Basic Sciences: Growth, Development and Reproduction

Development

Development is the journey a person goes on until they are able to reproduce. Development starts at the time of fertilization and is divided into:

1. Prenatal – embryonic weeks 1-8 when fetal weeks 9 til birth
2. Postnatal – birth until puberty

During the embryonic period, the embryo grows to 30mm, the rudiments of all the systems form and the cardiovascular system is functioning.

During the fetal period, the fetus grows by cell growth, division and increased production of ECM.

Tissue differentiation occurs – a progressive an irreversible process whereby cells change to an overtly specialized cell type.

Induction is the change in the developmental fate of one region caused by interaction with another e.g. lens development stimulated by the optic cup.

Cell migration is the movement of cells at a particular time to a particular place.

Cell death is programmed e.g. digit separation at a set time.

Pregnancy is timed from the last menstrual period LMP – 40-week pregnancy or 38 weeks from the time of fertilisation.

Congenital abnormalities are morphological defects occurring during prenatal development. They are classified into types:

- Disruption due to a factor interfering with normal development
- Deformation is an altered structure due to extrinsic pressures
- Malformation due to flawed organ or structure development
- Dysplasia is an abnormal organization of cells/tissue.

Female Reproductive System

The system is composed of the ovaries, uterine tubes (site of fertilisation), uterus (site of implantation), cervix, vagina and mammary glands.

Stages of ova production:

1. Primordial oocytes enlarge as the follicular cells proliferate as the zona pedullica, meiosis 1 occurs.
2. This layer is then a theca layer and the inner part secretes oestrogen
3. The follicular cells fill with fluid to form the tertiary follicle
4. The ovum is held by a cloud and moves to the surface of the ovary for release
5. LH causes final ova maturation makes the graffian follicle.
6. Meiosis 2 occurs when fertilisation occurs
7. The corpus luteum forms and secretes progesterone, when it dies it forms a corpus albicans.
The uterus has an endometrial lining with an epithelium and stroma with spiral blood vessels; this layer is lost during menstruation. The basilar layer containing straight arteries is retained. Glands in the wall begin saw shaped but become balloon shaped allowing implantation, they secrete mucus, lipids and glycogen.

Stages of the menstrual cycle:
1. Blood loss for days 1-4
2. Proliferative phase for days 5-15
3. Progestational phase for days 11-28

**Male Reproductive System**

Leydig cells are endocrine cells and make testosterone - needed for spermatogenesis and male characteristics and development.

The testis are surrounded by the tunica albuginea which is thickened at the mediastinum, a septa divide them into incomplete lobules.

Spermatagonia (2n) → primary spermatocytes –meiosis→ secondary spermatocytes → spermatids (n) → spermatooza by spermiogenesis, migrate into the seminiferous tubule lumen. Spermatagonia cells are of type a and b a→ a and b while b → b, supplies wont be exhausted.

Sertoli cells are bound by tight junctions on the basal border, the developing sperm move between them to reach the lumen. They produce ABP (androgen binding protein) which is complexed with testosterone and released with the sperm to enhance their development. Sertoli cells also remove residual sperm cytoplasm and regulate metabolite exchange.

Spermiogenesis – chromatin condenses, excess cytoplasm is shed, organelles are re-organised and an acrosome (Golgi structure) forms which contains hydrolase enzymes for egg penetration. Flagella from the centrioles migrate to form the tail, the tail neck contains many mitochondria for swimming. The whole sperm cycle takes 74 days.

Seminiferous tubules collect at the rete testis and unite to from the epididymis, has sterecillia to allow sperm movement. In the vas deferens, the ampulla glands secrete fructose and prostaglandins (cause female smooth muscle contraction).

The prostate adds a white milky fluid to the sperm which contains acid phosphatases. It has a capsule and smooth muscle to aid sperm movement. Carcinoma can develop in the peri-urethral gland.

Erectile tissue – 2 corpus cavernosa and 1 corpus spongiosum. They are vascular meshes surrounded by an inelastic tunica albicans. The blood flow is ANS controlled.
Implantation and Cleavage

The semen is made up of spermatozoa, which at this stage are fully formed but largely non-motile. They are stored primarily in the epididymis and also the ampulla of the deferent duct, but not in the seminal vesicle. The sperm are transported in the male genital tract by the action of cilia, muscular movements and fluid currents.

Seminal plasma, which makes up most of the volume of the ejaculate. The plasma is secreted by the prostate and seminal vesicle and contains prostaglandins (active on smooth muscle), fructose etc.

Motility, capacitation and fertility of sperm

Sperm are immotile while in testis and become partially motile in the epididymis. Sperm become fully motile when mixed with secretions from the seminal vesicle and prostate at ejaculation. Even when sperm become motile they are incapable of fertilisation until after capacitation.

The process of capacitation requires approximately 6-7 hours and is induced by substances from the female genital tract or cells from the cumulus oophorus. Capacitation involves the removal of plasma proteins (secreted by the epididymis) from the sperm and a change in the glycoproteins of the cell membrane.

Sperm remain motile for up to 7 days after ejaculation in humans, but fertility declines much sooner.

Transport of sperm in the female tract

During normal intercourse sperm are ejaculated in the upper, posterior part of the vagina. Substances in the semen liquefy the cervical mucous plug. Sperm then have to travel the whole length of the uterus and uterine tube (approx. 17.5 cm). Muscular movements may aid transport in the female tract.

Timing of intercourse for fertilisation

For fertilisation to be possible, intercourse must take place at a time when both fertile sperm and an oocyte are present (fertile life of sperm is 1-6 days and life of an oocyte is 6-28 hours). If conception is wanted, the fertile interval is from 1 day before ovulation to 1 day after ovulation. If conception is to be avoided, potentially fertile period is from 6 days before to 2 days after ovulation.

Fertilisation

Penetration of the corona radiata

Sperm first have to penetrate the corona radiata, which are cells surrounding the oocyte. Capacitated sperm pass freely through the corona, although penetration is possibly aided by the release of hyaluronidase from the acrosome of the sperm.

