3A Women's Health Revision Notes

How to Use

This **isn't** a complete overview of everything that you need to know for the 3A Women's Health module. There are quite a lot of topics that I haven't managed to cover this year, mainly due to time constraints. Because of this, these notes focus on what (I think) are the core topics of the module, with a lot of the key exam content included. Notes in the grey text boxes are probably less likely to come up in exams, but they add explanation and people may find them interesting anyway.

I would recommend making flashcards and testing yourself on what is written here; in my experience, it's a good way to retain the knowledge and is a fairly time-efficient way of getting through lots of content.

Feedback

Please use the link below to give honest feedback so that improvements can be made to future versions:

https://forms.gle/Ro42xS2wo7AXSgda9

- A Grocott, FY1

Contents

Not Covered:

- Postnatal depression
- VTE in pregnancy
- Anaemia in pregnancy
- Rhesus disease
- UTI in pregnancy
- Group B Strep infection
- Gonorrhoea in pregnancy
- Malpresentation
- Multiple pregnancy
- Oligo / Polyhydramnios
- Assisted conception
- Subfertility
- Ovarian torsion
- Lichen sclerosus
- Vulvar cancer
- Vaginal cancer
- Hydatidiform mole
- Adenomyosis
- Menarche
- Endometrial polyps
- Turner's syndrome
- Asherman's syndrome
- Prolactinoma
- PID
- Pre-menopausal syndrome
- Genital tract fistula
- Human sexuality
- Paget's disease of the nipple
- **Genitourinary Medicine**

1. Physiology of Pregnancy

Fertilisation, Early Embryology, Placenta, Maternal Physiological Changes

Oogenesis: *see "Normal Menstrual Cycle" - pp. 35-39*

Fertilisation: Fusion of haploid sperm and oocyte, typically occurring in the **ampulla** of the fallopian tube. This can be broken down into six stages:

1. **Capacitation** - final stage of sperm maturation - involves exposure of receptor sites involved in zona pellucida penetration.
2. **Acrosome reaction** - loss of the acrosome cap on the head of the sperm cell leads to release of lytic enzymes, which allows the sperm to penetrate the zona pellucida.
3. **Adhesion and entry** - cell membranes of sperm and egg fuse, and the head of the sperm if phagocytosed - it then breaks down to release the sperm nucleus.
4. **Cortical reaction** - modification of the zona pellucida to prevent polyspermy, induced by membrane fusion and mediated by cortical granules
5. **Meiosis II** - the oocyte completes meiosis II (which until this point is arrested in metaphase II) to give the second polar body.
6. **Syngamy** - the male and female pronuclei replicate DNA and shed their nuclear membranes as they move toward one another, before aligning at a common metaphase plate and undergoing **mitosis.**

Key Events in Embryonic Development:

- **Day 6-7:** implantation of blastocyst into endometrium
- **Week 3:** gastrulation - formation of trilaminar disc (**endoderm, mesoderm, ectoderm**) from the primitive streak
- **Week 3-8:** beginning of development of organ systems
- **Week 4:** neurulation - development of **neural tube** from the ectoderm
- **Week 23:** generally considered to be the threshold of viability.

Placental Functions:

1. **Exchange:**
    a. Gaseous - oxygen moves readily from maternal to foetal haemoglobin (HbF) due to HbF's higher affinity. CO_2 diffuses from foetal to maternal blood down the concentration gradient
    b. Nutrition - glucose moves from maternal to foetal circulation via facilitated diffusion; both amino acids and free fatty acids also cross from mother to foetus, the former through active transport.

2. **Endocrine**
    a. Human Chorionic Gonadotrophin (hCG) - produced by trophoblast cells - maintains the corpus luteum to allow for sufficient progesterone production until the placenta takes over.
    b. Human Placental Lactogen (hPL) - increases maternal free fatty acid and insulin levels, as well as inducing maternal insulin resistance.
    c. Progesterone - inhibits uterine contractility, thickens endometrium
    d. Oestrogen - stimulates myometrial growth, oxytocin receptor synthesis, and pregnancy-related breast changes.

Formation of the Placenta and Umbilical Cord:

1. Blastocyst implantation on **day 6-7** leads immediately to **trophoblastic invasion** into the highly vascular uterine wall.
2. By mid-late **week 2,** trophoblastic cells invade endometrial capillaries and venules and form **lacunae**, filled with maternal blood. The projections of invading cells are referred to as primary villi - they form branches which become secondary and tertiary villi.
3. Within the villi, cells of the **extraembryonic mesoderm** extend down and form foetal vessels.
4. The functional units of the placenta, **cotyledons,** are formed from **stem villi** and collections of their secondary / tertiary villi. These form the exchange surface between the maternal circulation and foetal circulation.
5. The umbilical cord is formed from a tube of **amniotic membrane** which surrounds the **connecting stalk** and **vitelline duct;** the two umbilical arteries carry deoxygenated blood from foetus to mother, and the single umbilical vein carries oxygenated blood in the opposite direction.

During systole, maternal blood flows out of flaccid invaded spiral arterioles into the **intervillous space** - it is here that it contacts the foetal exchange surface of the chorionic plate, before rejoining the maternal circulation via **collecting venules.** Maternal blood is supplied by the uterine arteries, branches of the internal iliac arteries.

Maternal Physiological Changes:

1. **Cardiovascular:**
    - Total peripheral resistance decreases significantly in early pregnancy, likely due to oestrogen and its effects on nitric oxide.
    - Cardiac output increases by 45% in the first trimester; this is mainly due to increased stroke volume. Cardiac preload is increased because of increased blood volume, which occurs mainly due to activation of the RAAS stimulated by the relative underfilling perceived by the kidneys as a result of the reduced systemic vascular resistance.
2. **Haematological:**
    - Red cell mass increases - this may be due to a combination of increased erythropoietin and human placental lactogen. However, a **physiological anaemia** is seen due to dilution from the even more increased plasma volume.
    - Increased total white cells.
    - Decreased platelet count.
    - Clotting factors VII, VIII, IX and X all increase in pregnancy, leading to a hypercoagulable state.

3. **Renal:**
    - Increased renal blood flow and glomerular filtration rate
    - Increased sodium reabsorption via RAAS to facilitate increased blood volume
    - Lower serum urea and creatinine due to raised GFR.
4. **Respiratory:**
    - Sensitisation of medulla to PaCO2 stimulates increased minute ventilation - this drives a steeper foetal-maternal concentration gradient to remove more foetal CO2.
5. **Immunological:**
    - Foetus avoids 'transplant rejection' through a few mechanisms:
        - General maternal immunosuppression - mechanism unclear.
        - Trophoblast cells, the only direct interface with maternal circulation, are **immunologically inert** and do not express HLA Class I and II molecules (important for antigen presentation).
    - *N.B. there is an interesting paper on this topic that goes way beyond the scope of the 3A exams: Warning, J.C., McCracken, S.A. and Morris, J.M. (2011) 'A balancing act: Mechanisms by which the fetus avoids rejection by the maternal immune system', REPRODUCTION, 141(6), pp. 715–724. doi:10.1530/rep-10-0360.*
6. **Reproductive:**
    - Uterus weight increases from approximately 40-100g to 800-1000g at term.
    - The uterine arteries and their branches undergo hypertrophy and dilation - uterine blood flow increases **tenfold** from pre-pregnancy levels.
    - Ovarian (gonadal) arteries supply a significant portion of the gravid uterus' blood; this is not seen in non-pregnant women.
    - The cervix becomes more vascular, and in the third trimester it loses collagen and accumulates water and glycosaminoglycans to allow for stretching at parturition; the vagina undergoes a similar process. Cervical mucus becomes thicker and eventually forms the **operculum** (mucus plug) to prevent infection.
7. **Breasts:**
    - Ductal proliferation occurs in response to high oestrogen levels.
    - Alveoli (subunits of breast lobules) grow under influence of progesterone and prolactin.
    - Prolactin stimulates milk production from alveolar cells - this is inhibited during pregnancy but facilitated directly after delivery by the sudden drop in oestrogen and progesterone.
8. **Gastrointestinal:**
    - Gastric emptying is slowed and bowel motility is decreased, as progesterone acts as a smooth muscle relaxant. This can lead to gastric reflux and constipation.
9. **Skin:**
    - Increased pigmentation due to raised melanocyte-stimulating hormone levels:
        - Chloasma / Melasma (face)
        - Areola

    - Linea nigra (increased pigmentation of linea alba)
- Striae gravidarum: disruption of collagen fibres due to adrenocortical hormones and mechanical stress.

10. Endocrine:

- Oestrogen and progesterone rise throughout pregnancy.
- Corticotropin releasing hormone (CRH) rises in the third trimester - this may play a role in labour.

Immediate Post-Fertilisation Events:

- **0 - 4 days:** cleavage of zygote into blastomeres, via mitosis; no cell *growth* occurs during this period, so the total volume of the embryo (still contained within the zona pellucida) remains unchanged. At the 8-cell stage, the blastomeres start to segregate into **embryoblast** and **trophoblast** precursors and flatten against the wall of the zona pellucida in a process called **compaction.** Eventually, the entire inner wall is lined by trophoblast cells, which is why the embryoblast is also referred to as the **inner cell mass.**
- **Day 3-4:** upon dividing into 16 cells, the conceptus is now called a morula.
- **Day 5:** blastocyst formation: the morula forms a cavity called a **blastocoel** by actively transporting electrolytes and taking on water via osmosis.
- **Day 5-6:** hatching: lytic enzymes allow the blastocyst to break out of the zona pellucida and hatching into the uterus.
- **Day 6-7:** implantation: blastocyst adheres to the endometrium; endometrial stromal cells differentiate into decidual cells to accommodate the blastocyst in a process called the **decidual reaction.** Additionally, the uterine wall becomes more vascularised. The trophoblast cells divide into the **cytotrophoblast** and **syncytiotrophoblast** (a membrane-less mass of cytoplasm and nuclei), and the latter begins to invade into the uterine wall.

Week 2:

- **Day 8:** the syncytiotrophoblast invades deeper into the uterine wall, assisted by proteolytic enzymes produced by the cytotrophoblast. The entire embryo is drawn into the uterine wall. Meanwhile:
    - The cells of the embryoblast differentiate into **epiblast** and **hypoblast** cells to form the **bilaminar disc.**
    - The formation of the amniotic cavity (between the epiblast and cytotrophoblast) begins.
    - The primary yolk sac (Heuser's membrane) forms when hypoblast cells spread and line the former blastocoel.
- **Day 9:** the embryo is fully implanted **within** the wall, and is surrounded by syncytiotrophoblast.
- **Day 10-11:** extraembryonic mesoderm cells form from Heuser's membrane. At this point, lacunae formed from the invading trophoblastic cells invade into maternal capillaries.
- **Day 11-12:** extraembryonic mesoderm expands.
- **Day 12-13:** the extraembryonic mesoderm splits into two layers, leaving a space which forms the chorionic cavity. This cavity grows rapidly to become the dominant constituent of the embryo by day 13 - at this point, the bilaminar disc, amnion, and yolk sac (surrounded by extraembryonic mesoderm) are suspended within the chorionic cavity by the connecting stalk.

Sources and Further Reading:

- Symonds, I. *et al.* (2019) '2,3,4', in *Essential Obstetrics and Gynaecology*. Elsevier, pp. 13–54.
- Schoenwolf, G.C. and Larsen, W.J. (2020) *Larsen's human embryology*. Philadelphia: Elsevier.

2. Management of Uncomplicated Pregnancy

Screening, Routine Appointments

There are **eight** routine appointments for parous women, and **eleven** for nulliparous women (additional three are highlighted). There is also the possibility of a 41 week appointment if the woman has not yet delivered.

1. **Before 10+0 weeks -** Booking visit:
    - Height and weight measurement
    - Screening offered (see below)
    - Blood pressure and urinalysis
    - Assess risk for GDM, pre-eclampsia, FGR, VTE, FGM
    - Offer **vaccines:** influenza at any time as required, pertussis at 16-30 weeks
2. **11+2 to 14+1 weeks -** Dating scan:
    - Estimate gestational age
    - Assess for multiple pregnancy
    - Foetal anomaly screening
3. **16 weeks:**
    - Blood pressure and urinalysis
4. **18+0 to 20+6 weeks -** Anatomy scan:
    - More detailed scan to assess for various anatomical anomalies e.g. anencephaly, meningocele, exomphalos - part of **screening programme.**
    - Assess position of placenta (low-lying, praevia)
    - Foetal movements typically felt at this point
5. **25 weeks:**
    - Blood pressure and urinalysis
    - Symphyseal-fundal height (SFH)
6. **28 weeks:**
    - Height and weight, blood pressure and urinalysis, SFH
    - Anti-D prophylaxis (first dose) for Rhesus negative women
7. **31 weeks:**
    - Blood pressure and urinalysis, SFH
8. **34 weeks:**
    - Blood pressure and urinalysis, SFH
    - Anti-D prophylaxis (second dose) for Rh-ve women.
9. **36 weeks:**
    - Blood pressure and urinalysis, SFH
    - Palpate abdomen to assess for breech presentation
10. **38 weeks:**
    - Blood pressure and urinalysis, SFH
    - Discuss possibility of prolonged pregnancy and its management
11. **40 weeks:**
    - Blood pressure and urinalysis, SFH

12. 41 weeks:
- Blood pressure and urinalysis, SFH
- Induction of labour offered

Screening in Pregnancy:

There are three elements of pregnancy screening in the UK: infectious diseases, sickle cell & thalassaemia, and foetal anomaly. All are offered at the **booking visit.**

1. **Infectious Diseases**
   - HIV (25% risk MTC transmission if untreated)
   - Syphilis (risk of miscarriage, stillbirth, congenital syphilis)
   - Hepatitis B (70-90% risk MTC transmission if HBeAg positive)
2. **Sickle Cell & Thalassaemia**
   - Sickle cell disease (immunosuppression, risk of miscarriage, anaemia, vaso-occlusive crises)
   - Thalassaemia (anaemia)
3. **Foetal Anomaly**
   - Down's syndrome (trisomy 21), Edwards' syndrome (trisomy 18), Patau's syndrome (trisomy 13) all screened for at **booking visit** with the **combined test:**
     1. Maternal age (e.g. chance of baby with T21 is 1/1500 at 20yo vs 1/100 at 40yo)
     2. beta-hCG, PAPP-A (pregnancy-associated plasma protein-A)
     3. USS scan (11+2 - 14+1) - nuchal translucency (NT), crown-rump length (CRL)
   - If mother is late-booking (**>14+0**), the **quadruple test** is used to screen for T21:
     - Maternal age, beta-hCG, AFP, inhibin-A, unconjugated oestriol
   - If **high chance** (>1/150), there are three options:
     1. No further testing
     2. Non-invasive prenatal testing (NIPT) - placental cell-free DNA
     3. Prenatal diagnosis (PND) - chorionic villus sampling (11-14 weeks), amniocentesis (15+ weeks)

Note - CRL must be 45-84mm to be eligible for combined test - if too low, then wait // too high, offer quadruple test.

