Exogenous hormones
    - Copper IUCD

- **Approach to Abnormal Uterine Bleeding**
  - ***History:***
    - Menstrual history (current & past):
      - Last menstrual period
      - Regularity & length of cycles
      - Duration & amount of menses
      - Any intermenstrual &/or post-coital bleeding
    - Any pain or dysmenorrhea
      - Dysmenorrhea may suggest adenomyosis or chronic pelvic inflammatory disease
      - Lower abdominal pain may be present in infections of the reproductive tract or pregnancy complications
    - Per-vaginal discharge
      - Foul-smelling coloured discharge may indicate infection of reproductive tract
      - Greyish tissues passed may suggest products of conception in an incomplete abortion
    - Systemic screen
      - Constitutional symptoms (*fever, LOA, LOW*)
      - Symptoms of anemia (*to assess severity*)
      - Thyroid symptoms (*lethargy, cold intolerance, constipation*)
      - Urinary symptoms (*hematuria may occur in locally invasive neoplasms; frequency or obstructive symptoms may be present due to mass effect of local pathology*)
      - Changes in bowel habits
      - Any other sources of bleeding
    - Past medical/surgical/gynaecological history
      - Any current medications
      - Any contraceptives currently used
      - Last Pap smear & mammogram (+ results)
    - Family history
    - Social history
      - Smoking, drinking
      - Sexual history (*especially if STD suspected*)
      - Desire for future fertility; desire for menses or amenorrhea (*affects management*)
  - ***Physical examination:***
    - General examination
      - Assess patient's vitals & look for pallor
      - Assess for supraclavicular lymphadenopathy
      - Neck examination for goitre
      - Breast examination
      - Chest & lungs for pleural effusion
    - Abdominal examination
      - Inspect for distension, past surgical scars
      - Palpate for organomegaly & abdominopelvic masses
      - Palpate for any lower abdominal tenderness
      - Percuss for shifting dullness
    - Pelvic examination
      - Inspect for any vulvar lesions
      - Speculum examination to inspect cervix (*any lesions, os open? products of conception seen?*) & vaginal walls
      - Take a Pap smear & swabs where indicated during speculum examination
      - Digital vaginal examination to elicit cervical excitation & feel for uterosacral & pouch of Douglas masses
      - Bimanual palpation to assess uterine size, define any abdominopelvic mass felt
      - Rectal examination where indicated to assess local invasion where malignancy is suspected

- *Investigations & work-up:*
  - Urine pregnancy test
  - Blood tests
    - Full blood count (*assess for anemia & platelets*)
    - PT/PTT (*rule out coagulopathy*)
    - Thyroid function test (*rule out hypothyroidism*)
  - Tests for sexually-transmitted diseases
    - Urine PCR for Chlamydia antigen
    - Endocervical & high vaginal swab (HVS) for gonococcal culture
    - Workup for bacterial vaginosis, Trichomonas & Candida where indicated
    - Consider HIV, VDRL & hepatitis B screening
  - Pelvic ultrasound
    - Assess for uterine pathology
    - Assess for viability & site of pregnancy
  - Endometrial biopsy
    - Done where endometrial hyperplasia or cancer is suspected (*see "Algorithm for Endometrial Evaluation" in "Gynaecologic Oncology"*)

- **Management of Abnormal Uterine Bleeding**
  - *Non-hormonal medical treatment:*
    - **Tranexamic acid**
      - Decreases heavy flow by 50%
    - **NSAIDS (e.g. mefenamic acid aka Ponstan)**
      - Decreases heavy flow by 30%
      - Helps relieve dysmenorrhea as well
  - *Hormonal medical treatment:*
    - **Combined oral contraceptive pills**
      - Decreases heavy flow by 43%
      - Helps relieve dysmenorrhea as well
      - Protects against risk of endometrial cancer in anovulatory DUB
    - **Progestin therapy**
      - Progestin-only pills aka POP (*norethisterone, medroxyprogesterone acetate*) decreases heavy flow by 80%
      - Depot progestin injections (*Depo-Provera*) decreases heavy flow by 70-90%
      - Subcutaneous implantable Etonogestrel (*Implanon*) decreases heavy flow by 70-90%
      - Levonorgestrel-releasing intra-uterine system (*Mirena*) decreases heavy flow by 70-90%; also helps with dysmenorrhea in adenomyosis
    - **For patients with DUB desiring fertility:**
      - Luteal phase progesterone (*e.g. Duphaston aka dydrogesterone*) for ovulatory DUB
      - Ovulation induction for anovulatory DUB
    - **GnRH agonists**
      - Induces pseudo-menopause to achieve amenorrhea
      - Option for heavy symptomatic abnormal uterine bleeding refractory to other medical treatments to allow for patient to restore a normal haemoglobin level + buy time to plan definitive treatment
      - Adverse effect on bone mineral density; use limited to 6 months at most
  - *Surgical treatment:*
    - **Dilatation & curettage + hysteroscopy**
      - Does not offer a permanent cure
      - Therapeutic for bleeding in short term + diagnostic (*provides better sample for endometrial histological assessment than endometrial sampling*)
      - Therapeutic measures can be undertaken for certain pathologies visualized (*e.g. resection of polyps & submucosal fibroids*)
    - **Endometrial ablation**
      - Reserved for older patients who do not desire fertility but wish to retain uterus with bleeding refractory to medical treatment
      - Best done for uterus <10 weeks size
      - Modalities: *transcervical resection of the endometrium (TCRE), roller ball diathermy, microwave endometrial ablation, novasure*
      - 60-70% success rate, can decrease heavy bleeding by 40%
      - Not definitive however, recurrence would require repeat ablation
    - **Hysterectomy**
      - Definitive treatment for bleeding refractory to medical treatment
      - Option in older patients with no desire for uterus preservation or future fertility

Post-Coital & Post-Menopausal Bleeding

Post-coital bleed (PCB) = per-vaginal bleeding after intercourse
Post-menopausal bleed (PMB) = per-vaginal bleeding after menopause
Both are assumed pathological until proven otherwise

- **Causes of PCB & PMB**
  - *Causes of post-coital bleeding:*
    - Vaginal causes (rare)
      - Vaginal trauma/lacerations
      - Vaginal growths/neoplasms
    - Cervical causes
      - Cervical trauma/lacerations
      - Cervical ectropion
      - Cervical polyps
      - Cervical cancer
  - *Causes of post-menopausal bleeding:*
    - Vulvar causes (rare)
    - Vaginal causes
      - Atrophic vaginitis (most common)
      - Vaginal growths/neoplasms
    - Cervical causes
      - Cervical growths/neoplasms
    - Uterine causes
      - Endometrial growths/neoplasms

- **Evaluation of PCB & PMB**
  - *Evaluation of post-coital bleeding:*
    - Requires evaluation of the entire lower genital tract
    - Direct examination under good light to look for visible lesions of the lower genital tract
    - Assessment of cervix:
      (*refer to "Cervical Screening (Pap Smear) Algorithm" in "Gynaecologic Oncology"*)
      - Visible lesion → biopsy
      - No visible lesion → Pap smear
  - *Evaluation of post-menopausal bleeding:*
    - Requires evaluation of the entire lower genital tract + evaluation of the endometrium
    - Direct examination under good light to look for visible lesions of the lower genital tract
    - Assessment of cervix (as for post-coital bleeding)
    - Transvaginal ultrasound to assess endometrial thickness & determine need for follow-up investigations:
      (*refer to "Algorithm for Endometrial Evaluation" in "Gynaecologic Oncology"*)
      - <5mm → observe
      - >5mm → endometrial biopsy

Dysmenorrhea

Painful menstruation; may be primary (no readily identifiable cause) or secondary (results from underlying organic pelvic disease)

Primary Dysmenorrhea

- **Pathophysiology of Primary Dysmenorrhea**
  - Occurs during ovulatory cycles, typically appearing within 6-12 months from menarche
  - Etiology attributed to uterine contractions with ischemia & production of prostaglandins
  - Evidence supporting involvement of prostaglandins in primary dysmenorrhea:
    - Menstrual fluid from women with primary dysmenorrhea contain higher than normal levels of prostaglandin
    - NSAIDs are effective treatment modalities
    - Anovulatory cycles often have painless menses (*secretory endometrium under the influence of progesterone have much higher levels of prostaglandin than proliferative endometrium*)

- **Clinical Features of Primary Dysmenorrhea**
  - Cramping lower abdominal pain:
    - Often begins a few hours before onset of menses
    - May persist for hours or days (usually 48-72 hours)
    - May radiate to thighs & lower back
  - Associated symptoms:
    - Nausea/vomiting
    - Fatigue, dizziness, headache
    - Altered bowel habits (diarrhea)
  - Pelvic examination should be <u>normal</u>

- **Management of Primary Dysmenorrhea**
  - ***Conservative management:***
    - Reassurance & explanation
  - ***Medical management:***
    - Paracetamol
    - NSAIDs (*ibuprofen, naproxen, mefenamic acid*)
    - Combined oral contraceptive pills
    - High-dose continuous progestins (*dydrogesterone, medroxyprogesterone acetate*)
    - Smooth muscle anti-spasmodics (*alverine, hyoscine*)
  - ***Alternative management:***
    - Transcutaneous nerve stimulation
    - Acupuncture
    - Psychotherapy, hypnotherapy
  - Dysmenorrhea refractory to NSAIDs & hormonal therapy:
    - Should re-assess patient to look harder for possible underlying organic pelvic disease
    - Ultrasound, exploratory laparoscopy, hysteroscopy are all modalities to be considered for a more thorough workup

Secondary Dysmenorrhea

- **Causes of Secondary Dysmenorrhea**
  - ***Endometriosis***
    - Pain tends to extend to pre- & post-menstrual phases or may even be continuous
    - Other symptoms: *deep dyspareunia*
    - Signs: *uterosacral tender nodules, pouch of Douglas nodularity, visible tender nodules in posterior fornix, palpable adnexal mass (endometrioma)*
  - ***Adenomyosis (occasionally fibroids)***
    - Other symptoms: *menorrhagia*
    - Signs: *enlarged bulky uterus which may be mildly tender*
  - ***Pelvic inflammatory disease***
    - Pain may extend into pre-menstrual phase
    - Other symptoms: *deep dyspareunia, intermenstrual bleeding, vaginal discharge*
    - Signs: *pelvic tenderness, may have adnexal mass (tubo-ovarian abscess, hydrosalpinx)*
  - ***Ovarian cysts (especially luteal & endometriotic cysts)***
    - Other symptoms: *may have mass symptoms if large*
    - Signs: *palpable adnexal mass*
  - ***Pelvic congestion***
    - Dull ill-defined pelvic ache worse premenstrually, relieved by menses
    - History of sexual problems usually present

Pelvic Pain

Acute Pelvic Pain

- **Gynaecologic Causes of Acute Pelvic Pain**
  - ***Physiological:***
    - **Mittelschmerz** (*midcycle pain resulting from ovulation*)
  - ***Adnexal accidents:***
    - Ovarian cyst torsion
    - Ovarian cyst rupture
    - Intra-cystic hemorrhage
  - ***Acute infections:***
    - Acute pelvic inflammatory disease
    - Endometritis
  - ***Pregnancy complications:***
    - Ruptured ectopic pregnancy
    - Incomplete/complete miscarriage

- **Non-Gynaecologic Causes of Acute Pelvic Pain**
  - ***Gastrointestinal causes:***
    - Acute appendicitis
    - Diverticulitis
    - Intestinal obstruction
  - ***Urinary system causes:***
    - Acute cystitis
    - Ureteral stones
    - Urethral syndrome
  - ***Other causes:***
    - Pelvic thrombophlebitis
    - Acute porphyria
    - Mesenteric adenitis

Chronic Pelvic Pain

Defined as pelvic pain of >6 months duration that has a significant impact on the daily function & quality of life of a patient

- **Causes of Chronic Pelvic Pain**
  - ***Gynaecologic causes:***
    - Endometriosis
    - Chronic pelvic inflammatory disease
    - Ovarian pain (*e.g. in ovarian remnant syndrome where an ovary or a remnant of it becomes retroperitoneal secondary to inflammation or previous surgery; cyst formation in these circumstances causes chronic pain*)
    - Adenomyosis
    - Uterine fibroids (*typically painless; however, large degenerating fibroids or those compression pelvic nerves may cause chronic pain*)
    - Pelvic congestion syndrome (*clinical entity seen in multiparous women with pelvic vein varicosities & congested pelvic organs; pain is worse premenstrually, upon standing & during sexual intercourse*)
  - ***Gastrointestinal causes:***
    - Irritable bowel syndrome (*most common*)
    - Inflammatory bowel disease
    - Hernia
    - Locally invasive GI malignancies
  - ***Urinary system causes:***
    - Urinary retention
    - Urethral syndrome
    - Trigonitis
    - Interstitial cystitis
  - ***Neuromuscular causes:***
    - Fibromyalgia
    - Nerve entrapments (*iliohypogastric, ilioinguinal, pudendal*)

- **Evaluation of Chronic Pelvic Pain**
  - ***History:***
    - Take a thorough pain history (+ relation to menstrual cycle)
    - Menstrual history
    - Screen symptoms of other systems (*bowel, urinary, musculoskeletal*)
    - Past medical, surgery, obstetric & gynaecologic history
  - ***Physical examination:***
    - Abdominal examination
      - Palpate for masses
      - Examine abdominal wall for myofascial trigger points & for nerve entrapment pain in corresponding dermatomes (T12, L1, L2)
    - Pelvic examination
      - Assess uterine size & version (*fixed retroverted uterus may suggest endometriosis*)
      - Feel for uterosacral & pouch of Douglas nodularity & tenderness
      - Palpate for adnexal masses
  - ***Investigations & work-up:***
    - Pelvic ultrasound
    - CT abdomen, GI endoscopy, cystoscopy & CT urogram are useful modalities for assessment of gastrointestinal & urinary system differentials
    - Diagnostic laparoscopy

- **Management of Chronic Pelvic Pain**
  - Treat any treatable underlying pathology identified
  - For no pathology or pathology not amenable to treatment identified:
    - Multidisciplinary team care
    - Medical treatment:
      - Hormonal treatment
      - NSAIDs
      - Tricyclic antidepressants
      - Serotonin-norepinephrine reuptake inhibitors
      - Anti-convulsants
    - Anesthesia
      - Nerve blocks
      - Trigger point injections of local anesthetic
    - Surgical treatment
      - Presacral neurectomy
      - Adhesiolysis
      - Unilateral adnexectomy
      - Hysterectomy

Vulvovaginitis

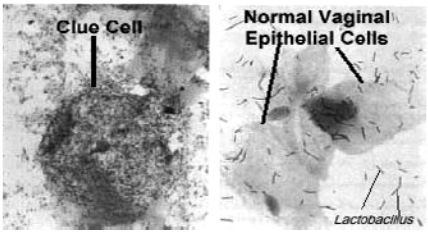
Bacterial Vaginosis

Most common cause of vaginal discharge

- **Microbiology & Pathophysiology**
  - Involves disruption of normal healthy vaginal microflora (*e.g. Lactobacillus jensenii, Lactobacillus crispatus*) by a characteristic set of BV-complex microorganisms:
    - *Gardnerella vaginalis*
    - Genital mycoplasmas (*Mycoplasma hominis, Ureaplasma urealyticum*)
    - Vaginal anaerobic bacteria (*Prevotella, Bacteroides, Mobiluncus*)
  - Risk factors & associations for developing BV:
    - New sexual partner
    - Smoking
    - Use of intrauterine device
    - Frequent douching

- **Clinical Features**
  - ***Asymptomatic***
  - ***Symptomatic presentation:***
    - Vaginal odour
    - Vaginal discharge (*profuse, milky, non-adherent*)
  - ***Complications:***
    - For non-pregnant women, increases risk of:
      - Pelvic inflammatory disease
      - Postoperative infections (*e.g. after hysterectomy, termination of pregnancy*)
      - HIV transmission
    - For pregnant women, increases risk of:
      - 2nd trimester miscarriage
      - Preterm labour

- **Diagnosis & Evaluation**
  - **Amsel criteria** (requires ≥3 of 4 features)
    - Characteristic vaginal discharge (*homogeneous, watery, white/grey coloured, thin*)
    - **Whiff test** positive (*fishy odour after alkalinizing vaginal discharge with a drop of 10% potassium hydroxide*)
    - Presence of >20% clue cells (*vaginal epithelial cells with edges blurred by bacteria*) on microscopy of wet mount preparation
    - Vaginal pH >4.5



- **Management**
  - ***Antimicrobial therapy:***
    - Metronidazole PO 500mg twice daily x 7 days
    - Clindamycin cream 2% with one applicator (5g) intravaginally at bedtime x 7 days
  - ***Partner screening:***
    - Generally <u>not</u> recommended for BV

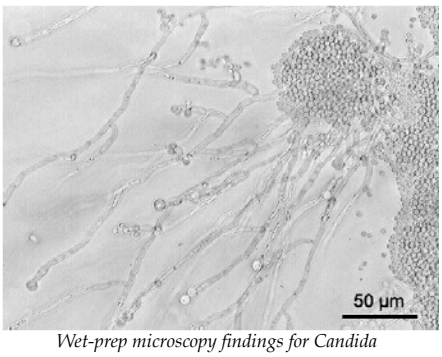
Vulvovaginal Candidiasis

2nd most common cause of vulvovaginal-related symptoms; up to 75% of women acquire vulvovaginal candidiasis at some point in time

- **Microbiology & Pathophysiology**
  - Caused by fungal pathogens:
    - *Candida albicans* (most common)
    - *Candida glabrata*
  - Risk factors & associations for developing candidiasis:
    - Highly-estrogenized vaginal epithelium:
      - High-dose oral contraceptives
      - Pregnancy
      - After menarche, before menopause
    - Immunosuppresion:
      - Diabetes mellitus
      - Long-term steroid use
      - HIV
    - Disruption of normal vaginal flora:
      - Frequent douching
      - Antibiotic use

- **Clinical Features**
  - ***Symptomatic presentation:***
    - Vaginal itching, burning sensation, irritation
    - Vaginal discharge (*odourless, white, thick & curdy with appearance of cottage cheese*)
    - Dysuria may also be present
    - Vaginal speculum examination often reveals vulvovaginal erythema with evidence of acute on chronic excoriation
  - ***Recurrent vulvovaginal candidiasis:***
    - Defined as ≥4 episodes within 1 year (5% of cases)

- **Diagnosis & Evaluation**
  - ***Microscopy of wet mount preparation***
    - Reveals budding yeast cells, pseudohyphae or mycelial tangles (in 50-70% of cases)
  - ***Fungal culture***
    - May be considered in cases with suggestive clinical findings but absent wet-prep microscopy evidence



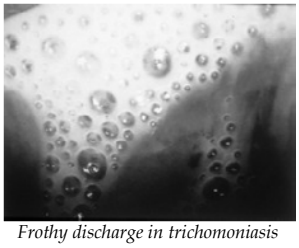
Wet-prep microscopy findings for Candida

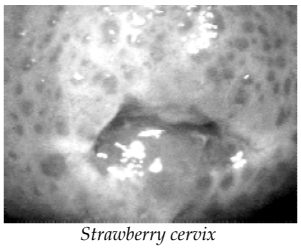
- **Management**
  - ***Antimicrobial therapy:***
    - Clotrimazole 500mg (as vaginal pessary or cream)
    - Fluconazole PO 150mg single dose
  - ***Partner screening:***
    - Can be considered & treatment instituted where appropriate even though vulvovaginal candidiasis is <u>not</u> thought to be sexually transmitted in most cases

Trichomoniasis

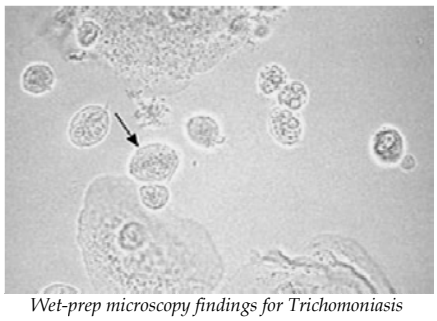
- **Microbiology & Pathophysiology**
  - Caused by protozoan *Trichomonas vaginalis*

- **Clinical Features**
  - ***Asymptomatic*** (up to 50% of cases)
  - ***Symptomatic presentation:***
    - Vaginal odour (*"musty"*)
    - Vaginal discharge (*green-yellow, frothy*)
    - May have vaginal irritation, dyspareunia, dysuria
    - Vaginal speculum examination may reveal a cervix with punctate hemorrhages (*"strawberry cervix"*)
  - ***Complications:***
    - For non-pregnant women, increases risk of:
      - Pelvic inflammatory disease
      - Postoperative infections (*e.g. after hysterectomy, termination of pregnancy*)
      - HIV transmission
    - For pregnant women, increases risk of:
      - 2nd trimester miscarriage
      - Preterm labour


Frothy discharge in trichomoniasis


Strawberry cervix

- **Diagnosis & Evaluation**
  - ***Microscopy of wet mount preparation:***
    - Reveals motile trichomonads
  - ***Culture:***
    - Using Fineberg Whittington medium


Wet-prep microscopy findings for Trichomoniasis

- **Management**
  - ***Antimicrobial therapy:***
    - Metronidazole PO 2g single dose
    - Tinidazole PO 2g single dose (*for cases resistant to metronidazole*)
  - ***Partner screening:***
    - Indicated in trichomoniasis (along with appropriate treatment) so as to prevent reinfection

Sexually Transmitted Infections

Genital Herpes

- **Microbiology & Pathophysiology**
  - Caused by Herpes Simplex Virus (HSV); 2 serotypes:
    - HSV 1 (*most commonly associated with oral lesions/cold sores; contributes to about 30% of primary genital herpes*)
    - HSV 2 (*causes 70% of primary genital herpes & 95% of recurrent genital herpes*)
  - Transmitted through intimate oral, genital or anal contact
    - Virus enters body through microabrasions in the skin or mucosa, thereafter travelling along sensory nerves to end up in the dorsal root ganglion where it remains dormant until reactivation occurs
    - Infected mother can transmit herpes to her neonate during delivery

- **Clinical Features**
  - ***Acute genital herpes***
    - Anogenital vesicles
      - Multiple, bilateral & painful
      - Erythematous base
      - Heal spontaneously within 2-3 weeks without residual scarring
    - Systemic signs & symptoms
      - Fever, headache, malaise
      - Lymphadenopathy
    - Acute cervicitis may also be present
  - ***Recurrent genital herpes***
    - Lesions are usually fewer, unilateral & less painful
      - Heal spontaneously within 5-7 days in immunocompetent individuals
    - Systemic signs & symptoms less likely to be present

- **Diagnosis & Evaluation**
  - ***Diagnostic tests:***
    - Viral culture
      - Requires live cells from swab taken from the herpetic lesion
      - Expensive, time-consuming & relatively low-sensitivity (50-80%)
    - Viral PCR
      - Expensive but highly accurate
      - Typically used for testing cerebrospinal fluid in suspected herpes simplex encephalitis, not routinely done for genital herpes
    - Type-specific serology tests for antibodies

- **Management**
  - ***Pharmacological therapy:***
    - Symptomatic relief of pain with analgesics
      - Topical lignocaine gel
    - Antiviral agents
      - Acyclovir (*200mg 5 times daily x 7-10 days for 1st acute episode of genital herpes; 400mg twice daily for long-term suppression in cases of recurrent herpes*)
      - Famciclovir, valacyclovir
  - ***Other considerations:***
    - Do urine pregnancy test
    - Offer testing for other sexually transmitted diseases
    - Advice on barrier contraception

Human Papillomavirus

- **Microbiology & Pathophysiology**
  - Human papillomavirus; many serotypes (about 200):
    - Serotypes 6 & 11 commonly associated with genital warts
    - Serotypes 16 & 18 commonly associated with cervical cancer & penile cancer
  - Transmitted via close contact
    - Occurs even when no visible lesions are present
    - Mother-to-infant transmission is rare

- **Clinical Features**
  - ***Genital warts (condylomata acuminata)***
    - Can be found on the vulva, vagina, cervix, urethra & perianal region
    - May bleed due to mechanical abrasion (*e.g. post-coital bleed in the setting of cervical or vaginal warts*)
    - Differential diagnoses:
      - Condylomata lata (*caused by syphilis; should be considered if lesions look atypical or fail to respond to treatment for HPV*)
      - Malignancy (*consider if lesions look atypical or remain persistent despite treatment*)
  - ***Cervical cancer***
    (*see "Gynaecologic Oncology"*)

- **Diagnosis & Evaluation**
  - Diagnosis is usually made on clinical grounds

- **Management**
  - ***Pharmacological therapy:***
    - Provider-applied topical therapy:
      - Podophyllin resin 10-25%
      - Trichloroacetic acid
      - Bichloracetic acid 80-90%
    - Patient-applied topical therapy:
      - Podofilox 0.5% solution or gel
      - Imiquimod 5% cream
  - ***Surgical treatment:***
    - Cryotherapy
    - Surgical excision
    - Electrocautery
    - Laser vaporization
    - Intralesional interferon
  - ***Vaccination:***
    - **Gardasil**
      - Quadrivalent vaccine (*protects against HPV serotypes 6, 11, 16 & 18*) manufactured by Merck
      - Approved for use between 9 & 26 years of age
    - **Cervarix**
      - Bivalent vaccine (*protects against HPV serotypes 16 & 18*) manufactured by GlaxoSmithKline
      - Approved for use between 9 & 45 years of age
  - ***Other considerations:***
    - Do urine pregnancy test
    - Offer testing for other sexually transmitted diseases
    - Advice on barrier contraception

Chlamydia

- **Microbiology & Pathophysiology**
  - Caused by *Chlamydia trachomatis*
    - Obligate intracellular bacteria
    - Infects columnar epithelial cells of the endocervix, urethra, endometrium, fallopian tubes & rectum
    - No effective immunity conferred even though antibodies are produced after 1 episode of infection, hence multiple reinfections are possible
  - Several serotypes exist:
    - Oculogenital biovars A, B, Ba, C
      - Conjunctivitis
      - Trachoma
    - Oculogenital biovars D to K
      - Paratrachoma
      - Genital infections
      - Non-gonococcal urethritis
      - Ophthalmia neonatorum
    - LGV biovars L1, L2 & L3
      - Lymphogranuloma venereum

- **Clinical Features**
  - ***Asymptomatic***
    - Asymptomatic carriage in 70% of infected females & 50% of infected males
  - ***Symptomatic Chlamydia infection:***
    - Non-gonococcal urethritis
    - Mucopurulent cervicitis (*30% of untreated cases progress further to more severe upper tract infections*)
    - Acute salpingitis
    - Pelvic inflammatory disease
    - Fitz-Hugh-Curtis syndrome (perihepatitis)
    - Proctitis
  - ***Pregnancy-related complications & sequelae:***
    - Subfertility
    - Ectopic pregnancy
    - Preterm labour
    - Chorioamnionitis
    - Post-partum endometritis
    - Ophthalmia neonatorum & neonatal pneumonia from intrapartum transmission

- **Diagnosis & Evaluation**
  - ***Diagnostic investigations:***
    - Tissue culture
      - Requires live cells, expensive
      - Not routinely done
    - Urine antigen test
    - PCR
      - Done using urine or endocervical swab sample

- **Management**
  - ***Pharmacological therapy:***
    - Doxycycline 100mg twice daily x 7 days
    - Azithromycin 1g single dose (*safe in pregnancy*)
    - Ofloxacin 400mg once daily x 7 days
    - Erythromycin 500mg twice daily x 14 days (*safe in pregnancy*)
  - ***Other considerations:***
    - Do urine pregnancy test
    - Offer testing for other sexually transmitted diseases
    - Advice on barrier contraception
    - Contact tracing
    - Abstain from sexual contact within 7 days after last sexual partner starts on treatment to minimize risk of reinfection

Gonorrhea

- **Microbiology & Pathophysiology**
  - Caused by *Neisseria gonnorhoeae*
    - Gram negative diplococci
    - Infects the same columnar epithelial cells as *Chlamydia trachomatis*, additionally able to infect the pharynx in about 10%, establishing throat carriage
    - No effective immunity conferred even though antibodies are produced after 1 episode of infection, hence multiple reinfections are possible

- **Clinical Features**
  (*mostly similar to Chlamydia*)
  - ***Asymptomatic***
    - Asymptomatic carriage in most infected females & only 5% of infected males
  - ***Symptomatic gonococcal infection:***
    - Gonococcal urethritis
    - Mucopurulent cervicitis (*15% of untreated cases progress further to more severe upper tract infections*)
    - Acute salpingitis
    - Pelvic inflammatory disease
    - Fitz-Hugh-Curtis syndrome (perihepatitis)
    - Proctitis
  - ***Pregnancy-related complications & sequelae:***
    - Subfertility
    - Ectopic pregnancy
    - Preterm labour
    - Chorioamnionitis
    - Post-partum endometritis
    - Ophthalmia neonatorum & neonatal pneumonia from intrapartum transmission

- **Diagnosis & Evaluation**
  - ***Diagnostic investigations:***
    - Gram stain of discharge or endocervical swab
      - Visualization of gram negative diplococci in polymorphonuclear cells (neutrophils)
      - Highly sensitive for diagnosis of gonorrhea in men, but only 50% sensitive in women
    - Bacterial culture
      - Gonococcus is fastidious & requires culture on chocolate agar (Thayer-Martin or Transgrow media culture)
      - Takes longer while but has good sensitivity (90%) and specificity (97%)
    - PCR
      - Done using urine or endocervical swab sample