Penetration of the zona pellucida

The sperm now makes contact with the zona pellucida via a specific reaction between the gametes where a ligand (ZP3) in the zona binds to a specific receptor on the head of the sperm. The acrosome reaction is induced by the contact and release of acrosomal enzymes (acrosin) allows sperm to penetrate the zona due to the lytic actions of the enzymes. After penetration, zona reaction (hydrolysis of the zona) blocks any further sperm entry.

Fusion of cell membranes and sperm entry

Following adhesion, the plasma membranes of the sperm and egg fuse (takes just a few minutes). The entry of the sperm takes about 15 minutes and in humans all of the sperm enters the oocyte, although the mid-piece and tail play no further role.
Formation of the female and male pronuclei
The entry of the sperm induces the oocyte to undergo the 2nd meiotic division to form the second polar body and the definitive oocyte, which is known as the female pronucleus upon subsequent chromosome re-arrangement. The male pronucleus forms after about 60 minutes and is derived from the head of the sperm.

Cleavage
The first cell divisions of the zygote are known as cleavage. This process is not accompanied by an increase in the amount of cytoplasm hence the size of the cells decreases. Cell division appears to be under the control of the cytoplasm, with a normal amount of cytoplasm (stimulated during fertilisation) required for cleavage to occur. The first stages of differentiation do not occur until nears the end of cleavage.

At the end of cleavage the zygote is referred to as a morula (= mulberry) as it looks like a blackberry collection of cells. At the 12-16-cell morula stage the zygote enters the uterus and the first signs of differentiation are evident. Towards the end of the 4-5th day the morula absorbs fluid, swells and fluid-filled spaces between the cells coalesce to form a cavity. A process of compaction segregates inner cells from the outer cells.

The zygote is now termed a blastocyst and consists of:
- an outer shell of about 55 cells – the trophoblast
- cavity – the blastocoele
- inner cell mass of about 5 embryonic cells

Time and position of implantation
Initially the blastocyst lies free within the uterine cavity, but as the blastocyst escapes from the zona pellucida its ‘sticky’ surface cells adhere to the endometrium of the uterine wall. This first stage of implantation occurs at day 5-7 following fertilisation. Implantation of the blastocyst occurs in the upper, posterior part of the uterus. The trophoblast produces a number of enzymes, which breaks down the cells of the endometrium. The digested products of the endometrium are used as nourishment for the early embryo. By the 10-12th day the blastocyst is completely covered by endometrium.

The trophoblast
The trophoblast of the blastocyst is initially thin and flattened but when contact is made with the maternal endometrium, the trophoblast cells proliferate to form a thickened layer. The outer most cells fuse with each other to form a multinucleated syncytium called the syncytiotrophoblast. The inner cells remain unfused and are called the cytotrophoblast and continue to divide throughout pregnancy.

Maintaining the uterine epithelium
If pregnancy occurs, maternal hormones maintain the endometrium for 7 days after implantation (14 days after ovulation). Secreted human chorionic gonadotrophin (HCG) acts like luteinising hormone (LH) and maintains the corpus luteum. The corpus luteum continues secreting progesterone, which maintains the epithelium of the uterus and prevents menstruation and loss of the embryo. The placenta later takes on the role of secreting progesterone and the corpus luteum gradually regresses.
If pregnancy fails to occur, maternal hormones maintain the secretory phase of the uterine epithelium for 14 days after ovulation.
Placental Physiology

Fertilisation
Sperm penetrate the zona radiata, pellucida and plasma membrane. The morula’s nutrition is controlled by progesterone. Implantation occurs 6 days after fertilisation. The blastocyst burrows into the endometrial wall = the placenta. As the placenta develops, there is further erosion of the endometrium.

At 2 weeks – erosion of the endometrial capillaries → lacunae → intervillous space = haemochorial placenta bathed in maternal blood and glandular fluid. The cytotrophoblast layer proliferates → primary chorionic villi → break through the maternal syncitiotrophoblast layer.

8 weeks – the placenta is mature. The villi enlarge and blood vessels penetrate into the villi fingers. Further invasion of the endometrial spiral arteries allows spurs of maternal blood to enter the intervillous space.

At term the placenta weighs 600g, is 20cm in diameter and is 2-3cm thick.

5 layers separate maternal and fetal circulation:
1. Microvillus membrane of the trophoblast
2. Synctiotrophoblast cells
3. Basal membrane of the trophoblast
4. Mesoderm CT
5. Epithelium of fetal blood vessels

Transport – materno-fetal exchange
Passive diffusion:
- High for hydrophobic solutes, the rate depends on maternal/fetal blood flow
- Low for hydrophilic substances, rate independent of blood flow
- Na+ passes well via Na+/H+ (mf) and Na+/PO4- (m) channels
- Cl- through maternal chloride channels
- Ca2+ via fetal calcium ATPase

Carrier mediated – transcellular transport requires 2 proteins
Endo/Exocytosis – large proteins are transported using coated pits.

Endocrinology: Placental steroidogenesis
Progesterone:
- Source = corpus luteum for 1st 3 months then the placenta
- Stimulates secretion from the fallopian tube and endometrial glands
- Maintains uterus lining and inhibits contractions (blocks Oxytocin receptors and prostaglandin production)
- Substrate for fetal cortisol and aldosterone production
- Stimulates alveolar pouch development
- Increases maternal ventilation
- Prevents ovarian cycling

Estrogens (estradiol, estrone, estriol):
- Stimulate growth of uterine myometrium
- Stimulate breast ductal development
- Augments progesterone production
- Relaxes the myometrium
- Softens pelvic ligaments and pubic symphysis
HCG:

- Source = placental synctiotrophoblast cells
- Maintains the corpus luteum for 3 months
- Enhances uterine quiescence (decreases Oxytocin production)
- Stimulates relaxin secretion
- When the corpus luteum packs up, levels fall until the placenta takes over the production, often a time of miscarriage
- Inhibits LH secretion
Physiology of Pregnancy

At full term the mother has a 14kg weight gain
4Kg = adipose tissue
4Kg = fetus
1Kg blood, breast tissue, placenta, amniotic fluid, ECF, uterus.

