• Chromosomes in sperm (haploid) = 23X or 23Y (as males have XY in their germ cells)

• Chromosomes in oocyte (haploid) = 23X (as females have XX in their germ cells)

• Fertilisation occurs when sperm (haploid cells) fuses with oocyte (haploid cell) to form a gamete (diploid cell) with a full set of 23 pairs of chromosomes (22 pairs of autosomal and 1 pair of sex chromosomes)

• So it is the type of sperm (X or Y) which fertilises the egg which determines chromosomal sex

• Possibilities:
  • 46 XX => female chromosomal sex
  • 46 XY => male chromosomal sex (it is the Y which causes male development)

• However there are other factors involved which determine our “gender” e.g. hormonal regulation, genetic mutations, etc

• Ways of defining sex:
  
  ➢ **Chromosomal sex**: 46 XX = female; 46 XY = male chromosomal sex (Y=> male)
  
  ➢ **Gonadal sex (internal reproductive tract)**: if Y is present and functional we get development of testes; if Y is absent or non-functional, we get development of ovaries
  
  ➢ **Genital sex (external reproductive tract)**: if Y is present and the testes develop it secretes hormones (e.g. Mullerian factor and androgens e.g. testosterone) we get development of male external genitalia e.g. penis and scrotum + secondary male characteristics. If Y is absent => testicles absent => testicular hormones absent => then we get development of female external genitalia e.g. vagina and clitoris + female secondary characteristics
  
  ➢ **Gender**: perceived genital sex + rearing of individual as male or female => results in gender identity.

**Bipotential gonad**

• Everyone is born with the potential to be either male or female. Everyone is born with both the Wolffian duct / Mesonephric duct (male duct system) and the Mullerian duct / Paramesonephric duct (female duct system).

• **What determines sex is the presence or absence of the SRY gene on the male Y chromosome.** The SRY gene (on Y chromosome) is what causes testis to develop.
• Lack of Mullerian inhibiting factor causes Mullerian ducts to develop into female reproductive tract e.g. oviducts (fallopian tube) and uterus

• Absence of testosterone causes:
  
  ➢ Degeneration of Wolffian ducts (male reproductive tract)

  ➢ Undifferentiated external genitalia to develop into female genitalia

Summary

• Chromosomal sex: 46XX (female) or 46XY (male)
• Gonadal sex: internal reproductive tract sex
• Genital sex: external reproductive tract sex
• “Gender”: way the child is raised
Clinical example: Androgen insensitivity syndrome (testicular feminisation syndrome)

- Congenital insensitivity to androgens e.g. condition that results in the partial or complete inability of the cell to respond to androgens (male sex hormones)
- X-linked recessive disorder which only affects male karyotypes (male chromosomal sex)
- Disorder of male karyotype (46XY) => male chromosomal sex => testis develop
- Testosterone is secreted, however the tissues of the developing genital tract are unresponsive to it
- The unresponsiveness of the cells of the developing genital tract to the presence of androgenic hormones (androgen resistance) can impair or prevent the development of male reproductive tract and masculinization of the male external genitalia in the developing fetus, as well as the development of male secondary sexual characteristics at puberty
- Testis develop due to presence of SRY on Y chromosome (but do not descend – as this is under control of testosterone) => testes release androgens (testosterone from Leydig cells) and Mullerian inhibition factor (from Sertoli cells)
- Androgen induction of wolffian duct does not occur (due to androgen resistance) => internal male reproductive tract does NOT develop
- Androgen induction of undifferentiated external genitalia is dysfunctional => external female genitalia may develop
- Mullerian inhibition does occur (as anti-mullerian released from Sertoli cells) => degeneration of internal female reproductive tract
- Therefore individuals with complete androgen insensitivity are born with male chromosome sex, phenotypically external female genitalia (with short vagina), with an absent uterus and ovaries.
- Often brought up as females due to the external “genital sex”
- Commonly present at puberty with primary amenorrhea (never menstruated), and lack of pubic hair (absent pubarche)
- There are two types of AIS, which are determined by the level of insensitivity to androgen. They are:
  - **Complete androgen insensitivity syndrome (CAIS)**, where there is total insensitivity to androgen and a child (chromosomally male) develops external genitals that are entirely female. However the production of Anti-Mullerian from the testis results in the absence of uterus and ovaries = > infertile as no male or female internal sex organs. Most children born with CAIS are brought up as girls (but have male chromosomal sex)
To preserve the number of chromosomes in the offspring, each gamete must have half the usual number of chromosomes present in other body cells. Otherwise, the offspring will have twice the normal number of chromosomes, and serious abnormalities may result. In humans, chromosomal abnormalities arising from incorrect spermatogenesis can result in Down Syndrome (trisomy 21 most commonly – Non disjunction), Klinefelter’s Syndrome (47XXY), and spontaneous abortion.

Spermatogenesis takes place within several structures of the male reproductive system.

The initial stages occur within the testes (seminiferous tubules) and progress to the epididymis where the developing gametes mature and are stored until ejaculation.

Maturation of sperm occurs in the epididymis

A spermatozoon

A spermatozoon is a motile sperm cell e.g. mobile male gamete (haploid)

A spermatozoon joins an ovum to form a zygote (a zygote is a single cell, with a complete set of chromosomes, that normally develops into an embryo)

Features of spermatozoon:

- **Acrosome:** containing enzymes that play an important role in the penetration through the zona pellucida of the oocyte
• Released by the hypothalamus and travels to the anterior pituitary by the portal system
• Stimulates the anterior pituitary to produce and release LH and FSH
• Under negative feedback control from testosterone

Luteinizing hormone (LH) and follicular stimulating hormone (FSH)

• Glycoproteins secreted by anterior pituitary
• Secretion of LH and FSH is stimulated by gonadotropin-releasing hormone (GnRH) from the hypothalamus
• Secretion of LH and FSH is under negative feedback control from testosterone
• Production is non-cyclical in males (in contrast to females) => constantly fertility in males
• Luteinizing hormone (LH):
  - Acts on Leydig cells to stimulate testosterone secretion
  - Regulated by negative feedback from testosterone
• Follicle stimulating hormone (FSH):
  - Acts on Sertoli cells to enhance spermatogenesis
  - Regulated by negative feedback from inhibin
  - Regulated by positive feedback from activin which stimulates FSH production
  - Regulated by negative feedback from testosterone

Testosterone

• Produced in Leydig cells in response to LH stimulation
• Steroid hormone derived from cholesterol
• Secreted into blood and seminiferous tubules for sperm production
• Negative feedback on hypothalamus and pituitary gland => high levels of testosterone feedback the hypothalamus to decrease GnRH and feedback to the pituitary to decrease LH and FSH
• Testosterone Effects:
  - Before birth: masculinises internal reproductive tract, induces development of male external genitalia, and promotes descent of testes
- Seminal vesicles: **Produce semen (semen fluid)** into ejaculatory duct, supply fructose (alkaline), secrete prostaglandins (stimulates motility), secrete fibrinogen (clot precursor). Produce most of the fluid in semen.

- Prostate Gland: **Produces alkaline fluid** (neutralizes vaginal acidity), produces clotting enzymes to clot semen within female, contracts to aid ejaculatory force (peristalsis), phosphatases

- Bulbourethral Glands: **Secrete mucus** to act as lubricant

### Delivery of sperm to female

- Testes:
  - Produce sperm in **seminiferous tubules**
  - Sperm is transferred to rete testes. The rete testis is an anastomosing network of delicate tubules that carries sperm from the seminiferous tubules to the efferent ducts. The efferent ducts connect the rete testis with the initial section of the epididymis.
  - The epididymis is composed of tightly coiled ducts lying just outside each testis connecting efferent ducts to vas deferens. The epididymis is for **storage and maturation** of sperm.

- Route of sperm: spermatogenesis (seminiferous tubules) => rete testis => epididymis => vas deferens => efferent ducts => prostatic urethra => +/- female vagina

- Erection: blood fills corpora cavernosa (corpus cavernosum) - under parasymathetic control => point

- Emission: contraction accessory sex glands and vas deferens (peristalsis) so semen expelled to urethra

- Ejaculation: contraction of smooth muscles of urethra and erectile muscles (under sympathetic control => shoot)

- Problems if premature or retrograde ejaculation e.g. neuropathy (e.g. DM), prostate surgery or anticholinergic drugs (blocking of parasympathetic NS => problems with erection)

### Fertilisation in ampullary region of Fallopian Tube
- An obstruction preventing sperm release, due to injury or infection
- Congenital absence of the vas deferens e.g. due to CF
- Vasectomy
- Non-obstructive azoospermia (testicular failure) the testicles are producing such low numbers of sperm that they don’t reach the vas deferens

• In the first three conditions, sperm are produced by the testes, but are unable to be ejaculated because of the blockage or absence of the vas deferens. The man can still ejaculate seminal fluid (semen) but this fluid will not contain any sperm. It is possible to collect sperm directly from the epididymis.

• In cases of non-obstructive azoospermia (complete absence of sperm in semen), very small amounts of sperm may be produced and can be collected directly from the testes (seminiferous tubules). This is done by performing multiple testicular biopsies at random. In these cases a biopsy will normally be sent to the laboratory for analysis as to the possible cause of the problem.

**Intracytoplasmic Sperm Injection (ICSI)**

- Indications: very low sperm count (severe oligozoospermia; if non severe oligozoospermia then can use intra-uterine insemination) or azoospermia (if collected by surgical sperm aspiration)

- Intra-cytoplasmic sperm injection (ICSI) involves injecting a single sperm directly into an egg in order to fertilise it (in-vitro e.g. out of body). The fertilised egg (embryo) is then transferred to the woman’s uterus. The major development of ICSI means that as long as some sperm can be obtained (even in very low numbers), fertilisation is possible.

- **Type of IVF (in-vitro fertilisation)** e.g. an egg is fertilised by sperm outside the body

- Procedure: Sperm collected (e.g. via surgical sperm aspiration) and injected into stripped oocyte obtained during IVF.
• This is when you have had a miscarriage (=> FH –ve) but there is still some tissue left in the uterus

• This occurs when the products of conception (POC) are only partially expelled => retained products of conception

• Lower abdominal pain

• Heavy vaginal bleeding with clots/tissues

• Cervical shock +ve: The patient may be in cervical shock. The vaso-vagal effect of the products of conception passing through the cervix causes a reflex bradycardia and vasovagal syncope. In this situation the remaining products of conception should be removed using a sponge-holding forceps. The shock normally resolves spontaneously. Other causes of shock such as hypovolaemia may also occur and are associated with a tachycardia.

• Tenderness and pain +ve

• Cervix open (cervical os open) – this distinguishes from missed where cervical os is closed

• Products of conception (POC) may be present in cervix (cervical canal)

• FH –ve (this distinguishes from inevitable miscarriage)

Complete miscarriage

• This means that you have lost your pregnancy and your uterus is empty

• History similar to incomplete followed by cessation of bleeding

• Uterus smaller than < gestation age => as no products of conception in uterus

• Cervix closed (cervical os closed)

• FH –ve

Septic miscarriage

• Infection following a miscarriage

• Can cause septic shock (vasogenic shock due to peripheral vasodilation) e.g. presenting with tachycardia, hypotension, cold clammy skin, increased CRT etc

Missed miscarriage ("silent miscarriage")
- NB: Although hCG is sensitive to ectopic pregnancies, it is clearly not selective! Beta-hCG is raised in normal pregnancies or hydratiform mole or rare germ cell tumours.

- **Diagnostic laparoscopy**

- **Diagnostic laparotomy for Tx as well as Dx if pt is shocked and there is clinical suspicion**

**Treatment of Ectopic pregnancy**

- **Conservative management:** *'Wait and see' (expectancy)*. Not all ectopic pregnancies are life-threatening or lead to a risk to the mother. In many cases the ectopic pregnancy resolves by itself with no future problems. The pregnancy often dies in a way similar to a miscarriage. A possible option is to see how things go if you have mild or no symptoms. You would need to have treatment if symptoms become worse. Also, you will need close observation and repeated scans and blood tests to check on how things are developing.

- **Laparoscopic salpingotomy:** Surgeons use laparoscopy to gain access to the pelvis and can incise the affected Fallopian and remove only the pregnancy

- Laparoscopic salpingectomy: surgical removal of the affected fallopian tub with the pregnancy

- **Methotrexate:** Early treatment of an ectopic pregnancy with methotrexate is a viable alternative to surgical treatment. If administered early in the pregnancy, methotrexate terminates the growth of the developing embryo, this may cause an abortion, or the developing embryo may then be either absorbed by the woman's body or pass with a menstrual period.

- **Laparotomy if ectopic pregnancy is ruptured:** A laparotomy is a surgical procedure involving a large incision through the abdominal wall to gain access into the abdominal cavity.

**Gestational Trophoblastic Disease**

- Gestational trophoblastic disease (GTD) forms a group of disorders which **range from hydatidiform mole to malignant conditions such as choriocarcinoma.**

- If there is any evidence of persistence of GTD the condition is referred to as gestational trophoblastic neoplasia (GTN).

- **Cure rates are excellent for this condition.** This is due to central registration and monitoring in the UK, the use of beta human chorionic gonadotrophin (beta-hCG) as a biomarker, and the development of effective treatments.

- GTD is classified as follows:
In complete molar pregnancies, all the genetic material comes from the father. An empty oocyte lacking maternal genes is fertilised. This is an ovum not carrying any chromosomes or genetic material. Under normal circumstances, the fertilised empty ovum would die and not implant in the uterus. But rarely, the ovum doesn't die and implantation takes place. Most commonly (75-80%) this arises from a single sperm duplicating within an empty ovum. Therefore there is no maternal DNA present => no fetal tissue develops. However, the trophoblast cells grow and develop as a disorganised mass of tissue but the embryo does not develop. This is a complete hydatidiform mole. There is no tissue resembling an unborn baby (a fetus) at all.

In partial molar pregnancies, the trophoblast cells usually have three sets of chromosomes (triploid). Two sperm are believed to fertilise an ovum (with genetic material) at the same time, leading to one set of maternal and two sets of paternal chromosomes. This means that there is too much genetic material present => also results in the development of too much trophoblastic tissue. The growth of the trophoblastic tissue overtakes the growth of any fetal tissue and the fetus does not develop normally. There is usually evidence of fetal tissue or fetal blood cells in a partial molar pregnancy. An embryo (fetal tissue) may be present at the start.

Both complete and partial molar pregnancies (hydratiform moles) are 'non-viable' pregnancies. A pregnancy that results in a partial hydatidiform mole is called a molar pregnancy.

NB: Trophoblasts are cells forming the outer layer of a blastocyst. They develop into a large part of the placenta (foetal part). They are formed during the first stage of pregnancy and are the first cells to differentiate from the fertilized egg.

Clinical Features

- Pregnancy symptoms:
  - Amenorrhoea (periods stopping) and +ve pregnancy test
  - Nausea
  - Vomiting: abnormally high levels of beta-HCG may cause hyperemesis gravidarum (abnormally high levels of bHG can also cause thyrotoxicosis)
  - Breast tenderness

- Vaginal bleeding: vaginal bleeding early in the pregnancy. This is the most common symptom. Many women suspect that they are having a miscarriage. MAY BE HEAVY.

- Uterus larger than dates: patient may feel bigger than expected for gestational age. This is because a molar pregnancy grows more quickly than a normal pregnancy would, due to the abnormally developing trophoblastic tissue (placental tissue)
genetic material) at the same time, leading to one set of maternal and two sets of paternal chromosomes.

- Choriocarcinoma is a malignant, trophoblastic cancer, usually of the placenta. It is characterized by early hematogenous spread to the lungs. It belongs to the malignant end of the spectrum in gestational trophoblastic disease (GTD).