- **Management**
  - ***Pharmacological therapy:***
    - Ceftriaxone IM 250mg single dose
    - Ciprofloxacin PO 500mg single dose
    - Amoxicillin PO 1g single dose + probenecid 2g
  - ***Concomitant treatment of Chlamydia empirically:***
    - Recommended as 20-40% of gonococcal cervical infections have concomitant *Chlamydia* infection
    - Azithromycin PO 1g single dose
  - ***Other considerations:***
    - Do urine pregnancy test
    - Offer testing for other sexually transmitted diseases
    - Advice on barrier contraception
    - Contact tracing
    - Abstain from sexual contact within 7 days after last sexual partner starts on treatment to minimize risk of reinfection

Other Sexually Transmitted Infections

- **Syphilis**
  - Caused by *Treponema pallidum*
    - Spirochete bacteria
  - ***Clinical features:***
    - Primary syphilis
      - Chancre (*painless genital ulcer*)
      - Regional lymphadenopathy (*inguinal*)
    - Secondary syphilis
      - Systemic rash (*usually involves palms & soles*)
      - Generalized lymphadenopathy
      - Condylomata lata (*warts in anogenital areas*)
      - Mucous patches (*lesions on mucous membranes, e.g. snail patch ulcers in mouth*)
    - Tertiary syphilis
      - Neurosyphilis (*general paresis of the insane, tabes dorsalis, Argyll Robertson pupils*)
      - Gummatous syphilis (*granulomatous lesions progressing on to necrosis, leaving gumma – ulcers, perforations - on skin, mucous membranes & bone*)
      - Syphilitic aortitis (*vasculitis of the thoracic aorta leading to aortic regurgitation, ascending aortic aneurysms, coronary artery ostia narrowing*)
    - Congenital syphilis (*vertical transmission*)
      - Hutchinson's triad (*interstitial keratitis, 8th nerve deafness, Hutchinson's teeth – notched incisors*)
      - Neonatal bullous rash (*may go on to develop lesions resembling secondary syphilis, gumma & neurosyphilis*)
  - ***Treatment:***
    - IM benzathine penicillin G

- **Chancroid**
  - Caused by *Haemophilus ducreyi*
  - ***Clinical features:***
    - Chancroid (*aka soft chancres; painful genital lesions*)
    - Usually accompanied by regional lymphadenopathy
  - ***Treatment:***
    - Azithromycin PO 1g single dose
    - Ceftriaxone IM 250mg single dose

- **Granuloma inguinale (donovanosis)**
  - Caused by *Klebsiella granulomatis* (used to be named *Calymmatobacterium granulomatis*)
  - ***Clinical features:***
    - Subcutaneous red raised nodules which break down to form painless ulcers that subsequently enlarge with prominent granulation tissue formation, tissue loss & scarring
    - Spread to inguinal region causes periadenitis (*pseudobubo formation*) and pelvic fibrosis
  - ***Treatment:***
    - Doxycycline PO 100mg twice daily x 3 weeks

- **Molluscum contagiosum**
  - Caused by Molluscum contagiosum, a poxvirus
  - ***Clinical features:*** waxy papules
  - ***Treatment:*** cryotherapy, topical imiquimod

- **Pediculosis pubis**
  - Caused by *Phthirus pediculosis*, a crab louse
  - ***Treatment:*** permethrin 1% cream rinse

- **Scabies**
  - Caused by *Sarcoptes scabiei*, a mite
  - ***Treatment:*** permethrin 5% cream, ivermectin

Pelvic Inflammatory Disease

Infection of the female upper reproductive tract (endocervix, uterine cavity & endometrium, fallopian tubes, intraperitoneally)

- **Etiology & Associations**
  - ***Causative organisms:***
    - *Chlamydia trachomatis*
    - *Neisseria gonnorhoeae*
    - Genital mycoplasmas:
      - *Mycoplasma hominis*
      - *Ureaplasma urealyticum*
      - *Mycoplasma genitalium*
    - Other endogenous lower reproductive tract &/or gastrointestinal tract organisms (*often isolated from pelvic abscesses complicating PID*):
      - *Escherichia coli*
      - Anaerobes (*Bacteroides, Prevotella,* anaerobic *Streptococci*)
      - *Gardnerella vaginalis*
  - ***Risk factors for PID:***
    - Sexual behavior-related risk factors:
      - Young age (*highest rates amongst sexually active adolescents & young adults*)
      - Multiple sexual partners
      - Recent new partner (*within previous 3 months*)
      - Past history of sexually transmitted infections
    - Uterine instrumentation:
      - Termination of pregnancy
      - Insertion of intrauterine device (*IUD-insertion related infections usually occur within the first 3 weeks following insertion*)
      - Hysterosalpingography
      - In-vitro fertilization, intrauterine insemination

- **Pathophysiology of PID**
  - PID-causing organism usually gains entry via the lower reproductive tract as a result of sexual intercourse or uterine instrumentation
    - Acute cervicitis caused by Chlamydia or gonococcus can lead on to PID in 30% & 15% of untreated cases respectively
  - Ascending infection subsequently involves more structures & regions:
    - Endometrium
      - Not usually a problem in non-pregnant women as the endometrium is shed regularly
      - In pregnancy, infection of endometrium can result in miscarriage, preterm labour, chorioamnionitis & post-partum endometritis
    - Fallopian tubes
      - Results in acute salpingitis
    - Pelvic intraperitoneal cavity
      - Results in pelvic & tuboovarian abscesses
    - Abdominal intraperitoneal cavity
      - Distant abscesses, peritonitis (*e.g. in the setting of tuboovarian abscess rupture*)
      - Fitz-Hugh-Curtis syndrome (*perihepatic inflammation & adhesions as a result of PID; classically can visualize "violin-string" adhesions when mobilizing the liver intraoperatively*)
  - Scarring of infected areas as a result of PID can lead to long-term sequelae even after resolution of the acute episode of infection:
    - Chronic pelvic pain
    - Ectopic pregnancy (*6x more likely*)
    - Subfertility (*14 times more likely*)

- **Clinical Features of PID**
  (*the following delineates typical features of symptomatic PID; many cases of PID can be asymptomatic, which may come to clinical attention as a result of associated sequelae*)
  - ***History:***
    - Presenting symptoms:
      - Local symptoms (*vaginal discharge, abnormal uterine bleeding, pelvic pain, dyspareunia, dysuria, abdominal pain*)
      - Systemic symptoms (*fever, nausea/vomiting*)
      - Last menstrual period
    - Past gynaecological & obstetric history:
      - Previous episodes of PID
      - History of reproductive tract instrumentation (*recent uterine procedures, TOP, IUD insertion*)
      - Previous ectopic pregnancies
      - History of subfertility
      - Previous obstetric events (*miscarriage, preterm labour, chorioamnionitis, post-partum endometritis*)
      - Last Pap smear & results
    - Past medical, surgical & drug history:
    - Sexual history:
      - Number of sexual partners
      - Use of (barrier) contraception
  - ***Physical examination:***
    - General examination:
      - Vitals (*temperature, HR, BP, RR, SpO_2*)
      - Assess for pallor & general well-being
    - Abdominal examination:
      - Palpate for abdominal tenderness, rebound tenderness & guarding
      - Palpate for pelviabdominal masses
      - Percuss for shifting dullness
    - Pelvic examination:
      - Inspect external genitalia for evidence of lower tract sexually-transmitted infections
      - Speculum examination to visualize cervix & vaginal canal (*take relevant swabs for gram stain & culture; do Pap smear where applicable*)
      - Digital vaginal exam/bimanual exam to assess for uterine size, adnexal masses & cervical motion tenderness (*tenderness elicited upon digital deflection of cervix to one side, felt on the side ipsilateral to the side of deflection; due to stretching of inflamed broad ligament & adnexa*)

- **Diagnosis & Evaluation**
  - ***Urine pregnancy test*** (to exclude ectopic pregnancy)
  - ***Routine haematological tests:***
    - Full blood count (*anemia, leukocytosis*)
    - CRP & ESR
  - ***Microbiological investigations:***
    - Endocervical & high vaginal swabs for gram stain & cultures (*including chocolate agar*)
    - Urine FEME & urine culture
    - Urine Chlamydia antigen test
    - Offer other STI screening (HIV, hep B, VDRL)
  - ***Pelvic ultrasound:***
    - Visualize any adnexal masses suggestive of tuboovarian abscesses & fluid in the pouch of Douglas

- **Management of PID**

  - ***Initial resuscitation & stabilization:***
    - ABCs, establish IV access, do necessary initial investigations, establish monitoring of vitals
    - Other initial considerations:
      - Analgesia
      - Remove IUCD if present & send it for culture
    - Admission for inpatient management if:
      - Diagnostic uncertainty exists
      - Severe symptoms & signs
      - Presence of tuboovarian abscess &/or sepsis
      - Inability to tolerate or failure to respond to oral antibiotic therapy
      - Pregnancy

  - ***Antimicrobial therapy:***
    - Inpatient empirical antibiotic regime: (i) + (ii) + (iii)
      (i) Cefoxitin IV 2g 4 times daily <u>or</u> ceftriaxone IV/IM 1g once daily
      (ii) Doxycycline IV 100mg twice daily
      (iii) Metronidazole IV 500mg twice daily
      → until patient condition improves, then continue on oral therapy with:
      (iv) Doxycycline PO 100mg twice daily + metronidazole PO 500mg twice daily x 14 days
    - Outpatient empirical antibiotic regime (i) + (ii) + (iii):
      (i) Ceftriaxone IM 250mg single dose <u>or</u> cefoxitin IM 2g single dose with oral probenecid
      (ii) Doxycycline PO 100mg twice daily x 14 days
      (iii) Metronidazole PO 500mg twice daily x 14 days
      ****Note: review at 72 hours is recommended to assess improvement on outpatient treatment*

  - ***Surgical intervention:***
    - Indications for surgery in PID:
      - Drainage of tuboovarian abscess
      - Adnexal mass of uncertain diagnosis
      - Treatment for other sequelae of PID (*e.g. salpingectomy for ectopic, hysterectomy for refractory chronic pelvic pain, adhesiolysis for intestinal obstruction from adhesions*)

  - ***Other general considerations:***
    - Contact tracing, partner screening & treatment
      - Avoid sexual intercourse until both parties have completed treatment
    - Contraceptive counselling:
      - Barrier contraceptives advisable to reduce risk of STI transmission
      - IUD not advisable due to heightened risk of infection and ectopic pregnancy
      - Consider hormonal contraception
    - Counsel on long-term sequelae:
      - Risk of subfertility correlates with duration of untreated illness & number of episodes of PID (*1st episode prompt treatment usually have well-preserved fertility; impaired fertility risk doubles with each subsequent episode*)
      - Chronic pelvic pain affects 30% of women following PID to varying extents
      - Increased risk of ectopic pregnancy in subsequent pregnancies, hence early booking visit to ascertain viable intrauterine pregnancy via ultrasound is advisable

Principles of Contraception

Technically speaking, contraception refers to the prevention of fertilization, whereas interception refers to the prevention of implantation (but both are broadly considered under contraception);

- **Importance of Contraception**
  - ***Maternal benefits:***
    - Allows for a satisfying & safe sex life with the freedom to decide if, when & how often to reproduce
    - Prevents unplanned pregnancies which carry with it a whole host of unnecessary maternal complications:
      - Risks involved with abortions
      - Obstetric complications
      - Peripartum complications
    - Barrier methods protect against sexually-transmitted diseases
  - ***Fetal benefits:***
    - Allows optimization of fetal outcomes with proper pre-conception care permitted when timing of pregnancy can be controlled
    - Planned pregnancies can also have earlier antenatal care instituted to optimize care & allow for early detection of pregnancy complications & fetal anomalies
  - ***Public health benefits:***
    - Decreases pregnancy-related maternal & fetal morbidity & mortality
    - Improves reproductive health of the population as a whole (physical, mental & social well-being)
    - Barrier methods help prevent transmission of sexually-transmitted diseases

- **The Ideal Contraceptive**
  - 100% effective
  - Acts only on the genital tract (no systemic side effects)
  - Removed from the act of coitus
  - No short term or long term side effects
  - Immediate return of fertility when stopped
  - Simple, cheap & freely available
  - Requires minimal motivation, maintenance & supervision

- **Assessment of Contraceptive Efficacy**
  - ***Pearl Index***
    - Defined as the number of failures per 100 woman years (HWY) of exposure:

$$\text{Rate per HWY} = \frac{\text{Total no. of accidental pregnancies} \times 12 \times 100}{\text{Total no. of months of use}}$$

    - Limitation of this statistical analysis is the assumption that the rate of failures for each contraceptive method remains constant over a given period of time
  - ***Life table analysis***
    - Calculates a failure rate for a specified period
    - Eliminates the time-related biases present with the Pearl Index, for example:
      - Fertile couples getting pregnant & dropping out of the study early
      - Couples becoming more skilled at using a form of contraceptive over time

Risk of Contraceptive Failure During 1st Year of Use

Contraceptive Method		*Theoretical %*	*Typical %*
No contraceptive method		85	85
Male sterilization		0.1	0.15
Female sterilization		0.5	0.5
Copper IUCD		0.6	0.8
Mirena		0.1	0.1
Norplant		0.2	0.2
Depot medroxyprogesterone acetate		0.3	6.7
Combined oral contraceptive pill		0.3	8.7
Progestin-only pill		0.5	8.7
Diaphragm with spermicide		6.0	16.0
Male condom		2.0	17.4
Cervical cap	*Nulliparous*	9.0	16.0
	Multiparous	26.0	32.0
Spermicide alone		15.0	29.0
Rhythm method		19.0	25.3
Coitus interruptus		-	18.4

- **Overview on Contraceptive Options**
  - ***Hormonal contraception***
    - Oral contraceptives
      - Combined oral contraceptives (COCs)
      - Progestin-only pills (POPs)
    - Progestin depot injections
      - Depot medroxyprogesterone acetate (aka DMPA, Depo-Provera)
    - Progestin implants
      - Norplant
      - Implanon
    - Levonorgestrel-releasing intrauterine system
  - ***Non-hormonal contraception***
    - Copper intrauterine contraceptive device
    - Male barrier contraception
      - Male condoms
    - Female barrier contraception
      - Female condoms
      - Cervical caps
      - Diaphragms
    - Spermicides (*usually used together with above mentioned barrier methods*)
  - ***Behavioral contraception***
    - Rhythm method
    - Coitus interruptus
  - ***Surgical sterilization***
    - Male sterilization (*vasectomy*)
    - Female sterilization (*tubal ligation*)

- **Factors to be Considered In Choosing Contraceptive Options**
  - ***Patient factors:***
    - Reproductive factors
      - Future reproductive intention
    - Social factors:
      - Sexual habits (multiple partners?)
      - Motivation & compliance
      - Education & socioeconomic factors
    - Medical factors:
      - Age of patient
      - Existing medical/surgical/gynae conditions
  - ***Non-patient factors:***
    - Methods available
    - Government policies

Hormonal Contraception

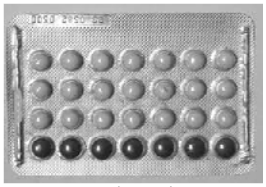
Combined Oral Contraceptive Pills

- **Composition of COCs**
  - Combination of synthetic estrogens & progestins
  - ***Synthetic estrogen options:***
    - Ethinyl estradiol (EE)
    - Mestranol
  - ***Progestin options:***
    - 1st generation progestins (*estrane family*)
      - Megestrol
      - Chlormadinone
      - Medroxyprogesterone acetate (Provera)
      - Ethynodiol
      - Norethisterone (aka norethindrone)
      - Norethynodrel
    - 2nd generation progestins (*gonane family; varying degrees of androgenic & estrogenic activity as well*)
      - Levonorgestrel (LNG)
      - Norgestrel
    - 3rd generation progestins (*gonane family; minimal androgenic activity*)
      - Desogestrel
      - Norgestimate
      - Gestodene
    - 4th generation progestins (*minimal androgenic activity*)
      - Drospirenone
      - Dienogest (Visanne)

- **Mode of Action of COCs**
  - ***Inhibition of ovulation***
    - Hormones (especially estrogen) administered effect negative feedback inhibition of pituitary gonadotropin production
    - Blocks LH surge, hence inhibiting ovulation
  - ***Affects tubular transport of ovum***
  - ***Thickens cervical mucus***
    - Effect of progestin
    - Blocks sperm penetration
  - ***Induces endometrial thinning & atrophy***
    - Effect of progestin
    - Inhibits implantation

- **Administration of COCs**
  - ***2 different types of dosing regimen:***
    - Monophasic: *fixed dose of estrogen + progestin throughout the cycle*
      - Microgynon 30: *30μg EE + 150μg LNG*
      - Nordiol: *50μg EE + 150μg LNG*
      - Yasmin: *30μg EE + 3mg drospirenone*
    - Multiphasic: *bi-/triphasic dose variations of estrogen + progestin throughout the cycle to mimic normal cycle & reduce the total hormonal dose per cycle of administration (no proven advantage over monophasic however)*
      - Triquilar: *EE + LNG*
      - Trinordiol: *EE + LNG*
      - Qlaira: *estradiol valerate + dienogest*
  - ***Types of administration:***
    - 21-day pack: *21 combined E + P pills*
      - To be taken from day 5 to day 26 of cycle, followed by a 7-day pill-free interval
      - Menstruation occurs during the 7-day pill free period (withdrawal bleed), allows woman to experience normal menses & be sure that she is not pregnant
    - 28-day pack: *21 combined E + P pills with 7 sugar pills*
      - Uninterrupted pill-taking continuously with the 7-day sugar pill interval substituting the 7-day pill-free period of the 21-day pack
      - Easier for woman to keep track of pills (*don't need to remember & count number of pill-free days before starting on the next pack*)

21-day pack



28-day pack

  - ***Missed pills – what to do?***
    - Single active pill missed:
      - Take the pill as soon as remembered
      - Take the next pill at the usual time (*e.g. if pill taken at 8am every morning but forgotten until 5pm when it was taken, the next pill should still be taken at 8am again the following day*)
    - ≥2 active pills missed:
      - At least <u>7 days of continuous pill-taking</u> is needed to effectively suppress endogenous FSH production
      - After ≥2 active pills are missed, FSH starts rising & recruiting follicles, necessitating a new round of 7 continuous days of pill-taking before full contraceptive efficacy is restored
      - If ≥7 active pills left in the pack: *continue taking the rest of the pills + barrier contraception for at least 7 days in the meantime*
      - If <7 active pills left in the pack: *discard pack & begin on a new pack + barrier contraception for at least 7 days in the meantime*
  - ***Efficacy of COCs:***
    - Highly efficacious (0.1-3.0% failure rate)
    - Most failures are due to non-compliance, hence need for careful instructions & reinforcement of routine

- **Benefits of COCs**
  - ***Contraceptive benefits:***
    - Highly effective in pregnancy prevention, with regular withdrawal bleeding providing reassurance
    - Decreased incidence of ectopic pregnancy
    - Removed from the act of coitus
    - Readily reversible, with speedy return of fertility
  - ***Non-contraceptive benefits:***
    - Menstrual benefits:
      - Regulates menses
      - Reduces menstrual loss (*any long-term progestin thins the endometrial lining*)
      - Relieves dysmenorrhea (*anovulatory cycles tend to have less dysmenorrhea*)
    - Cancer benefits:
      - Decreases incidence of epithelial ovarian cancer (*reduced ovulation reduces repeated damage to the ovarian epithelium*)
      - Decreases incidence of endometrial cancer (*reduces number of cycles a woman might experience with unopposed estrogen action on endometrium*)
    - Other gynaecologic benefits:
      - Decreases incidence of benign breast diseases
      - Possibly protective against benign ovarian cysts, fibroids, endometriosis & osteoporosis

- **Side Effects of COCs**
  - ***Minor side effects:***
    - Estrogen-related: *nausea, vomiting, headache, giddiness*
    - Progestin-related: *weight gain, acne, facial pigmentation*
    - E&P-related: *breast fullness & tenderness*
    - Others: *breakthrough bleeding, loss of libido, depression*
  - ***Major side effects:***
    - **<u>Effects on circulatory system:</u>**
      - Venous thromboembolism, coronary arterial disease & stroke (*both hemorrhagic & ischemic*)
      - Primarily related to estrogen dose (↑ *clotting factors,* ↓ *anti-coagulants,* ↑ *platelet aggregation*)
      - Risk is much more significant for the high-dose (50µg) estrogen pills vs the lower dose estrogen pills (30µg)
      - VTE: *OR 3.25 for non-Europeans, 4.15 for Europeans; applies only to current users; unrelated to duration of use; COCs should hence be stopped 4 weeks prior to major surgery*
      - Coronary arterial disease: *RR 1.8 (4.2 for high-dose pills), applies to current users; young women have non-significant increased risk (RR 1.1), especially in the absence of risk factors*
      - Stroke: *lower-dose COC (<50µg EE) does not increase risk of hemorrhagic stroke in women <35, small increase for women >35; ischemic stroke risk has overall small increased risk (OR<3.0) but lower in the women <35 age group*
    - **<u>Effects on liver disease:</u>**
      - 19-norsteroids alter liver function & cause cholestasis, hence best avoided in women with active hepatitis or history of cholestatic jaundice or symptomatic gallstone disease
      - Long term COC use also increases risk of developing benign hepatic adenomas (10-20x)
    - **<u>Effects on breast cancer:</u>**
      - Current users: slight increased risk (RR 1.24)
      - <10 after stopping: small increased risk of having breast cancer diagnosed
      - ≥10 years after stopping: no increased risk
      - Women starting COCs before 20 years old: higher risk (RR 1.59)
  - ***Other systemic side effects:***
    - Carbohydrate metabolism:
      - Impairs glucose tolerance & induces peripheral insulin resistance (progestin effect)
      - Cautious use in latent diabetes; can be used with drug/dietary modifications in young diabetes; avoid use in advanced or long-standing diabetics
      - Long term use does not in itself cause diabetes
    - Lipid metabolism:
      - 19-norsteroids increase LDL & decrease HDL
      - However, estrogens counteract this effect
    - Vitamin levels:
      - Decreases vitamins B_2, B_6, B_{12} & folic acid
      - Increases iron levels
    - Pregnancy outcomes
      - No increase in spontaneous abortion or fetal abnormalities in former users of COCs
      - No proven teratogenic potential (*if pregnancy occurs during use of COCs*)

- **Drug Interactions of COCs**
  - ***Drugs which reduce COC efficacy:***
    - Anticonvulsants: *phenytoin, phenobarbitone*
    - Antibiotics: *rifampicin, griseofulvin*
    - Sedatives: *chlordiazepoxide*
  - ***Drugs requiring dose adjustment if COC is taken:***
    - Anticoagulants (*needs increased dose*)
    - Tricyclic antidepressants (*needs increased dose as COCs can aggravate depression*)
    - Insulin & oral hypoglycemic (*needs increased dose*)
    - Corticosteroids (*needs decreased dose*)

- **Contraindications to Use of COCs:**
  - ***Absolute contraindications:***
    - Circulatory disorders (*thrombotic disorders, coronary artery disease, stroke*)
    - Hepatic disorders (*impaired liver function, existing hepatic adenoma*)
    - Estrogen-dependent malignancies (*breast cancer, existing endometrial cancer*)
    - Pregnancy or breast-feeding (*interferes with lactation*)
    - Any undiagnosed abnormal uterine bleeding
  - ***Relative contraindications:***
    - Smokers >35 years old
    - Metabolic diseases (*diabetes, hypertension, obesity*)
    - Migraine
    - Gallbladder disease
    - Cardiac disease
    - Planned elective surgery

- **Combined Patches**
  - ***Ortho Evra***
    (norelgestromin/ethinyl estradiol transdermal system)
    - Applied once weekly x 3 weeks (usually on buttock)
    - Start on day 1 or within 1st week of menses
    - Similar side-effect profile & efficacy as COCs

Progestin-Only Pills

- **Composition of POPs**
  - Estrogen-free oral contraceptive pills containing low-dose progestin (aka progestogen aka synthetic progesterone)
  - Progestin options (*see "Combined Oral Contraceptive Pills"*)

- **Mode of Action of POPs**
  - ***Thickens cervical mucus***
    - Blocks sperm penetration
  - ***Induces endometrial thinning & atrophy***
    - Inhibits implantation
  - ***Inhibits ovulation (in 50% of cases)***

- **Administration of POPs**
  - ***Administration:***
    - Taken daily at the same time each day throughout cycle
  - ***Missed pills – what to do?***
    - Missed for <3 hours
      - Take the pill as soon as remembered
      - Take the next pill at the usual time the following day
      - No need for barrier contraception
    - Missed for >3 hours
      - Take 1 pill as soon as remembered (*even if >1 pill have been missed*)
      - Take the next pill at the usual time the following day
      - Use barrier contraception for at least 2 days
  - ***Efficacy of POPs:***
    - Less efficacious than COCs (0.5-10.0 per HWY)

- **Benefits of POPs**
  - ***Contraceptive benefits:***
    - Immediately effectively (<24 hours)
    - Decreased incidence of ectopic pregnancy
    - Removed from the act of coitus
    - Readily reversible, with speedy return of fertility
    - Does not affect lactation
    - Suitable for patients with medical contraindications to exogenous estrogens
  - ***Non-contraceptive benefits:***
    - Menstrual benefits:
      - Reduces menstrual loss (*any long-term progestin thins the endometrial lining*)
      - Relieves dysmenorrhea
    - Cancer benefits:
      - Decreases incidence of endometrial cancer (*reduces number of cycles a woman might experience with unopposed estrogen action on endometrium*)

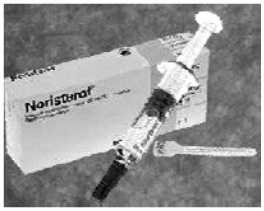
- **Side Effects of POPs**
  - ***Menstrual problems:***
    - Increased menstrual irregularity (*biggest side-effect of any progestin-only contraceptive*)
  - ***Progestogenic side-effects:***
    - Breast engorgement & tenderness
    - Headache, nausea
  - ***Androgenic side-effects***
    - Acne, hirsutism
    - More so with the 19-nortestosterone derivatives (*norethisterone, Levonorgestrel etc*)
    - Newer progestins actually have anti-androgenic properties & are licensed for even the use of acne treatment (*Dienogest, drospirenone*)

- **Contraindications to use of POPs**
  - Breast cancer
  - Liver disease
  - Undiagnosed abnormal uterine bleeding
  - Previous ectopic pregnancy

Progestin Depot Injections

- **Mode of Action of Progestin Depot Injections**
  - Similar to progestin-only pills

- **Administration of Progestin Depot Injections**
  - ***Administration:***
    - Depot medroxyprogesterone acetate (**Depo-Provera**)
      - Intramuscular injection
      - Continuous release occurs over 12 weeks
      - 150-300mg every <u>3 months</u>
    - Norethisterone enanthate (**Noristerat**)
      - Intramuscular injection
      - Continuous release occurs over 8 weeks
      - 200mg every <u>2 months</u>



  - ***Efficacy of Progestin Depot Injections***
    - Highly effective (*failure rate of 0.1-0.6% in 1st year*)

- **Benefits of Progestin Depot Injections**
  - ***Contraceptive benefits:***
    - Similar to progestin-only pills plus:
    - Less need for patient compliance (*vs taking pills*)
    - <u>BUT</u> return of fertility is delayed (median time of 10 months)
  - ***Non-contraceptive benefits:***
    - Similar to progestin-only pills plus:

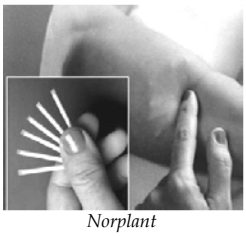
- **Side-effects of Progestin Depot Injections**
  - Menstrual irregularities:
    - Irregular menstrual spotting (60-70%)
    - Eventual amenorrhea (50-80%)
  - Weight gain
  - Delay in return of fertility (median time of 10 months)
  - Possible bone loss for long term use

- **Contraindications to use of Progestin Depot Injections**
  - Breast cancer
  - Suspected pregnancy
  - Undiagnosed abnormal uterine bleeding

Progestin Implants

- **Mode of Action of Progestin Implants**
  - Similar to progestin-only pills

- **Administration of Progestin Implants**
  - ***Administration:***
    - Levonorgestrel implant (**Norplant**)
      - 6 rods placed subdermally in arm
      - Sustained release of Levonorgestrel
      - Change every 5 years
      - Removed using a forceps through a small skin incision made in the arm
    - Etonogestrel implant (**Implanon**)
      - 1 rod placed subdermally in arm
      - Sustained release of Etonogestrel
      - Change every 3 years
      - Removed using a forceps through a small skin incision made in the arm


Norplant

Implanon

  - ***Efficacy of Progestin Implants:***
    - Highly efficacious (*failure rate 0.2/100 users in 1st year*)
    - Almost similar efficacy as sterilization in 1st 3 years

- **Benefits of Progestin Implants**
  - ***Contraceptive benefits:***
    - Similar to progestin-only pills plus:
    - Less need for patient compliance (*vs taking pills*)
  - ***Non-contraceptive benefits:***
    - Similar to progestin-only pills plus:
    - No significant effect on liver, kidney, thyroid, lipid metabolism & hemostasis

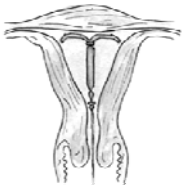
- **Side Effects of Progestin Implants**
  - ***Menstrual irregularities:***
    - Prolonged spotting
    - Breakthrough bleeding
    - Amenorrhea
  - ***Minor side-effects:***
    - Headache, dizziness, nausea
    - Weight gain, acne
  - ***Insertion & removal requires minor surgical procedure***

