

Lecture - Fetal Development

From Embryology

Embryology - 22 Oct 2015    Translate [Expand]

Introduction

The fetal period (9-36 weeks) is about continued differentiation of organs and tissues, most importantly this period is about growth both in size and weight.

The long Fetal period (4x the embryonic period) is a time of extensive growth in size and mass as well as ongoing differentiation of organ systems established in the embryonic period and do so at different times. For example, the brain continues to grow and develop extensively during this period (and postnatally), the respiratory system differentiates (and completes only just before birth), the urogenital system further differentiates between male/female, endocrine and gastrointestinal tract begins to function.



Note - Some of the content of this lecture has been discussed in earlier systems development lectures.

[Click Here](#) to play on mobile device

[Lecture - Print PDF](#)

Lecture Objectives

1. Understanding of fetal growth - length and weight
2. Understanding of fetal systems development/changes
3. Understanding of fetal abnormalities

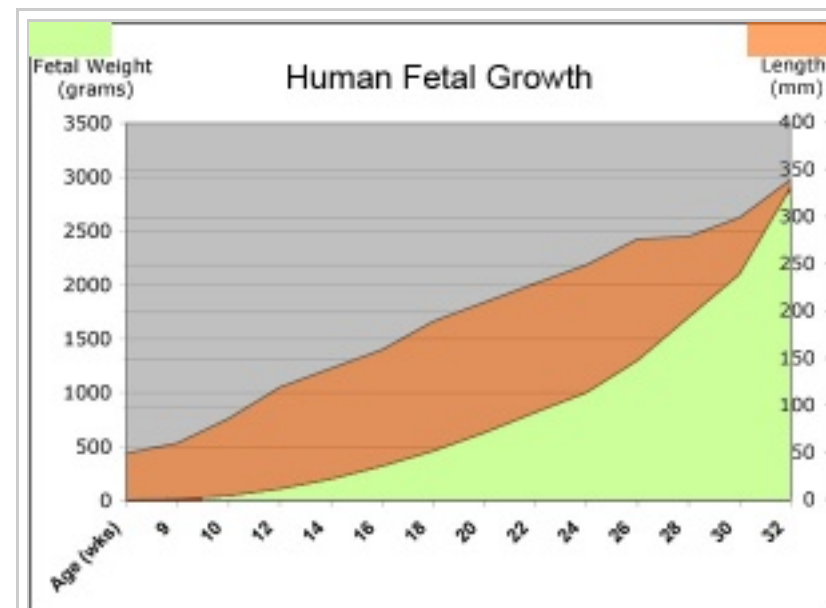
- First Trimester (1 - 12 weeks) - embryonic and early fetal
- Second Trimester (13 - 24 weeks) - organ development and function, growth
- Third Trimester (25 - 40 weeks) - organ function and rapid growth

Lecture Resources

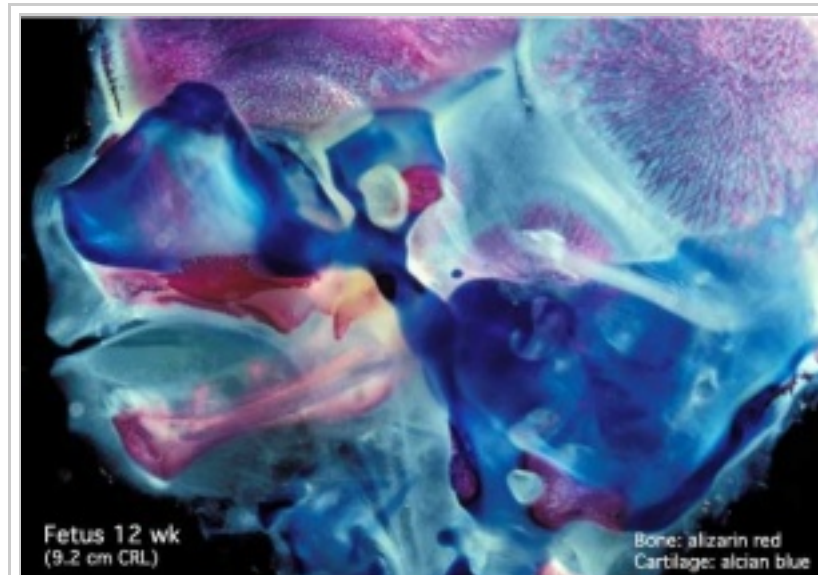
[Movies\[Expand\]](#)

Musculoskeletal

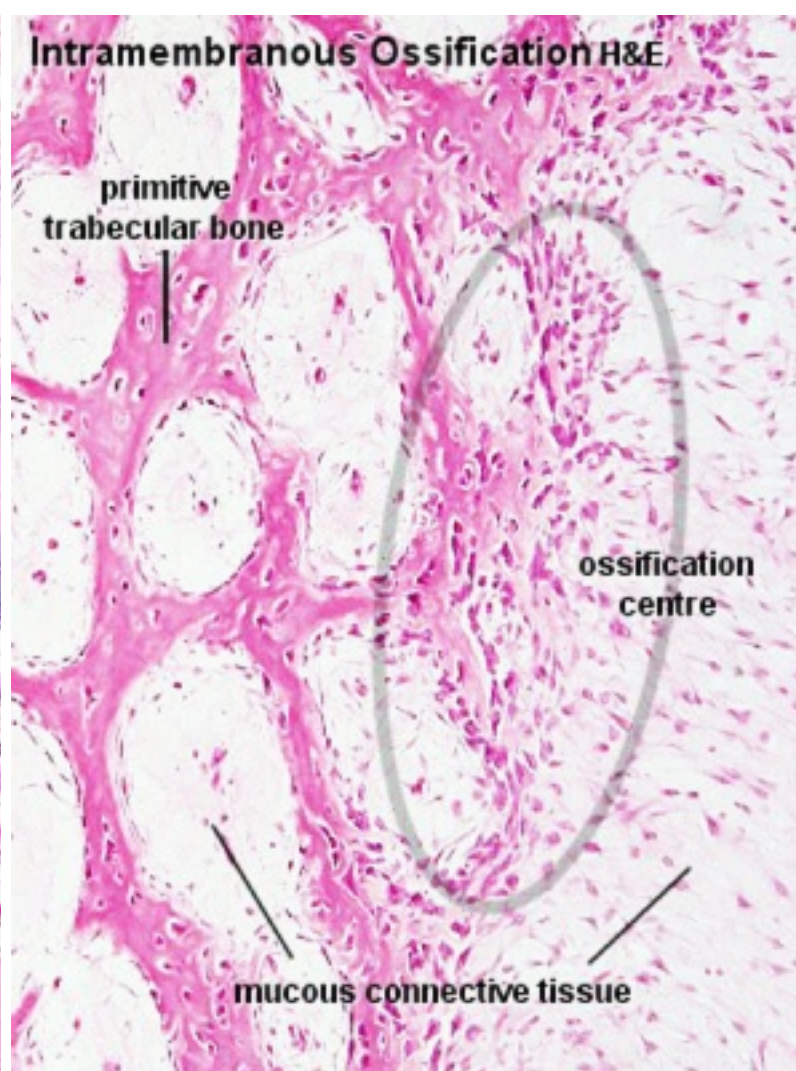
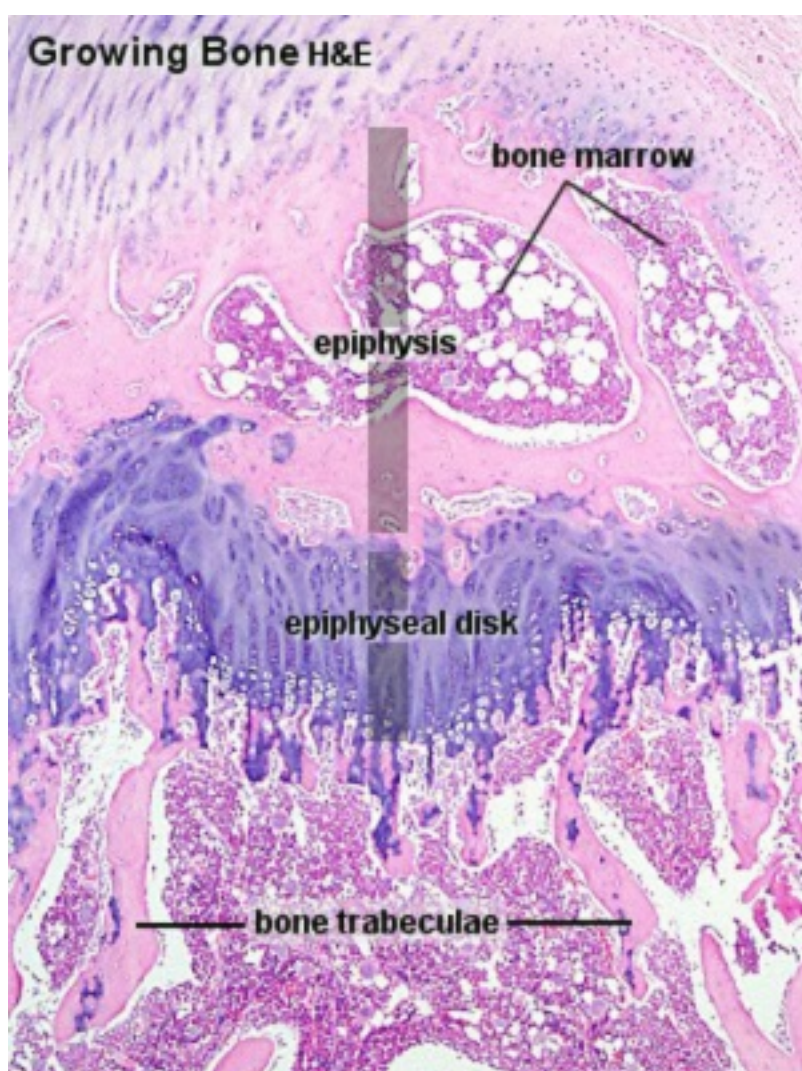
- Ongoing process of ossification.
 - endochondral and intramembranous
- growth in long bone length
 - Achondroplasia (common form of short limb dwarfism) third trimester ultrasound very shortened long bones.
- increased limb length
- continues postnatally
 - rapid growth during puberty
- relocation of haemopoietic stem cells to bone marrow



