CHAPTER-1

GENERAL EMBRYOLOGY
(Part-1 of 2)
OVULATION TO IMPLANTATION

The objectives for this section:

1. Understand the main phases of the ovarian cycle and relate these to hormonal and structural changes.

2. Know when ovulation occurs in the menstrual cycle.

3. Understand the role of the corpus luteum and how this is affected by a fertilised and non fertilised ovum.

4. Know the location where fertilisation takes place and how this is achieved.

5. Have a basic knowledge of the formation and progress of the blastocyst until implantation has taken place.

THE OVARIAN CYCLE

🕮 Revise: The principles of miosis and mitosis, gametogenesis; oogenesis and spermatogenesis

After the female has gone through puberty the ovaries start to perform a twin function; the production of the sex steroid hormones and **gametogenesis**. The effect of the hormones secreted cause the female to undergo regular monthly sexual cycles. These are controlled by the Hypothalamus by producing **Gonadotropin-releasing hormone (GnRH).** This hormone acts on the anterior pituitary (the epiphysis) gland, which in turn secrete a group of hormones called the **gonadotropins**. These are; **follicle-stimulating hormone (FSH) and Luteinizing hormone (LH)** and have the effect of stimulating and controlling the changes of the ovaries.

With each ovarian cycle about 5 to 15 **primordial follicles** begin to grow under the influence of FSH. Usually only one of these follicles will reach full maturity resulting in one **oocyte** being discharged.

The oocyte is enveloped by a group of cells and at this stage is called the **Graafian Follicle**. The follicle cells start to secrete estrogens which have two main functions:

(a) cause the uterine endometrium to proliferate; and
(b) to stimulate the pituitary to secrete LH.

(Locate a figure which shows the stages of human development from ovulation to implantation during week 1.) On day 7 the blastocyst has embedded into the uterine mucosa.

OVULATION

With a sudden surge of LH the follicle becomes fully matured and the oocyte is released. This phase of the cycle is called **ovulation**. In some women, ovulation is accompanied by slight pain, sometimes referred to as 'middle pain' because of its position in the menstrual cycle. Usually this event is accompanied by a slight rise in body temperature

CORPUS LUTEUM

After the oocyte has been release the follicular cells become vascularised and under the influenced of LH the remainder of the Graafian follicle (without the oocyte) is known as the **corpus luteum**. The function of the corpus luteum is to secrete progesterone. This hormone together with estrogens prepares the uterine mucosa for implantation of the embryo, provided fertilisation has taken place.

When the oocyte is released from the graafian follicle is surrounded by some granulosa cells. It is deposited near or within the fimbriae of the open end of the **fallopian tube**. The rhythmic contractions of the uterine tube propel the oocyte towards the lumen of the tube at the **ampulla**. Usually it is at the ampulla part of the fallopian tube that the fertilisation takes place. A fertilised oocyte will reach the uterine cavity within 3 to 4 days. If however fertilisation fails to occur, the corpus luteum reaches maximum development within approximately 9 days after ovulation and then start to decrease in size and forms a mass of small fibrotic scar, known as **corpus albicans**.

If the oocyte is fertilised, degeneration of the corpus luteum is prevented by **Chorionic Gonadotropin Hormone (hCG)** which is secreted by the **trophoblast** of the developing embryo. By the end of the 3rd month the corpus luteum may be up to ½ of the total ovary size. The corpus luteum continues to secrete progesterone until the end of the 4th month. After the 4th month progesterone starts to be secreted from the trophoblastic part of the placenta, therefore maintaining the pregnancy. The secretion of progesterones and estrogens also prevent further ovulations from taking place, whilst pregnancy is progressing.

CORPUS ALBICANS

The lack of progesterone secreted by the corpus albicans leads to a breakdown in the endometrial lining heralding the onset of the menstrual bleed.

FERTILISATION (day 1)

The process of fusion of the male and female gametes is known as fertilisation. This usually occurs in the **ampullary region of the fallopian tube**. The spermatozoa may remain alive in the female reproductive tract for about 24 hours and the oocyte may die with 12 to 24 hours after ovulation, if not fertilised. The spermatozoon with aid of enzymes secreted by its acrosome penetrates the **corona radiata** and **zona pellucida** of the oocyte. The 23 maternal and 23 paternal double stranded chromosomes split longitudinally thus providing the zygote with the normal diploid number of chromosomes. The determination of the sex of the offspring depends on the sex chromosome supplied by the sperm. An 'X' carrying **gamete** from the male will produce a female (XX) embryo and a 'Y' carrying gamete will produce a male (XY) embryo.

BLASTOCYST FORMATION (day 5)

The fertilised oocyte is now called the **Zygote** and it start to undergo a series of mitotic divisions resulting in an increase in the number of cells. After three to four divisions the zygote assumes the appearance of a mulberry, hence its new name; **Morula**. This is approximately 3-4 days after fertilisation and its location is around the entrance to the uterine cavity. The morula then undergoes a series of organisational changes; an inner mass of accumulated cells will go on to form the embryo proper and an outer cell mass the trophoblast which later will contribute to the placenta. This is now called the **Blastocyst**.

IMPLANTATION

About the 7^{th} day after fertilisation, the blastocyst is now in the uterine cavity and will now start to penetrate the epithelial cells of the endometrial mucosa.

SELF ASSESSMENT QUESTIONS

1. Discuss the endocrine changes associated with the ovarian cycle

2. What is the function of FSH and LH

3. At which point in the menstrual calendar does ovulation occur

4. Draw a simple graph of the menstrual cycle and plot the following:

    a. FSH
    b. LH
    c. Estrogens
    d. Progesterone

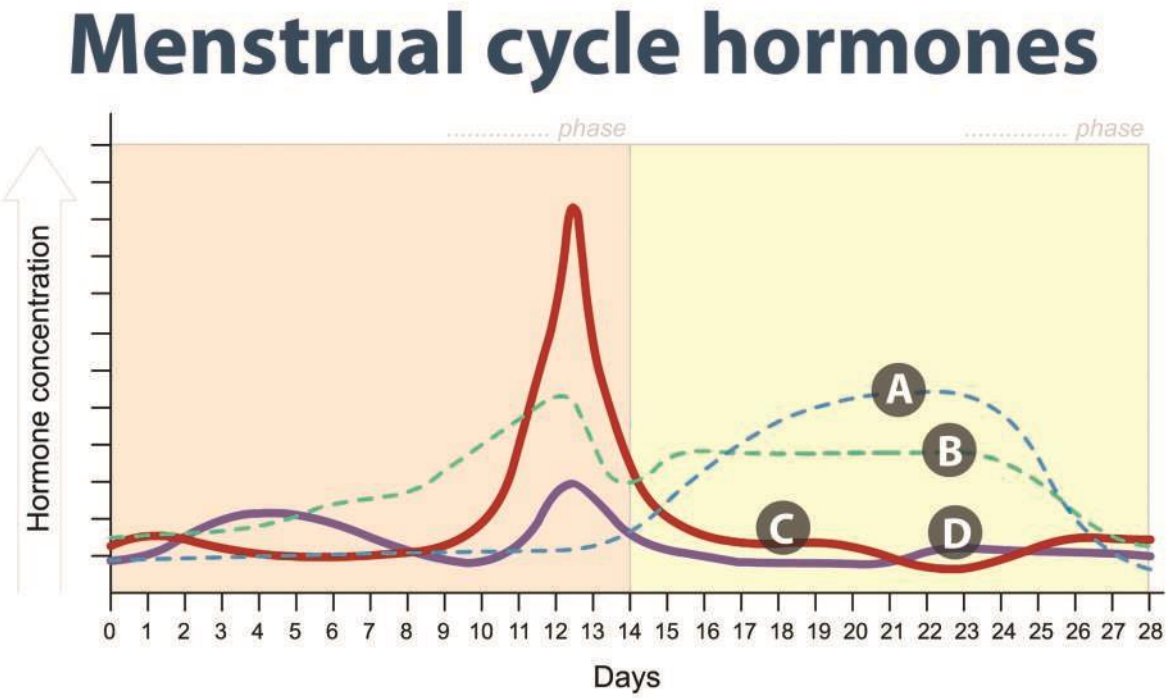
5. Extend the above graph to show how these hormones will be affected if fertilisation takes place.

6. Describe the function of the corpus luteum. What replaces its function after the 4th month into pregnancy?

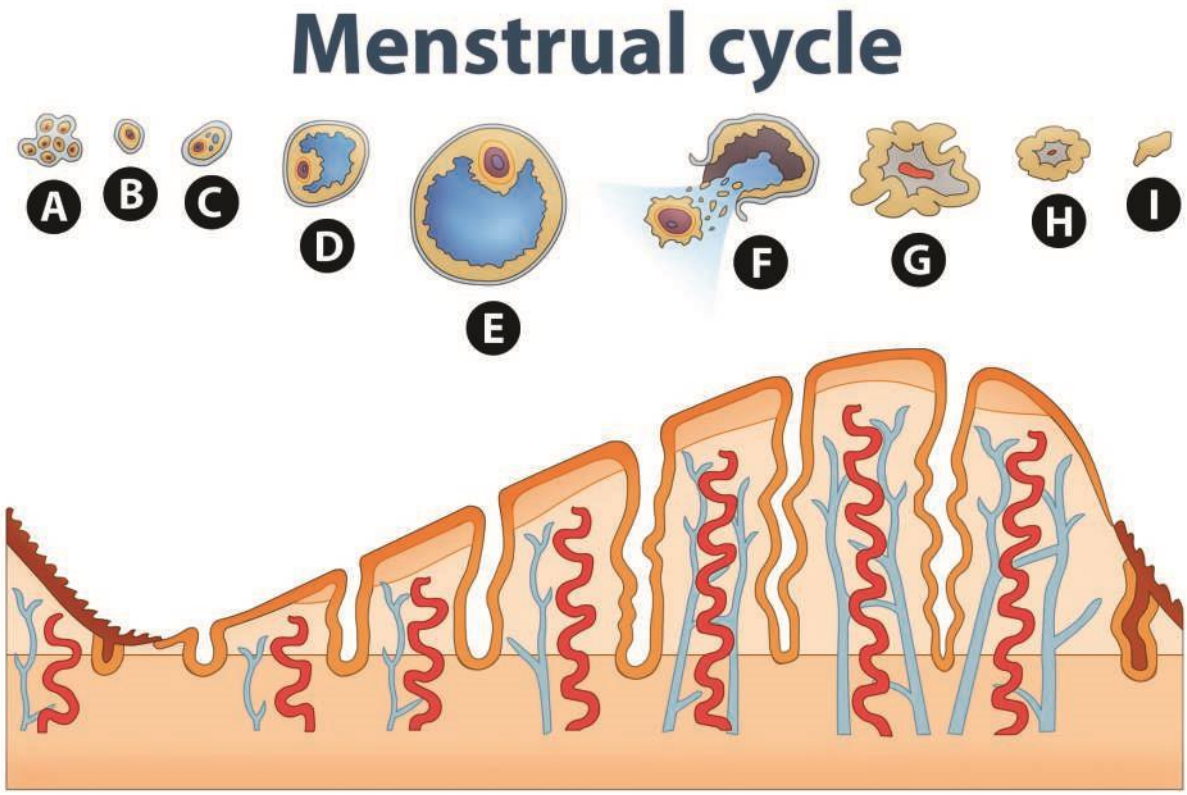
7. Where does fertilisation usually occur? State some abnormal areas of implantation.

