Rapid Review of Embryology

First Edition

Ahmed M. Ayesh

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"After going through the impressive project,

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it gives a good and excellent selection and analysis.

The final assessment gives us very impressive outcome for further studies".

Professor. **Fatma E. Farah**

Hepatologist

MRCB, FRCB,

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20 / 3 / 2017

Khartoum - Sudan

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Dedication

To

My mother, ***Omnia.***

My sister, brothers & family.

With love ,,,,,,

Preface

It is a great pleasure to present the first edition of *'Rapid Review of Embryology'* that provides a high-yield and simplified review of embryology. As conveying conceptions is believed to be much easier through illustrations, we endeavored to present the inclusive facts of the human development as concise and illustrative as possible. Sorting some information into tables and adding questions after each chapter will hopefully provide undergraduate medical students with quicker revision and recall.

Rapid Review of Embryology is designed into two main parts;

Part I : General embryology.

Part II : Special -systemic- embryology.

For his support and guidance, my special thanks are credited to;

Dr. Hosam Eldeen Elsadig Gasmalla, MBBS, M.Sc, Assistant Professor of anatomy, Faculty of Medicine, Alneelain University.

Teachers and medical mates, it would be my honour to receive your suggestions or comments and take them into consideration.

Finally, I hope the book would be as beneficial for students and other honorable readers as aimed.

Ahmed Mohamed Ayesh

" The one who sees things from the beginning will have the finest view of them "

Aristotle ¸384 – 322 B.C

Contents

Introduction

- **Embryology** is the science concerned with the normal development of the embryo in his intrauterine life and congenital disorders that occur before birth.

- **Clinical importance of embryology** (4Ps);

  i. Prevents **teratology** (birth defect).

  ii. Prenatal (before birth = prepartum) diagnosis and surgical treatment.

  iii. Procedures to reduce incidence of infertility.

  iv. Provides a basis for understanding pathology, gynecology, histology and anatomy.

- **Intrauterine life consists of 3 periods:**

  i. Germinal period (first 2 weeks).

  ii. Embryonic period includes: 3_{rd} week + organogenesis (4 – 8 weeks).

  iii. Fetal period (9_{th} week – birth).

> ***Note that:*** The term (embryo) is just used at the first 8 weeks, then replaced by (fetus).
>
> - **Conceptus** is a zygote, embryo or fetus and associated membranes.

- **Embryologic terminology;**

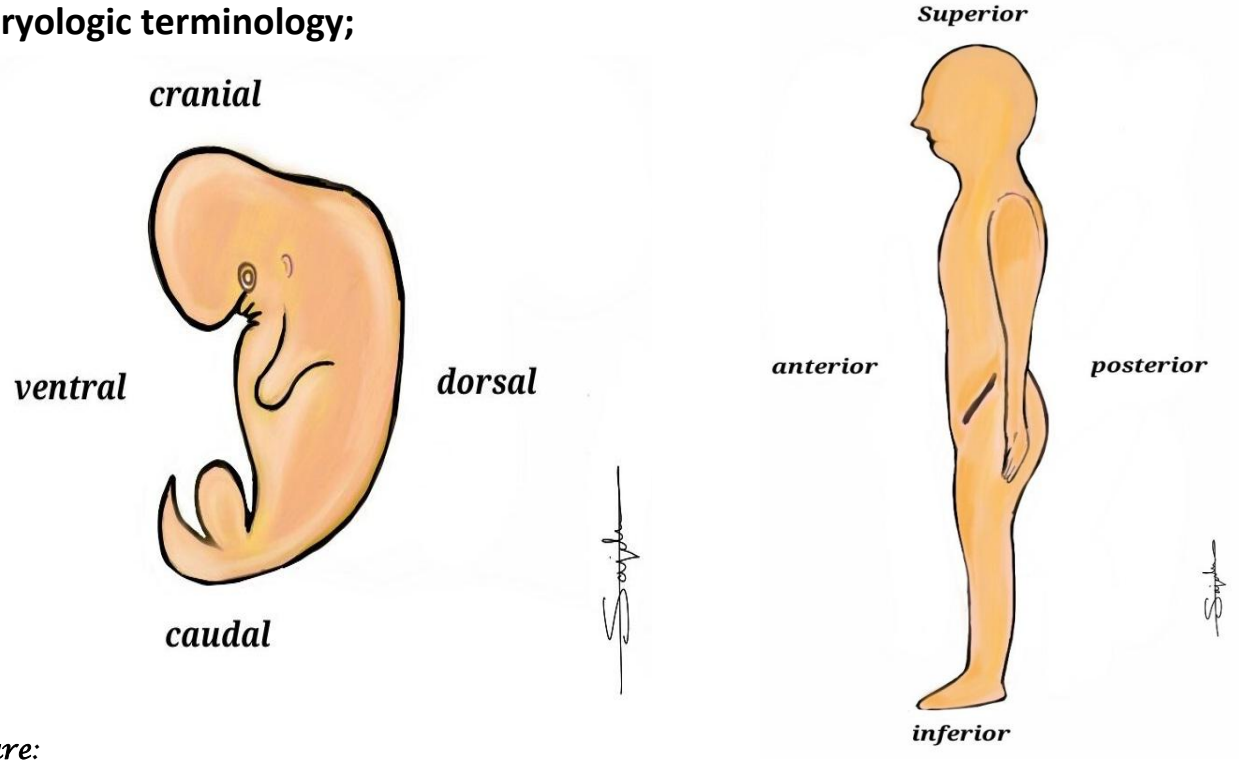


Figure:
Lateral view of an embryo & adult illustrating descriptive terms of directions & positions, respectively.

Part 1

General Embryology

>>>>>> Upon completing this part, you should be able to:

- Differentiate between the mitotic and meiotic divisions.
- List the process that occurs during the first week of development.
- Identify the structures which appear during the week of “twos”.
- Mention the structures formed at the week of gastrulation.
- Explain the mechanism of the embryonic folding and its results.
- Term the derivatives of the ectoderm, mesoderm and endoderm.
- Describe the formation of the fetal membranes and its roles\anomalies.
- Talk about the embryological basis of twins and its types.

Chapter 1 || Cell Division

☐ Cell division has two scenarios, either (i) mitotic or (ii) meiotic.

☐ There are two types of cells:

i. **Somatic** cell**:** Contains 23 **pairs** of chromosomes (**di**ploid number, **2**n).
ii. **Gamete** cell: Contains 23 chromosomes (haploid number, n). ***N:** No. of chromosomes.

MITOTIC DIVISION

☐ Parent cell divides into two identical daughter cells, each cell contains diploid number of chromosomes, occurs **only** in the somatic cells, as follows;

i. **Interphase:** DNA replication.

ii. **Prophase:** Each chromosome formed of two sisters/identical chromatids → shorten and thicken, joined at the centromere, spindle fibers appear, centrioles move to the opposite poles (in animal cells only).

iii. **Prometaphase** (end of prophase): Nucleolus and nuclear membrane disappear.

iv. **Metaphase:** Chromosomes line up on equatorial plane and become attached to spindle fibers by its centromere.

V. **Anaphase:** Chromatids split into two and move to opposite poles.

vi. **Telophase:** Spindle fibers disappear, nucleolus and nuclear membrane reappear and the **cytokinesis** (cytoplasm division) occurs.

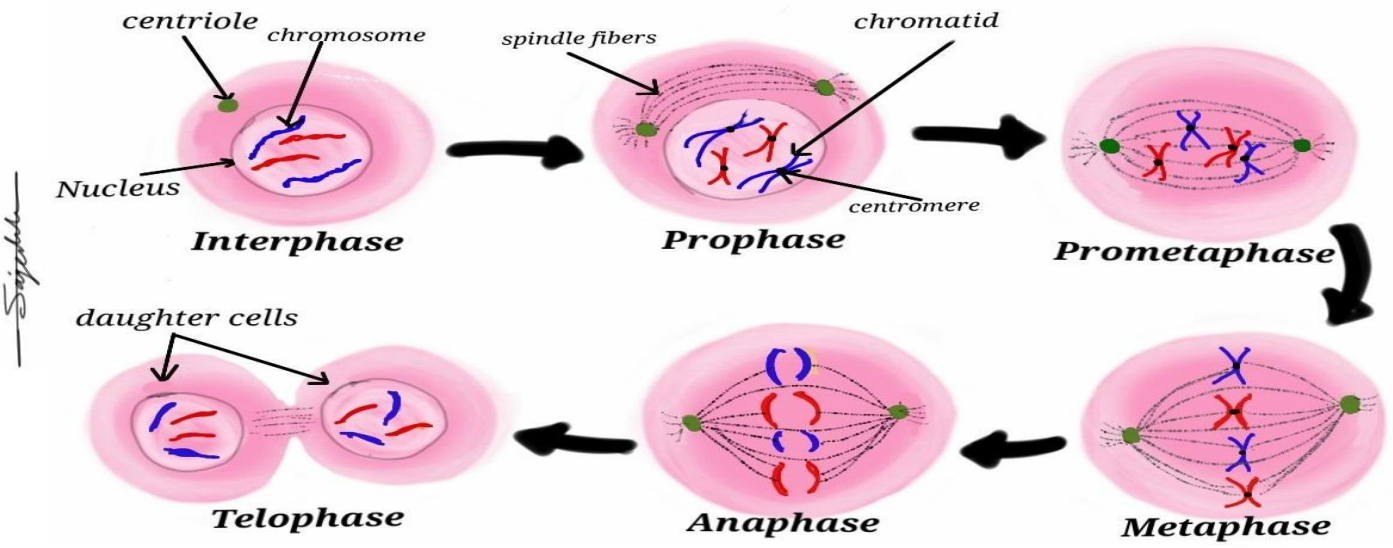


Fig. 1.1 Stages of mitotic division .

MEIOTIC DIVISION: Occurs only in gametes (eggs or sperm). It consists of meiosis **I** and meiosis **II** respectively, results in the production of 4 gametes, each one of them contains a haploid number of chromosomes (N).

☐ **Meiosis I:** DNA replication.

i. **prophase I**. **Synapsis** (Pairing of homologous chromosomes) and **crossing over** (interchange of Chromatids fragments) occurs → exchange in genetic material.

ii. **Metaphase I**. Homologous (same) pairs attached to spindle fibers, Chromosomes line up on the metaphase plate.

iii. **Anaphase I**. The homologous chromosomes are separated then move to the opposite poles as spindle fibers shorten.

iv. **Telophase I.** Nuclear membrane reforms, spindle fibers disappear → cytokinesis occurs.

☐ **Meiosis II:** Is similar to mitosis but remember that two haploid cells enter meiosis **II**. Chromosome splits into Chromatids. At the completion of meiotic division, each of the four daughter cells has specific chromosomes as by the crossing over.

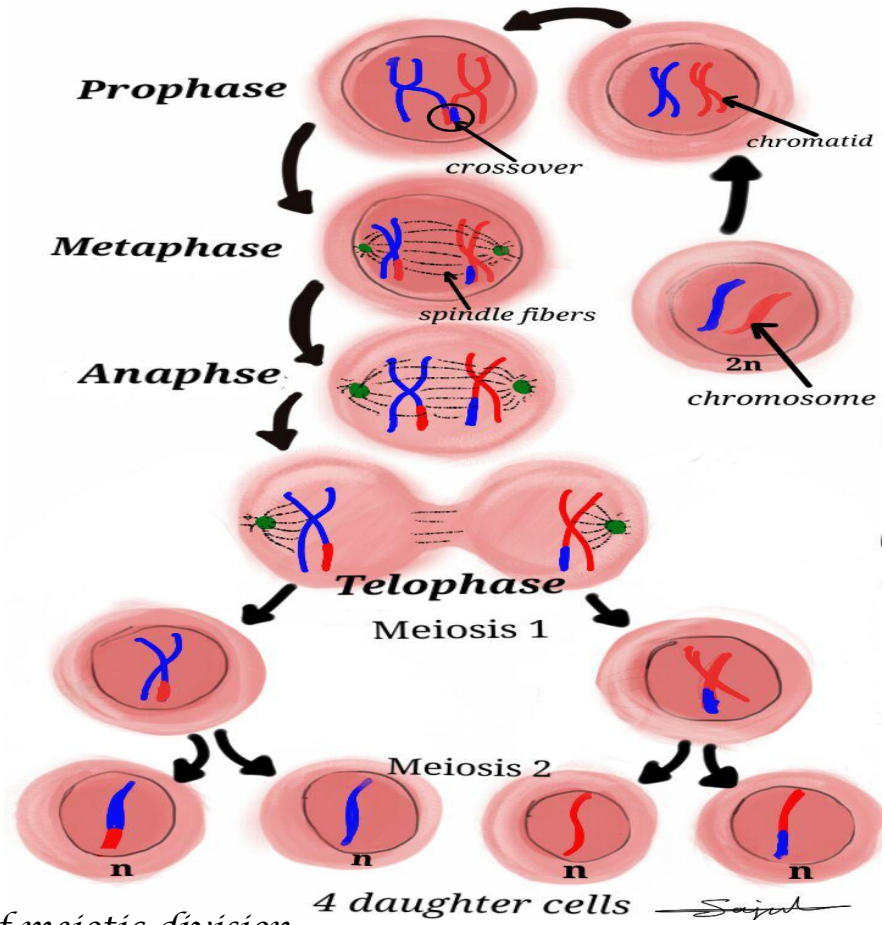


Fig. 1.2 Stages of meiotic division.

NOTES

- **Chromosomal abnormalities: (i)** numerical **(ii)** structural
- **Variation in chromosome number:**

I. Euploid number: cells with an exact multiple of (n).

Ex: diploid (2n), triploid (3n), etc.

II. Aneuploid number: cells with an odd number of chromosomes.

Ex: trisomy (2n+1), monosomy (2n-1), tetrasomic (2n+2), etc.

Down syndrome (trisomy21):

- A genetic disorder **caused by** the presence of an extra Chromosome 21.
- People with Down syndrome (Have 47chromosomes) **Characterized by;** growth retardation, flat face, small head and ears, short web neck, poor muscle tone, eyes slanting upward and cardiac defects.

Chapter 2 || Gametogenesis

☐ It is defined as the formation (=genesis) of male and female gametes from germ cells which occurs in the gonads (testis and ovary).

The Male Genitalia

I. **Testis:** Produces and secretes spermatozoa (exocrine function) and testosterone hormone into the blood (endocrine function), is covered by tunica albuginea, suspended in the scrotum by the spermatic cords.

ii. **Genital ducts:** Epididymis (storage and **full** maturation of spermatozoa) continues as the vas deferens (nutritive to spermatozoa by fructose) which joins the duct of the seminal vesicle to form ejaculatory duct which opens into the prostatic urethra.

iii. **Accessory glands:** Seminal vesicle, prostate and bulbourethral glands which secrete the semen (seminal fluid).

iv. **Penis:** Urination and sexual activity (passage for the semen).

N.B. Primordial germ cells (**PGCs**)

Are the precursor of gametes which are diploid cells, they originate from epiblast (*2nd* week) then, move through the primitive streak to the wall of the yolk sac (*4th* week) finally, they migrate towards the gonads region (6^{th} week) where PGCs differentiate into mother cells (spermatogonia & oogonia).

SPERMATOGENESIS: It begins at puberty till old age, takes approximately 74 days, occurs in the seminiferous tubules of the testis and includes two steps:

i. **Spermatocytogenesis:** Spermatogonia (2n) ⟶ spermatids (n).

ii. **Spermiogenesis:** Spermatids ⟶ (by morphological changes) mature sperms (immotile).

- ☐ Condensation of the nucleus of spermatid to form **sperm head**.
- ☐ Formation of **acrosome** (head cap) from Golgi apparatus.
- ☐ Elongation of the Centrioles to form an axial filament.
- ☐ The mitochondria form a spiral sheath around the body.
- ☐ Splitting of the cytoplasm.

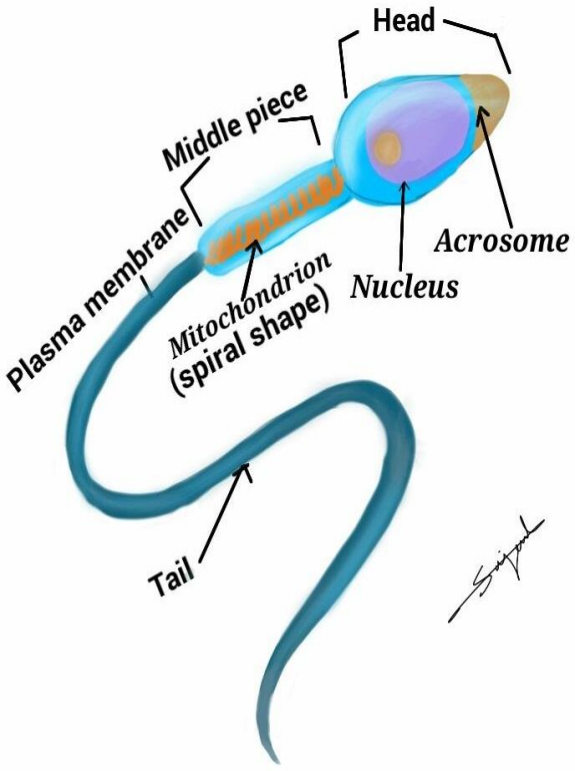


Fig. 2.1 Mature sperm.

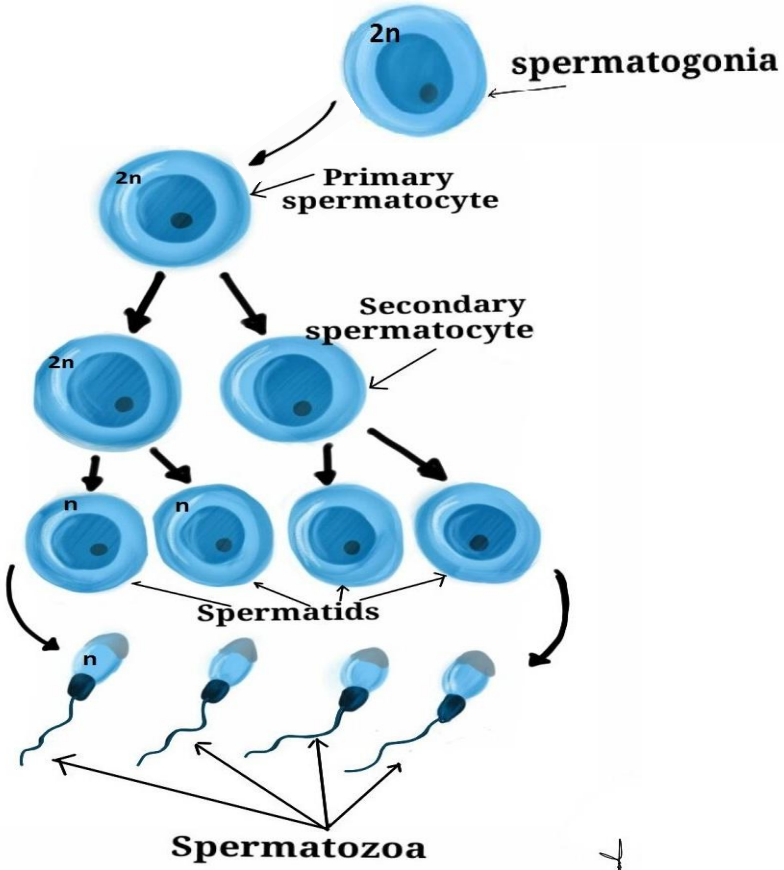


Fig. 2.2 Stages of spermatogenesis.

Histological correlation;

- The epididymis is lined by a thin layer of circular **smooth muscle** which is responsible for transporting the sperms from testicular seminiferous tubules to the vas deferens through the epididymis. Sperms acquire motility after leaving the epididymis.
- The seminiferous tubules are lined by **Sertoli cells** for support, protection, nutrition and regulation of spermatogenesis.

The Female Genitalia

i. **Ovaries:** Located in the lateral wall of the pelvis. Consist of a cortex and medulla. The ovaries produce ova (exocrine) and the female sex hormones (endocrine).

ii. **Genital ducts:**

- ☐ Uterine tube: Consists of {fimbria, infundibulum, ampulla, isthmus and intramural part}.
- ☐ Uterus: Includes three parts {fundus, body and cervix}.
- ☐ Vagina: Site of copulation in female.

iii. **Vulva:** External genital organ.

OOGENESIS

- Formation of mature ovum which begins before birth till menopause (around 50 years). It occurs in the cortex of the ovary.

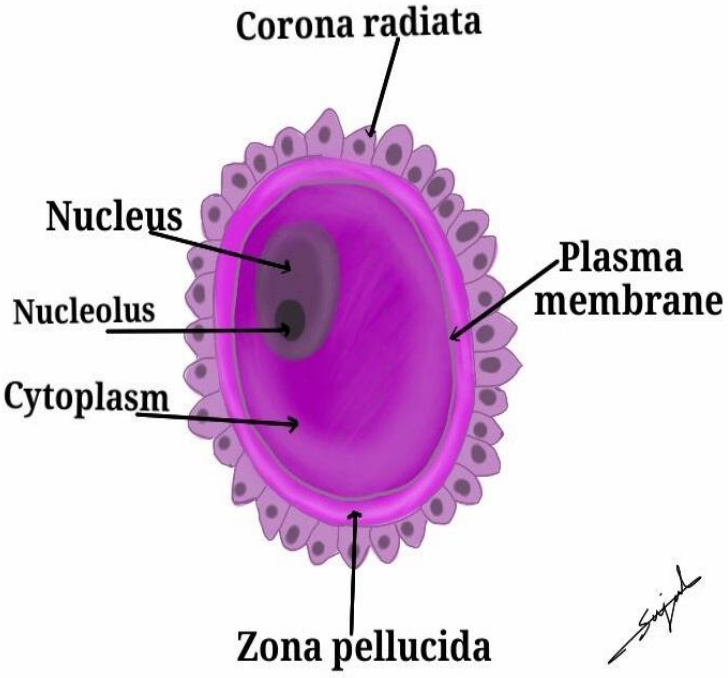


Fig. 2.3 Mature oocyte.

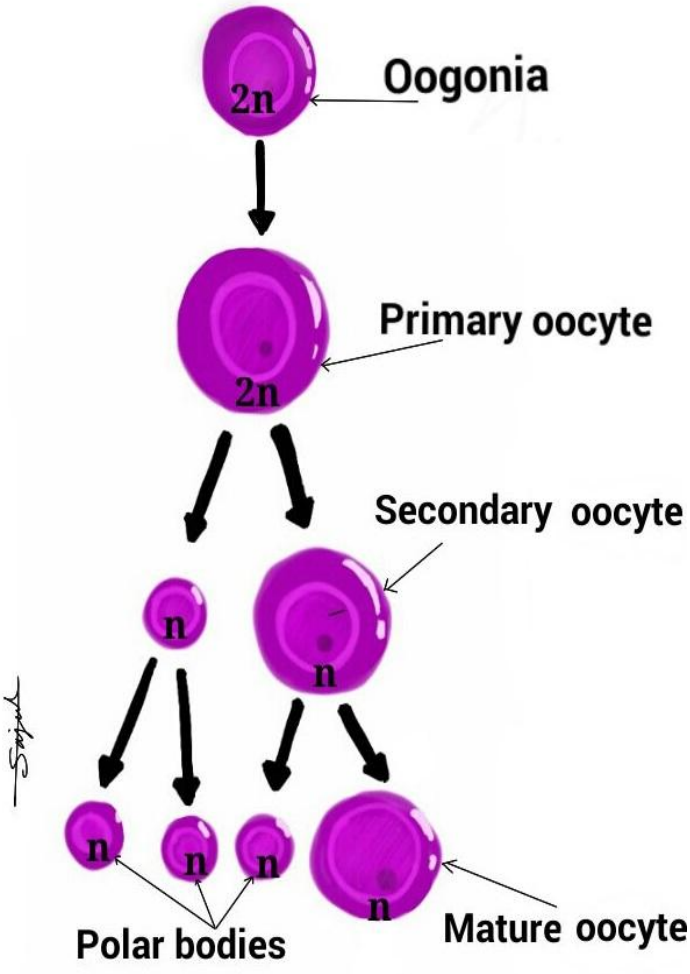


Fig. 2.4 Stages of oogenesis.

i. The secondary (2_{ry}) oocyte arrests in metaphase of meiosis II until fertilization then, transformed into mature oocyte.

ii. **Primordial follicle**: primary (1_{ry}) oocyte + single layer of flat cells.

iii. **Primary follicle:** 1_{ry} oocyte + single layer of cuboidal cells.

iv. **Secondary follicle:** 1_{ry} oocyte + multilayer of cuboidal cells.

v. **Growing secondary follicle:** 2_{ry} oocyte + follicular cavity (antrum).

vi. **Mature Graafian follicle** (Fig. 3.1).

Physiological correlation; ***"Gonadotropins"***

Follicular stimulating hormone (FSH) and luteinizing hormone (LH) are known as Gonadotropins (GTHs) for their effects on the male and female gonads. They are glycoproteins released from the basophilic cells of the anterior pituitary gland.

Chapter 3 || First Week of Development

OVARIAN CYCLE

>> Sequence of changes occurs every 28 days in the cortex of the ovary from puberty till menopause, includes;

i. The **follicular** phase (oogenesis)**:**

- ☐ Primordial follicle ⟹ **FSH** ⟹ mature vesicular (Graafian) follicle.
- ☐ It takes 14 days.
- ☐ Secretion of **estrogen** from mature Graafian follicle.

ii. **Ovulation:**

- ☐ Increase in LH release in response to estrogen.
- ☐ Rupture of mature Graafian follicle (under influence of LH surge).
- ☐ Escape of the 2_{ry} oocyte into the uterine tube on the 14_{th} day.

iii. The **luteal** phase**:**

- ☐ Ruptured follicle ⟹ **LH** ⟹ corpus luteum (yellow body).
  - fertilization occurs ⟶ corpus luteum of pregnancy.
  - Corpus luteum ⟶ fertilization doesn't occur ⟶ corpus albicans.
- ☐ The corpus albicans (white body) degenerates after 10 days.
- ☐ The corpus luteum secretes **progesterone** (to prepare the endometrium of the uterus for implantation) and estrogen.
- ☐ The corpus luteum of pregnancy persists up to 5 months then, it degenerates.
- ☐ Its function shall be carried by the **placenta**.

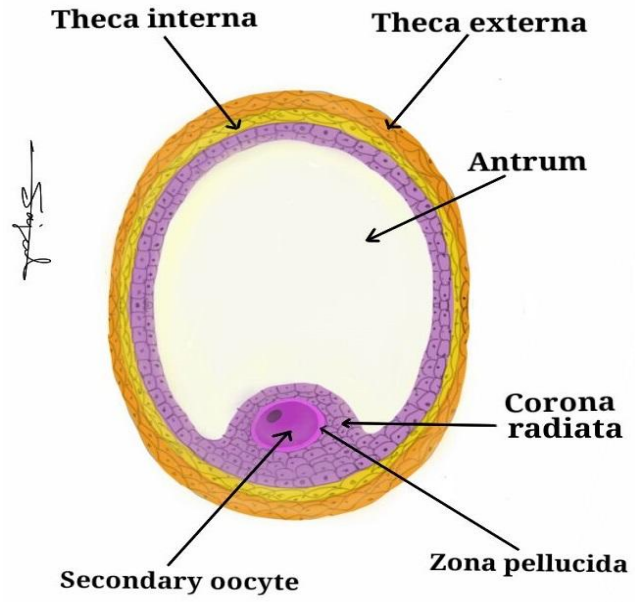


Fig. 3.1 Mature Graafian follicle.

MENSTRUAL CYCLE

>> Series of events occurs in the endometrium of the uterus accompanied (parallel) with the ovarian cycle, consists of;

i. The **menstrual** (bleeding) phase:

- ☐ It occurs in the first (4-5) days.
- ☐ Slough of the superficial functional layer of the endometrium causes **hemorrhage.**
- ☐ The thickness of the endometrium is 0.5 mm.

ii. The **proliferative** (follicular, estrogenic) phase:

- ☐ It lasts up to 10 days so, **ovulation** occurs at the end of this phase.
- ☐ The surface epithelium covers the shed parts.
- ☐ The arteries, veins and glands get straight and longer.
- ☐ The endometrium thickens (4 mm).

iii. The **progestational** (secretory, luteal) phase:

- ☐ This phase persists for 10 −14 days.
- ☐ The arteries, veins and glands become tortuous and very long.
- ☐ The endometrium consists of 3 layers (Fig. 3.2) and becomes (7 mm) thick.

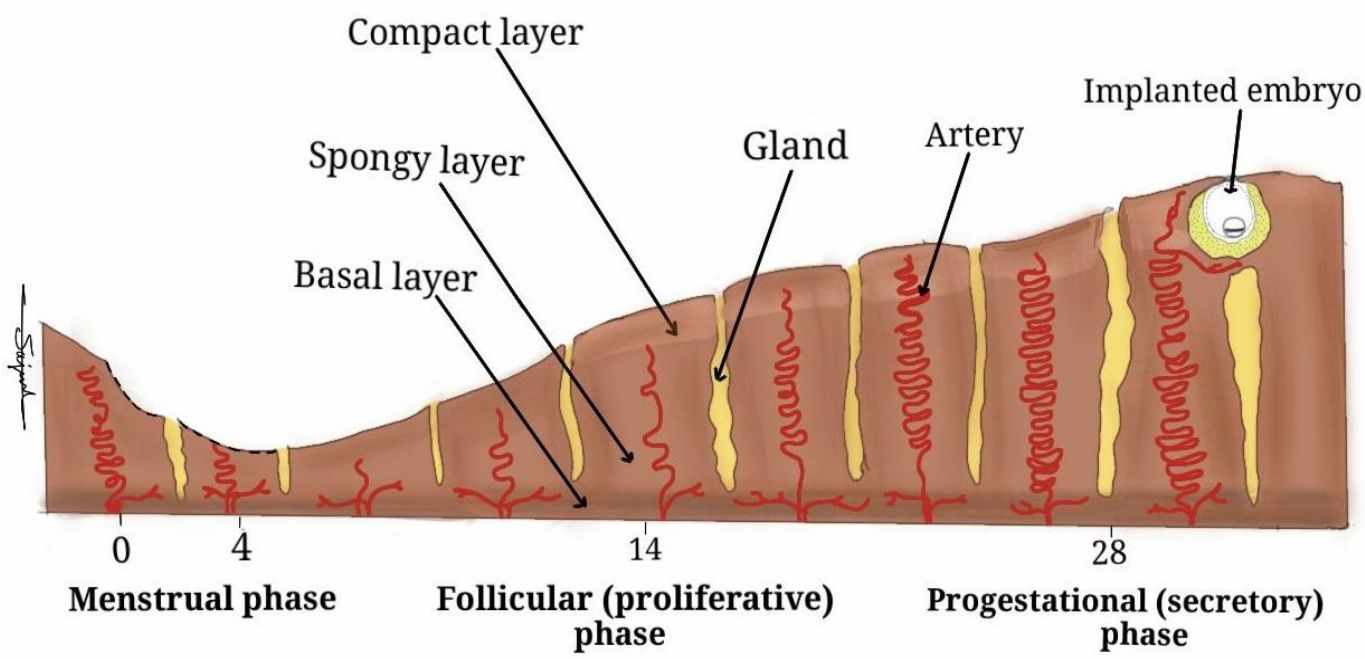


Fig. 3.2 Changes in the endometrium during menstrual cycle.

FERTILIZATION

>> Meeting and union of the sperm (n) and 2ry oocyte(n) to form the **zygote** (2n), usually occurs in the **ampulla** of the fallopian (uterine) tube, includes;

i. **Penetration of the corona radiata:**

- ☐ 300–500 million sperms reach the cervix of the vagina, only 300–500 sperms migrate to the surface of the ovum by contractions of the smooth muscle fibers of the uterine wall. Only one sperm fertilizes the ovum.

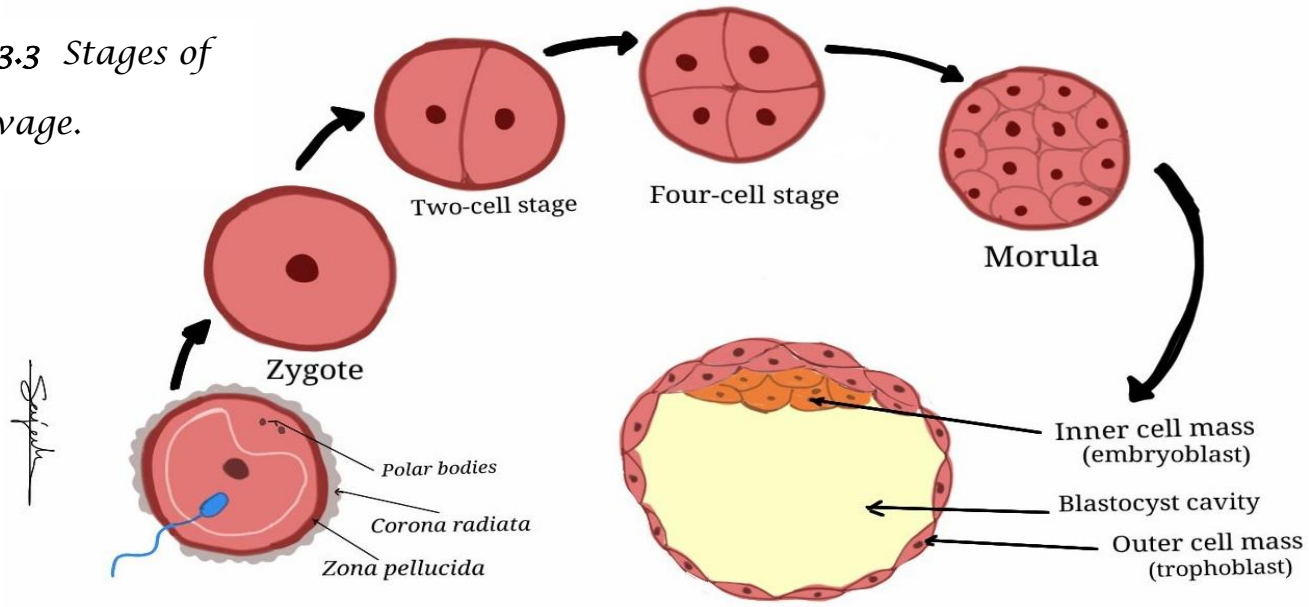
ii. **Penetration of the zona pellucida:**

- ☐ Preparation of the sperms to be able to penetrate the ovum by increasing their motility and maturation (**capacitation**). It lasts for 6 hours.
- ☐ Penetration of the zona pellucida occurs under the effect of the "acrosin" enzyme released from the acrosome (**acrosomal reaction**).
- ☐ Zona pellucida becomes impermeable to other sperms (zonal block).

iii. **Formation of the zygote:**

- ☐ The sperm's penetration into the *2ry* oocyte → completing the *2nd* meiotic division → a mature ovum + *2nd* polar body.
- ☐ The female ♀ pronucleus (nucleus of the mature ovum) fuses with male ♂ pronucleus (nucleus of the sperm) to produce the **zygote**.
- ☐ **Male gamete** determines the sex, either ♂ (XY) or ♀ (XX).
- ☐ Identification of the heredity characters.
- ☐ Stimulation and initiation of the segmentation **(cleavage).**

Fig. 3.3 Stages of Cleavage.