Metabolism
Carbohydrate – increased levels of estrogens, progesterone, hpl, PRL and cortisol cause elevated plasma insulin, tight regulation of fasting glucose (4-4.5mmol/l), and reduced glucose tolerance.

Lipid – reduced FFA's/glycerol. At term, fat storage and mobilization increase FFA. Glucose is reserved for the fetus by maternal fat utilization. At the placenta, FFA transfer increases and fetal hepatic lipogenesis occurs.

Amino acids and proteins – amino acid catabolism decreases due to increased placental transfer and gluconeogenesis.

GI tract function
The hypothalamus increases the activity of the feeding center, cravings and distaste can occur. Ang2 and PRL increase drinking (drpsogenic effect). Dietary intake increases by 837kg/day. The mother needs extra Ca++ and Fe.

Oesophagus – increased intragastric pressure causes dyspepsia in 70% of women
Stomach – acid secretion, motility and emptying is decreased
Duodenum – Ca++ absorption is enhanced
Illeum – peristalsis decreases causing better absorption
Colon – smooth muscle relaxes, water reabsorption increases causing constipation.

Cardiovascular
Blood components – plasma volume increases (42%), red blood cell mass increases by 21% - the hematocrit decreases. White cell count is raised – increased neutrophiles and coagulation factors but decreased lymphocytes (decreases the risk of rejection but makes the mother more prone to infection).

Blood pressure – systolic and diastolic pressures decrease due to reduced peripheral resistance. This can cause supine hypotension.

Circulation – increased blood flow to the placenta (750ml/min), skin for heat dissipation, breasts, GI tract and kidneys (up by 80% in the 1st trimester).

Cardiac function – 40% increase in cardiac output due to a 30% increase in stroke volume (60 ->80) and a 20% increase in heart rate (70 -> 80bpm).

Respiratory function
Oxygen consumption – increases by 20% 220->260ml/min - needed by the fetus and placenta.

Lung function – 40% increase in tidal volume, inspiratory capacity and minute volume. Expiratory reserve and airway resistance both decrease by 40% to compensate. 2cm of lower rib flare is evident.
Renal function
Renal enlargement – the kidneys enlarge by 1cm, plasma renal flow increases by 35%, GFR by 50% and Na+ and water reabsorption increase.

Excretion – increases for fructose, lactose, ribose and xylose causing glycosuria. K+ excretion decreases due to progesterone. Amino acid excretion increases.

Bladder – urination increases due to increased production and abdominal pressure.

Circulatory effects – decreased plasma osmolarity (10mosmol/kg) this leads to a resetting of the hypothalamic osmoreceptors.

Pharmacology of Contraception

Estrogens are produced by the ovaries. Our natural levels are too low to produce contraceptive effects. We use synthetic mestranol and ethinyloestradiol.

Actions:
Endocrine – development of secondary sexual characteristics, myometrial hypertrophy and mucus secretion during ovulation.

CNS – depressant, nausea

Metabolic – Increase Na+ and water retention → oedema and raised bp
  -- Increase circulating triglycerides and HDL, lowers LDL decreasing atheroma
  -- Increase coagulation and clotting factors → thromboembolism

Progesterones – we have 1 natural one and 5 synthetic ones.

Combined pill:
Benefits
  • Reliable
  • Decrease dysmenorrhoea, iron deficiency, pmh, benign breast disease and pelvic inflammatory diseases

Side effects:
  • Nausea and vomiting
  • Headache
  • Fluid retention
  • Breast tenderness
  • Depression
  • Decreased libido
  • Decreased liver function, jaundice
  • Venous thromboembolism
  • Increased risk of breast cancer

If a person has 2 or more risk factors for arterial disease e.g. smoking or obesity do not prescribe the pill to them.
Risk of thromboembolism increases by 5-10% in women taking progesterone. The risk doubles using 3rd generation drugs.

Emergency contraception – 2 tablets taken <72 hours after intercourse then another 2 taken 12 hours later, they prevent implantation. They contain 50ug ethinylestradiol and 250ug levonorgestrel.

Problems – missed pill, take asap. D+V use extra protection for 7 days. Drug interactions occur between some antibiotics and antiepileptics.

Reasons to stop treatment immediately – sudden severe chest pain or breathlessness, calf pain in 1 leg, severe stomach pain or headache, jaundice, severe depression, detection of a risk factor, or BP> 160-95.

Protein hormone production by HGH-N
HPL (placental lactogen):
- Increases maternal insulin secretion
- Made by syncytiotrophoblast cells
- Impairs maternal glucose tolerance
- Increases glucose and amino acid transfer to the fetus
- Increases maternal IGF-1
- Is lypo and proteolytic

PRL-R – causes breast development and inhibits pituitary GH secretion

HGH-V:
- Produced by syncytiotrophoblast cells
- Inhibits pituitary GH secretion
- Stimulates maternal growth – uterine and acromegalic

Decidual PRL is found in amniotic fluid (4000ng/ml) in high concentrations:
- Regulates amniotic fluid
- Regulates pulmonary surfactant production
- Lowers myometrial contractility
- Prevents immune rejection

Embryo to 18 days

1. At week 2, cells of the inner cell mass rearrange into 2 layers – the upper epiblast and the lower hypoblast
2. The epiblast cells divide to form the amniotic cavity
3. The hypoblast cells migrate and line the cytotrophoblast forming the primary yolk sac
4. The primary yolk sac constricts to form the secondary yolk sac and around it the chorionic cavity which fills with fluid.