Please refer to your labelling supplement handbook and label any images associated with the above chapter.

Identify the different hormones in the diagram below:



Name the different structures below:
Identify the menstrual cycle phase in which these occur:



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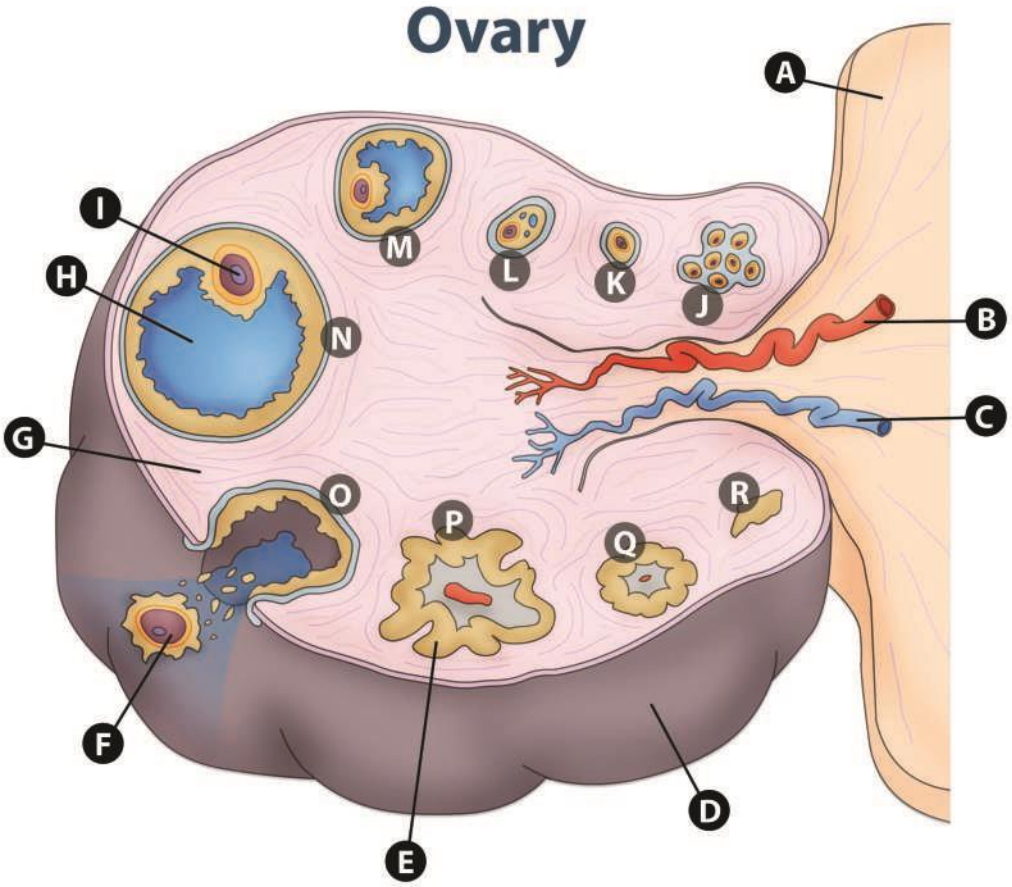


Uterus at time of implantation

CONTENTS

Objectives

1. To know the main phases of the uterine cycle

2. To understand what changes take place in the uterus during each of the above phases.

3. To understand what hormonal factors are responsible for the different stages in the menstrual cycle.

📖 Anatomy of the uterus: Blood supply, lymph drainage, ligament attachments, nerve supply, endocrine function.

UTERUS AT TIME OF IMPLANTATION

The wall of the uterus consists of three layers

a) The endometrium (mucosa lining the inside wall of the uterus)
b) The myometrium (a thick layer of smooth muscle
c) The perimetrium (the peritoneal covering lining the outside wall)

From puberty (11-13 years) until menopause (45-50) the endometrium undergoes cyclical changes which occur approximately every 28 days. This is under the direct hormonal control of the ovaries whose activity is regulated by the pituitary.
The pituitary secretes Follicle Stimulating Hormone (FSH) which stimulates the ovaries to mature a follicle to become an ovum and Luteinizing Hormone (LH) to develop and mature the corpus luteum.

During the menstrual cycle the endometrium undergoes three stages:

a) Follicular or proliferative phase
b) The secretory or progestational phase
c) The menstrual phase

Follicular or proliferative phase

The proliferative phase begins at the end of the menstrual phase, is under the influence of oestrogen and parallels growth of the ovarian follicles. During this period the endometrium undergoes growth and the spongy mucus layer becomes thicker with a rich blood supply.

The Secretory of Progestational Phase

The secretary phase begins 2-3 days after ovulation under the influence of progesterone produced by corpus luteum. At the time of implantation the mucosa of the uterus is in the secretory phase when the uterine glands and arteries become coiled and the tissues becomes succulent. If fertilisation does occur then the endometrium assists in implantation and contributes to formation of the placenta. If fertilisation does not occur, the shedding of the endometrium begins which marks the initiation of the menstrual phase.

The Menstrual Phase

If fertilisation does not occur, it is followed by the menstrual phase (2-3 days) when the compact and spongy layers are expelled from the uterus. The basal layer of the endometrium is retained and serves the function as a regenerative layer in the rebuilding of the glands and arteries (in the proliferative phase).

SELF ASSESSMENT QUESTIONS

1. How may layers does the uterine walls consist of and what is their function?

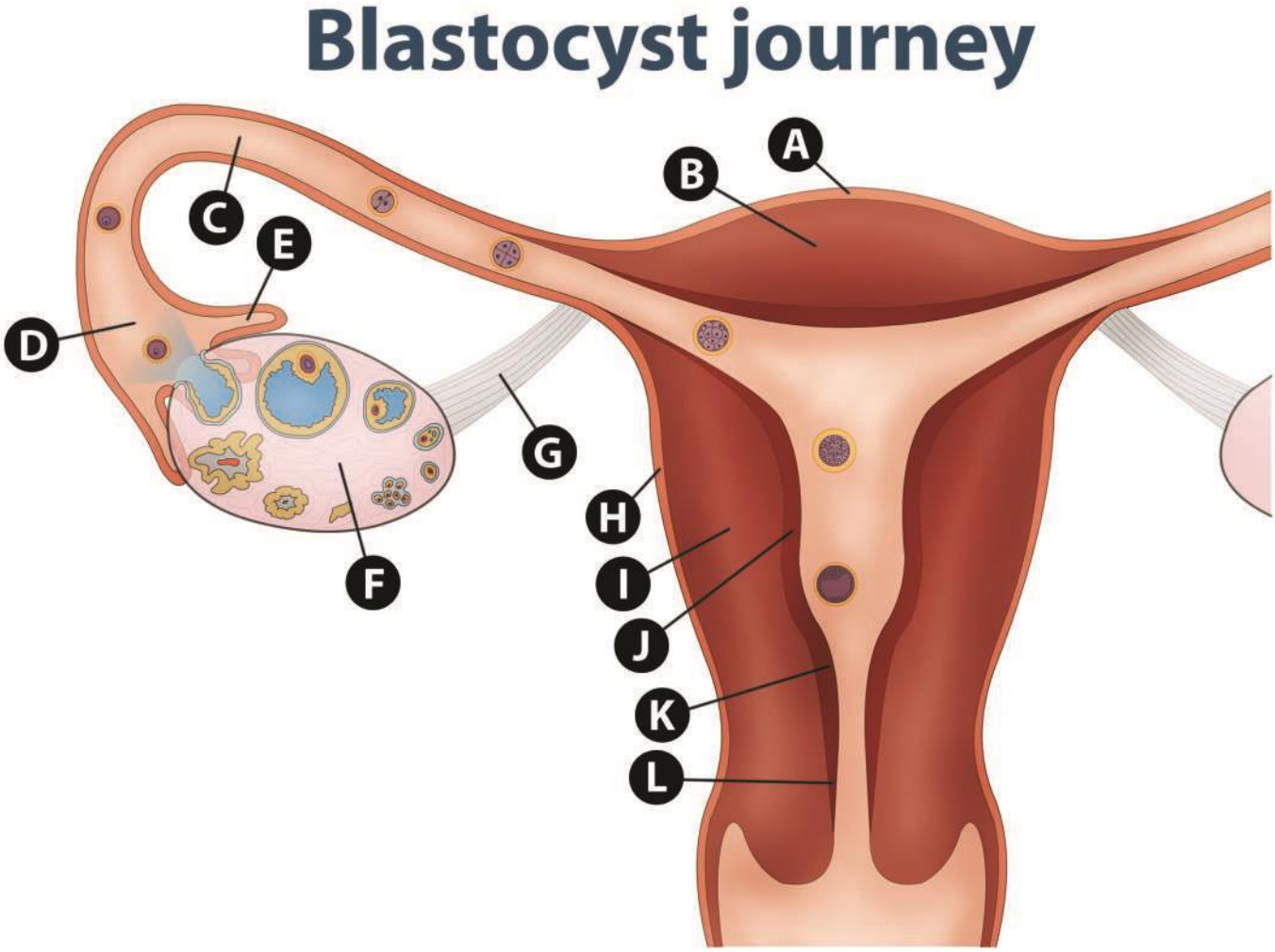
2. Name the three phases of the uterine growth and state what happens to the uterine mucosa during progression through the menstrual cycle?