CLEAVAGE

>> One of the early growth phases defined as a series of mitotic divisions of the zygote. It occurs in the uterine tube.

- ☐ The cells of the zygote increase in number and become smaller.
- ☐ The zygote cleaves after 30 hours from fertilization into **blastomeres** (embryonic cells) 2− cell, 4−cell, 8− cell and so on.
- ☐ 3 days after fertilization, the blastomeres reach a 16-cell (**morula**) stage.
- ☐ Zona pellucida degenerates on day 5 to allow the implantation of the embryo.
- ☐ Formation of **blastocyst** (blastomeres without zona pellucida).
- ☐ When the blastomeres reach 128 cells, it's called **blastula.**
- ☐ Now, blastula consists of;

  i. **Embryoblast** (blast=primitive cell)**:** Gives origin to the developing of the embryo.

  ii. **Trophoblast:** Gives origin to the fetal membranes (placenta, yolk sac and amnion).

  iii. **Blastocele** (blastocyst cavity).

N.B. After the sperm enters into the cytoplasm of the secondary oocyte, its mitochondria and tail split and degenerate → *all mitochondrial DNA within the zygote is of* ***maternal*** *origin.*

- As the mitochondria is also called 'powerhouse', it's amazingly believed that **your energy arises from your *mother*.**

Chapter 4 || Second Week of Development

☐ **Remember that:** This week is also called "the week of ***twos***".

BILAMINAR GERM DISC

☐ The embryonic disc differentiates into *two*:

i. Dorsal **epiblast** (epi=above) layer of columnar cells.

ii. Ventral **hypoblast** (hypo=below) layer of cuboidal cells.

☐ The Trophoblast becomes *two* layers:

i. Outer **syncytiotrophoblast**.

ii. Inner **cytotrophoblast.**

☐ Formation of *two* cavities:

i. **Amniotic** cavity, dorsal to the epiblast.

ii. **Yolk sac** cavity, ventral to the hypoblast.

☐ Also, *two* membranes will appear:

i. **Amnioblastic** membrane: Derived from cytotrophoblast and lines the amniotic cavity.

ii. **Exocoelomic** membrane: Derived from hypoblast and lines the yolk sac.

☐ The 1_{ry} (extra embryonic) mesoderm is derived from the epiblast, and then appears between the Exocoelomic membrane and cytotrophoblast, it contains the chorionic cavity **(extra embryonic coelom)** which splits into *two*:

i. Extraembryonic **somatic** mesoderm (lining the cytotrophoblast).

ii. Extraembryonic **splanchnic** mesoderm (enclosing the yolk sac).

☐ By the end of this week, maternal blood enters the trophoblastic lacunae and becomes in direct contact with syncytiotrophoblast. Then, the primitive **uteroplacental circulation** begins**.**

☐ The extra embryonic coelom becomes in junction (traverses) with the chorionic cavity at the **connecting stalk** (primitive umbilical cord).

☐ Primary stem villi appear.

- ☐ The cells of the cytotrophoblast penetrate the outer layer (syncytiotrophoblast) to form projections-like fingers called **chorionic villi.**

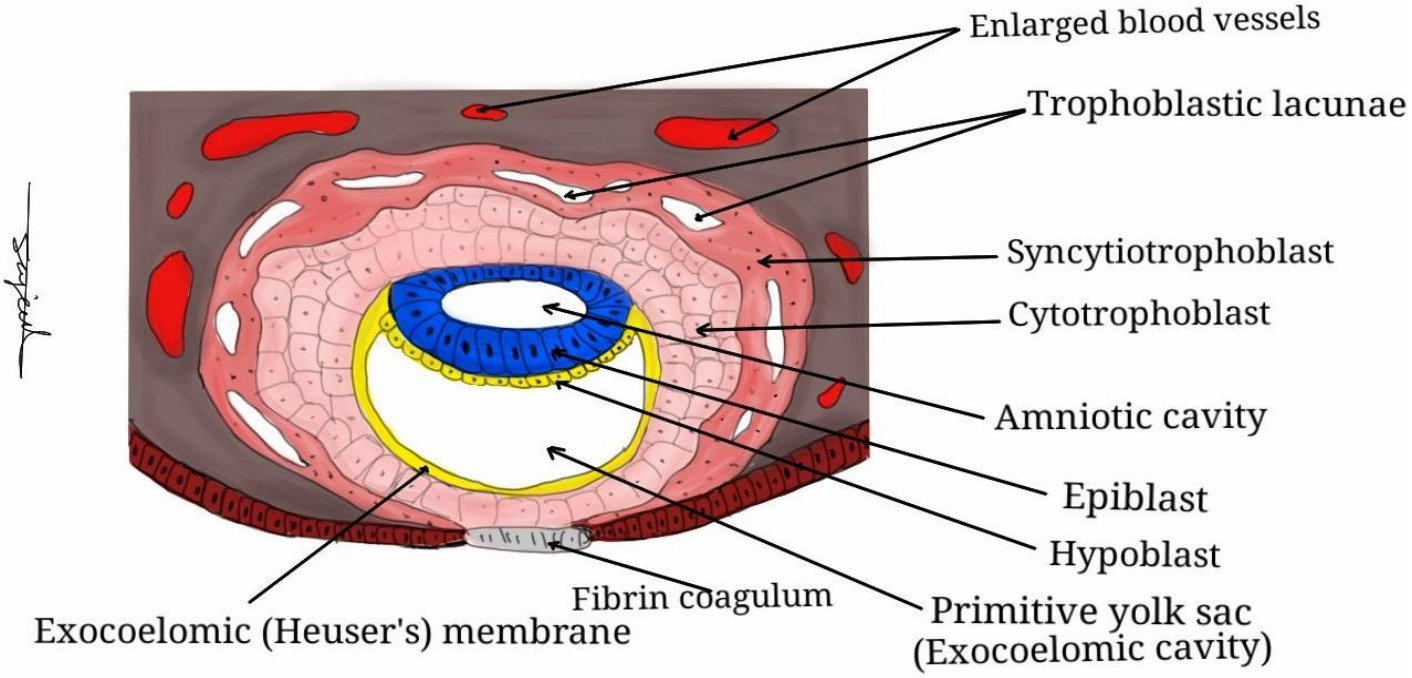


Fig. 4.1 Development of the blastocyst (9_{th} day).

IMPLANTATION

>> Attachment of the blastocyst to the functional layer of the endometrium of the uterus. It's completed at the end of the *2nd* week.

- ☐ Syncytiotrophoblast cells invade, ingest and erode the epithelium of the endometrium.
- ☐ Embedding of the blastocyst occurs in the upper part of the body of the uterus.
- ☐ If the implantation takes place in other sites in the uterus except for the upper part, it's called **placenta previa,** as follows;

  i. Placenta previa **lateralis**: On the lateral wall of the uterus.

  ii. Placenta previa **marginalis**: On the margin of the internal os.

  iii. Placenta previa **centralis**: At the center of the internal os.

- When implantation occurs outside the uterus, it's called **ectopic** (aberrant) **pregnancy** which includes;

  i. Tubal pregnancy: in the uterine tube (most common).

  ii. Ovarian pregnancy.

  iii. Abdominal pregnancy: in the intestine.

N.B. By the end of the implantation, the endometrium of the uterus is called **decidua**

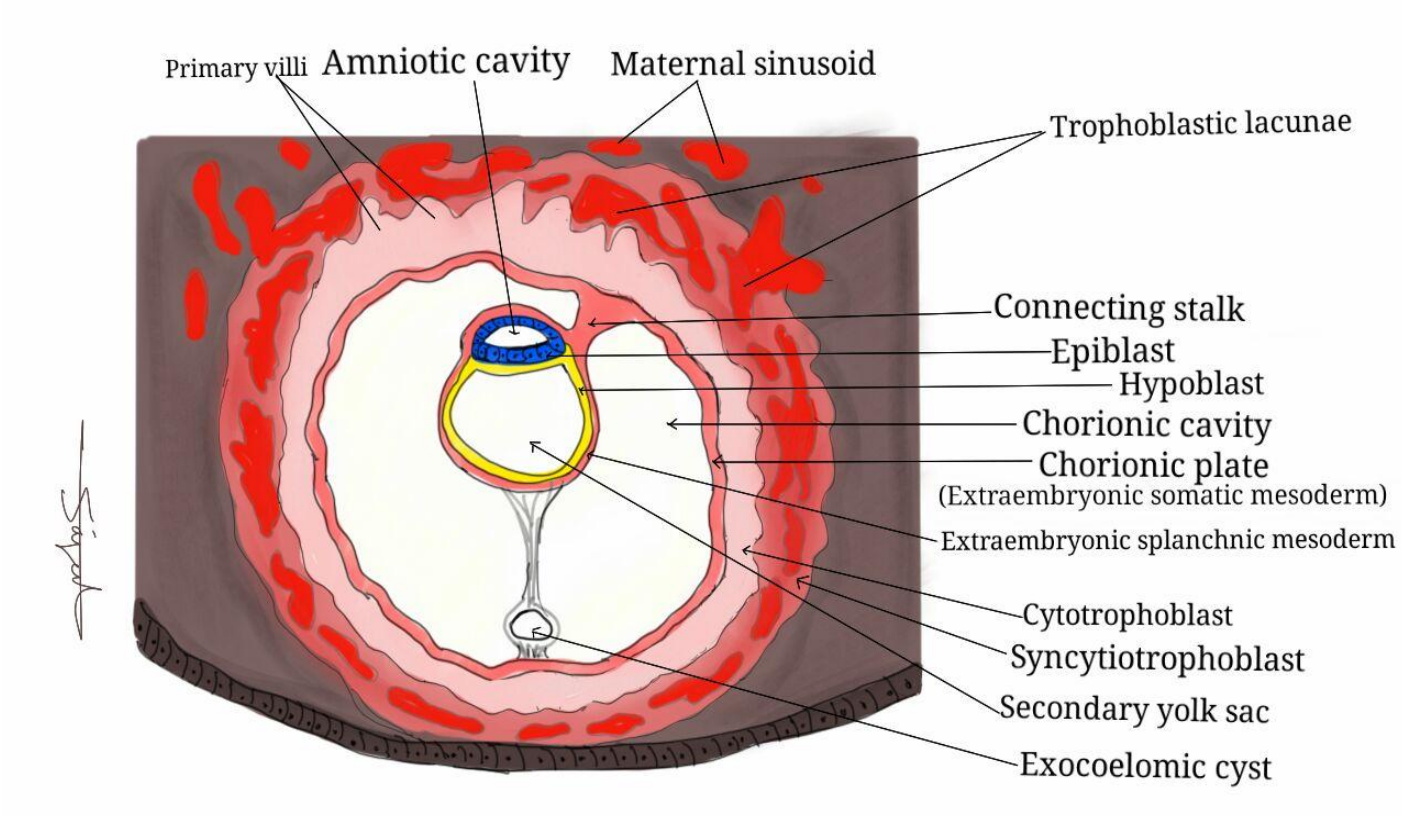


Fig. 4.2 Human blastocyst at the end of the 2nd week.

Chapter 5 || The Embryonic Period

- It begins with the third week of development known as the week of **gastrulation;** establishing of the trilaminar germ disc.

PRIMITIVE STREAK

- Proliferation of epiblast (**ectoderm**) cells leads to the appearance of **primitive streak**.
- The primitive streak includes the primitive node (Hensen's node), primitive pit and primitive groove.
- Both the epiblast and the hypoblast (endoderm) fuse caudally at the **cloacal membrane** (future anus).
- Also, the endoderm and ectoderm layers become in contact cranially at the **prechordal plate** (future mouth). It becomes a part of the **oropharyngeal membrane.**
- The prechordal plate is cluster of columnar endodermal cells.
- **Cardiogenic area:** Is a region of the **mesoderm** forming the heart.

NOTOCHORD

- The Hensen's node extends at the midline between the endoderm and ectoderm to form the **notochordal process**. It elongates toward the caudal direction till it reaches the prechordal plate by lengthening of primitive pit through it, which's then canalized and transformed into **notochordal canal**.
- The floor (endoderm) of the notochordal canal disappears leading to transitory communication between the yolk sac and amniotic cavity called **neurenteric canal**.
- Regeneration (repairing) of the endodermal cells of the floor of the notochordal canal → **notochordal plate**. Its (notochordal plate) cells increase and detach (separate) from the endoderm → **notochord** (solid cord of cells extending from the primitive node to the prechordal plate).
- Fate of notochord will be:

    i. **Apical ligament.**

    ii. **Nucleus pulposus** of the intervertebral disc.

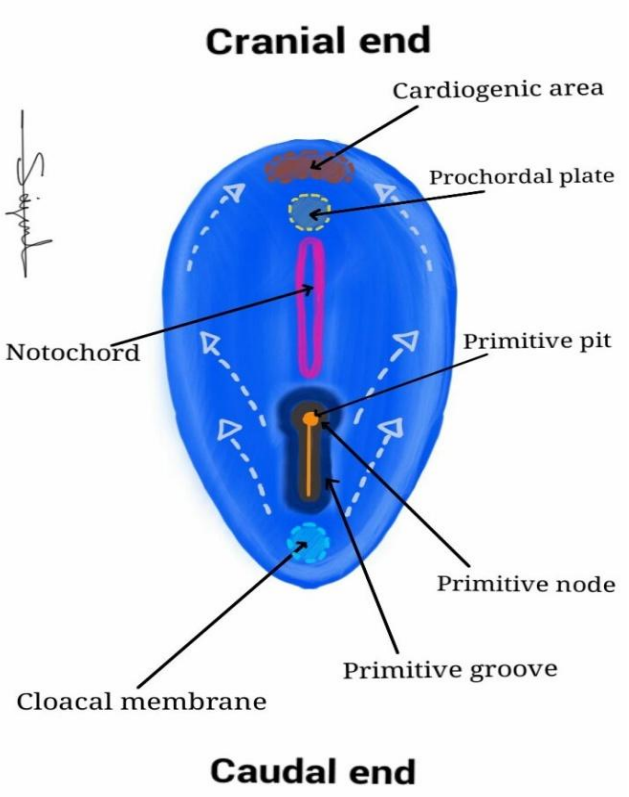


Fig. 5.1 Dorsal view of the embryonic disc during gastrulation.

TRILAMINAR EMBRYONIC DISC

- The ectoderm, 2_{ry} mesoderm and endoderm are derived from the **epiblast**, as follows;
  - i. Some epiblastic cells displace the hypoblast and are transformed into inner **endoderm** (for nutrition).
  - ii. Other cells invaginate through the primitive streak and lie between the epiblast and endoderm, creating the **mesoderm**.
  - iii. Formation of the outer embryonic **ectoderm** (protective layer) by the remaining cells.
- All of these layers will form various organs and tissues found in the human being.
- The ectoderm layer differentiates into surface ectoderm (future epidermis) and neural plate.

NEURULATION: Formation of the neural tube.

- Overgrowth of ectodermal cells → condensation and thickening of the area cephalic to the primitive streak → **neural plate**.
  Rising (elevation) of the lateral margins of the neural plate → **neural folds**.
  Gradually, the **neural groove** is formed while the midregion becomes depressed.
- Gathering (fusion) of the neural folds forms the **neural tube** (future **CNS**) that's located beyond (dorsal) to the notochord. Then, separates from the surface ectoderm.

- ☐ The neural tube connects with the amniotic cavity by anterior and posterior **neuropores**. These openings provide nourishment to the embryo.
- ☐ Closure of the cranial (anterior) neuropore occurs at the **middle** of the 4th week while the caudal (posterior) one closes by the **end** of the same week.
- ☐ Later on, two constrictions appear at the **cephalic end** of the neural tube, dividing it into three vesicles; forebrain, midbrain and hindbrain. The **caudal end** → spinal cord.
  The **lumen of the neural tube** → spinal cord's central canal & brain's ventricular system.
- ☐ Two imprisoned **neural crest** are formed where the neural folds unite. Soon, it shifts and lies at the dorsolateral sides of the neural tube.
- ☐ Derivates of the neural crest are;

  i. Sympathetic ganglia.

  ii. Dorsal root ganglia.

  iii. Sensory ganglia of V, VII, IX and X cranial nerves (**1975**).

  iv. Chromaffin cells of adrenal medulla.

  v. The pia and arachnoid maters.

  vi. Schwann, pigment, glial and C (of the thyroid gland) cells and melanocytes.

  vii. Many connective tissues especially in the head.

  viii. Mesenchyme of the pharyngeal arches.

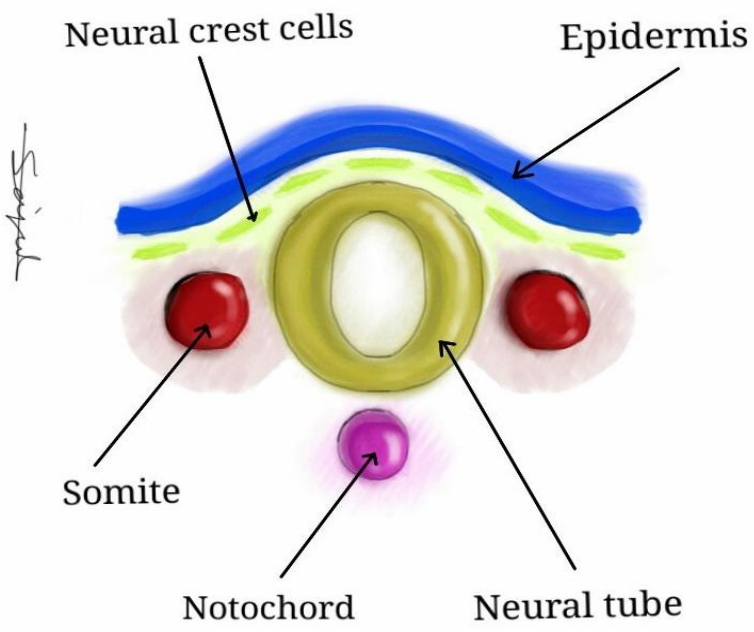


Fig. 5.2 *Cross (transverse) section through the embryonic disc at day 21.*

Neural Tube Defects (NTDs): Failure of closure of the neural tube.

- Either cranially (Anterior neuropore) → **anencephaly** OR caudally (posterior neuropore) → **spina bifida**. The most common site of the later within the lumbosacral region (see Chapter 7).
- Up to 70% of NTDs can be reduced by the **folic acid** supplementation before and during pregnancy.

SECONDARY MESODERMAL LAYER

i. Close to the notochord, there is Medial **paraxial mesoderm**; it forms the **somites**.

☐ Formation of the somites begins on day 20 and continues till the end of the *5th* week. It's useful to indicate and determine the **embryo's age**.

Crown-rump length {CRL}

Is an ultrasound measurement of the probable age, size and length of the fetus
⟹ Predict the expected date of *parturition*.

☐ There are 42 – 44 **pairs** of somites (4 occipital, 8 cervical, 12 thoracic, 5 lumbar, 5 sacral and 8 – 10 coccygeal). Each somite differentiates into;

a. **Sclerotome** (future axial skeleton).

b. **Dermatome** forms the skin's dermis.

c. **Myotome** forms the skeletal muscle.

ii. **Intermediate mesoderm**; gives rise to organs of the urogenital system.

iii. **Lateral plate mesoderm**; characterized by the appearance of U-shaped cavity known as **intraembryonic coelom** (future **p**ericardial, **p**leural and **p**eritoneal cavities). This cavity divides the lateral plate into **somatic** (parietal) and **splanchnic** (visceral) layers. The intraembryonic coelom becomes in direct continuity with the Extraembryonic coelom on each side.

N.B. The mesodermal cells fill the space between the endodermal and ectodermal layers ***except***;

i. Cloacal membrane ii. Notochord

iii. Oropharyngeal membrane

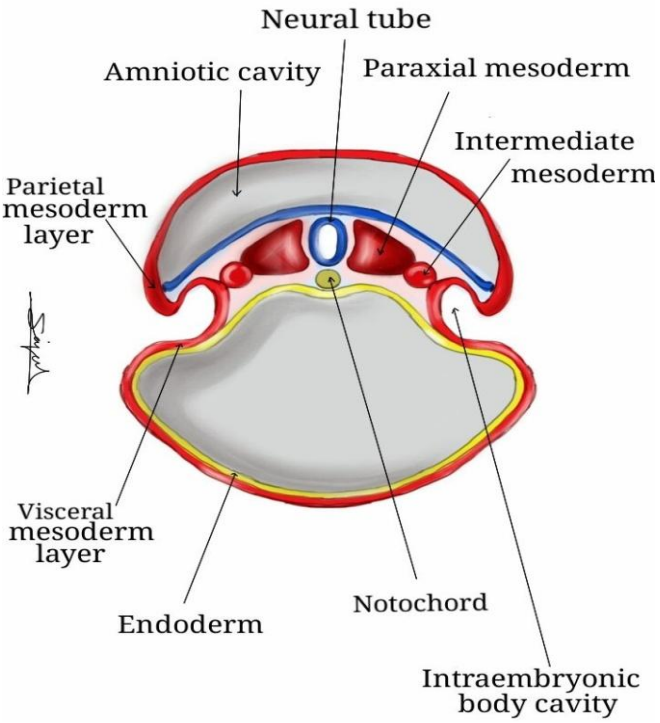


Fig. 5.3 Cross section at day 21 shows the differential mesoderm.

FOLDING: Formation of the tail, head and 2 lateral flexions (folds). It starts by the end of the 3rd week.

☐ Also defined as the conversion of flat germ disc into the normal convex shape of the embryo. This process occurs by;
Differential growth of the neural tube → cephalocaudal direction.
Growing of the somites → transverse or lateral direction.

☐ **Results of the folding;**

i. The endodermal layer becomes → ventral in position → rolls (bends) down forming → the **gut tube** (future GIT). It forms the foregut, midgut and hindgut.

ii. The amnion expands ventrally to the head and tail endings, the definitive yolk sac constricts and communicates with the midgut by the **vitelline** (vitello-intestinal) **duct**.

iii. Formation of the **head** and **thoracic bulges** and **stomodeum** (primitive mouth) results from ectodermal depression that separates it from the foregut by the oropharyngeal membrane.

iv. Appearance of the **cloaca** (dilation of the terminal part of the gut tube) and **cloacal membrane.**

v. From the yolk sac, the **allantois** (allanto-enteric diverticulum) will originate. It connects with the cloaca.

vi. Growing of the extraembryonic mesoderm results in formation of the **connecting stalk** (future umbilical cord). It is being carried at the ventral side of the embryo after folding.

Vii. The septum transversum, primordial heart, pericardium, cloacal and oropharyngeal membranes move and become ventral to the embryo.

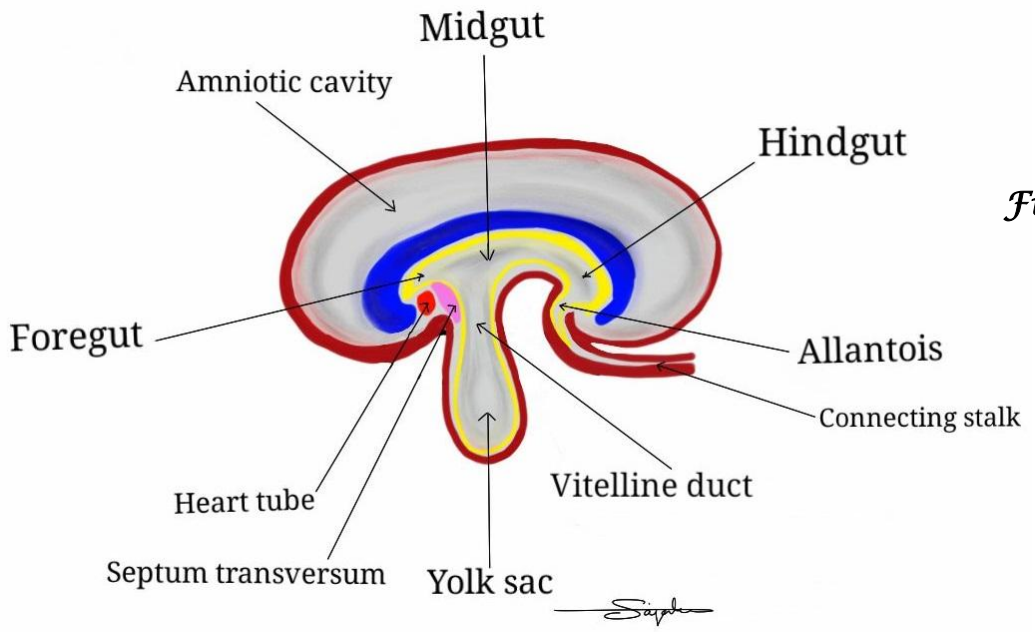


Fig. 5.4 Longitudinal section Showing the embryonic folding (day 25).

DERIVATIVES OF THE GERM LAYERS

Endoderm

i. Epithelial lining of the primitive GIT,respiratory tract, urinary bladder and urethra.

ii. **Parenchyma** of the liver,pancreas,thymus,thyroid and parathyroids.

iii. Epithelial part of the tympanic cavity (middle ear), auditory(eustachian) tube and upper part of anal canal.

Mesoderm

i. Vascular system; heart, arteries, veins and lymphatic vessels.

ii. Connective tissue, dura mater, spleen and adrenal cortex.

iii. Genital organs and others (see above).

Ectoderm

i. Nervous system.

ii. Epidermis of skin, hair and nails.

iii. Glands of Pituitary, sweat, mammary and adrenal medulla.

iv. The enamel of the teeth and eye lens.

v. Epithelium of the nasal cavity, anterior part of the oral cavity and lower anal canal.

NUTRITION OF THE EMBRYO

i. At the first two weeks, from the endometrial blood vessels and glands via **diffusion**.

ii. Then, through the **trophoblastic lacunae** and primitive uteroplacental circulation by the beginning of the third week via the villous system.

iii. Finally, the **placenta** is formed at the *4th month* and it's responsible for nutrition of the fetus.

N.B. In the embryonic period;

- The embryo has a distinctly human appearance at week 8.
- Most malformations and birth defects are induced so, it's also known as "teratogenic period" .

Chapter 6 || The Fetal Period

- Characterized mainly by the rapid fetal growth.
- Accurately, the duration of normal pregnancy is considered to be 266 days or 38 weeks after fertilization.
  Remember that the ovulation occurs during the 14_{th} or 15_{th} day.
  Therefore, it was expected to be (266 + 14) 280 days or 40 weeks after the last normal menstrual period (LNMP).
  For several purposes, each 3 months = trimester. So, there are 1st, 2nd and 3rd trimesters.

FETAL MEMBRANES

Allantois

- Defined as a protrusion from the yolk sac. Early, it extends through the connecting stalk. After folding, it connects with the hindgut. Allantois originates as a diverticulum from the endoderm around the 16_{th} day. The proximal part of the allantois → **apex of the urinary bladder**, whereas the distal part (urachus) → **median umbilical ligament** or fold.

Decidua

- Endometrium of the uterus after implantation, consisting of 3 parts;
  i. Decidua **basalis**; between the conceptus and the uterine wall. It shares in the placental formation.
  ii. Decidua **capsularis**; connects the conceptus with the uterine cavity.
  iii. Decidua **parietalis**; lining the wall of the uterus.

N.B. Both the decidua capsularis and parietalis will atrophy and disappear.

Amnion

- It forms on day 8 in three phases as follow:
  i. **Blastocystic** phase whereas the amnion lies between the epiblast and trophoblast.

ii. In the **chrionic vesicle** stage, it is floored by the ectoderm and roofed by the primary mesoderm.

iii. A clear, watery amniotic fluid (contained in the amniotic cavity) surrounding all the embryonic aspects after **folding**, increases in volume (1 Liter at term).

- **Functions** of the amniotic fluid;

i. **Protection** of the fetus from injuries, shocks or strikes.

ii. **Thermal insulator**

iii. Aids the **movement** of the fetus and **development** of muscles, GIT and lungs.

iv. Plays an important role during labour by **dilating** the cervix of the uterus. As well as cleaning (washing) the birth canal.

- **Anomalies** of the amniotic fluid; It occurs due to abnormal volume of the amniotic fluid, either more than 2 L (**polyhydramnios**) or less than 0.5 L (**oligohydramnios**).

Connecting Stalk

- The amnion is attached to the chorion **only** by the mesodermal band called ''connecting stalk. The latter, appears in the chorionc vesicle phase and it's suspended from the conceptus (Fig. 4.2). Later on, it becomes the umbilical cord.

- **It contains**;

i. Allantois.

ii. Umbilical vessels.

Umbilical Cord

- The connection between the umbilicus of the fetus and **central** part of the fetal surface of the placenta (50 – 60 cm long). It includes:

i. Connecting stalk containing the allantois and umbilical vessels (two arteries and one vein), see Fig. 6.2 .

ii. Yolk sac (vitelline duct), it is obliterated by the end of the third month.

iii. Protective layer for vessels formed by amnion (**Wharton's jelly**).

iv. Remnants of the extraembryonic coelom.

- **Anomalies** of the umbilical cord (twisting) are common because it's longer than the cord. There are:

  i. The cord attached either to the amnion "**velamentous attachment**" or to the preipheral part (edge) of the placenta "**battledore placenta**".

  ii. **Abnormal long or short cord**.

  iii. **True** (fatal) **or false knot**.

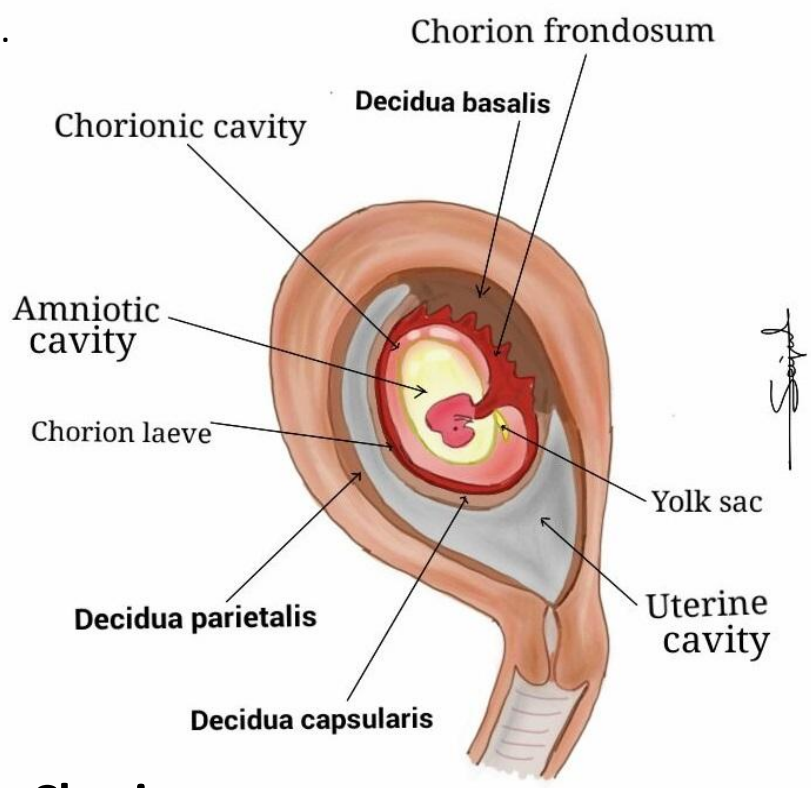


Fig. 6.1 The relation between fetal Membranes and the decidua (early fetal period).

Chorion

- The covering of the chorionic vesicle (Fig. 4.2). It is composed of:

  i. Outer layer "**syncitiotrophoblast"**.

  ii. Middle layer "**cytotrophoblast"**.

  iii. Inner primary mesodermal layer "**extraembryonic somatic mesoderm"**.

- The **divisions** of the chorion;

  i. Chorion **frondosum**: Has many **villi**, long, towards decidua basalis and forms the fetal part of the placenta.

  ii. Chorion **laeve**: Smooth, short, towards decidua capsularis and gets atrophied.

- The **degrees** of the choroinic villi;

  i**. Primary** villi (Fig. 4.2) : Syncitiotrophoblast + cytotrophoblast.

ii. **Secondary** villi: Primary villi + extraembryonic mesoderm.

iii. **Tertiary** villi: Secondary villi + fetal capillary blood vessels.

Yolk Sac

- ☐ **Primary** yolk sac: It appears within the blastocyst stage, roofed by the hypoblast and floored by the exocoelomic membrane (Fig. 4.1).
- ☐ **Secondary** yolk sac; It forms in the chorionic vesicle stage, perfectly lined with endoderm and characterized by the presence of the connecting stalk (Fig. 4.2).
- ☐ As a result of folding, its name changes into **definitive** yolk sac.
- ☐ **Roles** include: Nutrition (during weeks 2-3), giving the primordial germ cells (see Chapter 2), blood **(RBCs)** development (on its wall in week 3) and protection.
- ☐ **Fate:** by week 10, it shrinks as pregnancy advances and gets smaller.

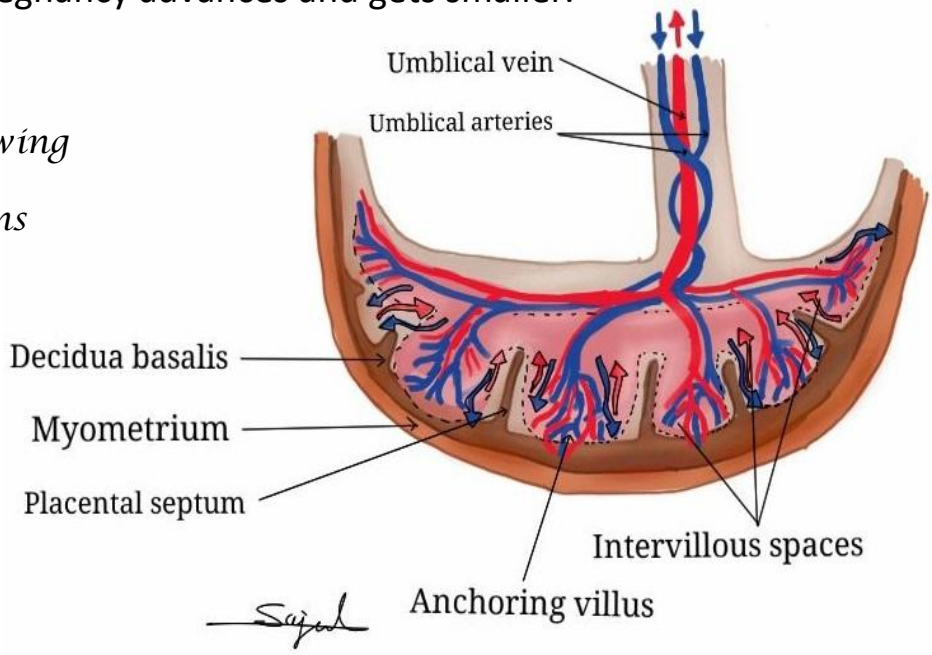


Fig. 6.2 Longitudinal section showing The maternal and fetal portions Of the full term placenta.