Gastrulation generates 3 germ layers from the epiblast layer:
1. Epiblast cells converge in the midline to form the primitive streak and the axis are decided
2. An accumulation of cells at the cranial end = primitive node
3. Epiblast cells near the streak change shape and migrate between the epiblast and hypoblast layers, invading the hypoblast
4. These cells migrate laterally and cranially → embryonic mesoderm
5. Cells from the primitive node form the prechordal mesoderm which stimulates forebrain development (Lim 1 gene)
6. The notochordal area → notochord (HNF-3beta)

7. After 18 days, the primitive streak gradually regresses caudally then degenerates after 4 weeks.

Ectoderm → skin, nervous tissue and its derivatives
Mesoderm → muscle, blood and connective tissue
Endoderm → gut, lung epithelia and its derivatives

Paraxial mesoderm → somites
Intermediate mesoderm → excretory ducts and tubes
Lateral plate mesoderm → splanchnopleuric mesoderm which covers the viscera and the somatopleuric mesoderm → body wall lining and limb mesenchyme.

At 3 weeks, faint ectoderm depressions appear at the cranial and caudal ends of the embryo. The endo- and ectoderm fuse to form a bilaminar membrane = blind ends of the gut. The cranial buccopharyngeal membrane breaks down → oral cavity (week 4) and the caudal cloacal membrane breaks down → anus and urogenital openings (week 7).

Clinical point – cloacal extrophy occurs when the cloacal membrane is too large to fuse in the midline leaving the bladder and anorectal canal exposed through the abdominal wall.

The notochord develops from the notochordal process, it becomes the prime signaling center that stimulates neurulation. It develops until it is a solid rod = definitive notochord (sonic hedgehog gene).

**Neural and body folds**

**Neurulation**
1. Induced by signals from the underlying notochord
2. Midline ectoderm thickens → neural plate, the cells become narrow and columnar
3. Medial plate cells anchor to the underlying notochord and form a hinge
4. The ectoderm causes an extrinsic motive pressure forcing the paired neural folds to meet and fuse → neural tube
5. Neural tube closure proceeds bidirectionally leaving open cranial and caudal neuropores (pax-5 and sonic hedgehog)
6. On day 24 the cranial neuropore closes
7. On day 26 the caudal neuropore closes
8. The overlying ectoderm separates from the neural tube (N-CAM and N-adherin)

Spina bifida occurs if the neural folds fail to fuse → an open vertebral canal. In S.B occulta a pigmentation is seen in the lumbosacral region. IN S.B meningocoel, the spinal cord protrudes.

Anencephally is an open cranial vault formed because the cranial neuropore fails to close. It is often fatal.

Neural crest cells are embryonic migratory cells that detach from the dorsal neural tube, migrate to numerous locations and give rise to a wide range of structures including the PNS, facial cartilage and bone, CT and endocrine cells. Hirshprung's disease is an abnormally dilated colon lacking parasympathetic enteric ganglia as the neural crest cells didn't migrate into the gut wall.

**Somites**
Formation – somites develop from paraxial mesoderm which forms thick, long bands on either side of the notochord. It divides into discrete paired blocks of segmental mesoderm = somites besides at the cranial region. They form cranially → caudally until 44 are formed. They give rise to a segmented body plan and the axial skeleton, epaxial, hypaxial and limb skeletal muscle and dermis of the neck and trunk.
Differentiation – signals cause the somites to loose their epithelial organization (sonic hedgehog) and develop into sclerotomes while the epithelial cap → dermomyotomes.

**Sclerotome** – ventral cells surround the notochord → vertebral bodies while dorsal ones surround the neural tube → vertebral arches and ribs.

The **dermomyotome** of each somite → skeletal muscle and dermis. Cells at the lip proliferate and generate the myotomes → epaxial and hypaxial muscle (wnt family, BMP-4). Lateral cells → limb muscles. The dermotome separates from the myotomes and contributes to the dermis of the neck and back.

Congenital scoliosis occurs due to defective induction of sclerotomes, 1 side of vertebral body is not formed → lateral bending of the spine.

**Embryonic folding**

**Head fold** – the disc buckles rotating the pericardium into the chest region. A small portion of the yolk sac is incorporated into the embryo as the foregut which ends blindly at the cloacal membrane.

**Tail fold** – occurs later than the head fold and results from growth of the neural tube. As the embryo grows, the tail region projects over the cloacal membrane. A small portion of the yolk sac is incorporated into the embryo as the hindgut.

**Lateral folding** – the lateral sides fold inwards and meet in the midline creating a cylindrical embryo. As the abdominal wall forms, a part of the yolk sac is incorporated into the embryo as the midgut.

Folding causes ectoderm to cover the entire embryo except at the body stalk, fusion of the lateral edges of endoderm creates the gut tube.

**Yolk sac**
- Provides nutrition to the developing embryo for the 1st 2-3 weeks
- Is essential for the 1st phase of haematopoiesis
- Yolk sac lining cells are sites of differentiation of the primordial germ cells

**Allantois**
- Is an extension of the yolk sac
- Is another site of early blood formation
- During folding it opens into the developing hindgut
- Becomes the medial umbilical ligament in the adult

**Amnion**
- Is formed early in development
- It surrounds the entire embryo and body stalk
- Initially forms amniotic fluid
- Absorbs amniotic fluid and transfers it to the fetal circulation
- Prevents outside pressure affecting development prior to skeletal formation.
Branchial Arch Development

The branchial arches are thickenings of mesenchymal tissue that form on each side of the developing pharyngeal foregut. They appear before the completion of the body folds and during closure of the neural tube.

Branchial arch apparatus components = branchial arches, pharyngeal pouches, branchial clefts and branchial membranes.

**Branchial arch formation** – 6 arches form but only 5 are well defined – the 5th arch either never forms or develops and quickly regresses. The 1st arch splits into the maxillary and mandibular processes soon after formation (otx2).

Each arch consists initially of a mesenchymal core lined on the outside with ectoderm and the inside with endoderm. They are separated by brachial clefts externally and pharyngeal pouches internally. Neural crest cells migrate into each arch and surround the core. They guide specific cranial nerves into the arches and proliferate rapidly to produce distinct arch swellings.