T21: high beta-hCG, low PAPP-A, high NT (>3.5mm) // low AFP, high inhibin-A, low unconjugated oestriol
T18: low beta-hCG, low PAPP-A, high NT
T13: low beta-hCG, low PAPP-A, high NT

Sources and further reading:

- NICE Guideline 201 (NG201): Antenatal Care
- NHS infectious diseases in pregnancy screening programme: GOV.UK
- NHS fetal anomaly screening programme (FASP): GOV.UK
- Screening for Down's Syndrome, Edwards' Syndrome and Patau's Syndrome: GOV.UK

3. Antepartum Haemorrhage

Low-lying Placenta, Vasa Praevia, Placenta Accreta Spectrum, Placental Abruption

Placenta Praevia:

Definition:

- **Placenta praevia:** placenta covers the internal os of the cervix.
- **Low-lying placenta:** placenta lies within 20 mm of the internal os (but does not cover it).
- Note: previously different grades were applied to degree of os coverage / proximity to os. This has recently been simplified to the above.

Aetiology and Pathophysiology:

- Occurs when blastocyst implants in the lower segment of the uterus.
- Bleeding occurs due to placental trauma (or can be spontaneous):
    - Sexual intercourse
    - Vaginal examination
    - Cervical dilatation in labour

Risk Factors:

- Previous caesarean section
- IVF pregnancy
- Previous placenta praevia

Presentation:

- Painless antepartum haemorrhage (PV bleeding after **24 weeks** gestation; <24 weeks = threatened miscarriage, >24 weeks = antepartum haemorrhage) with a **soft / non-tender uterus.**

Investigations:

- Usually diagnosed when asymptomatic at the **20 week anatomy scan.**
    - Follow up scan indicated at **32 weeks** if praevia / low-lying.
    - Further follow up scan at **36 weeks** if not resolved.
- Otherwise diagnosed when symptomatic by transvaginal ultrasound.

Investigation of antepartum haemorrhage:

1. Full blood count, group + save
2. Kleihauer test (for fetomaternal haemorrhage) in Rhesus -ve women
3. Transvaginal / transabdominal ultrasound

4. CTG for foetal monitoring

Differentials for antepartum haemorrhage:

- Placental abruption
- Onset of labour
- Cervical ectropion
- Vasa praevia

Management:

- **Antenatal:**
  - Conservative management with follow up scanning as described above.
    - PP often spontaneously resolves as the uterus grows and lower pole stretches in later pregnancy.
  - Single course of **oral corticosteroids** is indicated between 34 and 36 weeks.
- **Delivery:**
  - Placenta praevia: Aim to deliver by **caesarean section** at 36-37 weeks for uncomplicated placenta praevia.
    - High risk of massive obstetric haemorrhage (12x background risk).
  - Low-lying placenta: trial of labour is offered, particularly if 10-20mm from os; caesarean section is also offered.

Vasa Praevia

Definition:

- Malformation of foetal vessels (umbilical vein + arteries), leading them to run through placental membranes instead of the umbilical cord.

Pathophysiology:

- Exposed foetal vessels are liable to rupture and haemorrhage in labour due to cervical dilatation or movement of the presenting part, particularly if they overlie the cervical os.

Epidemiology and Risk:

- Uncommon, estimated between 1 in 1200 and 1 in 5000 pregnancies
- If undiagnosed, mortality is very high: if SROM occurs, foetal mortality is 60%.

Presentation:

- Antepartum haemorrhage; resulting in antenatal diagnosis
- Labour: vaginal bleeding after SROM at onset of labour with foetal distress.

Investigations:

- Antenatal: transvaginal ultrasound scan
- Labour: vaginal examination (palpable foetal vessels overlying os).

Management:

- Antenatal detection:
    - Corticosteroids at 32 weeks due to high risk of prematurity
    - Elective CS (34-36 weeks, although optimal timing is contested).
- Undetected:
    - Category 1 caesarean section.

Classification of vasa praevia:

Type 1 - foetal vessel connected to velamentous* umbilical cord.
Type 2 - foetal vessel connected to succenturiate** placental lobe.

*velamentous cord = cord inserted into foetal membranes, not placenta
**succenturiate lobe = accessory lobe connected to main body of the placenta

Placenta Accreta Spectrum:

Definition:

- Range of pathologic adherence of the placenta (accreta, increta, percreta).
    - Placenta **accreta:** abnormal invasion of the placental villi through the decidua leading to **adherence to** the myometrium.
    - Placenta **increta:** abnormal invasion of the placental villi through the decidua and **into** the myometrium, through to the outer **serosa.**
    - Placenta **percreta:** abnormal invasion of the placental villi through the entire uterine wall; it may then invade other organs.

Pathophysiology and Aetiology:

- Defective endometrial-myometrial interface (usually due to scarring) causes failure of **normal decidualisation** - this allows the placental villi (trophoblast) to invade further.
- This leads to massive obstetric haemorrhage in labour if not detected and managed appropriately.

Risk Factors:

- Previous caesarean section (commonest)
- Other uterine surgery
- Increased maternal age

Presentation:

- Typically detected in antenatal period:
    - Women with previous CS found to have **low-lying placenta** are specifically screened with ultrasound scanning.

Management:

- Caesarean section at 35-37 weeks.
    - This may be *uterus-preserving* if the accreta is limited and placenta can be safely separated.
    - Otherwise, RCOG guidelines recommend caesarean section **hysterectomy** with placenta left in situ in the uterus.

Placental Abruption:

Definition:

- Premature separation of the placenta from the decidua.

Aetiology and Pathophysiology:

- Occurs due to a combination of chronic processes and an acute trigger.
- Chronic processes such as placental thrombosis and infection cause hypoperfusion, placental infarction, and **shallow trophoblast invasion.**
    - This predisposes the placenta to premature separation.
- This is followed by a non-specific acute trigger (mechanical force within the abdomen) which causes the poorly adherent placenta to separate from underlying decidua.
- Separation causes rupture of maternal decidual vessels - blood can then accumulate between placenta and decidua.
- Note - In normal placental separation, bleeding is stemmed by placental contraction; this is not possible when the foetus is in situ and the myometrium is stretched.

Further Pathophysiology:

- Decidual bleeding causes excess thrombin production (due to tissue factor AKA clotting factor 3-mediated activation of the extrinsic clotting pathway).
- This leads to enhanced matrix metalloproteinase expression and endothelial injury, alongside release of proinflammatory cytokines.
- Thrombin has been shown to have **uterotonic** effects - this would explain uterine contraction and rupture

of membranes in response to abruption.
- High levels of systemic thrombin can lead to a consumptive coagulopathy i.e. **disseminated intravascular coagulation.**

Risk Factors:

1. Previous abruption (strongest risk factor)
2. Pre-eclampsia
3. Abdominal trauma
4. Smoking
5. Cocaine use

Types:

1. Concealed - blood remains behind the placenta, preventing a PV bleed.
2. Revealed - blood escapes from behind the placenta, causing a PV bleed.
3. Mixed - clot forms behind placenta alongside PV bleed.

Presentation:

- Antepartum haemorrhage.
- Abdominal pain.
- 'Woody' hard, contractile uterus

Investigations:

- See *investigation of antepartum haemorrhage*.
- Diagnosed **clinically** - ultrasound is not reliable for providing a diagnosis.

Management:

- **First Line:** category 1 caesarean section

Sources and Further Reading:

- Jauniaux, E., Alfirevic, Z., Bhide, A., Belfort, M., Burton, G., Collins, S., Dornan, S., Jurkovic, D., Kayem, G., Kingdom, J., Silver, R. and Sentilhes, L. (2018). Placenta Praevia and Placenta Accreta: Diagnosis and Management. BJOG: An International Journal of Obstetrics & Gynaecology, [online] 126(1), pp.e1–e48. doi:https://doi.org/10.1111/1471-0528.15306.
- BMJ Best Practice. [online] Available at: https://bestpractice.bmj.com/topics/en-gb/667/aetiology [Accessed 13 Sep. 2023].
- Royal College of Obstetricians and Gynaecologists (2011). Antepartum Haemorrhage Green-top Guideline No. 63. [online] Available at: https://www.rcog.org.uk/media/pwdi1tef/gtg_63.pdf.
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- Brandt, J.S. and Ananth, C.V. (2023). Placental abruption at near-term and term gestations: pathophysiology, epidemiology, diagnosis, and management. American Journal of Obstetrics and Gynecology, [online] 228(5). doi:https://doi.org/10.1016/j.ajog.2022.06.059.

4. Small for Gestational Age (SGA)

Causes and Management

Definition:

- Estimated foetal weight less than the **10th centile**.
    - Differs from intrauterine / foetal growth restriction (IUGR / FGR), which implies a **pathological** restriction of full genetic growth potential (RCOG definition).
    - Severe SGA is defined at EFW less than 3rd centile.

Foetal Measurement:

- Surveillance of foetal size can be performed with the following measurements:
    1. Symphyseal fundal height (measured regularly at routine antenatal appointments from 24+0 onwards).
    2. Foetal abdominal circumference.
    3. Femur length.
    4. Head circumference / biparietal diameter.
    5. Liquor volume / amniotic fluid index (normal = 5-25cm)

Risk Factors:

- **Major** - odds ratio >2.0 for SGA:
    1. Maternal age >40
    2. Smoker >11 cigarettes per day.
    3. Maternal cocaine use in pregnancy.
    4. Maternal daily vigorous exercise
    5. Previous SGA baby
    6. Previous stillbirth
    7. Maternal SGA
    8. Paternal SGA
    9. Chronic hypertension
    10. Diabetes with vascular disease
    11. Renal impairment
    12. Antiphospholipid syndrome
- **Minor** risk factors include nulliparity and previous pre-eclampsia.
- Further **major** risk factors that may arise during pregnancy include **pre-eclampsia, unexplained APH** and **low maternal weight gain.**

Investigations:

- Routine monitoring:
    - **First Line:** SFH measurement
    - SFH is plotted on a **customised growth chart.**
        - Adjusted to maternal height, weight, parity and ethnicity.
    - **Second Line:** USS scan (see *Foetal Measurement*).
- Any single **major risk factor:**
    - Serial (2 weekly) USS and umbilical artery Doppler from 26-28 weeks.
- Any single SFH <10th centile **or** slow / static growth:
    - Serial USS and umbilical artery Doppler.

Further Investigations into SGA:

- Umbilical artery Doppler:
    - Normal low-resistance placenta allows continuous positive flow from foetus to placenta throughout the cardiac cycle (i.e. in systole and diastole).
    - If end-diastolic flow is slowed / reversed, this suggests increased placental resistance, which implies placental compromise (for example due to pre-eclampsia) and is predictive of SGA.
- CMV and toxoplasmosis screening:
    - Indicated in severe SGA.
- MCA Doppler:
    - Measured in comparison to umbilical artery flow.
    - Hypoxic foetus diverts blood flow to the brain to spare cerebral function - this increases MCA diastolic flow in relation to UA diastolic flow.
    - MCA flow also increases in foetal anaemia.

Management:

- RCOG recommends umbilical artery Doppler as the **primary surveillance tool** for an SGA foetus.
- Current guidelines state, in general:
    - An SGA foetus should be delivered by **caesarean section** before **37 weeks** gestation.

Sources and Further Reading:

- Royal College of Obstetricians and Gynaecologists (2013). The Investigation and Management of the Small-for-Gestational-Age Fetus Green-top Guideline No. 31. [online] Available at: https://www.rcog.org.uk/media/t3lmjhnl/gtg_31.pdf.
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5. Hypertensive Disease of Pregnancy

Pregnancy-induced hypertension, Pre-eclampsia, Eclampsia, HELLP syndrome

Definition:

- **PIH:** new-onset hypertension, developing after **20 weeks** gestation.
- **Pre-eclampsia:** new-onset hypertension associated with proteinuria **or** systemic features*, developing after **20 weeks** gestation.

Pathophysiology and Aetiology:

- Systemic reaction to abnormally invasive placenta - *see text box.*

Presentation:

- **PIH:**
  - asymptomatic, headaches, blurred vision
- **Pre-eclampsia:**
  - asymptomatic, headaches, upper abdominal pain, blurred vision, reduced foetal movements // brisk reflexes, systemic hypertension

Investigations:

- **Initial:**
  - blood pressure measurement *(140/90mmHg, +30/+15 in pre-existing hypertension)*
  - urinalysis *(protein **2+** on dipstick, >30mg/mmol protein-creatinine ratio)*
  - sFLT : PlGF ratio *(>85 is diagnostic)*
- **Further:**
  - Bloods: FBC, U+E, LFT twice-weekly
  - Ultrasound scan: to assess foetal growth and AFI, 2-weekly
  - Umbilical Artery Doppler velocimetry: assess placental perfusion, 2-weekly
  - Cardiotocography: upon diagnosis, + if RFM, PV bleed, abdo pain, deterioration
  - Auscultation of foetal heart: offer at every appointment

Management:

- **Prevention:** 75mg aspirin OD from 12/40 onwards.
- First Line: labetalol (beta-blocker)
- Second Line: nifedipine
- Third Line: methyldopa
- **Plus:** consider early delivery at **37 weeks**

Complications:

- **Eclampsia:** Tonic-clonic seizures in presence of pre-eclampsia
  - **Investigations:** as above

    - **Management:** intravenous **magnesium sulphate**, emergency delivery via LSCS.
- **HELLP syndrome:** syndrome of **H**aemolysis, **E**levated **L**iver enzymes, **L**ow **P**latelets.
    - **Investigations:** as above
    - **Management:** as above, plus expedite delivery
- Placental abruption (see pp x-y)
- Disseminated intravascular coagulation

Diagnostic criteria of severe pre-eclampsia requiring urgent hospital admission:

1. Systolic BP > 160mmHg
2. Severe headaches, visual scotomata, N+V, oliguria, epigastric pain, pulmonary oedema
3. Rising creatinine, elevated liver enzymes, thrombocytopenia

Further pathophysiology:

1. Defective remodelling (adaptation from low to high flow vessels due to invasion of extravillous trophoblast cells after week 10) of maternal spiral arteries leads to inadequate oxygenation of trophoblastic tissue and subsequent **oxidative stress.**
    a. Stressed trophoblast releases pro-inflammatory cytokines + other factors including sFLT into maternal circulation
    b. Pro-inflammatory cytokines disrupt maternal endothelium, leading to systemic inflammatory response and reduced blood flow to maternal organs.
    c. **Hypertension** is thought to result from impaired renal blood flow and reduced glomerular filtration, as well as elevated sFLT (which reduces maternal endothelial nitric oxide production by binding to and impairing VEGF).
    d. **Proteinuria** arises from glomerular changes including disruption of the basement membrane and podocytes - the mechanism of this is not fully understood.
2. Defective remodelling directly results in placental hypoperfusion, leading to inadequate nutrient delivery to the developing foetus, causing IUGR.
3. Systemic features arise from maternal endothelial dysfunction and resulting vasodilatation, which affect maternal organs in a similar way to hypovolaemic shock.
    a. **Seizures** in eclampsia are thought to occur due cerebral vasospasm.