- **Contraindications to use of Progestin Implants**
  - Breast cancer
  - Suspected pregnancy
  - Undiagnosed abnormal uterine bleeding

Levonorgestrel-Releasing Intrauterine System (Mirena)

- **Mode of Action of Mirena**
  - ***Thickens cervical mucus***
    - Blocks sperm penetration
  - ***Induces endometrial thinning & atrophy***
    - Inhibits implantation
  - ***Inhibits sperm motility & function inside the uterus & fallopian tubes***
    - Inhibits fertilization
  - ***Does not affect ovarian function in most women***

- **Administration of Mirena**
  - ***Composition of Mirena:***
    - Silastic rod impregnated with 52mg of levonorgestrel
    - Slow release at 20µg/day for 5 years
  - ***Administration:***
    - Insertion should be done when sure that patient is not pregnant:
      - *Anytime when patient is very sure she has no possibility of being pregnant*
      - *Days 1-7 of menses*
      - *Post-abortion*
      - *Post-partum not recommended due to very high expulsion rates (wait till 6 weeks post-partum)*
    - Outpatient office procedure without anesthesia
    - Speculum is used to visualize cervix
    - Vulsellum forceps is used to grasp cervix
    - Under transabdominal ultrasound guidance, uterine sound inserted through the cervix to gauge the depth of the uterine cavity (≥*6mm required for use of Mirena*)
    - Mirena applicator is then inserted through the cervix & Mirena is placed within the uterine cavity
    - Removed after 5 years (*just pull on attached thread*)



  - ***Efficacy of Mirena:***
    - Highly efficacious (0-0.2% in 1st year)
    - Unsurpassed efficacy
    - Provides fertility control comparable to female sterilization

- **Benefits of Mirena**
  - ***Contraceptive benefits:***
    - Similar to progestin-only pills plus:
    - Less need for patient compliance (*vs taking pills*)
    - Lowest plasma concentration of hormone amongst all the hormonal methods of concentration
  - ***Non-contraceptive benefits:***
    - Menstrual benefits:
      - Reduction in menstrual flow (*reduces menorrhagia by 97% after 1 year of use*)
      - Effective relieve of dysmenorrhea (*used in adenomyosis, endometriosis*)
      - Treats endometrial hyperplasia
    - Other gynaecologic benefits:
      - Decreases growth & incidence of fibroids
      - Decreases incidence of PID
      - Decreases incidence of ectopic pregnancy
    - No significant effect on carbohydrate metabolism, coagulation, liver enzymes or lipid levels

- **Side-Effects & Complications of Mirena**
  - ***Menstrual irregularities:***
    - Prolonged spotting
    - Breakthrough bleeding
    - Amenorrhea
  - ***Minor side-effects:***
    - Headache, dizziness, nausea
    - Weight gain, acne
  - ***Insertion requires minor procedure:***
    - Crampy discomfort may be experienced
    - Risk of bleeding & uterine perforation
    - Risk of infection (*if at all, usually occurs in 1st 3 weeks*)
  - ***Expulsion (drop out) rate = 0.5%***

- **Contraindications to use of Mirena**
  - Breast cancer
  - Suspected pregnancy
  - Undiagnosed abnormal uterine bleeding
  - Active pelvic inflammatory disease
  - High risk of PID (*e.g. multiple sexual partners*)
  - Abnormal uterine cavity (*large fibroids, congenital abnormalities*)

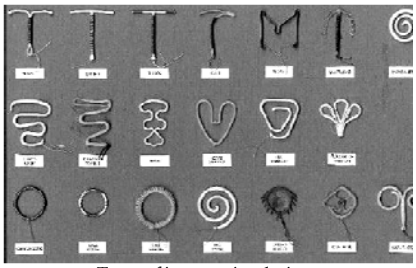
- **Management of Intrauterine Device Problems**
  - ***Missing thread***
    - Patients should be advised to check monthly for the thread to ensure that device in still in place
    - If suspected to be missing:
      - Speculum examine to look for thread
      - Pelvic ultrasound to look for device
      - X-ray may be required if pelvic ultrasound cannot locate device
  - ***Bleeding***
    - Observe & follow-up
    - Remove device if patient cannot stand it
    - If persistent following removal, investigation as per for abnormal uterine bleeding
  - ***Infection***
    - Remove device
    - Antibiotics

Non Hormonal Contraception

Copper Intrauterine Contraceptive Device

- **Mode of Action of Copper IUCD**
  - Interferes with sperm transport
  - Spermicidal
  - Interferes with embryo implantation

- **Administration**
  - ***Types of IUCDs:***
    - Many types available (*different in shapes, size, material*)
    - Main type used now is the Copper T-380



Types of intrauterine devices

Copper T-380

  - ***Administration of Copper IUCD:***
    - Similar to that for Mirena
  - ***Efficacy of Copper IUCD:***
    - Highly effective

- **Benefits of Copper IUCD**
  - ***Contraceptive benefits:***
    - Highly & immediately effective
    - Minimal patient compliance required
    - Removed from the act of coitus
    - Readily reversible, with speedy return of fertility
    - Does not affect lactation
    - Suitable for patients with medical contraindications to hormonal contraceptives

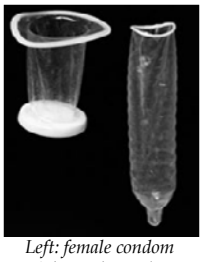
- **Side Effects & Complications of Copper IUCD**
  - ***Menstrual problems:***
    - Increased menstrual bleeding
    - Increased menstrual cramps
  - ***Other gynaecologic side-effects:***
    - Increased risk of PID
    - If pregnancy occurs, more likely to be ectopic
  - ***Insertion requires minor procedure:***
    - Crampy discomfort may be experienced
    - Risk of bleeding & uterine perforation
    - Risk of infection (*if at all, usually occurs in 1st 3 weeks*)
  - ***Expulsion of IUCD can occur***

- **Contraindications to use of Copper IUCD**
  - Suspected pregnancy
  - Undiagnosed abnormal uterine bleeding
  - Active pelvic inflammatory disease
  - High risk of PID (*e.g. multiple sexual partners*)
  - Abnormal uterine cavity (*large fibroids, congenital abnormalities*)

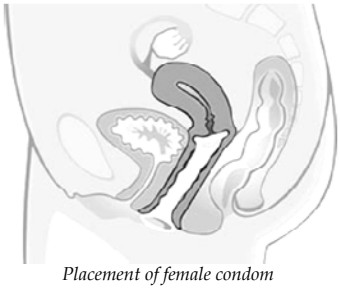
- **Management of Intrauterine Device Problems**
  - Similar to that for Mirena

Barrier Methods

- **Types of Barrier Methods**
  - ***Male condoms***
    - Worn over the penis before intercourse occurs
  - ***Female condoms***
    - Placed into the vagina before intercourse occurs
  - ***Cervical caps & diaphragms***
    - Needs to be fitted in place before intercourse occurs
    - Removed 6 hours after intercourse is over
  - ***Spermicide***
    - Usually used in conjunction with above mentioned barrier methods
    - Comes in various forms (tablets, cream, aerosols)

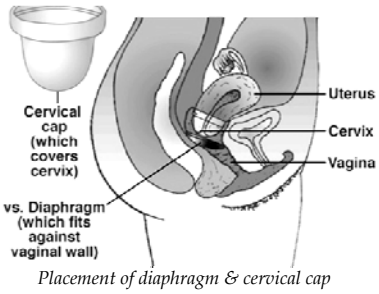


Left: female condom
Right: male condom



Placement of female condom

Diaphragm & cervical cap



Placement of diaphragm & cervical cap

- **Mode of Action of Barrier Methods**
  - Prevents sperm from reaching upper genital tract
  - Spermicides causes sperm cell membrane lysis

- **Advantages of Barrier Methods**
  - ***Contraceptive benefits:***
    - Immediately effective
    - Easily available & used
    - Does not affect fertility or lactation
    - No systemic side effects
    - Protects against sexually-transmitted diseases

- **Disadvantages of Barrier Methods**
  - ***Problem with patient compliance:***
    - Interferes with coital act, decreased sexual pleasure
    - Needs consistency in usage
    - Needs both partners to agree to its use
    - Cervical caps & diaphragms need pre-fitting & removal only after 6 hours post-intercourse
  - ***Possible allergy (to latex or spermicide)***

Behavioral Methods

- **Types of Behavioral Methods**
  - ***Calendar method***
    - Requires regular cycles
    - Monitor for at least 6 cycles first
    - Fertile period is from:
      [shortest cycle – 18] to [longest cycle – 11]
  - ***Basal body temperature method***
  - ***Cervical mucus (Billings technique)***

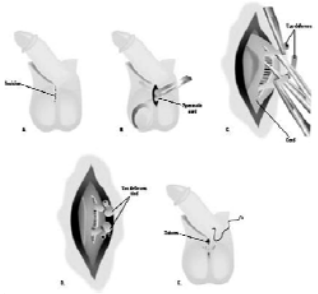
- **Mode of Action of Behavioral Methods**
  - Avoid intercourse during calculated fertile period

- **Advantages of Behavioral Methods**
  - Free, no side effects

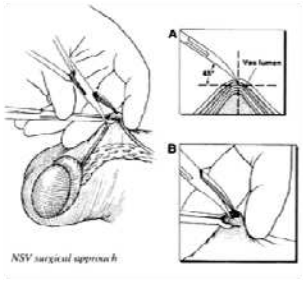
- **Disadvantages of Behavioral Methods**
  - Not very effective
  - Requires willingness to abstain during fertile period
  - Needs motivation & record keeping

Surgical Sterilization

- **Male Sterilization**
  - ***Vasectomy***
    - Interruption of the vas deferens
  - ***Techniques:***
    - No-scalpel vasectomy (*under local anesthesia in office*)
    - Outpatient surgical procedure



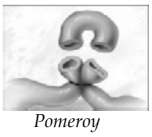
Conventional vasectomy



No-scalpel vasectomy

  - ***Efficacy:***
    - Highly effective (*more so than female sterilization*)
    - Need to wait for 3 months after procedure before sterility sets in completely (*should use barrier contraception in the meantime*)
  - ***Advantages:***
    - Similar to that for female sterilization
  - ***Disadvantages:***
    - Anti-sperm antibodies may develop, resulting in persistent infertility despite reversal of vasectomy should the male choose to down the road

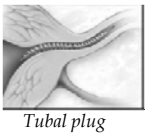
- **Female Sterilization**
  - ***Tubal ligation***
    - Interruption of the fallopian tubes
    - Performed when sure that woman not pregnant:
      - Woman is sure she is not pregnant
      - Follicular phase of menstrual cycle
      - Postpartum sterilization (PPS)
      - Post-abortion
  - ***Techniques:***
    - Abdominal approach
      - Via mini-laparotomy or laparoscopy
      - **Pomeroy technique** (*ligation & division of tubes*)
      - **Filshie clips** (*clips used to clamp tubes*)
      - **Falope ring** (*ring placed around tubes*)
    - Hysteroscopic approach
      - Tubal plugs anchored in the proximal portions of the tube to incite fibrosis



Pomeroy

Filshie clip

Falope ring



Tubal plug

  - ***Efficacy:***
    - Highly effective & immediate effect
  - ***Advantages:***
    - No side-effects
    - Does not interfere with coital act or breast-feeding
    - Permanent contraception
  - ***Disadvantages:***
    - Irreversible (*success of reversal of sterilization varies*)
    - Surgical procedure (*pain, bleeding, anesthesia risk*)
    - Small risk of failure (*0.1-0.4%*)
    - May regret later in life

Emergency Contraception

- **Indications for Emergency Contraception**
  - No contraception used before intercourse occurred
  - Contraceptive accident
  - Victim of sexual assault

- **Approach to Patient Presenting for Emergency Contraception**
  - ***Essential history to elicit:***
    - Last menstrual period
    - Cycle length
    - Timing of 1st act of unprotected intercourse (*patient may have had multiple episodes of unprotected intercourse before presentation*)
    - Relevant medical & surgical history (*to assess for contraindications to the options for emergency contraception*):
      - Drug allergies
      - Metabolic diseases (*DM, hypertension, lipids*)
      - Cardiovascular disease, stroke
      - Venous thromboembolic disease
      - Liver disease
      - Any undiagnosed abnormal uterine bleeding
      - Any malignancies (*especially breast*)
    - Relevant social history:
      - Sexual habits (*may be at risk of STDs, offer tests*)
      - Sexual assault requires counselling & police
  - ***Essential patient counselling:***
    - Possibility of failure (*especially if multiple episodes of intercourse have already occurred outside the protective period of the emergency contraception used*)
    - Possible side effects & complications involved
    - Importance of regular contraception
    - Importance of follow-up if delayed menses occurs

- **Options for Emergency Contraception**
  - ***Combined hormonal pill***
    - Known as the **Yuzpe regime**
    - Requirement:
      - Patient presents within 72 hours of intercourse
    - 2 tablets of 50µg EE + 500µg norgestrel (or 250µg levonorgestrel) given at presentation; repeated again 12 hours later
    - Failure rate = 2%
    - Side effects: *nausea, vomiting, breast tenderness*
  - ***Progestin-only pill***
    - Uses **Postinor**
    - Requirement:
      - Patient presents within 48 hours of intercourse
    - 750µg levonorgestrel given at presentation; repeated again 12 hours later
    - Failure rate = 3%
    - Side effects: *similar to above but less*
  - ***Copper intrauterine contraceptive device***
    - Requirement:
      - Patients presents within 5 days of intercourse
    - Copper IUCD inserted at presentation
    - Failure rate < 1%
    - Side effects: *as per for copper IUCD*

Termination of Pregnancy

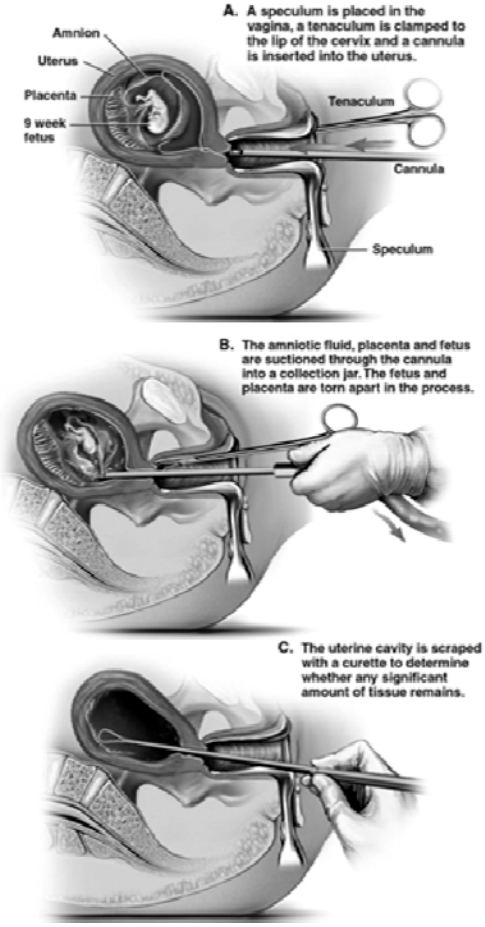
Abortion refers to the disruption of an established pregnancy, which may be spontaneous (a miscarriage) or induced (termination of pregnancy) via medical &/or surgical interventions

- **Abortion Legislation in Singapore**
  - ***Induced abortion*** = termination of pregnancy before 24 weeks gestation (i.e. before fetal viability)
  - ***Evolution of abortion legislation in Singapore:***
    - **Before 1967:**
      - Legal abortion restricted only to cases in which maternal life was endangered
    - **1967: Abortion Authorization Board set up**
      - Abortion extended to those with fetal malformations, mothers who were victims of sex crimes or intercourse with a mentally insane person
    - **1968: First Abortion Bill**
      - Law liberalized to allow abortion for family, social & economic reasons
    - **1974: New Abortion Act**
      - Abortion could be performed at the request of any female up to 24 weeks of pregnancy by a registered doctor with prescribed qualification in an approved institution
      - This is regardless of age
      - Does not require consent of anyone (including parental consent even in the case of minors)
    - **1986: Abortion Counselling Introduced**
      - Mandatory pre-abortion counselling
      - Consent for abortion procedure can only be given 48 hours after counselling is completed
  - ***Impact of legislations on legalized abortions in Singapore***
    - Total number of legalized abortion per year rose from 1913 (year 1970) to 23512 (year 1986) with increasingly liberal abortion laws
    - Following introduction of abortion counselling, total number of legalized abortions per year fell gradually until it reached a stable rate of ~12000 from year 2004 onwards
    - However, when fertility rates are taken into account, the falling fertility rates over time meant that the proportion of pregnancies abortion did not change despite the introduction of mandatory pre-abortion counselling (*still about 1 in every 4 pregnancies*)

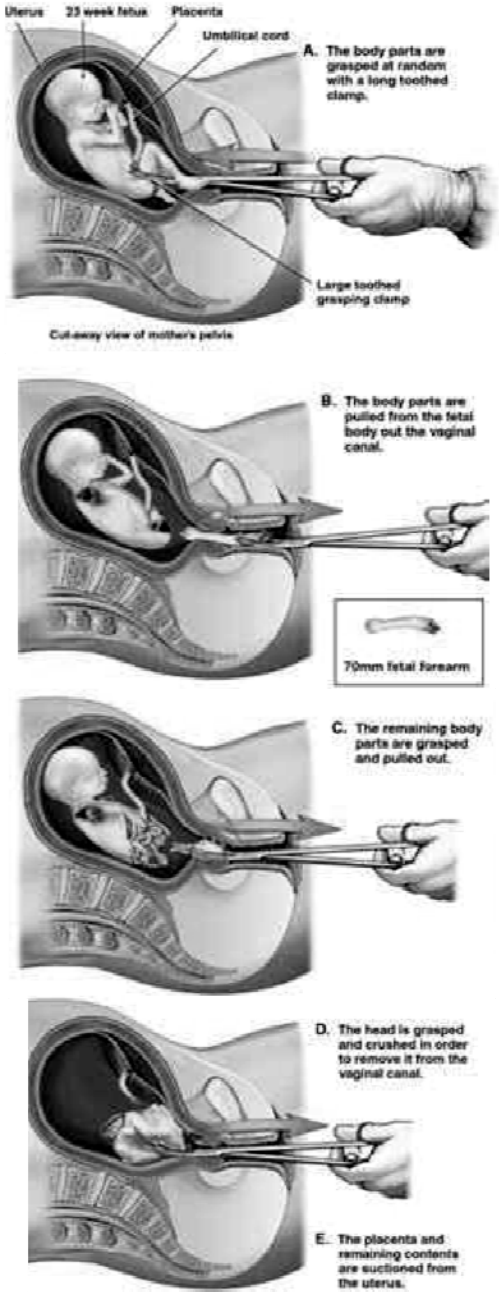
- **Indications for Induced Abortion**
  - ***Maternal indications:***
    - Cardiac disease
    - Malignancy
    - Renal disease
    - Psychotic state
  - ***Fetal indications:***
    - Genetic/chromosomal anomalies
    - Fetal anomalies
  - ***Social indications:***
    - Unwanted pregnancy

- **Pre-Abortion Assessment**
  - ***Confirm pregnancy viability & site***
    - Exclude ectopic pregnancy
    - Assess if fetus is viable (*if non-viable, patient is technically experiencing a missed miscarriage, in which case evacuation of the uterus can be offered as a management option; this would technically not be an induced abortion, hence all the legislations requiring pre-abortion counselling would not apply*)
  - ***Determine gestational age***
    - If too early to confirm viability of pregnancy, may need to follow-up patient with a repeat scan
    - Gestational age important to determine the method of induced abortion used (*see below*)
    - Gestational age >24 weeks is legally not allowed for an induced abortion except in special circumstances (*e.g. late detection of fetal anomaly which is not compatible with extra-uterine life*)
  - ***Determine parity***
    - Nulliparous women tend to require cervical priming before surgical termination of pregnancy
    - Nulliparous women also tend to have higher risk of cervical injury during surgical termination of pregnancy with sequelae of cervical incompetence
  - ***Determine maternal rhesus status***
    - Give anti-D Ig after abortion if rhesus negative & antibody negative to prevent isoimmunization
  - ***Mandatory pre-abortion counselling***
    - Involves watching a abortion counselling video
    - Consent for abortion can only be taken 48 hours later so patient has to return if she still wishes to proceed

- **Methods for Induced Abortion**
  - ***First trimester termination of pregnancy***
    - Medical abortion
      - Can be used up to 8 weeks gestation
      - Options include: misoprostol + mifepristone *(aka RU 486, an anti-progesterone; not available locally)* or misoprostol alone
      - Route of administration: *vaginal pessary*
      - Dosage of **misoprostol** for medical abortion: *loading dose of 800µg followed by 3 doses of 400µg given 3-hourly*
      - Success rate = 96%
    - Surgical abortion
      - Can be used anytime in 1st trimester
      - Done via **vacuum aspiration**
      - Pre-aspiration **cervical priming** using misoprostol may be needed especially in cases where difficulty of cervical dilatation is expected (*e.g. nulliparous*)
      - Route of administration: *vaginal pessary*
      - Dosage of misoprostol for cervical priming: *400µg given 3 hours before surgical abortion*
      - Alternative method of cervical priming is the use of **laminaria tents** (*osmotic dilators which gradually dilate the cervix as they enlarge in diameter through absorbing bodily fluid*)
      - Success rate >99%



  - ***Second trimester termination of pregnancy***
    - Medical abortion
      - Options include: misoprostol + mifepristone *(aka RU 486, an anti-progesterone; not available locally)* or misoprostol alone
      - Essential induces a "mini-labour"
      - Route of administration: *vaginal pessary*
    - Surgical abortion
      - Cervical preparation
      - **Dilatation & evacuation**



- **Complications of Induced Abortion**
  (*in general, 1st trimester abortions carry much lower risk of complications as compared to 2nd trimester abortions*)
  - ***Complications of medical induced abortions:***
    - Bleeding
    - Retained products of conception
  - ***Complications of surgical induced abortions:***
    - Immediate:
      - Bleeding, infection, anesthesia risk
      - Cervical injury
      - Uterine perforation
      - Bladder &/or bowel injury
      - Retained products of conception (*much less likely as compared to medical induced abortions*)
    - Long-term:
      - Cervical incompetence
      - Uterine rupture in subsequent pregnancy
      - Placenta accreta
      - Subfertility (*Asherman syndrome, tubal blockage*)
      - Chronic pelvic inflammatory disease
      - Rhesus isoimmunization
      - Psychological

- **Follow-up After Induced Abortion**
  - ***Immediate follow-up (1-2 weeks after abortion):***
    - Assess for retained products of conception
      - Any persistent per-vaginal bleeding?
      - Speculum examination for signs of RPOC (*opened os, visualized products of conception*)
    - Assess for infection
      - Any fever, lower abdominal pain, discharge?
      - Abdominal & pelvic examination for tenderness & discharge
    - Psychological support
    - Advice on contraception
  - ***Delayed follow-up (6-8 weeks after abortion):***
    - Assess for return of normal menses
    - Psychological support
    - Advice on contraception

INFERTILITY

Approach to Infertility

- **Definitions**
  - **Infertility** = inability to conceive following 1 year of unprotected intercourse
    - **Primary infertility** = when infertility occurs without any prior pregnancy
    - **Secondary infertility** = when infertility occurs after a previous conception
  - Average time required for conception in couples who will eventually attain pregnancy:
    - After 3 months of exposure → 57%
    - After 6 months of exposure → 72%
    - After 1 year of exposure → 85%
    - After 2 years of exposure → 93%

- **Incidence of Different Causes of Infertility**
  - Male coital factor (40%)
  - Female factor (30%)
    - Ovulatory factor
    - Tuboperitoneal factor
    - Uterine factor
    - Cervical factor
  - Both male & female factors (23%)
  - Unexplained infertility (7%)

- **History**
  - ***Conception attempts:***
    - Age (*especially woman's age, as age itself is related to decreasing fertility*)
    - Duration couple has tried conceiving so far
    - Any previous successful conceptions
  - ***Menstrual history:***
    - Age of menarche, last menstrual period
    - Regularity & length of cycles
  - ***Existing symptoms:***
    - Pelvic symptoms (*pelvic pain, dysmenorrhea, dyspareunia, abnormal uterine bleeding, vaginal discharge*)
    - Symptoms related to systemic causes (*galactorrhea, visual disturbances*)
  - ***Past medical, surgical & gynaecologic history:***
    - Previous infections (*STDs, PID, mumps*)
    - Known gynaecologic conditions (*PCOS, uterine fibroids, endometriosis etc*)
    - Past gynaecologic procedures (*pelvic surgery, tubal surgery, uterine instrumentation*)
    - Past exposure to radiation or chemotherapy (*husband as well*)
    - Drug history
  - ***Social history:***
    - Smoking & alcohol habits (*of husband as well*)
    - Occupation (*of husband as well*)
  - ***Coital history:***
    - Frequency of sexual intercourse
    - Any coital difficulties (*dyspareunia, ejaculatory problems*)

- **Physical Examination**
  - ***General examination:***
    - Height, weight, BMI (*overweight? underweight?*)
    - Signs of virilization & hirsutism
    - Signs of thyroid disease
    - Visual field testing for bitemporal hemianopia
  - ***Breast examination:***
    - Nipple discharge (*hyperprolactinemia*)
  - ***Abdominal examination:***
    - Palpable masses, tenderness
    - Scars from previous surgeries
  - ***Pelvic examination:***
    - Assess uterine size, version & mobility, presence of adnexal masses, tenderness & thickened uterosacrals

- **Range of Investigations for Infertility**
  - ***Hormonal investigations:***
    - Female: *day 2-3 FSH, LH, estradiol, testosterone & TSH + mid-luteal (day 20-22) prolactin & progesterone*
    - Male: *FSH, prolactin & TSH*
  - ***Infection screen:***
    - To assess for PID in female
  - ***Imaging studies:***
    - Pelvic ultrasound
      - Assesses uterine size & pathology (*fibroids, endometrial polyps, congenital anomaly*)
      - Assesses adnexal masses (*endometrioma, polycystic ovaries*)
    - Hysterosalpingography
      - Assesses uterine cavity
      - Assesses tubal patency
    - Saline sonography
      - Assesses uterine cavity
      - Assesses tubal patency
  - ***Diagnostic laparoscopy:***
    - Can aid in diagnosis for cases of infertility remaining unexplained despite more conservative investigations
    - Can assess for:
      - Pelvic adhesions
      - Signs of endometriosis
      - Tubal patency
  - ***Semen analysis:***
    - Baseline investigation to assess possible male factor infertility
  - ***Other tests:***
    - Basal body temperature monitoring
    - Post-coital test

- **Prioritizing Investigations in Infertility**
  - ***1st-line investigations:***
    - Hormonal tests + pelvic ultrasound + semen analysis ± infection screen
    - Convenient, non-invasive procedures which can guide the need for further evaluation (*e.g. abnormal semen analysis may require urologist referral*)
  - ***2nd-line investigations:***
    - Hysterosalpingography or saline sonography
    - More invasive procedures with attendant risks
    - Assesses uterine cavity & tubal patency
  - ***3rd-line investigations:***
    - Diagnostic laparoscopy
    - Surgical procedures with attendant risks

Etiologic Factors of Infertility

Male Coital Factor

- **Contributory Etiologies**
  - ***Problems with sperm production:***
    - Congenital abnormalities (*undescended testes, gonadal dysgenesis, congenital absence of vas deferens*)
    - Varicocele
    - Genital tract infections (*prostatitis, orchitis*)
    - Endocrine causes (*hypothalamic-pituitary dysfunction, hypothyroidism, hyperprolactinemia*)
    - Allergic reactions, anti-sperm antibodies
    - Surgery or trauma to genitalia or inguinal region (*e.g. previous inguinal hernia repair*)
    - Exposure to radiation
    - Exposure to toxins: excessive alcohol & smoking, heavy metals (*lead, cadmium*) or chemotherapeutic agents (*e.g. cyclophosphamide*)
    - Excessive genital exposure to environmental heat (*sauna, hot tubs, tight underwear, occupational exposure*)
  - ***Problems with sperm deposition:***
    - Abnormal location of urethral meatus
    - Ejaculatory problems (*e.g. premature ejaculation*)
    - Erectile dysfunction (*idiopathic, alcoholism, diabetes, hyperprolactinemia etc*)
  - ***Problems with sperm function:***
    - Use of lubricants toxic to sperm function
    - Poor intrinsic sperm function: low motility &/or abnormal morphology (*can be idiopathic or due to similar causes as for problems with sperm production*)

- **History & Physical Examination**
  - ***History:***
    - Check if patient has ever fathered a child before
    - Assess for possible causes of infertility
  - ***Physical examination:***
    (*usually done by urologist upon referral after an abnormal semen analysis report*)
    - Check location of urethral meatus
    - Assess testicular size
    - Assess for presence of varicocele

- **Diagnosis & Evaluation**
  - ***Semen analysis:***
    - Important considerations:
      - Semen analysis sample should be collected after a 2-4 day period of abstinence from sex
      - Entire ejaculate should be collected in a clean non-toxic container
      - Semen quality varies greatly between samples, hence an accurate appraisal of abnormal semen requires at least 3 analyses
    - Reference values for semen analysis report:

Characteristic	Reference Value
WHO Semen Analysis Guidelines 2009	
Semen volume	≥1.5ml
Sperm concentration	≥15 million/ml
Total sperm number	≥39 million per ejaculate
Sperm motility	Total motility (PR + NP) ≥40% Progressive motility (PR) ≥32%
Sperm morphology	≥4% normal forms (by 'strict' criteria)
Other Parameters not in WHO Guidelines 2009	
White blood cells	<1 million/ml
Immunobead test	<20% spermatozoa with adherent particles
SpermMar test	<10% spermatozoa with adherent particles

    - Relevant terminology of semen analysis:
      - **Aspermia** = *no ejaculate*
      - **Azoospermia** = *no measurable sperm in semen*
      - **Oligospermia** = *low sperm concentration/count*
      - **Asthenospermia** = *poor sperm motility*
      - **Teratospermia** = *abnormal sperm morphology*
  - ***Endocrine evaluation:***
    (*may be useful in men with abnormal semen analysis findings to elucidate possible underlying causes*)
    - Thyroid function test (*for hypothyroidism*)
    - Prolactin (*for hyperprolactinemia*)
    - Follicle-stimulating hormone (FSH)
      - Elevated FSH levels in a male generally indicates substantial testicular parenchymal damage (*as the hormone inhibin normally produced by the Sertoli cells of the testes provides the principle negative feedback control of FSH secretion by the anterior pituitary*)
      - Elevated FSH thus predicts a high likelihood of failure of most forms of treatment targeted at improving male fertility, but does <u>not</u> predict the likelihood of sperm recovery from testicular sperm extraction for assisted reproductive techniques

- **Management**
  - ***Conservative management:***
    - Coital advice:
      - Scheduled sexual intercourse (*once every 1-2 days during periovulatory period – days 12 to 16 of a 28-day cycle*)
      - Avoid use of toxic lubricants
      - Woman to lie on her back for at least 15 minutes after coitus to prevent rapid loss of semen from the vagina
    - Avoid environmental exposures:
      - Cut down on alcohol & smoking
      - Avoid excessive genital heat exposure
  - ***Treatment of underlying causes:***
    - Impaired sperm production due to hypothalamic-pituitary dysfunction or unknown cause:
      - Clomiphene
      - Gonadotropins (*e.g. hCG or hMG - human menopausal gonadotropin*)
      - Testosterone, mesterolone
    - Hyperprolactinemia:
      - Dopamine agonists (*bromocriptine, cabergoline*)
      - Surgical resection of pituitary adenoma
    - Infection:
      - Treat infection
    - Varicocele:
      - Venous plexus ligation
  - ***Assisted reproductive techniques:***
    (*indicated if infertility is refractory or not amenable to treatment by other modalities*)
    - Intrauterine insemination (IUI) with own or donor sperm
    - In-vitro fertilization (IVF) ± intracytoplasmic sperm injection (ICSI)

Female Ovulatory Factor

- **Contributory Etiologies**
  - ***Hypothalamic dysfunction:***
    - Systemic stresses (*poor nutrition, significant weight loss, excessive physical activity, severe emotional distress, chronic medical illness*)
    - Structural abnormalities (*congenital hypothalamic abnormalities, acquired space-occupying lesions or destructive lesions of the hypothalamus*)
  - ***Pituitary gland dysfunction:***
    - Hyperprolactinemia (*pituitary adenoma, drugs, primary hypothyroidism, chronic renal failure*)
    - Destructive lesions of the pituitary (*space-occupying lesions, Sheehan syndrome*)
  - ***Ovarian dysfunction:***
    - Premature ovarian failure (*dysgenetic gonads, mumps infection, post-radiation or chemotherapy, autoimmune*)
    - Hyperandrogenic disorders
      - Polycystic ovarian syndrome (PCOS)
      - Virilizing adrenal or ovarian tumours
      - Congenital adrenal hyperplasia

- **Diagnosis & Evaluation**
  - ***Test hormonal levels:***
    - FSH, LH, estradiol, testosterone & TSH (*taken on days 3-5 of cycle*)
    - Prolactin & progesterone (*taken in mid luteal phase – days 20-22 of cycle*)
      - Progesterone >5-10ng/ml indicates that ovulation has occurred this cycle
  - ***Pelvic ultrasound***
    - Assess ovaries for PCOS
  - ***Other adjunctive evaluations:***
    - Tanner staging (*for virilization*)
    - Basal body temperature charting
      - ≥0.3°C rise in basal body temperature is significant and indicates ovulation has occurred (*temperature is higher in the luteal phase*)

- **Management**
  - ***Treatment for systemic stresses:***
    - Put on weight if underweight
    - Moderate level of physical activity
  - ***Treatment for hyperprolactinemia:***
    - Dopamine agonists (*bromocriptine, cabergoline*)
    - Surgical resection of pituitary adenoma
  - ***Treatment for PCOS:***
    - Conservative measures:
      - Lose weight
    - Pharmacological measures:
      - Clomiphene
      - Metformin (*useful adjunct to clomiphene*)
    - Surgical measures:
      - Laparoscopic ovarian drilling
  - ***Assisted reproductive techniques:***
    (*indicated if infertility is refractory or not amenable to treatment by other modalities*)
    - IVF ± ICSI with own or donor oocyte

Female Tuboperitoneal Factor

- **Contributory Etiologies**
  - ***Congenital tubal obstruction***
  - ***Inflammatory causes:***
    - Endometriosis
    - Pelvic inflammatory disease
    - Previous ruptured appendiceal abscess
  - ***Iatrogenic causes***
    - Previous pelvic surgery (*causes adhesions & scarring*)
    - Previous tubal surgery (*e.g. salpingectomy*)

- **Diagnosis & Evaluation**
  - ***Pelvic ultrasound:***
    - Can visualize signs of tubal blockage (*hydrosalpinx*)
  - ***Hysterosalpingography (HSG):***
    - Can assess tubal patency
      - *Note: even if only 1 tube fills with dye during HSG, it may still be normal due to the dye following the path of least resistance*
    - Procedure:
      - Anesthesia is generally not required
      - Occlusive cannula placed in the cervix
      - Radiopaque water-soluble dye is then instilled to preliminarily assess tubal patency (*sequestration of oil-based dye within a blocked tube has adverse effects*)
      - Fluoroscopy used for image intensification
      - If tubal patency is confirmed, a further instillation of an oil-based dye is carried out (*demonstrated to have significant therapeutic effect for women with unexplained infertility*)
    - Risks of procedure:
      - Discomfort during procedure
      - Infection (*hence need a normal pelvic examination beforehand to rule out overt signs of lower tract infection + prophylactic doxycycline*)
  - ***Saline sonography:***
    - An alternative to HSG whereby saline is infused into the uterine cavity under ultrasound monitoring
  - ***Diagnostic laparoscopy:***
    - Can assess for pelvic adhesions, stigmata of chronic endometriosis & tubal patency

- **Management**
  - ***Expectant treatment:***
    - For unilateral tubal blockage (*pregnancy possible still*)
  - ***Surgical treatment:***
    - Tubal surgery:
      - Surgical options:
        - (i) Selective catheterization (*1st-line for proximal tubal occlusions*)
        - (ii) Microsurgical tuboplasty (*surgery for reversal of previous tubal ligation*)
        - (iii) Neosalpingostomy (*option for fimbrial occlusion by creating a new tubal opening*)
        - (iv) Tubal reimplantation (*option for occlusions of the intramural portion of the tube*)
      - Risk of ectopic pregnancy after tubal surgery:
        - → Repair of diseased tubes: *at least 10% risk*
        - → Anastomosis of healthy tubes: *3-5% risk*
    - Adjunctive surgical procedures:
      - Adhesiolysis
      - Ablation of endometriotic deposits
      - Resection of endometriomas (*cystectomy*)
  - ***Assisted reproductive techniques:***
    - IVF ± ICSI

Female Uterine Factor

- **Contributory Etiologies**
  - ***Congenital uterine abnormalities***
  - ***Structural uterine abnormalities***
    - Submucous ± large intramural fibroids
    - Endometrial polyps
    - Uterine synechiae, Asherman syndrome

- **Diagnosis & Evaluation**
  - ***Pelvic ultrasound***
  - ***Hysterosalpingography (HSG):***
  - ***Hysteroscopy***

- **Management**
  - ***Surgical treatment:***
    - Myomectomy for fibroids
    - Hysteroscopic excision of synechiae, endometrial polyps & submucous fibroids

Female Cervical Factor

- **Contributory Etiologies**
  - ***Structural cervical abnormalities:***
    - Congenital cervical incompetence
    - Acquired cervical incompetence (*e.g. after cone biopsy*)
  - ***Poor cervical mucus quality:***
    - A profuse watery cervical mucus (**spinnbarkeit**) exudes out of the cervix during the few days prior to ovulation which comes into contact with seminal ejaculate
      - Serves to protect sperm from the natural acidic pH & enzymatic activity of vaginal secretions
    - Alterations to the constitution of this cervical mucus can impair sperm function & survival:
      - Chronic cervicitis
      - Cervical infections

- **Diagnosis & Evaluation**
  - ***Evaluation of spinnbarkeit:***
    - Tested during the immediate pre-ovulatory phase (days 12-14 of a 28-cycle)
    - Parameters assessed:
      - Amount of cervical mucus
      - pH of cervical mucus (normally ≥6.5)
      - When litmus paper is used to touch mucus & lifted vertically, the mucus should extend in a thread to ≥6cm in length
  - ***Post-coital test (Sims Huhner test):***
    - Performed 2-12 hours after intercourse
    - Assesses number & fertility of spermatozoa that have entered the cervical canal
    - Poor correlation with fertility, poor predictive value

- **Management**
  - ***Treatment of underlying cause:***
    - Treat cervical infection (*e.g. doxycycline*)
    - Cryotherapy for chronic cervicitis refractory to medical treatment
  - ***Assisted reproductive techniques:***
    - Intrauterine insemination (IUI)
      - Useful as it helps bypass poor cervical mucus

Assisted Reproductive Techniques

In-Vitro Fertilization (IVF) & Intracytoplasmic Sperm Injection (ICSI)

- **Indications for IVF ± ICSI**
  - IVF ± ICSI essentially serves as a last resort treatment for many of the causes of infertility
    - Involves obtaining oocyte & sperm before carrying out fertilization of the oocyte in-vitro, with subsequent transfer of a successfully developed embryo into the uterine cavity for implantation
    - Donor sperm &/or oocyte may be used if either is not obtainable from the couple
  - ICSI is additionally useful for cases with poor sperm production &/or function:
    - Involves direct injection of a single selected good quality sperm into the harvested oocyte

- **Phases of IVF ± ICSI**

  i. ***Baseline investigations:***
    - Investigations for infertility:
      - Semen analysis
      - Hormonal blood tests
      - Pelvic ultrasound
      - HSG or saline sonogram
    - Screening blood tests (for both husband & wife):
      - HIV, Hepatitis B, Hepatitis C, VDRL
      - Mandatory by MOH guidelines
      - Results are only valid for 6 months

  ii. ***Ovarian stimulation:***
    - Aim of this phase is to assume exogenous control of & stimulate multiple follicular development
    - Procedure:
      - Begin in the mid-luteal phase (day 21)
      - Begin administering a GnRH agonist to shut down the endogenous hypothalamus-pituitary-ovary axis (*as a non-pulsatile GnRH exposure inhibits gonadotropin production by the pituitary, contrary to an endogenous pulsatile exposure which stimulates gonadotropin secretion*)
      - On day 2-3 of the subsequent cycle, begin administering a gonadotropin (*FSH &/or hMG*) to induce ovarian follicular development
      - Monitor follicular development with serial serum estradiol levels & pelvic ultrasounds (*follicular diameter ≥18mm considered mature*)
      - Once mean follicular size is 18mm, administer an injection of hCG (*usually 10000U*) to induce completion of oocyte maturation
    - Risks of ovarian stimulation:
      - **Ovarian hyperstimulation syndrome (OHSS)**: bloatedness, nausea/vomiting, shortness of breath, fluid retention (*may need hospitalization*)
      - Failed stimulation (*in 5% of cases, in which case procedure is cancelled*)

iii. Oocyte pick-up (OPU):

- Performed 35 hours after the hCG injection
- Procedure:
  - May be performed under conscious sedation
  - Transvaginal ultrasound guidance is used to direct aspiration of the multiple follicles in both ovaries
  - Harvested oocytes are then prepared & selected for subsequent fertilization
- Risks of oocyte pick-up:
  - Risks of sedation (*respiratory depression*)
  - Bleeding from ovaries, uterus or adjacent blood vessels
  - Injury to bowel & bladder
  - Infection

iv. Sperm collection & preparation:

- Fresh semen sample is collected on the same day as for oocyte pick-up
- Semen sample is then assessed, washed & prepared for fertilization

v. In-vitro fertilization:

(*2 main methods used for fertilization of harvested oocyte*)

- 2 main methods:
  - Conventional IVF: *thousands of sperm are incubated overnight with selected oocytes for fertilization to occur by itself*
  - Intracytoplasmic sperm injection (ICSI): *a single good quality sperm is selected by the embryologist & injected into the oocyte*
- Not all the oocytes harvested have to be fertilized; of oocytes not used, 2 options for patient:
  - Disposed of immediately
  - Made available for research
- Fertilized oocytes are then cultured & monitored for 2-3 days:
  - Successful fertilization can be identified by visualization of 2 pronuclei occurring 14-18 hours after insemination
  - Additional procedures following successful fertilization may be recommended based on individual circumstances (**Blastocyst culture**, **Laser Assisted Hatching**)
- Not all the embryos derived after fertilization will be usable; for abnormal embryos, 2 options for patient:
  - Observed until they cease development, following which they will be disposed of
  - Disposed of immediately
  - Made available for research

vi. Embryo transfer & embryo freezing:

- Normal embryos that have formed successfully from in-vitro fertilization can then be transferred to the uterine cavity 2-3 days after insemination
- Procedure:
  - Can usually be done without sedation
  - Under transabdominal ultrasound guidance, the embryos loaded in a soft catheter are introduced into the uterine cavity through the vagina & cervix
- Risks of embryo transfer:
  - Bleeding
  - Infection
  - Failed transfer requiring use of sedation or postponement of procedure
- Determining number of embryos transferred:
  - Up to 2 embryos are allowed to be transferred in most cases
  - Up to 3 embryos are allowed to be transferred if all 3 of the following criteria are met:
    - (i) all children conceived as a result of the procedure will be delivered & cared for in a hospital which has Level 3 neonatal intensive care facilities
    - (ii) patient is ≥37 years old
    - (iii) patient has undergone ≥1 previous stimulated assisted reproduction cycle which was unsuccessful or if there is no good quality embryo available
- Remaining good quality normal embryos not transferred will be frozen:
  - Can be kept & used for thawed embryo transfer in a subsequent menstrual cycle in the event of failure of the current attempt or for future additional pregnancies desired
  - Survival rate of frozen embryos is 83%
  - Storage of frozen embryos is limited to 10 years from the date of fertilization, subjected to an annual storage fee
  - Patient & spouse are to indicate from the onset a joint decision on what to do with their frozen embryos in the event that the marriage is terminated or patient becomes uncontactable (*either disposed of or made available for research*)

vii. Luteal support:

- Luteal support essential involves progesterone supplementation to maintain the endometrial lining for implantation & continuation of pregnancy
- Options:
  - Vaginal utrogestan
  - Pregnyl injections
  - Progesterone injections

viii. Day 17 pregnancy test:

- Mandatory, even in cases of per vaginal bleeding
- If pregnancy is unsuccessful & frozen embryos are available, can proceed with a frozen cycle
- All successful births resulting for assisted reproductive techniques (ART) is notifiable to MOH

- **Outcomes of IVF**
  - ***Possible pregnancy-related complications:***
    - Multiple gestation
    - Ectopic pregnancy
    - Miscarriage
    - Slight increased risk of fetal anomalies (4% vs 3% in spontaneous pregnancies)
  - ***Success rates of IVF:***

KK Hospital IVF/ICSI Success Rates 2010						
Age	***<30***	***30-35***	***36-37***	***38-39***	***≥40***	***Overall***
CPR (fresh)	48.5%	45.6%	29.3%	19.3%	12.1%	35.8%
LB (fresh)	37.9%	37.5%	23.6%	10.8%	4.3%	27.8%
CPR (thawed)	32.8%	39.4%	37.3%	24.3%	13.6%	33.7%
LB (thawed)	23.0%	27.2%	19.7%	14.8%	5.1%	21.4%

CPR = clinical pregnancy rate; LB = live birth

Intrauterine Insemination (IUI)

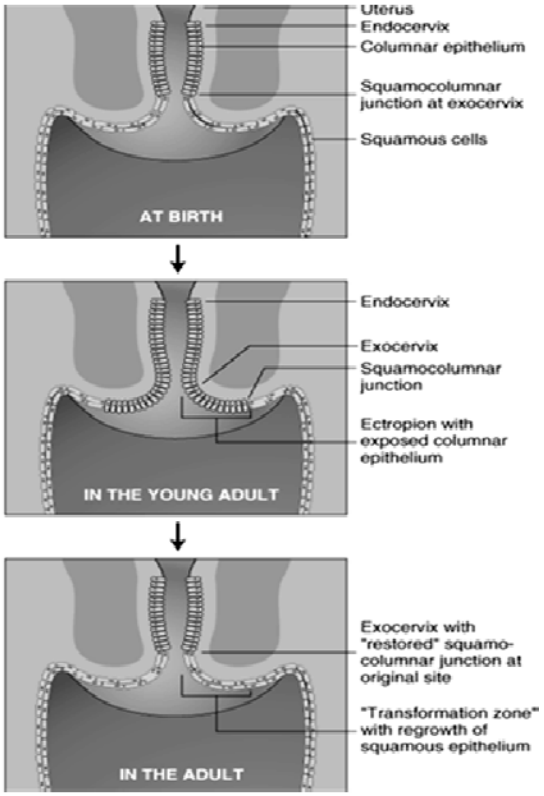
- **Indications for IUI**
  - IUI is useful as a penultimate measure (*before resorting to IVF*) in certain situations:
    - Essentially involves collection & preparation of sperm sample (*from husband or donor*), usually with concomitant ovarian stimulation in the wife to control timing of ovulation, before injection of prepared sperm into the uterus around the projected time of ovulation
    - Situations where IUI may be useful:
      - Mild male factor infertility
      - Cervical mucus factor infertility
      - Unexplained infertility

- **Phases of IUI**
  - ***i. Baseline investigations:***
    (*similar to as for IVF*)
  - ***ii. Ovarian stimulation:***
    (*similar to as for IVF; unlike for IVF, after hCG injection, stimulated follicles are not harvested, but rather allowed to rupture & ovulate as per normal*)
  - ***iii. Sperm collection & preparation:***
    (*similar to as for IVF*)
  - ***iv. Intrauterine insemination:***
    - Involves intrauterine placement of collected & prepared sperm timed at peri-ovulation (*36 hours after hCG injection*)
    - Procedure:
      - Office procedure, no sedation required
      - Prepared sperm is drawn up into a tuberculin syringe & attached to an intrauterine insemination catheter
      - Catheter is inserted into uterine cavity through the vagina & cervix, with the sperm subsequently injected

Cervical Dysplasia & Cancer

- **Epidemiology & Associations**
  - Cervical cancer is the most common malignancy in females in the world, but 5th most common locally (3rd most common gynaecological malignancy)
    - Due to effective screening programme in Singapore using Pap smear (**Papanicolaou smear**)
    - Cervical cancer is the only cancer considered to be preventable by screening
    - At least 80% coverage of a population by screening is required for effective reduction in national incidence of cervical cancer (as in the case of Singapore)
  - Mean age of presentation = 47 years
  - Risk factors for cervical cancer (*mostly related to exposure to human papillomavirus*):
    - Young age at 1st coitus (<20 years old)
    - Multiple sexual partners or sexual partner who has multiple sexual partners
    - High parity
    - Lower socioeconomic status
    - Smoking

- **Pathophysiology of Cervical Cancer**
  - ***Human papillomavirus (HPV) as the causative agent***
    - 95% of cervical cancers have HPV DNA
    - Many serotypes of HPV exist, but the ones with the highest risks for developing cervical cancer are serotypes 16 & 18 (*collectively accounting for 70%*)
    - Viral oncogenes implicated in carcinogenesis:
      - HPV genome normally has E2 gene which constitutionally inhibits expression of the E6 & E7 genes while virus is in a lytic state
      - Upon viral integration into the host cell genome, disruption of the E2 gene allows E6 & E7 expression
      - E6 gene product binds to host cell p53 tumour suppressor protein, promoting its degradation
      - E7 gene product binds to retinoblastoma tumour suppressor protein (pRB), freeing E2F cell cycle protein from its constitutional inhibition by pRB, promoting proliferation
  - ***HPV usually infects the transformation zone of the cervix***
    - At birth, the cervix comprises columnar epithelium (*lining the endocervical canal*) & squamous epithelium (*lining the ectocervix*), the junction between which is known as the **original squamocolumnar junction**
    - At puberty, under the influence of estrogen, the endocervical canal undergoes a certain degree of eversion (**cervical ectropion**), exposing the lower portion of the columnar epithelium
    - Acidification of the vagina at puberty results in squamous metaplasia of the exposed columnar epithelium in a radial pattern, beginning from the squamocolumnar junction inwards, producing a **new squamocolumnar junction** that moves progressively up the endocervical canal
    - This zone of squamous metaplasia is known as the **transformation zone**
    - Post-menopausally, the cervix may regress, causing the transformation zone to be retracted back into the endocervical canal

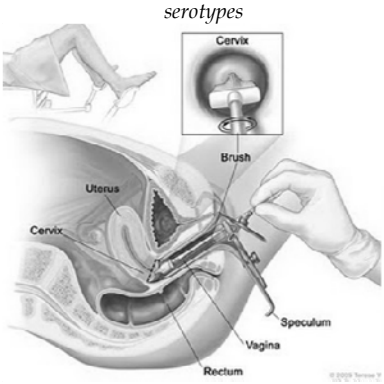


  - ***Stepwise carcinogenesis in cervical cancer***
    - Initial HPV exposure of the transformation zone
    - Dysplasia occurs with persistent HPV infection
    - **Cervical intraepithelial neoplasia (CIN)** develops:
      - CIN 1 = *abnormalities confined to ≤1/3 of the epithelium (spontaneous clearance rate 57%)*
      - CIN 2 = *abnormalities extend to between 1/3 & 2/3 of the epithelium (spontaneous clearance rate 43%)*
      - CIN 3 = *abnormalities extend to ≥2/3 of the epithelium (spontaneous clearance rate 32%)*

      (*note that CIN may be of squamous differentiation – squamous intraepithelial lesion, for which it may be low or high grade – or endocervical columnar differentiation – glandular intraepithelial lesion/adenocarcinoma-in-situ*)
    - Latent period between CIN & invasive carcinoma during which more cellular abnormalities accumulate, possibly influenced by further environmental factors (e.g. smoking)
      - *Natural history for squamous CIN is better defined, with a 10-25 year period before development of invasive squamous cell cancer*
      - *Natural history for adenocarcinoma-in-situ less well defined*
    - Eventual development of invasive carcinoma
      - Squamous cell carcinoma (80%)
      - Adenocarcinoma (15%)
      - Adenosquamous carcinoma (3%)
      - Others (2%)
  - ***Modes of spread of cervical cancer***
    - Direct invasion (*uterus, vagina, bladder, rectum, ureter*)
    - Lymphatic
    - Hematogenous (*lung, liver, bone, brain*)

- **Primary Prevention of Cervical Cancer**
  - ***Two HPV vaccines are currently available:***
    - **Gardasil**
      - Quadrivalent vaccine (*protects against HPV serotypes 6, 11, 16 & 18*) manufactured by Merck
      - Approved for use between 9 & 26 years of age
    - **Cervarix**
      - Bivalent vaccine (*protects against HPV serotypes 16 & 18*) manufactured by GlaxoSmithKline
      - Approved for use between 9 & 45 years of age
  - ***Recommended vaccination schedule:***
    - 3 doses, given at 0, 1 & 6 months
      - If 2nd or 3rd dose is delayed, no need for restarting, just continue
      - As long as all 3 doses are given within 1 year, efficacy can still be predicted
    - Most effective if vaccine is given <u>before</u> onset of sexual activity
      - Still recommended though, even after commencement of sexual activity, even after prior abnormal cytology or CIN
      - However, likely to be less effective
  - ***Public health perspective on HPV vaccination:***
    - Study done in 2011 comparing use of vaccine + screening (for both Gardasil & Cervarix) vs screening alone, looking at the outcome of incremental cost per life year saved in Singapore
    - Results showed incremental healthcare costs associated with vaccine + screening, but also additional life years saved with this policy
    - Overall incremental cost per life year saved with the use of vaccine + screening is far below GDP per capita of Singapore (*i.e. the money invested into saving one life each year is less than the money that one life can earn for the country per year*)
    - Hence addition of HPV vaccine on top of screening alone is a <u>very cost-effective</u> strategy compared to screening alone

- **Secondary Prevention of Cervical Cancer**
  - ***Cervical cancer screening modality***
    - Uses **Papanicolaou smear (Pap smear)**
      - During vaginal speculum examination (*without lubrication as lubricant may affect results*), the spatula or brush is used to sample the lining cells of the cervix
      - Both the endocervical canal & ectocervix have to be sampled
      - Sensitivity of screening can be further enhanced by added testing for HPV DNA
    - **Traditional/conventional smears**
      - Sample is smeared directly onto a glass slide before being treated & stained for microscopy
      - Lower sensitivity than liquid-based cytology (*false negative rates for high-grade intraepithelial lesions of 20%, higher rates for glandular lesions & invasive cancers*)
    - **Liquid-based cytology**
      - Method widely used nowadays
      - Sample is placed into a fixative solution, which is treated to remove blood, mucous & inflammatory cells before a monolayer smear is automatically prepared by a machine for microscopic evaluation
      - Advantages: *higher sensitivity & specificity, reduced inadequate sample rates, reading of slides can further be automated as well to further increase cost-effectiveness*
  - ***Cervical Screen Singapore (CSS)***
    - Recommendations:
      - 1st Pap smear for all women to be done at 25 years of age <u>or</u> within 1 year of sexual life if it commences after age of 25
      - 2nd Pap smear for all women to be done 1 year after the 1st Pap smear
      - Subsequent Pap smears are done 3-yearly (*so long as smears have been negative*)
      - Last Pap smear to be done at 65 years old
    - Special circumstances:
      - Virgo intacta (VI) women: *no need for smears; however, must counsel that cervical cancer can still occur (even though uncommonly) without HPV*
      - Vaccinated women: *smears following the recommendations are still indicated because the vaccine does not protect against all cancer-causing serotypes*



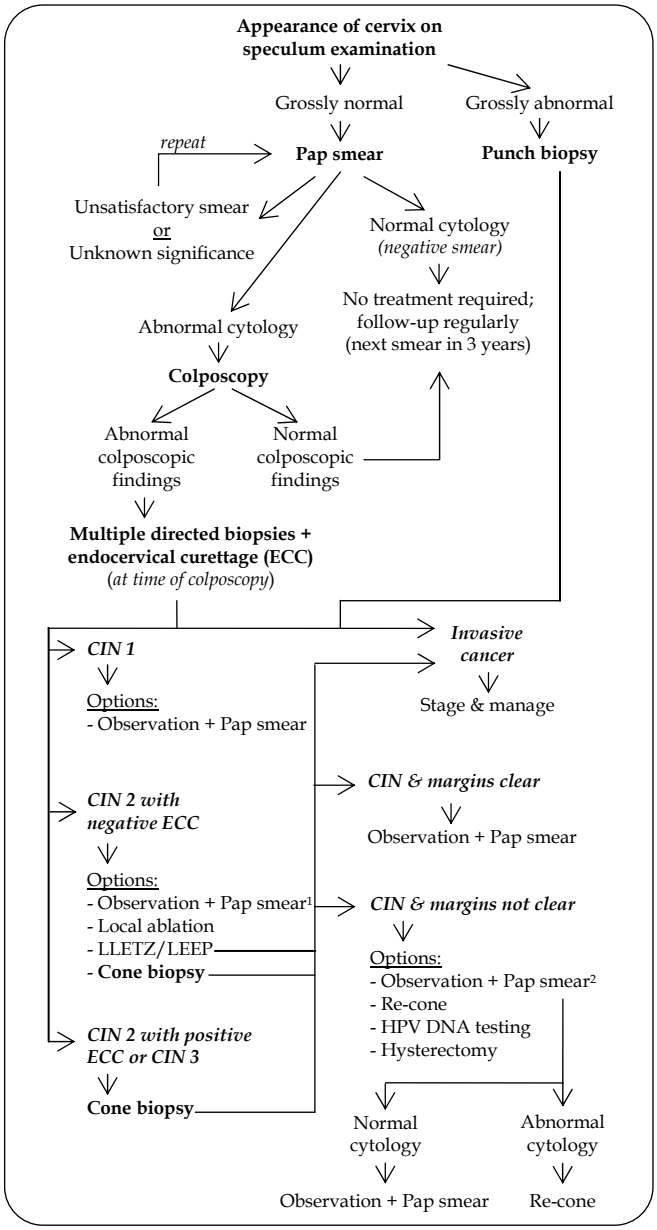
Performing a Pap smear

Liquid-based cytology

- **Clinical Presentation of Cervical Dysplasia & Cancer**
  - ***Asymptomatic***
    - Usually discovered on routine Pap smear (*see below for algorithm for evaluating an abnormal Pap smear*)
  - ***Local symptoms***
    - Abnormal vaginal bleeding (*most commonly post-coital, intermenstrual or post-menopausal bleeding*)
    - Vaginal discomfort
    - Vaginal discharge (*may be malodorous*)
  - ***Symptoms due to local invasion***
    - Dysuria, hematuria, per-vaginal leaking of urine (*fistula formation*)
    - Flank discomfort/mass (*hydronephrosis*)
    - Constipation
  - ***Metastatic symptoms***
    - Constitutional (*loss of weight & appetite*)
    - Lung (*dyspnea, hemoptysis*)
    - Liver (*abdominal discomfort, mass*)
    - Brain (*headache, nausea, focal neurological deficit*)
    - Bone (*bone pain, pathological fractures*)