- It is also classified as a germ cell tumor and may arise in the testis or ovary.

- Choriocarcinoma of the placenta during pregnancy is preceded by:
  - Hydatidiform mole (50% of cases)
  - spontaneous abortion (20% of cases)
  - ectopic pregnancy (2% of cases)
  - normal term pregnancy (20-30% of cases)

- Rarely, choriocarcinoma occurs in primary locations other than the placenta; very rarely, it occurs in testicles.

- Clinical features in females:
  - increased quantitative β-hCG levels (very high levels)
  - Vaginal bleeding
  - Shortness of breath
  - Haeemoptysis (coughing up blood)
  - Pleuritic chest pain
  - Chest X-ray shows multiple infiltrates of various shapes in both lungs

Cervical Incompetence

- The cervix is the narrow, tubular, lower end of the uterus that extends into the vagina eg. the neck of the uterus.

- When you’re not pregnant, the cervical canal remains open a tiny bit to allow sperm to enter the uterus and menstrual blood to flow out.

- Once you become pregnant, secretions fill the canal and form a protective barrier called the mucus plug. During a normal pregnancy, the cervix remains firm, long, and tightly closed until late in the third trimester.

- At that point it usually starts to soften, efface (grow shorter and thinner), and dilate (open up) as your body prepares for labour.
Atrial septation

- Atria start off as common chamber => single common communication into primitive ventricle
- 1st event in atrial septation => growth of septum primum
- Don’t want to completely separate just yet => apoptosis to create ostium secundum (hole in septum primum)
- Once this is in place => growth from septum secundum. The septum secundum grows downward from the upper wall of the atria immediately to the right of the primary septum and ostium secundum.
- Doesn’t completely fuse => formation of foramen ovale
- In the foetus, blood can flow through foramen ovale through ostium secundum into left atrium (right to left shunt), which allows blood to bypass pulmonary system
- In the foetus, blood must bypass the non-functioning pulmonary circulation => the reason for the foramen ovale (this is the same reason for the ductus arteriosus which allows a R to L shunt from the pulmonary trunk to the proximal descending aorta)
- Shortly after birth the septum secondum fuses with the septum primum, and consequently the foramen ovale is closed, but sometimes the fusion is incomplete and the upper part of the foramen remains patent
- Approximately 1/4 people have this “hole in the heart” which is usually kept close due to the large pressure difference from left to right
Congenital diaphragmatic hernia

- A diaphragmatic hernia may result from failure of fusion of its constituent parts (4 parts form the diaphragm)
- Most commonly on left side
- Usual cause is a defect in the formation of the pleuroperitoneal membrane
- Abdominal contents will herniate through into thoracic cavity
- Abdominal contents can compress on lungs => severe impact on lung development => pulmonary hypoplasia => small hypoplastic lung => decreased gas exchange
- Often on left side => left hypoplastic lung and shifting of apex beat to the right
• A woman’s reproductive (menstrual) cycle is controlled by the pituitary gland (LH and FSH).

• Hormones from the pituitary gland tell the follicles in the ovaries when to grow (FSH) and when to rupture (LH surge) and release an egg.

• The pituitary gland needs to be “switched off” before the woman can receive drugs to stimulate egg production (ovarian hyperstimulation).

• This is because these drugs stimulate the production of a “follicle.” A follicle is an immature egg, surrounded by a bubble of fluid, in the ovary. In IVF we want to stimulate as many follicles to grow as possible. If the pituitary gland is not “switched off” it may release a hormone (LH surge) that causes the follicles to burst (“spontaneous ovulation”) => we must suppress (down regulate) the pituitary release of LH and FSH, so that we can adequately hyperstimulate the ovaries and control when ovulation occurs.

• The drugs used to switch off your reproductive cycle are called gonadotrophin-releasing hormone analogues, or GnRH analogues for short. They may include **buserelin (similar to goserelin used in prostate cancer)**. You will need to take these drugs every day.

• **Buserelin (GnRH analogue) can be taken as a nasal spray or injection.**

• High doses of GnRH analogues cause reversible down regulation of the pituitary => suppression of LH and FSH.

• Having your reproductive cycle turned off trickles into your body thinking it is going through the **menopause**. Because of this, you may experience symptoms similar to those of the menopause such as:
  - Hot flushes and night sweats
  - Mood swings
  - Headaches
  - Dizziness
  - Lack of concentration
  - Dry mouth and vaginal soreness

• Other symptoms include nasal irritation (if on nasal buserelin)

• This **artificial menopause** (induced pituitary downregulation) is only temporary and will stop once the patient stops taking the drugs.

**Key points**

• Synthetic gonadotrophin releasing hormone analogue (**Buserelin**) is administered as a spray or injection and must be taken every day.
Reminder of menstrual cycle

Natural Family Planning (aka Fertility Awareness)

1. Calendar

- Ovulation occurs on 12-16 day (average) of menstrual cycle – usually 14 days before menstruation (Luteal phase is usually 14 days)

- Allows for survival time of ovum and sperm => intercourse must be avoided between day 10 and 20 of the menstrual cycle (for 28 day cycle)
No professional help required

- Short-term motivation
- **Provide protection against STI’s**

**Correct use of Male Condoms**

- Use a new condom every time
- Check the packet for “KITE Mark” and “use by” date
- Be careful not to damage it when removed from the packet
- Pinch the top and unroll over erect penis prior to genital contact to expel air
- After use, withdraw penis holding base of condom and take it away from the genital area
- No vaseline or oil based lubricants e.g. baby oil
- **The use of condoms lubricated with spermicide is generally not recommended (may increase STI transmission due to vaginal irritation)**

**Female barrier methods**

- **Spermicides should always be used in conjunction with female barrier method =>** kills sperm and blocks sperm progression (do not cause vagina irritation as spermicide is localised)

**Barrier Methods - Female**

- Female Condom ‘Femidom’
- Diaphragm
- Cap
Lymphogranuloma venereum: serotypes L1, L2, L3 (associated with MSM males who have sex with males). Genital ulcer, followed by painful lymphadenitis and lymphangitis (in contrast to the painless lymphadenopathy seen in syphilis).

**Diagnosis**

**Females**

- **Endocervical swab** (females) if patient being examined (e.g. symptomatic) OR **self-taken vulvovaginal swab** (VVS) if not being examined (e.g. asymptomatic)
- Rectal swab (if appropriate e.g. patient admits to anal sex)

**Males**

- **First pass urine** (males): in contrast to MSSU to assess for UTI or prostatitis
- Rectal swab (if appropriate e.g. patient admits to anal sex)

**Microbiology** use the PCR test

- **Combined GC/CT PCR** for diagnosis
- Very accurate

**Complications**

**Women**

- Pelvic inflammatory disease (PID)
- Increased risk of **ectopic pregnancy** & **infertility**
- Eye infections (adults and neonates) e.g. Chlamydia conjunctivitis or trachoma

**Men**

- Epididymo-orchitis
- **Reiter’s syndrome** / reactive arthritis (rare in females): the triad of
  - Arthritis
N.B. Gonorrhoea can cause severe neonatal conjunctivitis

**Diagnosis of Chlamydia (CT) and Gonorrhoea (GC)**

**Males**

- **First pass urine** for combined GC/CT PCR
- Urethral swab for culture (only at SRH sexual reproductive health clinic)
- Rectal and throat swabs for culture and/or GC/CT PCR

**Females**

- **Endocervical swab for culture or GC/CT PCR** (if patient is symptomatic and being examined)
- **Self-taken vulvovaginal swab for combined GC/CT PCR** (if patient is asymptomatic, and not being examined)
- Rectal and throat swabs for culture and/or GC/CT PCR

**Combined GC/CT PCR tests**

**Pros**

- Detects alive bacterial DNA
- Very sensitive tests
- Minimally invasive specimens required
- Doesn’t matter if the bacteria die in transit to lab

**REMEMBER TO TEST FOR CURE**

**Cons**

- Detect DNA of dead bacteria too => must wait 5-6 weeks to do test of cure
- Occasional false positives (problem if used to test a low-risk population)
- Cannot monitor changes in antibiotic resistance
Reproductive lecture notes: week 2

PATHOLOGY OF THE CERVIX, VULVA AND VAGINA

Anatomy review

- **Ovaries**: The ovaries are a functioning reproductive organ (female gonads), often found in pairs as part of the female reproductive system. Ovaries in female individuals are analogous to testes in male individuals, in that they are both gonads and endocrine glands.

  - Oogenesis starts in the germinal epithelium, which gives rise to the development of ovarian follicles, the functional unit of the ovary.

  - **Ovaries secrete oestrogen, testosterone and progesterone.** In women, fifty per cent of testosterone is produced by the ovaries and adrenal glands and released directly into the blood stream. The other fifty per cent is made from conversion of the adrenal androgens to testosterone in other parts of the body.

  - Oestrogen is responsible for the appearance of secondary sex characteristics for females at puberty and for the maturation and maintenance of the reproductive organs in their mature functional state. Oestrogen also causes proliferation of the endometrium. Oestrogen stimulates breast duct growth.

  - Progesterone prepares the uterus for pregnancy (and inhibits uterine contractions), and the mammary glands for lactation (stimulates lobule growth).
Transformation zone

- The area adjacent to the border of the endocervix (columnar) and ectocervix (squamous) is known as the transformation zone (TZ) or squamocolumnar junction (SC junction).

- The Squamo-columnar junction is the junction between ectocervical (squamous) and endocervical (columnar) epithelia.

- The SC junction moves throughout life => metaplasia of columnar cells to metaplastic squamous occurs => formation of metaplastic transformation zone.

- The transformation zone undergoes metaplasia numerous times during normal life. When the endocervix (columnar cells) is exposed to the harsh acidic environment of the vagina it undergoes metaplasia to squamous epithelium, which is better suited to the vaginal environment. Similarly when the ectocervix enters the less harsh uterine area, it undergoes metaplasia to become columnar epithelium.

- The original transformation zone is approximately at the external os premenarche (before first menstruation).

- Times in life when this metaplasia of the transformation zone occurs:
  - Puberty (menarche): the endocervix everts (moves out) of the uterus => columnar epithelium undergoes metaplasia to squamous => TZ moves into the vagina away from external os.
  - Menstrual cycle: with the changes of the cervix associated with the normal menstrual cycle.
  - Post-menopause: the uterus shrinks moving the transformation zone upwards (inwards) towards the uterus.

- Position of TZ also alters during life as physiological response to:
  - Menarche (part of puberty when the first menstrual cycle begins)
  - Menstrual cycle
  - Pregnancy
  - Menopause

- All these changes are normal and the occurrence is said to be physiological.

- However, all this metaplasia (particularly squamous cell metaplasia e.g columnar cells of the endocervix metaplasing to squamous cells) does increase the risk of cancer in this area => the transformation zone is the most common area for cervical cancer to occur.
• It may also give rise to **post-coital bleeding**, as fine blood vessels present within the columnar epithelium are easily traumatised.

**Nabothian cyst**

• Nabothian cyst = **distended endocervical gland** (mucus filled cyst), usually with overlying **squamous metaplasia**.

• They are most often caused when stratified squamous epithelium of the ectocervix (toward the vagina) grows over the simple columnar epithelium of the endocervix (toward the uterus).

• This tissue growth can block the cervical crypts trapping cervical mucus inside the crypts. The transformation of tissue types is called metaplasia.

**Pathology of the cervix**

**Inflammatory pathology**

**Cervicitis**

• Cervicitis = inflammation of the uterine cervix

• Non-specific acute or chronic inflammation.

• **Aetiology:**
  - Many cases are caused by sexually transmitted infections, most commonly **Chlamydia (CT)** and **gonorrhoea (GC)**, with chlamydia accounting for approximately 40% of cases *(CT is much more common than GC)*
  - **Strawberry cervix in Trichomonas vaginalis**
  - Non-infectious causes of cervicitis can include intrauterine devices (e.g. Mirena and IUCD), contraceptive diaphragms, and allergic reactions to spermicides or latex condoms

• **Clinical features:**
  - Often asymptomatic
  - May be associated with abnormal vaginal bleeding, unusual vaginal discharge, pain during sex (dyspareunia), and pelvic pain
  - Can lead to infertility due to simultaneous silent fallopian tube damage and blockage *(pelvic inflammatory disease)*
Human Papillomavirus (HPV) Infection

1. Genital Warts

- Low risk HPV (6 and 11)
- Genital wart (Condyloma Acuminatum): thickened "papillomatous" squamous epithelium with cytoplasmic vacuolation ("koilocytosis").
- Genital warts often look “mushroom” like
- Can be itchy
- Clinical diagnosis

- NB: A Koilocyte is a squamous epithelial cell that has undergone a number of structural changes, which occur as a result of infection of the cell by human papillomavirus. Koilocytosis is a term used in histology and cytology to describe the presence of koilocytes in a specimen. Koilocytes may have the following cellular changes:
  - Nuclear enlargement (two to three times normal size)
  - Irregularity of the nuclear membrane contour
  - A darker than normal staining pattern in the nucleus, known as Hyperchromasia

2. Cervical Intraepithelial Neoplasia

- High risk HPV (16 and 18)

- Infected epithelium remains flat, but may shows koilocytosis, which can be detected in cervical smears

3. Cervical cancer

- High risk HPV (16 and 18)

- Invasive squamous cell carcinoma (SCC): Virus integrated into host DNA

- The HPV produces oncoproteins that can cause cancer. The two primary oncoproteins of high risk HPV types are E6 and E7. The E6/E7 proteins inactivate two tumor suppressor proteins, p53 (inactivated by E6) and pRb (inactivated by E7).

Time Lines
• Appreciate that most cases of CIN will NOT advance to invasive cancers (HPV is cleared by the body’s immune system before this occurs)

• CIN 3 has the highest risk of progressing to cervical SCC (however only 12% will progress to malignancy!)

## Natural History of Cervical Lesions

<table>
<thead>
<tr>
<th>Biopsy Result</th>
<th>Regress</th>
<th>Persist</th>
<th>Progress to CIN3</th>
<th>Progress to Invasion</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIN1</td>
<td>57%</td>
<td>32%</td>
<td>11%</td>
<td>1%</td>
</tr>
<tr>
<td>CIN2</td>
<td>43%</td>
<td>35%</td>
<td>22%</td>
<td>5%</td>
</tr>
<tr>
<td>CIN3</td>
<td>32%</td>
<td>58%</td>
<td>--</td>
<td>&gt;12%</td>
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## Invasive Cervical Squamous Cell Carcinoma (cervical SCC)

• 75-95% of malignant cervical tumours are squamous carcinoma (commonly occurring at TZ)

• 2nd commonest female cancer (worldwide)

• Incidence reducing in UK due to screening (an hopefully will decrease even further soon due to HPV vaccination)

• Increasingly detected in younger women => often found in early asymptomatic stage

• Develops from pre-existing CIN, therefore most cases should be preventable by screening

• Some are rapidly progressive tumours

• Appreciate that the highest incidence is between 25 and 45 (cancer of the young!) => screening from 20 to 60 every 3 years

• Pain, PCB, and IMB
**Vulval intraepithelial neoplasia**

- Vulvar intraepithelial neoplasia (VIN)
- Paget’s disease of the vulva

**Vulvar intraepithelial neoplasia (VuIN)**

- Variable behaviour => less predictable than CIN.
- Three grades, like CIN
- Neoplasia of squamous cells
- Young women: often multifocal, recurrent or persistent causing treatment problems.
- Older women: greater risk of progression to invasive vulvar squamous carcinoma.
- Sometimes HPV related.
- Often synchronous cervical and vaginal neoplasia (CIN & VaIN).