Incidence and risk factors:

- Worldwide incidence estimated at 4.6% of pregnancies
- Risk factors include: nulliparity, previous pre-eclampsia, family history, BMI >30, age >40, multiple pregnancy, subfertility.

Sources and Further Reading:

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6. Maternal Medicine

Obstetric Cholestasis, Gestational Diabetes

Obstetric Cholestasis:

Definition:

- Obstetric condition causing increased serum bile acids and hepatic dysfunction.

Aetiology and Pathophysiology:

- Specific cause remains unknown - genetic susceptibility and response to increased oestrogen are established.
    - Oestrogen inhibits hepatic bile acid receptors in genetically susceptible women, leading to impaired bile acid homeostasis.
- Leads to deposition of **bile salts** in various tissues including **skin** and **placenta.**
- **Skin** deposition leads to pruritus (itching).
- **Placental** deposition causes raised foetal bile acid levels - this can cause acute foetal deterioration - thought to be either **foetal arrhythmia / cardiomyopathy** or **placental vasoconstriction.**

Presentation:

- Pruritus (sparing hands and face).
- Excoriations (scratch marks).

Investigations:

- Serum bile acids (raised above 19 micromol/L)
- Liver function tests

Management:

- **First Line:** emollient **plus** antihistamine
- **Second Line:** ursodeoxycholic acid
- **Plus:** consider expedited delivery
    - Dependent on serum bile acid concentration
    - For example: delivery at 35-36 weeks for women with peak bile acid concentration >100 micromol/L due to **increased stillbirth risk.**

Gestational Diabetes Mellitus (GDM):

Definition:

- Chronic hyperglycemia and insulin resistance due to pregnancy.

Aetiology and Pathophysiology:

- In normal pregnancy, local and placental hormones stimulate peripheral insulin resistance - the purpose of this is to spare glucose for delivery to the developing foetus.
- This is accompanied by lipolysis and gluconeogenesis, further increasing free fatty acid and glucose levels.
- Hypertrophy and hyperplasia of pancreatic beta-cells occurs to protect maternal glucose homeostasis.
- Failure of this protective mechanism due to beta-cell dysfunction, in combination with insulin resistance, leads to GDM.

Complications:

- **Maternal:**
    - Pre-eclampsia
    - Chronic type 2 diabetes (60%)
    - Increased risk of cardiovascular disease
- **Foetal:**
    - Macrosomia, leading to shoulder dystocia
    - Neonatal hypoglycaemia (due to dependence on maternal hyperglycaemia raising endogenous foetal insulin).
    - Childhood obesity (2x background risk).
    - Increased risk of metabolic syndrome and associated complications in later life.

Risk Factors:

- BMI > 30
- Previous macrosomia
- Previous GDM
- Family history of diabetes mellitus
- Ethnicity with high prevalence of diabetes.

Diagnosis:

- Women with **any one** of the above risk factors should be screened for GDM at 24-28 weeks.

- Women with **glycosuria** detected at a routine antenatal appointment should be screened at any time in their pregnancy.
- **First Line:** oral glucose tolerance test (OGTT)
    - Fasting blood glucose, followed by 75g carbohydrate drink, with a second blood glucose test **2 hours** later.
- **Diagnostic Criteria:** 5678
    - Fasting plasma glucose > 5.6mmol/L **or**
    - 2 hour glucose > 7.8mmol/L

Management:

- **First Line:** 2 week trial of diet, exercise and self-monitoring glucose levels
- **Second Line:** if not successful, **metformin**
- **If FPG >7.0:** start **insulin** immediately.
- **Plus:** extra growth scans at 28, 32, 36 weeks.

Sources and Further Reading:

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7. Labour and Parturition

Physiology, Management of Uncomplicated Labour, Induction

Labour is divided into three stages:

1. **First Stage** - onset defined by **progressive** contractions and cervical changes
    a. Latent first stage - effacement (thinning) of cervix, dilatation to 3cm
    b. Active first stage - dilatation from 3 - 10cm (i.e. fully dilated)
2. **Second stage** - from full dilation to delivery of the baby
    a. Passive second stage - head descends down pelvis
    b. Active second stage - mother bears down
3. **Third stage** - from delivery of baby to delivery of placenta and membranes
    - Should occur within 30 minutes of delivery of the baby
    - Can be **physiological** (i.e. no intervention) or actively managed (oxytocin injection after delivery of anterior shoulder).

Note - passage of the operculum (mucus plug) and spontaneous rupture of membranes (SROM) *should* coincide with the onset of labour but are not defining features.

Myometrial Activation: uterine contractions become synchronised and coordinated at term.

1. Endocrine cascade triggered by foetus leads to increased maternal oestrogen and decreased progesterone. Other contributing factors include uterine stretch, cortisol and the Ferguson reflex.
2. This leads to expression of CAPs (contraction-associated proteins) and increased production of oxytocin and prostaglandins.
3. CAPs increase expression of oxytocin receptors, prostaglandin receptors, gap junction proteins and ion channels to facilitate contractions.

- This is heavily simplified - the idea is that both agonists and receptors are increased to initiate labour.

Physiology of Uterine Contraction:

The uterine muscle contracts due to action potential spread; these action potentials open L-type calcium channels, increasing intracellular calcium and initiating downstream actin-myosin sarcomere contraction. The duration of a contraction is directly related to intracellular calcium levels; calcium-channel opening is increased by prostaglandin F2-alpha and oestrogen.

The **mechanism** of the second stage of labour can be broken down into seven stages:

1. **Descent** - the baby's head (providing it is in cephalic presentation) descends deeper into the pelvis until it is **no longer palpable** on abdominal examination.
2. **Flexion** - the baby's head flexes (chin to chest) to give the narrowest (suboccipitobregmatic) diameter.
3. **Internal rotation** - baby's occiput rotates anteriorly from the lateral position to give the normal **occipito-anterior** position.

4. **Extension** - baby's occiput contacts the maternal pubic rami - it then extends and crowns
5. **Restitution** - baby's occiput re-aligns with its shoulders, which lie in between the anterior-posterior and lateral positions
6. **External rotation** - baby's shoulders rotate into anterior-posterior position (i.e. perpendicular to mother's). At this point, the baby's head is delivered - it is aligned with its shoulders, so the face looks laterally at the mother's thigh.
7. **Delivery of shoulders** - the anterior shoulder is delivered first from beneath the pubic ramus; the head is then gently lifted anteriorly to deliver the posterior shoulder. The rest of the baby's body rapidly follows.

Monitoring in Labour:

Initial Assessment:

- Take a history, assess for risk factors, assess for pain.
- Pulse, blood pressure, respiratory rate, urinalysis
- Abdominal palpation to determine lie, presentation, engagement, contraction strength.
- Vaginal examination to determine station, position, cervical effacement and dilatation, presence or absence of membranes, caput or cranial moulding.

Progression of labour, foetal and maternal wellbeing are all recorded on a **partogram.** The measurements recorded are:

1. **Progress:** cervical dilatation, descent, contractions (frequency and duration)
2. **Foetal wellbeing:** heart rate*, amniotic fluid (liquor)
3. **Maternal wellbeing:** pulse, blood pressure, temperature, urinalysis

Heart rate can be monitored by **intermittent auscultation** with a Doppler probe (in low risk deliveries) or continuously with a cardiotocograph (CTG, in higher risk deliveries). CTG readouts can be interpreted as follows:

- **Normal:** no non-reassuring features
- **Suspicious:** one non-reassuring feature
- **Pathological:** two non-reassuring features **or** one abnormal features

Reassuring features of the CTG:

- Baseline heart rate: 110-160
- Decelerations (drops of 15 bpm for 15s): absent
- Accelerations (increases of 15 bpm for 15s): present
- Baseline variability: 5-25 bpm

	Baseline Rate	Accelerations	Decelerations	Variability
Non-reassuring	100-109 / +20 from start of labour	Absent	Repetitive variable for <30 mins / variable for <30 mins / repetitive late for 30 mins	<5 for 30-50 mins / >25 for <10 mins
Abnormal	<100 / >160	Absent	Repetitive variable with concerning characteristics >30 mins / repetitive late >30 mins / 3 min bradycardia	<5 for 50 mins / >25 for >10 mins / sinusoidal pattern

Analgesia in Labour:

- **Non-pharmacological:** breathing and relaxation techniques / use of birthing pool
- **Non-regional:** Entonox ('gas and air' - 50:50 mix of nitrous oxide and oxygen), intramuscular opioids e.g. diamorphine or morphine
- **Regional:** Epidural - local anaesthetic e.g. bupivacaine combined with fentanyl bolused into L3-4 epidural space, where it acts upon nerve roots to provide analgesia. N.B. a 'passive hour' without active pushing upon full dilatation is required.

Induction of Labour

Labour can be induced artificially, and is usually done so for the following indications:

1. Prolonged pregnancy >41 weeks
2. Preterm prelabour rupture of membranes (usually offered at 37+0)
3. Term prelabour rupture of membranes (offer 24hrs expectant management as well)
4. Maternal request
5. Maternal health issues e.g. pre-eclampsia, obstetric cholestasis
6. Intrauterine foetal death (IUFD)

Methods:

- Membrane sweep: finger passed through cervix to separate part of the **chorionic membrane** from the **decidua;** offered from 39+0.
- Bishop Score <6: prostaglandin E2 pessary (dinoprostone) **or** osmotic dilator
- Bishop Score >6: amniotomy (artificial rupture of membranes) +/- oxytocin infusion.

Sources and further reading:

- Symonds, I. and Arulkumaran, S. (2019) '11. Management of labour', in *Essential Obstetrics and Gynaecology*. Elsevier, pp. 155–183.
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- NICE Guideline CG190: Intrapartum care for healthy women and babies
- NICE Guideline NG207: Inducing labour
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8. Problems in Labour

Delay in Labour, Shoulder Dystocia, Instrumental Delivery, Caesarean Section

Delay in Labour:

Definition:

- **First Stage:** cervical dilatation of less than 2cm in 4 hours.
- **Second Stage:**
  - Nulliparous: >2 hour duration of second stage of labour.
  - Multiparous: >1 hour duration of second stage of labour.
- **Third Stage:**
  - Actively managed (oxytocin injection): >30 minutes without delivery of placenta.
  - Physiological: >60 minutes without delivery of placenta.

Pathophysiology and Aetiology:

- The 'Three Ps' of delayed labour are the **P**ower, **P**assenger and **P**assage.
- **Power:**
  - Uterine contractions - deviation from normal (i.e. 3-5 contractions of 30 seconds duration per 10 minutes).
- **Passenger:**
  - Size of foetus (head diameter, shoulder diameter etc.)
  - Foetal presentation (cephalic: vertex, brow, face vs breech)
  - Foetal position (occipito-anterior (normal), occipito-posterior, occipito-transverse)
- **Passage:**
  - Cephalopelvic disproportion

Investigations:

- Diagnosed by regular foetal monitoring in labour.
- Aberrant foetal position can be diagnosed on vaginal examination.

Management:

- **First Stage:**
  - Membranes intact - consider **amniotomy.**
  - Consider **oxytocin** infusion - requires continuous foetal monitoring (CTG).
- **Second Stage:**
  - Consider oxytocin infusion.
  - Offer **expedited delivery** i.e. instrumental delivery or caesarean section if vaginal delivery is improbable.
- **Third Stage:**
  - Controlled cord traction, IM oxytocin / ergometrine.

Shoulder Dystocia:

Definition:

- (RCOG) Vaginal cephalic delivery that requires additional obstetric manoeuvres to deliver the foetus after the head has delivered and gentle traction has failed.

Aetiology and Pathophysiology:

- Discrepancy between size of foetal shoulders and maternal pelvic inlet leads to impaction:
    - Anterior shoulder behind maternal pubic symphysis (commonest).
    - Posterior shoulder behind maternal sacral promontory (more rare).
- Delay in delivery can result in **hypoxic ischaemic encephalopathy (HIE)** due to compression of the umbilical cord against the maternal pelvis.
- Another notable complication is **brachial plexus injury** resulting in Erb's palsy (C5-6) or less commonly Klumpke's palsy (C8-T1).

Risk Factors:

1. Previous shoulder dystocia
2. Macrosomia (foetal weight > 4500g)
3. Maternal diabetes mellitus
4. High maternal BMI
5. Induction of labour
6. Prolonged labour.

Diagnosis:

- **Signs** include:
    - Difficulty delivering face / chin
    - Turtle-neck sign (head retracts into birth canal)
    - Failure of restitution
    - Failure of shoulder descent.
- Definitive diagnosis is made when **normal axial traction** cannot deliver the baby's body after the head has been delivered.

Management:

- **First Line:**
    1. McRoberts' manoeuvre (mother hyperflexes hips, bringing her thighs to her abdomen) **plus**
    2. Suprabupic pressure (to disimpact anterior shoulder) **plus**
    3. Discourage pushing (to prevent further impaction.
- **Second Line:**
    1. Deliver posterior arm

2. Attempt internal rotation manoeuvres.
3. If above fails - **all fours position** and repeat manoeuvres.

- **Third Line options (rare):**
  - Cleidotomy
  - Symphysiotomy
  - Zavanelli manoeuvre.

Instrumental Delivery:

Background:

- AKA assisted vaginal birth (by forceps or vacuum).
- 10-15% of deliveries in the UK; ⅓ of first deliveries for nulliparous women.

Types:

- Forceps delivery:
  - Interlocking blades fit around the baby's head and guide it down the birth canal, typically alongside medio-lateral episiotomy.
- Vacuum delivery:
  - Suction cup adheres to the baby's head to assist with delivery.

