- 2nd line is Metformin (CAN ADD TO CLOMIFENE)
- Lower birth rate than Clomifene but no increased risk of multiple pregnancy
- Good for treating hirsutism and if continued in pregnancy reduce risk of miscarriage and gestational DM
- Laparoscopic ovarian diathermy can lead to regular ovulations for many years
- Gonadotropins (LH/FSH) via subcut injections used in hypothalamic hypogonadism is weight is normal and if Clomifene fails
- In PCOS a low dose step up regime is used to minimise multiple pregnancy risk (monitored via US)
- LH/Hcg is then given to stimulate ovulation
- FINAL STRAW IS IVF

Risks of ovulation induction

1. Multiple pregnancy (also risk in IVF)
2. Ovarian Hyperstimulation Syndrome
   - gonadotrophins/ clomifene over stimulate follicles which become very large and painful
   - more common in IVF
   - young age, previous OHSS and PCO are risk factors
   - prevention is by using low gonadotrophin doses, US monitoring, withdrawing gonadotrophins fo a few days, cancelling IVF cycle
   - In severe cases can cause: hypovolaemia, electrolyte disturbance, ascites, thromboembolism, pulmonary oedema → hospital

Male subfertility

- In spermatogenesis LH (via testosterone from Leydig cells) and FSH control Sertoli cells which produce sperm
- Takes 70 days for sperm to develop fully
- Sperm analysed in semen analysis and in abnormal result must be repeated after 12 weeks

Normal sperm

- Volume: >1.5ml
- Sperm count: >15 million/ml
- Progressive motility: >32%
- Azoospermia (no sperm)
- Oligospermia
- Asthenospermia (low motility)

Causes of abnormal sperm

- Unknown
- Drugs (alcohol, smoking, anabolic steroids, industrial chemicals)
- Varicocele
Assisted conception

**IUI**
- Sperm injected directly into uterine cavity during normal cycle or with gonadotropin ovulation induction
- Requires tubal patency and is less successful than IVF but is cheaper

**IVF**
- Success rate is 35% in < 36 YO but <10% in 40s
- Normal ovarian reserve is required and is measured using serum levels of antimullarian hormone produced in ovary and using US of ovarian follicles
- GnRH Analogues given → LH and FSH → negative feedback → HPG axis shut down → induced menopausal state with low LH and FSH and a thin endometrium to prevent premature ovulation (long protocol)
- Note in short protocol, pituitary suppression is not reached before starting gonadotrophin injections and so GnRH antagonists are given during gonadotrophin injections
- FSH injections are then given and the development of the follicles if monitored via scan and endometrial thickening is checked
- Note at this stage Hyperstimulation of the ovaries is possible and is very serious!
- When a certain number of mature follicles is reached the FSH is stopped and 10 000 units of beta Hcg is given (LH analogue) → 36 hours later the eggs are surgically harvested from the ovaries (aspirated transvaginally under US control)
- The egg is then mixed with sperm produced 24 hours prior or ICSI can be used (High Risk!)
- Fertilisation takes place and embryo grows in culture medium for 2-6 days
- Usually 2 (max 3) embryos are then implanted into the uterus and the rest are frozen
- Progesterone is given until 4-8 weeks gestation

**ICSI**
- Used in male fertility problems
- Sperm injected into cytoplasm of oocyte

**Oocyte donation**
- For women who cannot conceive with their own eggs
- Donor goes through cycle of IVF and her retrieved oocytes are fertilized with recipients partners sperm → implanted into recipients uterus after preparation with oestrogen and progesterone

**Preimplantation Genetic Diagnosis**
- 2 cells from 8 cell preimplantation embryo removed → analysed using PCR and FISH for genetic abnormalities → useful if parents carriers e.g. CF or chromosomal abnormalities
Post coital Bleeding

- Always abnormal except first time!
- Ensure not menstrual loss!
- Need to exclude cervical ca!
- Causes: cervical carcinoma, cervical ectropion (abnormal cells out vaginal surface of cervix, cervical polyps, vaginitis, cervicitis (SEE CERVIX SECTION)
- Tx: inspect cervix, smear, remove any polyps and sent for histology, cryotherapy for ectropion
- If smear abnormal → colposcopy and biopsy to exclude cervical ca

Dysmenorrhoea

- Associated with high prostaglandin levels in endometrium and due to contraction and ischaemia
- Causes: Primary (no cause found- very common in adolescents- treat with NSAIDs/ COCP- pathology more likely if no response), Secondary (pelvic pathology present-pelvic US and hysteroscopy helpful- fibroids, Adenomyosis, endometriosis, PID, ovarian tumours- tx cause)

Precocious puberty

- Secondary sexual characteristics< 8 years or menstruation < 10 years
- Ix and Tx essential to investigate cause and prevent short stature
- 80% no cause found → GnRH analogues
- Meningitis, encephalitis, CNS tumours, hyper-thyro thyroidism → increased GnRH secretion
- Ovarian/ adrenal hormones producing tumour

Ambiguous Genitalia

- SEE CAH and Androgen insensitivity syndrome earlier!