Fetal length and weight changes



Fetal head (12 weeks)



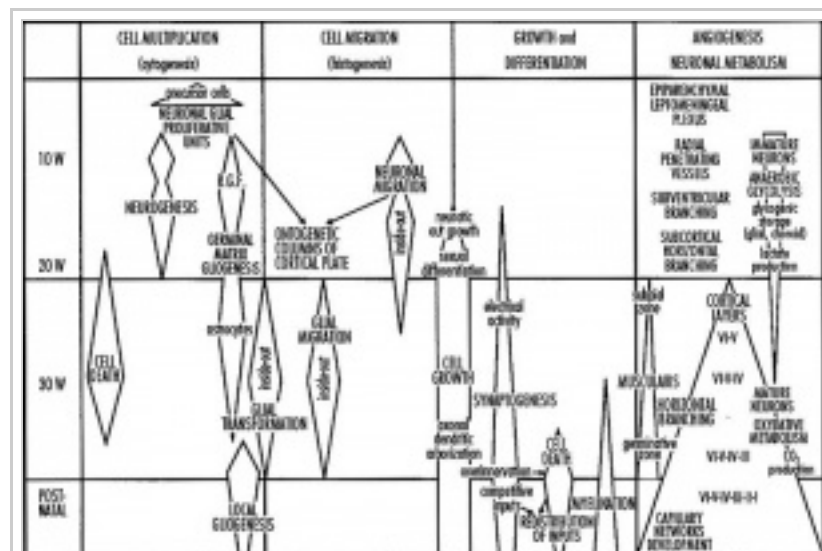
The collapsed tables below are for information purposes and are not examinable.

Table Of Ossification Of The Bones Of The Superior Extremity[Expand]

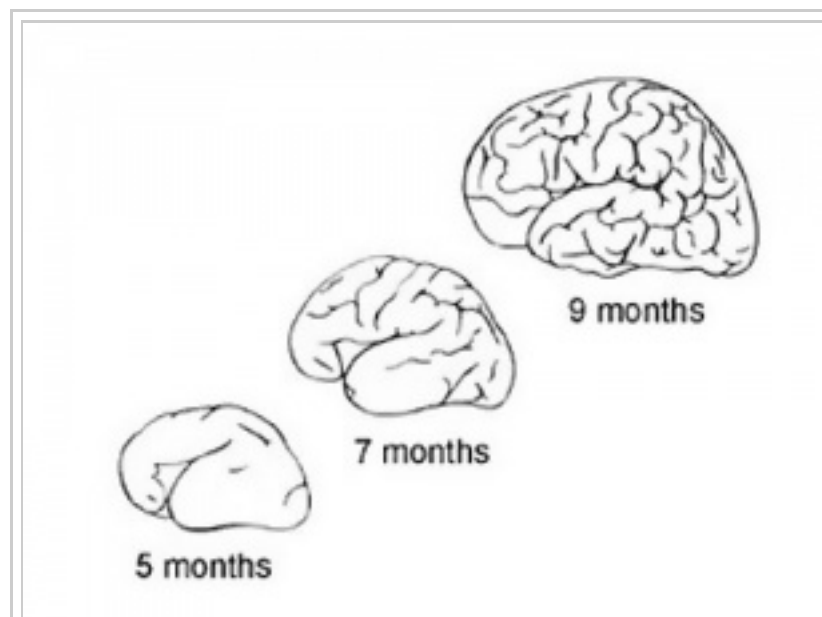
Table Of Ossification Of The Bones Of The Inferior Extremity[Expand]

Links: Bone Development Timeline | Bone Histology

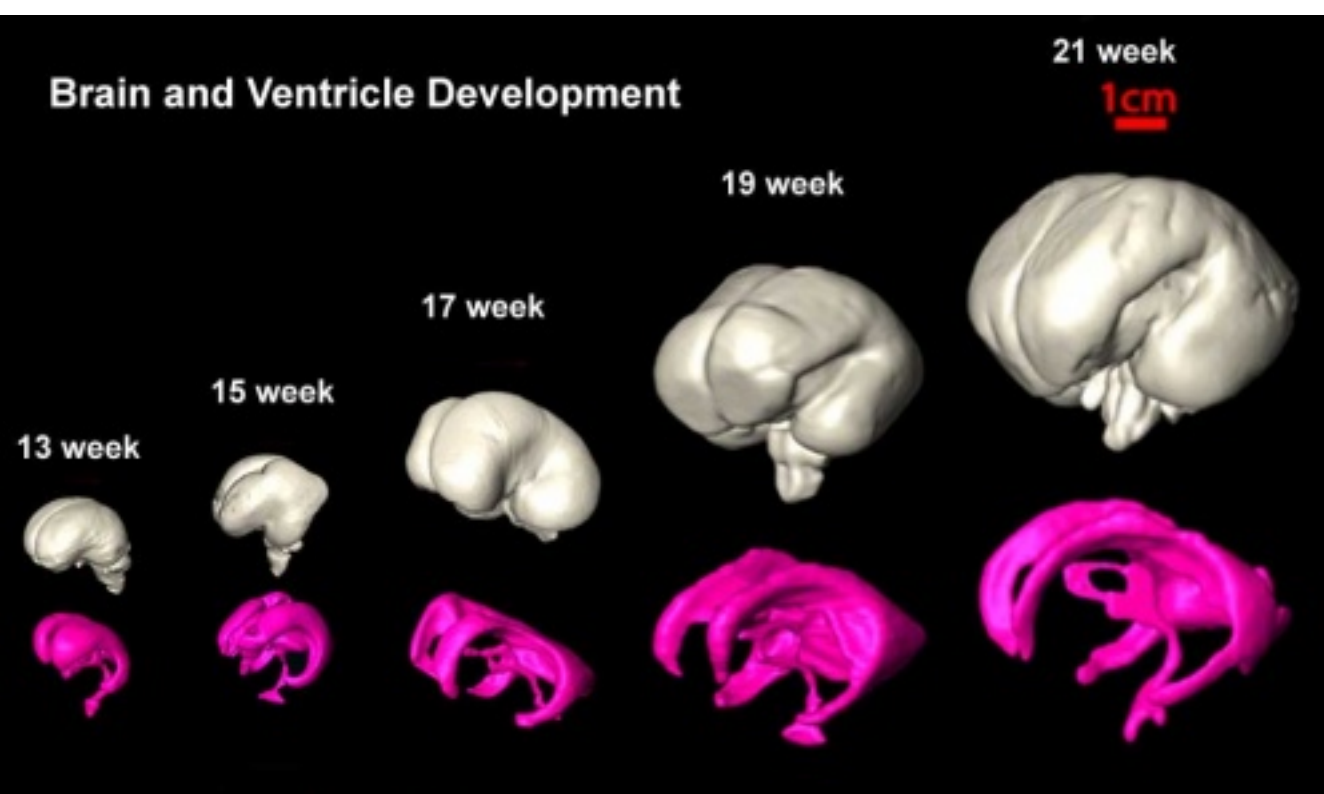
Fetal Neural



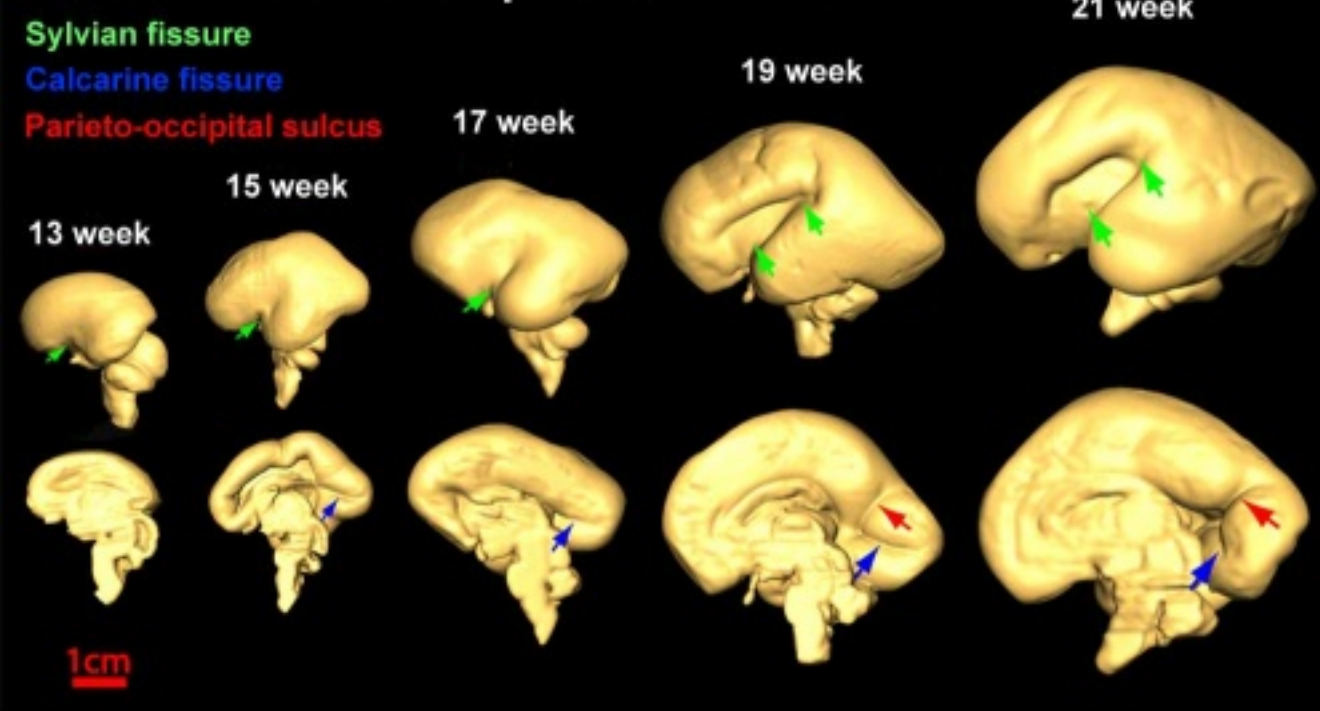
Timeline of events in Human Neural Development