Each arch contains:
- Cartilaginous skeletal element
- Skeletal muscle analagen
- Arch associated cranial nerve
- Aortic arch artery

Skeletal and muscle derivatives – cartilage of arches 1-3 are derived from neural crest contributions while 4 and 6 are derived from lateral plate mesoderm. Cranial paraxial mesoderm → musculature, muscles that form in each arch are innervated by a cranial nerve branch specific to that arch.

Cranial nerves – 4 cranial nerves (5, 7, 9, 10) from the hindbrain supply the arches.

Aortic arch arteries – a basket like arrangement of 5 pairs of arteries that arise from the aortic sac. Their endothelium is derived from mesoderm. Each artery supplies its own brachial arch and drains to the paired dorsal aorta.

Pharyngeal pouches – bulges where the arches project into the foregut. Each bulge is separated by outpockets of endoderm.
- 1st pouch → diverticulum → middle ear cavity and auditory tube
- 2nd pouch → palatine tonsils
- 3rd pouch ventral wing → thymus
- 3rd pouch dorsal wing → inferior parathyroids
- 4th pouch dorsal wing → superior parathyroids

Branchial clefts – are ectodermal infoldings separating each arch externally. During week 5, the 2nd arch overgrows 3 and 4 (sonic hedgehog, BMP7, FGF8) → cervical sinus. This is removed at week 7 to give a smooth neck. Only the 1st cleft contributes to adult structures – persists and the external acoustic meatus.

Clinical point – if the 2nd arch fails to grow caudally, a brachial fistula can be seen in the neck. If the cervical sinus remains, a lateral cervical cyst will be seen on the child.

Branchial membranes – formed where brachial cleft epithelia approaches a pharyngeal pouch – only the 1st brachial membrane gives an adult structure it → tympanic membrane.
**Face formation** – 5 facial processes exist at the end of week 5, these rearrange, merge and enlarge to form the face. Ectodermal thickenings called nasal placodes \( \rightarrow \) frontonasal process which invaginates into the nasal pits. The raised edges divide into medial and lateral nasal processes, which rearrange and merge to form lips, nose and cheeks.

Clinical points – cleft lip occurs if the maxillary and nasal processes fail to merge, occurs in 1:1000 births.

1st arch syndromes – mostly derived from neural crest cells failing to migrate enough in week 4. Treacher Collins \( \rightarrow \) malar and mandibular hypoplasia with malformed ears and slanting eye fissures. Pierre Robin syndrome – mandibular hypoplasia usually resulting in cleft palate and glossoptosis (posterior tongue).

**Respiratory System Development**

**Nasal and oral cavities** – on day 28, the buccopharyngeal membrane breaks down to leave a stomodeal chamber which divides into oral and nasal cavities. The nasal pits enlarge and fuse \( \rightarrow \) single nasal sac. The floor proliferates \( \rightarrow \) nasal fin which thins \( \rightarrow \) oronasal membrane. This ruptures \( \rightarrow \) primitive choana.

The primary and secondary palates form the adult nasal cavity.

**Lung bud formation** - at 4 weeks, a laryngeal groove forms in the midline of the pharyngeal wall. It evaginates into the respiratory diverticulum and becomes filled with mesenchyme forming a globular lung bud. 2 ridges appear which fuse as the tracheoesophageal septum \( \rightarrow \) trachea and oesophagus later on.

**Larynx and trachea development** – the lung bud maintains communication with the pharynx via the laryngeal orifice which changes shape due to mesenchymal infiltration from the 4th and 6th arches. The lumen of the orifice narrows and becomes the aretyoid swellings, recanalisation occurs to form the laryngeal ventricles, vocal folds and cords. The laryngeal muscles are derived from 4th and 6th arch mesoderm and innervated by the vagus nerve.

Clinical note – incomplete division of the tracheoesophageal septa \( \rightarrow \) tracheoesophageal fistula.

**Bronchi development** – the lung buds divide into 2 endodermal pouches – bronchial buds. These divide into secondary and tertiary bronchi, this branching process is regulated by ECM, FGF and BMP4. The pericardioperitoneal canal separates into peritoneal and pericardial cavities leaving a primary pleural cavity. As the lungs expand, the surrounding splanchnic and somatic mesoderm \( \rightarrow \) visceral and parietal pleural.

**Lung maturation**

1. Pseudoglandular period 5-16 weeks, the bronchi and bronchioles enlarge and become highly vascularised
2. Canalicular period 17-26 weeks – alveolar ducts form, some thin walled terminal sacs develop
3. Terminal sac period 26 weeks \( \rightarrow \) birth – the terminal sacs are formed and the air-blood barrier develops, type 1 and 2 cells grow, respiration is possible. Respiration occurs to train the muscles. Surfactant and amniotic fluid is aspirated and is essential for lung development
4. Alveolar period later pregnancy to childhood – alveoli grow and develop.

IRDS occurs if not enough surfactant is produced, alveoli collapse from the tension. Some alveoli are protein laden – hyaline membrane disease. Artificial surfactant and glucocorticoids are given.
Digestive System Development

Gut divisions and mesenteries
The embryonic gut forms from the incorporation of parts of the yolk sac during body folding. The gut is initially divided into foregut, midgut and hindgut and if suspended from body walls by mesenteries. Endoderm → gut epithelia and splanchnic mesoderm → smooth muscle and CT.

Foregut
Foregut → oesophagus, stomach, proximal duodenum the liver and biliary apparatus plus the pancreas. The celiac artery supplies the derivatives of the foregut.

The oesophagus forms caudal to the pharynx along with the trachea separated by the tracheoesophageal septum. As the oesophagus elongates the epithelium proliferates, obliterating the lumen of the oesophagus. Recanalisation occurs later.

The stomach is initially a small dilation in the caudal foregut, which enlarges dorso-ventrally. With enlargement, the stomach rotates 90° and the dorsal mesogastrium moves left forming the omental bursa. As the stomach enlarges further a double-layered overhanging sac if the formed, the greater omentum. The posterior wall grows more → stomach curvatures.

The duodenum develops from the caudal foregut and cranial midgut – therefore has a dual origin. The duodenum develops rapidly to form a C-shape loop, which rotates as the stomach rotates.