Assisted vaginal birth classification:
- Outlet - visible foetal scalp, skull has reached perineum, rotation less than 45 degrees.
- Low Cavity - station +2cm but not reaching perineum.
- Mid Cavity - less than 1/5th palpable abdominally, station +1 to 0cm

Forceps and Vacuum:
- Assisted deliveries require either **non-rotational** or **rotational** (if position is occipito-posterior or occipito-transverse) instruments.
- **Non-rotational:**
  - Neville Barnes forceps (low-cavity)
  - Simpson's forceps
  - Wrigley forceps (outlet, also used in caesarean sections)
  - Anterior cup
- **Rotational:**
  - Kjelland's forceps
  - Posterior cup e.g. Kiwi

Indications:

1. Suspected foetal compromise
2. Delayed second stage
3. Maternal exhaustion / distress
4. Medical contraindication to Valsalva

Risks and Complications:

- Forceps:
    1. Vaginal trauma
    2. Postpartum haemorrhage
    3. Obstetric anal sphincter injury (3rd degree tear)
    4. Facial / scalp laceration
- Vacuum:
    1. Vaginal trauma
    2. Postpartum haemorrhage
    3. OASI
    4. Facial / scalp laceration
    5. Retinal haemorrhage
    6. Cephalohematoma
    7. Subgaleal haemorrhage

Obstetric Injuries:

- 1st Degree Tear: skin only
- 2nd Degree Tear: perineal muscle
- 3rd Degree Tear: anal sphincter complex
    - Type A = less than 50% external AS
    - Type B = more than 50% external AS
    - Type C = internal and external AS injury
- 4th Degree: anorectal epithelium

Caesarean Section:

Classification of Urgency:

- Category 1 - within 30 minutes of decision - **immediate threat to life** of woman or foetus e.g. pathological CTG, placental abruption.
- Category 2 - within 75 minutes of decision - maternal / foetal compromise, **not immediately life-threatening** but birth must be expedited.
- Category 3 - no compromise, early birth indicated.
- Category 4 - elective.

Indications:

- Breech presentation (resistant to external cephalic version).

- Placenta praevia
- Placenta accreta spectrum
- Maternal choice
- Emergency: foetal bradycardia, abruption, uterine rupture, cord prolapse, foetal pH < 7.20, failure of instrumental delivery.

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9. Preterm Labour

(Preterm) Prelabour Rupture of Membranes (PROM, P-PROM)

Preterm Labour:

Definition:

- Onset of labour before 37 weeks gestation.

Aetiology and Pathophysiology:

- Similar mechanism to normal labour - probably due to:
    - Premature uterine stimulation
    - Premature withdrawal of pro-quiescent factors.
- Generally dictated by an inflammatory process causing **prostaglandin release**, such as:
    1. Intrauterine infection
    2. Placental ischaemia / decidual haemorrhage
    3. Uterine stretch
    4. Foetal / maternal stress

Further Pathophysiology:

- Intrauterine infection - host inflammatory mediators vs infection trigger labour.
- Uterine stretch (multiple gestation, polyhydramnios): myometrial stretch induces **gap junction formation**, as well as increasing **oxytocin receptors, inflammatory cytokines** and **prostaglandins.**
- Uteroplacental ischaemia (spiral artery maladaptation, microthrombosis, antepartum haemorrhage) - thrombin activation leads to uterine contraction.
- Foetal / maternal stress - activation of hypophyseal-pituitary-adrenal axis leading to increased ACTH release.
- Foetal fibronectin dissolution - extracellular matrix protein, adheres decidua to chorion; its breakdown allows their separation.

Prophylactic Treatment:

- Women with a history of **previous preterm birth** and **cervical length <25mm** are offered treatment with:
    - Vaginal progesterone **or**
    - Cervical cerclage (suture)

Diagnosis and Investigations:

- As in term labour:
    - History, abdominal and vaginal examination, observations, analgesia
- **Plus:**
    - Speculum examination to assess for P-PROM

    - Transvaginal ultrasound to measure cervical length **or** foetal fibronectin testing

Management:

- **First Line:** maternal corticosteroids (to aid foetal lung maturation):
    - Indicated if labour before **34 weeks**
    - Offer **betamethasone** or **dexamethasone,** 2 doses 12 hours apart.
- **Plus:** magnesium sulphate (neuroprotection - reduces incidence of intraventricular haemorrhage)
    - Indicated if labour before **30 weeks** (can be given up to 34 weeks)
- **Plus:** tocolysis (suppression of contractions)
    - Offer **nifedipine** before 34 weeks gestation.
- **Plus:** term labour management and monitoring.

Prelabour Rupture of Membranes (PROM) at term:

Definition:

- Spontaneous rupture of membranes before the onset of labour at term (after 37 weeks gestation).
- 60% of women with PROM go into normal labour within 24 hours.

Investigations:

- Speculum examination - only if doubt as to whether membranes have ruptured.
- Otherwise a clinical diagnosis based on history.

Management:

- Expectant management up to **24 hours** (with 4-hourly self-monitoring of temperature) **or:**
- Induction of labour; also offered if labour does not start with expectant management.
- Note: previous history of group B streptococcus infection warrants immediate induction for PROM, with intrapartum antibiotics (benzylpenicillin).

Preterm Prelabour Rupture of Membranes (P-PROM):

Definition:

- Rupture of membranes before 37 weeks without spontaneous labour.

Diagnosis:

- **First Line:** speculum examination
    - Shows pooling of amniotic fluid
- If no pooled amniotic fluid seen, offer **second line:** insulin-like growth factor binding protein-1 test **or** placental alpha microglobulin-1 test

Management:

- **First Line:** prophylactic antibiotics
    - PO erythromycin for 10 days / until established labour

Sources and Further Reading:

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10. Postpartum Haemorrhage

Causes and Management

Definition:

- Loss of more than 500ml of blood from the genital tract within 24 hours of delivering a baby.
- **Minor PPH:** 500-1000ml
- **Major PPH:** >1000ml
    - Moderate - 1000-2000ml
    - Severe - >2000ml

Aetiology and Pathophysiology:

- The causes of postpartum haemorrhage can be divided into **the four Ts** - tone, tissue, trauma, thrombin.
- **Tone** (uterine atony - **commonest cause of PPH**):
    - Inadequate contraction of the uterus after separation of the placenta leads to profuse bleeding from the decidua.
    - Causes include: multiple pregnancy, macrosomia, polyhydramnios, retained placenta, prolonged second stage of labour.
- **Tissue** (tissue retained in uterus):
    - Typically part of placenta, sometimes retention of part of foetal / maternal membranes.
    - Prevents proper uterine contraction and resulting vessel occlusion.
    - Causes include: placenta praevia, placenta accreta spectrum, succenturiate placental lobe, preterm delivery.
- **Trauma:**
    - Trauma to genital tract leading to bleeding - includes **caesarean section.**
    - Causes include: vulvovaginal tears, instrumental delivery, episiotomy.
- **Thrombin:**
    - Normal bleeding worsened by pre-existing / obstetric coagulopathy / thrombocytopenia.
    - Causes include: pre-eclampsia, HELLP syndrome, DIC, puerperal sepsis, von Willebrand disease, dilutional coagulopathy (resuscitation with high volumes of crystalloid).

Management:

- **Minor PPH:**
  - IV access with 14-gauge cannula
  - G+S, FBC, coagulation screen
  - Frequent observations every 15 minutes
  - Warmed crystalloid infusion.
- **Major PPH:**
  - As for minor PPH, plus:
  - Lie patient flat, give high flow oxygen
  - O-negative blood as soon as possible - warmed crystalloid until blood is available
  - **Ongoing haemorrhage:** blood component transfusion - FFP, platelets, cryoprecipitate - guided by blood counts and clotting profile.
- **Minor and Major PPH:**
  - Treatment of underlying cause; treated as for **atony:**
    - Fundal massage
    - Catheterisation
    - Oxytocin and ergometrine
    - Carboprost (uterotonic)
    - Misoprostol
  - Second line surgical measures, performed in a **stepwise** manner:
    - Intrauterine balloon tamponade
    - Haemostatic suturing (B-Lynch)
    - Uterine devascularization / arterial ligation
    - Hysterectomy

Sources and Further Reading:

- Royal College of Obstetricians and Gynaecologists (2016). Prevention and Management of Postpartum Haemorrhage (Green-top Guideline No. 52). [online] RCOG. Available at: https://www.rcog.org.uk/guidance/browse-all-guidance/green-top-guidelines/prevention-and-management-of-postpartum-haemorrhage-green-top-guideline-no-52/.
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Gynaecology and Breast Disease

1. The Menstrual Cycle

Physiology

A good understanding of the physiology of the normal menstrual cycle is essential when learning about its associated pathologies. It is easiest to break it down into its **ovarian, endocrine** and **uterine** components. However, if you are short on time, skip ahead to 'putting it all together.'

Ovarian:

- The menstrual cycle begins with **15-20** follicles - any of which could become the **Graafian** follicle which undergoes ovulation.
- A follicle consists of:
    1. A primary oocyte
    2. A zona pellucida - a protein coat surrounding the oocyte
    3. Granulosa cells - these express **FSH** receptors, which stimulates them to convert **androgens** produced by theca cells into **oestradiol**.
    4. A fluid-filled antrum.
    5. Theca cells - these express **LH** receptors, and produce **androgens.**
- After ovulation, the granulosa cells of the ruptured Graafian follicle undergo **luteinisation** to become the **progesterone**-secreting **corpus luteum** - this has a **10 day** lifespan before it begins atresia (continues secreting progesterone for 14 days).
- The menstrual cycle is therefore split into the **follicular** and **luteal** phases, separated by **ovulation.**
- *See text box for further detail on this.*

Endocrine

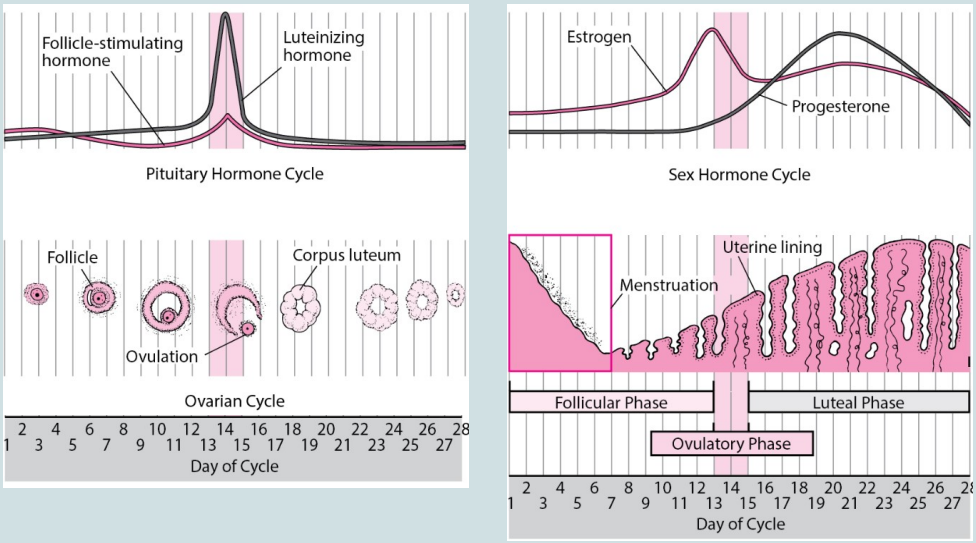
- The menstrual cycle is dictated by the **hypothalamic-pituitary-gonadal (HPG) axis.** This is the interaction between:
    1. Gonadotrophin-releasing hormone **(GnRH)** from the hypothalamus.
        - Travels from hypothalamus to anterior pituitary via hypophyseal portal vessel system.
        - Secreted in a **pulsatile** manner at varying frequencies i.e. higher frequency, lower amplitude in follicular phase, and lower frequency, higher amplitude in luteal phase.
        - Stimulates secretion of LH and FSH
        - Inhibited by LH and FSH (**negative feedback**)

2. Luteinising hormone **(LH)** and follicle-stimulating hormone **(FSH)** from the anterior pituitary.
    - Peptide hormones, collectively known as the gonadotrophins (and are produced by cells called gonadotrophs).
    - LH acts on theca cells, causing them to produce androgens.
    - FSH acts on granulosa cells, causing them to convert the androgens into oestrogen.
3. **Oestrogen** and **progesterone** from the follicles in the ovary.
    - Steroid hormones
    - At moderate levels, oestrogen exerts **negative feedback** upon LH secretion; however, at **high** concentrations it exerts **positive feedback.**
    - Oestrogen peaks mid-cycle; progesterone is low throughout the follicular phase, but peaks **7 days** before a menstrual bleed (i.e. day 21 of a 28 day cycle).
    - Progesterone exerts **negative feedback** on GnRH secretion, reducing the frequency of its pulsatile secretion during the luteal phase.

Uterine:

- The lining of the uterus (the endometrium) undergoes significant changes in order to prepare to accommodate a fertilised oocyte.
- The endometrium has three layers, which are also separated into two strata by their functionality in the menstrual cycle:
    - Stratum functionalis, composed of the **stratum spongiosum** and **stratum compactum.**
    - Stratum basalis - relatively inert in this context.
- The stratum functionalis proliferates under the influence of **oestrogen** in advance of ovulation:
    1. Stratum spongiosum thickens through mitosis
    2. Endometrial glands lengthen
    3. Connective tissue stroma regenerates
    4. Spiral arterioles lengthen
- After ovulation, progesterone acts upon the endometrium to cause it to secrete substances including **glycogen** and **mucous** - this makes it more accommodating to a potentially fertilised oocyte.
- If conception does not take place, there is no beta-hCG to maintain the corpus luteum, leading it to spontaneously regress. With the withdrawal of its progesterone, the stratum functionalis degenerates and causes a menstrual bleed:
    1. Spiral arteriolar constriction causes tissue ischaemia.
    2. Leukocyte infiltration into stratum functionalis takes place.
    3. Spiral arterioles rupture
- Local prostaglandin release plays a significant role in inducing the menstrual bleed.

Putting it all together:



Days 1-14: Follicular Phase, Menses and Proliferative Phase

- Increased frequency of pulsatile GnRH secretion leads to an increase in LH, and an initial increase in FSH.
- Oestrogen rises gradually as granulosa cells convert thecal androgens under the influence of FSH. Progesterone levels remain low after loss of corpus luteum. Moderate levels of oestrogen exert negative feedback on FSH secretion.
- Days 1-5:
    - Progesterone withdrawal due to degeneration of corpus luteum leads to sloughing of the stratum functionalis (a menstrual bleed).
- Days 6-14:
    - The endometrium undergoes its **proliferative** phase due to rising oestrogen levels.
- Meanwhile, 15-20 early antral (tertiary) follicles undergo development. At approximately day 7, a single **dominant** follicle is selected. *Note - it is thought that this occurs because rising oestrogen levels lower FSH levels through negative feedback - the dominant follicle is the one that can cope with lower FSH.*
- Day 13 - Rising oestrogen levels reach a ‘tipping point’, at which their negative feedback on LH secretion is **reversed** - the **LH** surge occurs, stimulating the oocyte to complete meiosis I and form a single **Graafian** follicle.
- Day 14 - Ovulation - The secondary oocyte erupts from its follicle, carried by antral fluid.