Brain Growth



Brain Fissure Development



- 19 weeks (GA 21 weeks) neuronal migration ends and the radial glial cells that aided the migration now become transformed into astrocytes and astrocytic precursors.^[1]

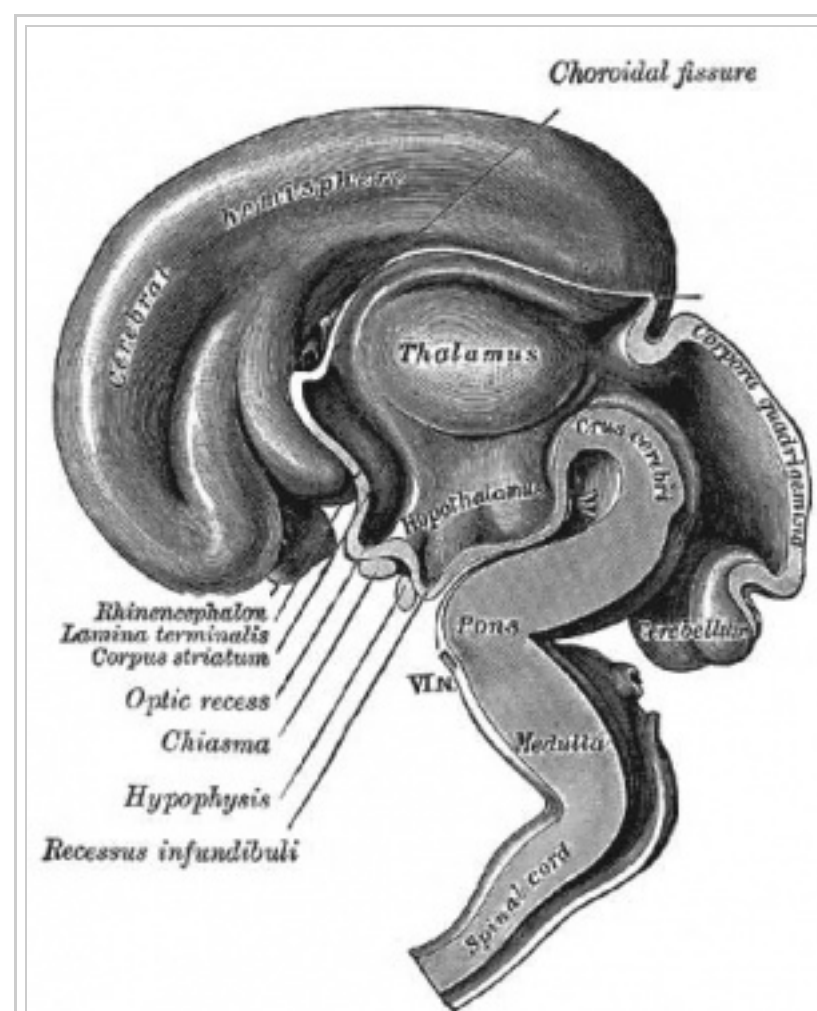
During the fetal period there is ongoing growth in size, weight and surface area of the brain and spinal cord. Microscopically there is ongoing: cell migration, extension of processes, cell death and glial cell development.

Cortical maturation (sulcation and gyration) and vascularization of the lateral surface of the brain starts with the insular cortex (insula, insular cortex or insular lobe) region during the fetal period. This cerebral cortex region in the adult brain lies deep within the lateral sulcus between the temporal lobe and the parietal lobe.

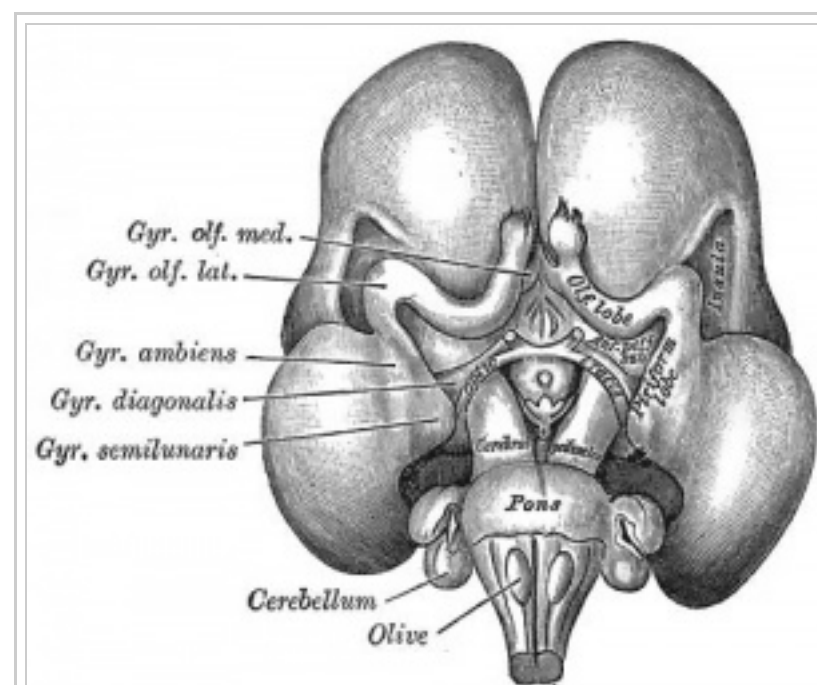
- sulcation** - The process of brain growth in the second to third trimester which forms sulci, grooves or folds visible on fetal brain surface as gyri grow (gyration). Abnormalities of these processes can lead to a smooth brain (lissencephaly).
- gyration** - The development of surface folds on the brain (singular, gyrus)

Insular Gyral and Sulcal Development^[2]

- 13-17 gestational weeks - appearance of the first sulcus
- 18-19 gestational weeks - development of the periinsular sulci
- 20-22 gestational weeks - central sulci and opercularization of the insula
- 24-26 gestational weeks - covering of the posterior insula
- 27-28 gestational weeks - closure of the lateral sulcus (Sylvian fissure or lateral fissure)
- Between 29-41 weeks volumes of: total brain, cerebral gray matter, unmyelinated white matter, myelinated, and cerebrospinal fluid (from MRI)
 - grey matter- mainly neuronal cell bodies; white matter- mainly neural processes and glia.
- total brain tissue volume increased linearly over this period at a rate of 22 ml/week.
- Total grey matter also showed a linear increase in relative intracranial volume of approximately 1.4% or 15 ml/week.
- The rapid increase in total grey matter is mainly due to a fourfold increase in cortical grey matter.
- Quantification of extracerebral and intraventricular CSF was found to change only minimally.



Human brain at three months (median sagittal section)



Human brain at four months (inferior surface)

(Text - modified from Huppi et al., (1998) Quantitative magnetic resonance imaging of brain development in premature and mature newborns. Ann Neurol 43(2):224-235.)

Neural development will continue after birth with substantial growth, death and reorganization occurring during the postnatally (**MH** - postnatal not described in this current lecture)

Links: Neural System - Fetal | Neuroscience - Regional specification of the developing brain
(<http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=neurosci&part=A1465&rendertype=figure&id=A1466>)

Fetal Cardiovascular

MH - covered in last week's lecture Late Vascular Development.

- the 3 septation events (atrial, ventricular and outflow tract) should be completed by the end of the first trimester.
- the 3 vascular shunts (foramen ovale, ductus arteriosus, ductus venosus) remain open until after birth.



Fetal Circulation

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Blood Cells

- fetal RBCs contain fetal haemoglobin (hemoglobin F or HbF).
- fetal neutrophils, monocytes, and macrophages are produced.
- mononuclear phagocytes do not mature until after birth

Immune System

- maternal placenta transfer of IgG not other immunoglobulin isotypes.
- fetal lymphocytes (mature T and B cells) produced not activated

MH - see postnatal lecture - maternal milk IgG and IgA antibodies, leukocytes, secretory IgA, lactoferrin, lysozyme, and oligosaccharides and glycoconjugates that are receptor analogs for microbial adhesins and toxins.