The liver and biliary apparatus arise from ventral endodermal outgrowths in the caudal foregut. The hepatic diverticulum (liver bud) extends into the septum transversum and as it expands to fill much of the abdominal cavity, the foregut connection narrows to form the bile duct. The gallbladder forms from a ventral outgrowth in the bile duct. As this diverticulum expands the stalk becomes the cystic duct. The entrance to the bile duct shifts to a posterior location as the duodenum rotates.

The pancreas develops as dorsal and ventral endodermal buds of tissue in the caudal foregut. As the duodenum rotates the ventral bud is carried posterior to the dorsal bud. The buds then fuse together.

Clinical notes – duodenal atresia is a complete occlusion of the duodenal lumen due to a recanalisation failure after proliferation. Vomiting occurs after birth, surgery is needed.

Duplex gallbladder – body of the gallbladder diverticulum divides early in development, usually asymptomatic.

MIDGUT
The midgut → small intestine, caecum and appendix, ascending colon and proximal two-thirds of the transverse colon. The superior mesenteric artery supplies the midgut derivatives. The midgut is suspended from the abdominal wall by the dorsal mesentery, which elongates to form the midgut loop. The loop extends into the umbilicus due to rapid growth of the midgut. Within the umbilicus the midgut rotates 90° around the artery and during this period the loops of the small intestines are formed.

Later the intestines return to the abdomen and the colon rotates through 180°. The caecum starts as a diverticulum in the caudal limb of the midgut loop. The apex of the diverticulum grows more slowly initially to form a small pouch, which lengthens to form the appendix.

Clinical note – Omphalocele is a herniation of viscera through an enlarged umbilical opening covered by amnion. Is often associated with other abnormalities which are fatal.
Meckels – remnant of the yolk stalk stays as a pouch of the ileum which can become inflamed or ulcerated. Causes appendicitis like symptoms.

**HINDGUT**

The hindgut → distal third of the transverse colon, the descending colon, sigmoid colon, the rectum and the upper part of the anal canal.

The inferior mesenteric artery supplies the hindgut derivatives. The end portion of the hindgut is a cavity called the cloaca, which is gradually divided into the anorectal canal and the urogenital sinus. The cloacal membrane also divides and as the anal membrane breaks down communication is established between the digestive tract and the amniotic cavity.

The cranial part of the anal canal if formed from endoderm of the hindgut, whilst the caudal segment is derived from the ectoderm derived anal pit. The anal membrane separates both segments.

Clinical note – Anal atresia is where the cloaca is too small so the anal membrane is shifted anteriorly and opens into the bladder or urethra.

**Development of the Genital System**

The SRY gene makes transcription factors needed for male development, found on the Y chromosome.

**Male gonadal development** –
1. Germ cells migrate into the area of the proliferating coelomic epithelium
2. Primary sex cords incorporate with the germ cells and are retained as medullary cords
3. The medullary cords → testis cords and join to the mesonephric duct at the rete testis caused by testosterone
4. Canalisation occurs at puberty
5. The paeamesonephric duct disappears caused by MIS (Mullerian inhibiting substance)
6. The genital tubercle elongates and takes the urethral fold with it
7. The urethral fold closes to form the penile urethra
8. The epithelium swells to form the scrotal swellings which fuse in the midline
9. Just before birth, the testes descend into the scrotum led by the gubernaculums taking all tissue layers with them.

**Female gonadal development** –
1. Germ cells migrate into the area of the proliferatingcoelomic epithelium
2. Primary sex cords incorporate with the germ cells but degenerate
3. Secondary sex cords wrap around the germ cells forming distinct follicles
4. The paeamesonephric duct → uterine tube while the mesonephric tube degenerates and leaves remnants
5. The 2 paeamesonephric ducts join to form the uterus and vagina (controlled by oestrogens)
6. The urethral folds enlarge to form the labium minus while the genital swelling enlarges to form the labium major
7. The genital tubercle enlarges then gets smaller → clitoris.
Musculoskeletal System Development

Development of the skull
Human skull develops from mesenchyme surrounding the developing brain and is divided into the neurocranium and viscerocranium. The cartilaginous neurocranium develops from a series of cartilaginous plates derived from neural crest cells which fuse undergo endochondral ossification. The membranous neurocranium develops from ossification sites that appear within the membranes covering the brain → flat bones of the vault of the skull. These calvarial bones are initially separated by sutures and fontanelles. The posterior and sphenoidal fontanelles close at 3 months while the anterior ones do at 1 and a half years. The cartilaginous viscerocranium derives from the first two branchial arches, whilst the membranous viscerocranium develops within the maxillary and mandibular processes of the developing face.

Clinical note – craniosyntosis is a premature closure of the sutures causing skull deformity e.g. Apert syndrome where the coronal sutures fuse causing a tower skull.

Development of the axial skeleton
The axial skeleton derives from sclerotome of the somites. Cells surround the notochord ad neural tube to subsequently form the body and arch respectively of each vertebra at week 6. The vertebra become intersegemental with the cranial sclerotome of 1 somite fusing with the caudal half of the preceeding sclerotome. The ribs originate within the ventral sclerotome and develop as costal processes of the developing thoracic vertebrae.

Clinical note – accessory ribs care ectopic growths in the cervical or lumbar regions. 3% of people have an extra 1 or 2 vertebrae, 2% have 1 less.

Development of the appendicular skeleton
Limb buds (week 5) are initially a mesenchyme core covered by ectoderm. The ectoderm is thickened at the distal border and forms the apical ectodermal ridge (AER), which induces the underlying mesenchyme, keeping cells in a proliferating and undifferentiated state (progress zone FGF 4, 8)). As the limb grows out, the cells furthest from the influence of the AER are able to differentiate (HOX). Cartilage elements are laid down in a proximo-distal sequence at 6 weeks. The fingers and toes form following cell death of the inter-digit mesenchyme. All the bones ossify via endochondral ossification starting in the centre of each cartilage template.