Placenta

- ☐ A temporary **fetomaternal** organ that appears by the beginning of the *4th month*, discoid-in-shape, nearly circular, thicker in its center and is 500 g at term.
- ☐ It has a maternal portion (decidua basalis) and a fetal portion (chorion frondosum).
- ☐ Also, it has two surfaces;
  i. Maternal (rough) surface: Attached to the uterine wall. Divided by the **placental septa** (protruding towards the intervillous spaces) into 15-20 irregular zones called **cotyledons**.

ii. Fetal surface: Smooth, covered by amnion giving the shiny appearance. The umbilical cord is attached to its centre.

- ☐ The tertiary villi of the villous chorion (chorion frondosum) contain the fetal vessels. There are two types;
  - i) **stem** (anchoring) villi for attachment into the decidua basalis and give branches on either sides named:
  - ii) **terminal** (free) villi that extends through the **intervillous space** (space between two neighbor villi) for exchanging substances.
- ☐ The decidua basalis contains the maternal vessels (spiral arteries).
- ☐ Maternal blood is the **only** content of the intervillous spaces.
- ☐ Fetal blood is completely separated from the maternal blood by a membrane which acts as a selective barrier called **placental barrier**. It comprises of 4 layers (layers of tertiary villi). In late pregnancy, only 2 layers persist (syncytiotrophoblast + fetal capillaries endothelium).
- ☐ Major **functions** of the placenta: (**AHMED**)
  - i. **A**llows the nutrients, gases and electrolytes to pass from and to the fetus.
  - ii. **H**ormone production, e.g., progesterone and estrogen.
  - iii. **M**etabolism, e.g., synthesis of fatty acids and glycogen.
  - iv. **E**xcretion of waste products from fetal blood.
  - v. **D**elivery of maternal antibodies providing passive immunity for the fetus.

Immunological correlated;

IgG is the only type of antibodies that can cross the placenta.

- ☐ The commonest **abnormalities** of the placenta;
  - i. Abnormal position. e.g., placenta **previa** (see Chapter 4).

ii. **Placentomegaly**: Is the enlargement of the placenta (more than 600 g).

iii. **Battledore** placenta: The umbilical cord is attached to the peripheral part of the placenta.

iv. **Velamentous** placenta: The umbilical cord is attached to the amniotic membrane.

v. Placenta **bipartita** or **tripartita**: the placenta is bilobed or trilobed.

vi. Placenta **succenturiata**: One main lobe and one or more small accessory lobes.

TWINING

- Twining is the delivery of two embryos together. There are 3 types;

- **Dizygotic** or fraternal twins (**DZ**): Constitutes 2/3 of the twins. Two sperms fertilize two different 2_{ry} oocytes → 2 zygotes → 2 blastocysts and therefore 2 amnions, 2 chorionic vesicles and 2 placentas. They may be of different sex, features and blood groups.

- **Monozygotic** twins (**MZ**): One sprem fertilizes a single 2_{ry} oocyte. They are **identical** and depends on the origin of the (splitting) of the twins as follow;

Stage of origin	Arrangement of the membranes
Two cell stage	**Same as DZ**
Blastocystic stage (most common)	**Two amnions , one chorion and one common placenta**
Bilaminar germ disc stage (rare)	**One amnion, chorion and common placenta**

Table 6.1 The arrangement of the fetal membranes according to the stage of splitting in MZ.

- **Conjoined twins** or Monsters; Incomplete separation of MZ. They may be **thoracopagus** (adhesion at the thoracic region), **craniopagus** (united in the head region), **pyopagus** (joined at the sacral region) or **xiphopagus** (joined at the xiphoid process).

Review Questions

1. ***All of the following events occur at the week of gastrulation, except:***

a) Appearance of the primitive streak

b) Formation of the notochord

c) Closure of the neural tube

d) Establishes of the trilaminar germ layers

2. ***The endoderm will give rise to the:***

a) Stomach

b) Spleen

c) Adrenal medulla

d) Pitutary gland

3. ***The primitive streak:***

a) Is formed during 2nd week of development

b) Is cephalic to the notochord

c) Is the first indication of the third week

d) Extends from the Hensen's node

4. ***Which of the following secrete progestrone ?***

a) Corpus luteum of pregnancy

b) Cytotrophoblast

c) Syncitiotrophoblast

d) None of the above

5. ***The cloacal membrane marks the site of the future:***

a) Umbilical cord

b) Mouth

c) Heart

d) Anus

6. ***Concerning to the gamete, it has:***

a) 46 chromosomes, 1N

b) 46 chromosomes, 2N

c) 23 chromosomes, 1N

d) 23 chromosomes, 2N

7. ***Each of the following are characteristics of the MZ twins except they:***

a) Are most common

b) Have two placentas

c) Are genetically identical

d) Usually have two amnions

8. ***All the following are mesodermal derivatives, except:***

a) Bones

b) kidneys

c) Skeletal muscles

d) Enamel of teeth

9. ***Which hormone prevents a second pregnancy during gestation?***

a) LH

b) Progestrone

c) FSH

d) hCG

10. ***What occurs as a result of fertilization ?***

a) Determining of the embyronic sex **b)** Initiation of the cleavage

c) Restored of the diploid number **d)** All of the above

11. ***In normal conditions, maternal blood becomes in contact with:***

a) Cytotrophoblast **b)** Syncytiotrophoblast

c) Extraembryonic mesoderm **d)** Both A and B

12. ***During the first week of gestation:***

a) The cells of the embryo increase in size **b)** Implantation is completed

c) The zona pellucida is degenerated **d)** The bilaminar disc is formed

13. ***True or false: The hypoblast forms the yolk sac ?***

a) True **b)** False

14. ***Name the correct order that involves in neurulation:***

a) Neural groove, neural plate, neural folds, neural tube

b) Neural tube, neural groove, neural plate, neural folds

c) Neural plate, neural groove, neural folds, neural tube

d) Neural plate, neural folds, neural groove, neural tube

15. ***Mention at least 3 functions of the placenta.***

16. ***Mention the normal and abnormal sites of implantation.***

17. ***Write the fate of notochord?***

Part 2

Special Embryology

Chapter 7 || The Axial Skeleton

Objectives:

- To explain each stage of development of each part of the axial skeleton and its anomalies.
- Give the origin of each part of the axial skeleton.

☐ The axial skeleton originates in general from **paraxial mesoderm**.

VERTEBRAL COLUMN

☐ During the 4_{th} week or notochordal stage, sclerotome (mesenchymal) cells multiply, migrate and enclose the notochord → **centrum**, neural tube → vertebral arches and in the body wall → the costal processes (Fig. 7.1).

☐ The centrum → the body of a vertebra,
vertebral (neural) **arch** → pedicles and laminae, spinous, transverse and articular processes.

☐ The vertebrae and arteries are intersegmental in position (unlike the intervertebral disc), which is explained by the **resegmentation process** (each definitive vertebra is composed of the caudal segment of sclerotome and the cranial segment of its neighbor).
The nerves are segmented because they arise opposite to the intervertebral disc.

☐ An intervertebral disc consists of **nucleus pulposus** (vestiges of the notochord) surrounded by circular rim of fibrocartilage called **annulus fibrosis** (mesodermal in origin).

☐ The thoracic and sacral curves appear firstly during the fetal period (primary curves) while the cervical and lumbar curves are established after birth (secondary curves).

☐ The cartilaginous stage occurs at the 6_{th} week, two chondrification centers are seen in the centrum (fuse together at week 8), one in each neural arch and one in each costal process. The transverse and spinous processes originate as a result of an extension of these centers.

☐ Vertebral **abnormalities**;

A. **Spina bifida occulta** (Fig. 7.5): Nonunion of the neural arches, covered by skin (occulta=hidden), asymptomatic (no clinical symptoms), discovered only on scans or x-rays (most common).

B. **Spina bifida cystica**: More severe type because it's visible defect, has two types (see Chapter 11).

C. **Hemivertebra:** Congenital missing of one half of the vertebral body usually resulting in **scoliosis** (lateral bending - curvature - of the vertebral column).

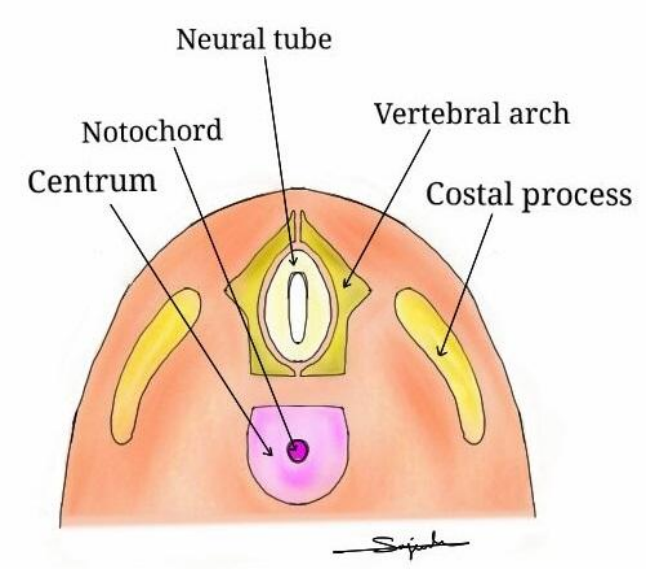


Fig. 7.1 Mesenchymal vertebra (5-7 weeks).

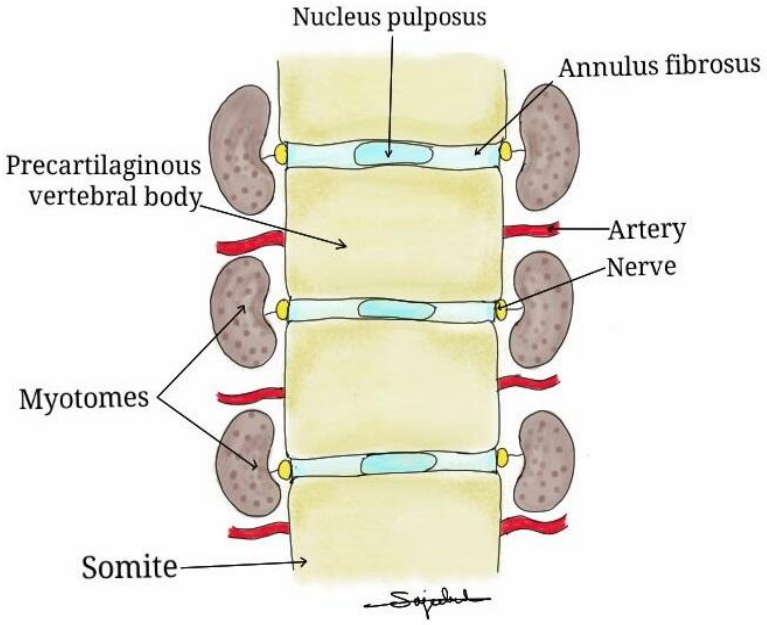


Fig. 7.2 Formation of the vertebral Column.

☐ The bony stage begins at the 8_{th} week and ends during the *25th* year, as follows;

Prenatal	**By the 8_{th} week, three** primary ossification centers **are formed, one in the centrum and one for each vertebral (neural) arch.**
At birth	Each vertebra is formed by three bony parts connected jointly by cartilage.
Postnatal (postpartum)	The two halves of the vertebral arch unite together by the first year of life.
	The centrum articulates with The vertebral arches during first 3 to 6 years, forming one bone.
	Five secondary ossification centers are seen after puberty at, a. Tip of spinous process b. Tip of each transverse process c. Two annular epiphyses on the upper and lower surfaces (rim) of the vertebral body.
	At about 25 years, all secondary centers fuse with the rest of the vertebrae, the epiphyses are formed.

Table7.1 The bony stage of the vertebral column at various periods.

RIBS

- ☐ They are developed from the thoracic costal processes of the vertebrae, chondrify throughout the embryonic period and ossify throughout the fetal period.

- ☐ Rib **defects** include;

  A. **Accessory** - extra- **lumbar ribs** (most common, usually causes no problems).

  B. **Cervical rib**: An extra rib usually attached to the C7 vertebra, present in 1% of individuals, may put pressure on the subclavian artery or the brachial plexus causing thoracic outlet syndrome.

STERNUM

- ☐ The sternum develops from somatic mesodermal cells in the ventral body wall as two **sternal bars**. By week 8, these latter are fused cephalocaudally in the median plane forming manubrium, sternebrae (body) and xiphoid process as cartilages.

- ☐ The ossification centers appear cephalocaudally before birth **except** in the xiphoid process which appears postnatally (during childhood).

- ☐ **Anomalies** of the Sternum;

  A. Cleft sternum: Failure of union of the sternal bars in the midline (very rare).

  B. Pectus excavatum or funnel chest**:** Sunken of chest wall posteriorly (fairly common).

  C. Pectus carinatum or pigeon chest**:** Protrusion of the sternum anteriorly (less common).

SKULL

- ☐ It can be classified functionally into: i. **neurocranium** or brain box and ii. **viscerocranium** or facial skeleton**,** each contains cartilaginous and membranous portions that will be ossified (converted into bone).

- ☐ **Membranous neurocranium** (skull cap or calvaria); Is derived from neural crest cells and comprises of flat bones (2 frontal, 2 parietal, squamous part of temporal and occipital bones) are separated from each other by **sutures** (dense connective tissue).
  Fibrous areas where several sutures or bones meet are called **fontanelle** (Fig. 7.3 A&B).
  Six* fontanelles and *five* sutures (unclosed) enable skull bones to deform during birth (molding**) and to expand postnatally.

☐ Closure of fontanelles:

The anterior (largest and most prominent one) and mastoid fontanelles - during ***2nd*** year.

Sphenoid and posterior fontanelles - about the ***2nd*** and ***6th*** month after birth, respectively.

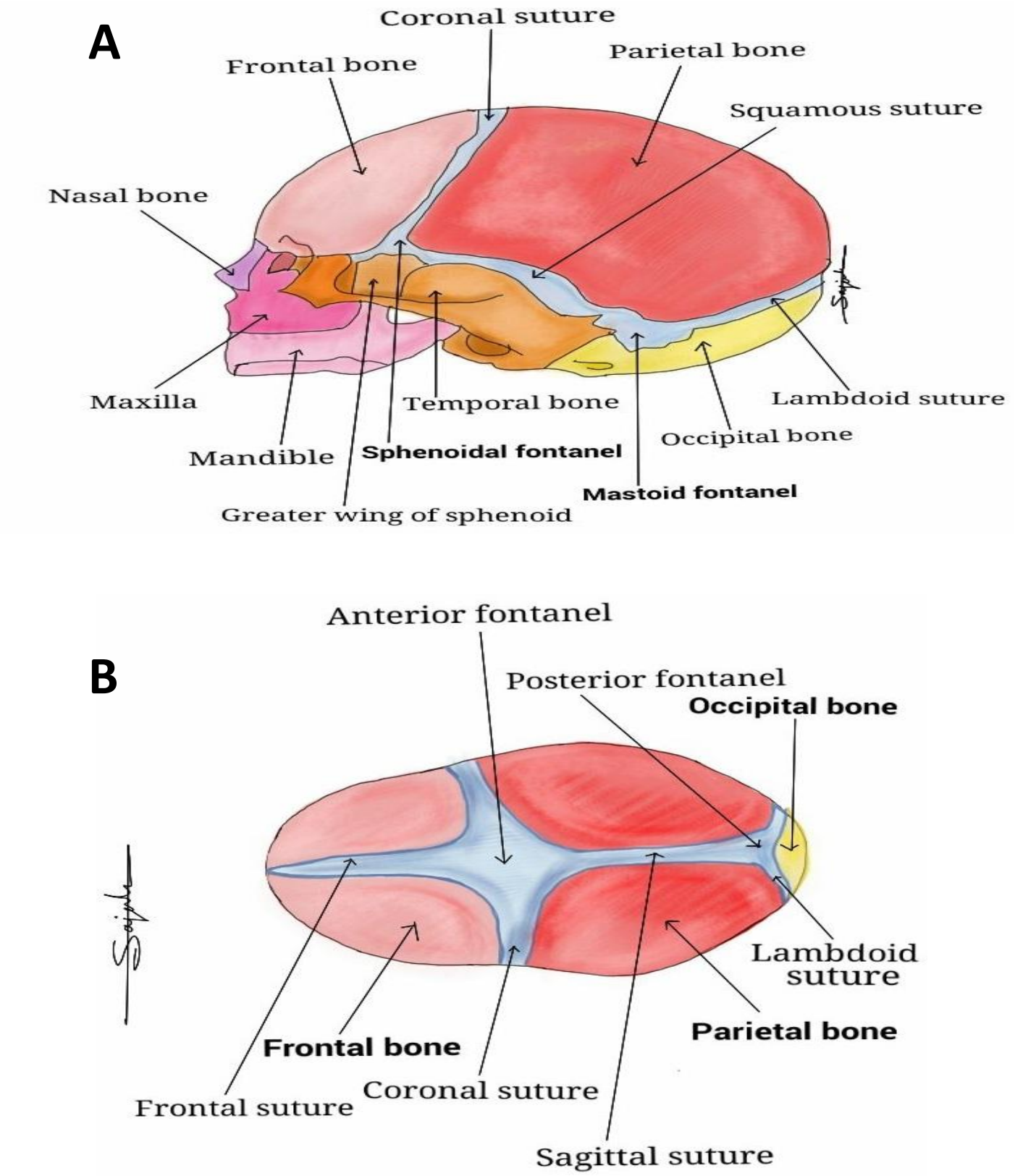


Fig. 7.3 *A newborn skull showing the membranous neurocranium.*
A) lateral view. B) superior view.

- **Cartilaginous neurocranium** or chondrocranium: Several cartilaginous condensation (3 lateral and 3 in the midline) derived from neural crest (**except** the basilar part of the occipital bone which is formed of mesodermal sclerotomes) are first seen. Later, chondrocranium undergoes endochondral ossification.

- From the rostral end, fusion of **trabeculae cranii** → cribriform plate of ethmoid bone.
  Hypophyseal C. develops around the hypophysis cerebri or pituitary gland (cranial limit of the notochord) and fuses → sphenoid bone.
  Parachordal C. arises around the notochord on each side and unite with three occipital somites → contribute to the formation of the base of the occipital bone.
  Ala orbitalis → lesser wing of sphenoid (ala = wing, orbitalis = lesser wing of sphenoid, above the orbit).
  Ala temporalis → greater wing of the sphenoid bone.
  Otic capsule develops around the otic vessels → mastoid and petrous parts of the temporal bone (otic = ear, lies within the petrous part of the temporal bone).
  Nasal capsules are formed around the nasal cavities → sharing in the formation of the ethmoid bone (Fig. 7.4).

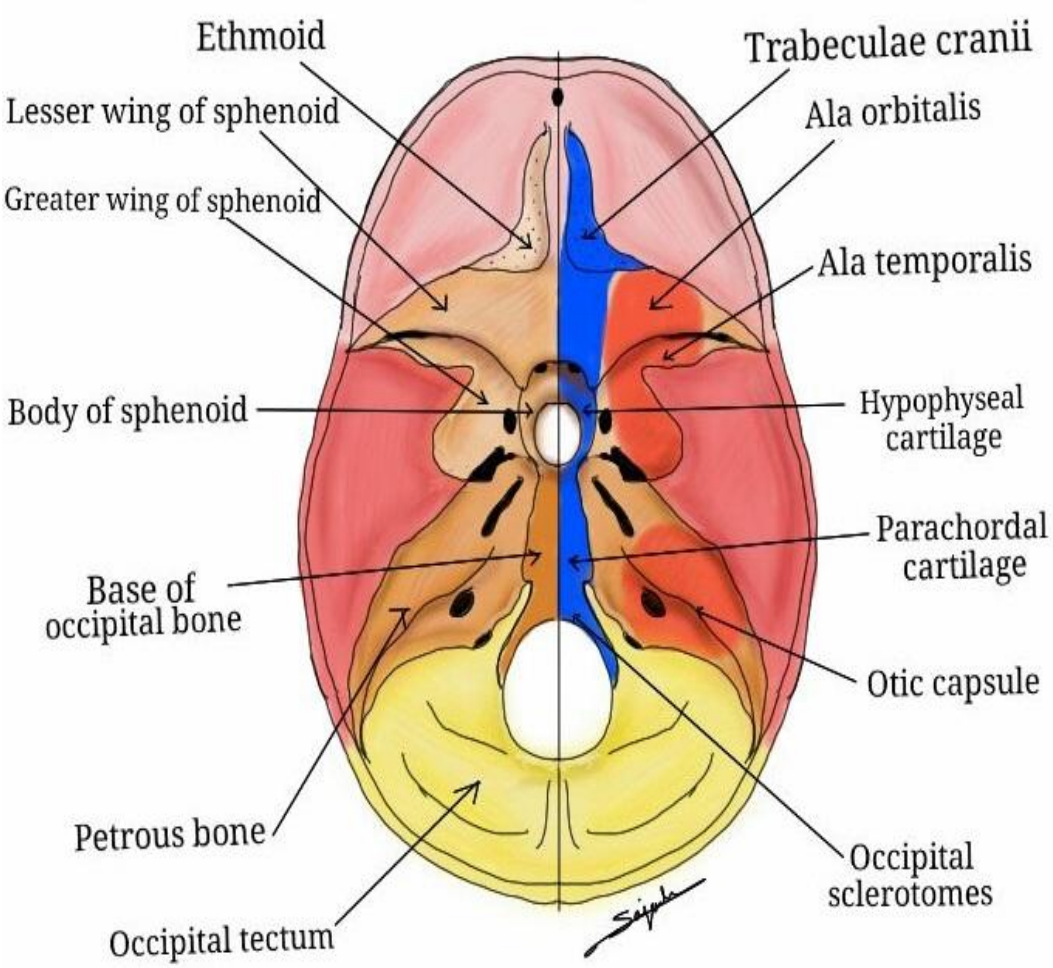


Fig. 7.4 Showing the chondrocranium (viewed superiorly).

- **Membranous viscerocranium;** Composed of the maxilla, mandible, zygomatic and squamous part of temporal bones, all of these originate from the ***1st* pharyngeal arch**.

- **Cartilaginous viscerocranium;** Formed mainly from both *1st* (incus and malleus) and *2nd* (stapes, styloid process and part of hyoid bones) pharyngeal arches.

- **Osteogenesis** or ossification is the formation of bone from mesoderm (connective tissue), occurs during the development via two ways;

  A. **Intramembranous ossification;** Mesenchyme ⟹ bone.
  Includes broad, flat bones, skull bones (**except** mandible) and intramembranous bones.

  B. **Endochondral ossification;** Mesenchyme ⟹ hyaline cartilage model ⟹ bone.
  Includes most skeletal and endochondral bones.

- Cranial **anomalies**;

  A. Acrania**:** A complete or partial absence of the neurocranium (rare).

  B. **Craniosynostosis:** Premature or early fusion (synostosis) of one or more cranial sutures, includes;

  1. **Scaphocephaly** or long skull**:** Synostosis of sagittal sutures leads to frontal and occipital expansion.

  2. **Brachycephaly** or short skull: Synostosis of coronal suture results in high, tower- like skull.

  3. Asymmetrical **plagiocephaly:** Unilateral synostosis of coronal suture results in a twisted skull.

  4. **Trigonocephaly:** Synostosis of the metopic (frontal) suture leads to deformity of the frontal bone.

  C. **Cranioschisis:** Failure of the cranium to close completely, if the brain's exposed to the amniotic fluid (**exencephaly**) and thus, degenerates, results in **anencephaly** (an = without).

  D. **Microcephaly:** Poor growth of the brain with the normal size of the face, usually associated with severe mental retardation.

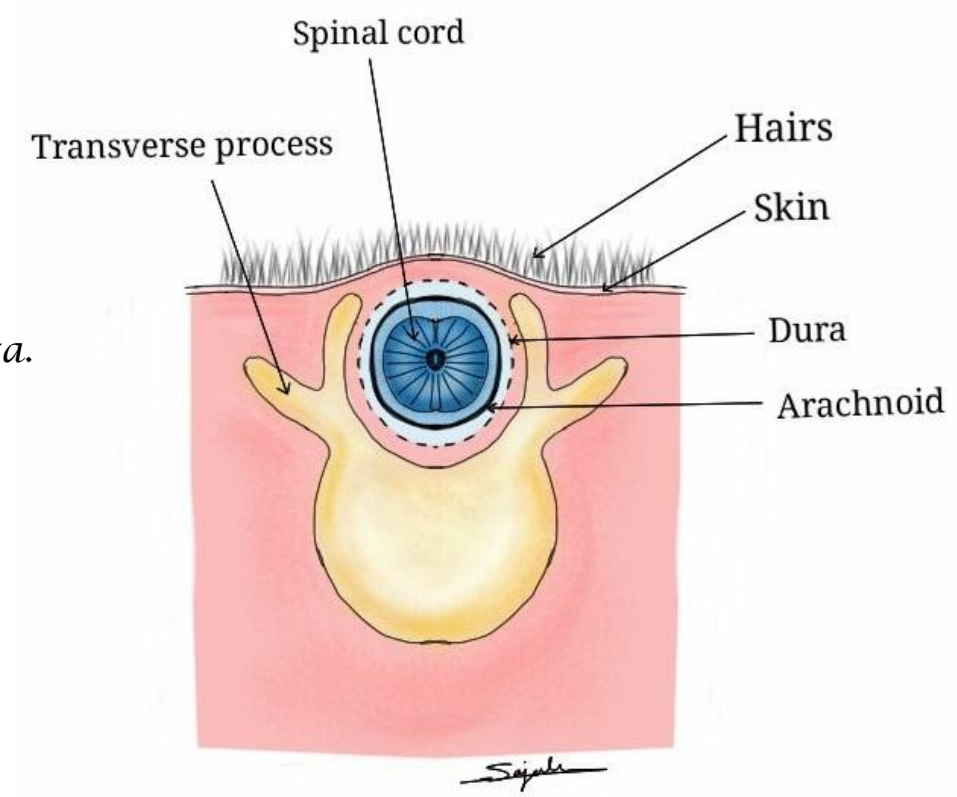


Fig. 7.5 *Spina bifida occulta.*

Chapter 8 || The Muscular System

Objectives:

- Identify the origin of each type of the muscles.
- Talk briefly about the musculature anomalies.

☐ Skeletal, smooth and cardiac muscles are derived generally from **mesoderm** except those of the iris which are derived from neuroectoderm.

SKELETAL MUSCLE

☐ Paraxial mesoderm forms blocks or segments known as **pharyngeal arches** or **somitomeres** (from 1 to 7 in the head region don't form somites), the remaining from the occipital region condense to form 42- 44 pairs of somites in the trunk region and form the axial skeleton, limbs and body wall, the last 5 to 7 somites surround the caudal end disappear later thus, the final count of somites is around 35 pairs.

☐ As mentioned previously, somites further differentiate into the sclerotome, myotome (myo=muscle) and dermatome (see Chapter 5).
Skeletal muscle originates from myotomic portions of somites.

☐ Muscles of the head and neck originate from somitomeres 1-7.

Related with neuroanatomy; ''Extraocular muscles''

Three muscles (Superior, medial and inferior recti) are innervated by the **third** cranial nerve because it has the same origin (somitomeres 1 and 2). Note the mnemonic (**LR6**) indicates that the **l**ateral **r**ectus muscle innervated by CN **VI** because it originates from somitomere 5; somitomere 3 gives origin to the **s**uperior **o**blique muscle which innervated by CN **IV** (**SO4**), **occipital myotomes** form the tongue muscles that has motor innervation via hypoglossal nerve (glossal=tongue) **except** the palatoglossus muscle (by CN X). Preotic myotomes refers to the somitomeres 1-3.

- Trunk musculature is developed from myotomes in the same region, each myotome divides into;
  a. dorsal epaxial (innervated by dorsal primary rami of spinal nerves)
  b. ventral hypaxial (innervated by ventral primary rami of spinal nerves).
  The **e**paxial (ep=above) → **e**xtensor muscles of the vertebral column and neck.
  Hypaxial (hyp=below) → scalene, prevertebral, geniohyoid, intercostal, abdominal and infrahyoid muscles, lateral and ventral flexors of the vertebral column, quadratus lumborum muscle, and pelvic diaphragm.

SMOOTH MUSCLE

- Most smooth muscles are derived from splanchnic (visceral) mesoderm **except** that of the mammary gland, sweat glands and pupil of the eye which are ectodermal in origin.

CARDIAC MUSCLE

- Cardiac muscle is derived from **splanchnic mesoderm** that encloses the primitive heart tube, later on called myocardium.

- Variation of some muscles is the most common **anomaly** of the muscular system, includes;

  A. **Prune belly syndrome**: Involving cells of the hypaxial, characterized by the absence of the abdominal musculature causing a weakness of the abdominal wall, that the abdominal organs are seeable and easily palpated.

  B. **Poland sequence**: Complete or partial absence of pectoralis major muscle usually associated with absence or displacement of the nipple and often digital defects.

  C. **Wryneck** or congenital torticollis: Shortness of the sternocleidomastoid muscle resulting in rotation and tilting of the head.

Chapter 9 || The Limbs

Objectives:

- Describe the formation, vasculature, musculature and rotation of the limbs.
- Name the abnormalities that related to the limbs development.

☐ By the end of the 4_{th} week, the limbs are oriented as elevations or bulges on the ventrolateral side of the embryo called **limb buds**.
The upper limb buds firstly appear (day 26-27) 1-2 days before the lower limb buds appear. Each limb bud comprised of a core of mesenchyme (differentiated from the parietal layer of lateral plate mesoderm → connective tissues and bones of the limb), covered by a layer of ectoderm. The latter thickens at the apex of each limb bud to form an **apical ectodermal ridge** (**AER**). The AER produces fibroblast growth factor (FGF) to interact with the limb mesenchyme, which enhances the growth, elongation and proliferation of the limb.

Related to molecular biology ***''Proliferation of the limb buds''***

- Bone morphology (type and shape) and patterning in the formation of the limbs are regulated and determined by ***HOX*** or homeobox genes.
- Initially, *FGF* activates the zone of polarizing activity (*ZPA*): a cluster of mesodermal cells aggregate at the base of the limb buds. The *ZPA* produces retinoic acid (vitamin A), which promotes expression of sonic hedgehog (*SSH*) genes controlling the limb's anteroposterior axis.

☐ At the *5th* week, Limb musculature is derived from somites (myotomes) as two condensations, anterior and posterior. The upper limb buds lie opposite somites C4 – T2 whereas the lower limb buds appear opposite L2 – S2 segments.

Limb / condensation	Anterior condensation	Posterior condensation
Upper limb	Flexor and pronator muscles	Extensor and supinator muscles
Lower limb	Flexor and adductor muscles	Extensor and abductor muscles

Table 9.1 Relation between muscles and condensations that form the upper and lower limbs.

- During the *6th* week, mesenchymes in the terminal ends of the buds flatten to form hand and footplates. The hand and footplates are separated from the future forearm and leg by first circular constriction (future wrist and ankle joints) respectively. There are some mesenchymal condensations in between the bones will form the future joints.

- By the end of the *6th* week, the hand and footplates condense to form digital rays, notches between digits appear as a result of apoptosis (programmed cell death) within the AER, apoptosis continues in the interdigital spaces. Finally, digits separation is completed at week 8.

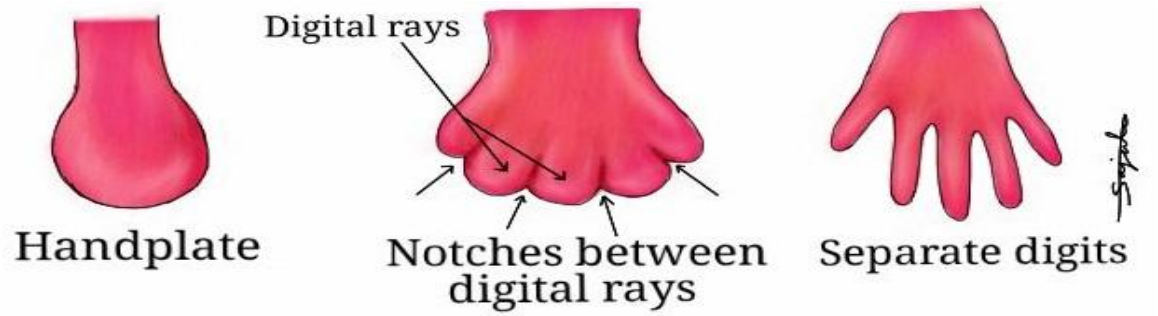


Fig. 9.1 Illustrations of the different stages for development of the hand from 4th week until the end of the embryonic period.

- Rotation of the limbs occur in the opposite directions early in the *7th* week, the upper limb rotates **90° laterally →** lateral position of the thumb, extensors compartment lie on the posterior and lateral side of the limb, flexors compartment lie anterior and elbow joints point dorsally.

  On the other side, the lower limb rotates **90° medially →** the future knee joint points ventrally, big toe lies medially, extensor muscles lie anteriorly and flexor muscles lie posteriorly.

- The subclavian artery on each side continues as the **axis artery** in the upper limb buds which terminates in a terminal plexus near the distal part of the limb bud. The terminal plexus forms the superficial and deep palmar arches. Initially, the axis artery buds the median and posterior interosseous arteries. Later on, it gives the radial and ulnar arteries. The axis artery remains in the adult as the axillary, brachial, anterior interosseous and deep palmar arteries.

- The umbilical arteries form the **axis artery** which runs in the lower limb and ends in a terminal plexus (future deep plantar arch). The axis artery gives rise to the anterior and posterior tibial arteries. Most of the axis artery disappears and persists in the adult as the sciatic, inferior gluteal, popliteal and peroneal arteries. The external iliac artery sprouts the femoral artery which gives rise to the profunda femoris artery.

☐ All limb's bones are derived from the somatic layer of the lateral plate mesoderm, primary ossification centers appear in these bones by the *8th* week and undergo endochondral ossification.

> ***N.B.*** The **clavicle** has some distinct characteristics;
>
> i. Undergoes both endochondral and membranous ossification.
>
> ii. Is the **only** long bone to undergo Intramembranous ossification.
>
> iii. First bone to be ossified, and last one to complete ossification.

☐ The joints develop from the **interzone** (mesenchymal region between the primordia of two bones). The latter also forms a capsule, synovial membrane and ligaments of the joint.