Fetal Respiratory

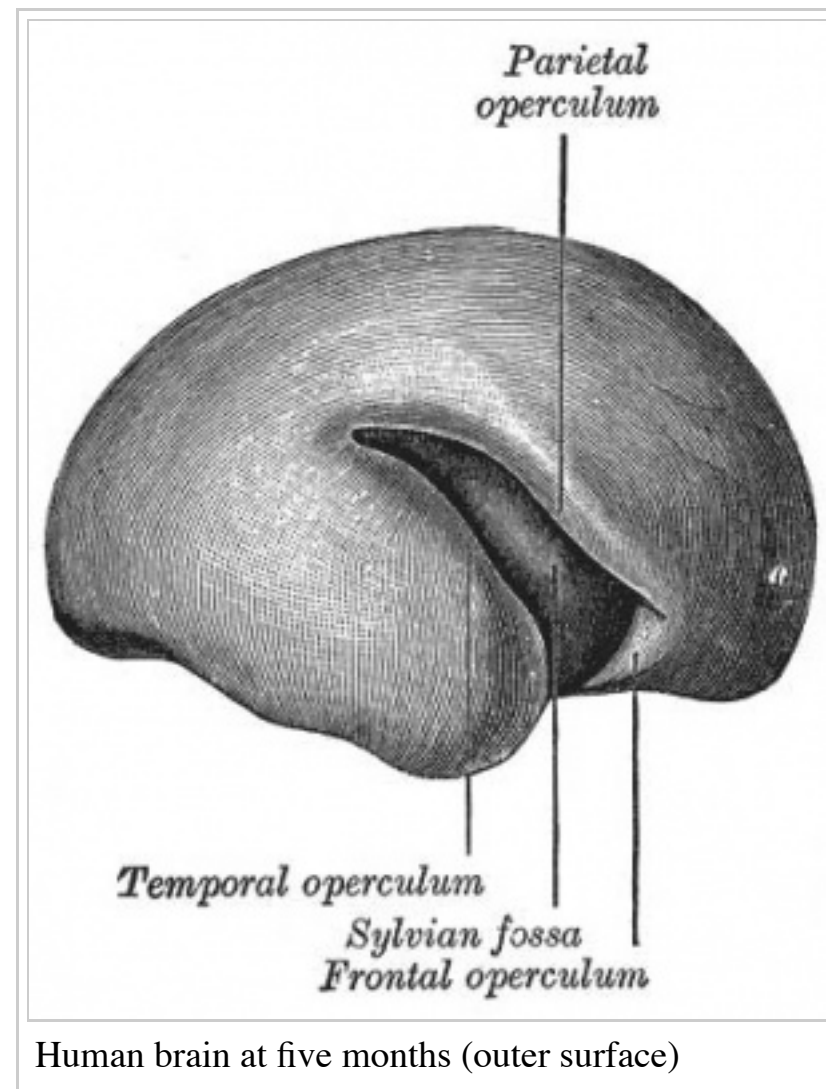
MH - covered also in Lecture - Respiratory Development.

Month 3 to 6 - lungs appear glandular, end month 6 alveolar cells type 2 appear and begin to secrete surfactant.

Month 7 - respiratory bronchioles proliferate and end in alveolar ducts and sacs.

Lung Stages

- **week 4 - 5** embryonic
- **week 5 - 17** pseudoglandular
- **week 16 - 25** canalicular
- **week 24 - 40** terminal sac



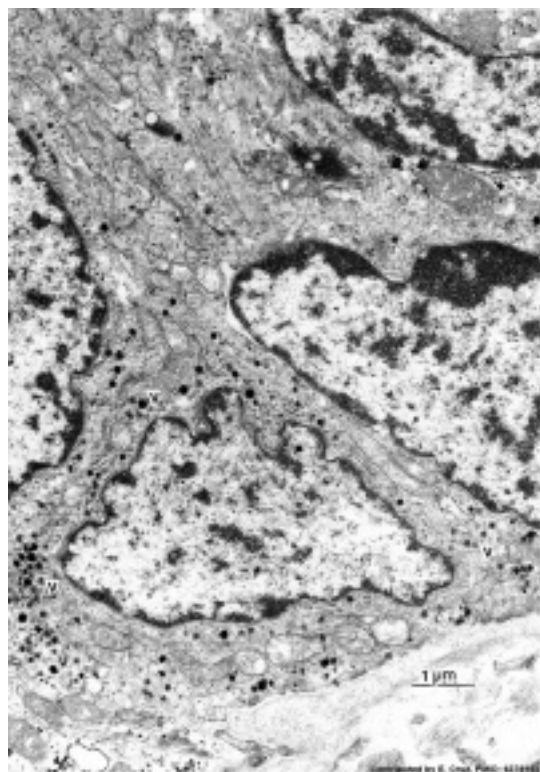
Human brain at five months (outer surface)

- late fetal - 8 years alveolar

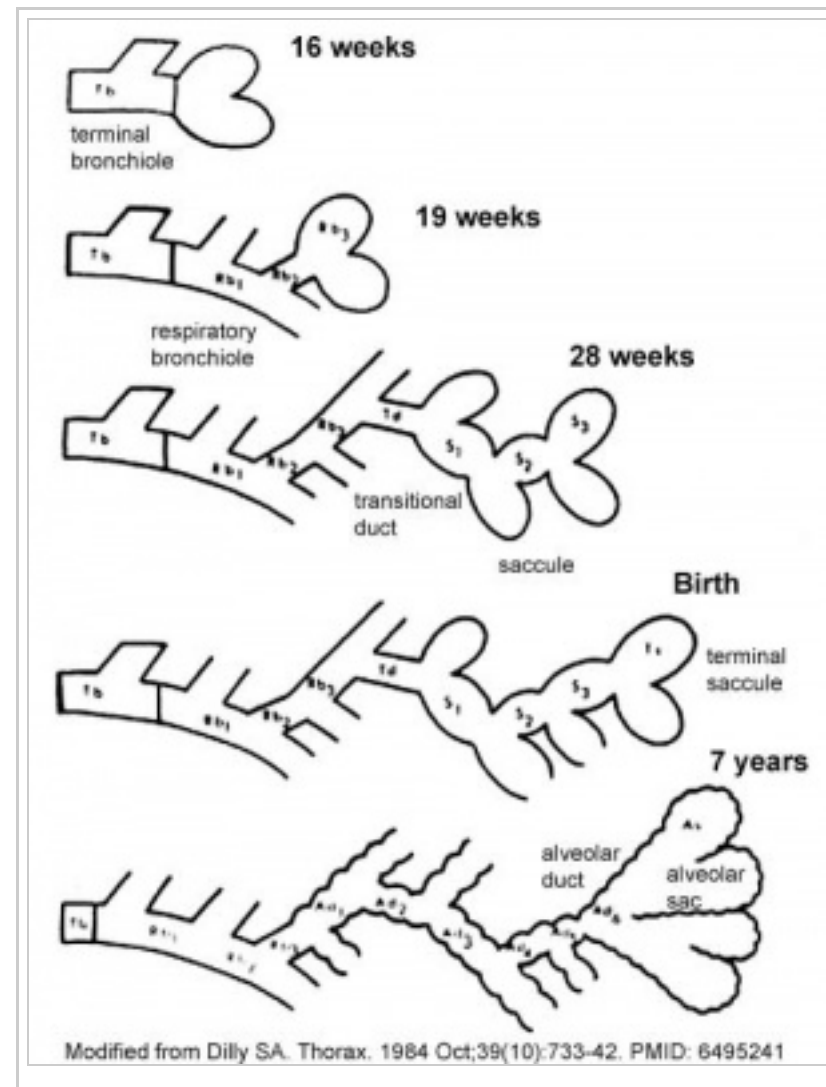
Pulmonary Neuroendocrine Cells

- develop in late embryonic to early fetal period.^{[3][4]}
- first cell type to differentiate in the airway epithelium.
- later in mid-fetal period clusters of these cells form neuroepithelial bodies (NEBs) located in the fetal lung at bronchiole branching points.
- may stimulate mitosis to increase branching. secrete 2 peptides - gastrin-releasing peptide (GRP) and calcitonin gene related peptide (CGRP)