Days 15-28: Luteal Phase and Secretory Phase

- Day 15 - the granulosa cells of the ruptured follicle become **luteinised**, forming the **progesterone-secreting corpus luteum.**
- The corpus luteum's progesterone acts upon the endometrium to cause it to enter its **secretory** phase - amongst other things, it secretes glycogen and mucous.
- Progesterone levels peak **7 days** before the next menstrual bleed - 7 days before CL completely degenerates.
- High levels of progesterone increase the volume and viscosity of cervical secretions; this begins the formation of the protective operculum.
- After 10 days, if no conceptus has implanted, the corpus luteum spontaneously regresses. This leads to diminishing progesterone levels:
    - Without progesterone's negative feedback on the hypothalamus, GnRH release frequency increases and facilitates a rise in gonadotrophins.
    - Progesterone withdrawal also stimulates the stratum functionalis of the secretory endometrium to be shed.
- As FSH and LH levels rise, and the menstrual bleed begins, the cycle restarts on Day 1.

Folliculogenesis and Oogenesis

- A developing female foetus will synthesise upwards of **6 million** oocytes whilst still in utero.
- This number decreases (by atresia) to approximately **300,000** by the time a female reaches puberty.
- Follicles are considered as either **pre-antral** or **antral.** The **antral** phase consists of **primordial, primary** and **secondary** follicles.
- Until puberty, each oocyte is part of a **primordial follicle**. This consists of:
    1. A single oocyte - arrested in **prophase I of meiosis.**
    2. A layer of flattened (squamous) **granulosa** cells
    3. A basal lamina (layer of extracellular matrix)
- Primordial follicles then undergo **recruitment** into **primary follicles**. Only a portion of primordial follicles undergo recruitment at any one time, enabling them to enter into the menstrual cycle. This involves:
    1. The granulosa cells undergo mitosis and change from a squamous to **cuboidal** shape
    2. Granulosa cells also start to express **FSH** receptors.
    3. The oocyte synthesises mRNA to encode proteins to form the **zona pellucida**, which is also produced by the granulosa cells.
    4. Therefore at this point, the components of the follicle are: a single oocyte, a surrounding zona pellucida, a layer of cuboidal granulosa cells and a basal lamina.
- The primary follicles then undergo transformation into the **secondary follicle**:
    1. The surrounding layer of granulosa cells thickens by mitosis.
    2. An outermost layer, comprising **theca cells**, forms around the basal lamina. This is accompanied by the formation of a network of blood vessels within the outer follicle, allowing delivery of nutrients and hormones.
- Secondary follicles then further develop into **tertiary follicles;** *as far as I understand, this is considered an intermediary stage between preantral and antral follicles, sometimes called an* ***early antral*** *follicle.*
    1. A fluid-filled cavity is formed within the granulosa cells - this is known as the **antrum.**
    2. One of these follicles undergoes **selection** during the midpoint of the follicular phase; it is then considered the **dominant** follicle.

- The dominant follicle must then develop into a final **Graafian** follicle. This is initiated by the **LH** surge, which takes the oocyte out of its **meiotic arrest,** allowing it to complete **meiosis I** and give the first polar body. It then proceeds and is arrested at **metaphase II.**
- A tertiary follicle with a complete antrum and a **secondary oocyte** is then called a **Graafian follicle** (an antral follicle). From deep to superficial, it consists of:
    1. A **secondary** oocyte (plus the first polar body).
    2. Zona Pellucida
    3. A surrounding **cumulus oophorus** of granulosa cells, attached to further granulosa cells but suspended in:
    4. A fluid-filled antrum
    5. Basal lamina
    6. Theca cells (interna and externa)
- The mature oocyte, alongside its surrounding **zona pellucida** and **cumulus oophorus** of granulosa cells, hatches from the antrum in the process of **ovulation.**

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2. Contraception

Regular, Emergency

Passmedicine has a dedicated question bank on this topic - I would recommend working through that in conjunction with this.

Regular Contraception:

Non-Hormonal:

Male Condom

- **Mechanism:** barrier
- **Efficacy (typical use):** 18% experience unintended pregnancy after 1 year.

Copper Intrauterine Device (Cu-IUD)

- **Mechanism:** copper ions prevent fertilisation by immobilising sperm and inactivating lytic enzymes required for the acrosome reaction. Localised endometrial inflammation can prevent implantation even if fertilisation does occur.
- **Efficacy (typical use):** 0.8% experience unintended pregnancy after 1 year.
- **Advantages:**
    1. Immediately effective upon insertion.
    2. No hormonal side effects
    3. High efficacy
- **Absolute Contraindications:**
    1. PID
    2. Gonorrhoea or chlamydia
    3. Unexplained vaginal bleeding / endometrial cancer
    4. Postpartum / post-abortion septicaemia
    5. Gestational trophoblastic disease
    6. Purulent cervicitis, pelvic TB
- **Side Effects:**
    - Breakthrough (intermenstrual) bleeding, increased duration / heaviness of periods
- **Other:**
    - Risk of pregnancy with Cu-IUD is very low; however, if pregnancy does occur then it is more likely to be ectopic.
    - Classed as a **LARC** (long-acting reversible contraceptive) alongside LNG-IUS, implant, injection.
    - Can be left in situ for 5 years.

Hormonal:

Combined Hormonal Contraception (Combined Pill)

- **Mechanism:** progestogen component exerts negative feedback on hypothalamus, reducing GnRH release frequency and therefore suppressing secretion of LH and FSH. Oestradiol component exerts negative feedback on pituitary secretion of LH and FSH. Together, follicular development, the LH surge, and crucially **ovulation,** are all suppressed.
- **Efficacy (typical use):** 9% experience unintended pregnancy after 1 year. (With perfect use, the annual failure rate is only 0.3% - this emphasises human error as an important factor in effective contraception).
- **Advantages:**
    1. Rapidly reversible if unintended side effects
    2. Regulates and tends to lighten periods.
- **Side Effects:**
    - Headache, mood disturbance, breakthrough bleeding.
- **Absolute Contraindications:**
    - UKMEC 4 contraindications (“condition which represents unacceptable health risk if the method is used.”):
    1. <6 weeks postpartum in breastfeeding women
    2. Aged 35, smoking >15 cigarettes per day
    3. Stage 2 hypertension (160/100)
    4. History of VTE
    5. Disease: Breast cancer, inherited thrombophilia e.g. Factor V Leiden, cardiomyopathy, cirrhosis, vascular disease, SLE, positive antiphospholipid antibodies.
    6. Migraine with aura

Progesterone-Only Pill (Mini-Pill)

- **Mechanism:** progestogen exerts negative feedback on hypothalamus, reducing GnRH release frequency and therefore suppressing secretion of LH and FSH. This suppresses follicle development, the LH surge, and ovulation. POPs also thicken cervical mucus to form a physical barrier to semen.
- **Efficacy (typical use):** 9% experience unintended pregnancy after 1 year.
- **Advantages:**
    - Rapidly reversible
    - Far fewer absolute contraindications than combined pill.
- **Side Effects:**
    - Breakthrough bleeding
- **Absolute Contraindications:**
    1. Breast cancer
- **Other:**
    - Effective after 2 days of administration.

Levonorgestrel Intrauterine System (LNG-IUS - commonly referred to as the Mirena)

- **Mechanism:** thinning of endometrium by downregulation of endometrial oestrogen receptors; this prevents implantation. Does not inhibit ovulation.
- **Efficacy (typical use):** 0.2% experience unintended pregnancy after 1 year.
- **Advantages:**
    - Extremely high efficacy
    - Can be left in situ for 3-5 years
    - Lightens periods
    - Systemic absorption is minimal, reducing systemic hormonal side effects.
- **Side Effects:**
    - Irregular menstrual bleeding
- **Absolute Contraindications:**
    1. PID
    2. Gonorrhoea or chlamydia
    3. Unexplained vaginal bleeding / endometrial cancer
    4. Postpartum / post-abortion septicaemia
    5. Gestational trophoblastic disease
    6. Purulent cervicitis, pelvic TB

Contraceptive Injection (Depo-Provera)

- **Mechanism:** progestogen exerts negative feedback on hypothalamus, reducing GnRH release frequency and therefore suppressing secretion of LH and FSH. This suppresses follicle development, the LH surge, and ovulation.
- **Efficacy (typical use):** 6% experience unintended pregnancy after 1 year.
- **Advantages:**
    - Long-acting - requires an injection every 13 weeks
- **Side Effects:**
    - Amenorrhea
- **Absolute Contraindications:**
    1. Breast cancer

Contraceptive Implant

- **Mechanism:** progestogen exerts negative feedback on hypothalamus, reducing GnRH release frequency and therefore suppressing secretion of LH and FSH. This suppresses follicle development, the LH surge, and ovulation.
- **Efficacy (typical use):** 0.05% experience unintended pregnancy after 1 year. This is a 10 times lower frequency than female sterilisation.
- **Advantages:**

    - Most effective contraception available.
    - Active for 3 years before replacement is required.
- **Side Effects:**
    - Irregular menstrual bleeding
- **Absolute Contraindications:**
    1. Breast Cancer

Note: a large study published in 2023 found that progestogen-only contraceptives also increase the risk of breast cancer (it was previously known that there was an increased risk associated with oestrogen-containing contraception): Fitzpatrick, D., Pirie, K., Reeves, G., Green, J. and Beral, V. (2023). Combined and progestagen-only hormonal contraceptives and breast cancer risk: A UK nested case–control study and meta-analysis. PLOS Medicine, 20(3), p.e1004188. doi:https://doi.org/10.1371/journal.pmed.1004188.

Emergency Contraception:

Levonorgestrel Pill

- **Mechanism:** exogenous progestogen, exerts negative feedback on hypothalamus to prevent the LH surge and delay ovulation in event of unprotected sexual intercourse (UPSI); can delay ovulation by **5 days** (the viable lifespan of ejaculated sperm). Not effective in the late luteal phase, in which case ulipristal acetate is required.
- **Efficacy:** effective up to 72 hours post-UPSI - **not** effective if taken after ovulation has occurred.
- **Note:** normal dose of 1.5mg can be **doubled** to 3mg if a woman is taking enzyme-inducing medications or has a BMI > 26.

Ulipristal Acetate Pill

- **Mechanism:** selective progesterone receptor modulator, inhibits ovulation (possibly by blocking hypothalamic progesterone receptors, which studies suggest play a role in producing the LH surge).
- **Efficacy:** effective up to 120 hours post-UPSI. Unlike levonorgestrel, it can delay ovulation even if LH surge has started, which is why it remains effective in the late follicular phase. **Not** effective if taken after ovulation.

Copper Intrauterine Device (Cu-IUD)

- **Mechanism:** copper ions prevent fertilisation by immobilising sperm and inactivating lytic enzymes required for the acrosome reaction. Localised endometrial inflammation can prevent implantation even if fertilisation does occur.

- **Efficacy:** most effective form of emergency contraception. Additionally, as implantation occurs on day 6-7 post-fertilisation, the Cu-IUD is licensed for insertion 5 days post-ovulation.
- **Contraindications:** same as regular insertion of IUD (see above).

Guideline Summary

1. Offer most effective method (Cu-IUD) first line;
    a. Can be taken **either** within 120 hours of first UPSI **or** within 120 hours of calculated date of ovulation; whichever is **later.**
2. If Cu-IUD not acceptable / appropriate, offer oral emergency contraception;
    a. If within 72 hours of UPSI - offer LNG or UPA.
    b. If 72-120 hours post-UPSI - offer UPA.

Sources and Further Reading:

- NICE CKS - Contraception - assessment (2023)
- Hacker, N.F., Gambone, J.C. and Hobel, C.J. (2016). *Hacker & Moore's essentials of obstetrics & gynecology*. 6th ed. Philadelphia, Pa: Elsevier.
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3. Early Pregnancy

Miscarriage, Abortion, Ectopic Pregnancy and Pregnancy of Unknown Location

Miscarriage:

Definition:

- Spontaneous loss of pregnancy before 24 weeks of gestation (NICE CKS).

Pathophysiology and Aetiology:

- Chromosomal abnormality (commonest) - typically autosomal trisomies.
    - Can result in failure of development of embryo within gestational sac.
- Hormonal factors:
    - PCOS, hyperprolactinaemia, diabetes, hyper/hypothyroidism
- Thrombophilia / autoimmunity:
    - Antiphospholipid syndrome, factor V Leiden - *induces placental thromboses leading to placental insufficiency.*
- Anatomical factors:
    - Bicornuate uterus, cervical insufficiency
- Infection:
    - Toxoplasmosis, syphilis

Risk Factors:

- Increased maternal age
- Previous miscarriage

Types:

- **Threatened:** vaginal bleeding in the first 24 weeks of pregnancy (with viable intrauterine pregnancy).
- **Incomplete:** non-viable pregnancy, bleeding begun, products of conception in uterus.
- **Complete:** all products of conception passed, bleeding has stopped.
- **Missed:** non-viable pregnancy on ultrasound (without pain / bleeding).
    - Mean gestational sac diameter >25mm with no yolk sac **or**
    - CRL >7mm with no cardiac activity
- **Inevitable:** non-viable pregnancy, bleeding begun, cervical os opened, POCs remain in uterus.

Presentation:

- Pelvic pain
- Vaginal bleeding

Differentials:

- The commonest causes of bleeding in early pregnancy are **miscarriage, gestational trophoblastic disease, implantation bleeding, ectopic pregnancy,** and importantly, **bleeding without an identified cause.**

Investigations and Management:

- **Diagnosis:**
  - Transvaginal ultrasound scan - to identify location, foetal pole and heartbeat.
- **Threatened Miscarriage:**
  - Manage conservatively: if no history of previous miscarriage, advise to return if bleeding persists after 14 days / becomes heavier. If there is a history of previous miscarriage, offer vaginal progesterone until 16 weeks of pregnancy completed.
  - Advise to take a pregnancy test 3 weeks after bleeding has stopped.
  - If bleeding is ongoing, offer a repeat scan.
- **Incomplete / Inevitable Miscarriage:**
  - First Line - expectant management (appropriate to 13 weeks gestation):
    - Allow 7-14 days for POCs to pass / bleeding to end.
  - Second Line - medical management:
    - mifepristone, followed by misoprostol 48 hours later.
  - Alternative Second Line - surgical management:
    - Vacuum aspiration under local **or** dilatation and evacuation under GA
  - Plus: pregnancy test 3 weeks post-miscarriage
- **Missed Miscarriage:**
  - As above, but use **misoprostol only** for medical management.

Contraindications to expectant management:

1. Heavy vaginal bleeding / increased risk of bleeding / increased vulnerability to heavy bleeding (coagulopathy)
2. Previous traumatic experience in pregnancy
3. Evidence of infection

Mechanism of mifepristone:

- Antiprogesterone; sensitises myometrium to prostaglandins, induces breakdown of decidua basalis.