3. If fertilisation and implantation does not take place what hormonal changes lead to
the menstrual phase?

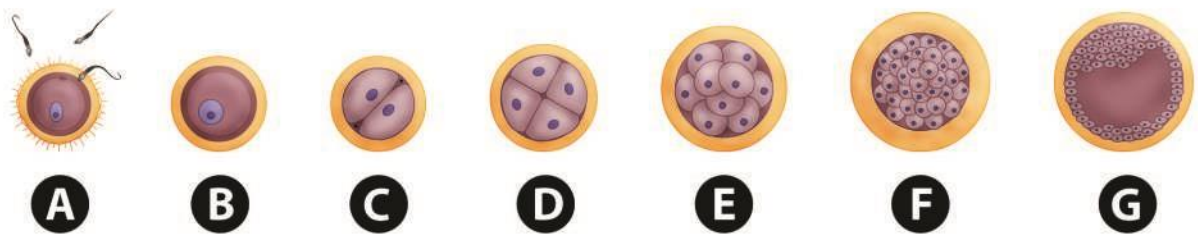
4. Following implantation of the embryo what contributes to the maintenance of the
uterine mucosa for the first 3 months of the pregnancy?

Please refer to your labelling supplement handbook and label any images associated with the above chapter.

Label the diagram below:



Label each of the stages following fertilisation:



BILAMINAR GERM DISC

Objectives

1. To understand the major events occurring in the 2nd week of development.

2. To know the names and structure of bilaminar germ disc.

THE BILAMINAR GERM DISC (2nd Week)

Eighth day of development

The blastocyst formation occurs when fluid secreted within the morula forms the blastocyst cavity. The **inner cell mass** which will eventually form the future embryo and foetus is called the **embryoblast.** The outer layer of the blastocyst, which will become the embryonic part of the placenta, is called the **trophoblast**.

At the 8th day of development the blastocyst is partially embedded in the endometrial stroma. In the area over the embryoblast, the trophoblast has differentiated into two layers

a) the cytotrophoblast (an inner layer)
b) the syncytiotrophoblast or syncytium (an outer layer)

The trophoblast cells divide in the cytotrophoblast and then migrate into the syncytiotrophoblast where they fuse and lose their individual cell membranes. **The cells of each of the germ layers form a flat disc and together they are known as the bilaminar germ disc.** At the same time a cavity appears and enlarges to become the amniotic cavity.

Ninth day of development

The blastocyst becomes more deeply embedded in the endometrium. The trophoblast shows considerable progress in development, particularly at the embryonic pole where vacuoles appear in the syncytium which fuse to form a cavity later to become the exocoelomic cavity or primitive yolk sac.

ABNORMAL IMPLANTATION SITES

In humans the blastocyst usually implants along the posterior or anterior wall of the uterus. Occasionally the blastocyst implants close to the internal os (where the uterus narrows and becomes the birth canal). At later stages of the development the placenta overbridges the os (known as Placenta Previa), and causes severe bleeding in the second part of the pregnancy and during delivery.

Sometimes implantation sites are found outside the uterus, resulting in extra-uterine or ectopic pregnancy. This may occur at any place in the abdominal cavity, ovary, or uterine tube. Ectopic pregnancy usually leads to death of the embryo and severe haemorrhaging by the mother during the second month of the pregnancy. In the abdominal cavity the blastocyst most frequently attaches itself to the peritoneal lining of the recto-uterine cavity (Douglas' pouch). The blastocyst also may attach itself to the peritoneal covering of the intestinal tract or to the omentum.

Very rarely the blastocyst develops in the ovary proper causing primary ovarian pregnancy but more commonly ectopic pregnancies involve the embryo being lodged **in the uterine tube**. If this is not addressed the tube will rupture at about the second month of the pregnancy resulting in severe internal haemorrhaging by the mother

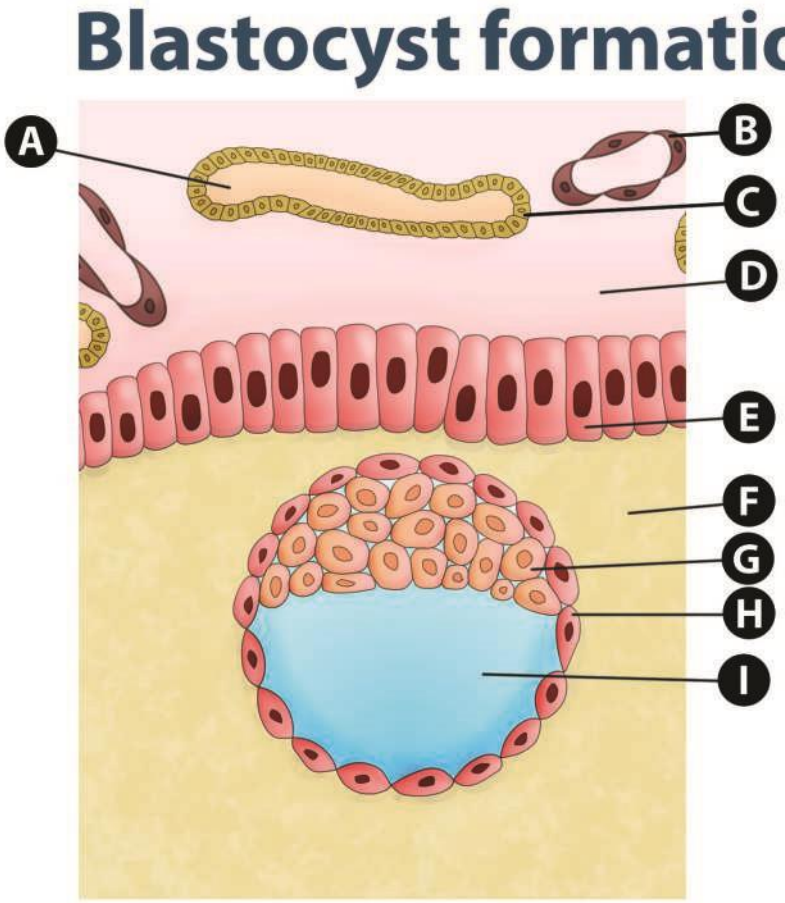
SELF ASSESSMENT QUESTIONS

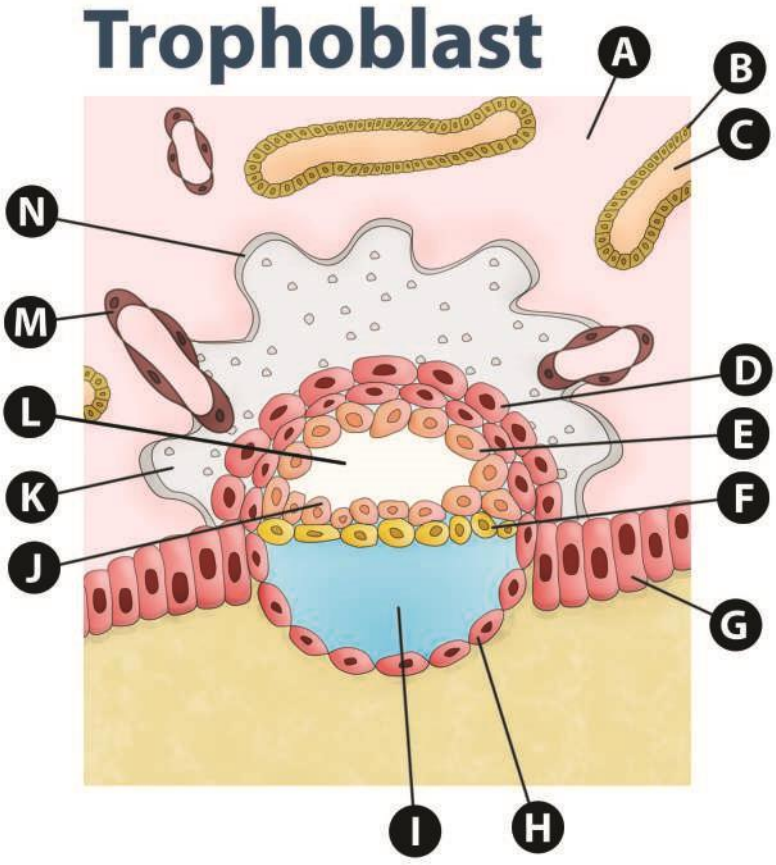
1. Name the two fluid-filled cavities found in the blastocyst by the 9th day of the embryonic development and state their principal function.

2. How is the embryoblast structured by the 9th day, ie how in many layers has the germ disc differentiated.

Please refer to your labelling supplement handbook and label any images associated with the above chapter.

Identify each of the structures below:





The Trilaminar Germ Disc

Objectives

1. Understand the changes that take place in the embryoblast which lead to the evolution of the trilaminar germ disk

2. Know the names of the three layers of the embryoblast and be able to list the main organ systems derived from each.

3. Have a basic knowledge of the process of invagination.

4. Understand basic structure and function of the trophoblast

Gastrulation: Formation of Embryonic Mesoderm and Endoderm

The most characteristic event occurring during the third week is gastrulation. This is the process that establishes all three germ layers in the embryo. Gastrulation begins with the formation of the primitive streak on the surface of the epiblast which looks like a narrow groove with slight bulging regions on either side. The cephalic end of the streak, known as the primitive node, consists of a slightly elevated area surrounding the small primitive pit.

In the transverse section through the region of the primitive groove new cells develop between the epiblast and the hypoblast. Cells of the epiblast migrate in the direction of the primitive streak to form the mesoderm and the intra-embryonic endoderm. As they arrive at the region of the primitive streak they detach to from the epiblast and slip underneath it. This inward movement is known as invagination. Once the cells have invaginated some displace the hypoblast, thereby creating the embryonic endoderm, while some come to lie between the epiblast and the newly created endoderm to form the mesoderm. Cells remaining in the epiblast then form the ectoderm. Thus, **the epiblast, through the processes of gastrulation, is the source of all three germ layers in the embryo.**

Formation of the notochord

The cells invaginating in the primitive pit move straight forward in the cephalic direction until they reach the prechordal plate. In this manner they form a tube-like process known at the notochordal or head process. The small central canal is considered as the forward extension of the primitive pit. This structure in turn becomes detached from the endoderm, which once again forms an uninterrupted layer in the roof of the yolk sac. The notochord now forms a midline axis, which will serve as the basis of the axial skeleton.

Further Growth of Germ Disc

The embryonic disc, initially flat and almost round gradually becomes elongated with a broad cephalic and a narrow caudal end. Expansion of the embryonic disc occurs mainly in the cephalic region.