- **Physical Examination**
  - General examination
    - Signs of metastatic disease (*cachexia, supraclavicular or inguinal lymphadenopathy, pleural effusion*)
    - Look for pallor (*complication of chronic bleeding*)
  - Abdominal examination
    - Palpate for hepatomegaly
    - Percuss for presence of ascites
  - Vaginal examination
    - Speculum examination to visualize cervix (*biopsy any gross abnormality; Pap smear if normal-looking*)
  - Rectal examination
    - Assess extent of local disease (*rectovaginal exam*)

- **Cervical Screening (Pap Smear) Evaluation Algorithm**



- ***Special issues in evaluation algorithm to note:***
  - [1]If colposcopic-directed punch biopsy results reveal CIN 2 with negative ECC, option of observation + Pap smear must be offered especially if patient is young (*to best preserve reproductive function*)
  - [2]If LLETZ or cone biopsy margins are found to be not clear, there is viability in offering observation + Pap smear to the patient as a management option as the follow-up Pap smear result has a greater bearing on the eventual outcome than the fact that the margins are not clear at present (*because any minor residual CIN tissue not excised usually clears spontaneously anyway*)

- ***Speculum examination & Pap smear***
  - During speculum examination prior to carrying out Pap smear, any gross abnormality of the cervix visible must have a **punch biopsy** performed on the spot; management plan according to punch biopsy results are as per for that after colposcopic-directed punch biopsy (*see below*)
  - Satisfactory Pap smear requires the following characteristics fulfilled:
    - Squamous, metaplastic & endocervical cells all seen on cytological examination (*indicates that a good representative sample of the entire transitional zone has been taken*)
  - Pap smear has good specificity but poor sensitivity:
    - If cellular atypia detected, high correlation with actual presence of cervical pathology present (hence follow-up colposcopy indicated)
    - If Pap smear normal, may well miss actual underlying pathology (false negative)
  - Based on Pap smear cytologic findings of cellular atypia, the grade of atypia detected has a certain degree of correlation to the underlying grade of CIN
    - Hence a Pap smear result can indicate that it is suggestive of CIN 1, 2 or 3
    - However, correlation with eventual findings on colposcopy is poor (30%), hence need to counsel patients accordingly when they present for colposcopy following abnormal Pap smear
  - Reporting of Pap smear results:

Terminology for Cervical Smear Reporting
(Cervical Screen Singapore Guidelines)

Specimen Adequacy
- Satisfactory for evaluation (note presence/absence of endocervical & transformation zone/metaplastic component)
- Unsatisfactory for evaluation (with reason specified)
- Specimen rejected/not processed (with reason specified)
- Specimen processed & examined, but unsatisfactory for evaluation of epithelial abnormality (with reason specified)

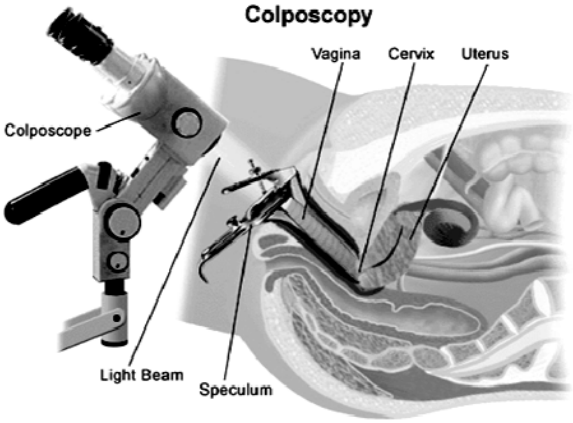
General Categorization
(i) Negative for intraepithelial lesion or malignancy
(ii) Epithelial cell abnormality
(iii) Other

(i) Negative for Intraepithelial Lesion or Malignancy
- Organisms (e.g. Trichomonas vaginalis)
- Reactive cellular changes associated with inflammation, radiation, intrauterine contraceptive device
- Atrophy

(ii) Epithelial Cell Abnormality
- Atypical squamous cells
  - Undetermined significance (ASC-US)
  - Cannot exclude high-grade lesion (ASC-H)
- Low-grade squamous intraepithelial lesion (LSIL)
  - Human papillomavirus effect
  - Mild dyskaryosis – indicative of CIN 1
- High-grade squamous intraepithelial lesion (HSIL)
  - Moderate dyskaryosis – indicative of CIN 2
  - Severe dyskaryosis – indicative of CIN 3
  - Severe dyskaryosis, cannot rule out invasive carcinoma
- Squamous cell carcinoma
- Atypical glandular cells (AGC)
  - Undetermined significance
  - Favour neoplastic
- Endocervical adenocarcinoma-in-situ (AIS)
- Adenocarcinoma

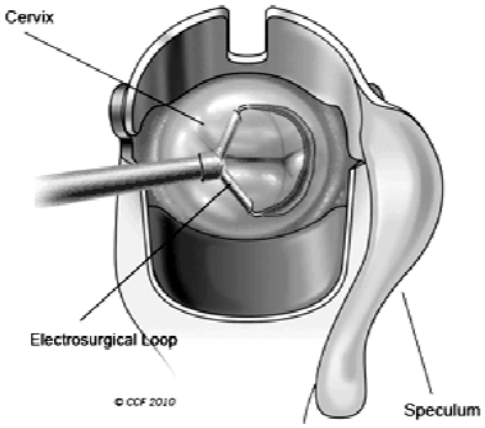
(iii) Other
- Carcinoma (others-specify or not further specified)
- Other malignant tumours (specify)

- ***Colposcopy***
  - Diagnostic procedure following abnormal Pap smear
    - *Confirms presence of CIN or even invasive CA*
  - Specific indications for colposcopy referral: (*refer to Cervical Screen Singapore Guidelines for more specific details for each specific finding*)
    - Any epithelial cell abnormality
    - 3 consecutive inflammatory smears
    - 3 consecutive unsatisfactory smears
  - Colposcope is a binocular microscope of low magnification (*usually x10 to x40*) with centered illumination & a focal length of 12-15cm
  - Colposcopic examination technique:
    - Office procedure, no analgesia or sedation
    - Speculum is used to expose the cervix
    - Cervix is cleansed with a cotton pledget soaked in 3% acetic acid
    - Green filter can accentuate vascular changes
    - Entire transformation zone should be seen
  - Colposcopic hallmark of CIN is a sharply delineated area of **acetowhite** epithelium (*turns white after treatment with acetic acid which dehydrates cell; areas of increased nuclear density exhibits increased light reflex*)
  - Within acetowhite areas, there may be abnormal vascular patterns commonly seen in CIN:
    - **Punctation** = *dots which are essential single-looped capillaries lying within the subepithelial papillae seen end-on*
    - **Mosaicism** = *fine network of capillaries disposed parallel to the surface in a mosaic pattern*
  - A trained colposcopist can, on visual inspection of the treated cervical epithelium, predict whether there is underlying CIN 1, 2, 3 or even invasive cancer
  - Multiple directed punch biopsy of the abnormal areas are then taken together with endocervical curettage (*to sample the endocervical epithelium as well*)
    - *note: endocervical curettage is not performed if the patient is pregnant at the time of colposcopy*

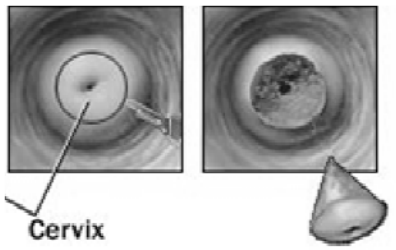


- ***Local ablation***
  - Therapeutic procedure for CIN 2 or even 3 (*after diagnosis is made on punch biopsy*)
  - Performed only if colposcopist is confident that there is no underlying invasive cancer & biopsy results also do not show any microinvasion
  - Outpatient procedure under local anesthesia
  - Options for ablation include:
    - CO_2 laser vaporization
    - Cryotherapy (*using liquid nitrogen*)
    - Cold coagulation (*misnomer, uses 100°C surface to thermally ablate abnormal area*)
  - Complications: *bleeding, scarring, failure (5-10%)*

- ***Large loop excision of transformation zone (LLETZ) aka Loop electrosurgical excision procedure (LEEP)***
  - Diagnostic & therapeutic procedure for CIN 2 with negative endocervical curettage findings
    - *Confirms absence of underlying microinvasion*
    - *Treats the CIN*
  - Outpatient procedure under local anesthesia
  - Wire loop through which electric current is passed is used to excise the cervical transformation zone & lesion to an adequate depth (~*8mm*) ensuring that the excision extends 4-5mm beyond the visible lesion
  - Complications: *bleeding, infection, cervical stenosis or incompetence (predisposing to miscarriage & preterm labour in future)*



- ***Cone biopsy (conization)***
  - Diagnostic & therapeutic procedure for CIN 2 & 3
    - *Confirms absence of underlying microinvasion*
    - *Treats the CIN*
  - Other indications for cone biopsy (*not explicitly stated in algorithm*):
    - Unsatisfactory colposcopy (*need to be able to visualize the entire transformation zone between the border with squamous epithelium & that with endocervical columnar epithelium*)
    - Microinvasion seen on punch biopsy
    - Adenocarcinoma-in-situ on Pap smear
  - Outpatient procedure under local anesthesia
  - Cone shaped-sample of cervix is excised using a scalpel (cold-knife conization) or CO_2 laser
  - Complications: *bleeding, infection, cervical stenosis or incompetence (predisposing to miscarriage & preterm labour in future)*



- **Diagnosis, Evaluation & Staging**
  - ***Diagnosis of cervical cancer*** is histopathological, which may be based on a sample obtained via:
    - Punch biopsy of a grossly visible cervical lesion
    - Colposcopic-directed biopsy of acetowhite areas
    - LLETZ or cone-biopsy
  - ***Staging of cervical cancer*** is clinical, supported by a limited range of investigations by FIGO guidelines:
    - Clinical examination (*especially vaginal & rectal*)
      - *Determine if lesion is visible clinically, & if so, measurement of the greatest diameter*
      - *Determine presence & extent of involvement of vagina & parametrium*
    - Cystoscopy & sigmoidoscopy
      - *Look for bladder & rectal mucosa involvement*
    - Intravenous urogram
      - *Look for hydronephrosis*
    - Chest X-ray
      - *Look for lung metastases*
    - Cross-sectional imaging (CT or MRI)
      - *Helps evaluate local extent of disease & detect nodal metastases; however results do not influence the FIGO stage of the cervical cancer*
      - *Also able to visualize hydronephrosis (hence if this is done, IVU is not required)*

International Federation of Obstetrics & Gynaecology (FIGO) Staging of Cervical Cancer (2009)

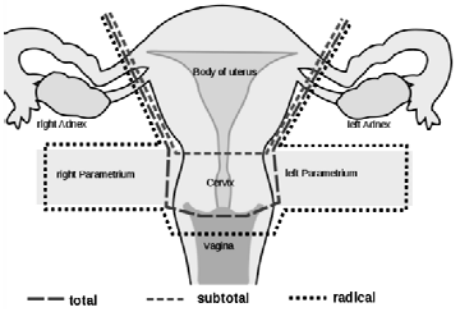
Stage	*Criteria*
Stage 0	**Carcinoma-in-situ (pre-invasive carcinoma)**
Stage I	**Carcinoma is strictly confined to the cervix**
Ia	Carcinoma diagnosed only by microscopy
Ia1	Stromal invasion ≤3mm in depth; extension ≤7mm
Ia2	Stromal invasion >3mm but <5mm; extension ≤7mm
Ib	Clinically-visible lesion confined to the cervix
Ib1	Lesion ≤4cm in greatest dimension
Ib2	Lesion >4cm in greatest dimension
Stage II	**Carcinoma invades beyond uterus but not to pelvic wall or lower third of vagina**
IIa	Involves upper two thirds of vagina, no parametrial involvement
IIa1	Lesion ≤4cm in greatest dimension
IIa2	Lesion >4cm in greatest dimension
IIb	Involves parametrium but not the pelvic side wall
Stage III	**Carcinoma extends to pelvic wall &/or involves lower third of vagina &/or causes hydronephrosis or non-functioning kidney**
IIIa	Involves lower third of vagina, no pelvic side wall involvement
IIIb	Involves pelvic side wall &/or causes hydronephrosis or NFK
Stage IV	**Carcinoma extends beyond true pelvis or involves bladder or rectal mucosa (proven by biopsy)**
IVa	Involves bladder or rectal mucosa
IVb	Spread beyond true pelvis &/or by metastasis into distant organs

Note: once FIGO stage has been assigned, further findings on cross-sectional imaging & surgery do not alter the stage; they however can be useful to plan treatment regimes

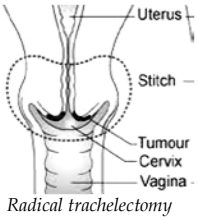
- **Management of Cervical Cancer**
  - ***2 main modalities – surgery & radiation:***
    - Surgery
      (*use limited up to stage IIa disease*)
      - Radical trachelectomy (*option for early disease with a desire for fertility preservation*)
      - Hysterectomy (*simple/total for stage Ia1, radical for Ia2 & early disease*)
      - Pelvic exenteration (*used in the setting of stage IVa tumours with rectovaginal/vesicovaginal fistula formation or recurrent disease following primary chemoradiation*)
      - Pelvic lymph node dissection (PLND) (*used in combination with radical trachelectomy or hysterectomy*)
    - Radiotherapy
      (*can be used in all stages of disease*)
      - Usually combined with cisplatin-based chemotherapy (chemoradiation) to increase sensitivity of tumour cells to radiation
      - Brachytherapy (intracavitary) &/or external beam radiation (teletherapy)
      - Can be also given to palliate symptoms (*e.g. bleeding*) in metastatic disease
  - ***Comparing surgery & radiotherapy***
    - Similarities:
      - Similar curative rates
      - Similar complication rates in terms of bladder, ureteric & intestinal fistulae & perforation
    - Advantages of surgery over radiotherapy:
      - Simple treatment session (*vs up to 6-week prolonged radiotherapy treatment*)
      - Accurate assessment for surgicopathological prognostic factors
      - Conserves ovarian function & prevents vaginal dryness
      - No risk of secondary malignancy
    - Advantages of radiotherapy over surgery:
      - Outpatient procedure
      - No anesthesia risk

Management of Cervical Cancer by FIGO Stage

Stage	*Management Options*
Microinvasive (Ia1)	Cone biopsy (*for fertility preservation*) Simple (total) hysterectomy Radiotherapy only (*if surgery not wanted by patient*)
Microinvasive (Ia2)	Modified radical hysterectomy with PLND Radical trachelectomy with PLND (*for fertility preservation*) Radiotherapy only (*if surgery not wanted by patient*)
Early (Ib & IIa)	Radical trachelectomy with PLND (*for fertility preservation*) Radical hysterectomy with PLND Primary chemoradiation (*if nodes positive*) Radiotherapy only
Locally advanced (IIb, III & IVa)	Primary chemoradiation Pelvic exenteration (*if rectovaginal or vesicovaginal fistula*)
Metastatic (IVb)	Chemotherapy Individualized palliative pelvic radiation



Types of hysterectomies



Radical trachelectomy

- **Prognosis of Cervical Cancer**
  - Stage I: 90% 5-year survival
  - Stage II: 80% 5-year survival
  - Stage III: 60% 5-year survival
  - Stage IV: 20% 5-year survival

Ovarian Neoplasms

Types of Ovarian Neoplasms

Secondary metastases account for 4-8% of ovarian malignancies; primary ovarian neoplasms can be classified based on cell population they are derived from:
(i) epithelial ovarian tumours (80-85%)
(ii) germ cell tumours (10-15%)
(iii) specialized gonadal stromal cell tumours (3-5%)

- **Epithelial Ovarian Tumours**
  (*derived from the mesothelial lining of the ovary & peritoneum; may be differentiated along the Müllerian or Wolffian pathway*)
  - ***Serous tumours***
    - Most common epithelial ovarian tumour
    - Resemble fallopian tube epithelium (Müllerian)
    - Bilateral in 10% of cases
    - Varying degrees of malignancy:
      - 70% benign (*serous cystadenoma*)
      - 5-10% borderline
      - 20-25% malignant (*serous cystadenocarcinoma*)
    - Pathology of serous tumours:
      - Grossly: *unilocular (small) or multilocular (large) cysts containing clear serous fluid*
      - Histologically: *psammoma bodies, papillary bodies*
    - Clinical implications:
      - Worst prognosis (for cystadenocarcinoma) alongside clear cell tumours amongst the epithelial ovarian tumours
  - ***Mucinous tumours***
    - Resemble endocervical epithelium (Müllerian)
    - Bilateral in <10% of cases
    - Varying degrees of malignancy:
      - 85% benign (*mucinous cystadenoma*)
      - Borderline
      - Malignant (*mucinous cystadenocarcinoma*)
    - Pathology of mucinous tumours:
      - Grossly: *multilocular, huge cysts containing mucous-like contents; often the largest of all ovarian masses, can grow to the extent of filling up the pelvis & abdomen in a patient*
      - Histologically: *locules containing mucin*
    - Clinical implications:
      - Described association with a mucocele of the appendix (*hence appendicectomy usually also performed during surgery*)
      - Rare complication occurs when a mucinous tumour ruptures & seeds the surface of the peritoneal & bowel surfaces, producing large quantities of mucus (**pseudomyxoma peritonei**)
  - ***Endometrioid tumours***
    - 20% of all ovarian neoplasms
    - Resemble endometrium (Müllerian)
    - Mostly malignant
    - Clinical implications:
      - 10-15% associated with endometriosis (*even though malignant transformation of endometriosis occurs in <1% of patients*)
      - 20% associated with primary endometrial cancer of the uterus
  - ***Clear cell (mesonephroid) tumours***
    - Uncommon (5% of all ovarian neoplasms)
    - Wolffian differentiation
    - Malignant
    - Pathology of clear cell tumours:
      - Grossly: *may be solid or cystic*
      - Histologically: *large sheets of epithelial cells with clear cytoplasm, tubules &* **hobnail nuclei**
    - Clinical implications:
      - Worst prognosis alongside serous cystadenocarcinomas amongst the epithelial ovarian tumours
      - 25% occur in conjunction with endometriosis
  - ***Brenner tumours***
    - Uncommon (2-3% of all ovarian neoplasms)
    - Resemble transitional epithelium (Wolffian)
    - Predominantly benign (<2% are malignant)
    - Pathology of Brenner tumours:
      - Grossly: *small (1-8cm) smooth solid mass*
      - Histologically: *nests of urothelial-like cells with* **coffee bean nuclei** *within a dense fibrous stroma*
    - Clinical implications:
      - 10% of Brenner tumours occur in conjunction with a mucinous tumour or a dermoid cyst in the same or contralateral ovary

- **Germ Cell Tumours**
  (*derived from the germ cells – ovum – of the ovary*)
  - ***Benign cystic teratoma (mature teratoma; dermoid cyst)***
    - Tumour differentiation into embryonic tissue
    - Most common benign ovarian neoplasm
    - Pathology:
      - Can take on a great variety of forms, with virtually all adult tissue types represented within the tumour mass
      - Commonly features ectodermal tissue types (*skin, hair, sweat & sebaceous glands, teeth, neural*) with some mesodermal (*bone, cartilage*) & rarely endodermal elements
      - Cyst lumen contains a nipple/mammary body/hillock-like protuberance (**Rokitansky tubercle**)
      - Rarely, may be composed of functional thyroid tissue (**struma ovarii**), which can lead to clinical hyperthyroidism
    - Clinical implications:
      - Rarely may result in acute abdominal pain if tumour ruptures & releases sebaceous material which causes peritonism
      - 15-20% bilateral
  - ***Malignant teratoma (immature teratoma)***
    - Tumour differentiation into embryonic tissue
    - 2nd most common malignant germ cell tumour
    - Majority seen in the 1st 2 decades of life
    - Pathology:
      - Neural elements most frequently seen, but cartilage & epithelial tissues also common
    - Grading system for malignant teratomas:
      - Grade 1 = *rare foci of immature neuroepithelial tissue occupying <1 per low power field (40x) in any slide*
      - Grade 2 = *1-3 per low power field per slide*
      - Grade 3 = *large amounts*
    - Clinical implications:
      - Do not produce any tumour markers
      - Grow rapidly (*like most malignant germ cell tumours*) & can cause pain early

- ***Gonadoblastoma***
  - No tumour differentiation
  - Benign tumour
  - Almost all gonadoblastomas are seen in women with dysgenetic gonads
  - Pathology:
    - Technically a mixed ovarian neoplasm composed of cells resembling those of dysgerminoma & others resembling granulosa & Sertoli cells
    - Psammoma bodies characteristically seen
  - Clinical implications:
    - 50% will eventually become dysgerminoma or other malignant germ cell tumours
    - Bilateral oophorectomy indicated if dysgenetic gonads present to prevent subsequent development of dysgerminoma
- ***Dysgerminoma***
  - No tumour differentiation
  - Most common malignant germ cell tumour
  - Majority seen in children & young women
    - Occasionally seen in patients with gonadal dysgenesis or testicular feminization syndrome (*in which case dysgerminoma may arise from a pre-existing gonadoblastoma*)
  - Pathology:
    - Grossly: *large, firm, bosselated external surface; soft & fleshy*
    - Histologically: *nests of monotonous tumour cells with clear glycogen-filled cytoplasm bound within fibrous septa filled with lymphocytes*
  - Clinical implications:
    - Produces lactate dehydrogenase (LDH)
    - Highly radiosensitive tumour (*but nowadays chemotherapy is first-line treatment instead*)
    - 10% are associated with other germ cell malignancies
    - 10% are bilateral
- ***Choriocarcinoma***
  - Tumour differentiation into extra-embryonic tissue
    - A non-gestational form of choriocarcinoma
    - Choriocarcinoma can occur in a gestational form in the setting of molar pregnancies or from the trophoblastic tissue of ectopic & normal pregnancies
  - Clinical implications:
    - Produces hCG
    - Rarely bilateral
- ***Endodermal sinus tumour (yolk sac tumour)***
  - Tumour differentiation into extra-embryonic tissue
  - Highly malignant tumour
  - Exclusively seen in young children & young women
  - Pathology:
    - Yolk sac differentiation
    - **Schiller-Duval bodies** (*central space surrounded by malignant cells*)
    - Immunohistochemical stain for AFP positive
  - Clinical implications:
    - Produces alpha-feto protein (AFP)
    - Rarely bilateral
- ***Embryonal carcinoma***
  - Clinical implications:
    - Produces both AFP & hCG
    - Rarely bilateral

- **Specialized Gonadal Stromal Tumours**
  (*derived from the bipotential gonadal stroma/sex cords*)
  - ***Granulosa-theca cell tumours***
    - Feminine differentiation of stromal cells
    - Can occur at any time, but most common in post-menopausal age group
    - Pure thecomas are rarely malignant; granulosa cell tumours are the most common malignant stromal cell tumours
    - Pathology:
      - Thecomas exhibit plump spindle cells with lipid droplets
      - Granulosa cell tumours comprise groups of lipid laden luteinized cells in a follicular pattern (**Call-Exner bodies**); cells exhibit **coffee bean nuclei**; strongly positive for inhibin
    - Clinical implications:
      - Functioning tumour producing female hormones, resulting in feminizing signs & symptoms (*precocious puberty, premenarchal uterine bleeding in infancy & childhood, menorrhagia, endometrial hyperplasia, endometrial cancer, breast tenderness, fluid retention*)
  - ***Sertoli-Leydig cell tumours (Arrhenoblastomas)***
    - Masculine differentiation of stromal cells
    - Commonly seen in young women
    - Low grade malignant potential (3-5% malignant)
    - Clinical implications:
      - Functioning tumour producing male hormones, resulting in virilizing signs & symptoms (*hirsutism, temporal baldness, voice deepening, clitoromegaly, muscular build*)
  - ***Gynandroblastomas***
    - Combination of granulosa-theca & Sertoli-Leydig cell
  - ***Lipid cell tumours (hilar cell tumours)***
    - Usually located in the ovarian hilus
    - Rarely malignant
    - Clinical implications:
      - Occasionally produce adrenal corticosteroids resulting in Cushing's syndrome
  - ***Fibroma***
    - Pathology:
      - Solid encapsulated smooth-surfaced tumour
      - Composed of interlacing bundles of fibrocytes
      - May occasionally contain theca cell elements (fibrothecoma)
    - Clinical implications:
      - Occasionally results in transudation of fluid from the tumour, resulting in ascites & subsequently flow of the ascitic fluid through transdiaphragmatic lymphatics to result in right-sided pleural effusion (**Meig's syndrome**)

- **Metastatic Tumours**
  - Usual features of metastatic tumours to the ovaries:
    - Bilateral involvement
    - Cytokeratin 7 negative (CK 7, a marker for primary ovarian neoplasm)
    - Friable & necrotic with vascular invasion
  - Common sites of primaries:
    - Breast
    - Gastrointestinal tract
      - Specific type of metastasis from gastric cancers histologically comprising signet-ring cells known as **Krukenberg tumour**
    - Uterus, fallopian tubes
    - Peritoneum

Clinical Approach to Ovarian Cancer

- **Epidemiology & Associations**
  - Most common gynaecological cancer in Singapore
  - Age-distribution depends on the histological subtype:
    - Epithelial ovarian tumours are more commonly seen in older women
    - Germ cell tumours usually seen in children & young women
    - Specialized gonadal stromal tumours vary in age distribution (*e.g. granulosa-theca cell tumours more common in post-menopausal women while Sertoli-Leydig cell tumours are more common in young women*)
    - Metastatic tumours to the ovaries more common in older women (*who are more likely to have primary malignancies elsewhere e.g. breast, gastrointestinal tract*)
  - ***Risk factors (for epithelial ovarian malignancies):***
    - Increased number of ovulatory cycles
      - Late age at menopause
      - Nulliparity
    - Hereditary predispositions
      - Family history of cancer of the bowel, breast &/or ovary
      - Breast-ovarian cancer syndrome (*BRCA1 on chromosome 17; BRCA2 on chromosome 13*)
      - Lynch II syndrome aka HNPCC (*MSH2, MSH6, MLH1*) (*adenocarcinomas of colon, endometrium, breast, ovary, stomach, pancreas etc*)
  - ***Protective factors:***
    - Use of oral contraceptive pills (*postulated to be due to decreased ovulatory events which decreases incidence of ovarian epithelial damage & regenerative proliferation*)
    - Tubal ligation & hysterectomy (*postulated to be due to prevention of unknown causative agent from entering the peritoneal cavity through the lower genital tract*)

- **Modes of Spread of Ovarian Cancer**
  - ***Trans-coelomic*** (*tumour exfoliates cells that disseminate & implant throughout the peritoneal cavity; distribution of intraperitoneal metastases tends to follow the circulatory path of peritoneal fluid*)
    - Pouch of Douglas (aka pelvic cul-de-sac)
    - Paracolic gutters
    - Hemidiaphragm
    - Liver capsule
    - Omentum
    - Bowel serosa & mesenteries
  - ***Direct invasion***
  - ***Lymphatic***
    - Pelvic nodes
    - Para-aortic nodes
  - ***Hematogenous***
    - Lungs
    - Liver parenchyma

- **Clinical Presentation of Ovarian Cancer**
  - ***Asymptomatic***
    - Ovarian mass may be picked up incidentally on radiographic studies
  - ***Mass symptoms***
    - Bloating, early satiety & abdominal distension (*due to tumour growth or malignant ascites*)
    - Constipation (*from rectal compression*)
    - Urinary frequency (*from bladder compression*)
    - Pelvic pain
    - Dyspareunia (*if mass sits in pouch of Douglas*)
    - Acute abdomen (*torsion, rupture, intracystic bleeding*)
  - ***Menstrual disturbances***
    (*usually due to functioning stromal tumours*)
    - Menorrhagia (*feminizing tumours*)
    - Oligomenorrhea/amenorrhea (*virilizing tumours*)
    - Post-menopausal bleeding (*feminizing tumours*)
  - ***Metastatic symptoms (late)***
    - Loss of weight, loss of appetite
    - Nausea, vomiting, inanition, colicky abdominal pain (*carcinomatosis peritonei resulting in ileus*)
    - Dyspnea (*lung mets*)
  - ***Symptoms related to primary malignancy***
    (*in the context of secondary metastases to the ovaries*)
    - Breast primary: lump, nipple discharge
    - GI primary: GI bleeding, change in bowel habits
    - Endometrial primary: abnormal uterine bleeding