Mechanism of misoprostol:

- Prostaglandin E1 analogue; degrades cervical collagen, stimulates uterine contraction.

Abortion:

The 1967 Abortion Act gives four legal grounds for termination of pregnancy (TOP):

1. Pregnancy before 24 weeks - continuation risks injury to physical / mental health of the pregnant woman / her children.
2. Necessary to prevent grave permanent injury to physical / mental health of the pregnant woman.
3. Continuation of pregnancy involves risk to the life of the pregnant woman.
4. Substantial risk of serious physical / mental disability to the child if it were born.

- **Medical:**
    - Up to 9+6 weeks - single dose mifepristone, followed by single dose PO / PV misoprostol 48 hours later
    - 10+0 to 23+6 weeks - single dose mifepristone, followed by **serial** misoprostol every 3 hours.
    - Analgesia - NSAIDs, opioids as required.
- **Surgical:**
    - Up to 13+6 weeks - cervical priming with misoprostol or mifepristone, followed by vacuum aspiration.
    - 14+0 to 24+0 weeks - cervical priming with mifepristone + misoprostol or osmotic dilator, followed by dilatation and evacuation.
    - Plus - oral doxycycline to prevent infection.
    - Analgesia - NSAIDs, local anaesthetic, conscious sedation.
- **Summary:**
    - Medical - mifepristone plus misoprostol taken 48 hours later
    - Surgical - misoprostol plus vacuum aspiration / dilatation and evacuation.

Note - abortion is a sensitising event, so **Anti-D** should be offered after 10+0 weeks to women who are Rhesus negative.

Ectopic Pregnancy:

Definition:

- Any pregnancy that implants outside of the endometrial cavity. 97% are implanted in a fallopian tube.

Pathophysiology and Aetiology:

- Fertilisation of the oocyte typically takes place in the ampulla of the fallopian tube; the conceptus must then travel into the endometrial cavity.
    - This occurs due to tubal **peristalsis** alongside **ciliary motion** and tubal fluid flow.
    - Any dysfunction in the above due to e.g. tubal surgery, salpingitis, PID can prevent the conceptus from implanting in the correct place.
- A pregnancy that implants in the fallopian tube will grow and eventually lead to rupture and catastrophic bleeding.
- Most tubal ectopics implant in the **ampulla** (widest point).

Risk Factors:

1. Previous ectopic pregnancy
2. Cu-IUD use (although background risk of pregnancy is obviously much lower).
3. Chronic salpingitis (tubal inflammation)
4. PID

Presentation:

- Typically presents at **6-8 weeks** after LMP; at this point the conceptus has grown to sufficient size to cause symptoms / signs.
- **Symptoms:** lower abdominal pain, amenorrhea, PV bleeding, urge to defecate, shoulder pain.
- **Signs:** lower abdominal tenderness / adnexal tenderness, cervical motion tenderness.
- **Note:** any female of childbearing age presenting with abdominal pain should be offered a UPT to exclude ectopic pregnancy.
- **Differentials** include miscarriage, appendicitis and ovarian torsion.

> The following signs / symptoms occur due to **intraperitoneal bleeding** and are indicative of rupture: urge to defecate, shoulder tip pain, cervical motion tenderness.

Investigations:

1. Urine pregnancy test
2. Transvaginal ultrasound scan

3. Serial serum beta-hCG if no pregnancy found on USS.

Management:

- **Expectant:** must meet certain criteria, and close monitoring required (see text box).
- **Medical:** oral methotrexate - as long as no surgical criteria are met. Take UPT three weeks later.
- **Surgical:** salpingectomy / salpingotomy; indicated if *any* of the following features are present:
    - Ruptured ectopic
    - Significant pain
    - Heartbeat on USS
    - >35mm diameter of pregnancy
    - Serum beta-hCG > 5000IU/L

Expectant management of ectopic pregnancy:
- No criteria for surgical intervention can be present
- Measure beta-hCG on days 0, 2, 4, and 7; if drop of more than 15% from previous measurement, repeat weekly until beta-hCG is less than 20IU/L. If not, refer for further management.

Choice of surgery:
Salpingectomy (removal of affected tube) is first line **unless** there are risk factors for infertility; in which case, salpingotomy (opening of tube for removal of ectopic) is recommended. Salpingotomy is less effective than salpingectomy. Advise UPT 3 weeks post surgery.

Pregnancy of unknown location:
- Diagnosed when UPT is positive but no pregnancy can be visualised on ultrasound scanning.
- In this circumstance, the pregnant woman must be closely monitored as there is still a chance of ectopic.
- Diagnosis and management are guided by **serial beta-hCG measurements:**
    - 2 measurements taken 48 hours apart
    - If second measurement is >63% greater than first: likely **viable intrauterine pregnancy**; offer a scan 7-14 days later
    - If second measurement is >50% less than first: likely **non-viable pregnancy**; advise UPT 14 days later
    - If the second measurement falls between these parameters: further review required for ?ectopic.

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4. Dysmenorrhea

Primary Dysmenorrhea, Endometriosis

Definition:

- Painful lower abdominal cramping that occurs before / during menstruation.

Differentials:

- Primary dysmenorrhea - dysmenorrhea in the absence of identifiable pelvic pathology.
- Secondary dysmenorrhea - dysmenorrhea due to identifiable pelvic pathology:
    - Endometriosis
    - Adenomyosis
    - Fibroids
    - Pelvic Inflammatory Disease (PID)
    - Endometrial polyps

Primary Dysmenorrhea:

Aetiology / Pathophysiology:

- Progesterone withdrawal leads to prostaglandin release - this sensitises to pain due to modulation of sensory neurons.
- Progesterone release also facilitates uterine contractions.
- Spiral arteriolar vasoconstriction and rupture causes painful tissue ischaemia.

Progesterone withdrawal and spiral arteriolar vasoconstriction:

- Endothelins are 3-peptide molecules which act as potent local vasoconstrictors, exerting their effect directly onto the smooth muscle cells found in the tunica media.
- It has been demonstrated *in vitro* that progesterone withdrawal leads to increased endothelin release by human uterine spiral arterioles.
- It is therefore theorised that spiral arteriolar vasoconstriction (and subsequent tissue ischaemia and stratum functionalis shedding) is related to increased endothelin release from upstream uterine arterial supply in response to progesterone withdrawal after the degeneration of the corpus luteum.

Presentation:

- Painful lower abdominal cramping, beginning before the onset of the menstrual bleed and improving as the bleed goes on.
- Onset is **6-12 months** after menarche - *a later onset e.g. a woman in her 20s / 30s would suggest a **secondary** cause.*
- Can include systemic symptoms such as nausea and vomiting, fatigue, bloating etc.

Investigations:

- Clinically diagnosed - if a secondary cause is suspected then this must be investigated appropriately.

Management:

- First Line: oral NSAID e.g. ibuprofen, naproxen +/- paracetamol
- Alternate First Line: COCP
- Second Line: NSAID / paracetamol **plus** COCP (or alternative hormonal contraception)

Endometriosis:

Definition:

- Presence of endometrial **glands** and **stroma** outside of the uterine cavity.

Prevalence:

- 10% of reproductive age women.

Pathophysiology and Aetiology:

- Uncertain; best current theory is **retrograde menstruation:**
    - Fragments of endometrial tissue pass from the uterine cavity into the pelvis via the open-ended fallopian tubes during menstruation.
    - This ectopic tissue is responsive to the normal hormonal fluctuations of the menstrual cycle, so undergoes painful inflammation at the end of the cycle.

Further pathophysiology and infertility associations:

- Possible endocrine and immunological explanations are being explored.
- For example, eutopic (normally located) endometrial tissue in women with endometriosis has a different immunological makeup to that of women without endometriosis; for example, altered gene expression related to inflammatory response.
- Endometriosis pain is thought to be due to:
    - Neuroangiogenesis - development of new blood vessels and (nociceptive) peripheral nerves.
    - Pro-inflammatory and pro-neurogenetic factors are increased in women with endometriosis.
    - Increased risk of central sensitisation and related CNS changes (akin to other chronic pain) - this might explain treatment-resistant pain.
- Endometriosis-associated infertility has multiple theorised pathways, such as altered hormonal levels / response, peritoneal inflammation and adhesion formation.

Presentation:

- **Symptoms** include: dysmenorrhea, acyclic / chronic pelvic pain, dyspareunia, dyschezia, subfertility.
- **Signs** include: fixed retroverted uterus, palpable mass on examination (endometrioma).

Investigations:

1. Clinical Examination - *can identify endometriomas (cystic lesions) / deep nodules.*
2. Transvaginal ultrasound - *endometrioma, deep pelvic endometriosis*
3. **Gold Standard:** Diagnostic laparoscopy - *biopsy-confirmed glands / stroma outside of endometrial cavity.*

Management:

- First Line: oral NSAID e.g. ibuprofen, naproxen.
- Alternative First Line: combined contraception (e.g. COCP) **or** progesterone contraception (LNG-IUS, implant, medroxyprogesterone).
- Second Line: GnRH agonist (e.g. leuprorelin) **or** GnRH antagonist (e.g. elagolix).
    - N.B. limited duration of treatment due to bone mineral density issues.
- Alternative Second Line: laparoscopy with ablation.

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5. Menorrhagia

Fibroids, Heavy Menstrual Bleeding (HMB)

Definition:

- Excessive menstrual blood loss, interfering with a woman's physical, social, emotional, material quality of life (NICE).

Differentials:

- Heavy Menstrual Bleeding (HMB) - primary, no identified cause (50% of cases)
- Secondary causes:
    - Fibroids
    - Endometrial polyps
    - Gynaecological cancer
    - Endometriosis / adenomyosis
    - **Systemic:** hypothyroidism, inherited coagulopathy (von Willebrand's).

Investigating HMB:

1. Full blood count - *anaemia*
2. Consider further investigations for a cause as guided by the history.

Management of HMB:

- First Line: offer LNG-IUS
- Second Line: tranexamic acid (anti-fibrinolytic) **or** alternative hormonal treatment e.g. COCP, POP.

Uterine Fibroids:

Definition:

- Benign uterine tumours made of smooth muscle and connective tissue; also known as leiomyomata.

Pathophysiology / Aetiology:

- (Probably) derived from myometrial stem cells; considered to be oestrogen-dependent tumours, they express higher than normal numbers of certain oestrogen and progesterone receptors.
- It is uncertain how fibroids lead to HMB - proposed mechanisms include **distortion of uterine lining** and **abnormal humoral factors** due to altered histology of the overlying endometrium.

- Fibroids can be:
    - Intramural - contained within the myometrium.
    - Submucosal - projecting inwardly.
    - Subserosal - projecting outwardly.
    - Pedunculated - attached on a stem.

Risk Factors:

- High BMI, age in 40s, black ethnicity, low serum vitamin D levels.

Fibroids and high BMI:
- Increased adiposity leads to increased peripheral aromatase levels - therefore increasing circulating oestrogen due to conversion of adrenal DHEA into oestradiol.
- The increased oestrogen has an inhibitory effect on the HPG axis, leading to anovulation, decreased progesterone levels and thus reduced progestogenic endometrial protection (menses).
- Fibroids are oestrogen dependent; high oestrogen and low progesterone stimulates their growth.

Presentation:

- **Symptoms** include: menorrhagia, pelvic pain / pressure, bloating, dysmenorrhea.
- **Signs** include: palpable mass or enlarged uterus on bimanual examination.

Investigations:

- First Line: transabdominal and transvaginal ultrasound scan

Management:

- First Line: offer treatment as per HMB (LNG-IUS, tranexamic acid, alternative hormonal contraception).
- Second Line: GnRH agonist e.g. leuprorelin **or** antiprogesterone e.g. mifepristone
- Alternative - surgical management:
    - Myomectomy (surgical removal of fibroids) - **fertility-preserving**
    - Uterine artery embolisation (deliberate infarction of fibroid tissue whilst preserving surrounding uterus; performed by interventional radiologist, via percutaneous femoral access).
    - Hysterectomy.

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6. Oligomenorrhea and Amenorrhea

Polycystic Ovary Syndrome

Definition:

- **Oligomenorrhea:** infrequent / irregular menstrual periods (defined variably as fewer than 6 - 8 per year).
- **Amenorrhea:** the absence of a menstrual period.
    - Primary amenorrhea: absence of a period at age 15 in the presence of normal secondary sexual characteristics **or** at age 13 with no secondary sexual characteristics.
    - Secondary amenorrhea: absence of a period for three consecutive cycles in a woman with a previously established menstrual cycle.

Causes of Amenorrhea:

- Primary:
    - Constitutional delay (familial)
    - Imperforate hymen
    - Hypo- / hyperthyroidism, hyperprolactinaemia, Cushing's syndrome
    - Androgen insensitivity syndrome
    - Turner's syndrome
- Secondary:
    - **Functional Hypothalamic Amenorrhea** - excessive exercise, weight loss, stress, eating disorders.
    - Premature ovarian insufficiency
    - Sheehan's syndrome, prolactinoma, hypopituitarism
    - Hypo- / hyperthyroidism

Polycystic Ovary Syndrome:

Definition:

- Endocrinopathy resulting in syndrome of ovarian cysts, oligomenorrhea and hyperandrogenism.

Criteria:

- PCOS is defined by the **Rotterdam Criteria** - a woman must meet **2 of the 3:**
    1. Hyperandrogenism
    2. Oligo- or anovulation

3. Polycystic morphology on ultrasound.

- Therefore PCOS can be diagnosed in the absence of ovarian cysts.

Aetiology and Pathophysiology:

- Complex and multifactorial; this is a simplified version (derived from the 2017 paper by Ibanez *et al.*):
    1. Disrupted balance between androgens, anti-Mullerian hormone and FSH levels leads to arrest in follicular development:
        a. Increased GnRH release frequency leads to high LH:FSH ratio.
        b. This results in high androgen:oestradiol ratio.
        c. Low oestrogen (due to reduced granulosa cell activity) prevents follicle selection and subsequent **ovulation**. Instead, multiple immature follicles remain and form cysts.
        d. Additionally, high androgens may inhibit sex steroid negative feedback on the HPG axis, leading to a 'vicious circle' of rising androgens.
    2. Insulin resistance and hyperinsulinaemia:
        a. Peripheral insulin resistance (skeletal muscle, adipose tissue) leads to hyperglycaemia and subsequent hyperinsulinaemia.
        b. High insulin levels stimulate theca cell androgen production and reduce sex-hormone binding globulin levels (SHBG); this means increased free circulating androgens.