Further Development of Trophoblast

The trophoblast in the meantime has rapidly progressed. The primary villus has obtained a mesenchyme core in which subsequently small capillaries arise. When these villus capillaries make contact with capillaries in the chorionic plate and connecting stalk, the villus system is ready to supply the embryo with its nutrients and oxygen.

Embryonic period (Weeks 3-8)

The embryonic period extends from the 3rd to the 8th week of development and is the period during which each of the three germ layers gives rise to its own tissue and organ systems. As a result of the organ formation the major features of the body form are established. As a result by the 2nd month the embryo begins to acquire distinguishable features.

Derivatives of the Ectodermal Germ Layer

The **ectodermal** germ layer gives rise to those organs and structures that maintain contact with the outside world:

a. The central nervous system
b. The peripheral nervous system
c. Sensory epithelium of ear, eye, and nose
d. Skin, hairs and nails
e. Pituitary, mammary and sweat glands

The spinal cord is formed along the neural groove which lies on top of the ectodermal layer between caudal and cephalic regions.

Derivatives of the Mesodermal Germ Layer

Components of the mesodermal germ layer are the paraxial, intermediate, and lateral plate mesoderm. Regularly organised segments called somites will give rise to the myotome (or muscle tissue), sclerotome (cartilage and bone), and dermatome (subcutaneous tissue of the skin). These tissues form supportive structures of the body. Other structures formed from mesoderm

are: the vascular system, the urogenital system, spleen and suprarenal glands.

Derivatives of the Endodermal Germ Layer

The endodermal germ layer forms the epithelial lining of the gastrointestinal tract, respiratory tract, and urinary bladder. It also contributes towards the thyroid, parathyroids, liver and pancreas by providing parenchyma tissue (functional part)

External appearance during the second month

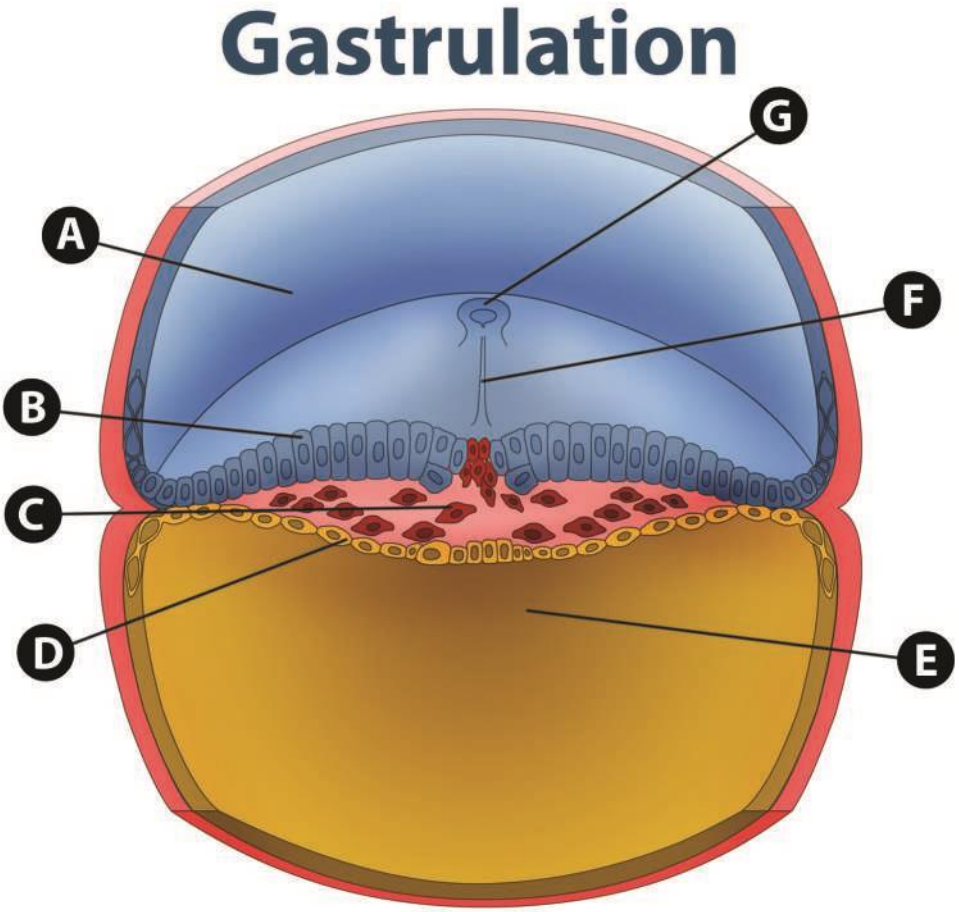
As a result of the formation of the major organ systems, the rapid growth of the central nervous system, the initial flat embryonic disc begins to fold in the cephalo-caudal direction, therefore establishing the head and tail folds. The rounded body form is also achieved by the disc folding in a transverse direction.

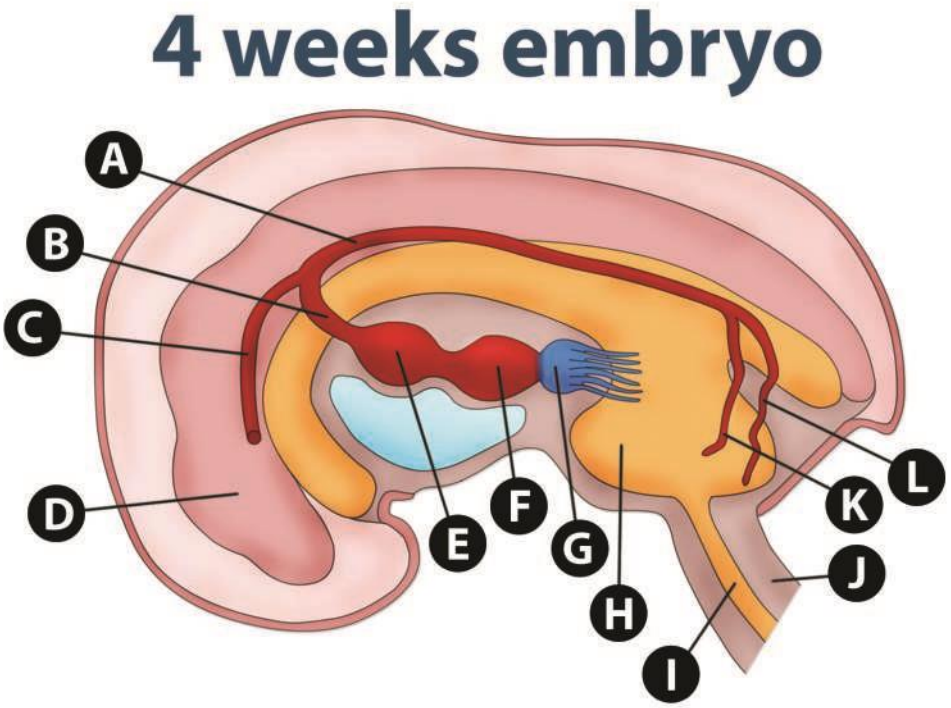
SELF ASSESSMENT QUESTIONS

1. How is the bilaminar germ disk transformed into the trilaminar germ disk?
2. Draw a longitudinal aspect of the trilaminar germ disc showing the relationship of the three layers to the amniotic and yolk cavities.
3. What do you understand by the terms: Notochord and primitive streak and what do these structures contribute towards?
4. What is the function of the trophoblast?
5. List the major organ systems derives from the ectoderm, mesoderm and endoderm.

Please refer to your labelling supplement handbook and label any images associated with the above chapter.

Identify each of the structures below:





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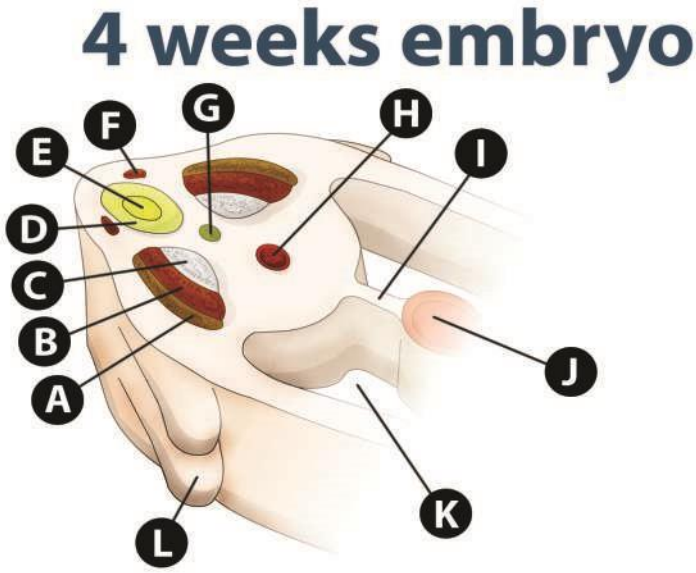

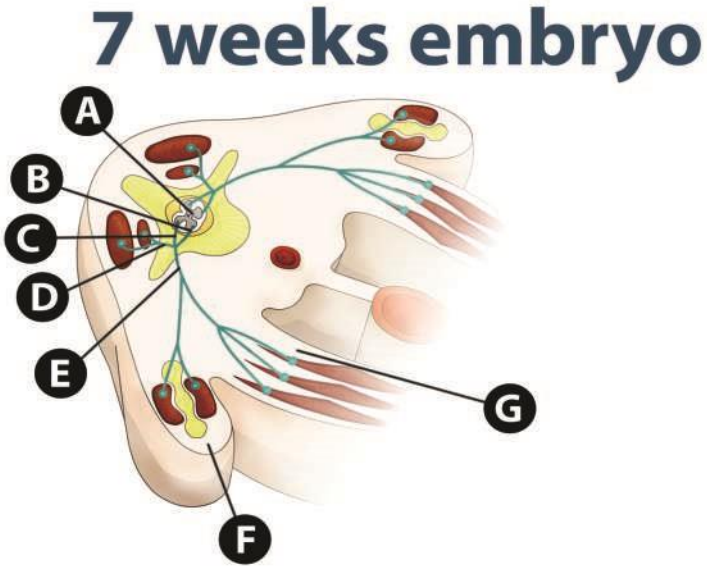

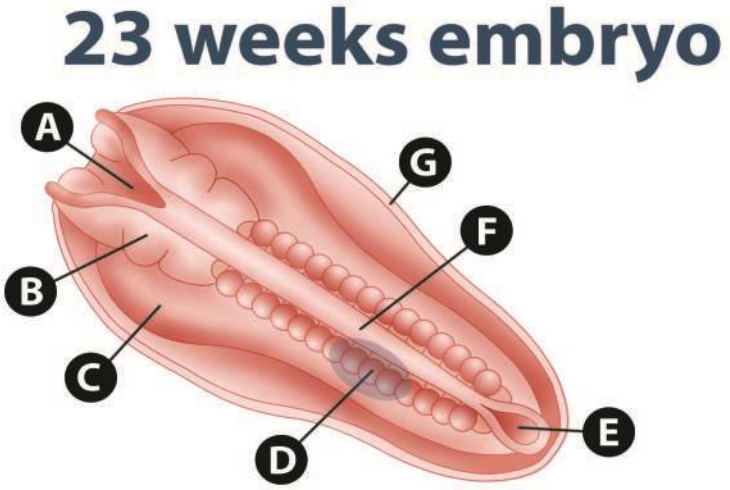

The Foetal Period

OBJECTIVES

a) Have a basic knowledge of the main developmental stages of the foetus.

b) Understand the modern diagnostics techniques used in identifying congenital and genetic anomalies.

c) Understand the variations of the menstrual cycle and ovulation.

d) Know how the delivery date is calculated.