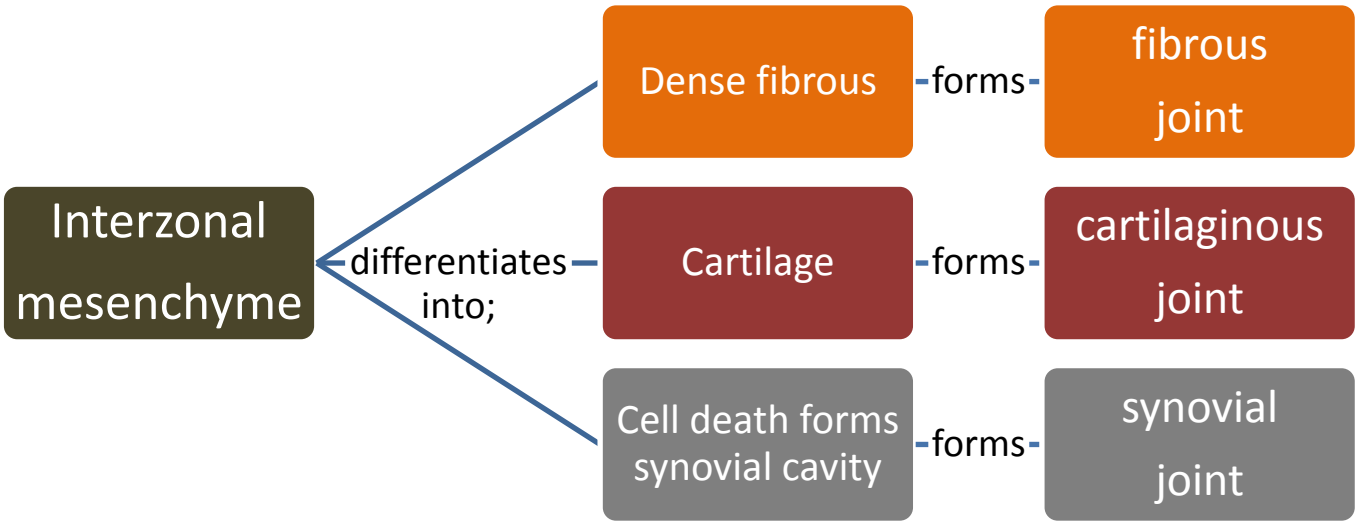


Fig. 9.2 Schema shows the formation of the type of joints.

☐ Most of the limb **defects** are caused by genetic disorders;

A. **Amelia** (A=without, melia= limb): Complete absence of one or more extremities.

B. **Meromelia** (mero=part): Partial absence of one or more limbs (e.g., **phocomelia**: small, irregular shape of the bone).
Micromelia (micro=small): Abnormally small or/and short extremities.

C. Some anomalies are seen in digits like; **Brachydactyly** (short digits), **polydactyly** (extra digits), **syndactyly** (fused digits) and **ectrodactyly** (missed digits).

D. **Cleft hand and foot**: Failure of growth of one or more digital rays leads to missing one or more central (between second and fourth) digits.
The foot or hand appears as two parts facing (oppose) each other.

E. Congenital dislocation of the hip joint. F. Some bones may be absent (e.g., radius).

Chapter 10 || Cardiovascular System

Objectives:

- Describe the initiation, development and partitions of the heart.
- Describe the beginning of the arterial and venous systems and their derivatives.
- Mention each stage of fetal circulation and changes after delivery.
- Define the significant anomalies of the cardiovascular system.

☐ The cardiovascular system or CVS is the first system to develop (during the 3_{rd} week), and function to provide the increasing demand (nutrients and oxygen) of the embryo. The CVS {Heart, blood vessels and cells} is mesodermal in origin.

HEMATOPOIESIS

☐ In the beginning, hematopoiesis (blood cell formation) was from the wall of the yolk sac (3-10 weeks), blood vessels and body mesenchyme (week 5) and liver (6_{th} week till birth). Since the 12_{th} week, blood cells originate from the spleen, thymus and lymph glands. Bone marrow hematopoiesis begins approximately during the week 30.
Note that there is overlapping in hematopoietic sites.

Bear in your mind >>
Hb **F** is the major and unique haemoglobin found in the **f**etus during gestation.

VASCULAR SYSTEM

☐ Mesenchymal (mesodermal) cells differentiate into angioblastic cells. The angioblasts group together to form blood islands. Blood vessels are developed via two mechanisms;
i. vasculogenesis -de novo formation- in which vessels develop from blood islands and
ii. angiogenesis (new vessels sprout or bud from pre-existing one), angio = blood vessel.
Endothelial cells arise from angioblasts.

CARDIAC DEVELOPMENT

☐ Initially, Cardiac progenitor cells lie within the epiblast, just lateral to the primitive streak. Through the latter, these cells migrate (during 16-18 days) into the visceral layer of lateral plate mesoderm forming a U - shaped cluster of cells in front of the neural plate and the oropharyngeal membrane , this is now called heart or cardiogenic field (Fig. 5.1).

- ☐ By day 19, the cardiogenic field mutates to form two parallel endocardial tubes. The pericardial cavity develops from intraembryonic coelom derived from lateral plate mesoderm (see Chapter 5).

- ☐ The heart invaginates within the pericardial cavity;
  it's suspended from the pericardial cavity by a mesentery called dorsal mesocardium.
  The latter forms the **transverse sinus** of pericardium.

- ☐ As the embryo undergoes folding by day 21, two endocardial tubes fuse in the midline to form a single, primitive heart tube. the heart and pericardial cavity migrate to the cervical region and eventually to the thorax.

- ☐ The heart starts to beat on the 22_{nd} day.

- ☐ In a 4-week embryo, Blood pumped out of the heart via the first aortic arches to a pair of the dorsal aortae that's in connection with the cephalic horns of the endocardial tubes.
  Venous drainage of the heart tube is carried by three pairs of veins; umbilical, cardinal and vitelline veins.

Cardiac Loop

- ☐ As a result of rapid lengthening and expansion of the heart tube, the latter gets divided into five chambers by four constrictions (see Fig. 10.1). These chambers bend (during week 4) under the influence of further elongation to form S-shaped **cardiac loop**.
  During the looping process, the heart tube loops to the *right* → the bulbus cordis and primitive ventricle lie ventral to the primitive atrium and sinus venosus.

- ☐ A congenital **dextrocardia** (situs inversus): the primitive heart tube loops to the *left* instead of the right, causing transposition of the heart and its great vessels to the right side as in a mirror image.

Heart chamber		Adult structure
Bulbus cordis	Distal part or **truncus arteriosus**	Roots of aorta and pulmonary trunk
	Conus cordis	Infundibulum of right ventricle and vestibule of left ventricle (smooth parts).
	Proximal part	Right ventricle (trabeculated part)
Primitive ventricle		Trabeculated (rough) parts of both ventricles.
Primitive atrium		Trabeculated (rough) parts of both atria.
Sinus venosus	Right horn	Smooth part of right atrium (sinus venarum).
	Left horn	Coronary sinus.

Table 10.1 Derivatives of the chambers of the primitive heart tube.

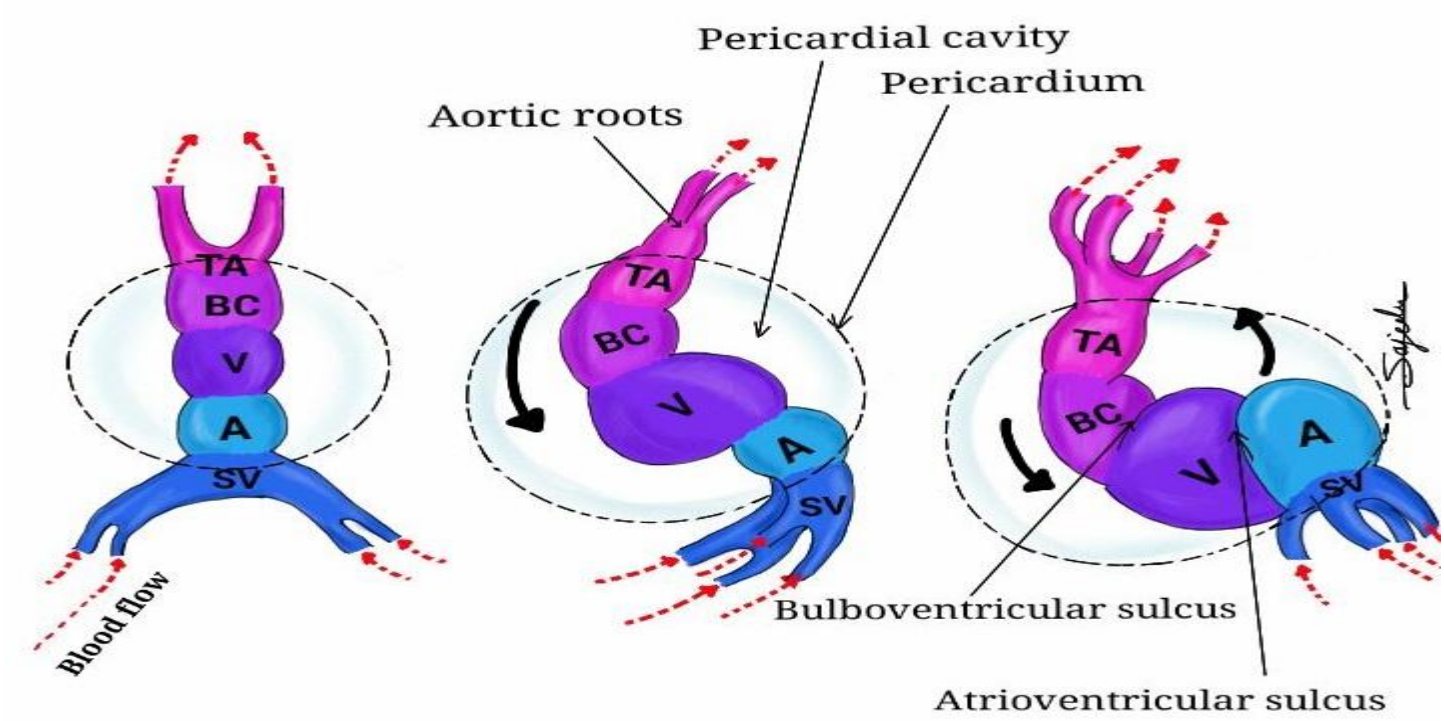


Fig. 10.1 *Ventral view of the primitive heart tube and its looping process. From the cranial end, TA= truncus arteriosus, BC= bulbus cordis, V= primitive ventricle, A= primitive atrium, SV= sinus venosus.*

☐ Bulbus cordis is separated from primitive ventricle by; **bulboventricular sulcus** (future interventricular sulcus).

Primitive atrium and ventricle are separated by; **atrioventricular sulcus**.

☐ Toward the end of the 4_{th} week, mesenchymal cells of the dorsal and ventral walls of the primitive atrium form the **endocardial cushions** on their respective sides.
The two endocardial cushions (future AV valves) increase in size, approach each other and fuse together to form septum that divides the **atrioventricular (AV) canal** into right and left AV canals.

☐ **Clinical considerations** of the AV canal;

A. **Persistent AV canal**: Non fusion of the AV cushions combined with interatrial and IV septal defects.

B. **Ostium primum defect**: Partial fusion of the AV cushions with the septum primum. The ostium primum is never closed.

C. **Tricuspid atresia**: Agenesis or failure of tricuspid valves to form. This anomaly blocks blood stream from the atrium to the ventricle on the right side. It's usually associated clinically with: **1.** patent foramen ovale, **2.** hypertrophy of left ventricle, **3.** interventricular septum defects (VSDs), and **4.** underdeveloped right ventricle.

D. **Ebstein's anomaly**: Displacement of the tricuspid valves towards the right ventricle leads to hypertrophy or enlargement of the right atrium.

Atrial Septum

☐ The primitive atrium partitioned into right and left atria by the **interatrial septum**.
It develops in several steps;

A. Descending of the incomplete **septum primum** from the roof of the primitive atrium towards the AV endocardial cushions. The remainder part between the septum primum and AV cushions is called **ostium** (=opening) **primum**.

B. With the further growing of the septum primum, it fuses with AV cushions to close the ostium primum leaving a cranial foramen (caused by apoptosis) called **ostium secundum**.

C. On the right hand of the septum primum, a C-shaped **septum secundum** appears and overlaps the ostium secundum. A gap left by the septum secundum called **foramen ovale** and it's valve formed by septum primum.

D. At birth, the foramen ovale functionally (passage of blood from the right atrium to the left atrium) closes due to anatomical fusion of the two septa and becomes **fossa ovale**. Later in life, the septum primum represents → fossa ovale;
septum secundum represents → **anulus ovalis** (fossa ovale's margin).

☐ There are four small pulmonary veins (2 from each lung bud) form the left and right pulmonary veins, union of the latter forming a single common pulmonary vein. Later, it opens and gets absorbed into the left atrium. Then, two pulmonary veins are absorbed and lastly, four separate branches are open in the left atrium.

☐ There is a vertical or dividing muscular line separates the posterior smooth wall of the right atrium from the anterior rough wall called **crista terminalis**, its lower part is formed by upper part of the right venous valve, but the upper part is formed from septum spurium. The crista terminalis is marked externally by the **sulcus terminalis**.

	RA	LA
Smooth part	Absorbed right horn of sinus venosus	Absorbed common pulmonary vein
Rough part	Right half of primitive atrium Right half of AV canal	Left half of primitive atrium Left half of AV canal
The Rt and Lt upper part of the atrioventricular canal, respectively		

Table 10.2 Summary of development of both atria.

☐ **Atrial Septal Defects** (ASDs) are most common in females than males;

A. **Patent foramen ovale**: In 25% of hearts, septum secundum fails to develop and the foramen ovale remains open between the two atria.

B. **Premature closure of the foramen ovale** in the intrauterine life results in hypertrophy of the right aspect of the heart and underdevelopment of the left aspect. Shortly, this fetus will die after birth.

C. **Ostium secundum defects**: a large opening between two atria caused by excessive resorption of septum secundum or septum primum or both.

D. **Common atrium** or (**cor triloculare biventriculare)** is the most serious condition. It defined as complete absence of the interatrial septum. Thus, the heart consists of one -common- atrium and two ventricles.

Interventricular Septum

☐ The **interventricular (IV) septum** consists of;

A. Thick **muscular part** arises as a median outgrowth from the floor (or near the apex) of the primitive ventricle. It ascends toward the AV cushions but doesn't reach it, leaving an opening called **IV foramen**.

B. Thin **membranous part** develops by a proliferation of mesenchymel cells that originate from the left bulbar ridge, right bulbar ridge and AV endocardial cushions. Fusion of the AV cushions with the bulbar ridges, and further proliferation of the membranous IV septum resulting in a closure of the IV foramen (at week 7).

☐ VSDs are the most common group of congenital heart disease (CHD), including;

A. **Membranous VSDs** (more serious).

B. **Muscular portion VSDs** (most common).

C. **Common ventricle** or (**cor triloculare biatriatum)** is an absence of the whole IV septum. So, the heart composed of one common ventricle and two atria.

Aorticopulmonary Septum

☐ Neural crest cells form the bulbar and truncal ridges. The ridges grow, twist around each other and finally fuse to form a spiral **aorticopulmonary (AP) septum** that divide the truncus arteriosus into ascending aorta and pulmonary trunk.

☐ **Anomalies** of the AP septum;

A. **Fallot's tetralogy**: A small diameter of the pulmonary trunk and large diameter of the aorta caused by unequal division of the conus. It's a group of four major cardiac defects, consists of; **[PROV]**

1. **P**ulmonary stenosis.
2. Aorta dextroposition (**o**verriding).
3. **V**SDs.
4. **R**ight ventricle hypertrophy.

B. **Persistent truncus arteriosus**: Failure of AP septum to develop; thus, truncus arteriosus wouldn't be divided into pulmonary trunk and aorta results in one large trunk leaving the heart. It's always accompanied by membranous VSD.

C. **Transposition of the great vessels**: Nonspiral or straight formation of the AP septum. It abnormally leads to the formation of the aorta from the RV and pulmonary trunk from the LV.

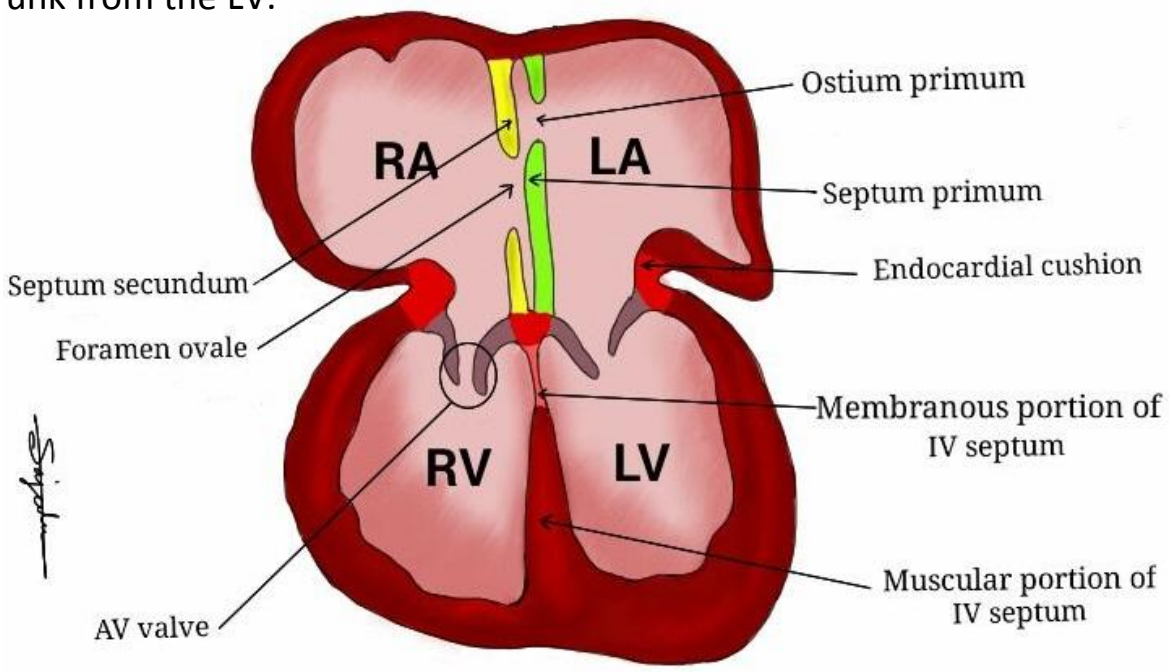


Fig. 10.2 Frontal section showing an embryonic heart at approximately 8 weeks.

Valves

- **Semilunar** (aortic and pulmonary) **valves:** Three swellings of mesenchymel tissue appear around the orifices of the pulmonary trunk and aorta, these swellings are excavated and reshaped.

- **AV** (mitral and tricuspid) **valves:** Develop similarly from tissue surrounding the orifices of the AV canals. Cusps of AV valves are connected by thick muscular bundles or strands to the wall of the ventricle. Later on, some of these bundles form the **papillary muscle** and **chordae tendineae**.

Conducting System

- At week 5, the right atrium is incorporated into the right wall of the sinus venosus. Cardiac myocytes from this region will form the **sinoatrial (SA) node**.
  Muscular ring around the AV canal incorporated into the left wall of sinus venosus.
  The AV bundle or bundle of His runs in the IV septum where it splits into right and left bundles.

☐ A congenital **ectopia cordis**: Failure of the sternum to develop, the heart is exposed and located outside the thoracic cavity (rare condition).

VENOUS SYSTEM

☐ During the *4th* week, three main pairs of veins drain into the left and right horns → sinus venosus → primitive atrium. As follows;

A. **Vitelline** veins: receive blood from the yolk sac and gut (poorly oxygenated).

B. **Umbilical** veins: return blood from the placenta (well oxygenated).

C. Short **common cardinal** or somatic (somatic=body) veins: Union of the anterior (drains cranial part of the embryo) and posterior (drains caudal part of the embryo) cardinal veins; carry blood from the embryo's body (poorly oxygenated).

☐ The sinus venosus open into the primitive atrium by **sinoatrial (SA) orifice** flanked – surrounded- by right and left venous valves.
The left venous valve fuses with the **septum secundum** and interatrial septum.
The right venous valve is divided into;
i. upper portion (disappears completely) *and* **ii.** lower portion: forms valves of the IVC (inferior vena cava) and coronary sinus. Fusion of these 2 valves at the cranial end of the SA orifice forms the **septum spurium**.

		Right side	Left side
Vitelline vein		Major part of the hepatic portal system + upper part of IVC	Regresses (5_{th} week)
Umbilical vein **(later, empty into the liver)**		Disappears (7_{th} week)	Persists as the only umbilical vein
Cardinal vein	**Anterior**	Upper part of SVC	Degenerates caudally
	Common (duct of Cuvier)	Lower part of SVC	Oblique vein of LA
	Posterior	Azygos vein	Disappears

Table 10.3 Fate of the major paired veins.

☐ After birth, the left umbilical vein fibroses and becomes the **ligamentum teres**.

☐ The posterior cardinal veins gradually disappear and are replaced by the subcardinal and supracardinal veins.

☐ From the *5th* to the *7th* weeks, additional small veins are formed:

A. Subcardinal veins → renal and gonadal (spermatic or ovarian) veins and part of IVC.
B. Sacrocardinal veins drain the lower limbs.

C. Supracardinal veins → azygos, intercostal and hemiazygos veins and part of IVC.

☐ The IVC is formed from five main segments as follows;

A. **Suprahepatic** segment *(proximal part of right vitelline vein)*.
B. **Hepatic** segment *(right vitelline – subcardinal anastomosis)*.
C. **Prerenal** segment *(right subcardinal vein)*.
D. **Renal** segment *(right subcardinal-supracardinal anastomosis)*.
E. **Postrenal** segment *(right supracardinal vein)*.

☐ Numerous anastomoses and communications link these veins such as;
Ductus venosus: develops within the liver; shunts blood from the umbilical veins to IVC. It gets obliterated after birth and becomes **ligamentum venosum**.

☐ **Right brachiocephalic** (innominate) **vein** develops from the uppermost part of the right anterior cardinal v.
left brachiocephalic vein represents the transeverse anastomotic vein between the anterior cardinal vs.

☐ **Internal jugular veins** arise as terminal part of the anterior cardinal vs.
External jugular veins are developed from the venous plexus in the face.

☐ **Right common iliac vein** arises from the most caudal part of the right posterior cardinal v .
Left common iliac vein: is the anastomosis between the posterior cardinal vs.

☐ **Venous system defects** include;

A. **Double IVC**: Is caused by persistence of the left Supracardinal v. as second IVC.
B. **Absence of the IVC**: Failure of the hepatic segment of the IVC to develop. Consequently, blood is drained via azygos and hemiazygos vs.
C. **Left SVC**: Due to persistence of the left anterior cardinal v. and obliteration of the right common and anterior cardinal vs.
D. **Double SVC**: In addition to persistence of the left SVC, the left brachiocephalic v. fails to form.

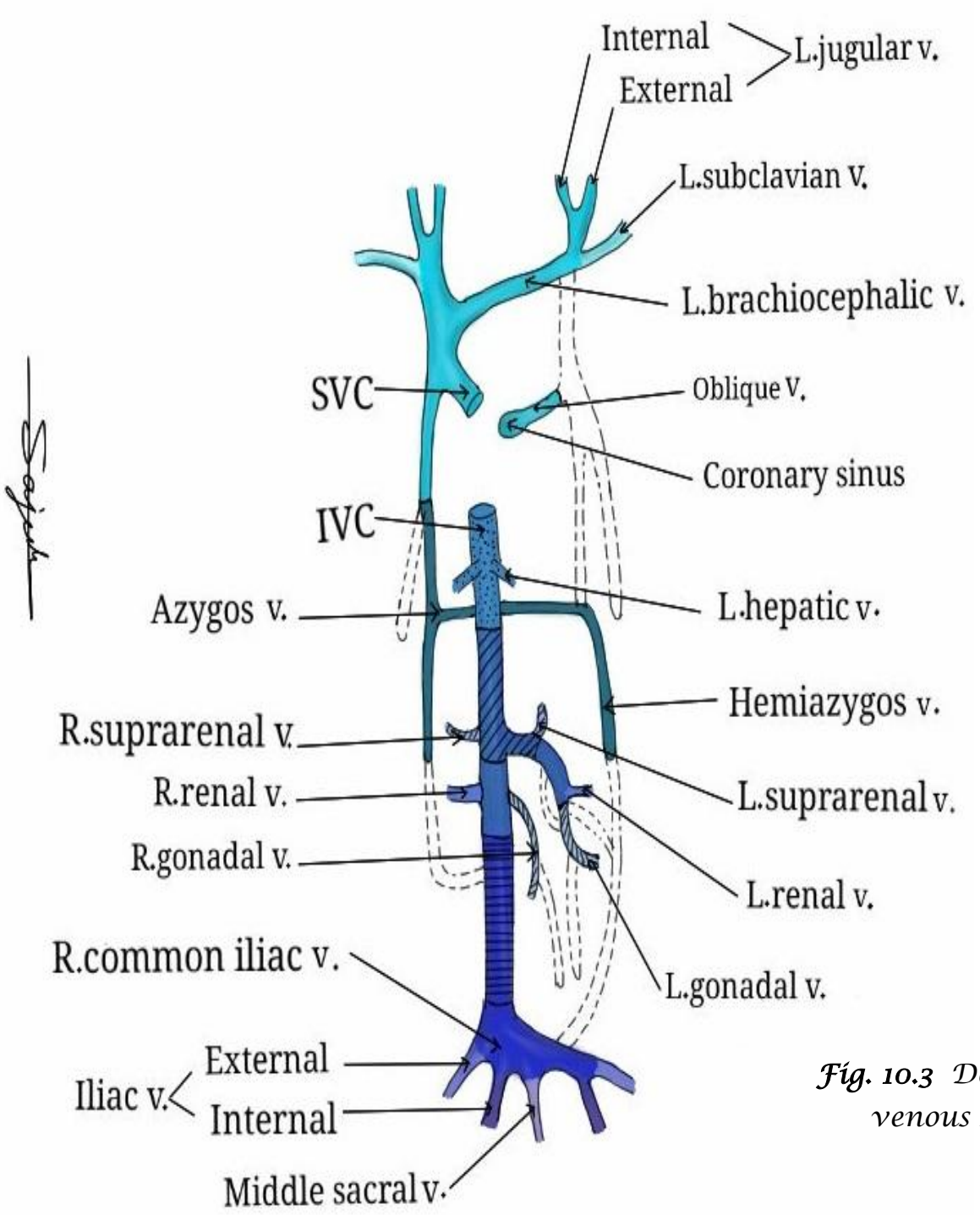


Fig. 10.3 *Development of the venous system.*

ARTERIAL SYSTEM

☐ It develops mainly from;

A. Six pairs of **aortic arches** arising from the **aortic sac** (dilation at the distal end of the ductus arteriosus), form the arterial pattern of the head and neck. The aortic arches begin from the aortic sac, terminate in the dorsal aortae and course within the pharyngeal arches (Chapter 15).

B. Right and left **dorsal aortae**, form the arterial pattern of the rest of the body.

Aortic arch	Arterial derivative	
1	Most of it has disappeared Small bit forms the **maxillary a.**	
2	Most of it has disappeared Small bit forms the **stapedial a.**	
3	Proximal part: **common carotid a.** Distal part: 1_{st} part of the **internal carotid a. (ICA)** **External carotid a.** sprouts as a new branch	
4	On the right side: **right subclavian a.** (proximal part) On the left side: **arch of the aorta**	
5	Regresses	
6	On the right side; proximally, **right pulmonary a.** distally, disappears	On the left side; proximally, **left pulmonary a.** distally, **ductus arteriosus**

Table 10.4 Aortic arch derivatives.

☐ In the adult, the ductus arteriosus is replaced by the **ligamentum arteriosum**.

☐ The remainder portion of the ICA is developed from the dorsal aorta.

☐ The distal part of the **Rt subclavian artery** is formed by Rt dorsal aorta and Rt 7_{th} intersegmental artery. Intersegmental a. are branches of Rt dorsal aorta.
Lt subclavian artery is formed by Lt 7_{th} intersegmental artery.

☐ With further development, a lot of modifications occur in the arterial system. For example, obliteration of the **carotid duct** (the dorsal aorta between the 3_{rd} and 4_{th} aortic arches).

☐ The Lt recurrent laryngeal nerve (a branch of the left vagus nerve) hooks around the distal part of the left 6_{th} aortic arch (ductus arteriosus).
But, the distal part of the Rt 6_{th} aortic arch disappears, and the 5_{th} aortic arch completely degenerates. So, the Rt recurrent laryngeal nerve moves up and hooks around distal part of the 4_{th} aortic arch (right subclavian a.).

☐ Caudal to the 6_{th} aortic arch, the right and left dorsal aortae fuse to form a single dorsal aorta.

Branches of the dorsal aorta can be subdivided into three distinct groups;

Embryologic structure		Adult equivalent
posterolateral branches (intersegmental arteries)		1. Neck: **vertebral a.** 2. Thorax: 11 posterior **intercostals** and 1 **subcostal a.** on each side 3. Abdomen: 5 **lumbar a.**, the fifth lumbar persists as **common iliac a**. 4. Pelvis: **lateral sacral a.** The most caudal end becomes the **median sacral a.**
Lateral branches		**Renal, suprarenal and gonadal** (ovarian or testicular) **a.**
Ventral branches	Vitelline arteries	**Celiac arterial trunk** supplies the foregut **Superior mesenteric artery** supplies the midgut **Inferior mesenteric artery** supplies the hindgut
	Umbilical Arteries	Proximal parts: **superior vesical** and **internal iliac a.** Distal parts: obliterate and become **medial umbilical ligaments**

Table 10.5 Fate of the dorsal aorta.

☐ Fusion of the paired ventral aortae forming the **aortic sac**. The latter, divides distally into right and left horns,

Rt horn subsequently → **brachiocephalic a.**

Lt horn → proximal part of the **arch of the aorta**.

At the proximal or lower part of the aortic sac, the ascending aorta and pulmonary trunk communicate with the 4_{th} and 6_{th} aortic arches, respectively.

☐ The **aorta** is formed from;

A. Ascending aorta (bulbus cordis).

B. Beginning of the arch of the aorta (Lt horn of the aortic sac).

C. The rest of the arch of the aorta (Lt 4_{th} aortic arch).

D. Descending thoracic aorta (Lt dorsal aorta).

☐ **Coronary arteries** are developed from two sources;

A. Angioblasts which are distributed over the surface of the heart.

B. The epicardium itself.

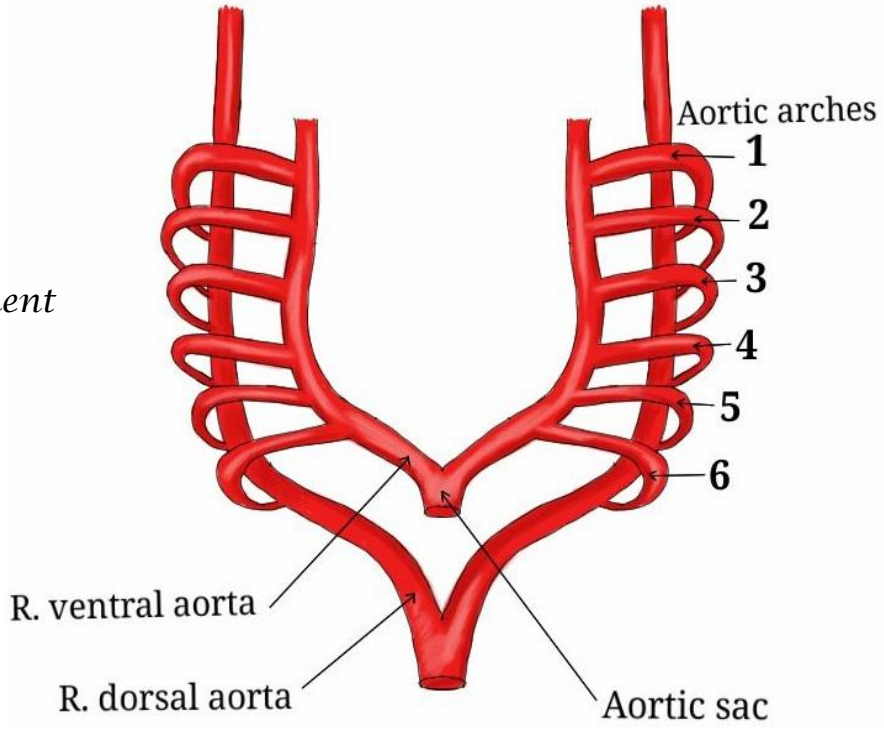


Fig. 10.4 *Initial stage of the development Of the arterial system.*

☐ Common **anomalies** of the arterial system;

A. **Patent ductus arteriosus** (patent=open): Non obliterated ductus arteriosus results in connection or channel between the left pulmonary trunk and the arch of the aorta, it's most seen in premature infants.

B. **Coarctation of the aorta:** Abnormal constriction of the aorta just distal to the left subclavian artery. The coarctation (=narrowing) is either superior to the ductus arteriosus (**preductal**) or inferior to it (**postductal**).

C. **Abnormal origin of the right subclavian artery**: It's formed from the dorsal aorta, and below the left subclavian artery. It courses posteriorly to the esophagus and trachea to provide the right arm. However, it is not important clinically.

D. In a **right aortic arch**, abnormal persistence of the Rt dorsal aorta accompanied by the distal part of the Lt dorsal aorta obliterates.

E. **Double aortic arch**: Developing of the abnormal right aortic arch in addition to a left one.

F. An **interrupted aortic arch**: Erasing or obliteration of the left *4th* aortic arch.

FETAL CIRCULATION

- Highly oxygenated blood comes from the mother (placenta) to the fetal liver via **Lt umbilical vein**. Poorly oxygenated blood returns back to the placenta through the umbilical a.
- In the liver, some blood enters the hepatic sinusoids, but most of it reaches the IVC via ductus venosus. Blood of IVC opens directly into the RA (through the mitral -bicuspid- valve). Then, it passes to the LA through the foramen ovale.
- Blood flows from the LA to the LV (through the mitral -bicuspid- valve). From the LV, blood is ejected to the ascending aorta to supply the heart, upper limbs, head and neck.
  A small amount of blood passes to the descending aorta.
- The deoxygenated blood drained by the SVC will enter the RA, where it passes (via the tricuspid valve) to the RV Then to the pulmonary trunk.
- On reaching the pulmonary trunk, most blood shunts (through the ductus arteriosus) to the descending aorta ⟹ umbilical arteries ⟹ placenta.
- Approximately 10% of blood in the pulmonary trunk goes to the lungs. Blood is sent back to the LA by the pulmonary veins.
- The placenta takes over the respiratory function until birth.
- At birth, many events occur such as cessation (occlusion) of the placental blood flow and expansion of the infant's lungs to begin its function (respiration). They cause closure and changes in the fetal circulation. It is summarized in Table 10.6.

Fetal structure	Adult remnant
Umbilical arteries	**Medial umbilical ligaments**
Left umbilical vein	**Ligamentum teres**
Foramen ovale	**Fossa ovale**
Ductus arteriosus	**Ligamentum arteriosum**
Ductus venosus	**Ligamentum venosum**

Table 10.6 Adult remnants of fetal circulation.