- **Physical Examination**
  - ***General examination***
    - Assess patient's vitals
    - Look for pallor, cachexia, supraclavicular & inguinal lymphadenopathy
    - Examine lungs for signs of mets (*pleural effusion*)
    - Examine breasts for any signs of a primary tumour (*breast lump, nipple changes/discharge, skin changes, axillary lymphadenopathy*)
  - ***Abdominal examination***
    - Look for organomegaly (*especially hepatomegaly*)
    - Palpate for abdominal or abdominopelvic masses (*primary GI tumour or pelvic mass*)
    - Assess for shifting dullness (*malignant ascites*)
  - ***Pelvic examination***
    - Speculum examination (*assess cervix, presence of blood*)
    - Bimanual palpation (*assess uterine size, feel for adnexal masses & their mobilities with respect to the cervix – ability to move mass without causing a concomitant cervical movement indicates that mass is not attached to uterus*)
    - Rectovaginal examination (*assess masses in the pouch of Douglas*)

- **Diagnosis, Evaluation & Staging**
  (*diagnosis of ovarian cancer is made only after intraoperative frozen section; hence pre-operative workup primarily focuses on evaluating the likelihood of malignancy which will determine threshold for an exploratory laparotomy; note that pre-operative attempts at diagnosis with measures such as paracentesis of ascitic fluid or aspiration of ovarian cyst fluid are not recommended due to the lack of reliability of the results & risk of tumour seeding*)
  - ***Pre-operative investigations & evaluation***
    - Routine pre-operative work-up:
      - Full blood count
      - Renal panel
      - PT/PTT, group & cross match
      - ECG, chest x-ray
    - Tumour markers:
      - **CA-125** (*tumour marker secreted by cells of mesothelial origin; most useful for non-mucinous epithelial ovarian tumours; levels >35U/ml in post-menopausal women calls for concern; more sources of false positives in pre-menopausal women – fibroids, PID, endometriosis, adenomyosis, pregnancy, menstruation, pleural & pericardial inflammation*)
      - **Alpha-fetoprotein, hCG, lactate dehydrogenase** (*germ cell tumour markers, more useful in younger women*)
    - Radiological investigations:
      - Ultrasound pelvis (*first line investigation, useful to characterize ovarian mass & determine degree of suspicion for malignancy – multiloculated complex cysts more suspicious*)
      - Chest x-ray (*to detect lung metastases*)
      - MRI pelvis (*useful when ultrasound findings are unclear; higher specificity over ultrasound – 73%, which is further improved by use of gadolinium enhancement – 93%; necrosis in solid tissue suspicious*)
      - CT abdopelvis (*useful for detection of metastases by evaluating liver, para-aortic region, omentum & mesentery*)
    - Investigations for possible primaries:
      - Endometrial biopsy (*especially if patient presents with abnormal uterine bleeding; concurrent tumours of endometrium & ovary can occur*)
      - Mammogram (*if breast lump found*)
      - Faecal occult blood test ± gastrointestinal endoscopy (*if prominent GI symptoms are present*)

Risk of Malignancy Index (RMI)

Criteria	*Scoring System*
Menopausal status (M)	
Pre-menopausal	1
Post-menopausal	3
Ultrasound features (U)	
Multiloculated Solid areas Bilateral lesions Ascites	None = 0 1 feature = 1 >1 feature = 3
Serum CA-125 titre	Absolute value in U/ml

Calculation & interpretation of RMI:

RMI = M x U x CA-125

Low risk RMI: <25 (<3% *risk of malignancy*)
Moderate risk RMI: 25-250 (*20% risk of malignancy*)
High-risk RMI: >250 (*75% risk of malignancy*)

  - ***Diagnosis of ovarian cancer*** is histopathological, often made at the point of surgical excision of a suspicious ovarian mass/cyst with intraoperative frozen section
    - *Refer to "Approach to Ovarian Masses/Cysts" for details on the clinical reasoning & decision making behind proceeding with surgery for an ovarian mass discovered on imaging or physical examination*
  - ***Staging of ovarian cancer*** is surgical, determined after a staging operation with various intra-abdominal samples obtained other than the primary ovarian mass:
    - Multiple cytological assays:
      - Free ascitic fluid (if present)
      - Peritoneal washings (50ml normal saline)
      - Pouch of Douglas
      - Both paracolic gutters
      - Both hemidiaphragms
    - Multiple intraperitoneal biopsies:
      - Pouch of Douglas peritoneum
      - Bladder peritoneum
      - Pedicles of infundibulopelvic ligaments
      - Both paracolic gutters
      - Bowel serosa & mesenteries
      - Omentum
      - Any adhesions
    - Extraperitoneal biopsies:
      - Pelvic & para-aortic lymph nodes

International Federation of Obstetrics & Gynaecology (FIGO) Staging of Primary Carcinoma of the Ovary

Stage	*Criteria*
Stage I	**Growth limited to the ovaries**
Ia	Growth limited to one ovary; no ascites. No tumour on the external surface; capsule intact
Ib	Growth limited to both ovaries; no ascites. No tumour on the external surfaces; capsules intact
Ic	Tumour either stage Ia or Ib but with tumour on the surface of one or both ovaries or with capsule(s) ruptured or with ascites present containing malignant cells or with positive peritoneal washings
Stage II	**Growth involving one or both ovaries with pelvic extension**
IIa	Extension or metastases, or both, to the uterus or tubes, or both
IIb	Extension to other pelvic tissues
IIc	Tumour either stage IIa or IIb, but with tumour on the surface of one or both ovaries or with capsule(s) ruptured or with ascites present containing malignant cells or with positive peritoneal washings
Stage III	**Tumour involving one or both ovaries with peritoneal implants outside the pelvis or positive retroperitoneal or inguinal lymph nodes, or both. Tumour is limited to the true pelvis but with histologically proven malignant extension to small bowel or omentum. Superficial liver metastases = stage III**
IIIa	Tumour grossly limited to the true pelvis with negative nodes but with histologically confirmed microscopic seeding of abdominal peritoneal surfaces
IIIb	Tumour of one or both ovaries with histologically confirmed implants of abdominal peritoneal surfaces, none exceeding 2cm in diameter; nodes negative for disease
IIIc	Abdominal implants >2cm in diameter or positive retroperitoneal or inguinal nodes, or both
Stage IV	**Growth involving one or both ovaries with distant metastasis. If pleural effusion is present, there must be positive cytologic test results to allot a case to stage IV. Parenchymal liver metastasis = stage IV**

- **Management of Primary Ovarian Cancers**
  (*management of primary ovarian cancer depends on the histological type; regardless, all would involve an initial surgical exploration*)
  - ***Initial surgical exploration:***
    - Frozen section of ovarian mass to clinch histopathological diagnosis
    - Thorough surgical staging with multiple cytological assays, intra- & extraperitoneal biopsies
  - ***Definitive management of epithelial ovarian cancer:***
    - In patients with no gross evidence of disease beyond the ovary, standard operation is **total hysterectomy, bilateral salpingo-oophorectomy (THBSO), infracolic omentectomy & thorough surgical staging**
    - In patients with advanced disease, additional **cytoreductive surgery (debulking)** is performed (*removal of primary tumour & all metastases where possible; where not feasible, individual tumour nodules should be reduced to ≤1cm in diameter; this has been shown to improve outcomes when adjuvant chemotherapy is given*)
    - Patients with grade 1 or 2 tumours confined to one or both ovaries after surgical staging **do not need further treatment**
    - Patients with grade 3 tumours &/or tumour spread beyond the ovaries need **adjuvant chemotherapy**:
      - IV carboplatin + paclitaxel <u>or</u> intraperitoneal cisplatin + paclitaxel (*only useful for patients with minimal residual disease*)
      - Patient response monitored using serial CA-125 levels during follow-up visits
  - ***Definitive management of dysgerminomas:***
    - In patients with only one ovary involved, contralateral ovary & the uterus can be preserved
    - Patients with tumour spread beyond the ovary need **adjuvant chemotherapy**:
      - Bleomycin + etoposide + cisplatin
    - **Radiotherapy** was previously mainstay of treatment (*as dysgerminomas are uniquely radiosensitive*), but is now reserved for recurrent chemoresistant disease
  - ***Definitive management of immature teratomas:***
    - Surgical removal of primary tumour with preservation of contralateral ovary in young patients to preserve fertility
      - Immature teratomas are graded 1 to 3 by a special system (*see "Types of Ovarian Neoplasms"*)
    - Patients with stage Ia grade 1 immature teratomas **do not need further treatment**
    - All other patients should receive **adjuvant chemotherapy**:
      - Bleomycin + etoposide + cisplatin
  - ***Definitive management of other germ cell tumours:***
    - Endodermal sinus tumours, choriocarcinomas & embryonal carcinomas are treated with **surgical resection of the primary tumour** followed by **adjuvant chemotherapy**:
      - Bleomycin + etoposide + cisplatin
  - ***Definitive management of stromal tumours:***
    - In most patients, best treated by **THBSO**
    - In young patients with stage I disease, **conservation of uterus & contralateral ovary** is appropriate
    - Stromal tumours are not very chemosensitive

- **Prognosis of Ovarian Cancer**
  - ***Prognosis of epithelial ovarian cancer:***
    - Stage I: 75-95% 5-year survival
    - Stage II: 65% 5-year survival
    - Advanced-stage disease: 20%
  - ***Prognosis of dysgerminomas:***
    - Stage I: 95% 5-year survival
    - Stage II: 80% 5-year survival
    - Stage III: 60-70% 5-year survival
  - ***Prognosis of immature teratomas:***
    - Grade 1: 95%
    - Grade 2: 80%
    - Grade 3: 60-70%
  - ***Prognosis of other germ cell tumours:***
    - Overall: 70-80%

Approach to Ovarian Masses/Cysts

Clinically, ovarian neoplasms usually come to clinical attention as an abdominopelvic mass on physical examination or ovarian cyst on pelvic ultrasound investigation; careful consideration of the differential diagnoses in each setting is central to the course of management & decision to perform an exploratory abdominal surgery to obtain a frozen section histological diagnosis of the ovarian mass/cyst

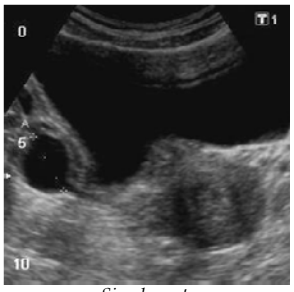
- **Differential Diagnoses of Abdominopelvic Masses**

Gynaecologic		Non-gynaecologic	
Benign	***Malignant***	***Benign***	***Malignant***
Non-neoplastic ovarian cysts - Mesothelial - Follicular - Inflammatory **Benign ovarian neoplasms** - Epithelial - Germ cell - Stromal **Tubal** - Hydrosalpinx - Pyosalpinx **Uterine** - Pregnancy - Leiomyoma - Adenomyosis	**Ovarian cancer** - Epithelial - Germ cell - Stromal - Non-specific - Metastatic **Tubal cancer** - Fallopian tube cancer **Uterine cancer** - Endometrial cancer - Leiomyo-sarcoma	**Gastrointestinal** - Diverticular abscess - Appendiceal abscess or mucocele **Urinary system** - Pelvic kidney - Ureteral diverticulum - Bladder diverticulum **Others** - Benign nerve sheath tumours	**Gastrointestinal malignancy** - Colorectal - Small bowel **Urinary system malignancy** - Bladder **Others** - Lymphoma - Retro-peritoneal sarcoma - Metastases

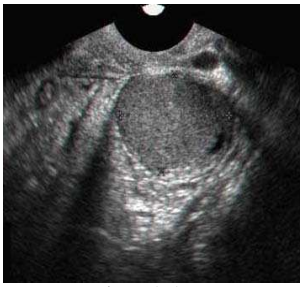
- **Differential Diagnoses of Ovarian Cysts**
  - ***Non-neoplastic ovarian cysts***
    - Cysts of mesothelial origin
      - **Germinal inclusion cysts** (*formed by the invagination of ovarian surface mesothelium into the cortex or stroma of the ovary; cystic enlargement results from accumulation of serous fluid secreted by the mesothelium; no evidence of association with epithelial ovarian cancer*)
    - Cysts of follicular origin (functional cysts)
      - **Follicular cysts** (*develop from partially-developed follicles that undergo atresia; extremely common, mostly physiological; may be multiple; undergo spontaneous regression*)
      - **Corpus luteal cysts** (*develops after corpus luteal hematoma formed after ovulation; lined by luteinized granulosa cells with theca cells in deeper layers; if persistent, continued secretion of progesterone results in delayed menstruation presenting as continuous vaginal bleeding; may rarely rupture & result in massive intraperitoneal hemorrhage*)
      - **Theca lutein cysts** (*formed by intensely luteinized theca interna cells when corpus luteum is under the influence of high hCG levels; usually small but may be multiple & large, especially when in association with multifetal gestation, gestational trophoblastic neoplasia & patients on gonadotropin treatment – ovarian hyperstimulation syndrome*)
      - **Polycystic ovary syndrome** (*multiple eccentrically-placed follicular cysts within ovary associated with chronic anovulation & generalized hyperandrogenism – see "Polycystic Ovary Syndrome"*)
    - Cysts of inflammatory conditions
      - **Tubo-ovarian abscess** (*abscess formed as a result of pelvic inflammatory disease*)
      - **Endometriotic cyst** (*aka endometrioma or chocolate cyst; occurs in endometriosis where ectopic endometrial tissue implants on ovaries & form a cyst enclosing stale blood*)
  - ***Benign ovarian neoplasms***
    - Epithelial origin
      - Serous tumours
      - Mucinous tumours
      - Endometrioid tumours
      - Brenner tumours (urothelial tumours)
    - Germ cell origin
      - Benign cystic teratomas
      - Gonadoblastomas
    - Specialized gonadal stromal origin
      - Granulosa-theca cell tumours
      - Sertoli-Leydig cell tumours (arrhenoblastoma)
      - Gynandroblastomas
      - Lipid cell tumours (hilar cell tumours)
      - Fibromas
  - ***Ovarian cancer***
    - Epithelial origin
      - Serous tumours
      - Mucinous tumours
      - Endometrioid tumours
      - Clear cell tumours (mesonephroid)
      - Brenner tumours (*rarely malignant*)
    - Germ cell origin
      - Immature teratomas
      - Dysgerminomas
      - Endodermal sinus tumours (yolk sac)
      - Choriocarcinoma
      - Embryonal carcinoma
    - Specialized gonadal stromal origin
      - Granulosa cell tumour (*most common malignant stromal tumour)*
      - Rest of stromal tumours are rarely malignant

- **Basic Clinical Approach to Abdominopelvic Masses**
  - ***History***
    - Mass symptoms
      - Abdominal &/or pelvic pain (*site, radiation, character, pain score, cyclical or non-cyclical*)
      - Dyspareunia (*endometriosis, PID, ovarian masses in pouch of Douglas*)
      - Bloating, early satiety, abdominal distension (*large mass, associated ascites*)
    - Menstrual history
      - Pre- or post-menopausal (*different differential diagnosis sets for each demographic – e.g. endometriosis, adenomyosis & pregnancy can be excluded if post-menopausal*)
      - Last menstrual period (*important to rule out pregnancy in any presentation of an abdominopelvic mass, lower abdominal pain or menstrual abnormalities*) ± pregnancy symptoms
      - Any menstrual cycle disturbance (*corpus luteal cysts can delay menstruation & cause continuous vaginal bleeding; virilizing ovarian stromal tumours can cause oligomenorrhea*)
      - Any menorrhagia (*feminizing ovarian stromal tumour, adenomyosis, fibroids*)
      - Any abnormal uterine bleeding (*PCOS, endometrial cancer*)
      - Any dysmenorrhea (*adenomyosis, endometriosis, chronic PID*)
    - Constitutional symptoms
      - Any fever (*PID, diverticular abscess*)
      - Any per-vaginal discharge (*PID*)
      - Any loss of weight & appetite (*malignancy*)
      - Symptoms of anemia (*if menorrhagia or chronic occult GI bleed*)
    - Systemic screen
      - Any breathlessness (*lung mets*)
      - Any breast lumps, last mammogram (*breast primary with secondary ovarian mets*)
      - Bowel symptoms, nausea/vomiting, change in bowel habits, melena/hematochezia (*GI causes; ovarian mass causing constipation*)
      - Urinary symptoms, hematuria
    - Past medical/surgical/gynae/obstetric history
      - Any past malignancies
      - Any known past gynae conditions (*including subfertility, PID, sexually-transmitted infections*)
    - Drug history
      - Use of oral contraceptives (*protective*)
      - Use of tamoxifen (*increases risk of endometrial cancer; chronic use also increases endogenous gonadotropin production due to antagonism of estrogen receptors responsible for negative feedback on the pituitary, which may cause theca lutein cysts*)
      - Use of gonadotropins (*theca lutein cysts*)
    - Social history
  - ***Physical examination***
    - General examination
      - Vitals
      - Assess for supraclavicular lymphadenopathy
      - Breast exam for lumps & nipple discharge
      - Auscultate lungs for pleural effusion
    - Abdominal examination
      - Inspect for distension, scars
      - Palpate for masses & organomegaly
      - Percuss for shifting dullness
      - Auscultate for bowel sounds & over any masses for bruit
    - Pelvic examination
      - Speculum examination (*examine cervix, look for any blood or discharge*)
      - Digital vaginal examination (*assess for cervical excitation, uterosacral tenderness*)
      - Bimanual palpation (*determine uterine size, characterize abdominopelvic mass & determine if it is uterine or adnexal – uterine mass when moved will cause cervix to move as well*)
      - Rectovaginal examination (*assess pouch of Douglas for masses or nodularity*)
  - ***Initial investigations & evaluation***
    (*choice of initial workup depends on differentials derived from the history & physical examination*)
    - Non-radiological investigations
      - **Urine pregnancy test** (*indicated in any pre-menopausal woman to rule out pregnancy*) ± **serum β-hCG levels**
      - **Full blood count** (*look for anemia*)
      - **Urine analysis & culture** (*if urinary symptoms are present, to rule out UTI*)
      - **PID workup**: urine PCR for *Chlamydia*, endocervical swab culture for gonorrhea + **sexually-transmitted disease workup**: HIV, VDRL, hepatitis B (*if PID suspected*)
      - **CA-125** (*used complementary to ultrasound findings to risk-stratify any ovarian cyst found*)
      - **Germ cell tumour markers**: AFP, hCG, LDH
      - **Other tumour markers**: CEA (*for suspected colorectal malignancy*)
    - Radiological investigations
      - **Ultrasound pelvis** (*to evaluate uterine or adnexal mass & endometrial thickness; if pregnancy test positive, used to confirm intra-uterine pregnancy & look for possible gestational trophoblastic disease*)
      - **Cross sectional imaging**: CT, MRI (*to assess GI & urinary system pathologies; can be used in certain cases of ovarian cysts in addition to ultrasound for greater specificity – MRI – & assessment of abdominal metastases – CT*)

- **Principles of Approaching Ovarian Masses/Cysts**
  - ***Basic didactic approach:***
    - Age/menopausal status of the patient is the most important factor in helping to narrow the differentials
      - Pre-menopausal: *usually functional cysts (follicular origin) or endometriotic cysts*
      - Post-menopausal: *higher incidence of neoplasms, but even then, mostly benign*
    - Most masses in any age group are benign, but need to be treated as malignant until proven otherwise
  - ***Ultrasound findings suggestive of benign disease:***
    - Simple ovarian cyst: *unilocular, no solid elements, thin-walled sonolucent cyst with smooth & regular borders (<1% risk of malignancy regardless of menopausal status or cyst size)*
    - Ovarian endometriotic cyst: *round & homogenous-looking cyst with low-level echoes within ovary (92% sensitivity & 87% specificity)*
    - Benign cystic teratoma: *hypoechoic attenuating component with multiple small homogenous interfaces (90% sensitivity & 98% specificity)*
    - Hydrosalpinx: *tubular-shaped sonolucent cyst*

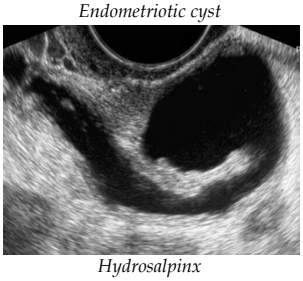


Simple cyst



Endometriotic cyst

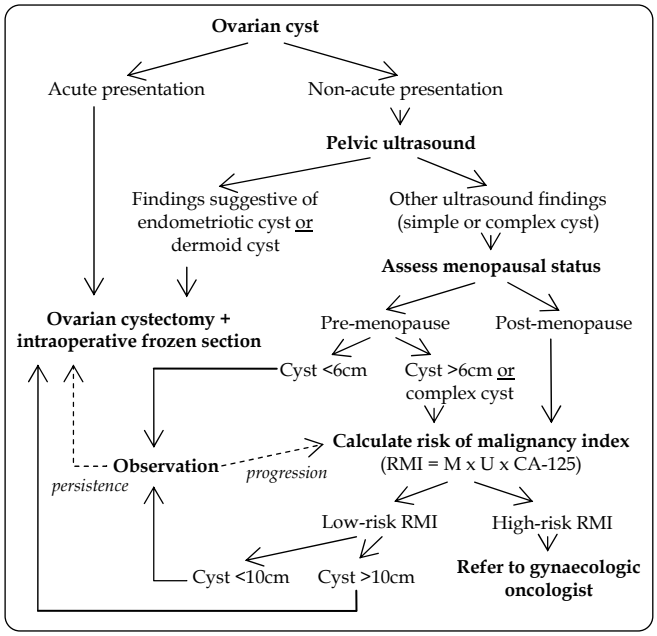
Benign cystic teratoma



Hydrosalpinx

  - ***Clinical utility of CA-125 in assessment of ovarian cysts:***
    - Use limited in pre-menopausal women due to multiple sources of false-positives:
      - Benign gynae conditions (*endometriosis, adenomyosis, fibroids, PID, pregnancy*)
      - Serosal inflammation (*pleuritis, pericarditis*)
    - Useful for differentiation between benign & malignant disease (used to calculate RMI) in the following settings:
      - *Pre-menopausal simple cyst >6cm or complex cyst*
      - *Post-menopausal women*
    - Even when elevated, monitoring serial CA-125 also helps in differentiating benign & malignant causes:
      - Benign diseases causing elevated CA-125 tend to plateau in CA-125 levels over time
      - Malignant disease causing elevated CA-125 will have continually rising CA-125 levels
  - ***Overview of management options:***
    - **Conservative**: observation with follow-up ultrasound ± CA-125 measurements indicated when risk of malignancy is low
      - **Oral contraceptive pills** can be considered for women with low risk for malignancy as it has been shown to decrease lifetime risk of epithelial ovarian neoplasms & increase likelihood of resolution of benign ovarian cysts
    - **Cystectomy + intraoperative frozen section** indicated for persistent low-risk cysts or ultrasound-diagnosed dermoid or endometriotic cysts
      - Contralateral ovary must be carefully inspected to exclude a bilateral lesion
      - If frozen section diagnoses mucinous cystadenoma: *additional appendicectomy performed as it is associated with coexistence of an appendiceal mucocele*
      - If frozen section diagnoses gonadoblastoma: *ovarian karyotyping required as most would have dysgenetic ovaries, in which case bilateral oophorectomy is indicated to prevent subsequent development of dysgerminomas; uterus can be preserved for future fertility using embryo transfer*
    - **Referral to a gynaecologic oncologist** has been well-established in multiple series to improve overall survival rates for women with ovarian cancer compared to those who were not, hence cysts with high risk for malignancies should be referred

- **Management Algorithm for Ovarian Cysts/Masses**



- ***Acute presentation of ovarian cysts***
  - Complicated ovarian cysts:
    - Ovarian torsion
    - Cyst rupture
    - Cyst hemorrhage (*especially with corpus luteal cysts in patients with coagulopathy, can lead to massive intra-peritoneal bleeding*)
  - Requires immediate surgical intervention, with which a histopathological diagnosis can be obtained
- ***Managing pre-menopausal simple cysts***
  - Studies revealed that simple cysts <6cm can often resolve spontaneously (50-75%), hence observation is appropriate (*most are usually functional cysts*)
  - Simple cysts >6cm can then be subjected to further work-up with CA-125 measurements for calculation of RMI:
    - If low-risk RMI, simple cysts <10cm in diameter have been found to be most often benign, with no survival outcome benefit associated with cystectomy for it
    - Only simple cysts >10cm would require cystectomy
- ***Managing pre-menopausal complex cysts***
  - Physiological forms of complex cysts may resolve spontaneously but many are persistent, hence observation as 1st-line measure with cystectomy reserved for persistent cyst is appropriate
  - In cases where suspicion for malignancy is significant (*ultrasound &/or MRI suggestive; calculated RMI high-risk*), referral to a gynaecologic oncologist is indicated
- ***Managing post-menopausal simple cysts***
  - Simple unilocular cysts <10cm in diameter have significant rates of spontaneous resolution (69.4%) & extremely low risks of malignancy (<0.1%)
  - Hence such cysts with a normal CA-125 may be observed, with cystectomy reserved for persistent cysts
- ***Managing post-menopausal complex cysts***
  - Most would require referral to a gynaecologic oncologist for laparotomy with definitive histopathological diagnosis as 36-39% are malignant (*especially if CA-125 levels >35U/ml*)
- ***Managing ovarian cysts in pregnancy***
  - Most common differentials in pregnancy:
    - Benign cystic teratomas
    - Corpus luteum cysts or theca lutein cysts
  - Risks involved:
    - Risk of malignancy 1 in 12000 to 47000; 4-7% of persistent masses
    - Risk of complication (torsion, rupture) 1-6%
  - Management principles:
    - 1st line: conservative, with serial ultrasound monitoring ± serial CA-125 monitoring (*normal CA-125 levels in pregnancy peak in 1st trimester & decrease consistently thereafter*)
    - For benign-looking cysts with symptoms of pain or mass-effect compression of other organs, laparoscopic cystectomy should be considered, preferably done in 2nd trimester
    - For malignant-looking cysts, surgical removal by laparotomy should be done in 2nd trimester

Uterine Corpus Cancer

Endometrial Cancer

- **Epidemiology & Associations**
  - 2nd most common gynaecological cancer in Singapore
  - ***Risk factors*** (*mostly related to unopposed estrogen exposure*):
    - Nulliparity
    - Late age at menopause
    - Polycystic ovary syndrome (*chronic anovulatory cycles leading to chronic estrogen exposure without corresponding progesterone counteraction*)
    - Obesity (*increased extra-ovarian aromatization of circulating androstenedione to estrone*)
    - Granulosa-theca cell tumour (*estrogen secreting*)
    - Chronic estrogen-only hormone replacement therapy
    - Chronic tamoxifen use (*selective estrogen receptor modulator that is agonist in the endometrium, hence promotes endometrial proliferation like estrogen does*)
    - Family history of breast, colon &/or ovarian cancer (Lynch II syndrome aka HNPCC)
      - 5% of endometrial cancers occur in women with Lynch II syndrome
      - Of women with Lynch II syndrome, 40% develop endometrial cancer
  - ***Protective factors:***
    - Use of oral contraceptive pills

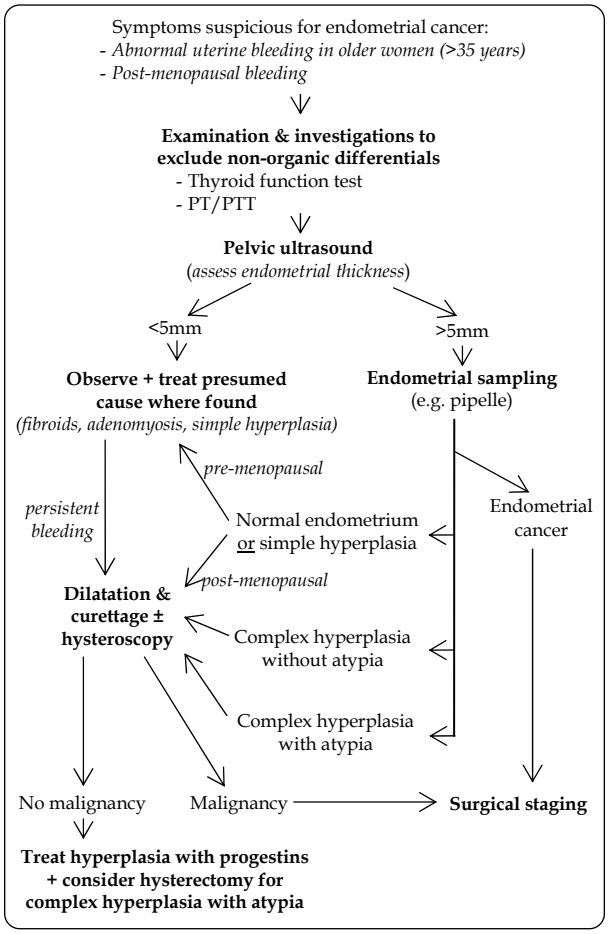
- **Pathophysiology of Endometrial Cancer**
  (2 *main subtypes of endometrial cancer*)
  - ***Type 1 endometrial cancer (80%)***
    - Associated with prolonged unopposed estrogen stimulation (*as described above*)
    - Usually develops from a pre-existing endometrial hyperplasia & intraepithelial neoplasia
    - Histological subtypes tend to be lower grade:
      - Endometrioid adenocarcinoma (grades 1 & 2)
    - Tend to have a relatively better prognosis than type 2
  - ***Type 2 endometrial cancer (20%)***
    - Not associated with estrogen exposure
    - Precursor lesions rarely identified
    - Histological subtypes tend to be high grade:
      - Endometrioid adenocarcinoma (grade 3)
      - Serous carcinoma
      - Clear cell carcinoma
      - Squamous cell carcinoma
    - Tend to have a worse prognosis than type 1