Outline Of The Development Of The Foetus

The foetal period extends from the ninth week until birth and is characterised by a rapid growth of the body and maturation of the organ systems. Growth is particularly striking during the 3rd, 4th and 5th months - when the foetus grows approximately by 5cm per month. Increase in weight is most evident during the last two months of gestation - approximately by700 gms per month.

A significant change is the relative slow down in the growth of the head. In the 3rd month it is about ½ of the crown-to-rump length. By the 5th month the size of the head is about 1/3 of the crown-to-rump and at birth ¼ of the crown-to-heel length. During the 5th month, foetal movements are clearly recognised by the mother and the foetus is covered with fine, small hairs. A foetus born during the 6th or 7th month has difficulties surviving, mainly because the respiratory and central nervous systems have not differentiated sufficiently.

In general, the length of pregnancy for a full-term foetus is considered to be 280 days or 40 weeks after onset of the last menstruation or more accurately, 266 days or 38 weeks after fertilisation.

Prenatal Diagnostic Techniques

A variety of parental screening techniques are available, including ultra-sonography, amniocentesis, and chorionic villus biopsy. These procedures are used for determining placental and foetal growth, congenital malformations, and chromosomal abnormalities. They are not normally routinely performed but are reserved for those considered to be at high risk as such procedures may be dangerous for the foetus or mother.

Calculation Of Delivery Date

In women with regular 28 day menstrual cycles the method is rather accurate but when the cycles are irregular significant miscalculations may be made. Please bear in mind that the time between ovulation and the succeeding menstrual bleeding is constant, that is 14 days (+/- 1 day), but the time between ovulation and the preceding menses is highly variable from month to month and from person to person. A further complicating factor occurs when the woman has a short bleeding about 14 days after fertilisation as a result of the erosive activity of the implanting trophoblast. Due to the above factors it is not always possible to determine the exact delivery date but usually it will fall within 10 to 14 days of calculation.

SELF ASSESSMENT QUESTIONS

1. Describe the main features of a nine week foetus and compare these with a fully mature one.

2. List the main diagnostic techniques and state the purposes these may be used for.

3. How many days after ovulation is menstrual bleeding observed.

4. List possible methods of identifying the time of ovulation

Please refer to your labelling supplement handbook and label any images associated with the above chapter.

The Placenta, the umbilical cord and foetal circulation and teratogens

The Structure of Foetal Membranes and Placenta

The placenta consists of 2 components:

a) Foetal portion which is derived from the chorion frondosum or villus chorion. (previous cytotrophoblast and syncytiotrophoblast)

b) Maternal portion derived from the decidua basalis (a portion of the endometrium)

The space between the chorionic and decidual plates (between the foetal and maternal portions) is filled with intervillus lakes of maternal blood. The villus trees (foetal tissue) grow into the maternal blood lakes and are bathed in them. The foetal circulation is at all times separated from the maternal circulation by:

a) a syncytial membrane (a chorion derivative)
b) the endothelial cell of the foetal capillaries

The intervillus lakes of the fully grown placenta contain approximately 150 ml of maternal blood which is renewed 3 or 4 times per minute. The villus area varies from 1 - 14 m^2, thus facilitating exchange between the mother and child.

The function of the placenta

Main functions of the placenta are:

a) exchange of gasses
b) exchange of nutrients and electrolytes
c) transmission of maternal antibodies providing the foetus with passive immunity
d) production of hormones such as progesterone, estradiol, oestrogen and chorionic gonadotropin
e) detoxification of some drugs

The amniotic fluid

The amniotic fluid is produced by dialysis of maternal and foetal blood through blood vessels in the placenta and by excretion of foetal urine into the amniotic sac.

After being swallowed by the foetus, the amniotic fluid is absorbed into the foetal bloodstream. Excess amniotic fluid is removed by the placenta and passed into the maternal circulation.

The amnion provides a large sac with amniotic fluid in which the foetus is suspended by its umbilical cord. The function of the fluid is therefore to:

a) absorb jolts
b) allow for foetal movements
c) prevents adherence of the embryo to surrounding tissues

The umbilical cord

The umbilical cord contains

a) 2 umbilical arteries (right and left UAs)
b) 1 umbilical vein
c) Wharton's jelly (a protective cushion of mucous connective tissue for the umbilical vessels)

Angiogenesis and Haematopoiesis

Parts of the mesoderm differentiates into angioblasts, which form angiogenic cell clusters.

Angiogenesis: Angioblasts around the periphery of the angiogenic cell clusters give rise to the endothelium of the blood vessels. Angiogenesis occurs initially in the extraembryonic visceral mesoderm (located around the yolk sac), and later in the mesoderm of the foetus.

Haemopoiesis: Angioblasts within the centre of the angiogenic cell clusters give rise to blood cells. Haematopoiesis occurs initially in the extraembryonic visceral mesoderm (located around the yolk sac) and later in the foetal liver, spleen, thymus and bone marrow.

Foetal Circulation

The foetal circulation involves three shunts:

- The ductus venosus
- Ductus arteriosus
- Foramen ovale.

When the placental circulation is fully established the foetal circulation takes the following route:

Umbilical vein supplies oxygenated blood to the foetus ➔ into the foetal abdomen ➔ bypasses the liver through the ductus venosus and joins ➔ the inferior vena cava ➔ into the right atrium, through the ➔ foramen ovale into ➔ left atrium and ventricle, and from the right atrium ➔ into pulmonary artery, bypasses pulmonary circulation by connecting into the arch of the aorta via the ductus arteriosus. Blood that has gone into the left chambers of the heart is propelled ➔ into aorta and foetal circulation. Deoxygenated blood return back to the placenta ➔ via the descending aorta ➔ into Umbilical arteries (near the bifurcation) ➔ into the foetal part of the placenta. ➔

A number of changes occur in the neonatal circulation when placental blood flow ceases (at the time of parturition), and lung respiration begins.

(it is recommended that you attempt to draw or trace the above circulatory route)

CLINICAL NOTES

Amniotic fluid anomalies

1. An increased amount of amniotic fluid is called **hydramnios** and is associated with encephaly and oesophageal atresia (imperforation).
2. A decreased amount of amniotic fluid is called **oligohyramnios** and is related to renal agenesis.

Twins

Foetal membranes in twins vary according
to their origin and time of formation.

Dizygotic Twins

70% of the twins are **dizygotic** or **fraternal** twins and they have 2 amnions, 2 chorions and 2 placentas. (the placentas may sometimes be fused).

Monozygotic Twins

The monozygotic twins usually have
2 amnions, 1 chorion and 1 placenta.

Conjoined Twins

In cases of conjoined (Siamese) twins in which the foetuses are not entirely split from each other there is 1 amnion, 1 chorion and 1 placenta.

Placenta Previa: Occurs when the placenta attaches to the lower part of the uterus and covers the interal os. Uterine blood vessels may rupture during the advanced stages of pregnancy, causing a potentially fatal haemorrhage in the mother and placing the foetus in jeopardy as a result of the compromised blood supply.

Erythroblastosis fetalis: (Haemolytic disease of the newborn) Occurs when foetal erythrocytes are Rh-positive but the maternal erythrocytes are Rh-negative. When the fetal erythrocytes cross the placental membrane and enter the maternal circulation, the mother's body forms anti-Rh antibodies that cross the placenta membrane and destroy the foetal erythrocytes.

Congenital Malformations

Many factors may interact with the differentiating and growing embryo. The result however is not necessarily a gross malformation. In some instances the teratogenic agent may be so toxic or may affect a vital organ system of the embryo or foetus so severely that death results. In other cases the environmental influence may be so mild that the embryo or foetus is able to survive but some of its organ systems are affected. This may result in partial or total growth retardation or other functional impairment, for example, mental retardation.

A variety of agents are known to produce congenital malformations in approximately 2-3% of all live-born infants. These agents include viruses such as rubella and cytomegalovirus; radiation; drugs, such as thalidomide (antinauseant, sleeping pill), aminopterin (antimetabolite), isotretinoin (Vit-A analogue); large doses of salicylates; anticonvulsants, antipsychotics and antianxiety compounds; social drugs such as PCP, LSD, cigarettes and alcohol; hormones such as diethylstilbestrol; maternal diabetes and chromosomal abnormalities such as trisomy 21 (Downs syndrome).

In the case of radiation and chemical factors, the malformations produced depend on the stage of gestation and organ differentiation during which the mother was exposed to the agent. In this respect most major malformations are produced during the embryonic period of development. Although a large number of birth defects have been described and attributed to specific factors little is known about how an agent actually produces a defect or how a defect may be prevented or reversed. Therefore the medical approach to this problem is postnatal repair or early detection (via amniocentesis, α-foetal protein, or ultrasound techniques) and subsequent termination of those embryos found to be severely malformed.