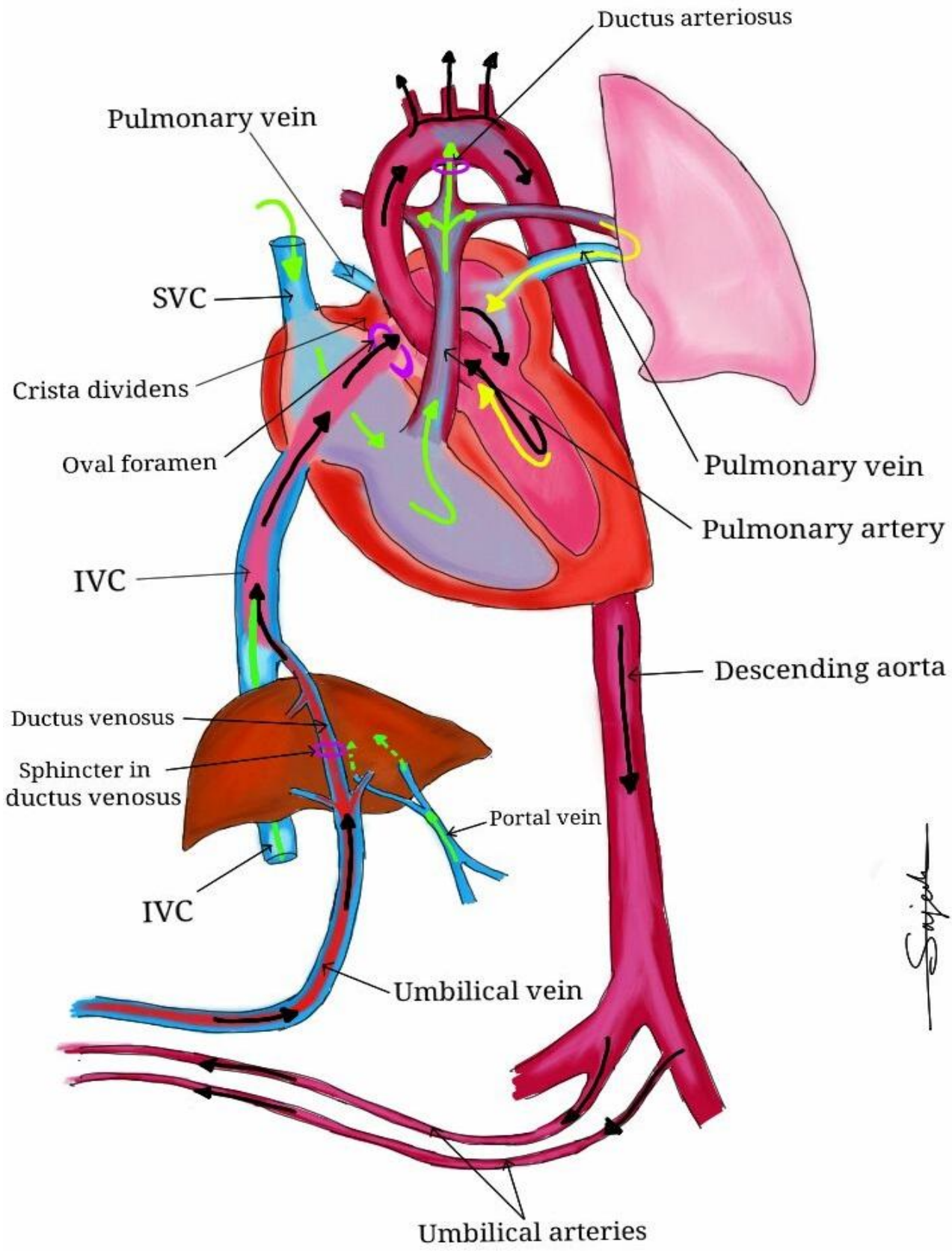


Fig. 10.5 Fetal circulatory system (before birth).

LYMPHATIC SYSTEM

- ☐ The lymphatic system develops at the end of *5th* week of intrauterine life.
- ☐ Lymphatic vessels arise as sac which originates from the endothelium of developing veins.
- ☐ Six lymph sacs are formed; 2 jugular, 2 iliac, 1 retroperitoneal and 1 cisterna chili. The Rt and Lt thoracic ducts connect the jugular lymph sacs with the cisterna chyli.
- ☐ Cranial portion of the Rt thoracic duct → **right lymphatic duct**.
  Caudal portion of the Rt thoracic duct, cranial portion of the Lt thoracic duct and the anastomosis between paired thoracic ducts → **thoracic duct**.
- ☐ Rt and Lt thoracic ducts connect with the venous system and empty into the junction or angle between the subclavian and internal jugular veins.
- ☐ The lymph nodes arise early from an aggregation of the mesenchymal cells along the course of the lymphatic vessels. The lymph nodules are not formed until birth.

Chapter 11 || Nervous System

Objectives:

- Describe the organization and function of nervous system.
- To understand the details of development of neural tube, neural crest cells and their derivatives.
- Outline the formation of various parts of the brain and spinal cord.

☐ Formation of the neural tube (see neurulation, Chapter 5).

☐ The nervous system divides into the central nervous system (CNS) and the peripheral nervous system (PNS). The latter also consists of the somatic nervous system (SNS) and autonomic nervous system (ANS). ANS includes sympathetic and parasympathetic components, each of which contains preganglionic and postganglionic fibers.

SPINAL CORD

☐ It is formed from the caudal one third of the neural tube. The latter consists of a thick, columnar, pseudostratified neuroepithelium or neuroectoderm.
These neuroepithelial cells constitute three layers or zones;

A. Inner ependymal or **ventricular** layer.

B. The neuroepithelial cells proliferate and differentiate into neuroblasts (primitive neurons) which migrate to form the intermediate or **mantle** layer.
This layer forms the gray matter of the CNS.

C. Outer **marginal** layer forms the white matter of the CNS.
It contains the axons of the nerve fibers that arise from the neurons.

☐ The **sulcus limitans** divides the intermediate layer into;
i. dorsal **alar plates** (sensory areas) and **ii.** ventral **basal plates** (motor areas).
The two alar plates (future dorsal horns) connect each other at the **roof plate** of the central canal and the two basal plates (become ventral and lateral horns) join at the **floor plate**. The latter contains the ventral median fissure.

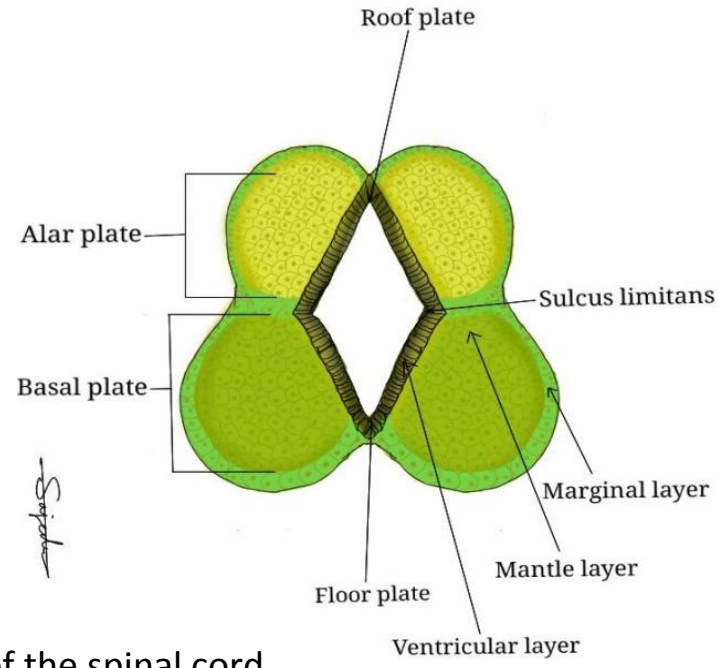


Fig. 11.1 Evolution of the spinal cord.

☐ The neuroectoderm differentiates into;

A. Ependymal cells, line the central canal of the spinal cord.

B. Neuroblasts, give rise to the nerve cells (unipolar, bipolar and multipolar cells).

C. Glioblasts, form both astroblasts and oligodendroblasts.

Microglial cells; small, supporting, phagocytic and the only type of cells in the CNS which are mesenchymal (mesodermal) in origin. They reach the nervous system within the invading blood vessels.

☐ Oligodendrocytes and Schwann cells produce the myelin in the CNS and PNS, respectively.

☐ A length of the spinal cord differs with age, further explanation in the following table;

Growth and positional changes of the spinal cord	
3rd month of development	**The spinal cord fills the whole length of the vertebral canal.**
At birth	**The spinal cord terminates at the 3$_{rd}$ lumbar vertebra.**
In the adult	**The caudal end of the spinal cord extends to the L1-L2 intervertebral disc.**

Table 11.1 Relation between the spinal cord and vertebral canal during various stages.

☐ **Anomalies** of spinal cord include;

A. **Spina bifida occulta** (see Chapter 7).

B. **Spina bifida cystica** has two severe types (see Fig. 11.2):

i. **Meningocele**: Bulging of the meninges through the defect.

ii. **Meningomyelocele**: Protrusion of the meninges and spinal cord through the defect.

C. **Spina bifida with Rachischisis** or **myeloschisis**: Exposing of the spinal cord to the surface of the back due to an open neural tube (the most severe condition of spina bifida).

- ☐ Neural crest derivatives (see Chapter 5).
- ☐ Spinal nerves arise from each segment of the spinal cord. By week 4, motor nerve fibers arise from nerve cells in the basal plates. These fibers arranged in bundles forming ventral nerve roots. The bundles of the dorsal nerve roots originate from spinal ganglia. Ventral primary rami form the major nerve plexuses (cervical, brachial and lumbosacral).

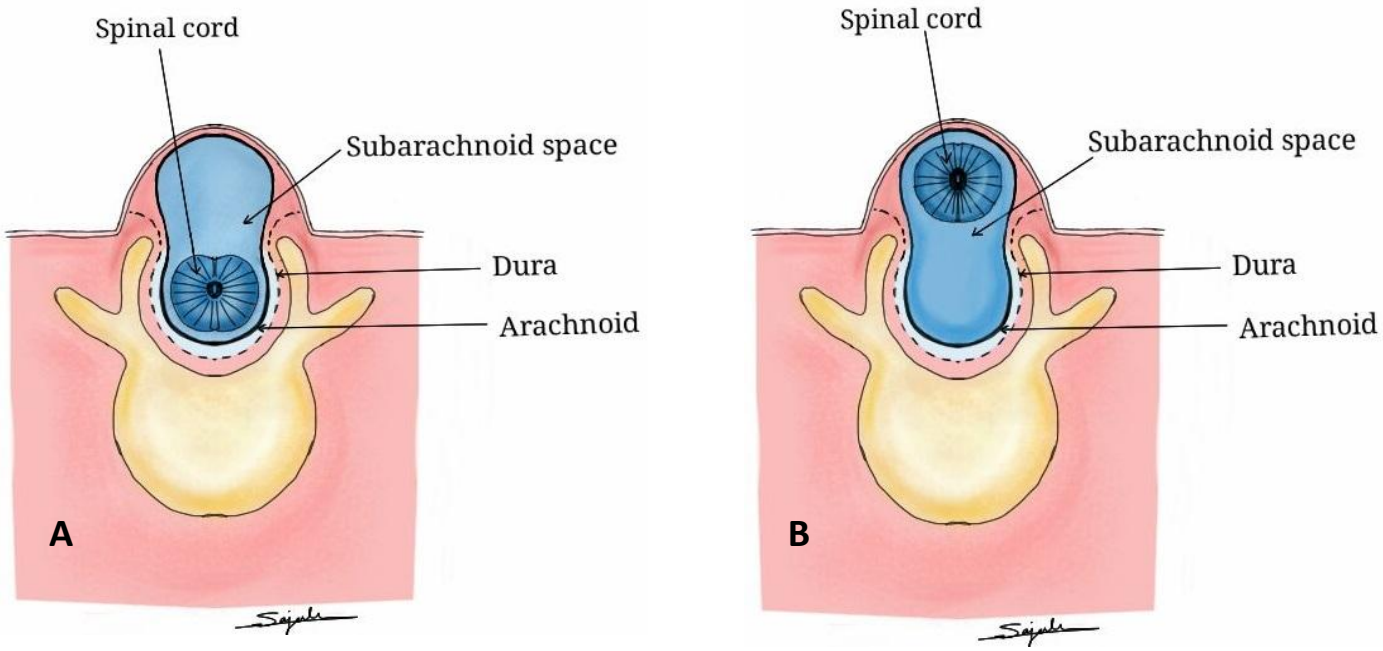


Fig. 11.2 Diagrammatic sketches showing A, Meningocele. B, Meningomyelocele.

BRAIN

- ☐ It develops from the cranial two third of the neural tube as brain swelling.
- ☐ Primarily, two constrictions appear in this swelling, dividing it into *three* chambers or vesicles during the *3rd* week of intrauterine life: forebrain (**prosencephalon**), midbrain (**mesencephalon**) and hindbrain (**rhombencephalon**).
- ☐ At week 4 of development, the embryonic brain bends as a result of rapid growth and undergoes 2 flexures:

i. Cervical flexure at the junction between the spinal cord and hind brain and

ii. Cephalic flexure at the midbrain region.

The **pontine flexure** grows in the opposite direction between the myelencephalon and the metencephalon.

☐ Secondarily, *five* vesicles are seen during the *5th* week.

The prosencephalon subdivides into **telencephalon** anteriorly and **diencephalon** posteriorly, caudal rhombencephalon → **myelencephalon** , rostral rhombencephalon → **metencephalon** and the mesencephalon remains unchanged.

Primary vesicles	Secondary vesicles	Adult structures	Fate of neural canal
Prosencephalon	Telencephalon	Cerebral hemispheres	Lateral ventricles
	Diencephalon	Optic cup and stalk, pituitary, thalamus, hypothalamus, subthalamus and epithalamus	Third ventricle
Mesencephalon	Mesencephalon	Midbrain	Cerebral aqueduct
Rhombencephalon	Metencephalon	Cerebellum and pons	Fourth ventricle
	Myelencephalon	Medulla oblongata	
		Spinal cord	Central canal

Table 11.2 Overview of the embryonic brain development.

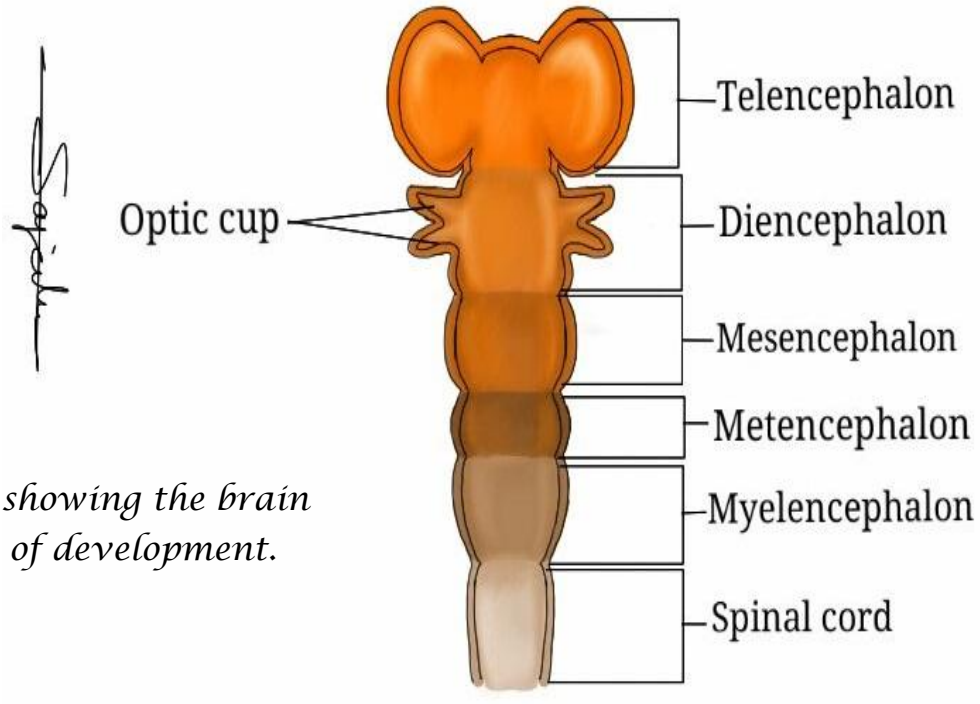


Fig. 11.3 Schematic drawing showing the brain vesicles during the 5th week of development.

☐ The brain has two divisions,

A. **Higher centers** (cerebral hemispheres and cerebellum).

B. **Brain stem** (midbrain, pons and medulla oblongata).

☐ Bilateral **cerebral hemispheres** (cerebral cortex and white matter) begin to develop at the 5th week as cerebral vesicles. At the same week, the **corpus striatum** appears and forms the **basal ganglia** (caudate nucleus, claustrum, amygdaloid nucleus and putamen).

☐ The right and left hemispheres are interconnected by fiber bundles known as cerebral **commissures** that run in and cross the median part of the telencephalon lamina terminalis. These three commissures are listed according to the first appearance as; **anterior**, **hippocampal** (or fornix) and **corpus callosum** (largest one) commissures. The cerebral cortex → **crus cerebri**.

☐ The diencephalon, which develops from two alar plates and a roof plate, gives rise to; **thalamus** (forms the thalamic nuclei, lateral and medial geniculate bodies), **hypothalamus** (forms the hypothalamic nuclei and mammillary bodies), **epithalamus** (forms the pineal body or gland, habenular and posterior commissures), **subthalamus** (forms the subthalamic nucleus, thalamic and lenticular fasciculi) and optic cups and stalks (will discuss later in Chapter 16).

☐ The **pituitary gland** or **hypophysis** develops from two diverticula;

A. **Rathke's pouch**; an upward elongation of the ectodermal roof of the primitive mouth (stomodeum) forming the adenohypophysis or the anterior lobe (adeno=gland). The latter gives rise to the pars anterior, pars intermedia (intermediate lobe) and pars tuberalis.

B. **Infundibulum**; a down growth from the neuroectoderm of the floor of the diencephalon forming the stalk of the pituitary and neurohypophysis or posterior lobe (pars nervosa).

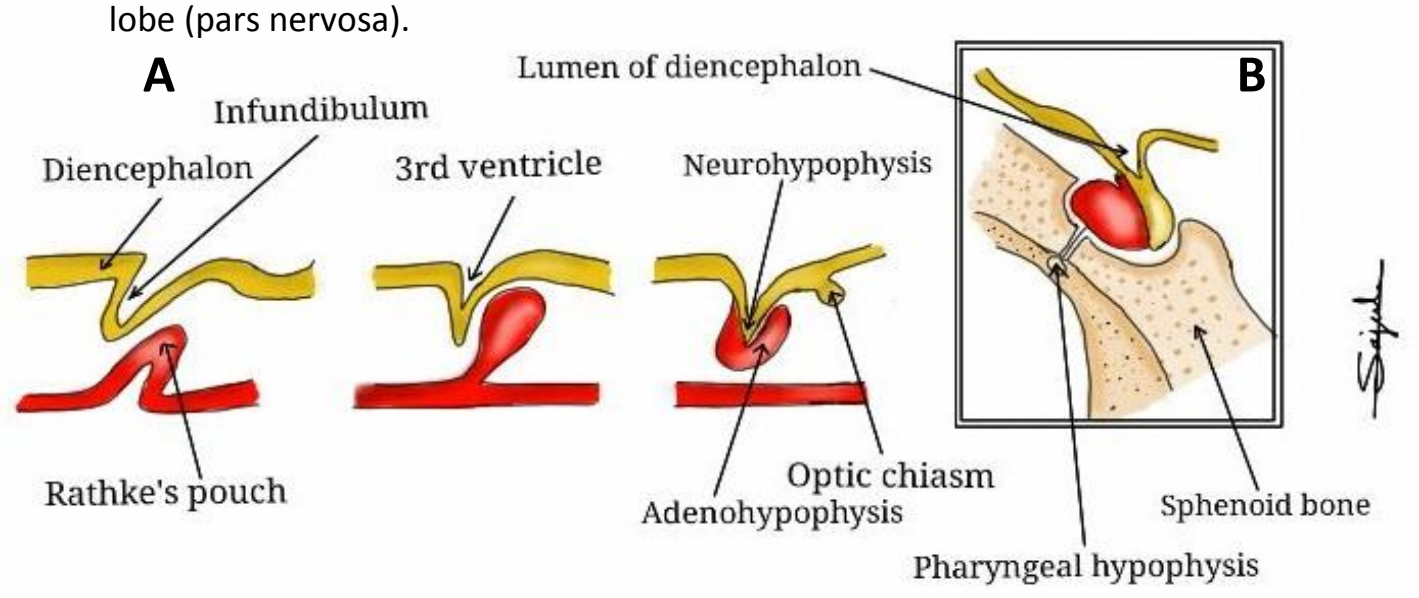


Fig. 11.4 A) Normal development of the hypophysis, B) Pharyngeal hypophysis.

☐ **Anomalies** of the hypophysis,

A. **Agenesis** is the complete absence of the whole hypophysis.

B. **Pharyngeal hypophysis**: A remnant of the stalk of the Rathke's pouch persists attached to the roof of the pharynx, see Fig. 11.4 (B).

C. **Craniopharyngiom** is a tumor develops from remnants of Rathke's pouch.

D. Duplication of pituitary gland is less frequent.

☐ With further development of the midbrain, it includes,

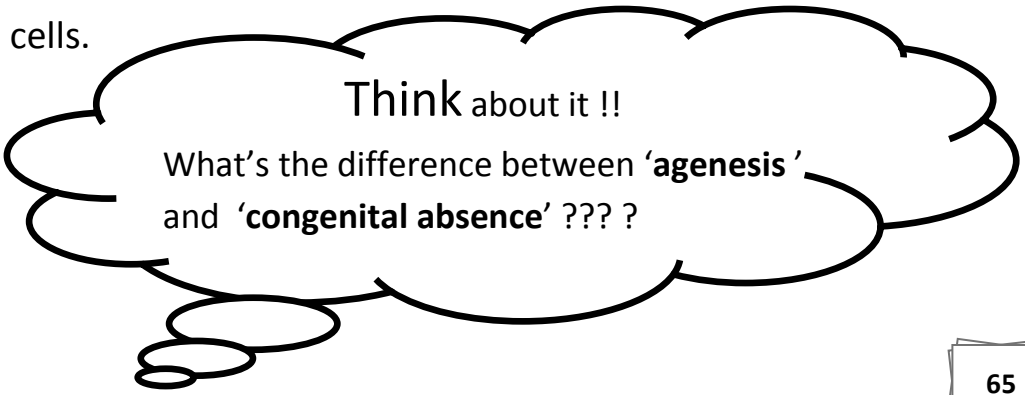
A. Alar plate gives rise to the superior and inferior colliculi.

B. Basal plate forms the Edinger-Westphal nucleus, oculomotor (CN III) nucleus, substantia nigra and red nucleus.

C. The nucleus of the trochlear (CN IV) nerve.

☐ The metencephalon has both alar and basal plates.
Alar plates of pons → cochlear, vestibular, spinal, principal, trigeminal, solitary and pontine nuclei. Basal plates → superior salivatory, facial (CN VII), trigeminal (CN V, motor) and abducent (CN VI) nuclei.

☐ Thickenings of the dorsolateral parts of the alar plates form the **rhombic lips** that develop into cerebellum. In a 6 week embryo, the rhombic lips compress and thicken to form the **cerebellar plate**. At week 12, this plate is separated by a transverse fissure into caudal (flocculonodular lobe) and cranial (vermis and cerebellar hemispheres) parts. Flocculonodular lobe is the most primitive (oldest) part of the cerebellum. The cerebellar plate consists of three layers like that of the spinal cord. In the third month, the ventricular layer gives rise to the **internal germinal layer** that forms the deep cerebellar nuclei (emboliform, globose, fastigial and dentate nuclei), Purkinje cells and Golgi cells. The marginal layer gives rise to the **external germinal layer**. The latter gives origin to the basket, granule and stellate cells.



- Spinal trigeminal, inferior olivary, solitary, dorsal column (gracile and cuneate), cochlear and vestibular nuclei; all of these are derived from alar plates of the myelencephalon. The basal plates will form the dorsal nucleus of the vagus nerve (CN X, motor), the inferior salivatory nucleus of the glossopharyngeal nerve (CN IX), nucleus ambiguus and hypoglossal (CN XII) nucleus.

- The **choroid plexuses** are a continuation or modification of the ependymal roof or layer that invaginate by vascular pia matter (tela choroidea) and secrete about 500ml of cerebrospinal fluid (**CSF**) per day. The CSF circulates through the ventricular system of the brain. Ultimately, the CSF is absorbed (returned) into the venous system via the arachnoid villi.

- Both lateral ventricles communicate with the third ventricle via the interventricular foramina (foramen of **Monro**). The fourth and third ventricles connected by the cerebral aqueduct of **Sylvius**.

- **Hydrocephalus** is an excess amount of the CSF within the brain ventricles or subarachnoid space causing dilation or enlargement of the head. Usually, it is due to **congenital aqueductal stenosis** (obstruction of the cerebral aqueduct of sylvius).

- The ANS originates from the;
  (i) **basal plates** of the neural tube (preganglionic fibers of both sympathetic and parasympathetic neurons) and (ii) **neural crest cells** (postganglionic fibers of sympathetic and parasympathetic neurons).

- The preganglionic parasympathetic neurons arise from nuclei of the brain stem (travel through CN X, IX, VII and III) and spinal cord (S2 – S4). The postganglionic parasympathetic neurons arise from peripheral ganglia (neurons).

- The preganglionic sympathetic neurons lie in the lateral horns of the spinal cord between T1 and L3 and pass through white communicating rami. Its postganglionic fibers pass from the sympathetic trunk (bilateral chains parallel to the vertebral column) or preaortic (e.g., mesenteric and celiac) ganglia to spinal nerves via gray communicating rami.

☐ 12 pairs of cranial nerves arise in the 4th week of development;

CN I. **Olfactory nerve**: Originates from nasal placode (a local thickening of embryonic ectoderm) within the telencephalon.

CN II. **Optic nerve**: Develops from the cells of the retina that lie in the diencephalon.

CN III. **Oculomotor nerve**: Arises from the basal plate of the cranial mesencephalon.

CN IV. **Trochlear nerve**: Exits from the basal plate of the caudal mesencephalon.

CN V. **Trigeminal nerve**: Derives from the basal plate of the anterior pons (motor division) and neural crest cells (sensory division).

CN VI. **Abducent nerve**: Derives from the basal plate of the posterior pons.

CN VII. **Facial nerve**: Is derived from the basal plate of the pons (motor part) and neural crest cells (sensory part).

CN VIII. **Vestibulocochlear nerve**: Is formed from the otic placode.

CN IX. **Glossopharyngeal nerve**: Is derived from the neural crest cells (sensory branch) and the basal plate of the medulla (motor branch).

CN X. **Vagus nerve**: The basal plate of the medulla forms the motor division whereas the neural crest cells give rise to the sensory division.

CN XI. **Accessory nerve**: Emerges from the basal plate of the cervical segments (C1 – C6).

CN XII. **Hypoglossal nerve**: Appears from the basal plate of the medulla.

☐ Common cranial **defects** include;

A. **Cranium bifidum**: Open cranium + cyst filled with CSF. It is caused by ossification defects in the cranium or bony skull (often in the occipital region). Cranium bifidum may occur with;

1. **Meningocele**, cyst contains meninges.
2. **Meningoencephalocele**, cyst contains meninges + brain tissue.
3. **Meningohydroencephalocele**, cyst contains meninges + brain tissue + part of the ventricular system.

B. **Holoprosencephaly** refers to a defect in the prosencephalon formation causes a wide range of anomalies in the brain and face. It is often characterized by hypotelorism (fused eyes), small forebrain, midline cleft lip and merge lateral ventricles.

C. **Arnold Chiari malformation** involves the cerebellum. It is defined as herniation of the vermis through the foramen magnum ⟹ obstructs the flow of CFS ⟹ hydrocephaly.

D. **Microcephaly**, **exencephaly** and **anencephaly** (meroencephaly), return to Chapter 7.

E. Partial or complete absence (**agenesis**) of the corpus callosum.
Usually is asymptomatic.

Chapter 12 || Digestive System

Goals:

- To understand one of the three main divisions of the GIT and associated organ development.
- Explain the folding, rotations, and relations during GIT development.
- Describe briefly the GIT abnormalities.

☐ As a result of embryonic folding, the primitive gut tube (endoderm covered by splanchnic mesoderm) is developed from the yolk sac by the 4th week and extends from the oropharyngeal membrane cranially to the cloacal membrane caudally.
It divides into foregut, midgut and hindgut (Fig. 5.4, page 21).

☐ The epithelial lining and glands of the primordial gut originate from **endoderm**.
The surrounding muscles and serous coats originate from the **splanchnic mesoderm**.

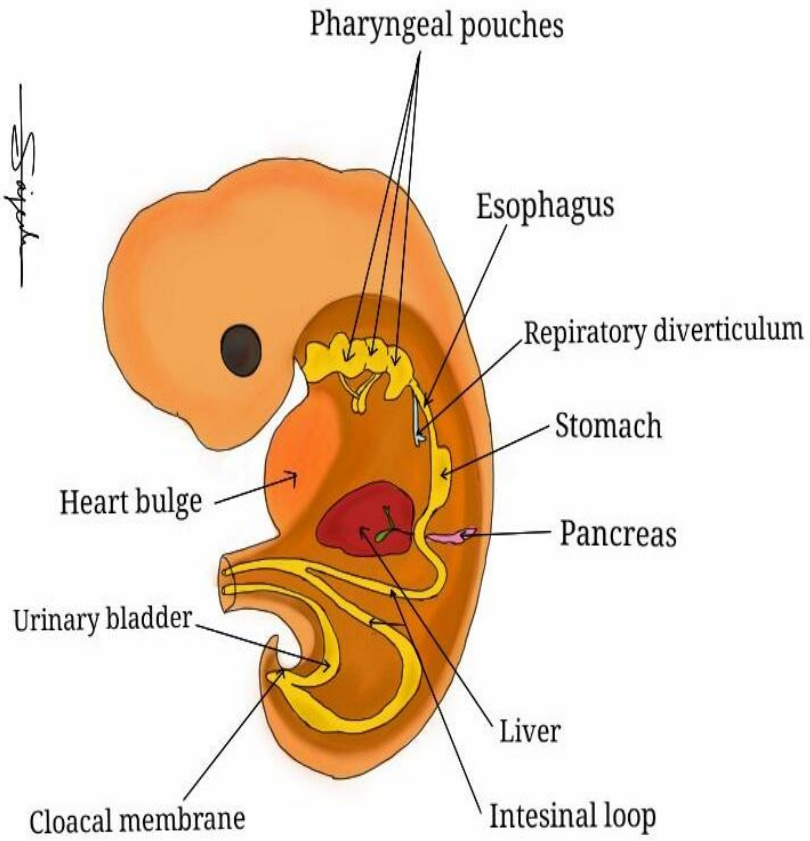


Fig. 12.1 *Embryo during the 5_{th} week showing formation of the digestive system.*

FOREGUT

☐ It extends from the pharynx to the second part of the duodenum (biliary orifice).

☐ The main arterial supply of the foregut is the celiac trunk.

Esophagus

☐ The **esophagus** arises just caudal to the pharynx. Tracheoesophageal septum partitions the proximal foregut into the respiratory primordium ventrally and short tube esophagus dorsally (see Chapter 13). Rapid elongation of the esophagus occurs due to the descent of the heart, lungs and diaphragm.

☐ The upper 2/3rd of the esophagus is coated by striated muscle whereas the lower 1/3rd is smooth muscle. Only the intra-abdominal portion of the esophagus is supplied by the celiac trunk.

☐ **Abnormalities** of the esophagus include;

A. **Esophageal atresia** is a blind or closed-ended esophageal tube caused by defects in the tracheoesophageal septum. In more than 85% of situations, esophageal atresia is accompanied by **tracheoesophageal fistulas** (TEFs).
To clarify in general, fistula is a connection between 2 epithelial linings.
Esophageal atresia prevents the passing of amniotic fluid to the intestine ➡ accumulation of excess amniotic fluid ➡ polyhydramnios.

B. **Esophageal stenosis** or esophageal narrowing, usually in the distal 1/3rd.

C. Congenital or **esophageal hiatal hernia,** very short esophagus ➡ part of the stomach is pulled up through the esophageal hiatus of the diaphragm reaching the thorax.

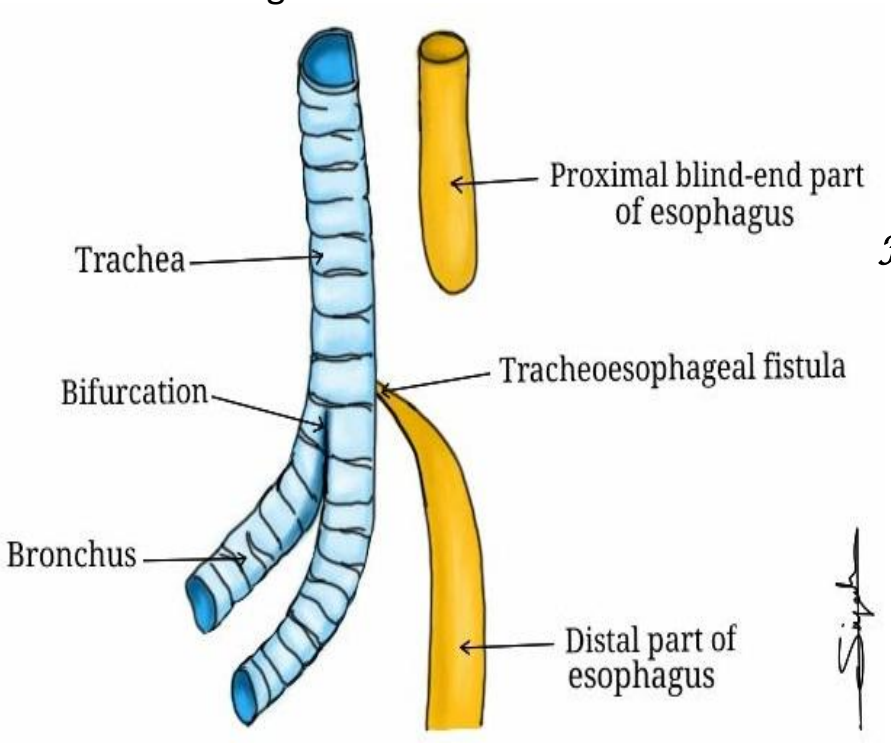


Fig. 12.2 Esophageal atresia and tracheoesophageal fistula (most common type).

☐ A slight dilation (fusiform in shape) of the distal foregut during week 4 indicates the primitive **stomach** (Latin, gastro). The dorsal border of the primitive stomach grows faster than the ventral border, forming the greater and lesser curvatures, respectively.
Greater curvature is connected to the posterior abdominal wall by **dorsal mesogastrium** (future greater omentum).
The lesser curvature is attached to the anterior body wall by the **ventral mesogastrium** (future lesser omentum).
The **omental bursa** (lesser peritoneal sac) is a small irregular space behind the stomach enclosed between two layers of the greater omentum, it becomes in contact with the greater omentum through an omental or epiploic foramen of Winslow.
The gastrophrenic, gastrosplenic and lienorenal ligaments are derived from the dorsal mesogastrium.