**Vulvar Invasive Squamous Carcinoma**

- **Keratinising Squamous Cell Carcinoma (SCC)**
  - Usually elderly women.
  - Can arise from normal epithelium or VIN.
  - Mostly well differentiated
  - Spread to **inguinal lymph nodes** (vulva drains into these lymph nodes), which is most important prognostic factor.
  - Surgical treatment: radical vulvectomy and inguinal lymphadenectomy.
    - 90% 5 year survival if lymph node negative
    - <60% 5 year survival if lymph node positive

**Vulvar Paget’s disease**

- Type of Extramammary Paget’s disease (EMPD)
- Rare, slow-growing, usually **noninvasive intraepithelial adenocarcinoma** (cancer)
• Low grade dyskaryosis (CIN I)
  
  ➢ Less specific (~30%
  
  ➢ Repeat a further one or two smears before referral to colposcopy e.g. repeat smear in 6 months

**Colposcopy**

• Detailed examination of cervix with x10 magnification

• A microscope (colposcope) with a strong light will be used to look at your cervix. The colposcope doesn’t enter the vagina and remains outside your body.

• If any abnormal areas are identified on STAINING, a small sample of tissue (a biopsy) may be removed for closer examination.

• However, the colposcopist will sometimes be confident that the screening test has been correct without the need for a biopsy, and may decide to proceed immediately to treatment

• The colposcopist will put a number of different solutions on the cervix and look for changes that indicate the presence or otherwise of changes to the cells.

• Acetic acid picks out abnormal epithelium

• If abnormal areas seen then the biopsied - remove a cone of abnormal tissue for histological assessment

• You may have treatment at the same time as your colposcopy. Or you may go back to the colposcopy clinic for treatment once they have the results of your biopsy.

• Can also be used to
  
  ➢ destroy abnormal tissue by **laser** (laser burns away the abnormal cells) or **cold coagulation**

  ➢ remove abnormal tissue by **LLETZ** (large loop excision of transformation zone) – form of diathermy under local anaesthetic. The treatment uses an electric current to cut away the tissue containing the abnormal cells.
The incidence will likely further decrease in the future due to the HPV vaccination.

**Cervical Screening: can it be improved?**

- HPV 16/18 accounts for 70% of Cervical Cancer
- HPV Vaccination: HPV 16/18 vaccine
- **Prophylactic vaccination** - prevention of CIN and invasive Cancer by prevention of HPV infection
- Started September 2008
  - 12/13y girls
  - **Course of three IM injections**
  - Will immunity alter distribution of other HPV types? Cross protection?
  - Should boys have been vaccinated as well as girls? More expensive however to generate a herd immunity will take longer only vaccinating girls.
  - Will boosters be necessary? Ab levels higher with vaccine than natural immunity.

**Why increase to first invite to 25y?**

Argument for:
- HPV infection high
• Rapid counting of specific chromosomes e.g. to assess for Downs

• PCR can also be used to look for specific mutations

When do you need chromosome analysis?

• Raised Maternal Age / Parental Anxiety

• Increased Risk of Chromosome Abnormality on Screening
  
  ➢ Abnormal Nuchal Thickness (increased in Downs) or abnormal serum markers at 12 weeks (PAPP-A and b-HCG)
  
  ➢ Abnormal serum screening at 16-18 weeks (triple blood test which measures hCG, oestriol E3 and AFP)

• Abnormality Detected on Ultrasound Scanning e.g. heart malformation

• Known Parental Chromosome Abnormality

Chromosome Analysis

Standard Karyotype (in metaphase)

• Full high quality analysis for all sample types

• Requires cell culture => approximately 2 weeks (long time) => not really practical antenatally

• CVS can give direct result quickly, however quality usually poor

Array CGH

• Works on DNA

• Covers whole genome

• Result, potentially < 1 week

• Risk of finding variation of uncertain significance (polymorphism)

Fluorescence in-situ Hybridisation (FISH)

• Only analyses one chromosomal location => usefull for detection of common chromosome aneuploidies
4. Amniocentesis

5. Fetal Blood Sampling

Genetic test

1. **Direct karyotype or FISH may be available**

2. Why not QF-PCR?

**NB: We dont know what the mutation could end up as => direct karyotype is the best option; however this will take time.** Potentially could use FISH. Why is QF-PCR not suitable? FISH is preferred in high risk situations.

Don’t we know that it could either be trisomy 4 or trisomy 9? **NOT AS SIMPLE AS ABOVE!** See below. With Robertsonian translocations there is a wide range of possibilities.

‘Ideal’ Timeline for Management
Gene testing (NOT chromosome) in pregnancy

Chromosome Analysis or Array CGH (Comparative genomic hybridization)

- General Analysis of the Genome
- A diagnosis may be suspected

For FISH or DNA analysis

- You need to suspect a diagnosis
- Useful for common chromomse deletions
- This tells you where to look
- However FISH can be used to tag individual genes to **assess for chromosome aneuploidies**

QF-PCR

- You need to suspect a diagnosis
- Only analyses specific loci e.g. **point mutations**
- Result in 24 hours (4 hours is technically feasible)
- However QF-PCR can be used to tag individual genes to **assess for chromosome aneuploidies**

Next generation sequencing

- DNA testing (often via PCR)
- Now available
- Sequence whole genome (<£1,000)
- Or just all known exons (= £500)
- Will be cheaper by next year
- DNA testing finds lots of polymorphisms
- If you sequence the whole genome, you will drown in data, 8,000,000 polymorphisms and you will REALLY need clinical data to tell you which genetic changes are important => Not currently feasible in prenatal diagnosis
• Parental chromosome abnormality e.g. Robertsonian translocation or Reciprocal translocation

• X-linked disorders => re-implantation of female embryos

• Other single gene disorders e.g. Cystic fibrosis and Huntingtons disease

**PGD: the Dark Side**

When is PGD appropriate

• Childhood lethal disorders?

• Severe learning difficulties?

• Moderate learning difficulties?

• Adult onset disorders - eg Huntington's?

• Adult onset predisposition - eg cancer?

• Short stature?

• Hair colour?

• Good tennis player?

**Summary**

• Tell us (the geneticists) early if we are needed: if possible at the pregnancy planning stage

• Tell us before you do an invasive testing procedure: it may be an inappropriate test

• We are here to understand the genetics: You only need to remember the principles and our telephone number

• Which sampling test should we perform? What genetic test should we perform? The answers to these questions are dependent upon the risk to fetus, gestation at which you can do test and speed of test result. **ASK A GENETICIST!!!!**

• **Chorionic villous sampling/biopsy (CVS or CVB)** can be done at **11 weeks (up until 15 weeks)** gestation but carries a risk of miscarriage of 1-2%. The deadline for doing a surgical termination of pregnancy is around 13 weeks, so if a mother wishes for this if fetus is affected, then a CVS gives you a result in time (hopefully). Chorionic villus is also a slightly weird tissue to work with genetically, and can result in false +ves due to confined placental mosaicism.
• Women’s breasts start to involute at age 18: **Lobular involution is the physiological atrophy** of the breast epithelium and is known to increase with increasing age. The stroma is replaced with fat as age increases.

• Lots of individual variation: may still have dense breasts aged 80 => US may be preferred.

• Don’t generally do mammography <40 unless suspicion of cancer (US is preferred as first line Ix under 40).

### Advantages of Mammography

- Images whole both breasts
- **High sensitivity for detecting Duct carcinoma in situ** *(microcalcifications, not breeched basement membrane)* & *invasive cancer*
- Only screening modality known to reduce population mortality

### Disadvantages of Mammography

- Non-specific: only 1 in 5 to 1 in 10 actually have breast cancer when detected (screen +ve)
- Uses **ionising radiation**
- **Can be uncomfortable**
- ~ 10% of cancers are probably over diagnosis

### Ultrasound

- Useful in symptomatic clinic => useful in breast x-ray
- Indications: palpable mass, work up of mammographically detected lesion, image guided biopsy, breast inflammation (e.g. abscess), breast problems during pregnancy (breasts very dense, breast of proliferation), breast problems during pregnancy (breasts very dense, breast of proliferation), breast problems during pregnancy (breasts very dense, breast of proliferation), breast problems during pregnancy (breasts very dense, breast of proliferation)

• Advantages:
  - **Useful for woman <40 with dense breasts (or for woman >40 with dense breasts)**
  - **No ionising radiation**
  - Not uncomfortable for patient
  - Good sensitivity and specificity for detecting invasive cancer
  - Quick if examination tailored to one area
  - **Can differentiate cystic from solid**
  - Cheap
  - Image guided biopsy very easy

### Biopsy methods

- There are four types of biopsies:
  - **Fine-needle aspiration (FNA):** for fluid filled masses e.g. cyst
  - **Core-needle biopsy:** for solids
  - Surgical biopsy
  - **Vaccum**
- The latter three are the most commonly used on the breast.
• Mammography
  ➢ Age >40
  ➢ If clinical or US findings are suspicious
  ➢ Screening: woman aged 50-70 every 3 years, mammography

**Spiculate masses**

• In oncology, a spiculated mass is a **lump of tissue with spikes or points on the surface**. It is **suggestive but not diagnostic of malignancy**, i.e. cancer.
• **Suspect carcinoma**
• Surgical scar can occasionally look similar, as can radial scar (complex sclerosing lesion)

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**Axillary US**

• US axilla
• Abnormal nodes identified by cortical thickness and shape
• **Core biopsy** or FNA of abnormal nodes identifies about 40% of node positive women pre-operatively
• Chemo/radio/surgical
• **Sentinel lymph node biopsy**: A sentinel lymph node is the first lymph node(s) to which cancer cells are most likely to spread from a primary tumour. A sentinel lymph node biopsy (SLNB) can be used to help determine the extent, or stage, of cancer in the body. A surgeon injects a radioactive substance, near the tumor to locate the position of the sentinel lymph node. The surgeon then uses a device that detects radioactivity to find the sentinel node. Once the
Adjuvant therapy

Tamoxifen (oestrogen receptor antagonist) in breast tissue; but oestrogen stimulant in endometrial tissue => can cause endometrial hyperplasia and Endometrial Ca): Taken post-operatively (usually). Effective if oestrogen-receptor positive e.g. oestrogen receptor protein measurable in primary tumor. ER (oestrogen receptor) +ve tumours are stimulated to grow by oestrogen. Used in premenopausal woman. Usually 5 years.

Aromatase inhibitors (AIs) are a class of drugs used in the treatment of breast cancer and ovarian cancer in postmenopausal women. Anastrozole is one of the drugs. In contrast to premenopausal women, in whom most of the estrogen is produced in the ovaries, in postmenopausal women estrogen is mainly produced in peripheral tissues of the body. Because some breast cancers respond to estrogen (ER +ve), lowering estrogen production at the site of the cancer (i.e. the adipose tissue of the breast) with aromatase inhibitors has been proven to be an effective treatment for hormone-sensitive breast cancer in postmenopausal women.

Oophorectomy (surgical removal of ovaries) => decrease oestrogen (useful for ER +ve tumours) and decrease progesterone (useful for PgR +ve tumours)

Immunotherapy with monoclonal ABs:

- Trastuzumab (Herceptin): a monoclonal antibody to HER2 (human epidermal growth factor receptor 2) for HER2 +ve breast cancers

Clinical Decision Making

- CPC: Clinical Pathological Conference
- MDT: Multidisciplinary Team Meeting
- Review preoperative decision
- Review operative pathology
- Plan subsequent management
- Management of recurrent disease.

Breast Screening

- Only mammography shown to work (2 views)
- Scotland programme 50-70yrs, every 3 years (in contrast to cervical screening which is 20-60 years every 3 years)
- About 4% recalled => Just under 1% have cancer
- Regular attenders probably reduce risk by 50%
- Women over 70 => no evidence. Benefits not shown, harm gets worse (overdiagnoses & shorter life expectancy & breast cancer less aggressive as you get older)
- Some evidence that women in 40s should have mammography

BREAST PATHOLOGY 1

Assessment of a patient with breast disease

Triple assessment:
progesterone dramatically decrease. This leads to many of the symptoms commonly associated with menopause. With this reduction in the stimulation by oestrogen and progesterone => there is a reduction in the glandular tissue of the breasts. The connective tissue of the breast becomes dehydrated and inelastic, and the breast tissue, which was prepared to make milk, shrinks and loses shape => atrophy. This leads to the "sagging" of the breasts often associated with women of this age.

Tanner stages of female pubertal development

• Thelarche = breast development (usually occurs first)

• Pubarche = development of pubic hair (often the second noticeable change in puberty, usually within a few months of thelarche)

• Menarche = first menstrual bleed (typically occurs about two years after thelarche)

Normal breast anatomy

• 2\textsuperscript{nd} to 6\textsuperscript{th} rib

• Sternal edge to anterior axillary line + axillary tail (don’t forget about the axillary tail e.g. on examination)
• Lies on pectoralis major fascia and serratus anterior fascia

• Blood supply: Axillary artery (subclavian artery becomes axillary artery), internal thoracic artery & intercostal arteries

• Lymphatic drainage
  ➢ Axillary nodes → Supraclavicular nodes → Cervical nodes
  ➢ Internal mammary
  ➢ ALWAYS EXAMINE LYMPH NODES

• Glandular tissues
  ➢ Lobules (mammary glands): produce milk during pregnancy and breastfeeding and pathological states (e.g. hyperprolactinaemia). Stimulated to grow primarily by progesterone. Stimulated to produce milk by prolactin. Lobules endocrine control = PP.
  ➢ Lactiferous ducts: connect the lobules of the mammary gland to the tip of the nipple. They carry milk from lobules during breastfeeding. Stimulated to grow by oestrogen. Stimulated to contract and eject milk by oxytocin. Ducts endocrine control by OO.
  ➢ Nipple: outlet of milk during breastfeeding.

• Other tissues
  ➢ Skin
  ➢ Adipose tissue: fills the spaces around the ducts and lobules
  ➢ Fibrous tissue: surrounds and supports breasts, making them feel firm
  ➢ Blood vessels
  ➢ Lymphatics
  ➢ Nerves
• Woman 30-50

Pathology

• **Cysts** are usually 1mm to several cm.

• Usually multiple cysts.

• Development of excess fibrous tissue, hyperplasia of epithelia lining of the mammary ducts and cyst formation

Management

• Exclude malignancy: triple assessment and mammogram >40 years; US<40 years

• Reassure

• Excise if necessary

Classification of Breast Tumours

Benign tumours

• Lipoma (benign fatty tumour)

• Lymphangioma (benign tumour of the lymphatic system which often involves the skin)

• Haemangioma (benign tumour of blood vessels)

• Squamous papilloma (benign papilloma that arises from the stratified squamous epithelium of the skin, lip, oral cavity, tongue, pharynx...)

• Myoepithelioma (benign tumour of glands which may rarely originate in breasts)

• ID (intraductal) papilloma: small, noncancerous (benign) tumor that grows in a milk duct (intraductal) of the breast, **can cause nipple discharge including blood stained**

• Adenoma: benign tumour of glandular origin

Malignant tumours
DCIS can progress in grade e.g. low grade DCIS => intermediate grade DCIS => high grade DCIS => G3 (high grade) ductal carcinoma. DCIS can also directly progress from either grade to invasive ductal carcinoma e.g from low grade DCIS to G1 (low grade) ductal carcinoma.