Neonatal Human

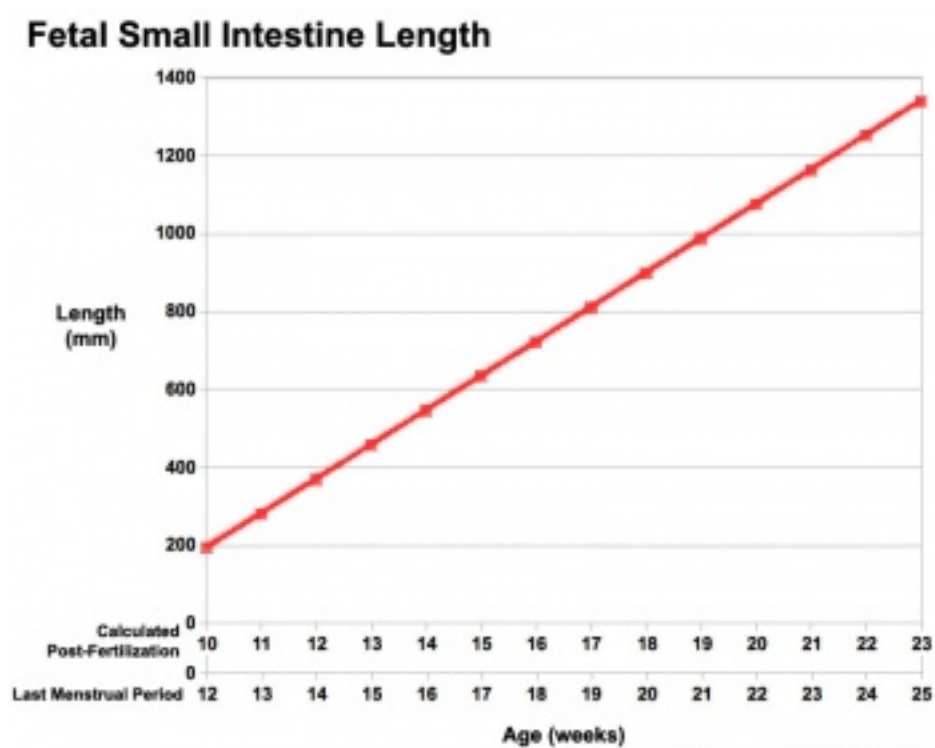


Fetal Rabbit

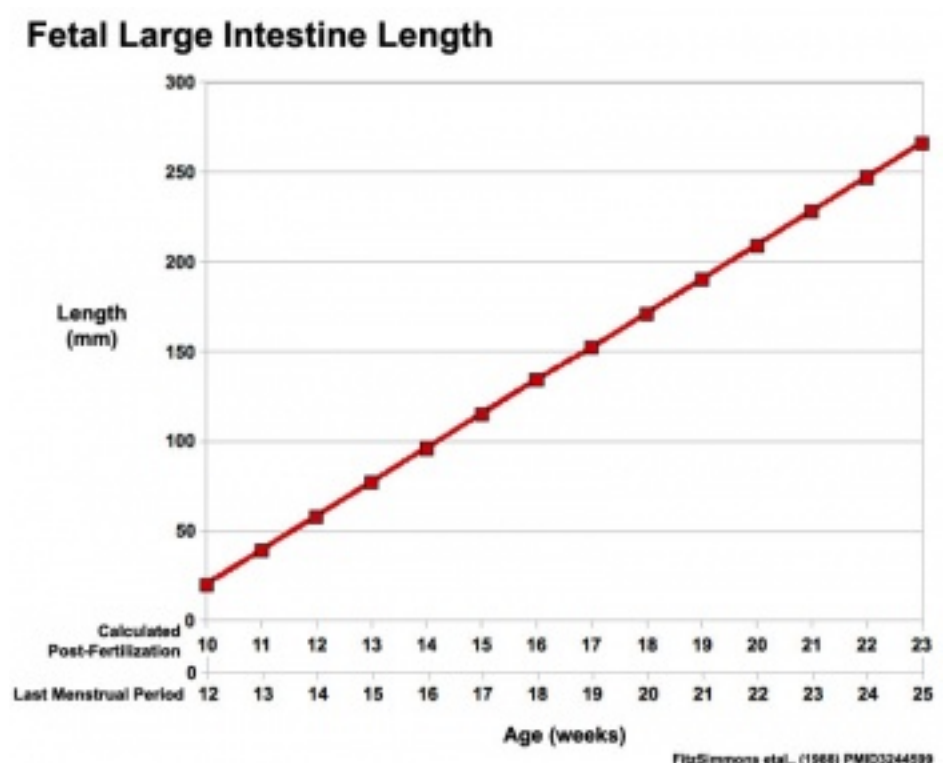


Pulmonary neuroendocrine cell (EM)^[5] Neuroepithelial body^[5]

Gastrointestinal Tract



Fetal small Intestine length growth



Fetal large Intestine length growth

Fetal developmental features include:

- initially herniated outside the ventral body wall
- the growth and rotation of intestines
- changes in mesenteries
- development of the blood supply and tract wall.

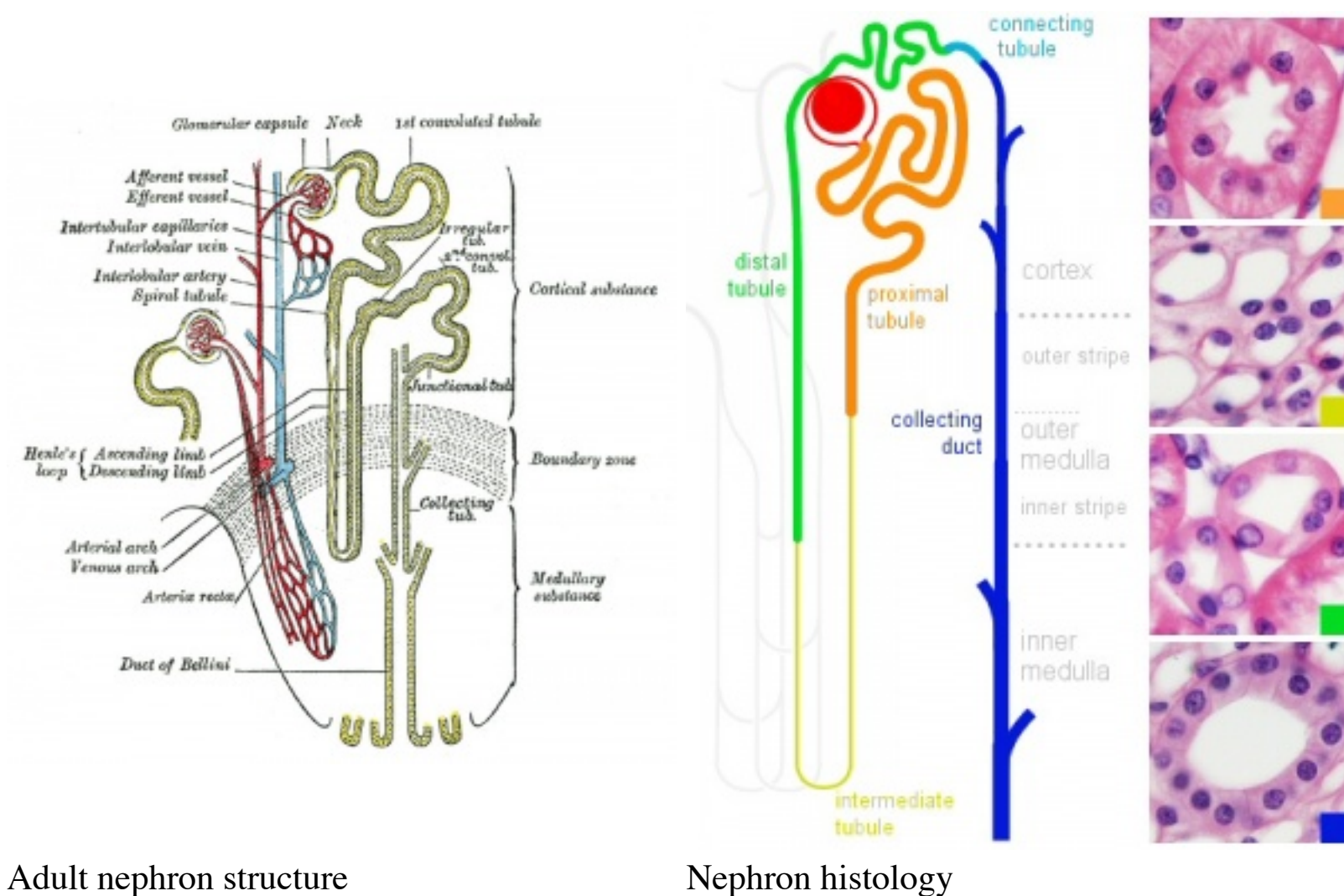
Initial functions:

- **amniotic fluid swallowing** - absorbed through the gastrointestinal tract and respiratory tract epithelium
- **meconium** - accumulation of both secretions and swallowed components within the large intestine

Links: Lecture - Gastrointestinal Development | Gastrointestinal Tract Development

Renal

- Nephron differentiation occurs mainly during the fetal period.
- Human total nephron number ranges between 617,000 and 1,075,000 (mean 850,000 nephrons).



Adult nephron structure

Nephron histology

Development has four developmental stages:

1. vesicle (V) stage (13-19 weeks)
2. S-shaped body (S) stage (20-24 weeks)
3. capillary loop (C) stage (25-29 weeks)
4. maturation (M) stage (infants aged 1-6 months)

Genital

MH - introduced in the Genital Development lecture.

Gonad Descent

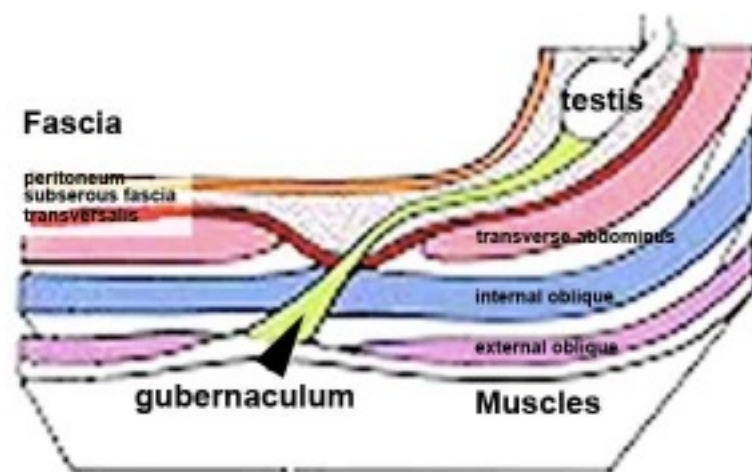
- Both kidney and gonads develop retroperitoneally, with the gonads moving into the abdomen or eventually into the scrotal sacs.
- During fetal development the gubernaculum and fetal growth in both male and female, changes the gonads' relative positions finally reaching their adult locations.

Both female and male gonads undergo anatomical descent.

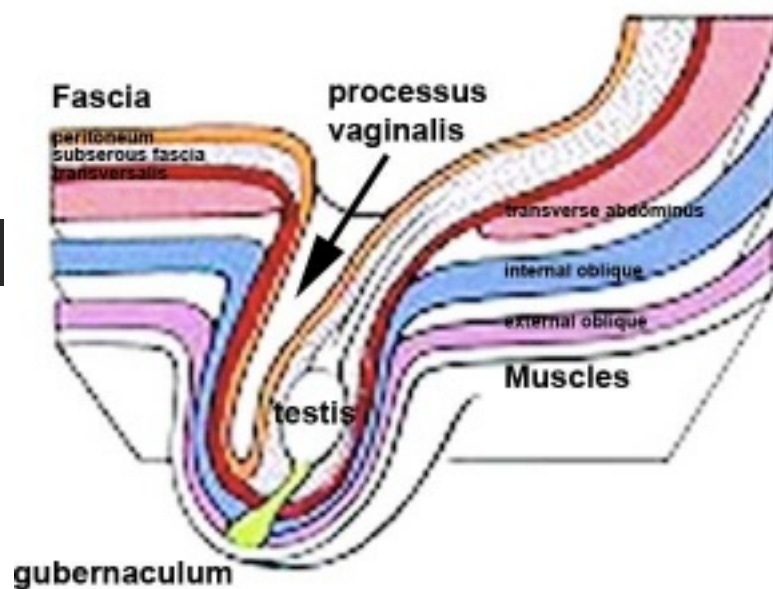
- **Ovaries** – undergo caudal and lateral shifts to be suspended in the broad ligament of the uterus, gubernaculum does not shorten, it attaches to paramesonephric ducts, causing medial movement into the pelvis.

- **Testes** – two anatomical phases in descent, transabdominal and transinguinal, under the influence of the shortening gubernaculum.

Beginning



End



The testis (white) lies in the subserous fascia (spotted) a cavity processus vaginalis evaginates into the scrotum, and the gubernaculum (green) attached to the testis shortens drawing it into the scrotal sac. As it descends it passes through the inguinal canal which extends from the deep ring (transversalis fascia) to the superficial ring (external oblique muscle). Descent of the testes into the scrotal sac begins generally during week 26 and may take several days. The animation shows the path of a single testis.