PMS

- Behavioural, psychological and physical changes occurring for 2 weeks before menstruation (during luteal phase)
- Tx: SSRIs, CBT, More extreme treatments if very severe e.g. GnRH analogues with add back HRT
Many different combinations with different strengths
- Tibolone a synthetic steroid can be used in women who desire amenorrhoea and treats symptoms
- Androgens e.g. testosterone can be used as sc implant/ patch → improves libido

Benefits and Risks of HRT

<table>
<thead>
<tr>
<th>Benefits</th>
<th>Risks</th>
<th>Uncertainties</th>
</tr>
</thead>
<tbody>
<tr>
<td>Helps symptoms</td>
<td>Oestrogen only → increased risk of endometrial ca</td>
<td>CVD</td>
</tr>
<tr>
<td>Prevents osteoporosis</td>
<td>Slight increased risk of breast ca (combined not oestrogen only)</td>
<td>Dementia</td>
</tr>
<tr>
<td>Reduces risk of colorectal ca</td>
<td>Oral HRT → increased risk of VTE and gallbladder disease</td>
<td>Ovarian ca</td>
</tr>
</tbody>
</table>

Duration of HRT

- Menopausal symptoms → up to 5 years then stop and see if recur
- Osteoporosis → lifelong (but may swap to bisphosphonates)
- Premature menopause → until 51 Yo

None HRT treatment

- Hot flushes/ sweats → progestogens only, SSRIs
- Osteoporosis → bisphosphonates, raloxifene (oestrogen receptor modulator), PTH peptides, calcium and VIT D supplements

Post-menopausal bleeding

- PV bleeding at least 12 months after last period
- Causes: endometrial ca, cervical ca, ovarian ca, endometrial hyperplasia, cervical polyps, atrophic vaginitis
- NOTE: regular bleeds with HRT are normal
- Ix: bimanual and speculum exam, cervical smear, transvaginal sonography, hysteroscopy + biopsy if endometrium > 4mm thick/ multiple bleeds
- Tx: treat cause or if atrophic vaginitis → oestrogen
2. Blood tests: FBC for anaemia (IDA is common), platelets (HELLP syndrome?), thalassemia/sickle cell, anti D antibodies, OGTT, Syphilis blood test, check rubella immunity, HIV and Hep B screening offered, haemoglobin electrophoresis, 

3. Screening for infection e.g. chlamydia, bacterial vaginosis, HIV, Hep B, syphilis, Rubella. Don’t do CMV/ toxoplasmosis unless signs of complications e.g. polyhydramnios

4. Urine M and C for asymptomatic bacteriuria (v.common) → TREAT

5. Urine analysis for glucose (DM), protein (renal disease e.g. hypertensive nephropathy or if after 20 weeks think preeclampsia) and nitrates (infection)

- Advice given on eating a balanced diet (avoiding alcohol especially in first trimester), stopping smoking, exercise advised, sleep in left lateral position

Later pregnancy screening

- Anomaly scan at 21 weeks to detect foetal abnormalities
- At 15-20 weeks can do a quadruple screen for Down Syndrome involving measurement of AFP, estriol, hCG and inhibin A
- Doppler US of uterine arteries at 23 weeks can screen for intrauterine growth restriction and pre-eclampsia
- Another scan at 32 takes place if placenta has been found to be low lying

Red blood cell isoimmunisation

- Mother mounts immune response against antigens on foetal RBCs which cross placenta and cause RBC destruction in baby
- Rhesus D allele is dominant so anyone who had D allele is rhesus positive
- Anyone who has dd is rhesus negative and will recognise D antigen as foreign
• 15% of Caucasian women are -ve

• Small amounts of foetal blood enter mother’s circulation across placenta during pregnancy and large amounts at sensitising events: delivery, TOP, evacuation of retained products after miscarriage, heavy bleeding, ECV, invasive uterine procedure e.g. amniocentesis, ectopic pregnancy etc...