- **Modes of Spread of Endometrial Cancer**
  - ***Direct extension***
    - Myometrium, serosal surface of uterus
    - Cervix, vagina, parametrium
    - Bladder, rectum
  - ***Transcoelomic*** (*exfoliated cells may pass through the fallopian tubes to gain access into the peritoneal cavity*)
    - Ovaries
    - Peritoneal surfaces
    - Omentum
  - ***Lymphatic***
    - Pelvic nodes
    - Para-aortic nodes
  - ***Hematogenous***
    - Lungs
    - Liver parenchyma

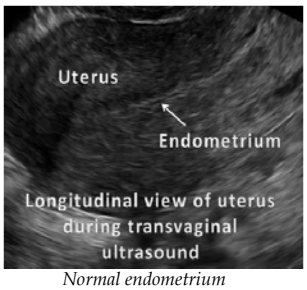
- **Clinical Presentation of Endometrial Cancer**
  - ***Asymptomatic***
  - ***Abnormal vaginal bleeding:***
    - Pre-menopausal women:
      - Menorrhagia
      - Intermenstrual bleeding
    - Post-menopausal women:
      - Post-menopausal bleeding
    - Anemic symptoms may result if bleed is significant & chronic enough
  - ***Metastatic symptoms (unusual at presentation):***
    - Dyspnea, hemoptysis, cough (*lung mets*)
    - Abdominal distension (*ascites*)

- **Physical Examination**
  - ***General examination***
    - Assess patient's vitals & check for pallor
    - Inspect for signs related to predisposing factors:
      - Obesity, cutaneous signs of diabetes mellitus
      - Hirsutism, acne (*PCOS*)
      - Petechiae/purpura/ecchymoses (*coagulopathy is a differential for abnormal uterine bleeding in pre-menopausal women*)
    - Neck examination for goitre (*as thyroid disorders, especially hypothyroidism, is a differential for abnormal uterine bleeding in pre-menopausal women*)
    - Breast examination (*check for lumps or previous mastectomy scars as breast cancers can occur in association with endometrial cancer; chronic tamoxifen use for breast cancer treatment is also associated with an increased risk of endometrial cancer*)
    - Respiratory examination for pleural effusion (*mets*)
  - ***Abdominal examination***
    - Inspect for any abdominal distension
    - Palpate for organomegaly
    - Palpate for any other masses (*enlarged uterus, colorectal cancer*)
    - Percuss for shifting dullness (*malignant ascites*)
  - ***Pelvic examination***
    - Speculum examination
      - May see blood coming through cervical os with or without blood clots presents
      - Assess cervix (*cervical cancer is a differential for abnormal uterine bleeding & post-menopausal bleed*)
      - Do a Pap smear (*picks up cervical cancer & may pick up underlying endometrial cancer in 50%*)
    - Bimanual palpation
      - Assess uterine size (*may be enlarged in endometrial cancer or if concomitant uterine pathologies such as adenomyosis of fibroids, both of which are differentials for menorrhagia, are present*)
      - Palpate for adnexal masses (*may have underlying granulosa cell tumour or concomitant endometrioid tumour of the ovary*)

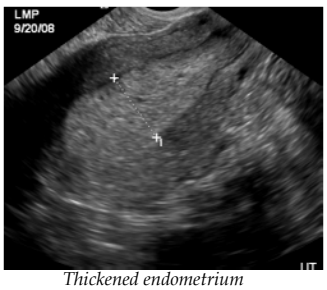
- **Algorithm for Endometrial Evaluation**



– ***Pelvic ultrasound***
  - In the context of a patient presenting with abnormal uterine bleeding or post-menopausal bleeding, the pelvic ultrasound is useful for investigating the possible organic etiology involved:
    - Assessment of endometrial thickness
    - Look for fibroids &/or adenomyosis
  - Endometrial thickness assessment:
    - 5mm is used as cut-off for endometrium that is suspiciously thick (*endometrial hyperplasia & cancer will almost invariably have endometrial thickness >5mm*)
    - Most useful in post-menopausal women
    - In pre-menopausal women, timing of the menstrual cycle may confound the finding (*thickness varies depending on the phase of the cycle*)

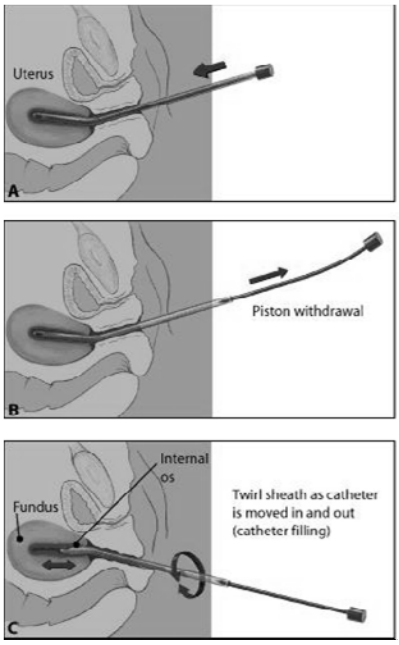


Normal endometrium

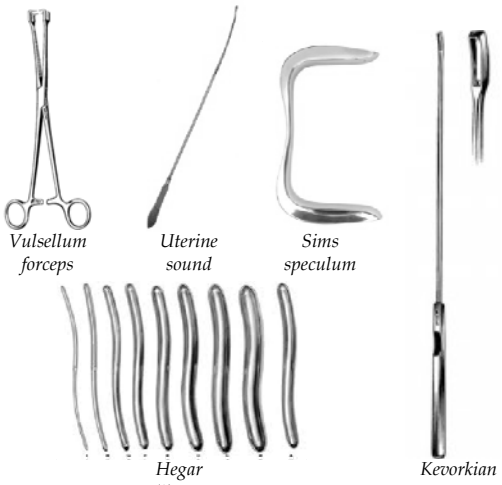


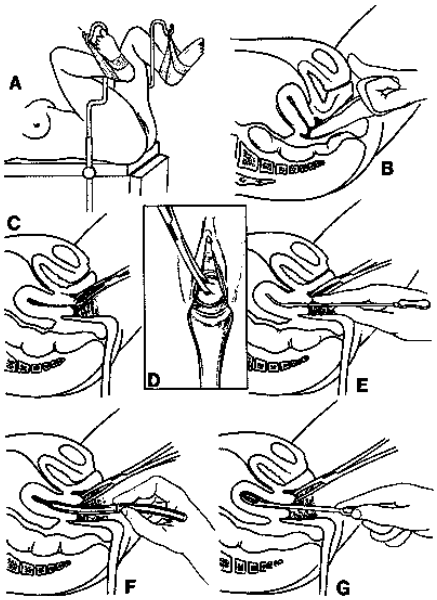
Thickened endometrium

– ***Endometrial sampling***
  - Performed in the office using a endometrial sampling instrument (e.g. pipelle) without anesthesia (*or at most local anesthesia*)
  - 1st-line before D&C due to various advantages:
    - Outpatient rather than surgical procedure
    - Minimal or no cervical dilatation needed
    - Lower risk of uterine perforation
    - Lower costs for patient incurred
    - *<u>however</u>, higher rates of false negatives due to sampling error*
  - Risks & complications:
    - Bleeding, infection
    - Uterine perforation, bowel & bladder injury
  - Possible results of endometrial samplings:
    - No abnormalities
    - Simple hyperplasia
    - Complex hyperplasia without atypia
    - Complex hyperplasia with atypia
    - Endometrial cancer
  - Management following endometrial sampling:
    - In pre-menopausal women with normal results: *threshold for more invasive endometrial biopsy is higher; hence it is appropriate to presume that abnormal bleeding is due to other benign pathologies discovered (fibroids, adenomyosis)*
    - In pre-menopausal women with simple hyperplasia: *similarly, no need for further testing, & medical treatment using progestins is appropriate*
    - In post-menopausal women with normal results or simple hyperplasia: *post-menopausal bleeding is almost always abnormal, thus threshold for more invasive endometrial biopsy is much lower; hence D&C is still indicated in case of a sampling error*
    - In cases of complex hyperplasia: *D&C follow-up in indicated to rule out cancer as the risk of malignancy is higher than in simple hyperplasia; once confirmed, cases without atypia can be treated with progestins whereas hysterectomy may be considered for cases with atypia as risk of subsequent cancer is very high*



– *Dilatation & curettage ± hysteroscopy*
  - Outpatient surgical procedure, can be done under paracervical block & local anesthesia
  - Dilatation & curettage technique:
    - Patient in dorsal lithotomy position
    - **Sims speculum** used to visualize cervix
    - Cervix is grasped using a **vulsellum forceps**
    - A thin metal rod (**uterine sound**) is passed through the cervix to gauge the depth of the endometrial cavity
    - Cervix is then dilated with a series of graduated dilators (**Hegar dilators**) passed to a depth as gauged by the sound
    - A sharp curette (**Kevorkian curette**) is then passed through the cervix to do a thorough curettage of the endometrial lining
  - Risks & complications:
    - Bleeding, infection
    - Uterine perforation, bowel & bladder injury
    - Cervical laceration
    - Uterine scarring (**Asherman syndrome**), resulting in subfertility & increased risk of placenta accreta
  - Possible histological results & subsequent management are similar to that for endometrial sampling





- **Diagnosis & Staging of Endometrial Cancer**
  – ***Pre-operative investigations:***
    - Full blood count (*assess for anemia*)
    - Chest x-ray ± CT/MRI (*look for mets*)
  – ***Diagnosis of endometrial cancer*** is histopathological, which may be based on a sample obtained via:
    - Endometrial sampling
    - Dilatation & curettage
  – ***Staging of endometrial cancer*** is surgical, assessed following a standard surgery (THBSO) is performed after histological diagnosis of endometrial cancer has been obtained

International Federation of Obstetrics & Gynaecology (FIGO) Staging of Endometrial Carcinoma (2009)

Stage	*Criteria*
Stage I	**Tumour confined to the corpus uteri (includes endocervical glandular involvement)**
Ia	No or less than half of myometrium invaded
Ib	Half or more of myometrium invaded
Stage II	**Tumour invades cervical stroma, but not beyond uterus**
Stage III	**Local &/or regional spread of tumour (positive peritoneal cytology to be reported separately but does not affect the stage)**
IIIa	Tumour invades serosal or adnexa or both
IIIb	Vaginal &/or parametria involvement
IIIc	Metastases to pelvic or para-aortic lymph nodes, or both
Stage IV	**Tumour involves bladder &/or bowel mucosa, &/or distant metastases**
IIIa	Tumour invasion of bladder or bowel mucosa, or both
IIIb	Distant metastases including intra-abdominal or inguinal lymph nodes, or both

Histological grading of endometrial cancer:
Grade 1 = well-differentiated
Grade 2 = moderately-differentiated
Grade 3 = poorly-differentiated

Note: histological grading does not change the stage of the tumour

- **Management of Endometrial Cancer**
  - ***Basic principles in management:***
    - Total abdominal hysterectomy + bilateral salpingo-oophorectomy (THBSO) is the cornerstone of treatment & staging for all diagnosed endometrial cancers
    - Peritoneal cytology is also performed
      - Used to affect staging in the 1988 FIGO staging
      - With the 2009 revised FIGO staging, it is reported separately without affecting the stage
    - Lymph node assessment selectively done in high-risk cases, which includes:
      - Grade 3 endometrioid adenocarcinoma
      - Serous carcinoma
      - Clear cell carcinoma
      - Outer myometrial invasion present
      - Cervical extension present
    - Adjuvant radiotherapy or chemotherapy used primarily for advanced cases
  - ***Management of early-stage disease (Stages I & II)***
    - THBSO + selective lymph node assessment
    - Adjuvant radiotherapy for the following:
      - Brachytherapy for high risk cases with negative nodes
      - External pelvic radiation for positive nodes
  - ***Management of advanced-stage disease (Stages III & IV)***
    - Treatment is <u>individualized</u>
    - THBSO wherever feasible
    - Adjuvant radio- &/or chemotherapy given:
      - Chemotherapy if pelvic &/or abdominal metastases incompletely resected
      - Whole abdominal radiation + chemotherapy if pelvic & abdominal mets completely resected
    - Hormonal therapy
      - High dose progestins can be considered for treatment of metastases in unresectable sites (*e.g. upper abdomen, liver, lung*)
      - Options: medroxyprogesterone acetate (Provera) 50mg TDS; Depo-Provera 400mg IM; megestrol acetate (Megace) 80mg BDS

- **Prognosis of Endometrial Cancer (Overall)**
  - Stage I = 90% 5-year survival
  - Stage II = 70% 5-year survival
  - Stage III = 50% 5-year survival
  - Stage IV = 20% 5-year survival

    Note: specific survival rates may vary depending on the histological subtype & grade of tumour as well

Uterine Sarcomas

Account for 3% of uterine corpus cancers; can arise from: (i) endometrial stroma (ii) mesenchymal tissues (iii) myometrial tissues; Uterine sarcomas may be:

- *homologous (malignant tissue is normally found in uterus – endometrial stroma, smooth muscle etc)*
- *heterologous (malignant tissue is not normally found in uterus – bone, cartilage, skeletal muscle, adipose tissue)*

- **Leiomyosarcoma**
  - May arise from leiomyoma (fibroid), but risk of malignant transformation in a fibroid is still <1%
  - Histologic criteria for distinguishing leiomyosarcomas from leiomyomas:
    - Mitotic count > 10 per 10 high power fields
    - Presence of coagulative necrosis
    - Presence of cellular atypia
  - Clinical features:
    - Mean age = 55 years old
    - Presents with pelvic pain, abnormal uterine bleeding, pelvic/lower abdominal mass or pressure symptoms on the bowel or bladder
    - Diagnosis is usually made at the time of surgery for a probable uterine fibroid
  - Management:
    - THBSO
    - Adjuvant pelvic radiation decreases local pelvic recurrence but does not prolong survival
    - Chemotherapy has very low response rates

- **Endometrial Stromal Tumours**
  - ***Endometrial stromal nodule***
    - Rare benign condition
    - ≤3 mitoses per 10 high power fields
    - Hysterectomy is curative
  - ***Endometrial stromal sarcoma***

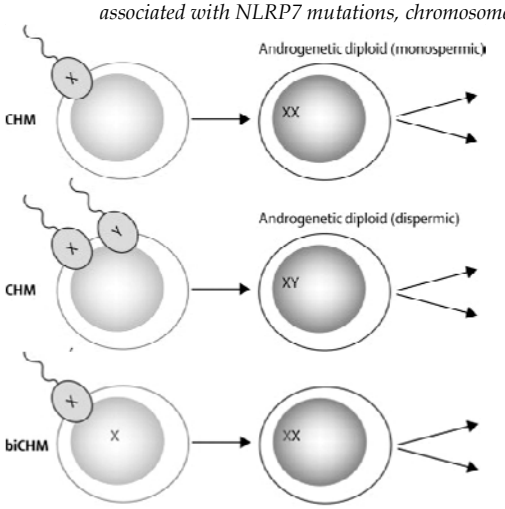
    (*previously known as endolymphatic stromal myosis*)
    - Low-grade lesion, with minimal to no cellular atypia
    - <5 mitoses per 10 high power fields
    - Evidence of vascular invasion almost always present
    - Treatment with THBSO is usually curative
    - Local & distant recurrences may occur 10-20 years later, but can be treated with good outcomes with various modalities:
      - Re-resection of recurrent disease
      - Hormonal treatment with progestins
      - Radiotherapy for pelvic disease
  - ***High grade endometrial sarcoma***
    - Diagnosis can be made by endometrial biopsy or dilatation & curettage for work-up of abnormal uterine bleeding (*patients are usually pre-menopausal*)
    - Malignant, often with very poorly-differentiated cells
    - ≥10 mitoses per 10 high power fields
    - Aggressive myometrial invasion & distant metastases are common at the point of presentation
    - Treated with THBSO + thorough exploration of the peritoneal cavity & retroperitoneum
    - Post-operative radiotherapy improves local control but does not improve survival
    - Treatment for metastatic disease:
      - Hormonal therapy with progestins
      - Chemotherapy

Gestational Trophoblastic Neoplasia

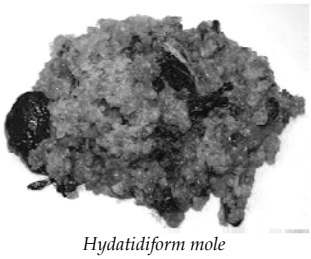
Unique spectrum of diseases resulting from aberrant conception; also known as "molar pregnancy"

Types of Gestational Trophoblastic Neoplasia

- **Hydatidiform Mole (Complete Mole)**
  - ***Pathophysiology:***
    - Benign
    - Abnormal conceptus without an embryo/fetus (i.e. only trophoblastic tissue present), with gross hydropic swelling of the villi & vesicle formation
    - Results from 1 of 3 possible ways:
      - **Androgenetic diploid (monospermic)**: *fertilization of an empty ovum by a 23X sperm followed by reduplication of the 23X set giving a completely homozygous diploid genome of 46XX derived entirely paternally*
      - **Androgenetic diploid (dispermic)**: *fertilization of an empty ovum by 2 sperms, resulting in a 46XX or 46XY heterozygous diploid genome derived entirely paternally*
      - **Biparental diploid**: *fertilization of a normal ovum by a sperm, but somehow still results in complete mole formation; this form is the usual form seen in hereditary recurrent hydatidiform moles associated with NLRP7 mutations, chromosome 19*



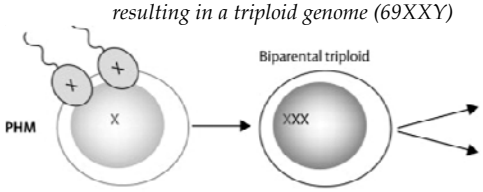
    - Characteristically produces <u>very high levels of hCG</u>, resulting in various effects:
      - Excessive pregnancy symptoms of nausea & vomiting or even hyperemesis gravidarum
      - May cause clinical hyperthyroidism (*as hCG has the same a-subunit as TSH, hence high levels as seen in complete moles can cause clinical hyperthyroidism*)
      - May cause formation of theca-lutein cyst of the ovaries
    - May be complicated by pre-eclampsia in early pregnancy (*before 20 weeks gestation*)
  - ***Clinical features:***
    - <u>History:</u>
      - Amenorrhea
      - Spontaneous abortion: irregular or heavy vaginal bleeding ± expulsion of molar vesicles from the vagina & lower abdominal pain (*usually in 1st or early 2nd trimester*)
      - Excessive nausea/vomiting or even hyperemesis gravidarum
      - Symptoms of pre-eclampsia: irritability, dizziness, photophobia, upper abdominal pain
      - Hyperthyroid symptoms: palpitations, nervousness, tremors, heat intolerance
    - <u>Physical examination findings:</u>
      - Signs of pre-eclampsia: *hypertension, papilloedema on fundoscopy, hyperreflexia, clonus, upper abdominal tenderness*
      - Signs of hyperthyroidism: *tachycardia, sweaty, tremors*
      - Obstetric examination: *uterus large for dates, absent fetal heart sounds*
      - Pelvic examination: *may see molar vesicles, may feel adnexal masses on bimanual palpation (theca-lutein cysts)*
    - <u>Investigation findings:</u>
      - Urine pregnancy test positive
      - β-hCG titres high for early pregnancy
      - Pelvic ultrasound: *no embryonic/fetal tissue,* **snowstorm pattern** *in uterus*
      - Urine protein positive (*in pre-eclampsia*)



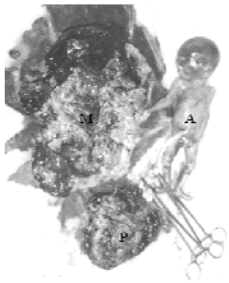
Hydatidiform mole

Ultrasound of hydatidiform mole

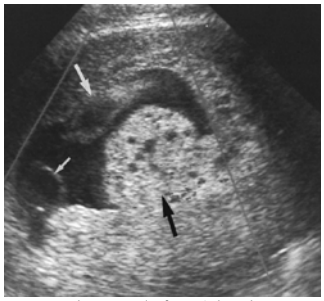
- **Partial Mole**
  - ***Pathophysiology:***
    - Benign
    - Trophoblastic neoplasia associated with a developing fetus, with placental areas showing typical changes of hydropic swelling & vesicles
    - Results from 1 of 2 possible ways:
      - **Biparental triploid (dispermic)**: *fertilization of a normal ovum by 2 sperms, resulting in a triploid genome (69XXX, 69XXY or 69XYY)*
      - **Biparental triploid (monospermic)**: *rarely, fertilization of a normal ovum by a sperm carrying an unreduced diploid paternal genome 46XY, resulting in a triploid genome (69XXY)*



    - Does not produce as much hCG as complete moles
    - May be complicated by pre-eclampsia in early pregnancy (*similar to complete moles, but usually presents later, at about 17-22 weeks gestation*)
  - ***Clinical features:***
    - History:
      - Amenorrhea
      - Usually presents with spontaneous abortion (*similar to complete mole*) or missed abortion
      - Symptoms of pre-eclampsia: irritability, dizziness, photophobia, upper abdominal pain
    - Physical examination findings:
      - Signs of pre-eclampsia: *hypertension, papilloedema on fundoscopy, hyperreflexia, clonus, upper abdominal tenderness*
      - Obstetric examination: *uterus small for dates, fetal heart sounds present if fetus still viable, absent if missed abortion has occurred*
      - Pelvic examination: *may see blood & products of conception if incomplete abortion is occurring*
    - Investigation findings:
      - Urine pregnancy test positive
      - β-hCG titres normal/slightly elevated for early pregnancy
      - Pelvic ultrasound: *fetal tissue seen, fetal heartbeat may be absent (in missed abortion), hydropic swelling of placenta*
      - Urine protein positive (*in pre-eclampsia*)
      - Immunohistochemistry strongly positive for **placental alkaline phosphatase (PLAP)**



Partial mole



Ultrasound of partial mole
black arrow: abnormal placenta with cysts
big white arrow: fetus
small white arrow: yolk sac

- **Invasive Mole (Chorioadenoma Destruens)**
  - ***Pathophysiology:***
    - Locally invasive, occasionally malignant
    - Hydatidiform mole in which hydropic villi invade the myometrium or blood vessels, or are transported to extra-uterine sites
      - Mostly confined to the uterus
      - 24-40% demonstrate distant metastases to lungs, vulva, broad ligament & brain
  - ***Clinical features:***
    - Diagnosis of invasive mole is usually made retrospectively on histological confirmation after a hysterectomy performed for persistent βhCG elevation following treatment for a complete mole

- **Choriocarcinoma**
  - ***Pathophysiology:***
    - Malignant epithelial tumour arising from trophoblastic tissue; may be:
      - Gestational: *arising from complete moles (50%), after abortions (25%), normal pregnancies (22%) & ectopic pregnancies (3%)*
      - Non-gestational: *arising as a germ cell tumour*
    - Comprises sheets of anaplastic cytotrophoblast & syncytiotrophoblast; grossly appear as a hemorrhagic friable mass with no identifiable villi
    - Widespread hematogenous metastasis:
      - Lungs (50%)
      - Vagina (30-40%)
      - Others: brain, liver, GIT, kidneys etc
    - Produces high levels of hCG (tumour marker)
  - ***Clinical features (of gestational choriocarcinoma):***
    - Usually presents with metastatic symptoms & complications following a gestational event:
      - Vaginal involvement: *vaginal bleeding*
      - Lung involvement: *cough, dyspnea, hemoptysis, cannonball mets on chest x-ray*
      - Brain involvement: *neurological signs & symptoms from hemorrhagic mets to brain*
      - GI involvement: *hematochezia*
    - May also present with persistent βhCG elevation following treatment for a complete mole

Clinical Approach to Molar Pregnancy

- **Epidemiology & Associations**
  - Geographical predisposition: *higher incidence in Asia, Africa & Latin America*
  - More common in extremes of reproductive ages: *<20 years or >40 years; malignant sequelae more common in older women*
  - Risk factors:
    - Previous molar pregnancy (*1-3% chance of a 2nd molar pregnancy, 40x greater than the average risk*)
    - Family history of molar pregnancies
  - Term pregnancy & live births have a protective effect

- **Clinical Features**
  - ***Features of benign molar pregnancies:***
    - Amenorrhea
    - Spontaneous abortion (*per vaginal bleeding, passing of grape-like vesicles per-vaginally, lower abdominal pain*)
    - Early-onset pre-eclampsia (*irritability, dizziness, photophobia, upper abdominal pain*)
    - Excessive nausea/vomiting (*complete mole*)
    - Clinical hyperthyroidism (*complete mole*)
  - ***Features of malignant molar pregnancies:***
    - Vaginal bleeding
    - Cough, dyspnea, hemoptysis
    - Neurological deficits
    - Hematochezia

- **Physical Examination**
  - ***General examination***
    - Assess patient's vitals & check for pallor
      - Hypertension: *pre-eclampsia*
      - Tachycardia: *excessive blood loss, hyperthyroid*
      - Tachypnea: *excessive blood loss, lung mets*
    - Respiratory examination may reveal abnormal findings (*lung mets*)
    - Neurological examination if neurological deficit is reported in the history (*brain mets*)
  - ***Obstetric examination (if patient supposedly pregnant)***
    - Assess uterine size
      - Large for dates in complete moles
      - Small for dates in partial moles
    - Auscultate for fetal heart sounds
      - Present in partial moles with viable fetus
      - Absent in complete moles or partial moles with dead fetus (missed abortion)
  - ***Pelvic examination***
    - Speculum examination
      - Cervical os may be open with blood coming through (*spontaneous abortion in benign molar pregnancies; choriocarcinoma*)
      - May see blood clots & grape-like vesicles
      - Firm discoloured mass in vagina (*vaginal mets*)
    - Bimanual examination
      - May find adnexal mass (*theca lutein cyst in complete mole or choriocarcinoma*)

- **Investigations**
  - ***Non-radiological investigations:***
    - Urine pregnancy test
    - Serum β-hCG (*disproportionately elevated in complete moles & choriocarcinomas*)
    - Full blood count (*check hemoglobin levels*)
    - Group & cross match
    - Urinary total protein (*check for proteinuria which may indicate pre-eclampsia*)
    - Lumbar puncture for CSF β-hCG quantification (*β-hCG does not readily cross blood-brain-barrier, hence serum:CSF β-hCG ratios < 40:1 suggests CNS involvement*)
  - ***Radiological investigations:***
    - Pelvic ultrasound (*diagnose form of molar pregnancy, assess for theca-lutein cyst*)
    - Chest x-ray (*cannonball mets in choriocarcinoma*)
    - CT head, abdopelvis (*look for mets in choriocarcinoma*)

- **Staging of Gestational Trophoblastic Neoplasia**

International Federation of Obstetrics & Gynaecology (FIGO) Staging of Gestational Trophoblastic Neoplasia

Stage	*Criteria*
Stage I	**Disease confined to uterus**
Ia	Disease confined to uterus with no risk factors
Ib	Disease confined to uterus with one risk factor
Ic	Disease confined to uterus with two risk factors
Stage II	**Tumour extends outside uterus but limited to genital structures (adnexa, vagina, broad ligament)**
IIa	Tumour involving genital structures with no risk factors
IIb	Tumour involving genital structures with one risk factor
IIc	Tumour involving genital structures with two risk factors
Stage III	**Tumour extending to lungs with or without known genital tract involvement**
IIIa	Tumour extending to lungs with no risk factors
IIIb	Tumour extending to lungs with one risk factor
IIIc	Tumour extending to lungs with two risk factors
Stage IV	**All other metastatic sites**
IIIa	All other metastatic sites with no risk factors
IIIb	All other metastatic sites with one risk factor
IIIc	All other metastatic sites with two risk factors

Risk factors:
1) *Serum hCG >100000U/ml*
2) *Duration of disease >6 months from TOP or antecedent pregnancy*

- **Management of Gestational Trophoblastic Neoplasia**
  - ***Management of benign molar pregnancies:***
    - **Evacuation of uterus**
      - Operative suction evacuation of the uterus followed by sharp curettage of the uterine cavity
      - IV oxytocin administered to help stimulate uterine contractions & reduce blood loss
      - Misoprostol (& any prostaglandins for that matter) avoided as it may cause dissemination of trophoblastic tissue into maternal circulation
      - Complications: *bleeding, uterine perforation, subfertility following procedure*
    - **Post-operative monitoring of β-hCG**
      - Weekly serum assays of β-hCG (*urine pregnancy test not used to monitor as β-hCG levels can drop to below detectable levels by this method*)
      - Normally, β-hCG levels should steadily decline to undetectable levels by serum assays within 12-16 weeks after evacuation
      - Persistently elevated β-hCG levels may indicate the presence of an undiagnosed invasive mole or choriocarcinoma
      - Patients should be advised to avoid pregnancy 9-12 months after evacuation & be given a reliable contraceptive method
    - **Chemotherapy**
      - Prophylactic chemotherapy is <u>not</u> indicated as 90% of patients have spontaneous remissions
      - Chemotherapy is employed if β-hCG levels plateau or rise during follow-up monitoring
    - **Hysterectomy**
      - Option in older women who have completed families to prevent risk of malignant sequelae
  - ***Management of malignant molar pregnancies:***
    - **Chemotherapy**
      - Regime for good prognosis GTNs: *methotrexate (+ folinic acid/leucovorin acid rescue regimen to decrease bone marrow toxicity)* <u>*or*</u> *actinomycin D*
      - Regime for poor prognosis GTNs: **MAC** *(methotrexate + actinomycin D + cyclophosphamide)* <u>*or*</u> **modified Bagshawe regime** *(etoposide + actinomycin D + vincristine + cyclophosphamide + methotrexate + folinic acid)*
    - **Radiotherapy**
      - For brain & liver metastases
    - **Hysterectomy**
      - Option for invasive mole with no metastases
    - **Post-operative monitoring of β-hCG**