Look up teratogens associated with human malformations and construct a table below:

Teratogen name	**Describe associated congenital malformations**
……	……. …….
……	……. …….
……	……. …….
……	……. …….
……	……. …….
……	……. …….
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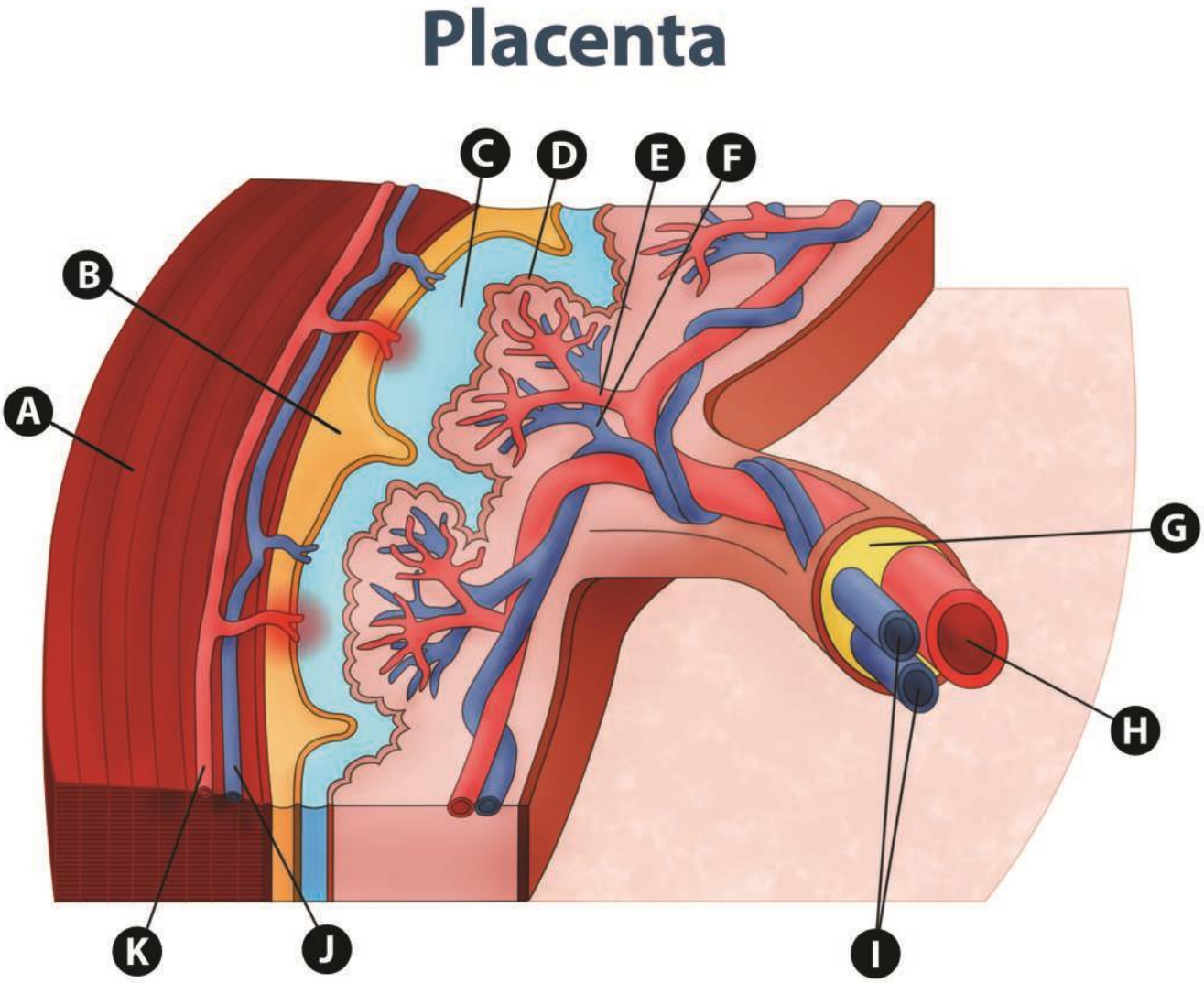
Identify each of the structures below:



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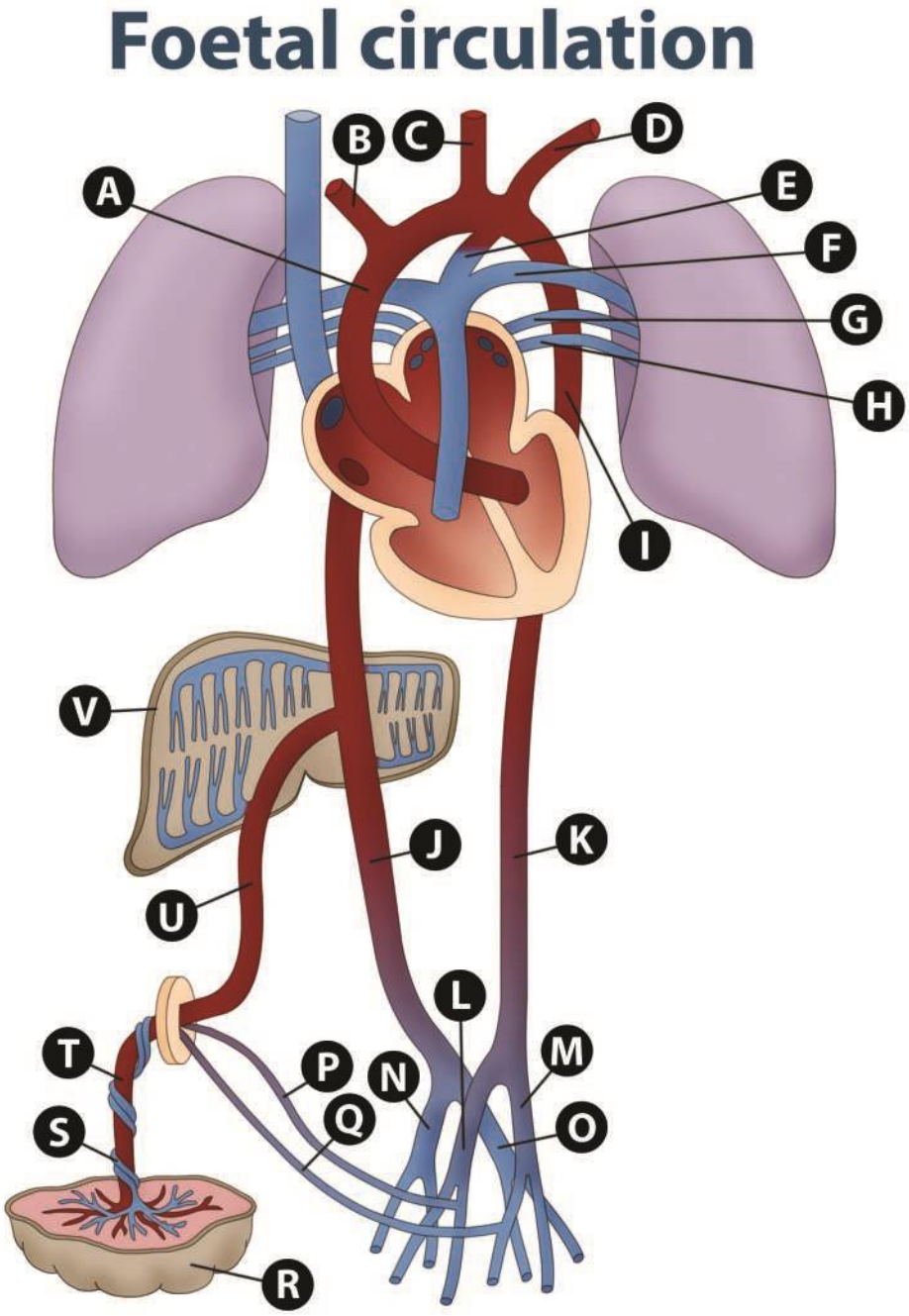


SELF ASSESSMENT QUESTIONS

1. Provide an outline of the structure of the placenta.

2. What are the main functions of the placenta

3. Describe the vascular structures which make up of the umbilical cord.

4. Briefly define the following terms:
   Dizygotic twins
   Monozygotic twins
   Conjoined twins

5. Draw an outline of foetal circulation starting from the placental part of umbilical vein and end back to the placenta with the umbilical arteries.

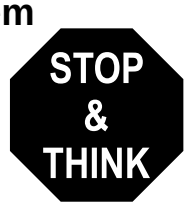
6. State the functions of: a) Ductus venosus, b) Ductus arteriosus, c) Foramen ovale.

7. List as many teratogenic agents as you can think

8. At what stage of the pregnancy is the developing embryo/foetus most susceptible to teratogens.

Please refer to your labelling supplement handbook and label any images associated with the above chapter.

The Development of Skeletal System & Muscular System



Objectives

A. To know the processes of Intramembraneous and Endochondral Ossification.

B. To know the structure and morphology of long bones

C. To have a basic understanding of the embryonic origins of muscular tissue

D. To be able to name and understand the different abnormalities arising from the development of the skeletal system

E. To be able to name and understand the different abnormalities arising from the development of the muscular tissue

Formation of the Skeletal System

The skeletal system develops from mesenchyme (non specialised embryonic connective tissue), which is derived from the mesodermal germ layer and from the neural crest.

There are two methods which lead to the formation of ossified bone:

a. Intramembraneous ossification
b. Endochondral ossification.

Intramembraneous Ossification

In contrast to endochondral ossification, intramembraneous ossification is a simpler and more direct method of bone formation. Osteoblasts are formed from osteoprogenitor cell clusters in a fibrous membrane. These clusters form the centre of subsequent ossification. The osteoblasts start to secrete intercellular substances composed of collagenous fibres that form a framework, (a matrix), in which calcium salts are deposited. The deposition of calcium salts is termed **ossification.** Subsequently, **traberculae** are formed when clusters of osteoblasts become completely surrounded by the calcified matrix. Adjacent traberculae are joined up to form the characteristic appearance of spongy or cancellous bone. The spaces between the traberculae are filled with red bone marrow.

The original connective tissue which surrounded the bone becomes the compact periosteal layer. The osteoblastic and osteoclastic processes do not stop after ossification, but bone continues to be destroyed and reformed, a process undertaken by osteoblasts and osteoblasts until the final adult size and shape is achieved.

Endochondral Ossification.