• If foetus is D positive (from father) and mother is negative then she will amount an immune response creating anti D antibodies (sensitization)

• If mother is again exposed in antigens e.g. another pregnancy, then she will create lots of antibodies, which can cross the placenta and destroy foetal RBCs → neonatal jaundice if mild or haemolytic anaemia of new-born if more severe or even in utero anaemia → foetal death

• Women are checked at booking and 28 weeks for antibodies

• Anti D is given to all mothers who are –ve at 28 weeks and within 72 hours of sensitising event to mop up any blood from foetus before it can be recognised by immune system and any antibodies formed

• Anti D is pointless after mother has already produced antibodies after sensitising event

• Post nata tally if baby found to be +ve after delivery → mother given anti D within 72 hours + kleihauer test performed to see if larger doses needed

• Anti D is not needed if foetus known to be –ve (both mother and father are negative) → although often still given due to sensitive possibility of non-paternity

• Pregnan cies at risk of foetal anaemia are assessed fortnightly using Doppler US of the peak velocity in systole of the foetal middle cerebral artery

• Very severe anaemia is detectable as hydrops or excessive foetal fluid

• If anaemia is suspected → fetal blood sampling from umbilical vein → treated with foetal blood transfusion through needle

Minor conditions of pregnancy

• Itching is common and non-pathological- check for jaundice, LFTS, bile acids

• Pelvic girdle pain

• Abdominal pain- common in pregnancy but beware of surgical/ medical pathology (UTIs and Fibroids can cause pain)

• Heartburn is common and antacids can be used (NOTE PRECLAMPSIA CAN PRESENT WITH EPIGASTRIC PAIN)

• Backache

• Constipation is common and a high fibre diet and stool softeners are used

• Ankle oedema is common BUT MAY BE A SIGH OF PRECLAMPSIA IF SUDDEN (Note that diuretics are contraindicated)

• Leg cramps

• Carpal tunnel syndrome

• Vaginitis due to candidiasis → imidazole pessaries

• Tiredness is almost universal
Ankle/foot/hand oedema  check kidney function (RF) + consider pre-eclampsia  ask if gets worse during the day as normal oedema in pregnancy will do

Physiological changes in pregnancy

- 10-15Kg weight gain
- Uterus increases in weight and muscle hypertrophies
- Cervix softens
- Blood volume increases by 50% and red cell mass increases
- Haemoglobin decreases and WBC count increases
- Increase in glomerular filtration rate (creatinine/ urea decrease)
- Thyroid enlargement

Detection of congenital Abnormalities

- Congenital abnormalities can be due to chromosomal abnormalities, single gene disorders structural deformities or due to drugs e.g. antiepileptic’s
- Account for 25 % of perinatal deaths and major cause of future disability
- Parental choice whether to carry out screening tests- info given at booking visit
- Remember difference between screening test (assesses risk) and diagnostic test (confirms whether have disease)
- A screening test should: have high sensitivity and specificity, be cheap, be accessible, be acceptable, have an effective diagnostic test associated and be looking at a serious treatable condition

Methods of prenatal testing

- Maternal blood testing: AFP is raised in NTDs and gastrochisis/fomphecele; levels of markers e.g. beta hCG, PAPP A, AFP and inhibin A can be altered in chromosomal abnormalities e.g. Downs
- US: confirm gestational age; screen of abnormalities e.g. nuchal translucency for Downs; aid CVS and amniocentesis; diagnose abnormalities at ‘anomaly scan’
- MRI: look at foetal intracranial lesions and differentiate between soft tissues
- Amniocentesis: removal of some amniotic fluid under US guidance after 15 weeks gestation  diagnose chromosomal abnormalities, infections e.g. CMV and inherited conditions e.g. CF
- CVS: sampling of chorion trophoblast from placenta after 11 weeks  allow to identify similar conditions to amniocentesis but done earlier so will allow earlier TOP. HOWEVER HIGHER RISK!
- Chromosomal abnormalities (more common with increasing age): Downs discussed below. Trisomy 18 (Edwards) and trisomy 13 (Pataus) are associated with major structural defects  foetus dies in utero or soon after birth. Also Turners and Klinefelters!
• Obtain IV access, cross match, give anti D, NBM
• If unstable + symptomatic + hCG>3000 → resuscitate → surgery (salpingectomy) often via laparotomy
• In subacute presentations laparoscopy is commonly performed and ectopic is removed from tubes (salpingostomy) or tube removed (salpingectomy)
• If ectopic is unruptured, with no cardiac activity and hCG<3000 → single dose methotrexate
• hCG levels monitored after methotrexate, salpingostomy to confirm ectopic resolution
• If small, unruptured, localisation is not clear, hCG levels<3000 and declining, and asymptomatic then observation may suffice