- Ductal carcinoma:
  - Low grade: G1 ductal carcinoma
  - Intermediate grade: G2 ductal carcinoma
  - High grade: G3 ductal carcinoma (progresses from high grade DCIS)

Lobar

Lobular carcinoma in situ:
  - Low grade: LCIS (Lobar carcinoma insitu)
  - Intermediate grade: Pleomorphic LCIS

Lobular carcinoma
  - Low grade: Lobular carcinoma (progresses from LCIS)
  - Intermediate grade: Pleomorphic lobular carcinoma (progresses from pleomorphic LCIS)

Tubular carcinoma
  - Low grade: Tubular carcinoma
- Triple assessment
- Tissue diagnosis (e.g. subtype of cancer)
- Grade
- Receptor status: ER (oestrogen receptor), PgR (progesterone receptor), HER2 (human epidermal growth factor receptor 2)
- Staging: TNM (important for Mx and prognosis)
- General fitness of patient
- Patients concerns and preferences

- Management options:
  - surgery
  - radiotherapy
  - chemotherapy
  - endocrine therapy (tamoxifen, oophorectomy, buserelin or goserelin, letrozole)
  - immunotherapy with MABs e.g. Herceptin (trastuzumab)
  - palliative care

**Breast cancer management**

- Surgery:
  - Breast: lumpectomy (wide local excision) or mastectomy
  - Axillary: sentinel node biopsy, sample, node clearance
  - reconstruction

- Radiotherapy – for all pts with breast conserving surgery (wide local excision)
- Chemotherapy
- Endocrine therapy
- Immunotherapy

- Bisphosphonates for prophylactic bone protection (e.g to protect against bone mets)
DIEP flap

• Latest variation in TRAM flap reconstruction
• Relies on two or three perforators from the deep inferior epigastric artery
• Leaves muscle and fascia intact
• No problems with abdominal wall closure.
• Less pain.

Complications of breast reconstruction

• Necrosis: skin, fat (fat necrosis)
• Flap failure
• Implant exposure
• Infection
• Scarring
• Capsular contracture
• Lymphoedema

BREAST ONCOLOGY

• Commonest cancer in women

• Increasing incidence => due to ageing population (in contrast to cervical SCC which is decreasing)

• 2nd commonest cause of death from cancer in women

• Survival improving: 5 year survival improved from 56% in 1970 to 81% in 2003-7

Presentation

• Screening: age 50-70 (screened every 3 years via mammography) => small, impalpable lump, microcalcifications, ductal carcinoma

• Symptomatic: most often lump in breast
  
  ➢ 84% operable

  ➢ 8% with distant metastases => incurable

  ➢ 8% locally advanced/inoperable

Treatment

• Surgery

• Radiotherapy

• Systemic therapy

  ➢ hormonal therapy

  ➢ cytotoxic chemotherapy

  ➢ immunotherapy
**Radiotherapy**

- **Postoperatively** to breast/chest wall and to nodal areas (axilla, supraclavicular fossa, internal mammary nodes) => used to kill any remaining cancer cells
- **Primary radical** for locally advanced
- **Palliatively** to painful bony mets, skin deposits, brain mets etc.
- **NB:** Neoadjuvant = therapy done before the main radical therapy – to aid the radical therapy

**Postoperative radiotherapy**

- Used after surgery to reduces the risk of local recurrence
- Reduces risk of local recurrence by about two thirds
- **Offered to ALL patients being treated conservatively e.g. wide local excision (lumpectomy)**
- Offered to mastectomy patients selectively e.g. large tumour, extensive nodal involvement, involved margins etc.

- **Acute side effects**
  - Skin erythema to moist desquamation
  - Tiredness and fatigue
  - Dysphagia if irradiating supraclavicular fossa
  - No alopecia

- **Late effects**
  - Local fibrosis and telangectasia
  - **Lung fibrosis** (rarely symptomatic)
  - **Cardiac damage** (fibrotic restrictive cardiomyopathy) => rarer now as treatment better planned

**Systemic therapy**

- Most operable, so why not curable?
• Gabapentin: bones have nerves! (gabapentin and amitriptyline are good for neuropathic pain)

• Bisphosphonates: long term bone protection, protects against hypercalcaemia of malignancy

BREAST TUTORIAL
Revision of anatomy and physiology

• Lobules have acini to manufacture milk and ducts to transport it.

• The lymph glands especially the axillary groups but also the internal mammary chain clear tissue fluid.

• Development and function of the breast is under the control of oestrogen (ducts) and progesterone (lobules). Breast morphology is influenced by these steroid hormones and changes with the normal menstrual cycle.

Symptoms and signs

• There are a limited number of breast symptoms: pain, lump, nipple retraction, nipple discharge and skin changes.

• Both benign and malignant conditions cause breast symptoms.

• In hospital outpatient practice, nine benign cases are seen for every malignant one.

Age and presentation

The benign disorders are particularly found in pre-menopausal women whereas some 80 per cent of breast cancers occur in patients who have passed the menopause

The age of a woman suggests the likely diagnosis of a breast lump:

• <30 years: normal lumpiness, fibroadenoma, rarely cancer

• 30-45 years: normal lumpiness, cyst (often fibrocystic e.g. fibroadenosis), sometimes cancer

• 45-60 years: cyst, cancer, normal lumpiness

• >60 years: cancer until proven otherwise

Evaluation
There are three methods of assessing benign and malignant breast disorders which together make up the ‘triple assessment’. These are

- Clinical: history and examination
- Breast imaging (mammography, ultrasound or MRI): mammography > 40 years and US < 40 years
- Cytology and/or histology

**Staging of breast cancer**

- Once breast cancer is diagnosed it needs to be staged using the TNM system and Nottingham prognostic score
- Other clinical evaluation and tests include: FBC, Biochem, LFTs, chest x-ray (and liver ultrasound and bone scan for more advanced cancers) - to evaluate organs to which breast cancer most commonly spreads, particularly bone marrow, liver and lungs.
- The majority of patients presenting with breast cancer in Britain are operable - that is the staging tests do not reveal evidence of metastases.
- Despite the absence of detectable metastases, breast cancer can recur even years after removal and initial treatment (likely due to undetectable micro occult mets)
- Invasive breast cancers need to be treated as if they were potentially ‘body-wide’ due to the possible presence of undetectable micro metastases for which ‘systemic’ adjuvant treatment (e.g. chemo, hormonal or MAB) is given either orally or intravenously.

**Treatment of breast cancer: summary**

Treatment is thought of in two categories:

- **Local or loco-regional treatment** (treatment given to the affected breast, chest wall and the first line lymph nodes in the axilla and along the internal mammary node chain) => Surgery +/- radiotherapy (i.e. XRT is definitely used in lumpectomy or wide local based excision, but not necessarily so for mastectomy)
- **Systemic or ‘body-wide’ treatment** which seeks to eliminate undetectable micrometastases => chemotherapy +/- endocrine therapy +/- immunotherapy

**Locoregional treatment**

- Conventionally loco-regional treatment is by surgery or radiotherapy or a combination of both.
• Recent outbreaks in UK cities, primarily amongst men who have sex with men (MSM)

• Diagnosis is usually made by serological tests e.g. by detecting ABs in the patients serum. The reason for this is the bacterium cannot be artificially cultured and are difficult to see by microscopy.

• There are two early clinical stages (primary and secondary), a latent stage (which can persist for a long time) and one late clinical stage (tertiary syphilis). Latent syphilis is typically asymptomatic.

• **Primary stage**: *isolated painless ulcer (chancre)*. May develop more than one.

• **Secondary stage**: “copper penny” generalised rash, Condylomata latum (wart like genital lesions), painless lymphadenopathy, fever and weight loss

• **Latent stage**: often asymptomatic, can persist for years and years, can affect near enough any organ

• **Tertiary stage**: cardiovascular syphilis (e.g. aortitis, aortic dissection), neurosyphilis (e.g. Argyl-Robertson pupil, Charcot joint, tabes dorsalis of the dorsal columns, dementia and other neuropsychiatric disorders)

### Non-specific serological tests

• Two types of test
  
  ➢ **VDRL** (Venereal Diseases Research Laboratory)

  ➢ **RPR** (Rapid Plasmin Reagin)

• Non-specific tests that indicate tissue inflammation

• May be **falsely positive** (e.g. SLE, malaria, pregnancy)

• Useful for **monitoring response to therapy**

• **Usually become negative after successful treatment**

### Specific serological tests

• **TPPA** (*T. pallidum* particle agglutination assay): a test for **specific IgG ABs**

• TPHA (*T. pallidum* haemagglutination assay): a test for specific IgG ABs (not used in Tayside)

• Specific for syphilis, but **remain positive for life** (IgG stays positive for life => natural immune response to generate immunity)
(a) What are the lesions?
   - Genital warts (often have cauliflower appearance)

(b) Which virus causes this condition?
   - HPV (6 and 11)

(c) Will sending a swab of the lesions for viral culture help to confirm the diagnosis?
   - No. HPV viral warts is a clinical Dx. No further Ix required.

(d) Is the girl just fussy or does she have reason to worry about herself?
   - Yes. They are a STD transmitted via close sexual contact between genital lesions
   - If the boy has one strain of HPV then he may have others e.g. oncogenic strains

(e) What treatment is available for the lesions in the photograph?
   - Podophyllin topical cream
   - Imiquimod
   - Cryotherapy

(f) Is there a vaccine available that might reduce the incidence of this infection?
   - Yes there are two vaccines available
   - One against oncogenic strains (HPV 16 and 18....)
   - One against oncogenic strains + strains which cause viral warts

Case 6

A 30 year old man attends your surgery with an ulcerated lesion on his penis (picture provided). The lesion is not particularly tender to touch. You can feel enlarged lymph nodes in both groins. The
(f) Six months later, you re-test the patient, and you receive the second lab report back. Has this patient been adequately treated?

- IgM = -ve
- VDRL = -ve
- Therefore treatment has been successful
- Follow up at 12 months (if HIV +ve requires life long follow up every 12 months)

(g) Would you suggest that this patient has tests for any other infections, and if so, which infections?

- STD screen:
  - CT/GC combined PCR on first pass urine
  - HIV, Hep B and syphilis serology +/- Hep C

Reproductive lecture notes: week 3

DOWNNS SYNDROME

- Three types:
  - trisomy 21 (non disjunction) – most common (95%)
  - partial trisomy 21 (unbalanced translocation) – 4% (in prenatal Dx, assess with karyotype of parent has known translocation)
  - mosaic trisomy 21 (some cells are normal, other cells have trisomy 21) – 1%

- Down syndrome is **most commonly caused by trisomy 21** (47, XX +21 for females; 47, XY, +21 for males). Trisomy 21= extra chromosome 21

- Affects 1 in 1000 babies

- Congenital (e.g. born with it)

- Downs syndrome is typically associated with physical growth delays, characteristic facial features and mild to moderate intellectual disability (**global developmental delay**)
• Children with Down’s syndrome can do sports and should not be stopped from taking part in sports or team activities.

  • Can have a normal life!

PHYSIOLOGY OF PREGNANCY AND LACTATION

Fertilisation and implantation

• Egg released by ovaries => captured by fimbriae of fallopian tubes

• Fertilised by sperm in the ampulla of the fallopian tubes

• Conceptus travels down the fallopian tube and the cells progressively divides and differentiates in the process called cleavage => results in formation of morula (day 4)

• The morula becomes a blastocyst as it enters the uterus (day 5)

• Implantation of the blastocyst (trophoblastic cells invade the endometrium) in the endometrium of the uterus occurs shortly after (day 6-9)

• Inner cell mass (embryoblast) becomes the embryo

• Outer trophoblastic cells differentiate and become the foetal part of the placenta
• **Advancing cords of trophoblastic cells** tunnel deeper into endometrium, carving out a hole for the blastocyst. The boundaries between cells in the advancing trophoblastic tissue disintegrate.

• When implantation is finished the blastocyst is completely buried in the endometrium

• **Blastocyst becomes fully buried in uterine lining by day 12**

![Diagram of endometrium, blastocyst, and placenta]

**Placenta**

**Placenta development**

• Placenta is derived from both trophoblast (derived from conceptus) & decidual tissue from **endometrium** (mucus membrane of uterus/endometrium which is perfectly designed for nourishing the foetus)

• Decidua = the mucous membrane of the body of the uterus (outer layer of endometrium)

• Decidual cells produce the nutrients that keep the foetus going. **Progesterone in the luteal phase is essential for the development of a suitable deciduas.**
• The respiratory function of the placenta makes supply of oxygen and removal of carbon dioxide possible.

• The exchange takes place between maternal oxygen-rich blood (received from maternal arteries e.g. uterine arteries) and the umbilical blood (umbilical vein) => AV shunt (occurs in intervillous space)

• Oxygen diffuses from the maternal vessels (uterine arteries) into the fetal circulation system (umbilical vein) as PO2 maternal uterine artery > PO2 fetal umbilical vein

• Carbon dioxide follows a reversed gradient from umbilical arteries to maternal circulation (uterine veins) (as PCO2 foetal umbilical arteries > PCO2 maternal uterine veins)

• Fetal, oxygen saturated blood, returns to the fetus via the umbilical vein.

• Partial pressures of oxygen in the umbilical vein are relatively low due to AV shunt (ineffective transfer) = > the levels of oxygen are much lower in the foetus.

• But how then is sufficient oxygenation of the fetus possible? The supply of the fetus with oxygen is facilitated by three factors:
  
  ➢ Fetal HbF (alpha 2, gamma 2) => increases ability to carry O2 (HbF has a greater affinity for O2 and a greater capacity for O2 compared to HbA, e.g. shift to the left of Hb dissociation curve). This allows HbF to "grab hold" of O2 from maternal HbA (alpha 2, beta 2).

  ➢ Higher Hb concentration in fetal blood (50% more than in adults)

  ➢ The Bohr effect (shift to right of Hb dissociation curve) allows rapid release of O2 in response to hypoxia, hypercapnia, and acidosis. The Bohr effect is very strong in HbF => even though HbF is shifted to the left compared to HbA, it has much greater capacity to shift to the right if needs be. Therefore the foetus is very good at compensating during hypoxia (due to greater capacity for carrying O2 and greater capacity to release O2 via the Bohr effect).
**Placenta: nutrients and waste products transport**

The placental exchange processes occur via classic membranous transport mechanisms:

- Passive transport (without energy consumption)
- Simple diffusion e.g. fatty acids (lipophillic)
- Osmosis e.g. water and the electrolytes which follow water
- Simplified transport
- Active transport

**Important exchanges**

- Water diffuses into the placenta along its osmotic gradient. Exchange increases during pregnancy up to the 35th week (3.5 litre / day).
- Electrolytes follow water (iron and calcium only go from mother to child).
- **Glucose, the fetus’ main source of energy, crosses the placenta via simplified transport** (high glucose need in 3rd trimester)
- Free diffusion of fatty acids (as lipophillic and can cross membranes)
- Diffusion of waste products is based on concentration gradient

**The placenta as a filter**

- One of the functions of the placenta is to act as a **filter**; allowing beneficial substances such as oxygen and nutrients to pass from the maternal circulation into the fetal circulation (AV shunt), but also trying to prevent harmful substances from making this journey.
- For example, the placenta allows the passage of some proteins and other bigger chemicals in the blood, including **maternal antibodies (IgG)**. Allowing her antibodies to pass across the placenta and into the fetus is important in providing protection for the fetus, and later the newborn baby, against the same infectious agents.
- **However, the placenta cannot prevent the transfer of alcohol, other drugs and viruses to the fetus.**
• hCG is produced by the **placenta** at implantation

• hCG is similar to LH (sister molecule)

• hCG prevents involution (degeneration) of **Corpus Luteum** (as similar to LH) => Corpus luteum is maintained and continues to produce progesterone and estrogen (essential for pregnancy and maintain decidua)

• hCG also stimulates Leydig cells (as sister molecule of LH) to produce testosterone in male foetuses (if presence of Y chromosome) => development of male sex organs

• Plateaus at approx 10 weeks gestation then levels decrease

• hCG can also cause **hyperemesis gravidarium**

• hCG also has structural resemblances to TSH and can cause **gestational thyrotoxicosis**

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**Human Chorionic Somatomammotropin (hCS)**

• hCS is also called human placental lactogen (hPL)

• Polypeptide placental hormone

• hCS is a hormone secreted by the **syncytiotrophoblast** (part of placenta) during pregnancy

• The syncytiotrophoblast is the epithelial covering of the highly vascular embryonic placental villi, which invades the wall of the uterus to establish nutrient circulation between the embryo and the mother.