Presentation:

- Hyperandrogenism: hirsutism, acne, hyperhidrosis.
- Oligomenorrhea - due to oligo-ovulation.
- Subfertility / infertility

Risk Factors:

1. Obesity
2. Family history
3. Premature adrenarche (pubic / axillary hair, apocrine sweat gland development).

Investigations:

1. Total serum testosterone - *elevated*
2. Sex hormone-binding globulin (SHBG) - *normal to low*
3. Free androgen index - *elevated*
4. **Rule-out tests:** LH and FSH (premature ovarian failure), prolactin (hyperprolactinaemia), TFTs (hypothyroidism); used to eliminate other causes of oligomenorrhea.
5. **Imaging:** ultrasound - *12 or more follicles on one ovary*.

Management:

- Dependent on whether or not fertility is desired at the time.
- **Not Desired:**
    1. First Line: COCP plus weight loss
    2. Second Line (in event of prolonged amenorrhea)
        a. Cyclical progesterone (taken for 14 days every 3 months) to induce a **withdrawal bleed** to protect endometrium.
        b. Also offer transvaginal USS to assess endometrial thickness
- **Fertility Desired:**
    1. First Line: weight loss **plus:**
        a. Clomifene **or**
        b. Letrozole (aromatase inhibitor).
    2. Second Line:
        a. Metformin

Mechanisms of PCOS Treatment:

1. COCP - regulation of menstrual cycle through stabilisation of oestrogen & progesterone levels. Also increases hepatic SHBG production (lowering free androgen index) and blocks some androgen receptors.
2. Metformin - improves peripheral insulin sensitivity to downregulate effects of insulin resistance described above.
3. Clomifene - selective oestrogen receptor modulator; blocks hypothalamic oestrogen receptors, thereby inhibiting HPG axis negative feedback and inducing FSH / LH secretion to lead to ovulation.
4. Letrozole - aromatase inhibitor, inhibits peripheral conversion of androgens into oestrogen, reducing HPG axis negative feedback to promote ovulation.

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7. Menopause

Physiology, Hormone Replacement Therapy (HRT)

Definition:

- Defined retrospectively as the point **12 months** after a woman's last natural menstrual period.
- **Perimenopause:** physiological changes and associated signs and symptoms during the period of time before the menopause.
- **Premature ovarian insufficiency:** onset of menopause before 40 years old.

Epidemiology:

- Average age of menopause is 51 years old; it typically occurs between 40 and 60 years old.

Aetiology and Physiology:

1. Declining reserves of oocytes and associated follicles leads to reduced **oestrogen** production in response to FSH and LH stimulation.
2. Therefore serum LH and FSH rise in response (lack of negative feedback).
3. Eventually insufficient oestrogen means the LH surge and subsequent ovulation do not occur, leading to anovulatory cycles.

Further Physiology:

- Low circulating progesterone due to anovulation leads to unpredictable breakthrough bleeding.
- The physiology of hot flushes is multifactorial and not fully understood, but is thought to be due to a combination of oestrogen withdrawal, thermoregulatory changes and alterations in neurotransmitter systems.
- Vaginal symptoms of dyspareunia (painful sexual intercourse), dryness and itch occur due to atrophic vaginitis secondary to low circulating oestrogen levels (epithelial thinning, muscular atrophy, reduced vascularity, loss of rugosity).

Presentation:

- **Symptoms** include:
    - Menstrual irregularity leading to amenorrhea
    - Vasomotor symptoms (hot flushes / night sweats
    - Mood disturbance
    - Sleep disturbance
    - Vaginal symptoms (dyspareunia, dryness, itch).

Complications:

- Osteoporosis - due to increased bone turnover (normal oestrogen levels inhibit osteoclast activity).
- Increased cardiovascular risk - due to alterations in LDL:HDL ratio, raised serum cholesterol, arterial stiffening (among many other factors that are not entirely clear).

Investigations:

- Typically diagnosed **clinically** - investigations are usually not indicated in women with menopausal symptoms over the age of 45.
- If indicated:
    - Serum FSH - *elevated*
    - Serum oestradiol - *reduced*

Management:

- Treatment can be beneficial for both symptomatic relief and cardiovascular / osteoporotic risk.
- HRT should be prescribed in the lowest effective dose for the shortest duration of treatment possible.
- First Line: lifestyle measures:
    - Regular excess
    - Weight loss (as necessary)
    - Avoidance of triggers (smoking, alcohol, spicy food).
- Second Line: hormone replacement therapy (HRT):
    - Women **with** a uterus:
        - Oral or transdermal (patch) **combined** oestrogen and progesterone e.g. tibolone for **systemic** i.e. vasomotor symptoms, mood disturbance.
        - Note - in situ Mirena can act as progesterone component of HRT.
        - Topical oestrogen gel for **local** i.e. vaginal symptoms.
    - Women **without** a uterus:
        - Oral or transdermal **oestrogen only** treatment for systemic symptoms.
        - Topical oestrogen gel for local symptoms.
    - HRT is prescribed in different regimens depending on the woman's stage of menopause.
    - For **perimenopausal women:**
        - Monthly or 3 monthly cyclical regime to produce a protective bleed:
            - Oestrogen daily, plus progestogen for 12 days every 4 weeks or 3 months.
    - For **postmenopausal women** (i.e. 12 months after LMP)**:**
        - Cyclical **or** continuous combined regime:
            - Cyclical (as above).
            - Continuous oestrogen and progesterone daily.

Risks of HRT:

- Systemic HRT is associated with increased risk of breast cancer. The longer its duration of use, the higher the associated risk.
    - Topical HRT is thought to have no effect on breast cancer risk due to minimal systemic absorption.
- Systemic HRT is associated with increased risk of venous thromboembolism.

Absolute Contraindications to HRT:

1. History of breast cancer, any oestrogen-dependent cancer, current undiagnosed PV bleeding, current endometrial hyperplasia.
2. History of idiopathic VTE (if not anticoagulated).
3. Thromboembolic disease e.g. MI, angina
4. Liver disease.
5. Inherited thrombophilia.
6. Pregnancy.

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8. Urogynaecology

Prolapse, Urinary Incontinence

Pelvic Organ Prolapse:

Definition:

- Herniation of one more pelvic organ into the vagina.

Normal Anatomy:
- Level 1 support:
  - Uterosacral ligaments - extend posteriorly from cervix / upper vagina to the sacral spine.
- Level 2 support:
  - Arcus tendineus fasciae pelvis (ATFP) - runs from ischial spines to pubic tubercle, attaching to sheets of suspensory 'slings' of fascial tissue e.g. pubovesicocervical fascia.
- Level 3 support:
  - Perineal body - fibromuscular mass, point of attachment for pelvic muscles.
  - Pubourethral ligaments.
  - Pelvic floor - (levator ani and coccygeus muscles).

Pathophysiology by Type:
- Uterosacral ligament weakness - uterine prolapse
- ATFP weakness - cystocele, rectocele
- Pubourethral ligament weakness - urethrocele

Aetiology:

- Loss of sufficient support for pelvic organs due to multiple factors including pregnancy, vaginal delivery and pelvic surgery.

Risk Factors:

1. Vaginal delivery (risk increased with increasing parity) - *damage to nerves, muscles and fascia*
2. Increasing age - *reduced elasticity of connective tissue*
3. High BMI - *raised intra-abdominal pressure*

Types of Pelvic Organ Prolapse:

1. Uterine prolapse - descent of cervix +/- uterus into the vagina.
2. Urethrocele - prolapse of the urethra into anterior vaginal wall.
3. Cystocele - prolapse of bladder into anterior vaginal wall.
4. Rectocele - prolapse of rectum into posterior vaginal wall.
5. Enterocele - prolapse of the small bowel through the Pouch of Douglas into the posterior vault of the vagina.

Presentation:

- **Symptoms** are related to the type of prolapse, as follows:
    - Uterine - vaginal pressure, dyspareunia, feeling of something descending into the vagina.
    - Urethrocele - stress incontinence.
    - Cystocele - recurrent UTI, difficulty passing urine.
    - Rectocele - difficulty defecating.
    - Enterocele - dragging sensation.
- **Signs** are seen on speculum examination:
    - Uterine - descended cervix / uterus
    - Vaginal (urethrocele, cystocele, rectocele, enterocele) - protrusion into vaginal vault anteriorly, anteriorly, posteriorly, posteriorly respectively.

Investigations:

- Typically diagnosed **clinically** based on characteristic symptoms and signs.

.**Management:**

- **Conservative:**
    - Pelvic floor exercises.
    - Avoidance of triggers e.g. heavy lifting, straining in constipation.
    - Weight loss, if overweight.
    - Topical oestrogen (counteracts urogenital atrophy - see ***Menopause***).
    - Pessaries
- **Surgical:**
    - Uterine - options include hysterectomy, sacro-hysteropexy (mesh), Manchester repair.
    - Vaginal vault - options include sacrospinous fixation, sacro-colpopexy (mesh).

Urinary Incontinence:

Definition:

- Involuntary passage of urine.

Types:

- Stress incontinence - urinary loss during a period of raised intra-abdominal pressure e.g. coughing, sneezing.
- Urge incontinence - urinary loss characterised by increased urge to pass urine - associated with detrusor muscle overactivity.
- Mixed incontinence - combination of the above.

Physiology of Continence

Storage phase:
- Impulses from the cerebral cortex are transmitted to the **pontine continence centre.**
- The pontine continence centre sends signals to sympathetic nuclei within T10-L2 sympathetic ganglia, which then sends further signals to the **detrusor** and **internal urethral sphincter** muscles via the sympathetic **hypogastric** nerve, stimulating:
    - Relaxation of the detrusor muscle.
    - Contraction of the internal urethral sphincter.
- Somatic innervation of the external urethral sphincter also contributes to continence during bladder filling.

Voiding phase:
- Afferent signals from the distended bladder ascend via the spinal cord to the **pontine micturition centre** and the cerebral cortex (conscious urge to pass urine).
- Efferent parasympathetic signals to the detrusor cause it to contract, transmitted via S2-4 **pelvic splanchnic** nerve.
- Inhibition of Onuf's nucleus (due to pontine micturition centre activity) reduces sympathetic storage-promoting activity.
- Conscious relaxation of external urethral sphincter via somatic pudendal nerve fibres allows passage of urine.

Summary of neurology:
- Sympathetic - T10-L2 hypogastric - detrusor relaxation, IUS closing
- Parasympathetic - S2-4 pelvic splanchnic - detrusor contraction, IUS opening
- Somatic afferent - S2-4 pudendal - sensation of bladder fullness
- Somatic efferent - S2-3 pudendal - closes / opens EUS.

Continence mechanisms in response to raised intra-abdominal pressure:
1. Reflexive contraction of the pelvic floor muscles elevates the IUS.
2. Augmentation of pelvic floor muscle closure by suspensory ligaments.
3. Urethrovaginal sphincter and compressor urethrae muscle contraction assists with urethral closure.

Aetiology and Pathophysiology:

- Stress incontinence:
    - Raised intra-abdominal pressure increases intra-vesical pressure.
    - IVP exceeds resistance of urethral sphincters leading to leakage.
    - This typically occurs due to downward movement of the internal sphincter secondary to pelvic floor weakness (**urethral hypermobility**).
- Urge incontinence:
    - Mechanism not fully understood - likely a combination of myopathy and neuropathy.

Risk Factors:

1. Increasing age
2. High BMI
3. High parity
4. Pelvic organ prolapse

Presentation:

- Stress incontinence - involuntary passage of urine during activities that raise intra-abdominal pressure (sneezing, coughing etc.)
- Urge incontinence - involuntary passage of urine **with associated urge** to pass urine, increased urinary frequency.

Investigations:

- First Line: urinalysis to rule out UTI, plus:
    - Bladder diary
    - Symptom questionnaire
- Second Line: urinary stress testing, e.g.
    - Cough stress test
    - Empty supine stress test

Management:

- Stress incontinence:
    - **First Line:** pelvic floor exercises (8 contractions x3 per day) + lifestyle measures e.g. reducing caffeine, weight loss, moderate fluid intake.
    - **Second Line:** (for some patients) - pseudoephedrine, topical oestrogen
    - **Third Line:** surgery such as **retropubic colposuspension.**
- Urge incontinence:
    - **First Line:** bladder training
    - **Second Line:** anticholinergic e.g. oxybutynin, solifenacin
    - **Third Line:** mirabegron (beta-3 agonist)
    - **Plus:** topical oestrogen if atrophic vaginitis present.

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9. Gynaecological Cancers

Endometrial, Ovarian, Cervical

Endometrial Cancer:

Epidemiology:

- 8000 new cases annually in the UK.
- Commonest gynaecological cancer.
- Median age of diagnosis is 63 years.

Histology:

- Multiple cell types - commonest is **endometrioid adenocarcinoma** (glandular secretory epithelium).
- Endometrial **hyperplasia:** raised gland:stroma ratio compared to normal endometrium.

Aetiology and Pathophysiology:

- Hormonal stimulation leads to **uninterrupted endometrial proliferation**, causing endometrial hyperplasia.
- The hyperplastic endometrial tissue then evolves and mutates from simple to complex forms, to premalignant **endometrial intraepithelial neoplasia** and eventually invasive **adenocarcinoma.**
- Endometrial cancer metastasises to **pelvic** and **para-aortic** lymph nodes.

Risk Factors:

- Obesity
- Age > 50
- Endometrial hyperplasia
- Unopposed **endogenous** oestrogen:
    - Early menarche, late menopause, nulliparity, anovulation leading to amenorrhea.
- Unopposed **exogenous** oestrogen:
    - HRT, hormonal contraception.

Presentation:

- Classic symptom is **post-menopausal bleeding** - this is considered endometrial cancer until proven otherwise.

Investigations:

- **First Line:** transvaginal ultrasound
    - Endometrial thickness >5 mm is abnormal
- **Second Line:** hysteroscopy with endometrial biopsy

Management:

- **Endometrial hyperplasia:**
    - **Without** atypical cells: reversal of risk factors e.g. weight loss, stopping HRT **+/-** progesterone therapy e.g. LNG-IUS.
    - **With** atypical cells: total hysterectomy with bilateral salpingo-oophorectomy (BSO)
- **Endometrial cancer:**
    - **First Line:** hysterectomy with BSO
    - **+/-** vaginal brachytherapy
    - **+/-** radiotherapy
    - **+/-** chemotherapy

Ovarian Cancer:

Epidemiology:

- 7000 new cases annually in the UK.
- Median age of diagnosis is 63 years.

Histology:

- There are multiple histological subtypes.
- Commonest subtype is **serous epithelial carcinoma** - derived from epithelium overlying the ovarian capsule and distal fallopian tube.
- 90% of ovarian cancers are epithelial in origin.
- Other subtypes originating from the cortex of the ovary include
    - **Sex cord stromal**
    - **Germ cell** (more prominent in pre-menopausal women).

Aetiology and Pathophysiology:

- The underlying cause of ovarian cancer is unclear, although there is an established relationship with BRCA1 and BRCA2 mutations.
- Metastasis can occur via **transcoelomic** (across a body cavity) spread as opposed to lymphatic / haematological. This means that ovarian epithelial cancers commonly metastasise to the liver, bowel and their associated mesentery.