Hyperemesis Gravidarum

• N and V in early pregnancy is so severe it causes dehydration, weight loss and electrolyte imbalance
• Most women who vomit in pregnancy only have mild (N and occasional morning V, no treatment) or moderate (more persistent vomiting, often admitted) nausea and vomiting of pregnancy (NVP)
• Seldom persist beyond 12 weeks
• More common in multiparous women

Treat

• Exclude UTI, Multiple pregnancies, molar pregnancies (in latter 2 → large placenta → increased hCG → hyperemesis)
• IV fluids
• Antiemetics
• Thiamine to prevent neurological damage (wernickes)
• Steroids in severe cases
• Psychological support

Gestational Trophoblastic disease

• Trophoblastic tissue from placenta that usually invades endometrium, proliferates more than normal and secretes excess hCG
• More common in extremes of reproductive age and in Asians
• CAUSES EARLY PREGNANCY BLEEDING
• Hydatidform moles are localised non-invasive proliferations and can be divided into complete/ partial moles.
• Complete moles are entirely paternal and are when a sperm fertilises an empty oocyte → diploid 46 XX ball of chorionic villi.
• A partial mole is triploid, from 2 sperm entering one oocyte → variable evidence of a foetus.
• Mole may show signs of malignancy: invasive if this is within the uterus locally or choriocarcinoma if metastasis occurs.
• If persistence of gestational trophoblastic disease (high hCG beyond 26 weeks) = gestational trophoblastic neoplasia → high risk patients get chemotherapy (100% 5 year survival).
• Symptoms are often of PV bleeding, hyperemesis and on examination the uterus is often large and early pre-eclampsia and hyperthyroidism may occur.
• Investigations: high hCG, US, histological diagnosis.
• Treatment: tissue removed by suction curettage (surgery) and thereafter serial blood and urine hCG levels are taken to monitor for malignancy.
• If partial can be OBSERVED AND TERMINATED IF REQUESTED.
• Management guided by national specialist centres.
• Pregnancy and COCP are avoided until hCG levels are normal.
• After every future pregnancy hCG levels are required to exclude recurrence.

SO NOTE THE THREE MAIN CAUSES OF EARLY PREGNANCY BLEEDING ARE MISCARRIAGE, MOLAR PREGNANCIES, AND ECTOPIC PREGNANCY!
Infections in pregnancy

Important because: maternal illness may be worse e.g. VSV, cause maternal complications e.g. pre-eclampsia in HIV, associated with preterm labour, vertical infections can be teratogenic, cause miscarriage or serious illness in child (like HIV and Hep B), increases risk of neuro damage and antibiotic use in pregnancy may be restricted

CMV

- 1% of women develop
- May cause IUGR, pneumonia thrombocytopenia and later hearing, visual and mental impairment or will die
- Diagnosis by maternal CMV Ig testing → if positive amniocentesis for vertical transmission
- Monitor foetus via US and blood sampling at 32 weeks
- Most maternal infection does not lead to problems in fetus
- TOP offered

Herpes Simplex

- Neonatal infection is rare but has high mortality
- Vertical transmission occurs during labour if vesicles present
- Diagnosis clinical/ swabs
- Refer to GUM
- C section if delivering within 5 weeks of primary attack, vesicles present from primary infection (normal delivery if vesicles from recurrent herpes)
- Mother given aciclovir towards end of pregnancy and neonates are given it too

Rubella

- Very rare in UK due to immunisations
- Maternal infection in early pregnancy causes fetal deafness, cardiac disease, eye problems and mental retardation
- TOP offered if non immune mother infected
- Screening done at booking to identify mothers who need vaccination at end of pregnancy (LIVE SO CANNOT GIVE DURING)

Toxoplasmosis

- Due to protozoa from soil, faeces, meat
- 0.2% of mothers
- Under half of foetuses develop mental retardation, convulsions and visual impairment
- Diagnosed in mum by serum IG → amniocentesis to check for VT
- Spiramycin for maternal infection
- TOP offered

Herpes zoster
Baby has small amount of colic and was put on IV gentamicin and penicillin IV for 7 days. Observations stable, raised CRP → neonatal unit. Baby check normal

PMH

Hypothyroidism

DH

Allergic to hydrocortisone

IV co-amoxiclav + metronidazole