Stomach

☐ The stomach undergoes 90° clockwise *rotation* around its longitudinal axis, which is responsible for the final position of the stomach in the adult and its anatomical relations with the foregut viscera. After this rotation, the original left side of the stomach faces anteriorly and its right side becomes the posterior surface. Hence, the left and right vagus nerves innervate the anterior and posterior walls of the adult stomach, respectively.

☐ Congenital **anomalies**;

A. **Pyloric stenosis** is caused by muscular hypertrophy (abnormal thickening) of the caudal sphincteric part of the stomach (pylorus). Severe stenosis ➡ obstruction of the food passage ➡ infant vomits (expels the stomach's contents) after feeding. This anomaly is treated by surgical excision of the thickened sphincter.

B. Thoracic stomach: Due to the abnormal short esophagus (rare), see page 70.

C. Hour glass stomach: Local constriction in the middle of the stomach dividing it into two portions.

D. Transposition of the stomach to the right side of the abdomen instead of the left side (situs inversus), rare.

Duodenum

☐ The duodenum originates from;

A. Terminal part of the foregut → upper part of the duodenum (supplied by the celiac trunk).

B. Cephalic part of the midgut → lower part (supplied by the sup. mesenteric a.).

It is worthy to note that the junction between the foregut and midgut is at the ampulla of Vater.

☐ When the rotation of the stomach takes place, a C-shaped duodenal loop rotates to the right → becomes retroperitoneal (external to peritoneum) in position.
The lumen of the duodenum becomes progressively obliterated, and are normally recanalized by the end of the embryonic period.

☐ Incomplete recanalization of the duodenum ⟹ partial occlusion of the lumen of the duodenum (**duodenal stenosis**). Otherwise, **duodenal atresia** is a complete occlusion/absence of the lumen (rare).

Liver & Biliary System

☐ Early in the *4th* week, the liver (Latin, hepatic), gallbladder and biliary duct system are appearing as an outgrowth (hepatic diverticulum or liver bud) from the distal part of the ventral foregut. The hepatic diverticulum grows into the large cranial part (primordial liver) and small caudal part (gallbladder).

☐ The liver is developed from two sources;

A. Endodermal **liver bud** → liver parenchyma or cells and sends hepatic cords to arrange themselves around the vitelline and umbilical veins and → liver sinusoids.

B. Splanchnic mesodermal **septum transversum** (Fig. 5.4, page 21) → fibrous capsule, hematopoietic, fibroblast (connective tissue) and Kupffer cells of the liver.

☐ The attachment between the liver and anterior abdominal wall (ventral mesentery) consists of;

A. The **lesser omentum**, it subdivides into hepatogastric and hepatoduodenal ligaments. The latter, contains the bile duct, hepatic artery and portal vein.

B. The **falciform ligament** which contains the left umbilical vein.

- Congenital **anomalies** of the liver are rare except for minor variations in liver lobulation but with no clinical importance.

- The connection between the foregut and hepatic diverticulum narrows forming the bile duct. A small solid outgrowth from the latter expands and gives rise to the cystic duct and gallbladder. Later on, the gallbladder and cystic duct canalize.

- Developmental abnormalities of the gallbladder include;

  A. A small **accessory hepatic ducts**.

  B. Duplication of the gallbladder (rarely).

  C. **Extrahepatic** and/or **intrahepatic biliary atresia**: Failures of the ducts to canalize. It is associated clinically with jaundice.
  Biliary atresia is the most common reason for liver transplantation.

  D. In **absent gallbladder**, the small caudal part of the liver bud fails to grow.
  In these conditions, there is no cystic duct and no gallbladder.

Pancreas

- The pancreas arises from endodermal cells of;

  A. A large **dorsal bud** originates directly from the caudal foregut. It forms most of the pancreas (upper part of the head, body and tail).

  B. A small **ventral bud** is an outgrowth near the liver bud. It gives rise to the lower part of the head and uncinate process.

- As the duodenum rotates, the ventral pancreatic bud also migrates dorsally and lies just below and behind the dorsal pancreatic bud, and the latter fuses with it forming the definitive adult pancreas. (Ventral bud + dorsal bud = definitive adult pancreas)

- The main pancreatic duct is formed by anastomosis of the ventral pancreatic duct and dorsal part of the dorsal pancreatic duct. The proximal part of the dorsal pancreatic duct either is regressed or persists as accessory pancreatic duct (opens into the duodenum as the minor papilla).

☐ Early in the *3rd* month, the pancreatic islets of Langerhans develop. However, insulin and glucagon secretions are released during the *5th* month of the fetal life (intra-uterine).

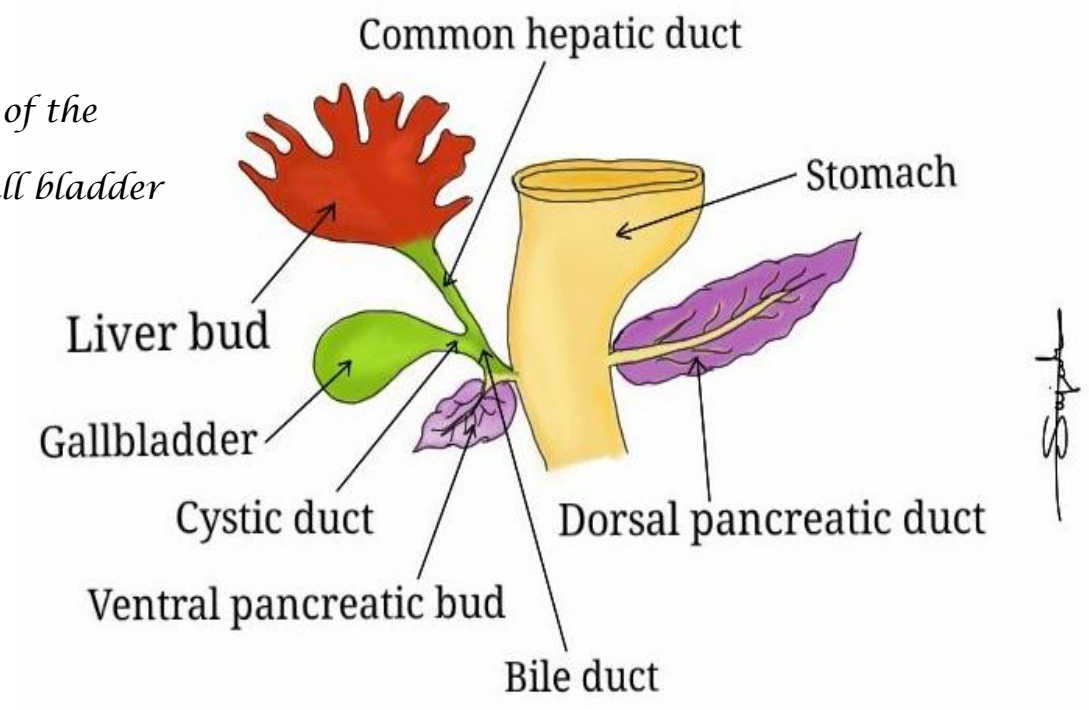


Fig. 12.3 *Development of the pancreas, liver, and gall bladder at week 5.*

☐ **Clinical considerations**;

A. **Annular pancreas** occurs when the ventral and dorsal buds fuse dorsally and ventrally forming a ring of pancreatic tissue around the duodenum, causing duodenal stenosis.

B. Most frequently, the **accessory pancreatic tissue** lies in the stomach or duodenal walls.

C. **Pancreas divisum** is a condition occurs when the main pancreatic duct fails to form. This patient is prone to pancreatitis.

Spleen

☐ In week 5, spleen arises from the mesodermal cells of the dorsal mesogastrium. These cells differentiate to form the capsule and connective tissue. The spleen is attached to; the stomach by the gastrosplenic ligament and to the left kidney by the splenorenal lig.

☐ Although the spleen is a lymphatic organ, it is described with the GIT system because this organ is derived from mesodermal cells located between the layers of the dorsal mesentery. Also, it supplied by a branch of celiac trunk.
In fact, the spleen is a hematopoietic organ until late in fetal life.

☐ **Accessory spleens** appear in 10% of people. One or more supernumerary small splenic masses may be present in one of the peritoneal folds.

MIDGUT

- It describes the region from lower part of the duodenum to the proximal 2/3rd of the transverse colon. The superior mesenteric a. supplied derivatives of the midgut. The midgut connects to the yolk sac via the vitelline duct or yolk stalk.

- At the 5th week, the midgut elongates rapidly forming a U-shaped midgut (intestinal) loop (Fig. 12.1) consisting of cranial limb, apex and caudal limb. Early in the 6th week, the intestinal loop herniates (bulges out) through the umbilicus into the extraembryonic coelom due to the large size of the liver and small room of the abdominal cavity at this time, and is known as the **physiological umbilical herniation**.

- As it returns to the abdominal cavity, the intestinal loop rotates a total of 270° anti or counterclockwise around the axis of the midgut artery. Thus, the physiological herniation is reduced by week 10.

- The cranial limb of the midgut loop greatly grows and coils and forms the jejunum and upper part of the ileum, the apex is attached to the yolk sac by way of omphaloenteric duct or yolk stalk and the caudal limb develops into the lower part of the ileum, cecal diverticulum or swelling, ascending and proximal two thirds of the transverse colon. Later, the cecal diverticulum gives rise to the cecum and appendix.

- Clinical correlates;

A. **Omphalocele** is a herniation of intestines (and may be liver and stomach) into the umbilical cord due to defects in the ventral body wall. It is also defined as persistence of the physiologically herniated loop of intestines outside the body (non-return).

B. **Gastroschisis** occurs when there is ventral abdominal wall defect which leads to protrusion of abdominal contents directly through the abdominal wall into the amniotic cavity. It is usually found lateral to the umbilical cord.

C. **Ileal** or **Meckel's diverticulum**: non obliteration or persistence of the proximal part of the vitelline duct, forming an outpouching of the ileum. Moreover, it often causes ulceration and bleeding.
Meckel's diverticulum may be connected to the umbilicus by a fibrous cord (vitelline ligament), or a vitelline cyst with vitelline ligaments on either side or vitelline duct remains patent in the vitelline fistula.

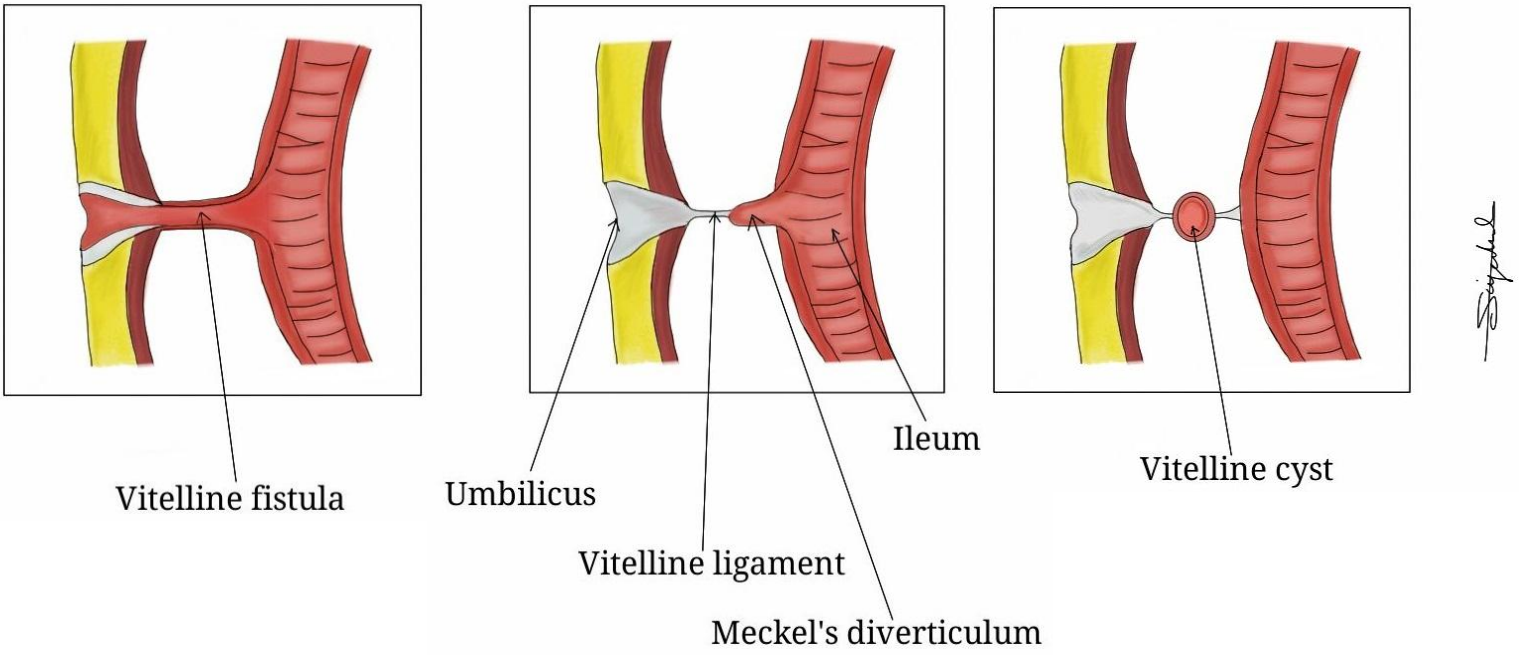


Fig. 12.4 Remnants of the vitelline duct.

D. **Stenosis and atresia** may occur anywhere over the intestines. These anomalies seem to be caused by lack of recanalization or vascular accidents (interruption of the blood supply).

E. **Duplication of the intestine** involves anywhere along the gut tube due to abnormal recanalization. The duplicated segment is found on the mesenteric border of the intestine.

F. **Nonrotation** or **malrotation of the midgut** is an incomplete rotation of the intestinal loop results in volvulus (twisting of the intestine) and causes duodenal obstruction. In this case, the entire large intestine lies on the left side and small intestine lies on the right side.

G. **Reversed rotation** occurs when the intestinal loop rotates in a clockwise direction. As a result, the duodenum lies anterior to the midgut artery (rather than posterior), and the transverse colon lies posterior (rather than anterior).

H. **Subhepatic cecum and appendix:** It is an attachment of the cecum to the inferior surface of the liver after its return to the abdomen. Thus, the cecum failed to migrate downward to its adult position (right iliac fossa).

I. Normally, the ascending colon is fixed to the posterior abdominal wall. If there is partial or incomplete fixation and a portion of the mesocolon persists, it gives rise to a **mobile cecum**. It may lead to volvulus of the cecum or retrocolic hernia.

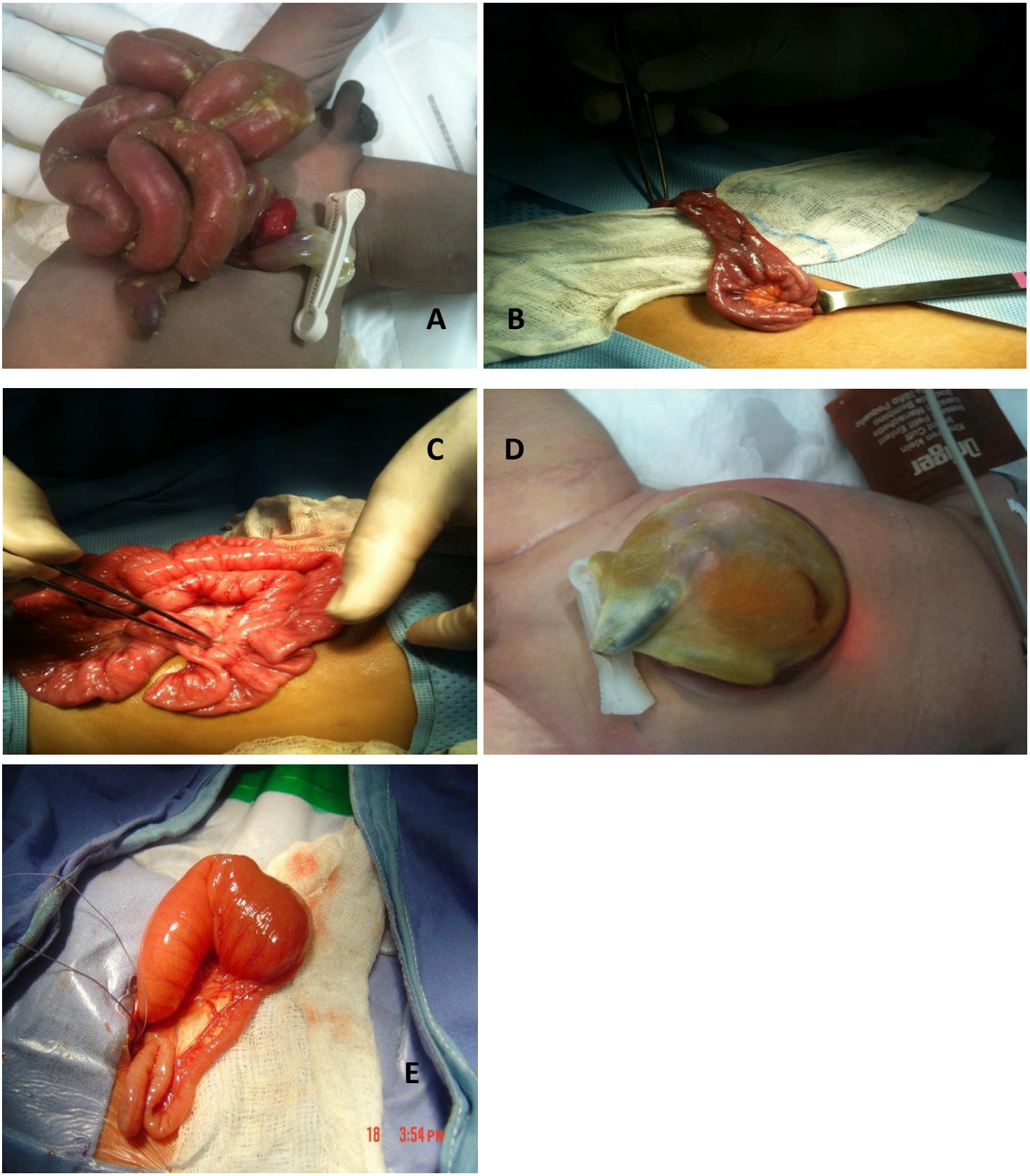


Fig. 12.5 A. Photograph of the infant with gastroschisis. B. Meckel's diverticulum. C. Intestinal duplication. D. Omphalocele. E. Intestinal atresia.

HINDGUT

- It forms the distal 1/3rd of the transverse colon, descending colon, sigmoid colon, rectum and upper part of the anal canal. The inferior mesenteric artery supplies all of the hindgut derivatives.

- The terminal end of the hindgut dilates and expands to form an endoderm lined cavity called the **cloaca** covered by surface ectoderm (proctodeum) forming the **cloacal membrane**.

- Later, the cloaca is partitioned by a layer of mesoderm, the **urorectal septum**, into urogenital sinus ventrally and anorectal canal dorsally (future rectum and upper part of the anal canal).
  The cloacal membrane itself is divided by the urorectal septum into a ventral urogenital membrane and a dorsal anal membrane.
  The urorectal septum lengths till it reaches the cloacal membrane and fuses with it to form the perineal body.

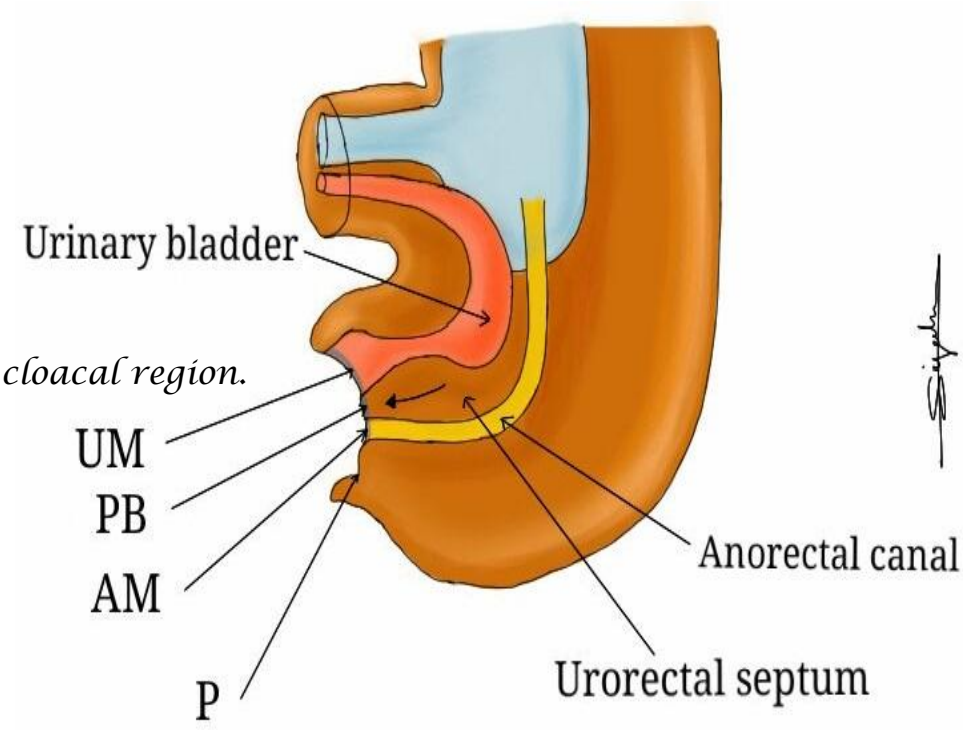


Fig. 12.6 *Diagram showing the cloacal region.*

UM= urogenital membrane;

PB= perineal body;

AM= anal membrane;

P= proctodeum.

- The upper 2/3rd of the anal canal originates from the hindgut.
  The lower 1/3rd derived from the ectodermal proctodeum (primitive anal pit).

- Cloacal membrane ➡ anal membrane ➡ pectinate line (in adult).

- Because of a dual embryological origin of the anal canal, there are several variations between upper and lower parts, the following table summarizes some of it.

	Upper part	Lowe part
Embryological origin	Endoderm	Ectoderm
Epithelial lining	Columnar	Stratified squamous
Arterial supply	Branch of hindgut artery (superior rectal)	Inferior rectal artery
Venous drainage	To portal venous system	To caval system
Lymphatic drainage	Internal iliac nodes	Superficial inguinal nodes
Innervations	By ANS, painless	By somatic innervations, very sensitive (inf. Rectal n.)
Anal columns	Present	Absent

Table 12.1 Comparison between the upper and lower parts of the anal canal.

▢ Hindgut **abnormalities**;

A. An abnormal extension of the urorectal septum leads to incomplete division of the cloaca. As a result, there is abnormal communication occurs between the rectum and urinary bladder (**rectovesical fistula**), or between the rectum and urethra (**rectourethral fistula**) in males or between the rectum and vagina (**rectovaginal fistula**) in females.

B. **Congenital megacolon** or **Hirschsprung disease**: An absence of parasympathetic ganglia which's derived from neural crest cells **(aganglionosis)** mostly in the wall of the sigmoid colon and rectum.

No parasympathetic ⟹ no relaxation of the colon ⟹ no peristalsis (movement of the intestinal contents) ⟹ megacolon (mega=big).

C. **Rectoanal fistulas**: Is a narrow fibrous tube extends from the rectum to the perineal surface.

D. **Imperforate anus:** Failure of the anal membrane to rupture or perforate.

E. **Anal agenesis** is a blind-ended of the anal canal inferior to the puborectalis muscle.

F. In the **rectal atresia**, both the anal canal and rectum are found but are separated.

G. **Anorectal agenesis** is a blind-ended of the rectum above the puborectalis muscle.

MESENTERIES

- The primitive gut tube and its derivatives are suspended within the peritoneal cavity to the dorsal and ventral body wall by the dorsal and ventral mesenteries, respectively.
  If the peritoneum encloses an organ completely, it is considered intraperitoneal, whereas the retroperitoneal organs are partially covered by peritoneum.

- Ligaments and mesenteries hold a route for blood vessels, nerves and lymphatics.

Embryonic mesentery	Adult derivatives
Ventral mesentery ''LFCT''	**Lesser omentum** (hepatogastric and hepatoduodenal ligaments)**, falciform, coronary and triangular ligaments of the liver.**
Dorsal mesentery	**Greater omentum** (splenorenal, gastrosplenic, gastrorenal and gastrocolic ligaments)**, mesoappendix, transverse mesocolon, mesentery of small intestine and sigmoid mesocolon.**

Table 12.2 Adult remnants of fetal mesenteries.

Chapter 13 || Respiratory System

Aims:

- Describe the normal growth of the respiratory system and anomalies related to it.
- Discuss the major events at various stages of lung maturation.
- Explain the development of the diaphragm and congenital anomalies.

☐ Basically, the respiratory system divides into;

i. **Upper part** which includes the nose, nasopharynx and oropharynx.

ii. **Lower part** which includes the larynx, trachea, bronchi and lungs.

Development of the upper respiratory tract is described in Chapter 15.

LOWER RESPIRATORY SYSTEM

☐ At 4-weeks old embryo, the laryngotracheal groove appears from the ventral surface of the primitive foregut.

This groove deepens and evaginates to form a laryngotracheal or **respiratory diverticulum** (Fig. 12.1).

The respiratory diverticulum still communicates with the primordial pharynx through the slit-like **laryngeal orifice**.

☐ As this endodermal diverticulum elongates caudally, it is invested or surrounded by splanchnic mesoderm.

However, *2* longitudinal tracheoesophageal ridges appear, approach each other and fuse to form the **tracheoesophageal septum**. The primitive foregut is partitioned by this septum into a ventral laryngotracheal tube and a dorsal esophagus.

☐ Endoderm ➡ the epithelial lining and associated glands of the lower respiratory system.

☐ Splanchnic mesoderm ➡ cartilage, connective tissue and smooth muscle of these structures.

☐ Improper or any defect in the formation of the tracheoesophageal septum leads to an umbrella term, esophageal atresia and/or TEFs (see Chapter 12).

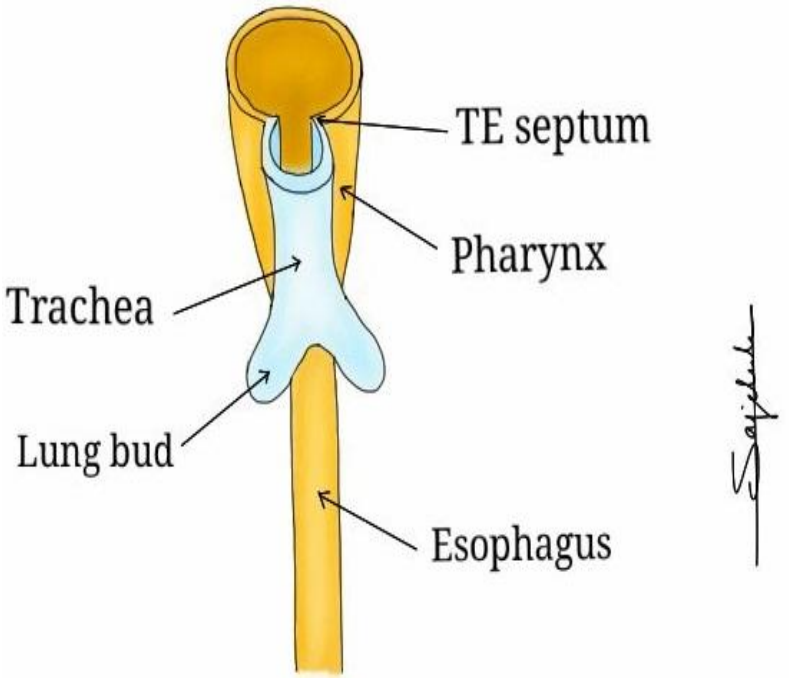


Fig. 13.1 Early development of the respiratory system.

- Endoderm ➡ the epithelium and glands of the **larynx.**
  Mesoderm of both the *4th* and *6th* pairs of pharyngeal arches ➡ laryngeal muscles and cartilages.

- The rapid proliferation of this mesoderm changes the laryngeal orifice (primordial glottis) into a T- shaped opening.

- Anyway, the laryngeal epithelium proliferates rapidly forming paired **laryngeal ventricles**. The latter, are bounded by tissue that becomes the **vocal cords** or folds.

- Laryngeal atresia is a rare anomaly occurs if recanalization of the larynx failed which triggers blockage of the upper airway of the fetus [congenital high airway obstruction syndrome].

- The respiratory diverticulum or lung bud forms the trachea and bifurcates into two lateral **bronchial buds**.

- In week 5 of development, each bud enlarges to form primary (main) bronchi. Subsequently, at week 6, the primary bronchi form three secondary (lobar) bronchi on the right lung and two on the left.

- By the 7_{th} week, the secondary bronchi subdivide into ten tertiary (segmental) bronchi on the right lung and eight on the left, which creates the bronchopulmonary segments.

- With the progressive expansion of the lungs, it invests into the primitive pleural cavity. Hence, the lung gets covered by;
    i. splanchnic mesoderm → the **visceral pleura**
    ii. somatic mesoderm lining the body wall → the **parietal pleura**
    iii. space between two layers of pleura is called the **pleural cavity**.

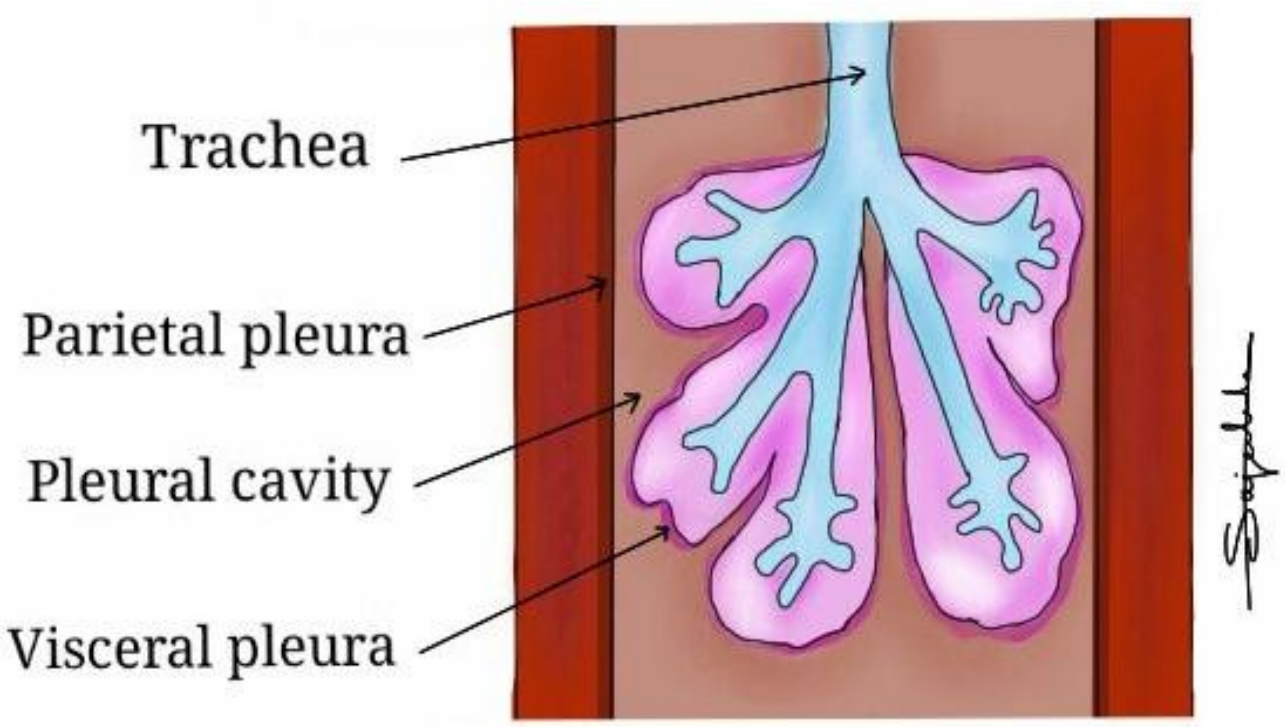


Fig. 13.2 *Expansion of the lung buds into the primitive pleural cavities, at week 6.*

☐ Maturation of the lungs has been explained in 4 stages;

Pseudoglandular Stage	**6 - 16 wk**	The terminal bronchiole resembles an exocrine gland. The absence of respiratory bronchioles and alveoli. Thus, fetuses born in this stage cannot survive.
Canalicular Stage	**16 - 26 wk**	Each terminal bronchiole branches into 2 or more respiratory bronchioles. Then branch into 3 to 6 alveolar ducts. Respiration is possible towards the end of this period. Otherwise, fetuses born before week 20 rarely survive because their systems are still immature.
Terminal Sac or saccular Stage	**26 wk to birth**	Many terminal sacs or primitive alveoli develop. The capillaries establish and intimate contact to the terminal sacs forming a blood-air barrier. By 26th week, epithelial cells lining the terminal sacs, type 1 pneumocyte (for gas exchange), will differentiate. At the end of 6th month, type 2 pneumocyte (surfactant production) will develop. Premature infants born at 24 to 28 weeks may survive with intensive care.
Alveolar Stage	**32 wk to 8 years**	Increase amount of surfactant during week 34. By the end of the fetal period, the alveolocapillary membrane becomes sufficiently thin to permit gas exchange. After birth, mature adult alveoli will well develop. Postnatal growth of the lungs is mainly due to increase in number of respiratory bronchioles and alveoli.

Table 13.1 Successive stages of maturation of the lungs.

☐ **Anomalies** of the bronchial tree and lung involve;

A. **Respiratory distress syndrome** (RDS) is caused by insufficient amount of surfactant. This is a critical cause of premature infant death.
RDS is also known as hyaline membrane disease.

B. Lung (pulmonary) agenesis is a complete absence of one or both lungs or a lobe due to a failure of development of the respiratory bud (rare).

C. **Lung hypoplasia** is poorly developed bronchial tree. It is commonly associated with congenital diaphragmatic hernia.

D. Accessory lung (rare).

E. Congenital **lung cysts** are formed by the dilation of terminal bronchi. These are multiple, small cysts that are filled with air or fluid.

F. Tracheal stenosis and atresia (extremely rare).

N.B. The diaphragm has a critical role in respiration, so it was discussed in this chapter.

DIAPHRAGM

☐ The diaphragm is a barrier between the peritoneal cavity and the pleural cavities. It is formed by sharing and fusion of four distinct sources:

1. **Septum transversum** ⟶ muscle and central tendon of the diaphragm.
2. **Pleuroperitoneal membranes** ⟶ primordial diaphragm.
3. **Dorsal mesentery of esophagus** ⟶ crura of the diaphragm.
4. **Mesoderm of the body wall** ⟶ peripheral muscular part.