• Produced from approximately week 5 of pregnancy

• Effects on mother:

  ➢ Its structure and function is similar to that of human **growth hormone**. It modifies the metabolic state of the mother during pregnancy to facilitate the energy supply of the fetus.

  ➢ hCS/hPL has **anti-insulin properties** => decreases insulin sensitivity in mother (e.g causes **insulin resistance**) => raises maternal **glucose serum levels** => more glucose for the fetus (major source of energy for foetus): particularly potent effect in third trimester (as hCS continues to rise through pregnancy and levels become high in third trimester)

  ➢ Involved in breast development and possibly lactation

  ➢ **Steadily increases throughout pregnancy so that is maximum in third trimester** => maternal insulin resistance => maternal hyperglycaemia => lots of glucose available for foetus in this rapid growth phase
• CO increases 30\%-50% above normal (beginning 6wk gestation and peaking approximately 24 wk)

• With twins CO increases more

• CO decreases in last 8 weeks (KEY POINT): becomes sensitive to body position and uterus compresses IVC

• Increases 30% more during labour.

• Flow murmurs are common due to increased CO

Heart rate

• Heart rate (HR) increases up to 90/min to maintain CO and manage to pump all the excess fluid

Blood pressure

• Blood pressure (BP) drops during 2nd trimester: uteroplacental circulation expands (resistance decreases) & peripheral resistance decreases

• With twins BP drops more

• Rises back up to pre-pregnancy BP in third trimester

Haematological changes

• Plasma volume increases (aldosterone effects) proportionally with cardiac output (50%): The plasma volume increases to provide for the greater circulatory needs of the maternal organs and the uteroplacental circulation

• Erythropoesis (RBC) increases (25%) => red cell volume increase is less than plasma volume increase

• Thus Hb (and HCT) is decreased by dilution (approximately 25%) => this decreases blood viscosity and can cause dilutional anaemia (as plasma volume increase > erythropoiesis increase)

• A pregnant woman will also become hypercoagulable (physiological change to prevent haemorrhage particularly PPH) due to increased liver production of coagulation factors, mainly fibrinogen and factor VIII. Therefore pregnant woman (and postpartum – in
particular) have increased risk for developing blood clots and embolisms. This hypercoagulable state along with the decreased ambulation (exercise involving legs) causes an increased risk of both DVT and PE

• Iron requirements increases significantly (partly due to increased erythropoisesis) => most women require iron supplements (amount from diet and iron stores is usually insufficient)

Respiratory changes

• In early pregnancy, the respiratory centre can't tolerate the unusual amount of carbon dioxide in the blood (excess CO2 from foetus). This accounts for the feeling of shortness of breath, dyspnea, or heightened awareness of the need to breathe reported by many pregnant women.

• Progesterone has a very interesting direct action on the mother's respiratory center (medulla oblongata of brain stem).

  Progesterone increases sensitivity of respiratory centre (medulla) to carbon dioxide => the pregnant woman is actually forced to hyperventilate, and "blow off" more carbon dioxide than she normally would. As a result, the removal of carbon dioxide from the fetus's bloodstream is facilitated!

• Progesterone signals the brain to lower CO2 levels by increasing CO2 sensitivity in respiratory centres

• Progesterone is responsible for a decreased amount of carbon dioxide in the blood of pregnant women.

• To lower CO2 levels, progesterone acts on respiratory centre to make it more sensitive to CO2 which results in:
Mechanical stretch of uterine muscles increases contractility by positively feeding back to the hypothalamus to increase oxytocin release.

Stretch of the cervix also stimulates uterine contractions and increases PG release.

- Braxton Hicks contractions, also known as prodromal labor or practice contractions, are sporadic uterine contractions that sometimes start around six weeks into a pregnancy. However, they are not usually felt until the second trimester or third trimester of pregnancy. They should be infrequent, irregular, and involve only mild cramping (usually painless). Braxton Hicks contractions are a tightening of the uterine muscles for one to two minutes and are thought to be an aid to the body in its preparation for birth. They are NOT part of labour.

Parturition: Initiation of Labour

- Braxton Hicks contractions: increase toward the end of pregnancy (preparation for true labour contractions)

- Eosstrogen from ovaries prepares the uterus for contractions:
  - Induces oxytocin receptors on uterus
  - Stimulates PG release
  - Increases gap junction in myometrium

- Fetal hormones released: oxytocin and PGs

- Oxytocin from foetus and mother’s posterior pituitary initiates and sustains contractions:
  - stimulate uterus to contract (“contractions”)
  - stimulate placenta to make prostaglandins (PGs) => PGs stimulate more vigorous contractions of uterus

- Distension/stretch of the cervix and uterus by foetus positively feedback to the placenta and posterior pituitary (via nervous APs) => even further increased release of oxytocin and PGs => more vigorous uterine contractions

- Strong uterine contractions and pain from the birth canal cause neurogenic reflexes from spinal cord that induce intense abdominal muscle contractions
PAPP-A (low PAPP-A is indicator of Down)

Second trimester (13-26 weeks gestation)

- Maternal blood sample at 15-20 weeks => the triple test
- The triple test usually performed at 16 weeks is an assay of:
  - HCG – increased in Downs
  - AFP (alpha-fetoprotein) – decreased in Downs
  - Estriol E3 – decreased in Downs

For both first and second trimester

- Incorporation of these measurements (NT, and triple test: HCG, AFP and E3) and results with maternal age and gestation to give a personal risk (maternal age is a big risk factor)
- >1:250 => high risk and requires further diagnostic investigation (e.g. amniocentesis >15 weeks or CVS <15 weeks). QF-PCR is usually the preferred prenatal tests, however in Robertsonian translocation we perform full karyotype.

Risk of Downs syndrome according to maternal age and serum levels

- Alpha-fetoprotein (AFP) is made in the part of the womb called the yolk sac and in the fetal liver, and some amount of AFP gets into the mother’s blood.
  - In neural tube defects (but not spina bifida occulta), the skin of the fetus is not intact and so larger amounts of AFP is measured in the mother’s blood => raised AFP (also raised in gastroschosis and omphalocoele)
  - In Down syndrome, the AFP is decreased in the mother’s blood, presumably because the yolk sac and fetus are smaller than usual.

- Estriol (E3) is a hormone produced by the placenta, using ingredients made by the fetal liver and adrenal gland. Estriol is decreased in the Down syndrome pregnancy. This test may not be included in all screens, depending on the laboratory.

- Human chorionic gonadotropin (hCG) hormone is produced by the placenta, and is used to test for the presence of pregnancy. A specific smaller part of the hormone, called the beta subunit beta-hCG is increased in Down syndrome pregnancies.
- **Placental abruption** (abruptio placentae): complication of pregnancy, wherein some of the placental lining has separated from the uterus of the mother. Causes uterine overdistension => initiates uterine contractions and labour (see above)

- **Placenta previa**: obstetric complication in which the placenta is inserted partially or wholly in lower uterine segment (low placenta). Placenta previa occurs when the placenta becomes implanted near or over the cervix. If the placenta does overlie the lower segment, as is the case with placenta praevia, it may shear off and a small section may bleed. It can sometimes occur in the later part of the first trimester, but usually during the second or third. It is a leading cause of antepartum haemorrhage (vaginal bleeding >24 weeks and before birth). The bleeding of placenta previa can increase the risk for preterm premature rupture of the membranes (PPROM), leading to premature labor. Placenta previa is painless (in comparison to placenta abruption which is painful). Associated with abnormal lies and previous C-section (due to fibrosis) and multiple pregnancy.

• Intercurrent illness:
  - Pyelonephritis / UTI
  - Appendicitis
  - Pneumonia
  - Pre-eclampsia

• Cervical incompetence: medical condition in which a pregnant woman's cervix begins to dilate (widen) and efface (thin) before her pregnancy has reached term. **Tx with cervical cerclage (sutures)**

• Precocious fetal endocrine activation

• Early induction of labour or caesarean birth

• Idiopathic

**Risk factors / associations with pre-term birth**

• Previous PTL (preterm labour)

• Multiple pregnancies

• IUGR: if causative agent(s) are any of the above
• Uterine anomalies
• Age (teenagers)
• Parity (=0 or >5):
  ➢ In the UK, gravidity is defined as the number of times that a woman has been pregnant and parity is defined as the number of times that she has given birth to a fetus with a gestational age of 24 weeks or more, regardless of whether the child was born alive or was stillborn.
  ➢ For example, a woman who is described as 'gravida 2, para 2' (sometimes abbreviated to G2 P2) has had two pregnancies and two deliveries after 24 weeks. A woman who is described as 'gravida 2, para 0' (G2 P0) has had two pregnancies, neither of which survived to a gestational age of 24 weeks.
  ➢ In Tayside we use Para X+Y, where X= the number of deliveries beyond 24 weeks (only include after the birth); the second is the number of pregnancies ending before 24 weeks without signs of life.
  ➢ Example 1: previous still birth at 32 weeks and a previous live birth at 40 weeks => Para 2+0. Remember that the first figure includes deliveries beyond 24 weeks, NOT necessarily live births
  ➢ Example 2: A woman at 8 weeks into her pregnancy => Para=0+0 (parity does not become 1 until after birth); if this woman has a miscarriage <24 weeks => Para 0+1. If this woman gave birth to a baby after 24 weeks (alive or stillborn) => Para 1+0
• Ethnicity
• Poor socio-economic status
• Smoking
• Drugs (especially cocaine)
• Low BMI (<20)

**SMALL FOR DATES PREGNANCY**

**Small for gestational age (SGA)**

• SGA = Infant with a birthweight that is less than 10th centile for gestation corrected for maternal height, weight, fetal sex and birth order.

• Note: large for dates > 90th percentile

• Small for dates may be due to
Small for gestational age (SGA): IUGR or constitutionally small

Wrong dates

Oligohydraminos: low volume of liquor amnii

Transverse lie

- Small for gestational age (SGA) can be due to:
  - **Intra uterine growth restriction (IUGR)** which is also called **pathological SGA**: pathological state where growth is normal in the early part of pregnancy, but slows in utero by at least two measurements, normally ultrasound. This is due to intrauterine growth restriction (IUGR). They have a wasted appearance with little subcutaneous fat. They are at greater risk of dying.
  - **Constitutionally small (familial)**: basically a genetic trait of the baby. Babies growth at all gestational ages is low. They are light-for-dates, but otherwise healthy. 50–70% of SGA fetuses are constitutionally small, with fetal growth appropriate for maternal size and ethnicity.

**Intra Uterine Growth Restriction (IUGR)**

- Intrauterine growth restriction (IUGR) refers to poor growth of a baby while in the mother's uterus during pregnancy. The causes can be many, but most often involve poor maternal nutrition or lack of adequate oxygen supply to the fetus (e.g., due to placenta dysfunction).

- Intrauterine growth restriction can result in baby being small for Gestational Age (SGA), which is most commonly defined as a weight below the 10th percentile for the gestational age. At the end of pregnancy, it can result in a low birth weight (LBW).

**Aetiology**

- Poor growth can be caused by:
  - **Maternal factors**
  - **Fetal factors**
  - **Placental factors**

- Maternal factors:
  - **Poor nutrition**
  - **Maternal disease** e.g. pre-eclampsia, hypertension, gestational diabetes, CV disease, respiratory disease
• Smoking
• Alcohol
• Drugs
• Poor weight gain during pregnancy
• Age

• Fetal factors:
  • Vertically transmitted infections e.g. rubella, CMV, toxoplasma
  • Congenital anomalies e.g. absent kidneys (renal agenesis)
  • Chromosomal abnormalities e.g. Down’s syndrome

• Placental factors:
  • Often secondary to hypertension e.g. preeclampsia
  • Infarcts
  • Placental insufficiency: Placental insufficiency or Utero-placental insufficiency is insufficient blood flow to the placenta during pregnancy.
  • Placenta abruption: complication of pregnancy, wherein the placental lining has separated from the uterine wall of the mother.
  • Multiple gestation
  • Uterine malformations

Classification of IUGR

• Symmetrical: small head and small abdomen: Symmetrical IUGR is less common and is more worrisome. It is less commonly known as global growth restriction, and indicates that the fetus has developed slowly throughout the duration of the pregnancy and was thus affected from a very early stage. The head circumference of such a newborn is in proportion to the rest of the body => “head sparing” has NOT occurred. Since most neurons are developed by the 18th week of gestation, the fetus with symmetrical IUGR is more likely to have permanent neurological sequelae. Common causes include:
  • Early intrauterine infections, such as cytomegalovirus, rubella or toxoplasmosis
  • Chromosomal abnormalities
  • Anaemia
7. LOSS OF BASELINE VARIABILITY (UNCOMPLICATED)

Baseline fetal heart rate variability of less than 5 beats/minute.
This may be caused by sedative or analgesic drugs used in labour.
In general the less baseline variability present, the greater the possibility of asphyxia.

8. LATE DECELERATIONS

Any deceleration whose lowest point is past the peak of the contraction (i.e. decelerations with "lag time").
This type of deceleration is usually associated with asphyxia; in general the longer the lag time the more serious is the fetal asphyxia.
This example of a Doppler ultrasound in a normal pregnancy shows a continuous, high forward flow (velocity) at the end of diastole throughout the cardiac cycle.
Multiple pregnancy

- Incidence:
  - Spontaneous twins 1:80
  - Spontaneous triplets 1:10,000
  - Higher incidence in infertility programmes (only 2 embryos should be implanted in IVF)

Multiple pregnancy classification

- Zygosity: refers to number of eggs fertilised to produce twins. Zygosity is the degree of identity in the genome of twins.
  - Mononzygotic => identical twins who came from one egg and one sperm
  - Dizygotic = non identical twins who came from two eggs and two sperms
- Chorionicity: refers to the placenta membrane (chorion) pattern of the twins
- Why is it important?
  - Monochorionic and monozygous (“identical”) twins are at higher risk of pregnancy complications
  - Monochorionicity of monozygotic (identical) twins. However the reverse is not true, as can have dizygotic twins with one chorion (chorionic membrane)
  - Dichorionicity (lambda sign on US) does NOT => dizygotic. Dichorionicity can occur in both monozygote and dizygotes. However, whether they are monogygotic or dizygotic, dichorionicity is reassuring as there are more complications in monochorinic pregnancies.
  - However dizygosity => dichorionicity.

Zygosity

- Zygosity is the degree of identity in the genome of twins. There are five common variations of twinning.
- The three most common variations are all dizygotic (fraternal or non-identical; come from separate eggs and separate sperms):
  - Male–female dizygotic twins are the most common result: 50 percent of dizygotic twins are male-female and the most common grouping of twins.
  - Female–female dizygotic twins
- Male–male dizygotic twins
- Share 50% of genetic code
- Will be dichorionic
- CANT BE MONOCHORIONIC

- The other two variations are monozygotic (identical; come from same egg and same sperm) twins:
  - Female–female monozygotic twins
  - Male–male monozygotic twins (less common)
  - Monozygotic “identical” twins will obviously be the same sex, and share the exact same genetic code
  - Can be monochorionic or dichorionic

![](image)

**Chorionicity**

- A chorionicity scan is used to find out if your twins share a placenta, or have separate placentas.