Risk Factors:

- BRCA1 / BRCA2 mutation
- Increasing age
- Family history

Presentation:

- The presentation of ovarian cancer is often vague and non-specific, meaning that it is often detected at an advanced stage of the disease.
- **Symptoms** include: vague gastrointestinal symptoms (bloating, early satiety, nausea, altered bowel habit), urinary frequency
- **Signs** include: palpable abdominal mass, ascites

Investigations:

- **First Line:** abdominal and pelvic examination
- **Second Line:** CA-125 (tumour marker) level
    - >35 IU/ml is highly suspicious for malignancy
- **Third Line:** transvaginal ultrasound

Management:

- **First Line:** surgical staging with radical hysterectomy, BSO, appendectomy, omentectomy, lymph node dissection, pelvic washout.
    - Fertility-sparing surgery can be used in some specific cases.
- **+/-** adjuvant chemotherapy
- **+/-** bevacizumab (anti VEGF monoclonal antibody).

Cervical Cancer:

Epidemiology:

- 3000 new cases annually in the UK, 75% of which are detected on screening.
- Median age of diagnosis is 50 years.

Histology:

- Most commonly **squamous cell** carcinoma of the **ectocervix** (part of the cervix projecting into the vagina).
- Also **adenocarcinoma** of the **endocervix** (part of the cervix lining the cervical canal).

Aetiology and Pathophysiology:

- Caused by infection with high-risk strains of **human papilloma virus** (HPV-16 and HPV-18).

- HPV infection spontaneously resolves within 2 years in 90% of women - at this point, risk returns to baseline.
- HPV causes dysregulated cell cycle regulation, leading to formation of a pre-malignant monoclonal cell population referred to as **cervical intraepithelial neoplasia (CIN),** which subsequently mutates further to become an invasive carcinoma.

Cervical Intraepithelial Neoplasia:

- **CIN1** - low grade, confined to lower **third** of epithelium.
- **CIN2** - moderate grade, confined to lower **two thirds** of epithelium.
- **CIN3** - high grade, severely atypical cellular changes in **more than two thirds** of epithelium.

Risk Factors:

- High-risk HPV (hrHPV) infection
- Cigarette smoking
- Immunosuppression.

Presentation:

- Typically detected by screening.
- **Symptoms** include: intermenstrual bleeding, postcoital bleeding, abnormal vaginal discharge.
- **Signs** include: mass, ulcerated lesion, bleeding on speculum exam.

Investigations:

- **First Line:** colposcopy with biopsy - suspicious features seen on colposcopy are **abnormal vascularity, white change with acetic acid** and **exophytic lesions.**
- **Plus:** HPV testing

Stages (simplified):

- Stage 1 - confined to cervix
- Stage 2 - extending beyond uterus
- Stage 3 - extending into lower third of the vagina **or** pelvic wall
- Stage 4 - spread beyond true pelvis **or** bladder / rectum involvement

Screening:

- Offered to women aged between 25 and 64.
- Normal recall intervals are:
    - 3-yearly for women aged 25-49
    - 5-yearly for women aged 50-64
- The first test is for hrHPV; if this is positive, further testing is indicated.

- **Negative hrHPV:**
    - Return to normal recall (age-based) without further testing at the time.
- **1st positive hrHPV:**
    - Use liquid-based cytology (LBC) to detect cellular atypia.
    - If cytology is **positive,** colposcopy is indicated.
    - If cytology is **inadequate**, cytology is repeated in 3 months.
        - If repeat cytology is inadequate, refer for colposcopy.
        - If colposcopy is normal, test hrHPV in 12 months.
    - If cytology is **negative,** perform the 2nd hrHPV test in 12 months.
- **2nd hrHPV:**
    - If **negative**, return to normal recall
    - If **positive,** offer a 3rd hrHPV test in a further 12 months (i.e. 24 months after the first positive test).
- **3rd hrHPV:**
    - If **negative,** return to normal recall
    - If **positive,** refer to colposcopy

Management:

- Treatment is highly variable and based on staging and the woman's wishes regarding fertility.
- Broadly:
    - Stage 1A1 (<3mm) can be managed with a **cone biopsy** if fertility is to be preserved; alternatively **radical hysterectomy** is indicated.
    - Treatment options for more advanced stages include:
        - Radical hysterectomy with lymph node removal, **plus** adjuvant therapy (chemotherapy / radiotherapy)
        - Radical trachelectomy (removal of cervix) with lymph node removal, **plus** adjuvant therapy.
        - Neoadjuvant chemotherapy, immunotherapy e.g. bevacizumab.

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10. Benign Breast Disease

Anatomy, Fibroadenoma, Fibrocystic Disease, Mastitis, Breast Abscesses

Breast Anatomy:

- Can be divided into **two regions:**
  - Circular body
  - Axillary tail - runs into axillary fossa
- Can also be divided **structurally:**
  - Mammary glands - consist of the functional apparatus of the breast in a highly branched structure:
    - **Lactiferous Ducts -** one per **lobe,** exiting at the nipple.
    - **Lobes -** 15-20 per breast, each made up of 20-40 **TDLUs.**
    - **TDLUs** (terminal duct lobular units) **-** secretory functional units, made up of approximately 100 **acini** that drain into a **terminal duct.**
  - Stroma - fibrous connective tissue, supports the structure of the breast and forms the **suspensory ligaments of Cooper.**
    - Each lobule is demarcated by a Cooper ligament.
- The ductal-lobular system is lined by **cuboidal and columnar** epithelial cells.
- The breast drain lymphatic fluid to three key sites:
  - **Axillary** lymph nodes (75%)
  - **Parasternal** lymph nodes (20%)
  - **Posterior intercostal** lymph nodes (5%).

Fibroadenoma:

Definition:

- Benign tumour of the breast.

Histology:

- Composed of **glandular epithelium** and **interlobular stroma** of a TDLU.
- Well-circumscribed, non-encapsulated.
- Does **not** infiltrate into the parenchyma of the breast.

Epidemiology:

- Most common in women under **30**.

Aetiology:

- Unclear - typically sex steroid-responsive (grow in pregnancy, shrink in menopause).

Presentation:

- Solitary, mobile breast lump with a regular border.

Investigations:

- **First Line:** breast imaging (USS or mammogram)
    - Typically stratified by **age** and **clinical suspicion:**
        - Women **<30:** breast ultrasound.
            - *Smooth, well-circumscribed mass with uniform hypoechogenic appearance.*
        - Women **>30** or **highly suspicious for cancer:** mammogram.
            - *Distinct, well-circumscribed mass.*

Management:

- None usually needed.

Fibrocystic Disease:

Definition:

- Condition causing multiple small breast lumps.

Epidemiology:

- Commonest benign breast disease.
- Most common in women aged 30-50.

Aetiology and Pathophysiology:

1. Normal menstrual cycle **oestrogen** fluctuation leads to **epithelial proliferation** and **stromal fibrosis** in the TDLUs.
2. This can lead to **obstruction** of ductules and terminal ducts.
3. Obstruction causes cyst formation or degeneration of the ductules.
4. Cyst rupture leads to inflammation and subsequent fibrosis.

Presentation:

- Bilateral diffuse, symmetrical lumpiness.
- Breast pain (mastalgia) - **often cyclical.**
- (Sometimes) nipple discharge.

Investigations:

- **First Line:** breast imaging (USS or mammogram)
    - Stratified by **age** and **clinical suspicion:**
        - Women **<30:** breast ultrasound.
            - *Cysts / solid mass*
        - Women **>30** or **highly suspicious for cancer:** mammogram.
            - *Circumscribed density*

Management:

- **First Line:** simple analgesia e.g. paracetamol, ibuprofen.

Mastitis and Breast Abscesses:

Definition:

- **Mastitis:** inflammation of the breast, typically due to infection.
    - Divided into **lactational** and **non-lactational** (duct ectasia)
- **Breast abscess:** discrete collection of pus due to infection.

Aetiology and Pathophysiology:

- Bacterial colonisation - **commonest** is *Staph. aureus.*
- **Lactational** mastitis:
    - Combination of breastfeeding-related nipple trauma and milk stasis predisposes the breast to local infection.
- **Duct ectasia** mastitis:
    - Blockage of lactiferous ducts due to **squamous metaplasia** leads to dilatation and inflammation.
    - Strongly associated with **cigarette smoking.**
- **Abscess:**
    - Progression of untreated infective mastitis; walled-off collection of infection forms.

Presentation:

- **Symptoms** include: fever, breast pain / tenderness (often during breastfeeding)
- **Signs** include: erythema, swelling, firmness.
- Duct ectasia is also associated with **nipple discharge.**

Investigations:

- Mastitis is usually a clinical diagnosis based on history and examination findings.
- Abscesses can be diagnosed with **breast ultrasound** and **diagnostic needle aspiration.**

Management:

- **Lactational Mastitis:**
  - **First Line:** continued breastfeeding / milk expression **plus** simple analgesia
  - **Second Line:** >24 hour duration / severe pain - add PO **flucloxacillin**.
- **Non-lactational Mastitis:**
  - **First Line:** PO flucloxacillin
- **Breast Abscess:**
  - **First Line:** needle aspiration and drainage **plus** flucloxacillin (dependent on local policy).

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11. Breast Cancer

Management, National Screening

Background:

- Breast cancer is the commonest cancer in the UK (15% of new cancer cases annually).
- There are approximately 56,000 new cases of breast cancer every year.

Types:

- **Pre-invasive:**
    1. Ductal carcinoma in situ (DCIS).
        - Neoplastic proliferation of epithelial cells - confined to duct without invasion through basement membrane.
        - Precursor to invasive breast cancer.
        - Comedo and non-comedo subtypes.
    2. Lobular carcinoma in situ (LCIS).
        - Neoplastic proliferation of epithelial cells, confined to **TDLU.**
- **Invasive** (penetration through basement membrane)**:**
    1. Invasive ductal carcinoma (**commonest - 75%**).
        - Neoplastic proliferation of epithelial cells that invades through the ductal basement membrane.
    2. Invasive lobular carcinoma
    3. Medullary carcinoma
        - More prevalent in the younger population.
        - Higher grade than IDC.
    4. **Many others** - including mucinous, tubular, papillary, inflammatory etc.

Histology:

- Invasive carcinoma can be graded using the **Nottingham criteria,** which consists of scoring of the following:
    - Gland formation
    - Nuclear atypia / pleomorphism
    - Mitosis counts (indicates rate of cellular reproduction)
- A higher grade carcinoma is one that is **markedly different** from normal breast tissue and is considered **poorly differentiated.**

Aetiology and Pathophysiology, Metastasis:

- Complex series of genetic mutations and deranged cellular signalling leads to generation of malignant cells.
- Breast cancer can be linked to inherited genetic mutations such as BRCA1.
- Malignant cells metastasise through a five step process:

1. Invasion through basement membrane
2. Intravasation (entry into circulation)
3. Circulation
4. Extravasation
5. Colonisation

- The commonest sites of breast cancer metastasis are bones, liver, lungs and brain.

Risk Factors:

1. Increasing age
2. Female sex (100:1 F:M incidence)
3. Family history
4. Inherited genetic mutations e.g. BRCA1
5. **Endogenous** oestrogen exposure:
    a. Early menarche
    b. Nulliparity / absence of breastfeeding
    c. Late menopause
6. **Exogenous** oestrogen and progestin exposure:
    a. Systemic hormonal HRT
    b. Systemic hormonal contraception

Presentation:

- **Symptoms** include: breast lump
- **Signs** include: nipple discharge, nipple retraction, skin changes e.g. peau d'orange, axillary lymphadenopathy.
- **Metastatic** features include: weight loss, bony pain, shortness of breath.

Stages:

- TNM staging (tumour, node, metastasis) - *see Cancer Research UK for full details.*
- Alternative staging:
    - Stage 1A: <2cm, isolated to breast
    - Stage 1B: <2cm, minor axillary LN spread
    - Stage 2A: <2cm, spread to 1-3 ipsilateral LNs.
    - Stage 2B: 2 - 5cm, minor axillary nodal spread **or** 2 - 5cm with 1-3 ipsilateral nodes **or** >5cm, no nodal spread
    - Stage 3A: 4-9 ipsilateral nodes **or** >5cm with 1-3 ipsilateral nodes
    - Stage 3B: spread to skin / chest wall
    - Stage 3C: >10 axillary nodes **or** supraclavicular spread **or** parasternal + axillary spread
    - Stage 4: distant metastatic spread to organs.

Screening:

- NHS screening programme: 3-yearly mammogram for women aged 50-71.

Investigations:

- **2 week wait criteria:**
    - Unexplained breast lump in a woman aged >30.
    - Unexplained axillary lump in a woman aged >30.
    - Unilateral nipple changes in a woman aged >50.
    - Skin changes suggestive of breast cancer, any age.
- **First Line:** breast imaging
    - >30 **or** highly suspicious for cancer: mammogram
    - <30: breast ultrasound
    - **Plus:** ultrasound of the axilla +/- needle biopsy
- **Second Line:** biopsy
    - Fine needle aspiration and cytology
    - **Plus:** oestrogen / progesterone receptor testing, HER2 receptor testing.
- If symptoms / signs suggestive of metastasis:
    - CT scan (CT thorax-abdomen-pelvis, CT head).

Mammogram Features:

- Pre-invasive: unifocal / widespread **microcalcifications**
- Invasive carcinoma:
    1. Irregular spiculated mass
    2. Clustered microcalcifications
    3. Linear branching calcifications.

Management:

- Dependent on histology, staging, receptor positivity, physiological reserve; but broadly:
- **First Line:** surgery
    - Tumour excision **or** mastectomy +/- breast reconstruction
    - **Plus** sentinel lymph node biopsy (no evidence of nodal spread) **or** axillary node clearance.
- **Plus:** radiotherapy
    - Whole breast / partial-breast
    - If tumour is invasive (i.e. not DCIS, LCIS), systemic third line therapy is indicated:
- **Adjuvant:** systemic therapy (guided by the PREDICT tool)
    - Oestrogen-receptor positive:
        - Pre-menopausal / male - **tamoxifen** (anti-oestrogen)
        - Post-menopausal - **anastrozole / letrozole** (aromatase inhibitor, prevents peripheral oestrogen synthesis).

        - Note - tamoxifen therapy can be continued long-term (5 years) before switching to an aromatase inhibitor.
    - HER2 (human epidermal growth factor receptor 2) positive:
        - Trastuzumab (Herceptin)
    - Chemotherapy:
        - Including a **taxane** and an **anthracycline**
        - E.g. ACT: doxorubicin, cyclophosphamide and paclitaxel.
- Note - systemic therapies can be **neoadjuvant** i.e. used to reduce tumour size before attempting surgery.

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