Gubernaculum - mesenchymal structure occurring associated with gonad development and involved in testes descent. Two factors - insulin-like peptide hormone 3 (INSL3) and androgen, have been shown to be involved with gubernaculum development.

Incomplete or failed descent can occur unilaterally or bilaterally, is more common in premature births, and can be completed postnatally.

Data from a recent study of male human fetal (between 10 and 35 weeks) gonad position.

- 10 to 23 weeks - (9.45%) had migrated from the abdomen and were situated in the inguinal canal
- 24 to 26 weeks - (57.9%) had migrated from the abdomen
- 27 to 29 weeks - (16.7%) had not descended to the scrotum

Postnatal Genital Development

- Not completed until puberty.



Testis Descent
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- Development of secondary sexual characteristics.
- Humans - earlier in female than male.
- Female - commencing menstrual cycle, follicle development, recommence meiosis.
- Male - decrease in MIS, Leydig cell testosterone, activation of spermatogenesis, begin meiosis.

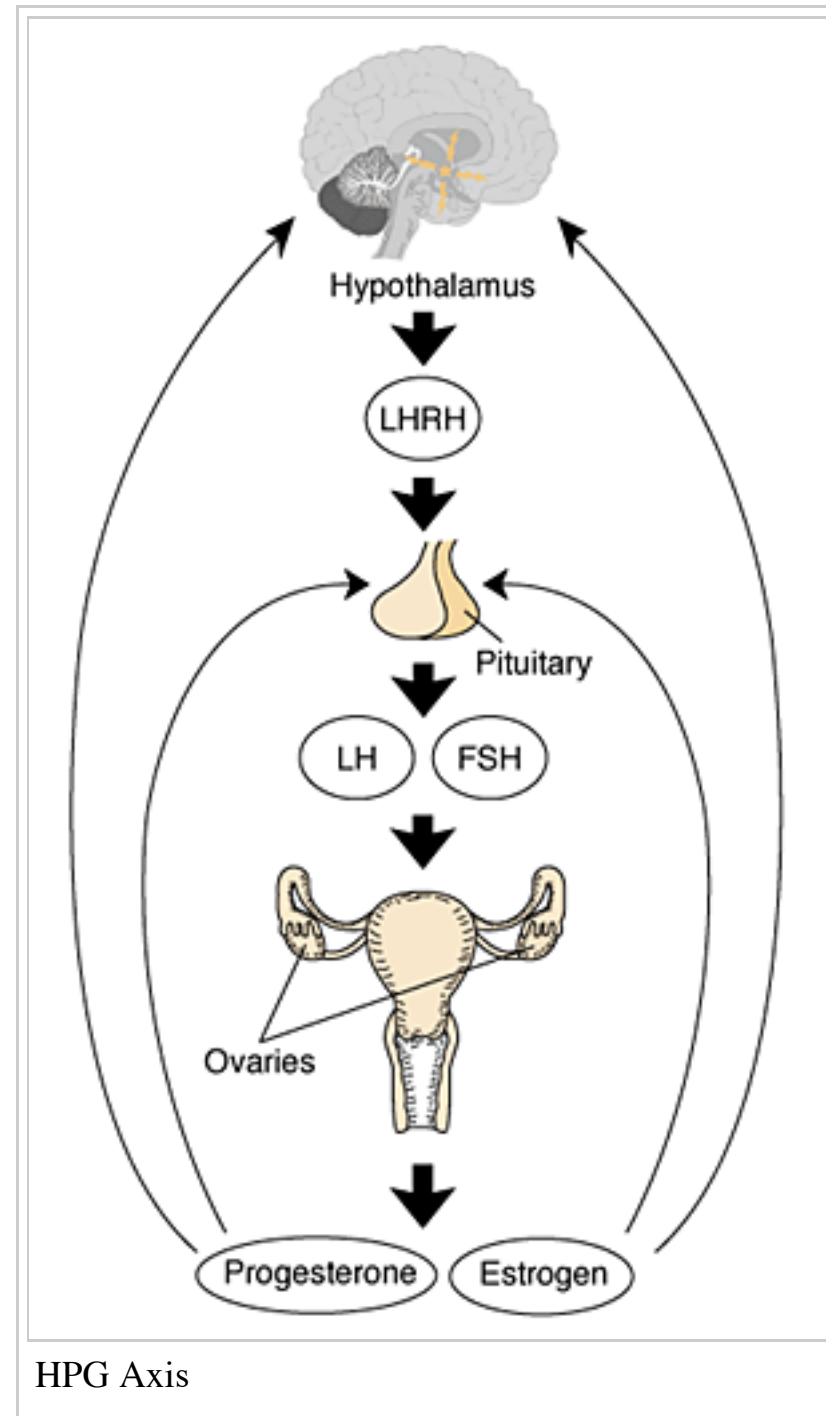
Endocrine

Pituitary Hormones

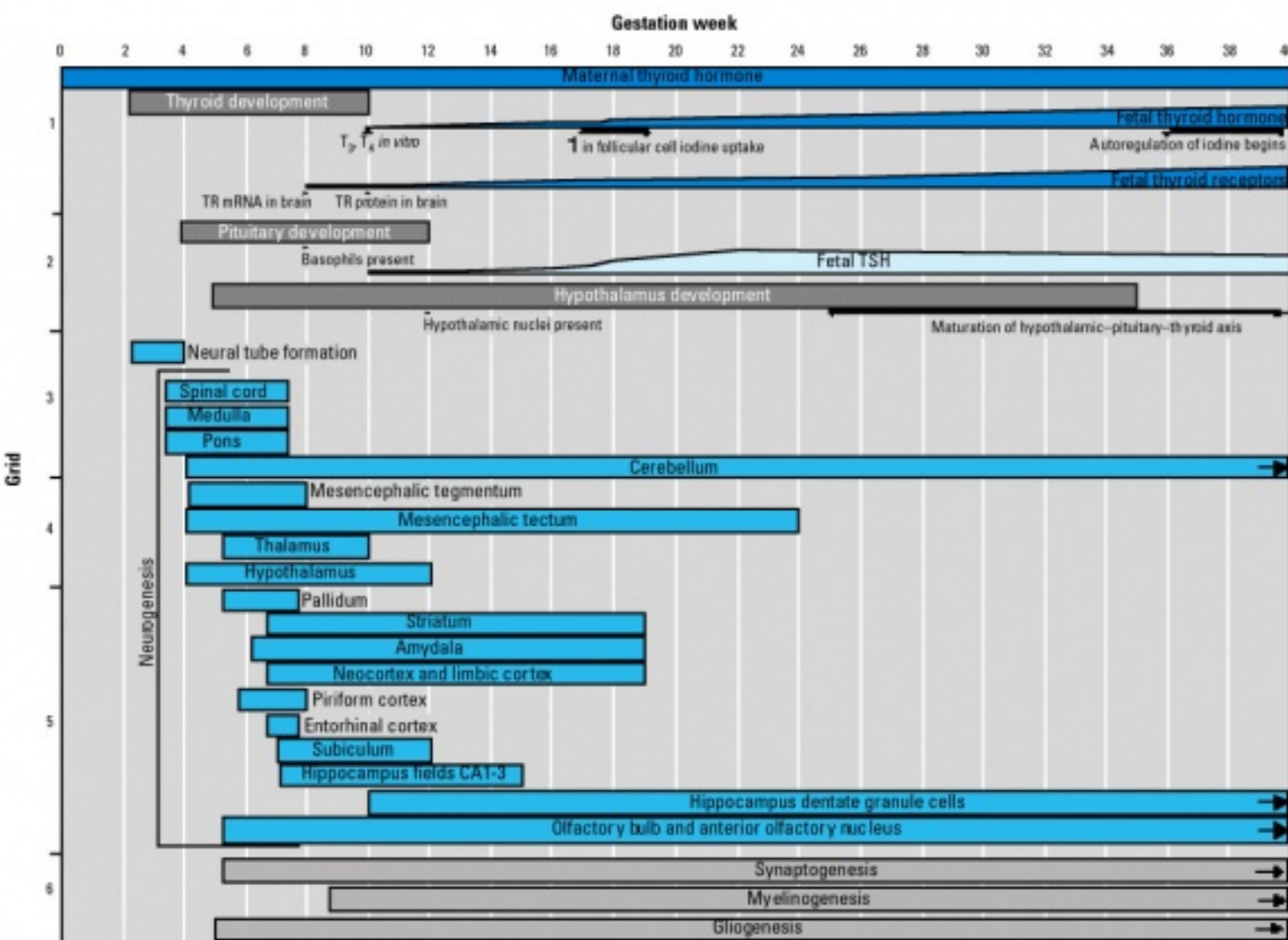
- HPA axis established by week 20
- Pituitary functional throughout fetal development

Thyroid Hormone

- required for metabolic activity, also in the newborn
- important for neural development
- placenta inactivates most of the maternal T4 to reverse T3 (rT3)
- Fetal to term up to 30% of the fetal thyroid hormones are of maternal origin.



HPG Axis



Parathyroid Hormone

- newborn has total calcium levels (approx 20 grams) accumulated mainly in the 3rd trimester (weeks 28–40)
- fetal parathyroid hormone (PTH) potentially available from 10–12 weeks and PTH does not cross the placenta
- fetus relatively hypercalcemic, active transplacental transport of Ca^{2+} to fetus
- maternal serum - calcium ions (Ca^{2+}), inorganic phosphate (Pi) and PTH concentrations are within the non-pregnant normal range throughout pregnancy.
- maternal bone turnover increases in the 3rd trimester.

(Based on Endocrinology - Materno—fetal calcium balance (<http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=endocrin&part=A742&rendertype=box&id=A876>))

Pancreatic Hormones

- maternal diabetes can affect fetal pancreas development (increase in fetal islet beta cells).