- **Monochorionic:** If they share a placenta (monochorionic), the pregnancy is at greater risk, and you’ll be monitored more closely, so that any complications can be prevented or
In addition, maternal GDM can result in foetal hyperglycaemia => fetal hyperinsulinaemia =>
increased anabolic state => large baby (macrosomia) and risk of neonatal hypoglycaemia
BM < 2.6 (when constant maternal glucose infusion is removed + high foetal insulin levels)

Consequences

- Overgrowth of insulin sensitive tissues => macrosomia (large foetus) => large for dates
  uterus => increased risk of preterm birth

- Hypoxaemic state in utero: Fetal hyperinsulinaemia and increased anabolism leads to
decrease level of arterial O2. This in turn results in an increase in EPO and polycythaemia
=> increase risk of neonatal jaundice

- Short term metabolic complications which may be life threatening e.g. neonatal
  hypoglycaemia (<2.6)

- Long term metabolic complications: Fetal metabolic reprogramming (thrifty phenotype)
  leading to increase long term risk of obesity, insulin resistance and diabetes

Gestational Diabetes: Screening and Diagnosis
Future development of Type 2 diabetes from GDM

- Risk up to 70%

- Main risk factors:
  - Obesity
  - Use of insulin during pregnancy
  - Fasting glucose levels abnormal during pregnancy
  - IGT (impaired glucose tolerance) post partum
  - Ethnic groups e.g. South Asian and Middle Eastern

Type 1 & 2 Diabetes in pregnancy: Additional management points

- Pre pregnancy counselling
- Fetal anomaly scan at 18 weeks
- Regular eye checks for retinopathy (fundoscopy) – pregnancy can accelerate damage
- BP and urinalysis (assess kidney function and assess for pre-eclampsia)
- Diabetic foot exam and peripheral vascular exam (as DM can cause peripheral vascular disease and neuropathy)

Key Points

- Large for dates aetiology:
  - Wrong dates
  - Multiple pregnancy
  - Macrosomia
  - DM => macrosomnia and polydraminos
  - Polyhydramnios
  - Fibroids
Metanephric Blastema = Nephron

- The metanephric blastema (metanephric mesoderm) is one of the two embryological structures that give rise to the kidney (the other is the ureteric bud, a protrusion of the mesonephric/Wolffian duct)
- The metanephric blastema mostly develops into nephrons (functional units of the kidneys)
- Nephrons components:
  - Bowman’s capsule
  - Proximal convoluted tubule
  - Loop of Henle
  - Distal convoluted tubule
Ascent of the kidney

- The kidneys develop in the pelvis

- As the pelvis and abdomen grow the kidneys slowly move upward and ascend to their final position (great ascent)

- The kidneys "migrate" from the pelvis into the abdomen, attaining their adult position by about week 9

- As the embryo continues to develop in a caudal direction, the kidneys are left behind and eventually come to lie in a retroperitoneal position at the level of L1 by the 9th week development

- Blood supply to kidneys is changing as well. As kidneys ascend into abdomen, they receive their blood supply from the aortic branches closest to them. This means that as the kidneys move up, their blood supply comes from higher and higher sources from the aorta. Normally the more caudal blood vessels degenerate as they are no longer needed. If this does not occur it is possible to have accessory renal arteries
• The genital tubercle ("projection") lengthens only a little, retracts again and, after 14 weeks, the clitoris is recognizable.

• From the genital swellings arise the labia majora

• The urethral folds also do not fuse. Out of them arise the labia minora (the urethral folds fold around the urethra orifice)

Abnormalities of urogenital system and hindgut

• The common origin of the urogenital system and the rectum/anal canal means that there may be connections and fistulae between them

• NB: The cloaca is the common end of the rectal tube and the urogenital tract.
• FBC: look for low platelets (thrombocytopenia) => HELLP requires immediate delivery
• Coagulation screen (PT/INR, APTT, and PLT) as can develop DIC
• Ultrasound (US/USS)

**Key Ix:** assess kidney, liver and haematological systems

**Management**

• Assess risk at booking

**Antenatal surveillance**

• Scans
  • BP monitoring and urine testing
  • **Aspirin:** only decreases risk by 15-30% (aspirin is a PG inhibitor => sometimes effective due to PG imbalance in PET)

**Scans**

• Normal scans:
  • **Dating scan (12 weeks):** estimates when baby is due + gestation + NT
  • **Anomaly scan (20 weeks):** assesses for any major physical anomalies
• If preeclampsia:
  • **Uterine artery Doppler at 20 weeks only:** can visualise notching: The presence of a notching in late in pregnancy is an indicator of increased uterine vascular resistance and impaired uterine circulation
  • **Umbilical artery Doppler:** assess diastolic flow (several scans)
  • Growth scans: several scans (assess for IUGR)

**Management**

• **Always consider delivery as this will resolve the preeclampsia:** The only known definitive treatment for eclampsia or advancing pre-eclampsia is delivery, either by **labor induction or**
• DIC: these women bleed a LOT
• Cortical blindness: rare
• Renal/hepatic failure: rare

Reproductive lecture notes: week 4

NORMAL LABOUR AND PUERPERIUM (POST-NATAL PERIOD)

• Labour is a physiological process during which the fetus, membranes (amnion and chorion membranes which surround and protect a developing fetus), umbilical cord, and placenta are expelled from the uterus

• Labour is associated with regular, painful uterine contractions of sufficient frequency, intensity and duration and accompanied by biochemical changes in the cervical tissue allowing **cervical effacement** (thinning and shortening of the cervix) and **full cervical dilatation** (stage 1) resulting in **delivery of the fetus** (stage 2) and **expulsion of the placenta** (stage 3).

• Interplay of three key factors (the 3 Ps):
  - **Power**: Uterine Contractions (power, frequency and duration) + retraction
  - **Passage**: Maternal Pelvis (shape, size)
  - **Passenger**: Fetus (form, size, lie, presentation, position)

Physiological considerations in labour

• **Progesterone keeps the uterus quiet** e.g. prevents early labour
  - Progesterone prevents formation of gap junctions => hinders contractibility of myocytes (SMCs of myometrium) => decreases uterine contractability

• **Oestrogen makes the uterus contract:**
  - Eostrogen simulates prostaglandin production => prostaglandins increase uterine contractions, increase sensitivity to oxytocin and soften the cervix
  - Increases oxytocin receptors => increases effects of oxytocin
  - Net effects => Increases uterine contractibility and promote cervical dilation and effacement

• **Oxytocin initiates and sustains contractions:**
PARTOGRAM

Mother information

Fetal well-being
- Fetal heart rate
- Character of liquor
- Moulding

Labour progress
- Dilatation
- Descent
- Uterine contraction

Medications
- Oxytocin
- Pain relief (e.g. pethidine)

Maternal well-being
- BP, Pulse, Temperature
- Urine – albumin, glucose, acetone
- Urine output
• Cocodamol: compound analgesic consisting of a combination of codeine phosphate (mild opioid) and paracetamol (acetaminophen)

• TENS (transcutaneous electrical nerve stimulation)

• Entonox (a mix of nitrous oxide 50% and oxygen 50%)

• Epidural: Epidural anaesthesia is a technique whereby a local anaesthetic drug is injected into the epidural space. Useful for prolonged labour.

• Spinal: Spinal anaesthesia is a technique whereby a local anaesthetic drug is injected into the cerebrospinal fluid e.g. SA space. Often first line for C-section; unless emergency => GA (as spinal is trickier to perform and more time consuming).

• Pudendal nerve (S2,3,4) block (perineal nerve block) – first line for instrumental deliveries (forceps or ventouse). It is also helpful just before an episiotomy.

• Combined spinal/epidural

• Remifentanyl: a potent ultra short-acting synthetic opioid analgesic drug

Operative vaginal delivery

As operative vaginal delivery can be associated with maternal and neonatal morbidity, strategies
that reduce the need for operative vaginal delivery should be used. Continuous support for women during childbirth can reduce the incidence of operative vaginal delivery (15 trials; n=13 357; RR 0.82; 95% CI 0.82–0.96), particularly when the carer was not a member of staff. Use of any upright or lateral position in the second stage of labour compared with supine or lithotomy positions was associated with a reduction in the number of assisted deliveries (20 trials; n=6135; RR 0.80; 95% CI 0.69–0.92). Epidural analgesia compared with non-epidural methods is associated with an increased incidence of operative vaginal deliveries, (presumably due to increasing the duration of the second stage of labour) (17 trials; n=6162; OR 1.38; 95% CI 1.24–1.53), but provides better pain relief than non-epidural analgesia (one trial; n=105; weighted mean difference –2.60; 95% CI –3.82 to –1.3.)
• Signs of obstruction
Reduced variability can be caused by:

- Foetus sleeping: this should last no longer than 40 minutes (most common cause)
- Foetal acidosis (due to hypoxia): more likely if late decelerations also present
- Foetal tachycardia
- Drugs: opiates, benzodiazepine’s, methyldopa, magnesium sulphate
- Prematurity: variability is reduced at earlier gestation (<28 weeks)
- Congenital heart abnormalities

Accelerations

- Accelerations are an abrupt increase in baseline heart rate of >15 bpm for >15 seconds
• **Swallowing amniotic fluid:** Amniotic fluid is "inhaled" and "exhaled" by the fetus. It is essential that fluid be breathed into the lungs in order for them to develop normally. Swallowed amniotic fluid also creates urine and contributes to the formation of meconium in the GI tract. Therefore amniotic fluid prepares the lungs, kidneys and GI tract for their extra-uterine job.

**Preparation: Labour and Delivery**

• Onset of labour => increased catecholamines

• Synthesis of lung fluid stops and fluid is reabsorbed via lymphatics

• Vaginal delivery: squeezes lungs => a process that helps clear amniotic fluid from the lungs and stimulate the circulation

• Therefore C-section births are at much greater risk of transient tachypnoea of the newborn due to excessive fluid in lungs

**The first seconds**

• Blue (due to decreased oxygen pressures in foetal circulation)

• Starts to breathe

• Cries

• Gradually goes pink (due to rising oxygen pressures)

• Cord cut

**Cardiorespiratory Adaptation: Lung Aeration**

• At birth, the baby's lungs are filled with amniotic fluid and are not inflated.

• The newborn is expelled from the birth canal (pressure helps to clear amniotic fluid, most amniotic fluid is cleared from lungs via lymphatic absorption), and its central nervous system reacts to the sudden change in temperature and environment. This triggers it to take the first breath, within about 10 seconds after delivery.

• Major physical stimulus for baby to take first breath = hypoxia and hypercapnoea

• Stimulus causes chest expansion and diaphragm contraction => huge negative intrathoracic pressure => results in large breaths
- Clamp between one and three minutes (if phototherapy is available)
- Clamping also reduces risk of PPH

- Closure of ductus arteriosus:
  - Decreased flow due to decreased pulmonary vascular resistance
  - **Increased** pO2 stimulates oxygen sensitive muscular layer
  - **Decreased circulating** PGE2 (major source of PGs are from placenta) due to increased lung metabolism (lungs metabolise PGs) and removal of placenta. Remember that prostaglandins cause the ductus arteriosus to remain open.

- Closure of foramen ovale:
  - SVR (systemic vascular resistance) is now greater than PVR (pulmonary vascular resistance) => *left atrium pressure > right atrium pressure*
  - This pushes the membrane flap closed

- Closure of ductus venosus:
  - Occurs due to falling PGs and rising O2 pressures
  - No flow
Benefits of breast feeding

• Passive immunity:
  - IgA => less colds, coughs, ear infections
  - Cells
  - Promotes healthy colonisation
  - Prevents against NEC

• Growth factors
• Bonding
• Maternal health
• Financial

Haematology

• Fetal haemoglobin (HbF= alpha 2, gamma 2)
  - Becomes disadvantageous
  - **HbF has a greater affinity for oxygen** (shift to left) due to lack of fetal hemoglobin’s interaction with 2,3-bisphosphoglycerate (2,3-BPG)
  - In adult HbA, increase in 2,3 BPG shifts curve to right => gives up O2 more readily => useful effect
Risk Factors for Venous Thromboembolism

- Age
- Marked obesity
- **Pregnancy: 10X**
- **Puerperium (6 weeks following birth): 20X** (appreciate that the time of greatest risk is in the 6 week period after pregnancy) – physiological mechanism to protect against PPH is believed to be the main cause
- Oestrogen therapy
- Smoker
- Previous DVT/PE
- Thrombophilia
- Surgery (C Section)
- Malignancy
- Heart Failure
- Recent MI
- Paralysis
- Immobility, recent surgery
- Infection
- IBD
- Etc

**Venous thrombosis in pregnancy**

**Virchow's triad**

- Stasis: pelvic mass, immobility, and oedema
- Vessel wall
- **Hypercoagulability** *(pregnancy is a hypercoagulable state):*
  
  - increased Factor VIII (low APTT)
- increased Von Willebrand Factor
- increased tissue factor
- decreased Protein S

DVT Prophylaxis

Physical:

- TED stockings (antiembolism stalkings; not the same as compresing stalkings)
- Physiotherapy
- Early mobilization

Pharmacological (anti-coagulation):

- Heparin: can be used for symptomatic DVT or prophylactically
- Warfarin: NOT during pregnancy as teratogenic!

LOW THRESHOLD FOR INTERVENTION

Prevention and management of venous thromboembolism: SIGN guidelines

ASSESSMENT OF RISK FOR VENOUS THROMBOEMBOLISM

VTE is a multicausal disease, the result of the coincidence of several risk factors which can be grouped as:

- inherent to the individual and may be inherited, eg thrombophilia
- inherent to the individual and can be acquired, eg obesity, cancer and certain drug use (eg oral contraceptive pill)
- the result of an intercurrent illness or procedure, or other cause of temporary reduced mobility, eg following major trauma or surgery, serious medical disorder, pregnancy, or long-haul travel.
## PREGNANCY AND THE Puerperium

### Antenatal thromboprophylaxis

- **D** All women should be assessed for risk factors for VTE when booking for antenatal care and at each subsequent maternity contact.

- **D** Women with a previous unprovoked VTE; or VTE linked to oestrogen (including pregnancy); or minimally provoked VTE (related to travel); or previous recurrent VTE; or other additional risk factors for VTE; should be offered antenatal thromboprophylaxis with LMWH.

- **D** Women considered to be at high risk of VTE because of multiple risk factors (three or more) should be offered thromboprophylaxis with LMWH antenatally (first trimester).

- **C** Vitamin K antagonists have adverse fetal effects and should generally be avoided in pregnancy. In women with mechanical heart valves, however, the risks and benefits of VKA and heparin should be assessed on an individual basis.

- **C** Women of childbearing age using VKA should be clearly informed of the risk of teratogenesis associated with these agents and should be advised to seek appropriate medical advice if they are planning to become pregnant or as soon as possible (and within two weeks following a first missed period) if they suspect that they may be pregnant.

- **D** Pregnant women considered to be at increased risk of VTE should be advised to wear AES when immobilised/hospitalised.

### Postnatal thromboprophylaxis

- **D** All women should be assessed after delivery for risk factors for VTE.

- **D** Women with multiple risk factors for VTE should be considered for postnatal thromboprophylaxis.

- **D** All women who have had an emergency Caesarean section and those who have an elective Caesarean section who have one or more additional risk factors for VTE, should receive thromboprophylaxis with LMWH for seven days.

- **D** Women with a previous VTE should receive LMWH for six weeks following delivery.