Clinical note – meromelia is the partial absence of a limb or limbs e.g. phocomelia – no long bones but hands/feet are present/ Syndactyly is a failure of the digits to separate causing webbing (HOX D13).

Muscular system
Craniofacial muscles form from unsegmented paraxial mesoderm and the precursors of each muscle move into the muscle forming regions due to growth and shape changes within the developing embryo.

The epaxial muscles derive from the epaxial myotome that form at the cranial lip of the dermomyotome of each somite. These myotomes differentiate to form the extensor muscles of the back and neck and are innervated by dorsal primary rami.

The hypaxial muscles derive from the hypaxial myotome that forms at the caudal lip of the dermomyotome of each somite. These myotomes differentiate to form the body wall muscles and are innervated by ventral primary rami.
The appendicular muscles are derived from cells that delaminate from the caudal border of each dermomyotome and migrate into the developing limb buds. Initially muscles cells are arranged into dorsal and ventral muscle masses, however these masses gradually cleave to form individual limb muscles (Pax3, c-met, ibx1).

The tongue muscles formed from cells that arise from the occipital somites and actively migrate into the developing tongue (Pax3, c-met, ibx1).

Multinucleated muscle fibres form after mononucleated myoblasts aggregate and orient within the muscle forming regions. These myoblasts fuse with each other during two waves (primary and secondary) and form immature myotubes. These myotubes gradually mature into muscle fibers and actively synthesise various contractile proteins (mrf’s e.g. myoD).

**Endocrine Development**

**Pituitary gland**
The pituitary gland develops from 2 sources of ectoderm.

**Neurohypophysis**
A downward ectodermal extension of the diencephalons forms the infundibulum or neurohypophyseal bud. This bud gives rise to the stalk and posterior lobe of the pituitary and is composed of neuroglial cells and nerve fibres.

**Adenohypophysis**
An ectodermal out-pocket known as Rathke’s pouch projects into the roof of the mouth at week four. The pouch grows dorsally towards the infundibulum, gradually losing the connection with the roof of the mouth. The anterior cells proliferates rapidly → anterior lobe. Small extensions wrap around the stalk of the infundibulum → pars tuberalis. The cells of the posterior wall form the thin layer called the pars intermedia.

Clinical note – crangiopharyngioma – remnant of Rathke’s pouch usually by the sella turcica, can cause hydrocephalus and pituitary disfunction.

**Thyroid Gland**
The thyroid first appears as a small mass of endoderm at the foramen caecum (at 1st branchial arch) and is the origin of the follicular cells. The mass descends through the neck at the end of the thyroglossal duct, which breaks down at week five and the gland continues its decent and finally lies inferior to the cricoid cartilage by the end of week 7. The caudal attachment of the duct may pertain as the pyramidal lobe. Parafollicular cells derive from neural crest cells within the fourth pharyngeal pouch. These cells fuse with the migrating thyroid and disseminate throughout the gland. The thyroid begins to function in the third month.

Clinical note – thyroglossal cyst is a midline neck mass (trapped duct remnants) which causes pharyngeal discomfort. May develop into a fistula.

**Parathyroids and Thymus**
The parathyroids and thymus glands derive from endoderm with the walls of the pharyngeal pouches. Neural crest cells are critical for its formation. Development of the thymus continues after birth. The thymus decreases in size after puberty, but is still important for maintaining health of the individual.
Adrenal Glands
The adrenal or suprarenal glands develop from two sources. The cortex is derived from lateral plate mesoderm as the medulla is from neural crest cells. The adrenal cortex starts as an aggregation of mesoderm between the root of the dorsal mesentery and the developing gonad. The mesothelial cells → fetal cortex. A second wave of mesothelial cells penetrates the fetal cortex → definitive cortex. Cells from the sympathetic ganglion (neural crest derived) invade the medial aspect to the fetal cortex to form the future medulla. These cells give rise to the secretory cells (chromaffin cells). Chromaffin cells are widespread throughout the embryo but only persist in the adrenal gland. The fetal adrenals are relatively 10-20 times larger than in the adult, mainly due to the size of the fetal cortex.

Pancreas
The pancreas develops as endodermal buds from the foregut region. As the future duodenum rotates the buds meet and fuse together to form the pancreas. In the third month the pancreatic islets develop from parenchymatous tissue and scatter throughout the enlarging process. Insulin production starts by the fifth month and maternal and fetal insulin levels remain independent as insulin doesn’t cross the placenta.

Lactation
Human milk provides a perfect balance of nutrients under an umbrella of protection mediated through its immune substances. It gives the baby the best start in life and reduces complications later on.

Short term benefits:
1. Decreases the incidence of infections
2. Decreases allergies and atopic illness
3. Generally improves health

Long term benefits:
1. Bonding – improved relationship
2. Improved cognitive function
3. Decreased blood pressure

Disadvantages – HIV transmission from mother to baby.

Sucking → hypothalamus → pituitary release of prolactin which turns on milk synthesis in the secretory glands (lactiferous cells) then this milk is made available by Oxytocin.

Its stages include a calibration stage where the mother’s milk production matches the baby’s needs (normally 700-800 ml/day). Suckling suppresses ovulation due to the increase in circulating prolactin. Suckling decreases when supplementary foods are given.

To improve breast feeding rates we need to alter politics, culture, attitudes and professional advice. The lower social classes need to be targeted - aim to get a happy hypothalamus.
Functional adaptation of the fetus and neonate

Trimester 1 = 0-12 weeks  
Trimester 2 = 13-27 weeks  
Trimester 3 = 28-40 weeks

Cardiovascular system
Maternal blood → uterus → placenta → umbilical vein → fetus → liver 50% ductus spenosum 50% → IVC → right atrium → foramen ovale → LA LV → iliac arteries → umbilical artery.

At birth the foramen ovale closes as the lungs inflate. If this doesn’t occur, we can use NO or viagra.

Respiratory system - At 24 weeks some respiration can occur – the limit of viability but surfactant is needed to prevent IRDS.