Gonadal Hormones

- testosterone - required during fetal development for external genital development and internal genital tract in male.
- estrogens - secreted inactive precursor converted to active form by placenta.

Links: Endocrinology - Control of steroid production in the fetal gonads

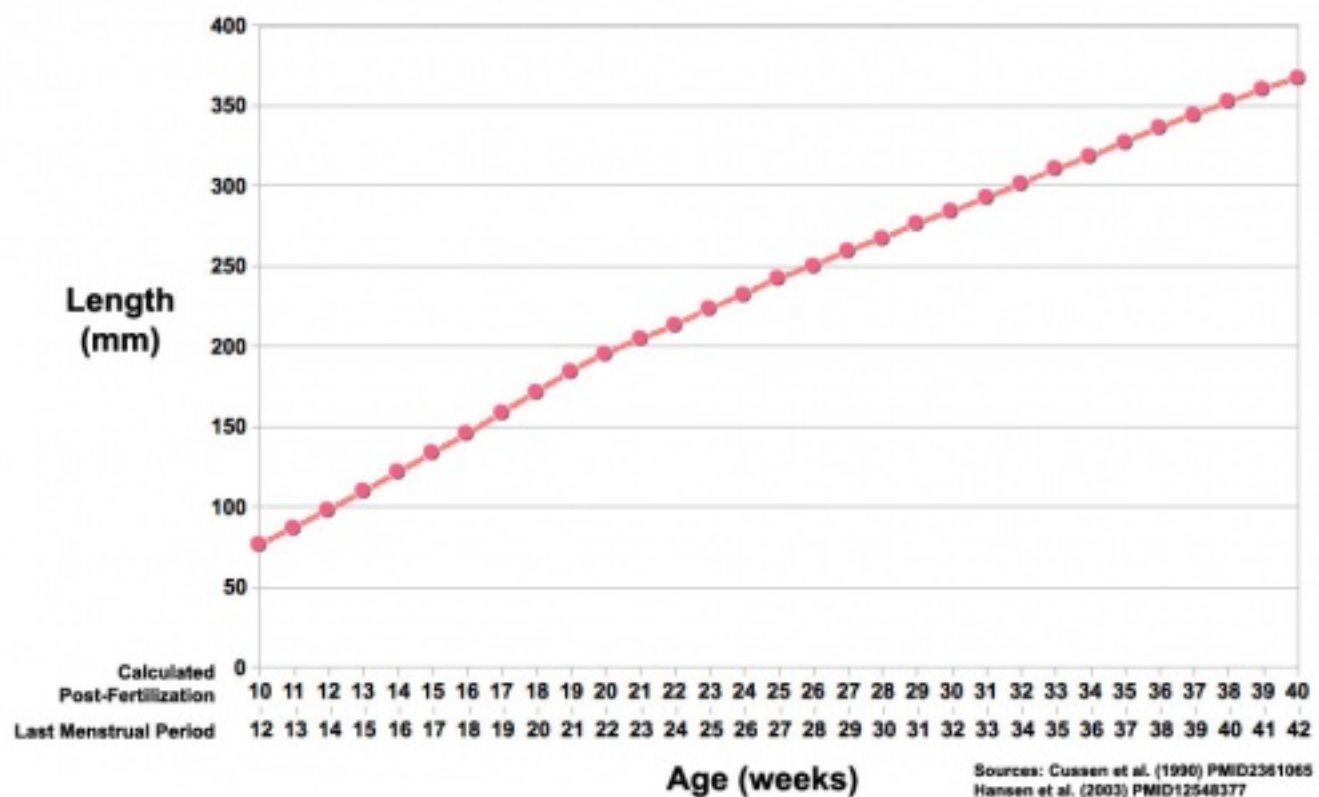
(<http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=endocrin&part=A972#A1056>) | Neuroscience - The Effect of Sex Hormones on Neural Circuitry (<http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=neurosci&part=A2124>)

Fetal Size

- Fetal length increases through both the second and third trimesters.
- Fetal growth parameters can now be accurately measured by ultrasound: biparietal diameter (BPD), abdominal circumference (AC) and femoral diaphysis length (FDL).

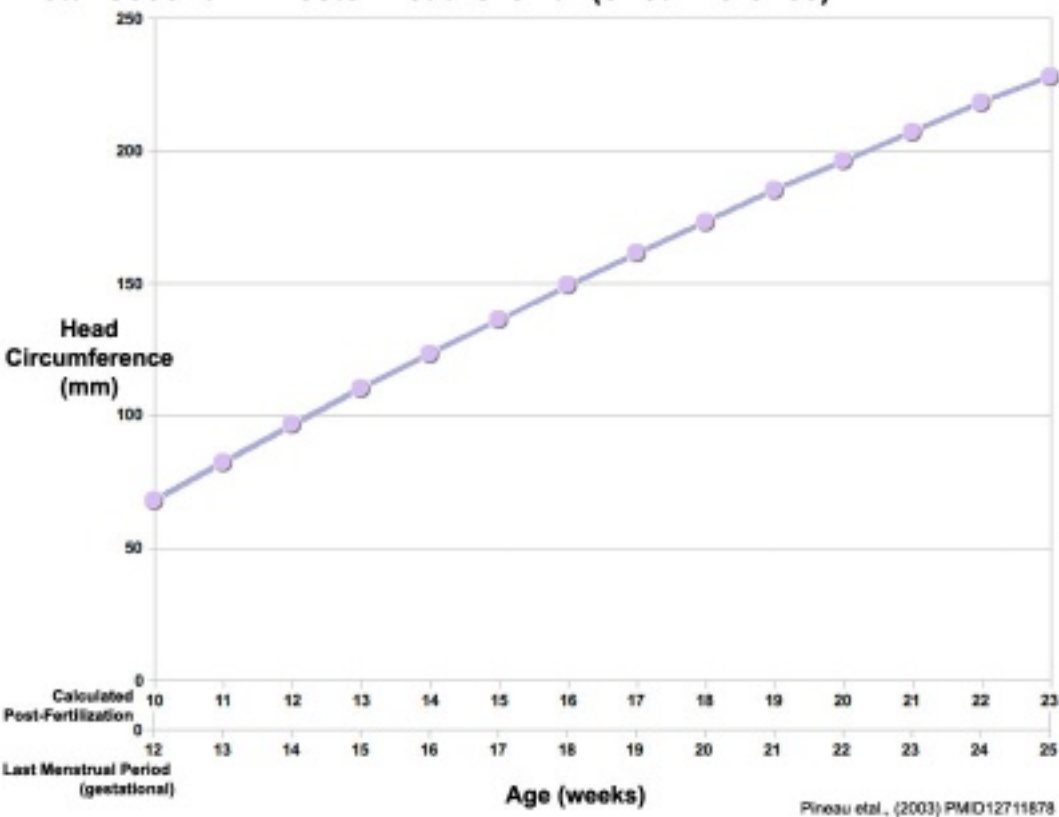


Fetal Crown-Rump Length (CRL)

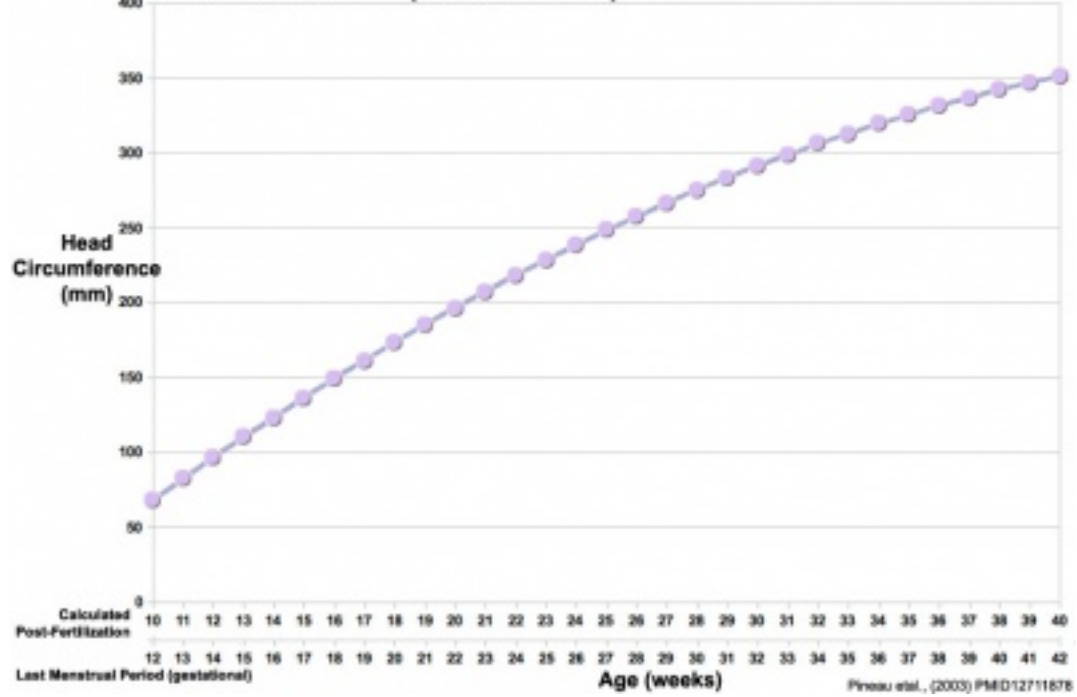


Head Size

Fetal Second Trimester Head Growth (circumference)