- **D** Women receiving prophylaxis antenatally should continue thromboprophylactic doses for six weeks following delivery.

---

APPRECIATE THAT THERE IS A REASONABLY LOW THRESHOLD FOR ANTICOAGULATING PREGNANT AND POSTNATAL FEMALES WITH HEPARIN

RCOG guidelines
**Vasa Prae via**

- **Vasa Prae via** = fetal vessels within the membranes due to **low set foetal vessels** (e.g. vessels near internal os)

- Fetal vessels crossing or running in close proximity to the inner cervical os => **these vessels course within the membranes** (unsupported by the umbilical cord or placental tissue) and these foetal vessels are at **risk of rupture when the supporting membranes rupture (ROM)**

- May result from either:
  - **Velamentous insertion** of the umbilical cord: cord normally inserts into middle of placenta, instead inserts **distally into fetal membranes**, then travels within membranes to placenta
  - **Succenturate lobe**: additional lobe of placenta, smaller than largest lobe

- **Bleeding from fetal vessels in the fetal membranes can occur**

- If these fetal vessels rupture the bleeding is from the fetoplacental circulation, and fetal exsanguination will rapidly occur, leading to **fetal death**

- Diagnosis: Can be diagnosed ante-natally using **US scan/doppler => allows early delivery**

- Fetal blood (200ml at term) therefore even a 100ml loss will be very significant to baby!

- Fetal death may be a complication: see a **sudden bradycardia on delivery** (due to hypoxia, occurs at delivery due to compression/damage of low set vessels)

- **If see a bradycardia (<120bpm) on delivery => query vasa praevia and act!!**

- Treatment: **Caesarean section if diagnosed ante-natally** (vaginal birth can cause rupture/compression of cord)
Persistence PPH (>1500ml)

Non surgical:
- Gauze packs & balloon tamponades (compress uterus)
- Tissue Sealants
- Factor VIIa
- Arterial Embolisation

Surgical:
- Undersuturing
- Brace Sutures
- Uterine Artery Ligation
- Internal Iliac Artery Ligation

Management of persistent PPH

- Summon a senior colleague
- Confirm placenta and membranes complete
- Urinary Catheter: empty bladder and measure urine output
- 500 micrograms Ergometrine IV: Avoid if cardiac disease or hypertension (vasoconstrictor, will exacerbate)
- Transfer to maternity operating theatre for EUA (examination under anaesthesia) => allows advanced techniques to assess for:
  - If vaginal / cervical / perineal trauma => ensure prompt repair
  - RPOC: retained products of conception
  - Uterine rupture
  - Uterus inversion (uterus turns inside out)
- PGF2α (Carbaprost: trade name = Haemabate) => causes uterus contraction
- D/W (discuss with) Haematology BTS (blood transfusion services): Blood products required
1\textsuperscript{st} trimester

- Risk of early miscarriage
- Organogenesis
- Period of greatest teratogenic risk: 4th -11th week (embryogenesis)
- Avoid drugs if at all possible unless maternal benefit outweighs risk to foetus

Teratogenic drugs

- ACE inhibitors/ARB e.g. lisonopril/rapimril (ACE-I) or losartan/valsartan (ARBs): can cause renal dysfunction and oligohydraminos
- Androgens
- Antiepileptics
- Cytotoxics
- Lithium
- Methotrexate
- Warfarin

2\textsuperscript{nd} + 3\textsuperscript{rd} trimesters

- Growth of foetus (end of embryogenesis)
- Functional development
  - Intellectual impairment
  - Behavioural abnormalities
- Toxic effects on foetal tissue
Around term

- Adverse effects of drugs on labour
  - Progress of labour
  - Adaptation of foetal circulation: Premature closure of ductus arteriosus e.g. due to NSAIDs (cause decreased PGs)
  - Suppression of foetal systems: Opiates => can cause respiratory depression
  - Bleeding: Warfarin (avoid all together in pregnancy => use heparin instead)

- Adverse effects of drugs on baby after delivery
  - Withdrawal syndrome: opiates, SSRIs
  - Sedation

Delayed effects

- Diethylstilbestrol (oestrogen)
  - Previously used to prevent recurrent miscarriage in pregnant women
  - Vaginal adenocarcinoma in girls aged 15-20 years whose mothers were exposed to diethylstilbestrol

Chronic conditions and pregnancy

- Need to discuss risk/benefit balance with patient: Ideally pre-conception
- Compliance with medication may be poor
- Many women avoid taking their asthma inhalers in pregnancy
- Up to 20% of women discontinue antiepileptic medication in pregnancy

Epilepsy

- Incidence of congenital malformations higher in untreated women with epilepsy than women without epilepsy
- Increased seizures in 10% of women
The mother’s breast is red, hot and swollen

The pain is intense but localised

The mother has flu-like symptoms

Her temperature is higher than 38.4 degrees Celsius.

Clinical features:

- Blocked duct: Tender spot, redness, sore lump without fever
- Breast infection: A tender spot or lump and a low grade fever
- A lump suggests abscess
- May have nausea, vomiting
- Infective mastitis may have:
  - cracked nipple
  - pus and blood in milk
  - red streaks from site back into breast
  - May develop into abscess (collection of pus)

Treatment:

- Continue breastfeeding – even in the infected breast!!!
- Frequent feeds on affected side
- Encourage removal of breast milk particularly where mother wants to stop breastfeeding
- Refer for skilled help
- Massage and expressing if needed
- Anti-inflammatory medication e.g. NSAIDS
- Antibiotics if no improvement:
  - Flucloxacillin – most caused by S. aureus
  - Erythromycin (if penicillin allergy)
- Abscess:
Birth weight of term baby

- Birth weight is often talked about
- Correlated with prognosis
- 3.5kg average
  - > 4kg = Macosomnia (large baby)
  - Less than 2.5kg is low
  - Less than 1.5kg is very low
  - Less than 1kg is extremely low

3rd trimester

- Last trimester: period of rapid growth and deposition of body fat (anabolic state for foetus and starvation/insulin resistant state for mother)

- Premature babies are very skinny with very little fat (remember that fat is very important for thermogenesis in neonates)
• Important in nutrition and organ dysfunction
• Last trimester very important in allowing the baby to withstand the stress of labour

Delivery at Term
• Triggers
  - Maternal: hormonal
  - Fetal: size, hormonal
• Spontaneous or induced: Induced labour to save mother or save baby from morbidity/mortality
• Vaginal
• C-Section (CS or caesarian)

Surviving labour
• Hypoxic environment during contractions => period of enormous hypoxic stress. Adults would probably die if subjected to this level of hypoxia. Foetal adaptations are important
• Foetal adaptations include respiratory and haematological adaptations e.g. HbF (left shift) and increased Hb concentration
• Fetal Hb (alpha 2, gamma 2) increases oxygen binding capacity, due to shift of the haemoglobin dissociation curve to the left => resulting in enhanced oxygen affinity in the blood. Fetal Hb is also more sensitive to the Bohr effect (shift to the right) in states of hypoxia and acidosis
• The combined increase in both capacity and affinity provides the fetus with high blood oxygen stores, something that may defer anaerobiosis in periods of reduced oxygen supply => particularly useful for periods of acidosis and hypoxia (due to HbF’s greater sensitivity to Bohr effect)
• Prolonged labour however reduces fetal reserves
• Factors that diminish potential for surviving labour:
  - Placental insufficiency
  - Growth restriction or excess
• Increased cortisol and adrenaline enhances adaptation
• Smoking cessation
• Alcohol limitation to recommended limit
• Drug use
• Diet: balanced
• Now good evidence that health as babies and toddlers strongly impacts on adult health: particularly diabetes, cardiovascular disease, some data on cancers now
• If there’s an opportunity to try to raise issues of lifestyle change, give it a go: however some will continue drinking, smoking etc
• Most parents highly motivated to change for their children

THE SICK TERM INFANT

Causes of sick term infant
• Asphyxia
• Cardiac
• Metabolic
• Infection
• Congenital anomalies
• Respiratory

Perinatal asphyxia
• Perinatal asphyxia, neonatal asphyxia, or birth asphyxia is the medical condition resulting from deprivation of oxygen to a newborn infant that lasts long enough during the birth process to cause physical harm, usually to the brain.
• Hypoxic damage can occur to most of the infant’s organs (heart, lungs, liver, gut, kidneys), but brain damage is of most concern and perhaps the least likely to quickly or completely heal.
• In the more pronounced cases, an infant will survive, but with damage to the brain manifested as either mental, such as developmental delay or intellectual disability, or physical, such as spasticity (cerebral palsy).
Bishops score

- **Bishop score (also known as cervix score)** is a pre-labor scoring system to assist in predicting whether induction of labor will be required.
- Also used to **monitor progression of labour**
- It has also been used to **assess the odds of spontaneous preterm delivery**.
- The total score is achieved by assessing the following five components on vaginal examination (4Cs + F):
  - Cervical dilation: max dilated at 10cm, dilates by approx 1cm per hour
  - Cervical effacement thinning and shortening of cervix
  - Cervical consistency (ripening)
  - Cervical position
  - Fetal station

- The Bishop score guides patients who would be most likely to achieve a successful induction. The duration of labor is inversely correlated with the Bishop score; a score that exceeds 8 describes the patient most likely to achieve a successful vaginal birth. **Bishop scores of less than 6 usually require that a cervical ripening method (e.g. vaginal PGs) be used before other methods.**
Methods of IOL

- **Prostaglandins**: PGE2 Dinoprostone or misoprostol: used for **cervical ripening** (paritcular if low Bishops score <6) and stimulation of uterine contractions. First line for medical induction.

- **Syntocinon (oxytocin) IVI (intravenous infusion)**: stimulates uterine contractions. Should not be used for at least 6 hours after last dose of PG. If the woman has fully dilated but uterine contractions are insufficient then can use syntocinon. Continuous CTG required.

- **Mechanical**
  - **Membrane sweep**: the practitioner moves her finger around the cervix to stimulate and/or separate the membranes around the baby from the cervix. This causes a release of prostaglandins which can help to kick-start labor.
  - **Extra-amniotic saline infusion**: Foley Balloon Catheter is inserted into the cervix and the distal portion expanded to dilate it and to release prostaglandins.

- **Amniotomy**: **Artificial rupture of membranes (AROM)**, also known as an amniotomy, may be performed by a midwife or obstetrician to induce or accelerate labor. The membranes may be ruptured using a specialized tool, such as an amnihook or amnicot, or they may be ruptured by the proceduralist's finger.

- **Key point:**
Aetiology of UI and POP
Overactive bladder (OAB) or urge incontinence

- Occurs due to overactive bladder e.g. twitchy detrusor muscle
- Causes urge to micturate which is frequently precipitated by a stimulus e.g. the hearing of running water
- Incontinence is associated with a **strong urge**

Treatment of OAB (urge incontinence)

**Conservative**

- **Lifestyle:** *avoid caffeinated drinks*
- **Physiotherapy:** *bladder training*
- **Drugs:** *Oxybutynin (and other antimuscarinic drugs)* block detrusor muscarinic receptors (stimulated by parasympathetic NS to void) and decrease the ability of detrusor muscles to contract. Remember the detrusor muscle receives parasympathetic stimulation (S2-S4) from the sacral plexus. Parasympathetic causes opening of sphincters (“rest and digest”).
  - **Remember that anti-muscarinic drugs can cause urinary retention**

**Surgical (rarely used)**

- **Botox injections**
- **Sacral nerve modulation**
- **Augmentation cystoplasty**
- **Bladder overdistension**

Investigation of urinary incontinence

- **History:**
  - Onset and timing and duration
  - Character: frequency, urgency (strong urge preceding urination?), stress (e.g. associated with coughing or sneezing?)
  - Radiation: bowel problems?
**Classification of pelvic organ prolapse**

- **1st degree** (in vagina)
- **2nd degree** (at vaginal interiotus)
- **3rd degree** (outside vagina)
- **Procidentia** (entirely outside vagina)

**Symptoms of pelvic organ prolapse**

- Any prolapse:
  - asymptomatic
  - worry
  - **coital difficulties** (sexual intercourse difficulties)
• Cystourethrocele (bladder/urethra prolapsed through anterior vaginal wall):
  ➢ stress urinary incontinence
  ➢ urinary retention
  ➢ recurrent UTI

• Uterine/vault prolapse
  ➢ backache
  ➢ ulceration if procidentia (completely out of vagina)

• Rectocele (rectum prolapsed through posterior wall):
  ➢ constipation
  ➢ dyschezia (difficulty defecating)

**Assessment of Prolapse Organ Prolapse**

**History**

• Age and Parity

• PC: urinary symptoms, bowel symptoms, sexual symptoms, other symptoms

• PMH: including past Obst and Gynaec history and past surgical history

• FH

• DH

• Allergies

• SH and occupational history

• Concerns and expectations

**Examination**

• Weight, height and BMI

• BP

• Urinalysis

• Abdominal Examination
Regression of the corpus luteum => progesterone levels will fall => shedding of the endometrium occurs (menstruation) => back to day 1 of the cycle

If fertilisation does occur, LH levels will decrease (due to rising progesterone released from corpus luteum), however luteal function will be maintained by the action of hCG (human chorionic gonadotropin), a hormone very similar to LH but secreted from the new placenta (trophoblastic cells)

Physiology

- Ovarian function is controlled by anterior pituitary hormones (LH and FSH) which are released in response to pulsatile secretion of GnRH from hypothalamus – cyclical.

- Ovaries produce oestrogen (mostly oestradiol E2), progesterone and testosterone (androgens also produced in adrenals).

- Negative feedback from oestrogen and progesterone on GnRH

- FSH causes production of oestrogens (granulosa cells) particular oestradiol E2

- LH causes production of androgens (theca cells)

- NB: More complicated mechanisms at work and there is a positive feedback at certain times e.g. LH surge just before ovulation
Many of these effects primarily occur due to oestrogen depletion in skin in urogenital tissues.

**Long Term Consequences**

- **Cardiovascular disease** (CVD) and Cerebrovascular disease due to decreased oestradiol (E2): CVD/stroke leading causes of death in women. Oestrogen reduces LDL, increases HDL, reduces cholesterol deposition and fat distribution => “normal” levels of oestrogen are CV and cerebrovascular protective. HRT is therefore protective.

- **Osteoporosis** (decreased BMD < -2.5) due to decreased oestradiol E2: loss bone mineral density (BMD) /architecture predisposing to fractures. Occurs due to loss of protective effect from oestrogen in premenopausal state (oestrogen protects bones). NHS spend almost £2bn a year on osteoporosis-related treatment. Hip fracture 30% mortality rate. 1 in 2 women by age 70 will have an osteoporosis related fracture. High burden to society. HRT is therefore protective.

**Management of the menopause**

- To minimise symptoms and reduce risk long term consequences (e.g. CV disease and osteoporosis)

- Lifestyle measures: healthy diet, regular exercise, stop smoking

- HRT if young onset or decreased QoL (e.g. due to symptoms). HRT’s aim is to restore normal levels of hormones. This is in contrast to COCP, which increases the levels of hormones in the body.