Nutrition and GIT - The placenta supplies all nutrients while the liver makes enzymes and the pancreas makes insulin. At birth the cord is clamped and glucagon is released due to hypoglycaemia stimulating glycogenolysis, gluconeogenesis and ketogenesis. If the placenta doesn’t supply all the necessary nutrients, the baby will be growth restricted.

Brain development 1. glial and neuronal development 2. axon and dentrite formation
Kidneys – make urine at 12 weeks → amniotic fluid, most nephrons form the last trimester.
Endocrine – early adrenal development. Thyroxine and cortisol surges aid growth by turning on genes.
Immune – antibodies pass through the placenta at 12 weeks and last until age 3 months.

Programming – stimuli or insults during development cause irreversible changes apparent in later life.

Endocrinology of puberty

Puberty = the process of becoming sexually mature  
Adolescence = the process of rapid physical and psychological changes

Puberty occurs in females normally between ages 9-13 and in boys 11-13. It is measured by growth of pubic hair, genitals and breasts in the female.
The testicular volume increases to 25mls and the uterine volume to 20mls.

Puberty is initiated by pulsatile releases of GnRH causing the release of LH and FSH.
In the male LH stimulates leydig cells to produce testosterone while FSH stimulates the sertoli cells.
In the female, LH stimulates theca cells while FSH stimulates the ovarian follicles.

Growth spurts occur at ages 0-2, 6-8 (small one) 10-12 in girls and 12-14 in boys, this growth mostly occurs in the legs.

Menarche will only occur after a critical weight – leptin from adipose tissue is needed to stimulate the HP axis.

Causes of delayed puberty:
• Constitutional delay – genetic late developer
• Hypogonadotrophic hypogonadism e.g. hormone deficiency or CNS disfunction
• Hypergonadotrophic hypogonadism – Kleinfelter of Turners syndrome
TREATMENT

- Investigations of bone age, chromosomes, hormone levels
- Testosterone supplements at age 14 for boys
- Oestrogen tablets for girls until puberty is established

Kallmann syndrome – X linked GnRH failure
Prader Willi syndrome – obese, poor growth, behavioural problems due to loss of paternal allele
Turner’s syndrome – neck webbing, lymphoedema.

Pernicious puberty –
- Isolated breast development – thelarche
- Isolated pubic hair development – adrenarche
- Central precocious puberty – idiopathic or secondary to intercranial tumours
- GN independent precocious puberty – testotoxicosis
- Rare causes – hypothyroidism, GN secreting tumours

Treatment:
- No treatment for thelarche
- Secondary precocious – treat underlying problem
- GN dependent precocious puberty – LHRH analogue
- GN independent precocious puberty – antiandrogens (flutamide).

NORMAL GROWTH

Growth rate – velocity is high at 0-3 then peaks again at 12-16.
Growth is influenced by genetic, nutrition, season, socio-economic group, the environment, race, diurnal patterns, sex and GH levels.

Model of growth:
1. Infancy component – nutrition
2. Childhood – GH and nutrition
3. Puberty – sex and growth hormones

Mean height for boys 174cm for girls 165 cm.
Growth is stepped if you measure it daily.
Yearly variations occur above and below the normal line.
More growth occurs in the summer months.
There is a worldwide variation in height – Africans are tallest and Asians are shortest.
People in higher socio-economic groups have greater height and weight.

Growth hormone release needs somatostatin to regulate the pulses, it is carried by GHBP and causes IGF release causing chondrocyte division. GH release is related to stage 4 sleep and is inhibited by REM sleep and illness.

Height is measured using a Harpenden stadiometer, the eyes must be in level with the external auditory meatus and 3 measurements made.
The skeleton can be disproportionate, an X-ray of the wrist can tell you the bone age.

Decimal age = decimal date of measurement – birth decimal date
A growth chart should show height plots, bone age, parental centiles and target height.
A referral will be made if the child is growing above the 99.6th or below the 0.4th centile.
Causes of short stature
- Familial short stature or delayed puberty
- Chronic systemic disease
- Psychological
- Intrauterine growth retardation – fetal programming
- Endocrine disorder
- Chromosomal abnormalities – turners, downs
- Skeletal dysplasia - chronic juvenile rheumatoid arthritis
- Other dysmorphic syndromes

History
- Pregnancy, delivery, birth age and weight
- Neonatal problems and nutrition
- Age of menarche
- Adverse psychological factors
- Family history – heights and timing of puberty

Examination
- Dysmorphic features and midline defects
- Height and sitting height
- Nutritional state
- Pubertal staging (Tanner and Whitehouse)
- Parental heights
- CV – peripheral pulses and bp
- Any asthma
- Inflammatory bowel disease
- Neurological problems
- Endocrine function
- Locomotion and skin

Investigations
- Height velocity
- Full blood count
- Thyroid function
- Urine
- Chromosome typing
- Electrolytes
- GH secretion
- Insulin levels

Causes of tall stature
- Familial and early puberty
- Obesity
- Endocrine disorder
- Soto syndrome – tall, clumsy, low IQ
- Marfan’s – tall with collagen defect
- Kleinfelter syndrome – XXY tall and infertile with learning difficulties
Infertility

Infertility = 1 year of unprotected intercourse without conception. 15% of couples will experience difficulties in conceiving. Infertility can be caused by – infection, ovulatory problems, sperm problems and unknown reasons.

Male investigation
Seminal fluid analysis for sperm number, quality, karyotype, motility, shape

Female investigations and problems
Tubal pathology – laparoscope
Endometriosis – laparoscope
Ovulatory disorder – hormone profile – diagnoses PCO

Assisted techniques
IVF
Egg sharing
Intracytoplasmic sperm injection
Donor sperm or oocyte treatment
Surrogacy

Please Note
These notes were written by K Kalami when a second-year medical student in 2003. They are presented in good faith and every effort has been taken to ensure their accuracy. Nevertheless, knowledge and medical practice changes over time and it is always important to check the information with your clinical teachers and with other reliable sources. Disclaimer: no responsibility can be taken by either the author or publisher for any loss, damage or injury occasioned to any person acting or refraining from action as a result of this information.