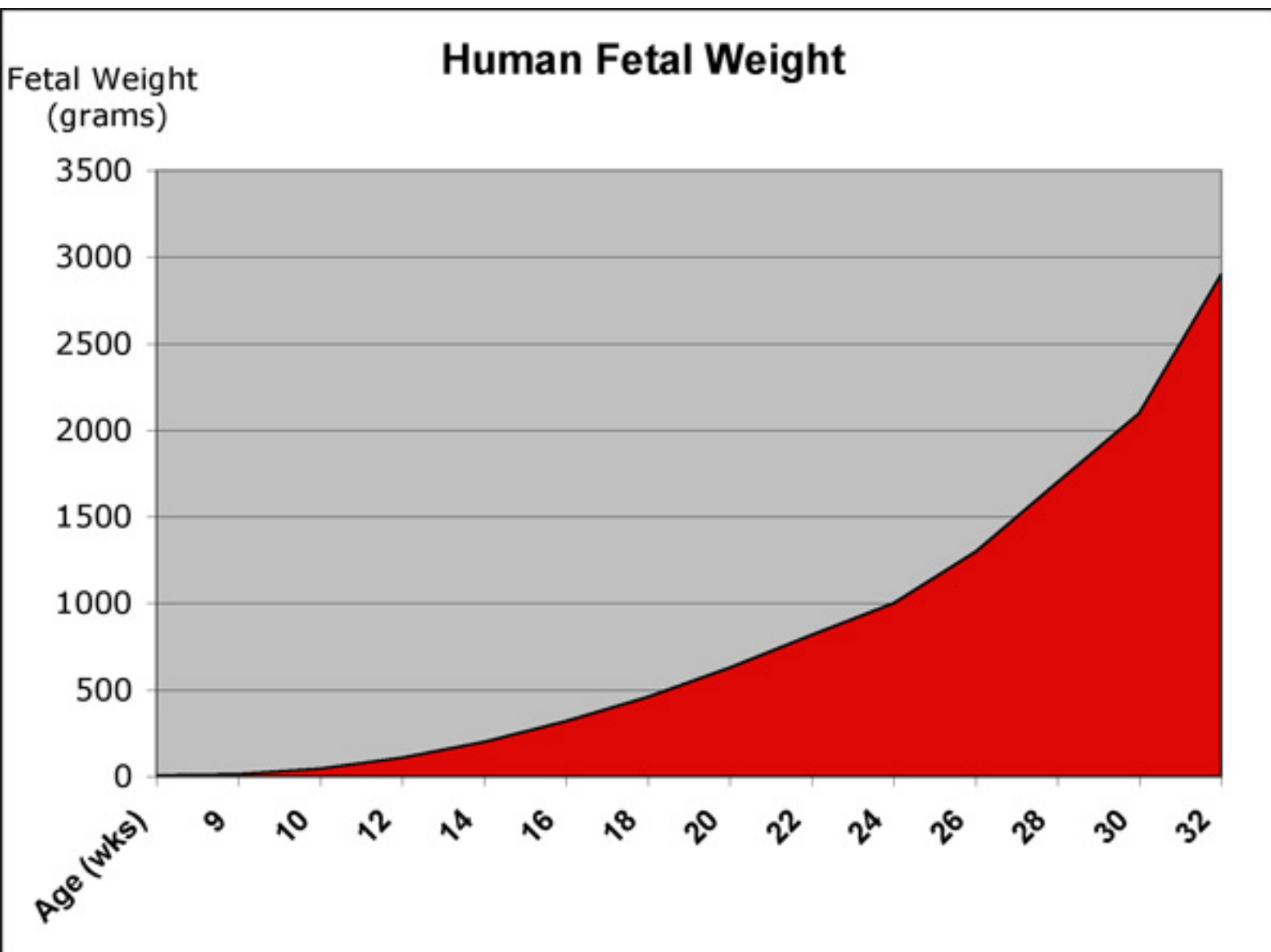


Fetal Head Growth (circumference)



Fetal Graphs: Crown-Rump Length (CRL) | Third trimester CRL | Head Circumference | Head Circumference 2nd Trimester | Liver Weight | Pancreas Weight | Thymus Weight | Small Intestine Length | Large Intestine Length | Length and Weight Changes | Fetal Development

Fetal Weight



See also Fetal origins hypothesis and Low Birth Weight.

Birth Weight

Birth weight (grams)	less 500	500 – 999	1,000 – 1,499	1,500 – 1,999	2,000 – 2,499	2,500 – 2,999	3,000 – 3,499	3,500 – 3,999	4,000 – 4,499	4,500 – 4,999	5,000 or more
Classification	Extremely Low Birth Weight	Very Low Birth Weight	Low Birth Weight	Normal Birth Weight				High Birth Weight			

The primary causes of VLBW are premature birth (born <37 weeks gestation, and often <30 weeks) and intrauterine growth restriction (IUGR), usually due to problems with placenta, maternal health, or to birth defects. Many VLBW babies with IUGR are preterm and thus are both physically small and physiologically immature.

Fetal Origins Hypothesis

- Maternal derived abnormalities relate to lifestyle, environment and nutrition and while some of these directly effect development.
- Growing evidence that some effects are more subtle and relate to later life health events.
- Original theory based on the early statistical analysis carried out by Barker of low birth weight data collected in the early 1900's in the south east of England
 - He then compared with these same babies later health outcomes.
 - Theory was therefore originally called the "Barker Hypothesis"
- recently been renamed as "developmental origins of health and disease" (DOHAD).

Links: Fetal Origins Hypothesis

Premature Birth

Year	< 34 weeks %	34-36 weeks %	total preterm %
1990	3.3	7.3	10.6
1995	3.3	7.7	11
2000	3.4	8.2	11.6
2005	3.6	9.1	12.7

Table data from: Prevention of preterm birth: a renewed national priority.
[6]

Australia Recommendations

Perinatal care at the borderlines of viability: a consensus statement based on a NSW and ACT consensus workshop (February 2005) published in The Medical Journal of Australia 2006.^[7]

- **< 23 weeks** survival is minimal and the risk of major morbidity is so high that initiation of resuscitation is not appropriate.
- **23 weeks** active treatment may be discussed, but would be discouraged in NSW/ACT neonatal intensive care units.
- **23 to 25 weeks** otherwise normal infant, there is an increasing obligation to treat. However, it is acceptable medical practice not to initiate intensive care if parents so wish, following appropriate counselling.
- **24 weeks** antenatal transfer to a tertiary centre for fetal reasons is indicated. The option of non-initiation of intensive care/resuscitation should be offered.
- **25 weeks** active treatment is usually offered, but the option of non-initiation of intensive care/resuscitation (presence of adverse fetal factors such as twin-to-twin transfusion, intrauterine growth restriction or chorioamnionitis) should also be discussed.
- **26 weeks +** otherwise normal infant the obligation to treat is very high, and treatment should generally be initiated unless there are exceptional circumstances.

Abnormalities

Teratology

How different environmental effects during the pregnancy may influence outcomes. A teratogen (Greek, teraton = monster) is defined as any agent that causes a structural abnormality (congenital abnormalities) following fetal exposure during pregnancy. The overall effect depends on dosage and time of exposure (see critical periods below).



Premature infant

Absolute risk - the rate of occurrence of an abnormal phenotype among individuals exposed to the agent. (e.g. fetal alcohol syndrome)

Relative risk - the ratio of the rate of the condition among the exposed and the nonexposed. (e.g. smokers risk of having a low birth weight baby compared to non-smokers) A high relative risk may indicate a low absolute risk if the condition is rare.

Mutagen - a chemical or agent that can cause permanent damage to the deoxyribonucleic acid (DNA) in a cell. DNA damage in the human egg or sperm may lead to reduced fertility, spontaneous abortion (miscarriage), birth defects and heritable diseases.












Fetotoxicant - is a chemical that adversely affects the developing fetus, resulting in low birth weight, symptoms of poisoning at birth or stillbirth (fetus dies before it is born).

Synergism - when the combined effect of exposure to more than one chemical at one time, or to a chemical in combination with other hazards (heat, radiation, infection) results in effects of such exposure to be greater than the sum of the individual effects of each hazard by itself.

Toxicogenomics - the interaction between the genome, chemicals in the environment, and disease. Cells exposed to a stress, drug or toxicant respond by altering the pattern of expression of genes within their chromosomes. Based on new genetic and microarray technologies.

Critical Periods

Critical periods of development refer to times when genetic or maternal effects can impact upon the developmental process. The timing of these effects will impact on different systems at different times.

Conceptus		Embryonic development (weeks)						Fetal period (weeks)			
1	2	3	4	5	6	7	8	9	16	20-36	38
											
		Neural									
		Heart									
		Upper limbs									
		Lower limbs									
		Ear									
		Eye									
				Palate							
				Teeth							
						External genitalia					
Loss	Major abnormalities						Functional and Minor abnormalities				

Links: Embryonic Development | Timeline human development | Movie - Human Development annotated cartoon | Human - critical periods | Human Abnormal Development

Systems with long periods of development or complex developmental origins are more susceptible to developmental abnormalities.

- Which systems will take a long time to develop?
- Which systems are complex in origin?

References

1. ↑ H J Kadhim, J F Gadisseux, P Evrard **Topographical and cytological evolution of the glial phase during prenatal development of the human brain: histochemical and electron microscopic study.** J. Neuropathol. Exp. Neurol.: 1988, 47(2);166-88 PubMed 3339373
2. ↑ A Afif, R Bouvier, A Buenerd, J Trouillas, P Mertens **Development of the human fetal insular cortex: study of the gyration from 13 to 28 gestational weeks.** Brain Struct Funct: 2007, 212(3-4);335-46 PubMed 17962979
3. ↑ E Cutz **Neuroendocrine cells of the lung. An overview of morphologic characteristics and development.** Exp. Lung Res.: 1982, 3(3-4);185-208 PubMed 6188605
4. ↑ E Cutz, J E Gillan, A C Bryan **Neuroendocrine cells in the developing human lung: morphologic and functional considerations.** Pediatr. Pulmonol.: 1985, 1(3 Suppl);S21-9 PubMed 3906540
5. ↑ ^{5.0} ^{5.1} R P DiAugustine, K S Sonstegard **Neuroendocrinelike (small granule) epithelial cells of the lung.** Environ. Health Perspect.: 1984, 55;271-95 PubMed 6376101
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