- **Prognosis of Gestational Trophoblastic Neoplasia**
  - Good prognosis GTNs: 95-100% cure rates
  - Poor prognosis GTNs: 50-70% cure rates

Vulvar & Vaginal Cancers

Vulvar Neoplasms

- **Vulvar Intraepithelial neoplasia (VIN)**
  - ***Squamous cell carcinoma in situ***
    - Associated with human papillomavirus infection & smoking; mainly seen in younger women
    - VIN III is also known as **Bowen's disease**
  - ***Adenocarcinoma in situ (vulvar Paget's disease)***
    - Adenocarcinoma-in-situ of the vulva
    - Cell of origin: primitive epithelial progenitor cells
    - Unlike Paget's disease of the breast, vulvar Paget's usually has no underlying malignancy (only 10-20%)

- **Squamous Cell Carcinoma of the Vulva**
  - ***Risk factors:***
    - Smoking
    - Human papillomavirus infection
    - Chronic lichen sclerosis
    - Lymphogranuloma venereum - *Chlamydia trachomatis*
    - Granuloma inguinale - *Klebsiella granulomatis*
  - ***Diagnosis for SCC of the vulva*** is via biopsy
  - ***FIGO staging for SCC of the vagina*** is surgical
  - ***Treatment:***
    - Early vulvar cancer: *deep local excision ± inguinal-femoral lymphadenectomy (unilateral or bilateral depending on staging)*
    - Advanced vulvar cancer: *radical surgery with urinary & bowel stoma formation or pre-operative chemoradiation to shrink tumour followed by conservative surgery*
  - ***Prognosis:***
    - Overall: 70% 5-year survival
    - Those with positive nodes: 50% 5-year survival
    - Those with negative nodes: 90% 5-year survival

- **Verrucuous Carcinoma of the Vulva**
  - Variant of squamous cell carcinoma of the vulva
  - Pathology:
    - Cauliflower-like growths
    - Invasion occurs with a broad "pushing" front
  - Metastases to regional lymph nodes rare, but locally aggressive & prone to local recurrence
  - Treatment:
    - Local excision with wide margins
    - Radiotherapy is contraindicated due to risk of inducing anaplastic transformation

- **Bartholin's Gland Carcinoma**
  - ***Various histological subtypes:***
    - Adenocarcinoma
    - Squamous cell carcinoma
    - Transitional cell carcinoma
  - ***Treatment:***
    - Hemivulvectomy + ipsilateral inguino-femoral lymphadenectomy
    - Post-operative radiation for large lesions to help decrease local recurrence rates

- **Other Cancers of the Vulva**
  - ***Malignant melanoma***
  - ***Basal cell carcinoma***

Vaginal Neoplasms

- **Vaginal Intraepithelial Neoplasia (VAIN)**
  - Relatively uncommon compared to vulvar (VIN) & cervical intraepithelial neoplasia (CIN)
  - Usually occurs in the upper third of the vagina
  - ***Risk factors:***
    - Human papillomavirus infection
    - Previous irradiation for cervical cancer
  - ***Diagnosis:***
    - Usually brought to clinical attention due to an abnormal Pap smear in a woman who has had a total hysterectomy or no cervical abnormality
    - Definitive diagnosis requires vaginal biopsy, directed using colposcopy or Lugol's iodine staining

- **Squamous Cell Carcinoma of the Vagina**
  - ***Epidemiology & associations:***
    - Uncommon malignancy
    - Mean age of presentation = 30 years
    - Up to 30% of patients have a previous history of CIN or cervical cancer treated ≥5 years ago
  - ***Diagnosis for SCC of the vagina*** is via punch biopsy
  - ***FIGO staging for SCC of the vagina*** is clinical
  - ***Treatment:***
    - Radiotherapy or chemoradiation is mainstay
    - Surgery has a limited role (*radical hysterectomy + partial vaginectomy + pelvic lymphadenectomy may be performed for early lesions in the posterior fornix*)
  - ***Prognosis:***
    - Stage I: 85-90% 5-year survival
    - Stage II: 55-65% 5-year survival
    - Stage III: 30-35% 5-year survival
    - Stage IV: 5-10% 5-year survival

- **Adenocarcinoma of the Vagina**
  - ***Types of adenocarcinomas of the vagina:***
    - Metastatic cancers to the vagina (most common):
      - Usually from a gynaecologic malignancy (*endometrial, ovarian, cervical*)
      - Occasionally from a distant site (*kidney, breast, colorectal*)
    - Primary adenocarcinoma of the vagina:
      - Most are clear cell adenocarcinomas
      - Rare few arise from malignant change in residual glands of Müllerian origin, Gartner's cyst or a focus of endometriosis
  - ***Clear cell adenocarcinoma***
    - Association with in-utero exposure to **diethylstilbesterol (DES)** due to maternal ingestion of DES during pregnancy
      - Mean age of diagnosis = 19 years
    - Treatment:
      - Radical hysterectomy + vaginectomy
      - Radiotherapy
    - Prognosis: *overall 80% 5-year survival*

- **Sarcoma of the Vagina**
  - ***Types of sarcomas of the vagina:***
    - Adults: leiomyosarcoma
    - Infants & children: **sarcoma botryoides**
  - ***Sarcoma botryoides***
    - An embryonal rhabdomyosarcoma
    - Lesions grossly resemble a bunch of grapes
    - Mean age of diagnosis = 2-3 years
    - Treatment: *conservative surgical resection followed by adjuvant chemotherapy ± radiotherapy*

MENOPAUSE

Changes in Menopause

- **Definitions & Terminologies**
  - ***Natural/Spontaneous Menopause***
    - Defined as the time of the final menstrual period (FMP) of a woman, confirmed after 12 consecutive months of amenorrhea in the absence of any obvious causes (*average age of natural menopause = 51 years*)
  - ***Induced/Iatrogenic Menopause***
    - Permanent cessation of menstruation after induced termination of ovarian function:
      - Chemotherapy, radiotherapy
      - Bilateral oophorectomy (surgical menopause)
  - ***Early Menopause***
    - Menopause occurring at ≤45 years of age
  - ***Premature Menopause***
    - Menopause occurring at ≤40 years of age
  - ***Perimenopause***
    - Period of time when menstrual cycle and endocrine changes occur around the time of natural menopause (*from a few years before the FMP to 12 months after it*)
  - ***Early Postmenopause***
    - Period of time within 5 years after the FMP

- **Hormonal Changes in Menopause**
  - ***Normal physiology of menopause:***
    - Most women normally ovulate about 400 times between menarche & menopause:
      - 1.5 million oocytes at birth
      - 400000 potentially responsive oocytes at the time of menarche
      - Most oocytes are then lost through atresia
    - When nearly all the oocytes have been ovulated or lost through atresia, the ovary becomes minimally responsive to pituitary gonadotropins (LH, FSH)
      - Production of ovarian hormones (estrogen, progesterone & androgens) then markedly decreases
  - ***Pattern of hormonal changes in menopause:***
    - Estrogen levels decrease differentially:
      - Estradiol (E2) levels decline (to 10-50pg/ml)
      - Estrone (E1) levels decline less, and may in fact increase due to continued production via peripheral conversion by adipose tissue of androstenedione produced by the ovaries & adrenal glands
    - Progesterone levels decline to low levels due to increasing anovulatory cycles during the perimenopausal period & thereafter
      - Leads to increased unopposed estrogenic exposure during the perimenopausal and postmenopausal period
    - Androgen (testosterone & androstenedione) levels gradually decrease
      - Postmenopausal women may still experience a relative increase in androgenic effects however due to a loss of estrogenic opposition to the effects of an albeit lowered androgen level
    - Gonadotropin (FSH & LH) levels are sustained at high levels due to release of negative feedback inhibitory control of estrogen on GnRH release from the hypothalamus

- **Clinical Consequences of Menopause**
  (*most are consequences of estrogen deficiency*)
  - ***General symptoms:***
    - Hot flashes (vasomotor symptoms)
      - Experienced by up to 85% of women, though only half of them are severely disturbed by it
      - Sudden intense feeling of warmth experienced predominantly over face, neck & chest with sweating ± chills
      - Average duration of each hot flash = 4 minutes
      - Worst in late perimenopause period
      - Worse in smokers than non-smokers
      - Due to pulsatile release of increased levels of gonadotropins (FSH & LH)
    - Psychological symptoms:
      - Mood disturbances, irritability, depression
      - Insomnia, fatigue
    - Dermatological symptoms:
      - Loss of skin collagen
  - ***Menstrual changes:***
    - Irregularity of menstrual periods
      - Periods become more irregular beginning from early perimenopausal period
      - Due to more frequent anovulatory cycles
      - As a result of anovulation, continued unopposed estrogenic effect on endometrial proliferation may also lead to menorrhagia and polymenorrhea when menstruation does occur
  - ***Urogenital changes:***
    - Atrophic vaginitis
      - Loss of estrogenic effect on vaginal epithelium causes it to become thin & dry with a less acidic (or even alkaline) secretion
      - Vagina shrinks in diameter & becomes more prone to splitting & tearing
      - Patient may experience dyspareunia, unpleasant dryness or discharge
    - Urinary incontinence
  - ***Long-term risks:***
    - Osteoporosis
      - Estrogen deficiency results in osteoclastic activity in bone to exceed that of osteoblasts, leading to increased rates of bone loss following menopause
      - 10-15 years following menopause, risk of fractures in women is 3-5x of that in men
      - Bone loss is most marked in trabecular bone (*vertebrae, femoral neck, and wrist*), hence placing these regions at increased risk for osteoporotic fractures (*vertebral compression fracture, hip fracture, Colles' fracture*)
    - Cardiovascular disease & stroke (*unclear*)
    - Dementia (*unclear*)
    - Cancers (*unclear*)
      - Perimenopausal period when incidence of anovulatory cycles become more common, risk of endometrial cancer is also increased (*increased estrogenic influence in the absence of opposition by progesterone*)

Management of Menopausal Women

Preliminary Evaluation of Menopausal Women

- **History**
  - ***Menopausal symptoms:***
    - General (*hot flashes, mood changes*)
    - Menstrual changes (*menstrual irregularity, abnormal uterine bleeding*)
    - Urogenital (*dyspareunia, vaginal dryness/discharge, urinary incontinence*)
  - ***Gynaecologic & obstetric history:***
    - Menstrual history (*last menstrual period, cycle length & regularity, average amount of menstrual blood loss*)
    - Previous gynaecologic conditions & treatments
    - Last Pap smear & mammogram (+ findings)
    - Any contraceptive use
    - Previous pregnancies & related conditions
  - ***Past medical, surgical & drug history:***
    - Diabetes mellitus, hypertension, dyslipidemia
    - Cardiovascular disease (*ischemic heart disease, stroke*)
    - Venous thromboembolism
    - Hepatic &/or gallstone disease
    - Any previous cancers (*especially breast & gynaecologic*)
    - Any previous fractures &/or known osteoporosis
    - Any previous surgical interventions
    - Long-term medications & drug allergies
  - ***Social history:***
    - Smoking, drinking
    - Functional status
  - ***Family history:***
    - Any cancers (*especially breast & gynaecologic*)

- **Physical Examination**
  - ***General examination:***
    - Height, weight, BMI
    - Blood pressure, quick cardiovascular examination
    - Pallor (*especially in context of abnormal uterine bleeding*)
    - Breast examination
  - ***Abdominal examination:***
    - Inspect for scars from previous abdominal & gynaecological surgeries
    - Palpate for tenderness & masses
    - Percuss for shifting dullness (*especially if pelviabdominal mass is felt on palpation*)
  - ***Pelvic examination:***
    - Inspect vulva for any pathology (*including pelvic organ prolapse & for stress urinary incontinence after asking patient to cough*)
    - Speculum examination to visualize cervix & vaginal vault (+ *Pap smear where indicated*)
    - Bimanual palpation to assess uterine size & presence of adnexal masses

- **Investigations**
  - ***Investigations to support diagnosis of menopause:***
    - Serum hormonal levels/amenorrhea panel (FSH, LH, estradiol, testosterone, prolactin)
      - Picture of elevated FSH & LH with low estradiol supports diagnosis of menopause
  - ***Baseline investigations:***
    - Full blood count (*assess for anemia*)
    - Serum fasting glucose & lipids
    - Urinalysis
  - ***Other symptom-specific investigations:***
    - For abnormal uterine bleeding (*menorrhagia, post-coital bleed, post-menopausal bleed etc*):
      - Pelvic ultrasound for endometrial thickness
      - Endometrial sampling
      - Endometrial biopsy via dilatation & curettage ± hysteroscopy (*gold standard*)
    - For urinary incontinence:
      - Urinalysis (*to rule out urinary tract infection*)
      - Urodynamic studies
  - ***Screening:***
    - Pap smear
    - Mammogram
    - Dual energy x-ray absorptiometry (DEXA) scan

Screening Recommendations

- **Cervical Cancer Screening**
  - ***Recommendations:***
    - Pap smear for women who ever had sexual intercourse to begin from age of 25 years old
    - Pap smear every 3 years provided results do not indicate otherwise
    - Last Pap smear at 65 years old provided results do not indicate otherwise
  - ***Special considerations:***
    - Virgo intacta (*never had sexual intercourse before*) do not need Pap smear (*but need to be counseled that they are not at zero risk of contracting cervical cancer*)
    - Women who have taken HPV vaccination still need to follow standard Pap smear screening recommendations (*as vaccines do not protect against every strain of HPV, just the most common ones*)

- **Breast Cancer Screening**
  - ***Recommendations:***
    - Mammography for women who are asymptomatic and without risk factors for breast cancer to begin from age of 40 years old
    - Mammography annually from 40-49 years old, then once every 2 years from 50-65 years old
    - After 65 years old, screening mammography may be less beneficial, hence no indication for further mammography on a generic basis
  - ***Special considerations:***
    - Women on hormonal replacement therapy have a slightly increased risk of breast cancer, hence should be screened annually from 40-49 years old, then once every 2 years from 50 years old onwards until 5 years after cessation of HRT
    - Women with increased risk of breast cancer (*BRCA, strong family history*) should have monthly breast self-exam + 6-monthly clinical breast exam + annual mammogram beginning from 5 years before the age of onset of the earliest breast cancer diagnosed in the family

- **Osteoporosis Screening**
  - ***Recommendations:***
    - **Dual energy x-ray absorptiometry (DEXA) scan** of lumbar spine & hip for women to be performed above the age of 65 years old
  - ***Interpretation of DEXA scan results:***
    - DEXA scan yields 3 main results:
      - Measured bone mineral density (*average BMD is 1.5g/cm²*)
      - **T-score** = *number of standard deviations from the average bone mineral density (BMD) of a healthy 30-year old individual of the same gender & ethnicity*
      - **Z-score** = *number of standard deviations from the average bone mineral density (BMD) of an age-matched control of the same gender & ethnicity*
    - T-score is used primarily to diagnose osteoporosis:
      - T-score of -2.5 to -1 = osteopenia
      - T-score of ≤ -2.5 = osteoporosis
    - Z-score is used to determine presence of pathological causes of decreased bone mineral density:
      - Z-score < -2 suggests presence of a pathological cause of osteoporosis (*long-term steroid use, hyperparathyroidism etc*)
  - ***Calculation of fracture risk:***
    - Using **WHO Fracture Risk Assessment Tool (FRAX)**, a risk calculation model which derives:
      (i) 10-year probability of hip fracture
      (ii) 10-year probability of major osteoporotic fracture
    - Parameters used in FRAX algorithm: (*http://www.shef.ac.uk/FRAX.index.aspx?lang=En*)
      (i) Nationality & ethnicity
      (ii) Age
      (iii) Gender
      (iv) Weight (kg)
      (v) Height (cm)
      (vi) Presence of previous fracture(s)
      (vii) Presence of parent who fractured hip
      (viii) Current smoking
      (ix) Use of glucocorticoids (*current or past use equivalent of ≥3 months of a dose of prednisolone ≥5g per day*)
      (x) Presence of rheumatoid arthritis
      (xi) Secondary osteoporosis (*presence of type 1 DM, osteogenesis imperfecta in adults, untreated long-standing hyperthyroidism, hypogonadism or menopause <45 years old, chronic malnutrition, malabsorption or chronic liver disease*)
      (xii) Ingestion of alcohol ≥3 units per day
      (xiii) Femoral neck BMD (g/cm²)
    - FRAX score is useful as an adjunct to determine indications for treatment/prevention of osteoporosis in combination with DEXA scan results (*see below for indications for pharmacological treatment of osteoporosis*)

Aspects of Management of Menopausal Women

- **Menopausal Symptoms**
  - ***Non-pharmacological options:***
    - Cool showers, environment, clothing
    - Relax, exercise, hobbies etc for mood changes
    - Psychological support & counselling
  - ***Pharmacological options:***
    - Systemic HRT
    - Tibolone
    - Phytoestrogens
    - Antidepressants

- **Urogenital Symptoms**
  - ***Non-pharmacological options***
    - Pelvic floor exercises
    - Pads/incontinence diapers
    - Lubricants
  - ***Pharmacological options***
    - Topical estrogen (*pharmacological option of choice for isolated urogenital symptoms in menopause*)
    - Systemic HRT (*effective for urogenital symptoms but should not be used for this indication alone*)
  - ***Surgical options***
    - Surgical treatment for stress urinary incontinence (*e.g. Burch colposuspension, tension-free vaginal tape etc*)

- **Osteoporosis**
  - ***General principles in management of osteoporosis:***
    - All women should be given advice on non-pharmacological methods of osteoporosis prevention ± calcium & vitamin D supplementation
    - Use of other pharmacological treatments for prevention of osteoporosis:
      - Beneficial effect of HRT or tibolone if either is already being used for another primary indication (*e.g. vasomotor symptoms*), but these should not be prescribed solely for purpose of osteoporosis prevention based on current recommendations
      - Raloxifene has preventive on top of its therapeutic effect for osteoporosis, hence can be used if patient has significant risk factors for osteoporosis development (*e.g. family history*)
    - Use of other pharmacological treatments for treatment:
      - Clear indications required:
        - → Hip or vertebral fracture
        - → Diagnosed osteoporosis (T-score ≤2.5)
        - → Diagnosed osteopenia (T-score -2.5 to -1) & age >50 years & 10-year probability of hip fracture >3% or 10-year probability of major osteoporotic fracture >20%
      - 1st-line option: *bisphosphonates*
      - Alternative options: *strontium ranelate, teriparatide, calcitonin*
    - DEXA scan for BMD monitoring should be done 2 years after initiation of treatment & at 2-yearly intervals thereafter (*monitoring at intervals shorter than 2 years not supported by current evidence*)
  - ***Non-pharmacological options:***
    - Healthy diet, regular exercise, quite smoking
    - Fall-prevention
  - ***Pharmacological options:***
    - Calcium & Vitamin D supplementation
      - Calcium 1500mg/day + Vitamin D 800IU/day for postmenopausal women not on HRT
      - Calcium 1000-1200mg/day + Vitamin D 400IU/day for premenopausal women or postmenopausal women on HRT
    - HRT
      - HRT has beneficial effects on prevention of osteoporosis in the long-term, but risks of long-term HRT use precludes this as a viable recommendation
    - Tibolone
      - Tibolone has similar beneficial effects for osteoporosis prevention as HRT but its similar side-effect profile also precludes it as a viable recommendation for osteoporosis prevention in the long-run
    - SERMs
      - Raloxifene is the best SERM based on current evidence (FDA-approved as well) for both prevention & treatment of osteoporosis
      - Raloxifene is thus a good option for (i) women who have been on HRT for the purpose of osteoporosis prevention but would like to switch to an alternative (ii) women with a family history of breast cancer & osteoporosis (*as raloxifene achieves osteoporosis prevention without breast cancer risk of HRT*)
      - Tamoxifen is not FDA-approved for osteoporosis prevention & has less data than raloxifene for clinical efficacy in this respect
    - Bisphosphonates
      - Initial treatment of choice for women with diagnosed osteoporosis
      - Alendronate has more significant GI side effects (*esophagitis*) than risedronate
    - Strontium ranelate
      - An option that is good at reducing risk of vertebral fractures in postmenopausal osteoporotic women, & to a lesser degree, the risk of other osteoporotic fractures
    - Teriparatide
      - High costs & risk of osteosarcoma limits its use to patients with very high risk of fractures or resistant to bisphosphonate treatment
    - Calcitonin
      - Unique role in acute treatment of osteoporotic fractures until fracture pain resolves, after which patient may be switched to a more effective long-term treatment (*bisphosphonates*)

- **Other Long-Term Sequelae of Menopause**
  - ***Cardiovascular disease***
    - HRT is not recommended as primary indication for coronary protection in women of any age
    - Screen for & treat diabetes mellitus, hypertension & dyslipidemia
  - ***Stroke***
    - HRT is not recommended for primary or secondary prevention of stroke
  - ***Dementia***
    - HRT is not recommended for prevention of dementia

Pharmacological Therapy for Menopause

Hormonal Replacement Therapy (HRT)

- **Research Findings on HRT**
  - ***Observational trials:***
    - Improves vasomotor symptoms
    - Lowers risk of osteoporosis
    - Lowers risk of coronary heart disease
    - Inconclusive effect on stroke
    - Lowers risk of Alzheimer's disease
  - ***Randomized control trials:***
    - Lowers risk of hip fractures
    - Inconclusive effect on coronary heart disease
    - Increases risk of stroke
    - Increases risk of venous thromboembolism
    - Increases risk of breast cancer

- **Current Accepted Effects of HRT**
  - ***Vasomotor symptoms:***
    - Effective for improving vasomotor symptoms
  - ***Urogenital symptoms:***
    - Effective for improving urogenital symptoms
  - ***Coronary heart disease:***
    - May lower CHD risk when initiated in younger & more recently postmenopausal women
    - Increases CHD risk when initiated in women >10 years postmenopause
  - ***Stroke:***
    - Increases risk of strokes
  - ***Venous thromboembolism:***
    - Increases risk of VTE
  - ***Endometrium:***
    - Estrogen-only HRT for >3 years increases risk of endometrial cancer up to 5-fold
  - ***Breast:***
    - Increases risk of breast cancer
  - ***Bone:***
    - Lowers risk of postmenopausal osteoporotic fractures

- **Types of HRT**
  - ***Combined HRT***
    - Combines an estrogen with a progestogen
    - 2 subtypes of combined HRT:
      - **Sequential combined HRT** = estrogen daily + progestogen on days 14-28 (*patient will still have cyclical withdrawal bleeding*)
      - **Continuous combined HRT** = estrogen + progestogen daily (*patient will not have any withdrawal bleeding*)
  - ***Estrogen-only HRT***
    - Estrogen given alone without any progestogen

- **HRT Dosages**
  - ***Estrogen options & dosages:***
    - Conjugated equine estrogen (CEE) 0.3mg
    - 17β-estradiol (0.5mg micronized oral <u>or</u> 14-25μg transdermal)
    - Ethinyl estradiol (EE)
  - ***Progestogen options & dosages:***
    - Medroxyprogesterone acetate (MPA) 1.5mg
    - Norethindrone acetate 0.1mg
    - Drospirenone 0.5mg
    - Micronized progesterone 50-100mg

- **Clinical Indications for Use of HRT**
  - ***Treatment of vasomotor symptoms:***
    - Currently the main indication for use of HRT
    - Principles guiding HRT use:
      - Lowest dose & shortest duration required
      - Decision to use HRT should be reviewed on a yearly basis to determine whether to continue or discontinue HRT
    - Type of HRT to use depends on patient:
      - Sequential combined HRT most suitable for early menopausal women (*who may still be experiencing irregular menstrual periods*)
      - Continuous combined HRT most suitable for postmenopausal women who have been amenorrheic for 1-2 years
      - Estrogen-only HRT most suitable for women who do not have a uterus (*e.g. post-hysterectomy*)
  - ***Women with premature menopause:***
    - Women experiencing menopause before age of 40 (*e.g. premature ovarian failure, early THBSO*) should be advised to start long-term HRT
      - Such women have not been exposed to the normal length of natural estrogen, hence health risks associated with HRT are not thought to apply until they reach the normal postmenopausal age
    - Type of HRT to use (*same considerations as for treatment for vasomotor symptoms*)

- **Contraindications to use of HRT**
  - ***Women at risk of HRT complications:***
    - Uncontrolled hypertension or diabetes mellitus
    - Significant cardiovascular disease
    - Venous thromboembolism (*current or past*)
    - Liver &/or gallstone disease
  - ***Undiagnosed vaginal bleeding***
  - ***Personal history of breast cancer***

HRT Alternatives for Osteoporosis

- **Selective Estrogen Receptor Modulators (SERMs)**
  - ***Mechanism of action:***
    - Bind to estrogen receptors in various tissues & produce varying effects (*agonistic in certain tissue types & antagonistic in others*)
    - Types of SERMs:
      - Raloxifene (Evista)
      - Tamoxifen
  - ***Drug effects:***
    - Vasomotor: *worsened by raloxifene*
    - Urogenital: *no significant effect*
    - Endometrium: *raloxifene does not have any effect; tamoxifen increases risk of endometrial cancer*
    - Breast: *competitively inhibits estrogen receptors in breast*
    - Bone: *decreases osteoclastic activity (estrogenic effect)*
    - Venous thromboembolism: *increased risk of VTE*
  - ***Clinical indications for use of SERMs:***
    - Raloxifene is FDA-approved for treatment & prevention of osteoporosis
      - Option for women currently on HRT for osteoporosis prevention who would like to discontinue HRT for various reasons
      - Option for women with family history of breast cancer
      - Not a good option for women with prominent vasomotor symptoms (*as raloxifene worsens it*)
    - Tamoxifen is not FDA-approved, but has data which suggests bone benefits (*but data is not as strong as for raloxifene*)

- **Bisphosphonates**
  - ***Mechanism of action:***
    - Specific inhibitors of osteoclasts to allow bone formation to exceed bone resorption, leading to progressive gains in bone mass
    - No significant effects for other menopause-related symptoms & health problems
    - Types of bisphosphonates:
      - Alendronate
      - Risedronate
  - ***Dosing of bisphosphonates:***
    - Alendronate 10mg/day or 70mg/week PO
      - Should be taken on an empty stomach, seated/standing upright for 30 minutes after
    - Risedronate 5mg/day or 35mg/week PO
  - ***Clinical indications for use of bisphosphonates:***
    - Most appropriate initial treatment for women with diagnosed osteoporosis
  - ***Side effects of bisphosphonates:***
    - GI effects (*esophagitis, possibly esophageal cancer*)
    - Osteonecrosis of the jaw
      - Especially in the context of IV use for cancer patients with a preceding dental procedure
    - Atrial fibrillation
    - Atypical femoral fractures (*diaphyseal, subtrochanteric*)

- **Teriparatide (Forteo)**
  - A recombinant form of parathyroid hormone
  - Given as a daily injection in the thigh or abdomen
  - High costs ($20/day) & risk of osteosarcoma limits this treatment to:
    - Very high fracture risk
    - Osteoporosis not responding to bisphosphonates

- **Calcitonin**
  - Given as a nasal spray
  - Less effects on bone compared to bisphosphonates
  - Has a unique role in the acute treatment of osteoporotic fractures, given until acute pain diminishes, after which it may be switched to alternate therapies

- **Strontium Ranelate (Protos)**
  - ***Mechanism of action:***
    - Promotes differentiation of precursors to osteoblasts while inhibiting osteoclastic differentiation
  - ***Therapeutic effects of strontium ranelate:***
    - Reduction of risk for vertebral fractures (37%) & to a lesser extent, non-vertebral fractures (14%) in osteoporotic postmenopausal women
    - Increases BMD in all sites in postmenopausal women both with & without osteoporosis
    - No significant effects for other menopause-related symptoms & health problems
  - ***Side-effects of strontium ranelate:***
    - Diarrhea (*main side-effect*)
    - Nausea, headache
    - Eczema

HRT Alternatives for Menopausal Symptoms

- **Tibolone (Livial)**
  - ***Mechanism of action:***
    - Selective tissue estrogenic activity regulator (STEAR)
    - Has effects on estrogenic, progesteronic & androgenic receptors
  - ***Drug effects:***
    - Vasomotor: *as effective as HRT for improvement*
    - Mood & sexual function: *relieves insomnia, improves mood & sexual function (possibly due to androgenic effect)*
    - Urogenital: *as effective as HRT for improvement*
    - Endometrium: *progesteronic effect (no stimulation, may cause atrophy)*
    - Breast: *similar risk of breast cancer as for estrogen-only HRT; does not increase mammographic density of breast*
    - Bone: *estrogenic effect (good for osteoporosis)*
    - Venous thromboembolism: *similar risk as for HRT*
  - ***Dosing of tibolone:***
    - Tibolone 2.5mg PO once a day
    - Start 1-2 years post-menopause, for up to 5 years
  - ***Clinical indications for use of tibolone:***
    - Serves as an alternative to HRT for treatment of menopausal symptoms where HRT would be indicated normally
    - Has added benefit of improving sexual function & libido compared to HRT

- **Phytoestrogens**
  - Systemic review reveals that there is no convincing evidence for any herbal medicinal products for treatment of menopausal symptoms
  - ***Types of phytoestrogens:***
    - Black cohosh
    - Red clover

- **Anti-depressants**
  - Paroxetine may be an effective & acceptable alternative to HRT in treatment of hot flashes
  - Citalopram alone is an efficacious treatment for perimenopausal & postmenopausal women with depression