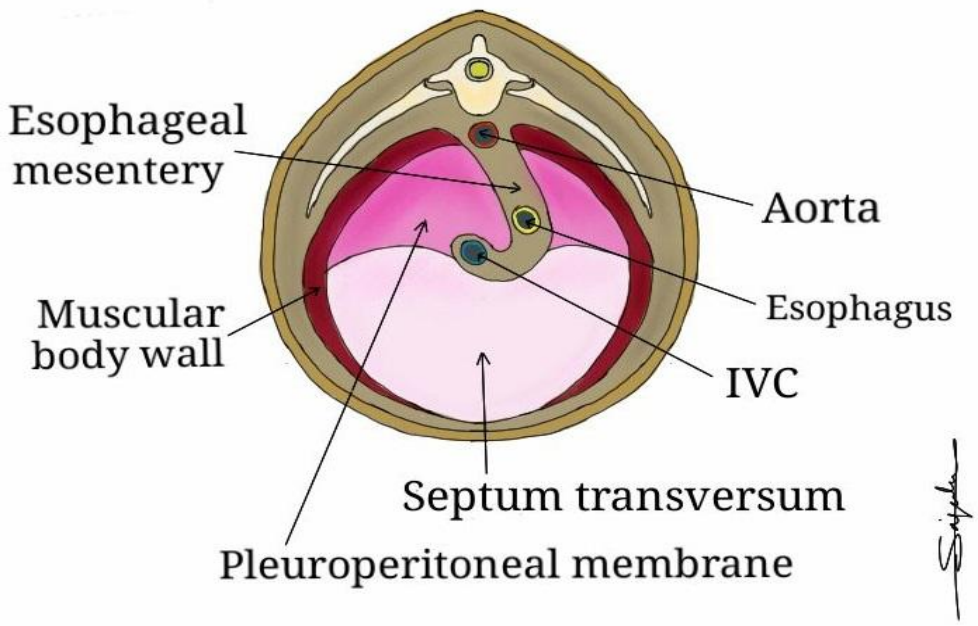


Fig. 13.3 Transverse section of a 4 month fetus showing the four components that forming a diaphragm.

☐ During week 4, the septum transversum lies opposite to the *3rd*, *4th* and *5th* cervical somites. Thus, the muscle of diaphragm develops from myoblasts of these somites, and it is innervated (motor) by the phrenic nerves that have the same origin (3, 4, 5).

Remember the mnemonic '' C3, 4, 5 keeps the diaphragm alive''.

☐ Rapid growth of the neural tube causes an apparent descent of the diaphragm to L1 level. Definitely, the phrenic nerves also descend and pass through the pleuropericardial membranes (future fibrous pericardium).

☐ **Abnormalities** of the diaphragm includes;

A. A **congenital diaphragmatic hernia** is a protrusion of abdominal viscera into the thoracic cavity. Usually, it is due to the incomplete formation and/or fusion of the pleuroperitoneal membranes with other diaphragmatic components. This hernia is most commonly found on the left side.
In that case, the abdominal contents compress the lung buds ➡ pulmonary hypoplasia/agenesis.

B. **Esophageal hiatal hernia** (see Chapter 12).

C. Eventration of diaphragm: An uncommon condition caused by the defective formation of diaphragmatic musculature forming a balloon-like pouch pushed up into the thoracic cavity. In fact, this is a herniation-like (not a true hernia), the diaphragm is intact but thin because there is no muscle.

Chapter 14 || Urogenital System

Targets:

- Describe the development of each organ of the urinary system.
- Discuss the formation of the genital system in both sexes.
- Define the congenital anomalies of both systems briefly.

☐ Functionally, the urogenital system is a dual term indicates, uro=urinary system (kidneys, ureters, urinary bladder and urethra) and genital= genital system of both sexes.
Based on the close anatomical and embryological relation between these two systems, both will be explained in the same chapter to make it easier for you to understand it.

☐ The urogenital system develops mainly from the **intermediate mesoderm**.

URINARY SYSTEM

☐ The intermediate mesoderm forms the **urogenital ridge** (a longitudinal elevation along the dorsal body wall) that gives rise to the **nephrogenic cord** (primordial urinary system).

Kidney & Ureter

☐ Developing of the kidney passes through ***3*** sets (Fig. 14.1); The *pronephros* (nonfunctional structures), *mesonephros* (functional briefly) and *metanephros* (permanent kidneys).

A. **Pronephros**: 7 – 10 cell clusters (pronephric tubules) in the neck region appear <u>early</u> at week 4, these *pronephric tubules* open into → *pronephric ducts* open caudally into → *cloaca*. Pronephric tubules degenerate at the end of week 4, however, the pronephric ducts persist as *mesonephric duct*.

B. **Mesonephros**: In this stage, differential mesoderm caudal to the pronephros gives rise to → *mesonephric tubules* that drain bilaterally into → *mesonephric* (Wolffian) ducts draining into → *cloaca*. The mesonephros appears <u>late</u> in week 4, it is functional for around four weeks and then most of it regresses by the end of the first trimester.

C. **Metanephros** begins to develop by week 5 in the sacral region, but it is functional nearly at week 10, it develops from;

1. The **ureteric bud** (an outgrowth from the mesonephric duct) → *collecting system* [upper most parts of **ureters** and **renal pelvis**]. Initially, the ureteric bud penetrates the metanephrogenic cap and undergoes repetitive branching and further development giving rise to → **major calyces**, **minor calyces** and **collecting ducts**.

2. The **metanephrogenic cap** (mass of metanephric mesoderm) → *excretory system*. M. cap differentiates into → small **metanephric vesicles** which later elongate to form → S - shaped **metanephrogenic tubules**. These tubules develop into → connecting tubule, distal convoluted tubule, loops of Henle, proximal convoluted tubule and Bowman's capsule. The latter will invaginate by a tuft of capillaries forming the **glomerulus** (Fig. 14.4).

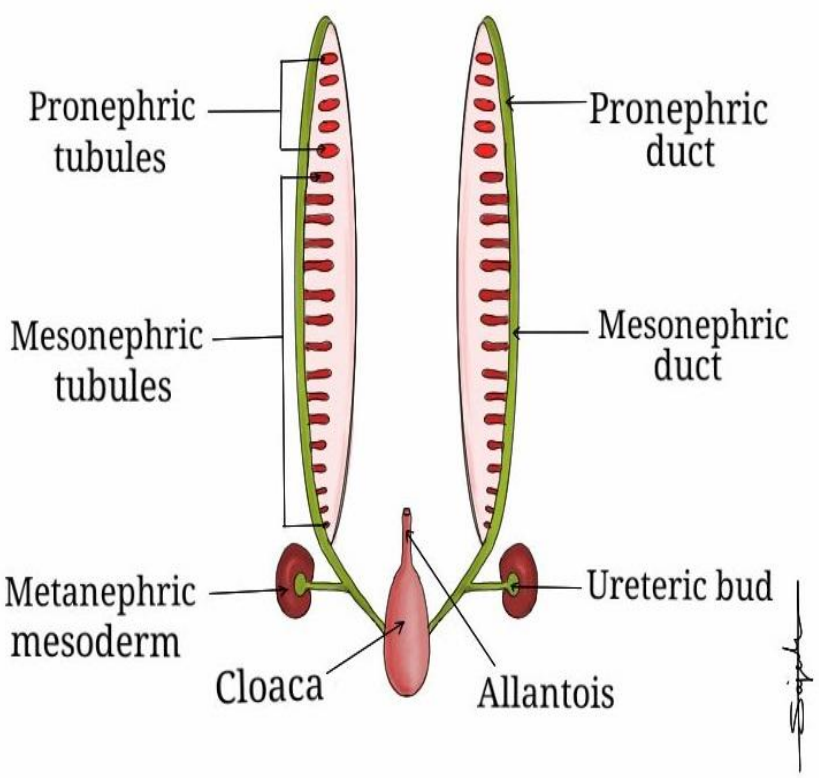


Fig. 14.1 Ventral view of an embryo at week 5 illustrates the sets of excretory systems.

☐ The nephron is formed until birth when there is about *1* million per kidney. Urine production starts at approximately 10 weeks of gestation. At birth, the kidney surface is lobulated, but this lobulation disappears during infancy and becomes smooth.

☐ Kidneys are a pelvic organ at first (S1-S2), then, and due to the rapid growth of the embryo in this region, it *ascends* on the posterior abdominal wall to reach the adult position (T12-L3). The kidneys *rotate* medially 90 degrees, thus, the hilum of the adult kidney faces medially (instead of ventrally).

☐ According to kidney traveling, it has varied blood supply.

Firstly from;

1. pelvic branches of the aorta.
2. new branches of the abdominal aorta (during its ascending).

These branches often degenerate.

Lastly from;

Permanent renal artery will develop at the level of L2.

Persistence of the first 2 vessels leads to **accessory** or supernumerary **renal arteries**.

☐ Common **abnormalities** of the kidney constitute;

A. **Renal agenesis**: Failure of the ureteric bud to develop. It may be unilateral (common in males and asymptomatic) or bilateral (less common, causes oligohydramnios and infants shortly die).

B. **Ectopic kidneys** are an abnormal position of one or both kidneys. For instance, failure of one or both kidneys to ascend and still remains in the pelvis (**pelvic kidney**). In some conditions, both pelvic kidneys get closer to each other and fuse to form a **pancake kidney**.

C. **Horseshoe kidney**: Fusion of the kidneys by its lower poles in the midline. The inferior mesenteric artery traps and prevents fused kidneys to ascend. Therefore, kidneys are arrested at the level of the inferior lumbar vertebrae.

D. **Polycystic kidney disease** **{PKD}** is a hereditary disease caused by the failure of fusion between the convoluted and the collecting tubules. In this case, kidney enlarges and contains many hundreds of cysts affecting kidney function. Infants can't survive unless dialysis and kidney transplantation are performed.

E. **Renal hypogenesis** is a congenital small kidney with normal morphology and reduced number of nephrons, usually unilateral.

F. **Bifid ureter** is a partial splitting of the ureteric bud. The ureters may fuse in the lower third before opening in the bladder. Usually, it is seen with the **double kidneys**.

G. **Double ureter** is due to complete dividing of the ureteric bud. It is also associated with the double kidneys.

H. **Ectopic ureter** is caused by the development of two ureteric buds, one bud has a normal position while the other may enter the bladder neck, vagina, urethra or epididymal region.

I. **Accessory** or supernumerary **renal arteries** (see above).

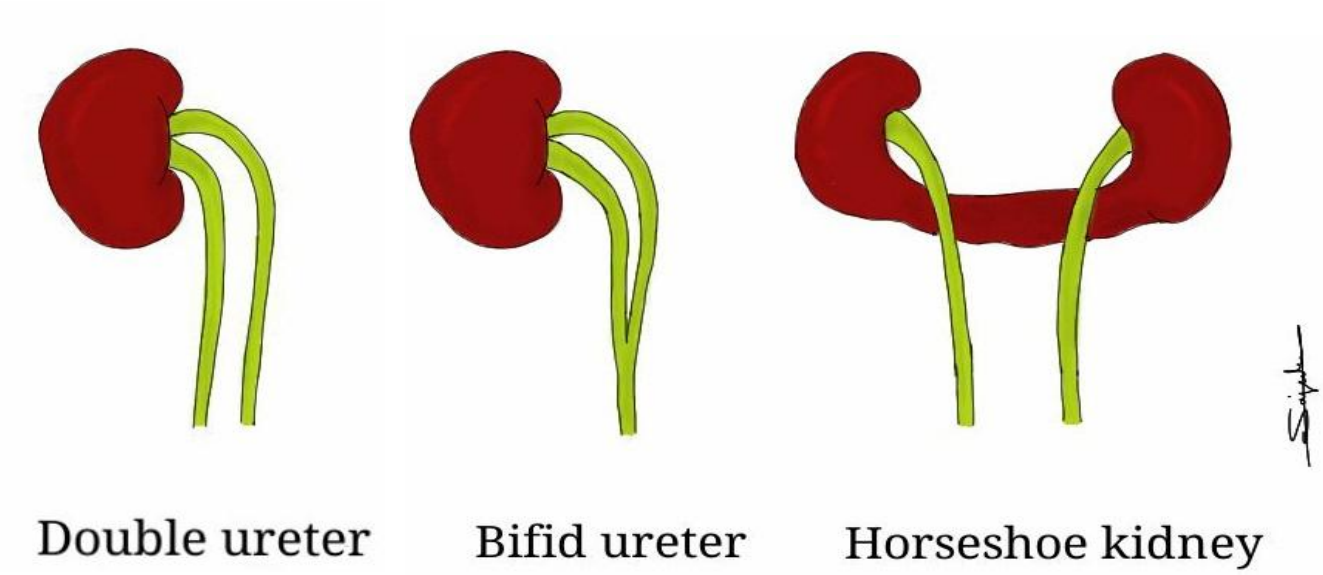


Fig. 14.2 Common congenital anomalies of the renal system.

Urinary Bladder

☐ The endodermal urogenital sinus (Chapter 12) is divided into 3 parts;

A. **Vesical** [Cranial] → most of the bladder.

B. **Pelvic** [Middle] → most of the prostatic urethra and entire female urethra.

C. **Phallic** [Caudal] → genital tubercle (primitive penis or clitoris).

☐ The urogenital sinus or bladder is continuous with the allantois.

Allantois ⇒ urachus (fibrosed allantois) ⇒ median umbilical ligament (adult remnant).

☐ Caudal portions of both mesonephric ducts and ureters (mesoderm) get absorbed into the bladder's dorsal wall forming → **trigone** of the bladder (connective tissue area).
Later on, this mesodermal area is replaced by endodermal *transitional epithelium*.

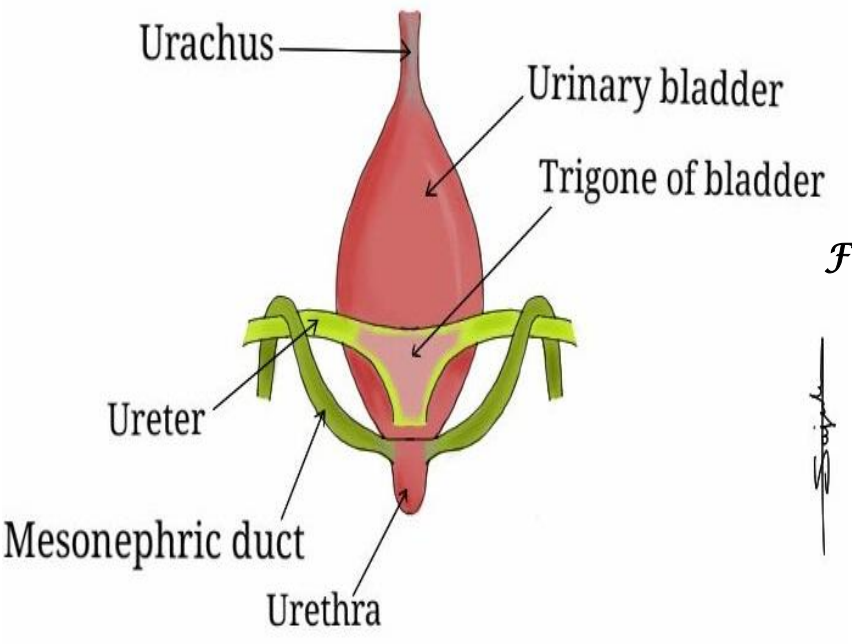


Fig. 14.3 Development of the urinary bladder.

- Indeed, in infants and kids, the urinary bladder is in the abdomen. By six years old, it *descends* to the greater pelvis. After puberty, it enters the lesser pelvis and becomes a *pelvic* organ.

- Common congenital **anomalies**;

  A. **Urachal fistula**: Non obliteration of the urachus ⟹ urine drains from the umbilicus.

  B. **Urachal cyst**: Persistence of only localized part of the urachus forming a cyst.

  C. **Urachal sinus**: Non obliteration of the distal part of the urachus.

  D. **Bladder exstrophy** (ectopia vesicae): The bladder is opened and exposed to the outside due to a defect in the lower part of the anterior abdominal wall. It is most common in the males. Clinically, it is associated with the *epispadias* and urine drainage to the exterior (rare).

  E. **Exstrophy of the cloaca**: A rare anomaly resembles the last one, but it results in a severe defect of the anterior abdominal wall. Note that both the bladder and hindgut are exposed.

Urethra

- In **males**,

Proximal part of the prostatic urethra = *endoderm of the mesonephric ducts*.
Distal prostatic, membranous and proximal penile urethra = endoderm of urogenital sinus.
The distal part of the penile urethra = *surface ectoderm*.

☐ In **females**,
Proximal part = *mesonephric ducts.*
Distal part = *urogenital sinus.*

☐ In both sexes, the connective tissue and smooth muscle surrounding the urethra are derived from *visceral mesoderm*.

Suprarenal Gland

☐ The suprarenal or adrenal gland consists of the cortex and medulla.

☐ Initially, the fetal cortex is developed from the coelomic mesothelial cells.
At week 6, a proliferation of the mesodermal cells surrounding the fetal cortex forms the adult cortex.
At birth, the fetal cortex degenerates.

☐ The adult cortex contains three layers or zone;
the zona glomerulosa and zona fasciculata are found at birth,
but the zona reticularis is formed at age 3.

☐ The medulla arises from the neural crest cells and differentiates into chromaffin cells.
Later, it migrates, aggregates, and invades the cortex.

#Exercise >>> *Fill the following table*;

Part / Fate	In **male**	In **female**
Mesonephric tubules		
Mesonephric duct		

GENITAL SYSTEM

☐ At fertilization, the genetic sex of an embryo is established.

From week 1 to week 6, male and female embryos still sexually undifferentiated.

At week 7, morphological characteristics of male and female indifferent embryo are developed.

By week 12, the external genitalia of both sexes can be distinguished.

During week 20, phenotypic (physical appearance) differentiation is complete.

Genetically correlated

Sex determining region on Y chromosome (**SRY**) gene is a key to sexual differentiation.

It is also known as testes determining factor (TDF).

Gonads

☐ Each of the testes or ovaries (gonads) is developed from two sources;

1. **Gonadal ridge** is a bulge formed by proliferation of the coelomic or surface epithelium and underlying mesoderm. Later, this ridge proliferates and forms the primitive gonadal cords. Now, the indifferent gonad is consists of an internal medulla and an external cortex.
2. **Primordial germ cells** (PGCs), see Chapter 2.

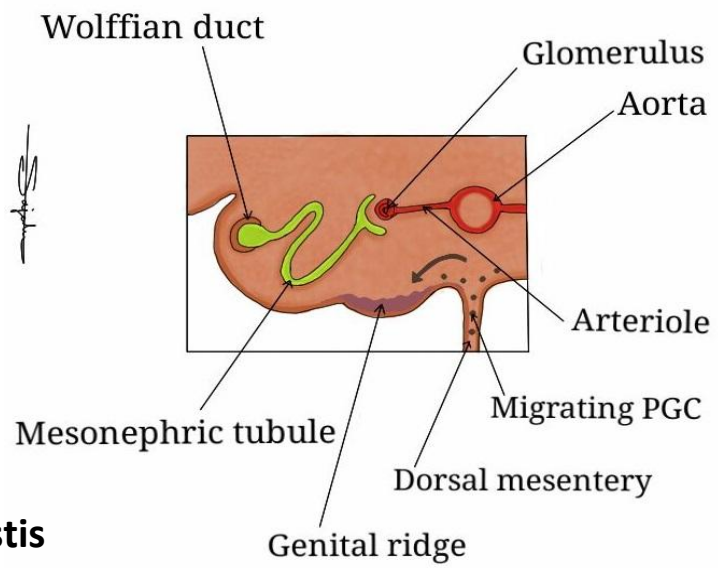


Fig. 14.4 Transverse section showing the genital ridge.

Testis

☐ Under control of SRY gene, the XY genotype (chromosome) of the embryo induces the formation of the testis. **Testosterone** is involved in this process.

N.B. 'Testis' is a singular word, whereas "testes" is a plural.

- ☐ The outer part of the mesenchyme condenses forming → **tunica albuginea** (fibrous connective tissue between cords and surface epithelium).
  The primitive sex cords elongate and become U – shaped → seminiferous tubules, tubuli recti and rete testes, which in turn join to the → ductuli efferentes.
  Seminiferous tubules remain as solid tubules (no lumina) until puberty, when lumina start to develop.

- ☐ Mesodermal cells between seminiferous tubules will form the interstitial cells of Leydig (testosterone production at week 8).

- ☐ Two types of cells are located within the walls of the seminiferous tubules;

  1. Sustentacular cells of Sertoli <<< the sex cords.
  2. Spermatogonia <<< primordial germ cells.

- ☐ Initially, the testes are developed (3_{rd} month) within the posterior abdominal wall, then, *descends* ⟹ deep inguinal ring (7_{th} month) ⟹ inguinal canal ⟹ superficial inguinal ring (8_{th} month) ⟹ scrotum (week 33).

- ☐ The **gubernaculum** is a fibrous band connects the testes to the scrotum. It persists as gubernaculum testes in adults.

- ☐ Causes of descent; (1) testosterone (androgen) production (2) increase of intra - abdominal pressure (3) shortness of the gubernaculum.

- ☐ The abdominal peritoneum is evaginated alongside the gubernaculum to form the processus vaginalis, which gets obliterated and becomes → **tunica vaginalis**.

- ☐ Commonest **anomalies** of the testes;

  A. **Cryptorchidism**: Failure of one or both testes to descent into the scrotum. The undescended testes may be in the abdomen or anywhere along its usual course. If uncorrected, this male becomes sterile.

  B. **Maldescended** (mal = wrong) or **ectopic testis** is a deviation or descending of the testis to an abnormal position. It is possibly found in the perineum, thigh (femoral triangle), in front of the pubis or anterior abdominal wall (superficial fascia).

  C. **Congenital inguinal hernia**: It occurs when a processus vaginalis persists and is not obliterated. Thus, a loop of intestine may protrude into the scrotum. It's mostly seen in males and is associated with *cryptorchidism*.

In some cases, obliteration of the processus vaginalis is irregular leaving a small cyst, and later, this cyst is filled with peritoneal fluid resulting in **hydrocele** of the testes.

Ovary

- ☐ If the embryo with an XX sex chromosome → under the influence of **estrogens** → induces development of the ovary.

- ☐ 1ry sex cords (containing clusters of primordial germ cells) → **rete ovarii**, and eventually degenerate.
  Surface epithelium continues to proliferate → 2ry sex cords 'cortical cords' (incorporated with the germ cells).
  Cortical cords break up into groups of cells called **primordial follicles**.
  Primordial follicles = oogonia (from germ cells) + covered by **follicular cells** (single layer of epithelium).

- ☐ Separating the surface epithelium from the follicles = *mesodermal* **tunica albuginea** (fibrous capsule).
  Stroma (connective tissue) of the ovary = *mesodermal* in origin.

- ☐ Ovaries originate within the posterior abdominal wall → *descent* into the pelvis.
  Gubernaculum is extending from the ovary to the uterus.
  Upper part of gubernaculum → *ovarian ligament*.
  Lower part becomes → *round ligament* of the uterus (attaching the labia majora).
  Processus vaginalis is obliterated.

- ☐ Dysgenesis of both ovaries is associated with Turner syndrome.

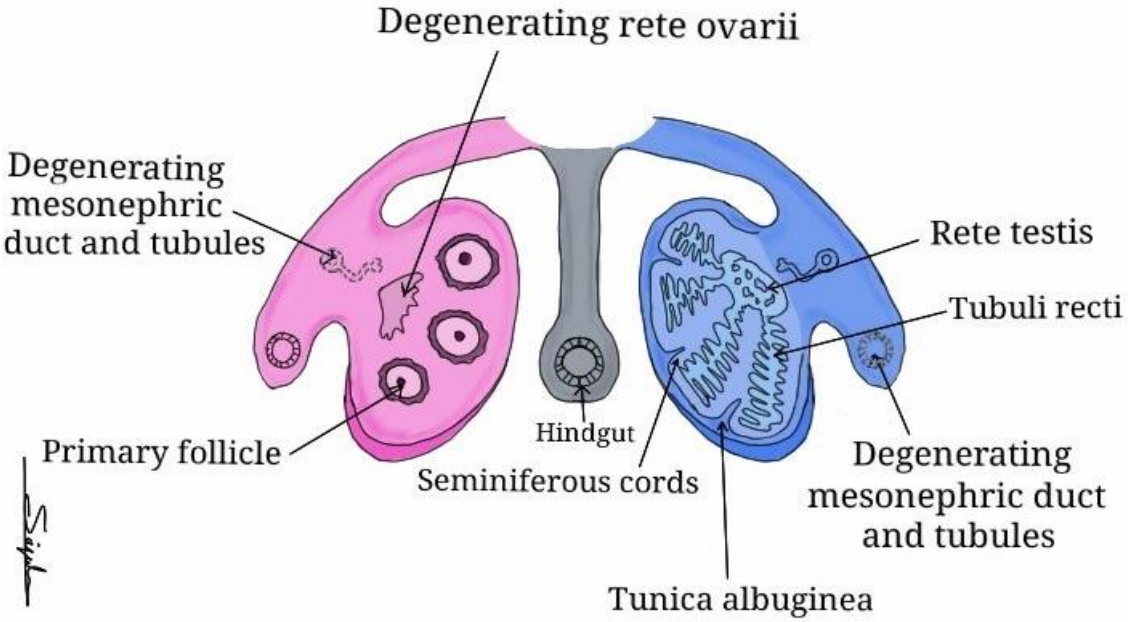


Fig. 14.5 Development of the gonads at week 20. On your left hand, the ovary, and the testis on the right.

Female Genital Ducts

- Early during development, paired of longitudinal invagination of epithelium appears laterally to the urogenital ridge (mesonephros), so it is called **paramesonephric** (müllerian) **duct**.
  Each duct has cranial (opens into abdomen), middle (horizontal) and caudal (opens into the urogenital sinus) portions.
  Cranial and middle portions → the **uterine tube**.
  At week 12, the caudal portions fuse → Y-shaped, the primitive **uterovaginal canal**.
  Uterovaginal canal develops into → uterus, cervix, fornix and upper *1/3* of the vagina.

- **Anomalies** of the uterus have many forms;

  A. **Double uterus** (uterus didelphys) is a complete failure of the paramesonephric ducts to fuse in a normal area ⟹ two uteri with a single or double vagina.

  B. **Bicornuate uterus** (cornu=horn) is a partial fusion of the paramesonephric ducts ⟹ uterus has two horns opening in a common vagina.

  C. **Bicornuate uterus with a rudimentary horn**: Inability of one paramesonephric duct to fuse. The rudimentary horn persists as an appendage and does not attach to the uterus.

  D. **Unicornuate uterus** occurs when one paramesonephric duct fails to form ⟹ uterus has a single uterine tube.

  E. **Uterus arcuatus** is a slightly indented (depression) at the fundus of the uterus.

  F. **Septate uterus:** Complete or partial absence of resorption of the septum between the two uterine horns.

- The primitive urovaginal canal connects with the urogenital sinus → sinus tubercle → paired endodermal sinovaginal bulbs.
  Union of these bulbs → thick cellular **vaginal plate** will canalize, form a lumen → lower 2/3 of the vagina.

- In other words, the vagina has a dual origin,
  1. Uterovaginal canal (mesoderm) → upper 1/3
  2. Vaginal plate (endoderm) → lower 2/3 and epithelial lining.

- **Vaginal atresia:** Vaginal plate fails to canalize.

- **Absence of the uterus and vagina** is due to failure of the primitive uterovaginal canal to develop ⟹ no sinovaginal bulbs ⟹ no vaginal plate.

- Two peritoneal folds attach the pelvic wall to the fusion site of the paramesonephric duct → **broad ligament**. Both the broad ligament and uterus divide the pelvic cavity into the **rectouterine** and **vesicouterine** pouches.

- The **hymen** is a thin tissue membrane separates the vagina from the urogenital sinus which contains the vaginal cells and epithelial lining of the sinus.
  It usually ruptures during the perinatal period and remains as a perforated thin mucosal fold.

- **Hymen variations** may be;
  Crescentic, annular, redundant, imperforate, cribriform, microperforate and septate.

- During conversion of the **mesonephric** (wolffian) **duct** into adult compartments, some of them remain as vestigial structures forming a cyst such as;
  epoophoron (cranial mesonephric tubules remnant), paroophoron (caudal mesonephric tubules remnant) and Gartner's cyst (mesonephric duct remnant). These are rarely seen.

Male Genital Ducts

- The mesonephric duct → **epididymis**, **ductus deferens**, **seminal vesicle** and **ejaculatory duct**.
  A few remainders of the mesonephric tubules → **efferent ductules** of the testis.

- Cranial part of the paramesonephric duct and primitive uterovaginal canal are regressed.

- Vestigial remnants of the male genital ducts may be;
  appendix testis (remnants of the paramesonephric duct), appendix epididymis (remnants of the mesonephric duct) and paradidymis (remnants of the mesonephric tubule).

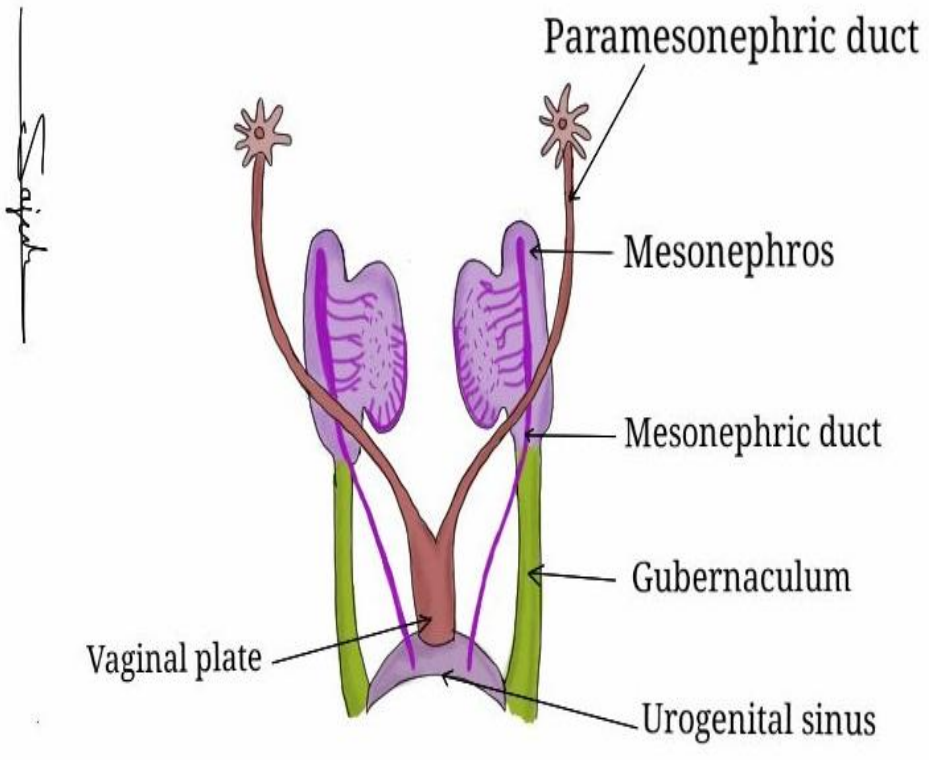


Fig. 14.6 Indifferent stage embryo showing the development of the genital ducts.

External Genitalia

- ☐ At week 4, mesodermal proliferation produces cloacal folds around the cloacal membrane. Cloacal folds fuse together cranially → **genital tubercle**, but divide caudally → **urethral folds** ventrally (surround the urogenital membrane) and **anal folds** dorsally (surround anal membrane).
  In the meantime, **genital** (labioscrotal) **swellings** develop on either side of the cloacal membrane.

- ☐ Agenesis of external genitalia (extremely rare): Genital tubercle fails to develop resulting in complete absence of the penis in male or clitoris in female.

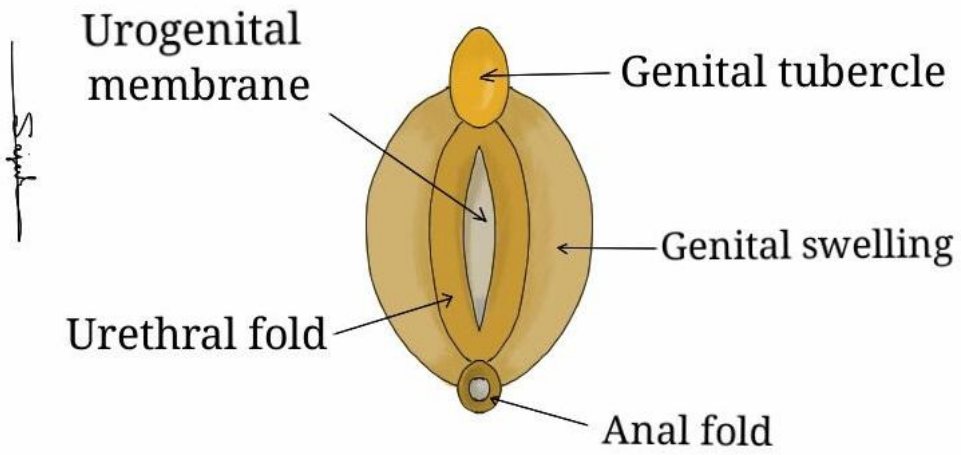


Fig. 14.7 Diagram illustrating the indifferent stage of the external genitalia at week 6.

Male External Genitalia

- ☐ The genital tubercle elongates rapidly to form the **phallus** which gives rise to → the penis (glans penis, corpora cavernosa and corpus spongiosum of penis).

- ☐ As the phallus elongates, the urethral folds are pulled to form → the lateral edges of the **urethral groove**. The endodermal lining of this groove → **urethral plate**. Fusion of the urethral folds → a canal, the **spongy** (penile) **urethra**. The latter does not extend to the phallus.
  Thus, migration of the ectodermal cells from the tip of the glans penis will form a short cord. This cord later canalizes and becomes a lumen extended to the penile urethra proximally.
  Thus, ectoderm → distal part of the penile urethra + external urethral meatus.
  The surface ectoderm fuses at the midline of the penis to form the **penile raphe**.

- ☐ The genital or scrotal swellings approach each other → **scrotum**.
  Line of fusion of these swellings is clearly visible as the scrotal septum.

- ☐ A fold of skin known as **prepuce** (foreskin) is formed from a circular ingrowth of ectoderm at the base of the glans.

- Congenital **anomalies**;

A. **Hypospadias** (most common): An incomplete fusion of the urethral folds at the midline resulting in abnormal openings of the urethra on the inferior surface of the penis instead of at the tip. Hypospadias may occur anywhere and in different degrees of severity such as; on the glans penis (glanular hypospadias) [the most common type], the body of the penis (penile hypospadias), junction of the penis and scrotum (penoscrotal hypospadias), scrotal hypospadias and perineal hypospadias. Usually, the penis poorly developed and curves ventrally (chordee).

B. Epispadias (rare): Abnormal urethral opening or meatus is found on the dorsum of the penis. It is often seen with exstrophy of the bladder.

C. In micro**penis**, the penis is too small and almost hidden. It is generally associated with hypopituitarism.

D. Bifid penis or **double penis** (very rare) is due to splitting of the genital tubercle. Usually, it is associated with exstrophy of the bladder.