This type of ossification is particularly observed in the long bones but also in the skull. In the early part of embryonic development, a cartilage model or template of the future bone is laid down by chondroblast, cells from mesenchyme. The cartilaginous model is covered by a membrane called the perichondrium. Initially a solitary vessel penetrates the perichondrium and therefore stimulating the osteoprogenitor cells to enlarge and become osteoblasts. The periosteal layer around the middle of the shaft (**diaphysis)** becomes ossified. The vessel also continues to penetrate the centre of the shaft triggering similar osteogenic processes where it now establishes the **primary ossification centre**. Similarly vessels now start to penetrate the ends of the diaphysis forming **secondary ossification centres.** A special region of cartilage remains between the diaphysis and the epiphysis called the **epiphyseal plate**.

The epiphyseal plates remain the only regions where longitudinal growth takes place until the bone reaches its full length. Cartilage is also laid over the end of the bones where it will form articulations with other bones.
The vertebral column and ribs are developed from the sclerotome compartments of the somites. A definitive vertebra is built up by condensation of the caudal half of one sclerotome and fusion with the cranial half of the subjacent sclerotome.

The skull has a complicated origin since it consists of the neuro-cranium and viscero-cranium each with its own membraneous and cartilaginous components.

The muscular system

Muscles are derived from mesoderm. Skeletal muscles are derived from paraxial mesoderm:

a) **Somites:** Give rise to muscles of the axial skeleton, body wall and limbs
b) **Somitomeres:** Give rise to the muscles of the head

Connective tissue derived from somites, somatic mesoderm, and neural crest provide for the establishment of muscle patterns.

Most smooth muscles as well as cardiac muscle fibres are derived from splanchnic mesoderm. This is mesoderm which is located towards the visceral cavity and endodermal aspects of the embryo.

CLINICAL NOTES

Many abnormalities of the skeletal system occur. These include vertebral spina bifida, skull and facial defects (cranial schisis and cranialstenosis, cleft palate). Major malformations of the limbs are rare but occur in high frequency in those mothers who have taken the anti-nauseant and sedative, thalidomide.

Spina bifida

There are several forms of spina bifida but principally it involves defects in the closure of the spinal theca. In its simpler form is seen as failure of the dorsal portions of the vertebrae to fuse with one another.

Most commonly are in the sacro-lumbar region where there may be partial or complete failure of the laminae to fuse. It is often identified by the external appearance of a tuft of hair over the affected area. This is called **spina bifida occulta.**

If more than one vertebral segments are affected, the meninges of the spinal cord may bulge under the surface of the skin. This is called a meningocele.

If the defect is large then part of the spinal cord may also bulge through and in this instance it is named **meningomyelocele.** This is a more serious defect and it will be accompanied by neurological symptoms.

In a rarer form of spina bifida results from failure of the neural groove to close, and the nervous tissue is then widely exposed to the surface.

Myelomeningoceles are usually associated with a caudal displacement of the medulla oblongata and of part of the cerebellum into the spinal canal. As the spinal canal is narrower and cannot accommodate the above structures it causes disturbances in the circulation of CSF. This leads to the development of **hydrocephaly.**

Cranial schisis (tear)

Abnormalities in the formation of the cranial vault vary from large defects that may be accompanied by anencephaly to small circumscribed defects.

Craniosynostosis (Craniostenosis)

These cranial abnormalities result from premature closure of one or more sutures.

Polydactyly

This is the presence of extra fingers or toes. This is usually bilateral.

Syndactyly

This is abnormal fusion of fingers or toes.

Lobster Claw

Characterised by an abnormal cleft between the 2nd and 4th metacarpals, the 3rd may be absent whist the remainder may be fused.

Club foot

The sole of the foot is turned inwards (inverted) and the foot is adducted and plantar flexed. Usually seen in the males and in some it may be hereditary.

Amelia, Meromelia, Micromelia

The absence or near absence of a limb to develop is known as **amelia**. Gross defects in the development of a limb is known as **meramelia,** and if the limb is present but abnormally small then it is referred to as **micromelia.**

Vertebral Column: Extra segments, Missing segments, Fusion.

It in not unusual to come across x-rays of spinal column and notice an extra segment especially in the lumbar and less frequently in the cervical regions. Conversely, a lumbar segment may be missing or the 5th vertebra may be fused onto the sacrum **(sacralisation).** The 1st sacral segment may be detached from the sacrum and may form a partial or full articulation with the rest of the lumbar spine. These abnormalities in some may be completely asymptomatic whilst in others may cause discomfort or mild disabilities.

Achondroplasia

An inherited disorder which affects the development skeletal growth. It is caused by a disturbance in endochondral ossification in the epiphyseal plates of the long bones. The extremities are short whilst the skull is almost unaffected. The individual's mental development is unaffected.

Acromegaly

This condition is caused by congenital hyperpituitarism and is characterised by disproportional development of the face, hands, and feet. In some cases where there is an overall rapid growth it results in **gigantism**.

Cervical rib

An overdeveloped costal process of the 7th cervical vertebra, may be unilateral or bilateral and it may vary in size from a small bony protrusion, often with a fibrous extension, to a complete supernumerary rib. It often exists without causing symptoms, especially in the young, but later on in life the tendency to gradual dropping of the shoulder girdle may lead to its causing neurological or vascular disturbance in the upper limb.

Muscle abnormalities

Absence or partial development of muscles is rather rare. The most commonly involved muscles are Pectoralis Major, Palmaris Longus, Serratus Anterior and Quadratus Femoris. Deviation of the head to one side may be caused by **Congenital Torticollis** a disorder of the Sternocleidomastoid muscle.

SELF ASSESSMENT QUESTIONS

1. Name the methods by which ossified bone is formed

2. Briefly describe the above processes

3. Name examples for the above processes

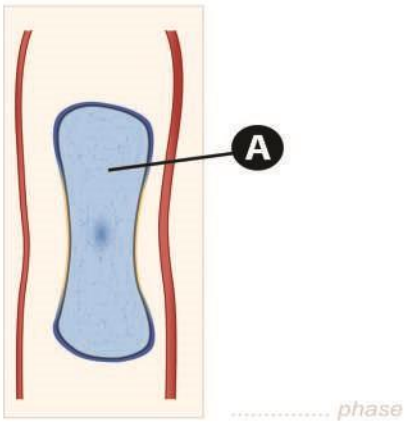
4. From which embryonic layer is muscular tissue derived

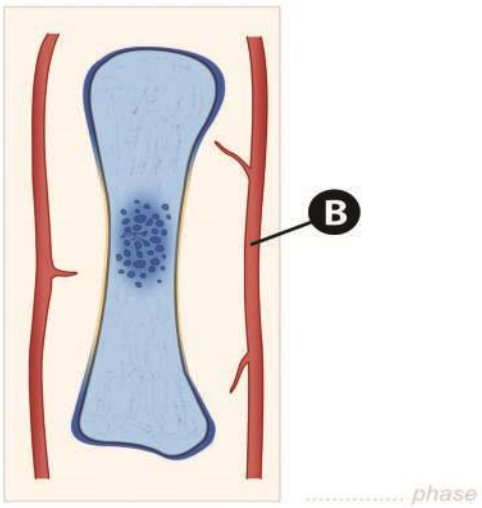
5. What is spina bifida occulta

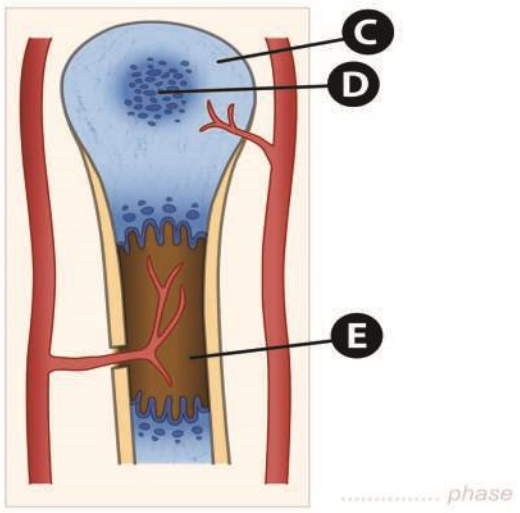
6. Briefly explain the following congenital abnormalities: Achondroplasia, Acromegaly, cervical rib, Congenital Torticollis.

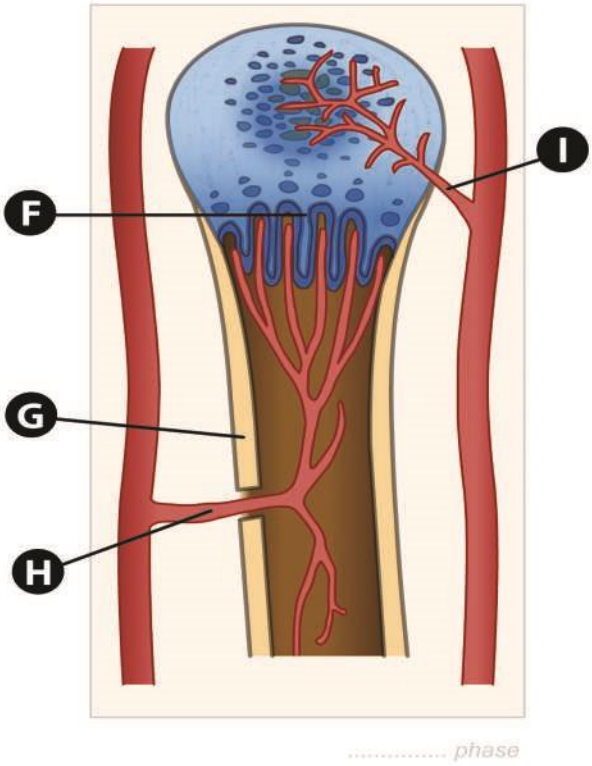
Please refer to your labelling supplement handbook and label any images associated with the above chapter.