- **Systemic: HRT**
  - Recomended for all early menopause <45 years
  - Recommended for all premature menopause < 40 years
  - Recommenddd for others where syptoms are affecting QoL

- **Local:** e.g. vaginal oestrogen cream

**HRT**

- Oestrogen-based therapy (HRT):
- Higher with combined HRT than oestrogen-only (although oestrogen is major risk factor, progesterones may contribute)
- More common in the first year of use
- Risk may be lowered by transdermal route/changing progestogen

**Stroke and CV disease:**
- In RCT’s HRT increased the risk of stroke (mostly ischaemic) compared with placebo
- Older women have a greater absolute risk of stroke
- Risk may depend on oestrogen dose
- No significant difference between E2 only/combined preparations
- HRT may raise BP

Therefore it is important to also perform a CV assessment at initial HRT consultation (similar consultation initiating COCP): migraine with aura, previous cerebrovascular accident or CV accident, CV risk factors, personal or family history of DVTs, personal or family history of O&G cancers, smoking status, BMI, BP

**HRT Uncertainties: CVD**
- Initially thought to be beneficial
- Re-analysis WHI study suggests a cardio-protective effect if HRT taken in the early menopausal years
- Increased risk of CVD in women who started combined HRT more than 10 years after the menopause
- No increased risk of CVD has been identified to date with oestrogen-only HRT
- Oestrogen can raise BP => may act as a CV risk factor
- Increased absolute excess risk the longer after menopause it is started.

**HRT Uncertainties: Alzheimer’s**
- Before age 60 observational studies suggest possible protection (but not an indication to take HRT)
➢ Chromosomal e.g. Turner's 45X, Down syndrome, Fragile X
➢ AI: Hypothyroidism, Addisons, DM, SLE, RA
➢ Enzyme deficiencies: Galactosaemia

Secondary causes

• Chemotherapy/radiotherapy
• Surgery: bilateral oophrectomy, hysterectomy
• Infection: TB, mumps

POF: Treatment

• Hormone replacement (HRT) required to keep tissues healthy and reduce long term complications
• HRT (higher doses) or COCP (optional pill free week) to age 52
• Sequential combined HRT as simulates natural cycle
• Testosterone as patch or implant
• Additional vaginal oestrogen may be needed

➢ Risks at this age are due to non-use of HRT (e.g. early CV disease and bone disease) rather than use (on HRT same risk as age-equivalent population for breast cancer, VTE etc; this is because we are just "normalising" hormone levels) => patients with POF should definitely be on HRT
• No studies have clearly shown best replacement hormones (HRT vs OCP)

PATHOLOGY OF THE OVARY AND FALLOPIAN TUBE

Anatomy reminder
Ovarian adenocarcinoma

- Surface epithelial-stromal tumour, also known as ovarian *glandular epithelial carcinoma* or *ovarian adenocarcinoma*

- **Most common type of ovarian cancer**

- It includes *serous adenocarcinoma*, *endometrioid adenocarcinoma* and *mucinous cystadenocarcinoma*.

- Less common tumors are malignant Brenner tumor and transitional cell carcinoma of the ovary.

Features of epithelial ovarian cancer

- **Presents late, vague symptoms:**
  
  - Dyspepsia like picture
  
  - Abdominal pain and swelling and bloating
  
  - Early satiety
  
  - Ascites
  
  - Pressure effects on other organs e.g. urinary symptoms

- Spreads throughout peritoneal cavity

- Poor prognosis: 5 year survival 43%

- 6th commonest female malignancy

- **Kills more women each year than all other gynaecological cancers combined**

Mucinous Adenocarcinoma

- Cancer of *endocervical type epithelium*

- Multiloculated cysts, solid areas, necrosis, haemorrhage.

- May extend through capsule

- Malignant mucinous epithelium

- Multilayered with mitotic figures.
➤ +/- Bleeding (esp post-coital bleeding)

➤ +/- pain

**Uterine fibroids**

- **Leiomyomas**: benign *smooth muscle tumours* (leiomyosarcomas = cancerous; very rare) with a fibrous component
  - Very common
  - Esp >40 years.
  - Usually few cm, but may be much bigger & multiple
  - Therefore common cause of pelvic mass

- Presentation:
  - May be asymptomatic/incidental finding
  - Menorrhagia (heavy menstruation loss >70ml)
  - Pelvic mass or “bulky uterus”
  - Pain/tenderness
  - Red degeneration: A rare complication of a fibroid during pregnancy is a problem medically as red degeneration. If red degeneration occurs there is haemorrhage within the *centre of the fibroid*. This usually happens in the middle trimester (three months) of pregnancy and is thought to result from the leiomyoma (fibroid tumour) growing rapidly and outgrowing its blood supply. Red degeneration can be very painful, usually requires treatment with strong painkillers, but nearly always settles down without causing serious problems or needing specific treatment. Can also occur in menopause.
    - ‘Pressure’ symptoms: leiomyomas can get very very large! e.g. bladder/bowel dyfunction

- Investigations:
  - Hb if heavy bleeding
  - Ultrasound usually diagnostic => smooth echogenic mass often multiple.
  - MRI for more precise localisation

- Management:
 Deposits on all peritoneal surfaces
 Omental disease/infiltration
 Malignant ascites with protein exudates

- Usually more insidious symptoms

**Often via non-gynaecology**

- Heartburn/indigestion
- Early satiety
- Weight loss/anorexia.
- Bloating
- ‘Pressure’ symptoms (especially bladder e.g. incontinence)
- Change of bowel habit
- SOB/ Pleural effusion
- Leg oedema or DVT
- Even generalised oedema if low albumin

- N.B There may not be a pelvic mass

Genetics of Ovarian Cancer

- Only 5% cases have genetic basis
- But always ask about family history

- **BRCA1 & 2: Breast & ovarian cancers**
- HNPCC (Lynch syndrome): Bowel, endometrial, ovarian cancer + many others
- Unfortunately screening not proven to detect early disease

Risk factors for ovarian cancer

- Increasing age
- Nulliparity
- Family history
The role of prophylactic salpingo-oophorectomy

• Women with a family history that appears to place them at high risk of developing ovarian cancer should be offered referral to a Clinical Genetics Service for assessment, confirmation of family history and consideration of genetic testing of an affected family member.

• Defining high risk: All women with non-mucinous ovarian (e.g. papillary serous cystadenocarcinoma) or fallopian tube cancer should be offered BRCA1 and BRCA2 mutation testing. Women with ovarian cancer who have a family history of breast or ovarian cancer should have a genetic risk assessment. BRCA1 and BRCA2 mutation analysis should be considered in a family where there is a 10% or greater risk of a mutation being present.

• Prophylactic salpingo-oophorectomy: “Women with genetic mutations of BRCA1 or BRCA2 genes should be offered prophylactic oopherectomy and removal of fallopian tubes at a relevant time of their life. Women at high risk in whom mutations have not been identified should have the opportunity to discuss the advantages and disadvantages of prophylactic salpingo-oophorectomy. Hormone replacement can be used after oopherectomy until the time of natural menopause without losing the benefits of breast cancer risk reduction. Women who decide to have prophylactic salpingo-oophorectomy should be offered counselling, support and information before and after surgery.”

Screening

• A large US study showed there is no benefit in screening.

• Screening for ovarian cancer in the general population should not be performed outwith the research setting.

BEAT ovarian cancer

• B for bloating that is persistent and doesn’t come and go

• E for eating less and feeling fuller

• A for abdominal pain

• T for telling your GP

Summary
DEFINITIONS

Primary amenorrhea: Failure to establish spontaneous periodic menstruation by the age of 16 years regardless of whether secondary sex characteristics have developed (e.g. Turners sundrom 45 X). Alterantive definition = no development of sexual charcteristics (e.g. thelarche) by age of 14.

Secondary amenorrhea: Absence of periodic menstruation for at least 6 months in women who have previously experienced menses.

FEMALE INFERTILITY

• Write brief notes about oogenesis

• Do quick summary of causes of female infertility similar to the male infertility lecture e.g pre-ovarian causes (hypothalamus and pituitary), pelvic causes, post-ovarian (obstructive)

• Use endocrinology block lectures

ESTROGENS AND OVARIAN FUNCTION

• The normal human ovary produces all 3 classes of sex steroids, estrogens, progestins and androgens; however, estradiol (E2) and progesterone, are the primary secretory products.

• Remember estrone (E1) is post menopausal oestrogen

Two-cell theory of estrogen production by the ovarian follicle:

• Thecal cells: produce androgens stimulated by LH.
• Granulosa cells: conversion of androgens to estrogens (mainly estradiol E2) by aromatisation, regulated by FSH.
• Both these cells (of the dominant follicle) develop into the corpus luteum

Estrogens are also produced by peripheral aromatisation of androgens:

• Important source of postmenopausal estrogens (mainly estrone E1)
• Source of androgens: adrenal cortex
• Major sites of aromatisation: liver and adipose tissue ($\uparrow$ estrone production with obesity).

Effect on pituitary:

• Slowly rising or sustained high levels of estrogen together with progesterone inhibit pituitary gonadotrophin (LH and FSH) secretion by NEGATIVE FEEDBACK.
• Rapid rise in estrogen concentration which occurs prior to ovulation stimulates LH secretion => POSITIVE FEEDBACK.
A Pain relief in labour

Following discussion, Julie opts for intramuscular injection of Diamorphine, 10 mgs.

1 What is Diamorphine and what are the actions of Diamorphine?


2 What are the side effects of Diamorphine injection?

Nausea, vomiting, constipation, dry mouth, biliary/resp depression, brady/tachycardia, palpitations, sedation, euphoria, peripheral vasodilatation, Pruritis.

3 Are there any effects on the fetus from Diamorphine?

Fetal respiratory depression.

After another two hours of labour, Julie is again showing signs of distress and is finding the effects of the Diamorphine injection wearing off. Following discussion, Julie requests an Epidural to be sited and the obstetric anaesthetist is called.

The Epidural is sited and Julie is now pain free and resting quietly.

4 What is an Epidural and how does it relieve pain?

*Epidural anaesthesia is inserted to the epidural spaces between L3 and L4.*

Usually contains levobupivacaine and opioids → nerve blocks by blocking sodium channels intracelluarly, hence preventing depolarization phase of action potential from happening
6 Why is an Epidural a good form of pain relief for Julie?

*Provides long lasting pain relief which can be topped up.* Helps with managing exhaustion and distress. It also allows active participation in labour as consciousness and contractions are maintained. This also avoids the risks associated with GA and there is less nausea associated.

7 What are the side effects on mother and fetus of Epidural Analgesia?

<table>
<thead>
<tr>
<th>Low Blood Pressure</th>
<th>(Lightheaded and Nausea)</th>
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<tbody>
<tr>
<td>Can lengthen labour</td>
<td>Headache</td>
</tr>
<tr>
<td>Pain (Technique of injection)</td>
<td></td>
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<tr>
<td>Decrease in blood pressure can cause a compromise in fetal blood and oxygen.</td>
<td>Can cause fetal bradycardia</td>
</tr>
<tr>
<td>Loss of Bladder Control (unable to tell it is full)</td>
<td></td>
</tr>
</tbody>
</table>

Progress of labour
To assess the progress of labour, a number of observations/assessments are made with regard to the mother and fetus. This information is documented on the partogram (see over).

8 What observations/assessments are made to assess the progress of labour?

- Fetal Heart and CTG
- Amniotic Fluid
- Bishops score: Cervical Dilatation, cervical effacement, cervical consistency, cervical position and foetal station
- Contractions: length, frequency, strength (intrauterine)
- Obstruction - Moulding
- Maternal Observations
Using the partogram, discuss the various observations/assessments recorded.

<table>
<thead>
<tr>
<th>Observation/Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amnitoic fluid (liquor) fluid is clear (C). If meconium present =&gt; label M. If blood present label B.</td>
</tr>
<tr>
<td>Positive caput and moulding</td>
</tr>
<tr>
<td>Dilated 7cm</td>
</tr>
<tr>
<td>1/5 palpable</td>
</tr>
<tr>
<td>Frequent but weak contractions</td>
</tr>
<tr>
<td>ROP</td>
</tr>
<tr>
<td>Dimorphine and epidural</td>
</tr>
<tr>
<td>BP fine</td>
</tr>
<tr>
<td>Urinalysis fine</td>
</tr>
</tbody>
</table>
• **Tumour stage (TNM system)** is based on depth of myometrial invasion and involvement of cervix, vagina, parametrial tissue and adnexae.

• 5 year survival rates are 96% for stage 1, 67% for stage 2 and 23% for stage 3. Other uterine tumours to be aware of:

**Fibroids**

- **Leiomyoma** – benign smooth muscle tumour of myometrium (fibroids).
- **Leiomyosarcoma** – rare, malignant counterpart to leiomyoma.

**Ovarian tumours**

<table>
<thead>
<tr>
<th>Tumour Origin</th>
<th>Name</th>
<th>Behaviour</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epithelial (60-70%)</td>
<td>Serous cystadenoma</td>
<td>Benign</td>
<td>Cystic tumour lined by benign (single layer) serous epithelium. Can be very large. <strong>Most common ovarian tumour</strong></td>
</tr>
<tr>
<td></td>
<td>Mucinous cystadenoma</td>
<td>Benign</td>
<td>Cystic tumour lined by benign (single layer) of mucinous epithelium. Can be very large.</td>
</tr>
<tr>
<td></td>
<td>Borderline tumour (serous or mucinous)</td>
<td></td>
<td>Some cystic tumours can show borderline change. Usually very good prognosis, but can metastasise.</td>
</tr>
<tr>
<td></td>
<td><strong>Serous carcinoma (most common ovarian cancer)</strong></td>
<td>Malignant</td>
<td>High grade carcinoma. <strong>Ca125 Peritoneal metastases common.</strong></td>
</tr>
<tr>
<td></td>
<td>Mucinous carcinoma</td>
<td>Malignant</td>
<td>Invasive tumour that produces mucin. Peritoneal involvement results in mucinous ascites (Pseudomyxoma peritonei)</td>
</tr>
<tr>
<td></td>
<td><strong>Germ Cell</strong></td>
<td></td>
<td>Usually a mixture of differentiated tissue types e.g. skin, hair, cartilage, teeth, fat and thyroid.</td>
</tr>
<tr>
<td></td>
<td>Mature teratoma (dermoid cyst)</td>
<td>Benign</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dysergimina</td>
<td>Malignant</td>
<td>Sheets of malignant germ cells.</td>
</tr>
<tr>
<td><strong>Metastases</strong></td>
<td>Metastases (type depends on primary tumour)</td>
<td>Malignant</td>
<td>Often bilateral. Ovarian metastases commonly originate from stomach/GI tract tumours. <strong>A Krukenberg tumor</strong> refers to a malignancy in the ovary that metastasized from a primary site, classically the gastrointestinal tract, although it can arise in other tissues such as the breast. Gastric adenocarcinoma (signet cells), especially at the pylorus, is the most common source</td>
</tr>
</tbody>
</table>

**Ovarian serous carcinoma is the most common type of malignant ovarian tumour.**

**Recent research suggests** that ovarian epithelial carcinomas actually arise from the
also has a family history of breast cancer.

- What is the likely diagnosis? Ovarian adenocarcinoma (serous cystadenocarcinoma)
- What is the relevant pathology?
- What is the prognosis for this patient?
- This patient will probably be referred to a geneticist. Why? Risk of BRCA1/2 mutation

**Para note**

- Some terminology uses: Para = X + Y (e.g. two numbers assigned to Para)
- X = number of pregnancies exceeding 24 weeks gestation (with a delivery of live or stillborn baby)
- Y = number of pregnancies ending before 24 weeks gestation

**Example 1**

- A woman at 8 weeks into her first pregnancy = para 0 + 0
- Parity does not become 1 until after delivery
- Para 1+0 = single pregnancy with delivery of baby(s) born after 24 weeks gestation (alive or stillborn)
- Para 0+1 = single pregnancy with loss of baby(s) before 24 weeks

**Example 2**

- A woman who has had a previously still birth at 32 weeks and a previous live birth at 40 weeks = para 2 + 0
- Remember that the first figure = deliveries beyond 24 weeks (live or stillborn)