Identify each of the structures below:



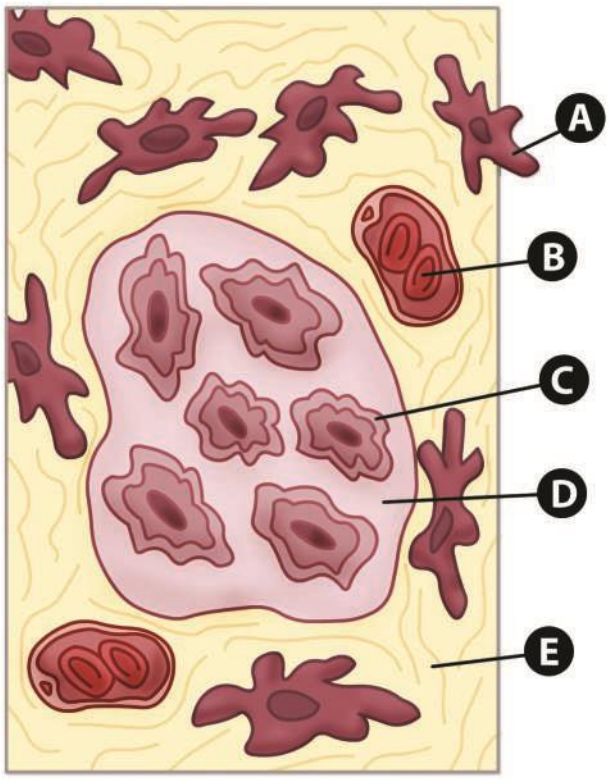


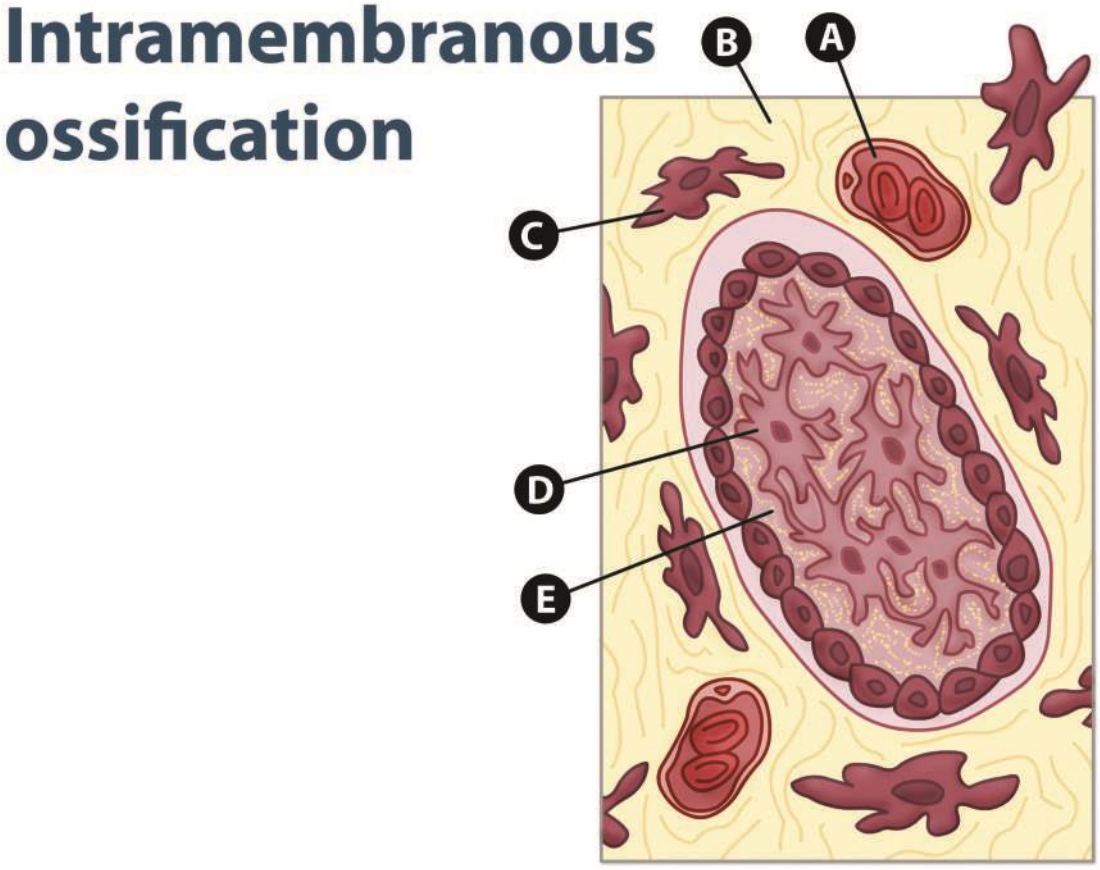




Endochondral ossification

Identify each of the structures below:





The formation of the Head and Neck

OBJECTIVES

A. To understand the principles behind pharyngeal or branchial arches.

B. To know the nerve supply of the different structures formed by the pharyngeal arches.

C. To understand the developmental anomalies that lead cleft palate and cleft lip and how these affect the neonate.

Early Embryonic Developments of the Head and Neck

The **pharyngeal (branchial)** arches consisting of bars or blocks of mesenchymal tissue and separated from each other by **pharyngeal pouches** and **clefts**, initially give the head and neck their typical appearances. Postnatally, the appearance of the teeth and paranasal sinuses provides the face with its own personal characteristics.

Each arch contains its own artery, nerve supply, muscle element, and cartilage bar or skeletal element.

The endoderm of the pharyngeal pouches gives rise to a number of endocrine glands and part of the middle ear.

In subsequent order the **pharyngeal pouches** give rise to:

a) **Middle ear cavity and auditory tube**
b) **The stroma of the palatine nostril**
c) **The parathyroid glands**
d) **The thymus**
e) **The ultimobranchial bodies**

The **pharyngeal clefts** give rise to only one structure:

a) **The external auditory meatus**

The thyroid gland originates from an epithelial proliferation in the floor of the tongue and descends to its level in front of tracheal rings in the course of development.

Pharyngeal Apparatus

The pharyngeal apparatus consists of:

a) **The pharyngeal arches**
b) **The pharyngeal pouches**
c) **The pharyngeal grooves**
d) **The pharyngeal membranes**

The **pharyngeal arches** (1,2,3,4,6) are comprised of mesoderm and neural crest cells. Each arch has a cranial nerve associated with it. The 5th pharyngeal arch degenerates in the human. (See diagram)

B. The **pharyngeal pouches** (1,2,3,4) are invaginations of the endoderm-lined foregut. (See table)

C. The **pharyngeal grooves** (1,2,3,4) are invaginations of surface ectoderm:

i. Pharyngeal groove 1 gives rise to the epithelial lining of the external auditory meatus.
ii. All other grooves are obliterated.

D. The **pharyngeal membranes** (1,2,3,4) are located at the junction of each pharyngeal groove and pouch:

i. Pharyngeal membrane 1 gives rise to the **tympanic** membrane
ii. All other membranes are obliterated.

The Thyroid Gland

The thyroid gland develops from the thyroid diverticulum, which forms in the floor of the foregut. The thyroid diverticulum migrates caudally to its adult anatomical position but remains connected to the foregut via the thyroglossal duct, which is later obliterated. The former sight of the thyroglossal duct is later indicated in the adult by the foramen cecum.

The Tongue

A. The anterior two thirds of the tongue forms from the median tongue bud and two distal tongue buds associated with pharyngeal arch-1:

i. General sensation is carried by the lingual branch of CN V (trigeminal).
ii. Taste sensation is carried by the chorda tympani branch of CN VII (facial)

B. The posterior one third of the tongue is associated with pharyngeal arches 3 and 4. General sensation and taste are carried by CN IX (glossopharyngeal).
C. The intrinsic muscles and the styleglossus, hyoglossus, and geniolglossus (intrinsic) muscles are derived from myoblasts that migrate to the tongue region from occipital somites. Motor innervation is supplied by CN XII (hypoglossal), except for that of the palatoglossus muscle, which is innervated by CN X (vagus).

The Palate

A. The intermaxillary segment forms when the two medial nasal prominences fuse together at the midline. The intermaxillary segment gives rise to the philtrum of the lip, for incisor teeth, and primary palate of the adult.

B. The secondary palate forms from outgrowths of the maxillary prominences called palatine shelves. These palatine shelves fuse at the midline.

C. The definitive palate is formed following fusion of the primary and secondary palates at the incisive foramen.

Formation of the Sinuses and Teeth

The teeth develop from an ectodermal and mesodermal component. The enamel (white layer on the surface) is made by the ameloblast. It lies on a thick layer of dentine produced by the odontoblasts (derivatives of the neural crest). The cementum is formed by cementoblast, another mesenchymal derivative found in the root of the tooth. Although the first teeth (called deciduous or milk teeth) appear 6 to 24 months after birth, the definitive or permanent teeth, which appear postnatally are formed mainly during the third month of development.

CLINICAL NOTES

1. **Pharyngeal Fistula**

A pharyngeal fistula occurs when pouch 2 and groove 2 persist. The fistula is generally found along the anterior border of the sternocleidomastoid muscle.

2. **Pharyngeal Cyst**

A pharyngeal cyst occurs when pharyngeal grooves that are normally obliterated persist. The cyst is usually located at the angle of the mandible.

3. **Cleft Palate**

Cleft palate occurs when the palatine shelves fail to fuse with each other or with the primary palate. The incisive foramen is considered the dividing land mark between the anterior and posterior cleft deformities.

Those anterior to the incisive foramen include the lateral cleft lip, the cleft upper jaw, and the cleft between the primary and secondary palates. Such defects are due to partial or complete lack of fusion of the maxillary prominence with the medial nasal prominence on one or both sides. Those which lie posterior to the incisive foramen are caused by failure of the palatine shelves to fuse and may lead to cleft (secondary) palate and the cleft uvula.

4. **Cleft Lip**

Cleft lip occurs when the maxillary prominence fails to fuse with the medial nasal prominence. This is the third category which is formed by a combination of clefts lying anterior as well as posterior to the incisive foramen. The anterior clefts may vary in severity from barely visible defects to clefts extending into the nose. In more severe cases the cleft extends to a deeper level thereby forming a cleft of the upper jaw. The maxilla is then split between the lateral incisor and the canine tooth. Frequently such a cleft extends to the incisive foramen. Similarly the posterior clefts may vary in severity from clefts involving the entire secondary palate to clefts of the uvula only.

Other variations of clefts are:

- Oblique facial cleft (extending from medial eye to the medial lip)
- Bilateral cleft lip (from the nasal swelling to the lip)
- Median cleft lip (nasal septum to the lip).

Cleft palate and cleft lip are distinct malformations, although they often occur together.

SELF ASSESSMENT QUESTIONS

1. What do you understand by the term; ‘the pharyngeal apparatus’
2. Where is the initial location of thyroid gland and where does it come to be situated in the neonate.
3. Name the nerve supply to the tongue in terms of :
    a. Taste sensation
    b. General sensation
    c. Motor supply

4. Briefly describe the formation of the palate
5. At what stage do the deciduous teeth form and when are they replaced by the permanent teeth
6. Describe the developmental processes which lead to the formation of cleft lip and cleft palate.

Please refer to your labelling supplement handbook and label any images associated with the above chapter.