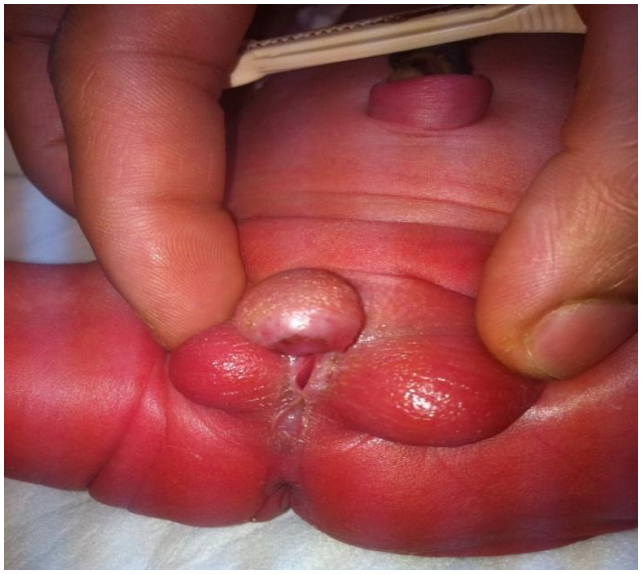


Fig. 14.8 Male with bifid scrotum and scrotal hypospadias with chordee.

Female External Genitalia

- The genital tubercle elongates slightly to become → the phallus → **clitoris** (glans clitoris, corpora cavernosa and vestibular bulbs).
- Urethral folds remain separated except the posterior part where the folds join → the frenulum of the labia minora, however, the largely unfused portion → **labia minora**. Opened urogenital groove → the vestibule.
- Genital swellings enlarge → **labia majora** and mons pubis.

- An **ambiguous genitalia** is referred to the disorder characterized by a small penis or a large clitoris. Thus, a baby may be born either female appearance with a large clitoris or male appearance with a small penis. If a child has both characteristics of male and female, he called *hermaphrodite*.

  Congenital adrenal hyperplasia is the most important reason of sexual ambiguity.

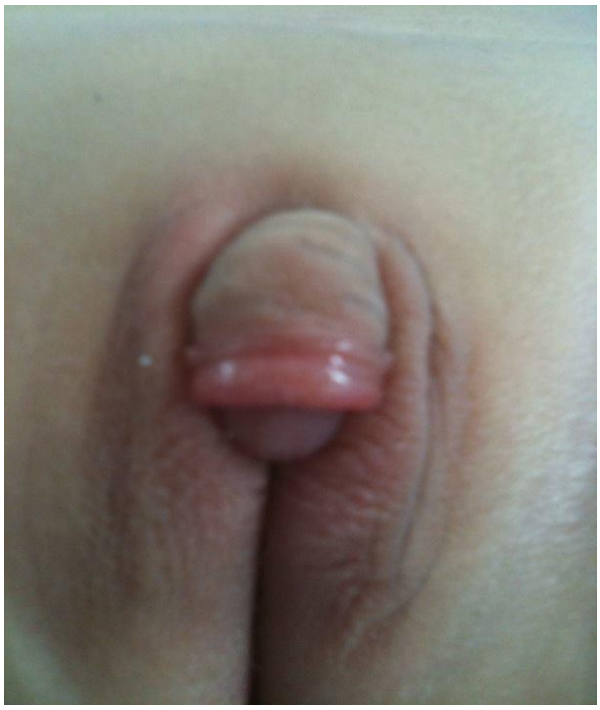


Fig. 14.9 Female with congenital adrenal hyperplasia with clitoromegaly and persistent urogenital sinus.

Chapter 15 || Head and Neck

Objectives:

- Identify the elements of the pharyngeal apparatus and list its derivatives.
- To understand the structures involved in the development of the face, palate and nasal cavities.
- To understand the stages in the development of the salivary and thyroid glands.
- To understand the development of the mouth and tongue.
- Describe the abnormal development of these structures.

PHARYNGEAL APPARATUS

☐ Pharyngeal apparatus is a group of the pharyngeal arches, pouches, clefts or grooves and membranes. It appears by the ***4th*** week as a branchial/pharyngeal apparatus and contributes to the formation of the head and neck.

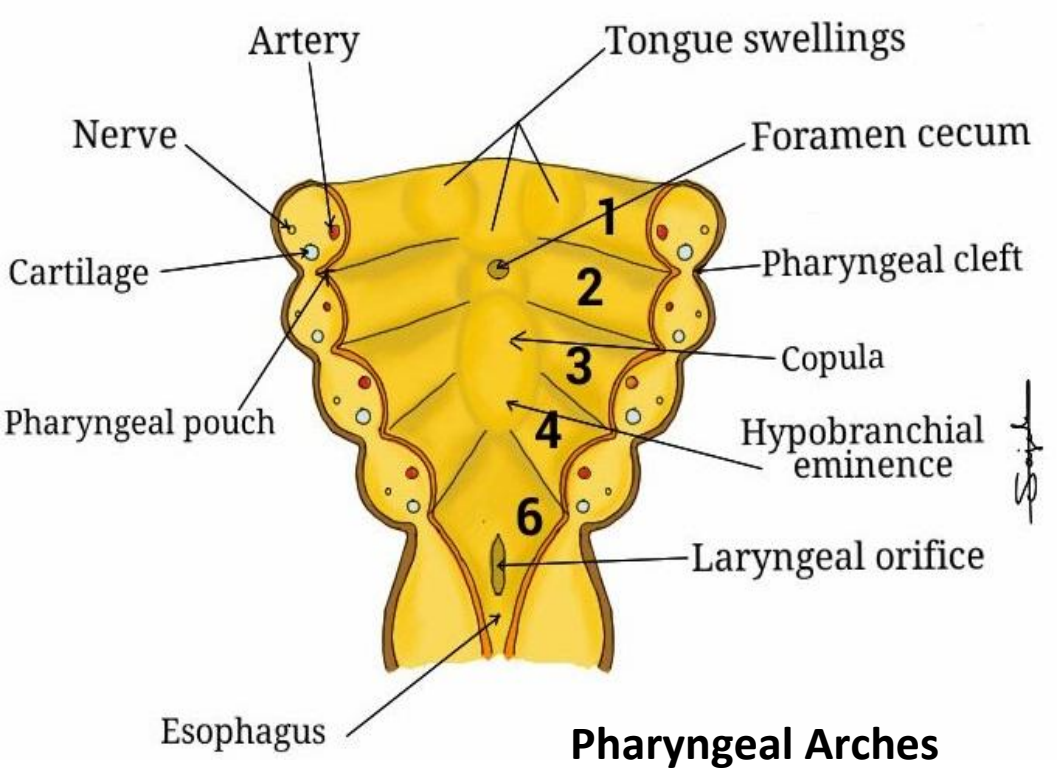


Fig. 15.1 *Cross section shows the pharyngeal apparatus at week 5.*

☐ Each pharyngeal arch is composed of a core of mesodermal cells covered by surface ectoderm (neural crest cells).
Mesodermal cells → muscular and vascular components.
Neural crest cells → the skeletal components (bone, connective tissue, ligament and cartilage).
Each arch has a specific cranial nerve for it.

Arch number	Skeleton	Muscles	Aortic arch	Cranial nerve
I (**M**andibular)	**M**axilla, **m**andible, **m**alleus, incus, zygomatic bone, squamous temporal bone, vomer, **M**eckel's cartilage, sphenomandibular ligament	Muscles of **m**astication, **m**ylohyoid, anterior belly of digastric, tensor tympani, tensor palatine	**M**axillary artery	**M**axillary and **m**andibular divisions of trigeminal (CN V)
II Hyoid	**S**tapes, **s**tyloid process, le**ss**er horn and **s**uperior body of hyoid bone, Reichert's cartilage, **s**tylohyoid ligament	Muscles of facial expressions, posterior belly of digastric, **s**tapedius, **s**tylohyoid	Hyoid and **s**tapedial arteries	Facial (CN VII)
III	Greater horn and inferior body of hyoid bone	Stylopharyngeus	Internal and common carotid arteries	Glossopharyngeal (CN IX)
IV	Thyroid cartilage	Muscles of soft palate (except tensor veli palatini), muscles of the pharynx (except stylopharyngeus), cricothyroid	Arch of aorta and right subclavian artery	Superior laryngeal (vagus)
V	Regressed			
VI	Cartilages of larynx (except thyroid cartilage)	Intrinsic muscles of larynx (except cricothyroid), upper muscles of the esophagus	Pulmonary arteries and ductus arteriosus	Recurrent laryngeal (vagus)

Table 15.1 Adult derivatives of pharyngeal arches.

Pharyngeal Pouches

☐ These are 4 pairs of the endodermal lining of the foregut. The 5th pair is absent.

Pouch number	Derivatives
I	Middle ear cavity, auditory tube and mastoid air cells
II	Palatine tonsils and tonsillar sinus
III	Inferior parathyroid gland and thymus
IV	Superior parathyroid gland and ultimopharyngeal body

Table 15.2 Derivatives of pharyngeal pouches.

☐ At week 5, the thymus and the inferior parathyroid glands lose their attachment with the pharynx → the thymus migrates to reach its final position (anterior to the thorax) and drags (pulls) the inferior parathyroid gland with it.
Development of the thymus continues until puberty → progressively atrophied.

☐ Neural crest cells incorporate into the ultimopharyngeal body → parafollicular cells of the thyroid.
In other words, pharyngeal pouch 4 ⟹ C cells.

Endocrinology correlation;

Parafollicular cells of the thyroid secrete **c**alcitonin. So, it is also called **C** cells.

Pharyngeal Grooves

☐ Are 4 ectodermal invaginations *covering* the pharyngeal arches.
Only, the first pharyngeal groove persists in adult as → **external auditory meatus**.
Other grooves (2, 3 and 4) → the cervical sinus at the neck region and finally are obliterated.

Pharyngeal Membranes

☐ Are located at the junction between the pharyngeal grooves and pouches.
1st pharyngeal membrane → **tympanic membrane**.
Other pouches are obliterated.

Use the mnemonic (**GAP**) to remember the origins of the pharyngeal apparatus.
As the arrangement of the germ layers from outside,

G = **g**rooves, ectoderm

A = **a**rches, mesoderm

P = **p**ouches, endoderm

- **Anomalies** of the pharyngeal region;

A. **Branchial or pharyngeal fistula**: Persistence of the cervical sinus as a narrow patent canal. The latter may open internally close to the tonsillar region or externally in front of the sternocleidomastoid muscle.

B. **Branchial cyst**: Non obliteration of a part of the cervical sinus forming a cyst. It is usually found just below the angle of the mandible.

C. **Ectopic thymus and parathyroids**: Abnormal migration of the thymus and parathyroid glands (usually inferior part). It is found anywhere along its descending path.

D. **First arch syndrome**: It is an abnormal formation of the first pharyngeal arch due to an incomplete migration of neural crest cells to arch 1.
It's associated with various anomalies of the ears, eyes, palate and mandible.
Manifestations of first arch syndrome include;

1. *'Treacher Collins syndrome'* [autosomal dominant genetic disorder]:
Is characterized by underdevelopment of the zygomatic bones (malar hypoplasia) and mandible, deformed external ears and defected lower eyelids (coloboma).

2. *'Pierre Robin syndrome'* [autosomal recessive disorder]:
Is characterized by small mandible (micrognathia), cleft palate, posterior displacement of the tongue (glossoptosis) and deformed eye and ear.

TONGUE

- The tongue (Latin, lingua) appears near the end of week 4 (Fig. 15.1).
Developmentally, it can be subdivided into;

A. **Anterior two thirds** originate from:

1. **Two lateral lingual swellings** (distal tongue buds).

2. **Single median lingual swelling** (median tongue bud or tuberculum impar).

These swellings develop from the pharyngeal arch ***1*** in the floor of the future pharynx. These 3 swellings overgrow → fusion of each other in the midline (future median sulcus) → oral part or anterior 2/3 of the tongue.

> ***N.B.*** The V-shaped **terminal sulcus** indicates the line of fusion between the anterior and posterior parts of the tongue.

B. **Posterior one third** develops from:

1. **Copula** ⇦ pharyngeal arch ***2***.
2. **Hypobranchial eminence** ⇦ arches ***3*** and ***4*** caudal to the copula.

- ☐ The anterior part of hypobranchial eminence extends to the midline and overgrows the copula and other arches. Thus, the copula disappears.
  Posterior 1/3 (pharyngeal part) of the tongue develops mainly from pharyngeal arch 3.
- ☐ Normally, only the inferior surface of the tongue is linked to the mouth floor by the frenulum.
- ☐ The extrinsic and intrinsic muscles of the tongue (see Chapter 8).

Related with neuroanatomy;

A. Ant. 2/3;
general sensation = trigeminal n. ⟶ mandibular branch ⟶ lingual n.
special (taste) sensation = Facial n. ⟶ chorda tympani n.

B. Post. 1/3;
general and special sensation = glossopharyngeal n.

- ☐ Congenital **anomalies** in tongue development;

A. **Ankyloglossia** (tongue tie): The frenulum is short and extends to the tip of the tongue. It is generally prevented tongue protrusion ⇨ breast feeding difficulty.

B. Macroglossia: Overgrowth of the lingual swellings ⇨ excessively large tongue.

C. Microglossia: Underdevelopment of the lingual swellings ⇨ abnormally small tongue.

D. Bifid tongue (**glossoschisis**): Partial fusion of the lateral swellings ⟹ groove in the midline of the tongue.

THYROID GLAND

- ☐ At week 4, the **thyroid diverticulum** arises as an endodermal proliferations in the floor of the primitive pharynx around the foramen cecum.
- ☐ As the tongue grows, the thyroid gland *descends* ventrally to the pharyngeal tube as a bilobed diverticulum until reaches the adult position in front of the trachea at the 7th week. However, it is still connected to the tongue via the **thyroglossal duct**. Later, this duct will obliterate.
- ☐ Congenital **anomalies** of the thyroid glands include;

A. **Thyroglossal duct cyst:** A part of the thyroglossal duct fails to obliterate leaving a cyst. Usually, found at the midline of the neck close to the hyoid bone, but anywhere else such as a lingual cyst. This cyst may also rupture forming a thyroglossal fistula.

B. Ectopic thyroid gland: Usually found along its descending course such as lingual thyroid gland or sublingual thyroid gland.

C. Agenesis of the thyroid gland.

D. Accessory thyroid tissue.

FACE

- ☐ Early in the week 4, the face develops as three swellings around the stomodeum;

A. Single **frontonasal prominence** (mesenchymal proliferation)

B. **Maxillary prominence** (paired)

C. **Mandibular prominence** (paired)

} ***1st*** pharyngeal arch derivatives

- ☐ By its name, the frontonasal prominence → forehead and nose.
  On each side of the frontonasal prominence, local ectodermal thickenings (**nasal placodes**) develop.

☐ At week 5, the nasal placodes depress → **nasal pits**.
Each nasal pit creates 2 limbs around itself → **medial** and **lateral nasal prominences**.

☐ Enlargement of the maxillary prominences → the cheeks and maxillae.

☐ **Upper lip:** *Fusion of*
lateral part = maxillary prominences, medial part = medial nasal prominences
If fusion fails to occur → **cleft lip** (1 of the most common facial anomalies).

☐ **lower lip and jaw:** *Fusion of*
mandibular prominences in the midline.

☐ The **nasolacrimal groove:** Is between the lateral nasal prominence and maxillary prominence. The grooves' ectodermal floor → solid epithelial cord → canalizes later on.
Ultimately, nasolacrimal groove → nasolacrimal duct and lacrimal sac.

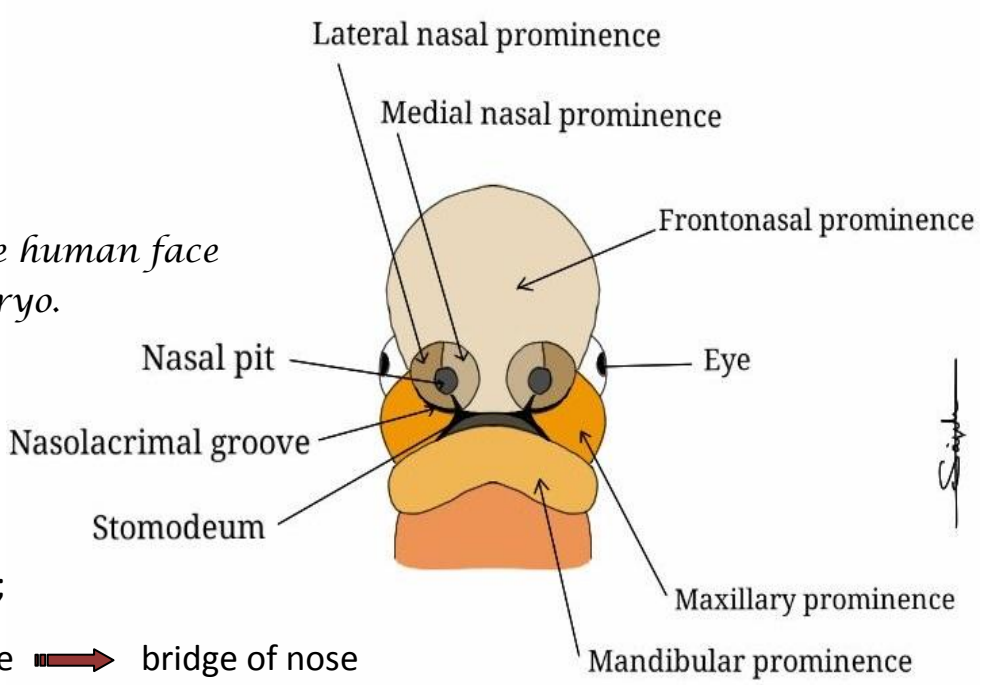


Fig. 15.2 Development of the human face at week 5 embryo.

☐ The **nose** is developed from;

A. Frontonasal prominence ⟹ bridge of nose

B. Medial nasal prominences ⟹ crest, tip and nasal septum

C. Lateral nasal prominences ⟹ alae of nose

D. Nasal pits ⟹ nostrils and nasal cavities

☐ The 2 medial nasal prominences fuse at the midline → **intermaxillary segment** →

1. Philtrum of the upper lip
2. Four incisor teeth
3. Primary palate

☐ Clinical **anomalies**;

A. **Cleft lip**: Is a common congenital anomaly due to lack of fusion between the maxillary and medial nasal prominences. It is uni or bilateral, and most common in males. It often occurs with cleft palate.

B. Median cleft lip: Is a rare anomaly produced by incomplete fusion of the medial nasal prominences in the midline.

PALATE

☐ *1ry* palate ⟸ intermaxillary segment which carries the incisor teeth.

☐ At week 6, *2ry* palate ⟸ fusion of 2 **palatine shelves** (mesenchymal outgrowth of the maxillary prominences) above the tongue.

☐ At the **incisive foramen**, the 1ry and 2ry palates merge to form → **definitive palate**.

☐ At the same time of fusion, the nasal septum descends vertically and fuse with the superior surface of the palate.

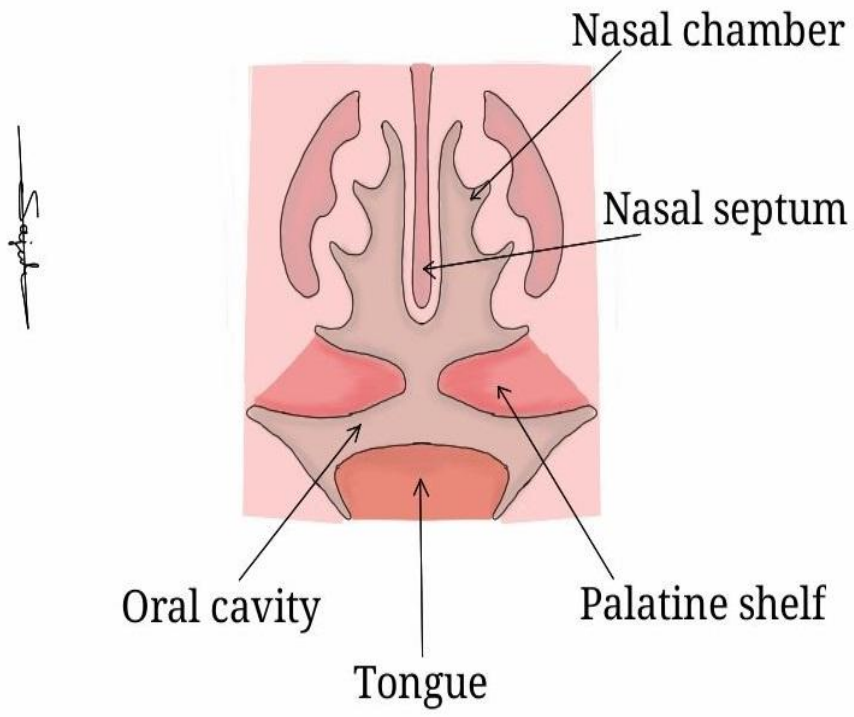


Fig. 15.3 Horizontal section through the head of a 8-week embryo showing development of the palate.

☐ Bone extends in the *1ry* and anterior portion of the *2ry* palates → **hard palate**.
Bone doesn't extends in the posterior portion of the *2ry* palate → **soft palate**, including the **uvula** (conical projection).

☐ Facial **anomalies** include;

A. **Cleft palate**: Non fusion of the palatine shelves in the midline.
It may be unilateral (most common) or bilateral. Most common in females.
Usually, causes cleft uvula.

B. **Oblique facial clefts:** Incomplete fusion between the maxillary prominence and medial nasal prominences.
In most cases, the nasolacrimal duct is opened to the surface.

MOUTH

☐ The mouth is developed from *2* sources;

A. **Stomodeum**, lined by ectoderm.

B. **Cranial end of the pharynx** , lined by endoderm.

☐ At first, the stomodeum and foregut are separated by the **oropharyngeal** or **buccopharyngeal membrane**.
This membrane ruptures by week 3 → continuity between the *2* cavities.

☐ **Abnormalities** of the mouth;

A. Macrostomia: Excessive large mouth due to incomplete fusion between the maxillary and mandibular prominences.

B. Microstomia: Very small mouth due to excessive fusion between the maxillary and mandibular prominences.

NASAL CAVITIES

☐ The **nasal placodes** invaginate → **nasal pits** → **nasal sacs**.

☐ At first, the nasal sacs and oral cavity are separated from each other by the **oronasal membrane**.
At week 6, this membrane ruptures → temporary communication between the oral and nasal cavities by means of the **primitive choanae.**

☐ After formation of the *2ry* palate, 3 elevations or swellings in the lateral wall of each nasal cavity develop = **superior**, **middle** and **inferior conchae**.
The **definitive choana** is located at the junction of the pharynx and nasal cavity.

- In the roofs of the nasal cavities, the ectodermal epithelium is specialized to → **olfactory epithelium**.

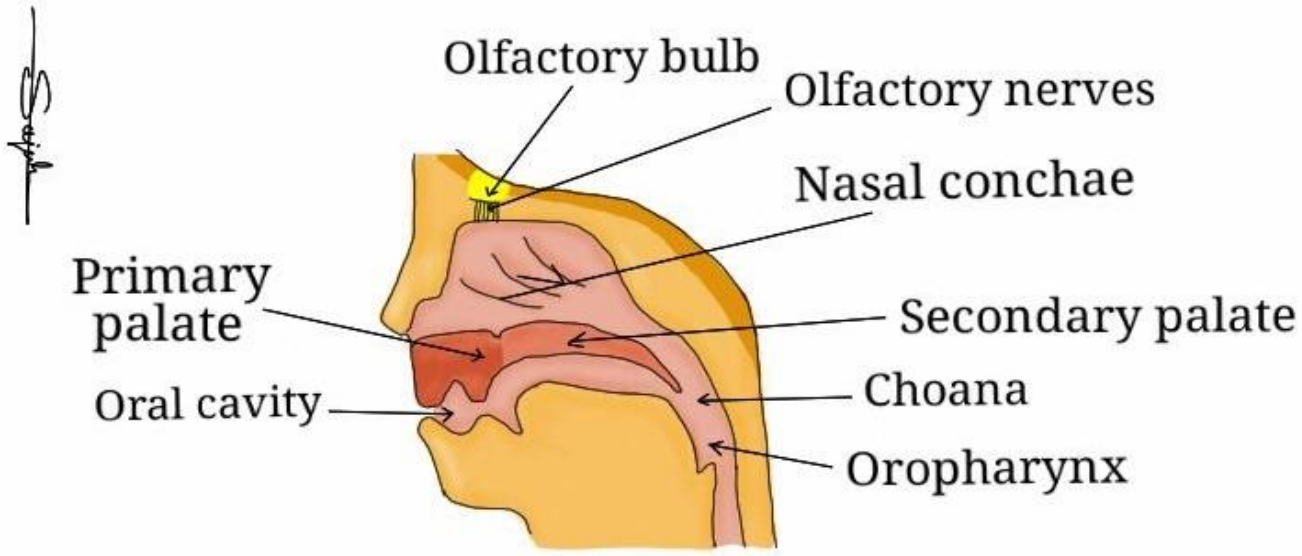


Fig. 15.4 Sagittal section of the face of a 12-week embryo showing the development of the nasal cavities.

- Paranasal sinuses develop postnatally except maxillary sinuses, develop prenatally. They are formed as outgrowths from the lateral walls of the nasal cavities → become filled with air → extend into the adjacent bones.

SALIVARY GLANDS

- **Parotid glands;**

  Early in *week 6*, buds arise from oral cavity's ectodermal lining, just close to the angles of the stomodeum.
  The distal part breaks into acini.
  At *week 10*, the proximal part canalizes → the parotid duct,
  but secretions begin by *week 18*.

- **Submandibular glands;**

  Late in *week 6*, buds arise from the endodermal floor of the stomodeum.
  At *week 12*, acini form, but its secretory activity commences at *week 16*.
  The proximal part canalizes → the submandibular duct.

- **Sublingual glands;**

  At *week 8*, small several endodermal buds in the paralingual sulcus.
  These buds appear as 1 gland having multiple ducts opening in the mouth floor.

Chapter 16 || Eye

Objectives :

- Identify the different structures of the eye and their formation.
- To understand the major congenital anomalies.

☐ The eye starts to appear at day *22* with the formation of the optic groove.
It is derived from;

1. **Neuroectoderm** of the diencephalon
2. **Mesoderm** between the neuroectoderm and surface ectoderm
3. **Surface ectoderm** of the head
4. **Neural crest cells**

> ***Genetically correlated***
>
> ***PAX6***
> is the master regulatory gene in eye development.

☐ Evagination of the neuroectodermal diencephalon → **optic vesicle**, which in turn →

A. Double layered **optic cup** → retina, iris and ciliary body.

B. **Optic stalk** → optic nerve, optic chiasm and optic tract.

☐ Invagination of the surface ectoderm forms the **lens placode**, which in turn → **lens vesicle**.
Lens vesicle → lens and the eyelids epithelium, conjunctiva and cornea.

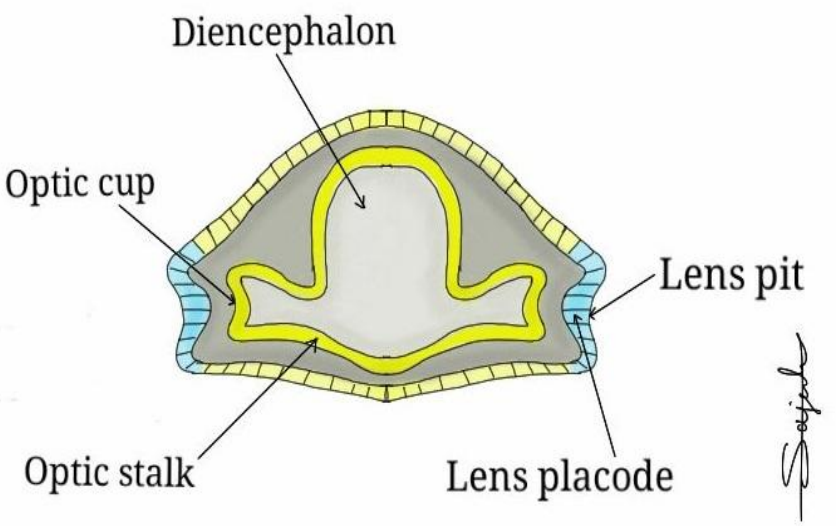


Fig. 16.1 Transverse section of the forebrain of a 5-week embryo.

- Mesoderm → portions of sclera and cornea, extraocular muscles and vitreous body.
- Neural crest cells differentiate into → portions of the sclera and choroid, sphincter pupillae, dilator pupillae and ciliary muscles.
- Hyaloid vessels are transported within the choroid (optic) fissure in the optic stalk proximally and in the vitreous body distally.
  Proximal part of the hyaloid vessels → central artery and vein of the retina in the adult.
  Distal part degenerate leaving → a hyaloid canal in the vitreous body.

Cornea

- The cornea develops from;
  1. Surface ectoderm ⟹ external corneal epithelium
  2. Mesenchyme or mesoderm ⟹ stroma
  3. Neural crest cells ⟹ corneal endothelium

Sclera

- An outer fibrous layer,
  it is developed from the → mesoderm and neural crest cells.
  The sclera is continuous anteriorly with the cornea and the dura mater posteriorly.

Iris

- Is originated from → *2* layers of the optic cup (epithelium) and the mesoderm (stroma).
  It contains the papillae muscles (dilator and sphincter).
- Mostly, color or pigmentation of the iris varies from light blue, gray, brown, to black in newborn infants. It is depended on the concentration and distribution of melanin in the iris.

Lens

- It originates from → surface ectoderm ⟹ lens placode ⟹ lens vesicle.
  Both the iris and lens are covered by the **iridopupillary membrane**.
  Normally, this membrane is resorbed prior to birth.

Ciliary body

- Its origin is similar to the iris.
  The ciliary body contains the ciliary muscle and ciliary processes.
  Aqueous humor is produced by the ciliary processes.

Choroid

- Is a vascular layer that develops from Mesenchyme surrounding the optic cup.

Retina

- The outer layer of the optic cup → the pigmented layer of the retina.
  The inner layer → the neural layer of the retina.
  These 2 layers are separated by; **intraretinal space** ➡ obliterated normally in adults.
  The inner neural layer of the retina → cons and rods, bipolar cells and ganglion cells.

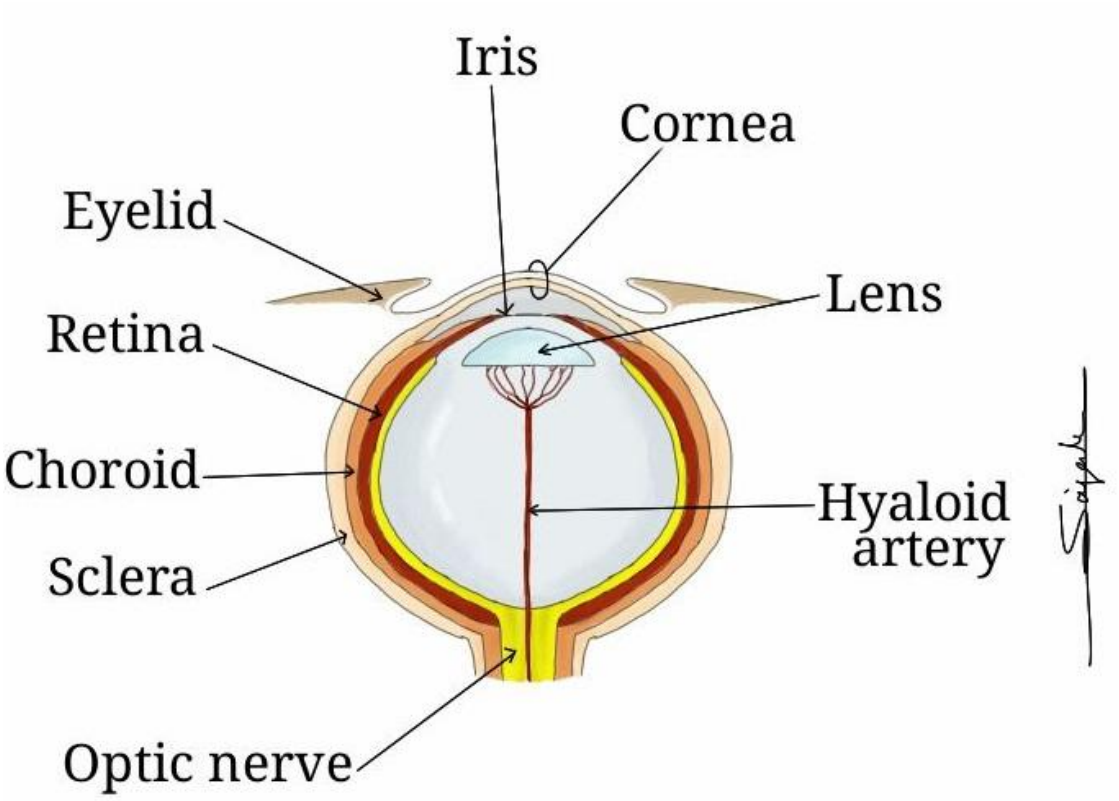


Fig. 16.2 Sagittal section of the eyeball of an embryo.

Eye Anomalies

A. **Coloboma iridis**: Failure to close of the choroid fissure → cleft in the iris.

B. **Congenital cataracts**: The most inherited anomaly. It is an opacity (cloudiness) of the normal lens.

C. In **microphthalmia**, the eye is very small. Usually associated with other ocular anomalies.

D. **Anophthalmia** is referred to the absence of the eye due to the failure of formation of the optic vesicle.

E. **Cyclopia** (single eye) and **synophthalmia** (fused eyes). Both of them are caused by failure in development of the midline cerebral structures (*holoprosencephaly*).

F. **Persistent iridopupillary membrane** is composed of web-like connective tissue that covers the pupil partially. Anyhow, it seldom interferes with vision.

G. **Congenital glaucoma**: An abnormal ⬆ increase in intraocular pressure due to abnormal development of the drainage pathway of the aqueous humor, chiefly the canal of Schlemm.

H. **Persistence of** the distal part of **the hyaloid artery** leaving a nonfunctional cord or cyst.

I. Congenital Aphakia (absence of the lens) and aniridia (absence of the iris) are extremely rare.

j. **Papilledema**: Edema (fluid accumulation) of the papilla (optic disk) due to and abnormal ⬆ elevation of the intracranial pressure.

K. **Detached retina**: Failure of the intra-retinal space to obliterate.
It may be congenital or due to trauma.

Chapter 17 || Ear

Objectives :

- Describe the development of the internal, middle and external ear.
- Enlist the common abnormalities related to the development of the ear.

☐ Anatomically, the ear consists of three distinctly parts: internal, middle and external ear.

Internal Ear

☐ The internal ear is the first part to be formed.
It develops at week 4 from the **otic placode** (ectodermal thickening adjacent to the rhombencephalon).
However, this placode will invaginate ⟹ **otic vesicle** divided into;

A. Dorsal **utricular portion** → utricle, semicircular ducts, *vestibular* ganglion CN VIII and endolymphatic duct and sac.

B. Ventral **saccular portion** → saccule, spiral organ of Corti or cochlear duct and *spiral* ganglion of CN VIII.

☐ The 2 portions together → **membranous labyrinth**.

☐ Otocyst or otic vesicle is surrounded by the connective tissue, the **otic capsule**.
This connective tissue ⟹ cartilaginous ⟹ ossifies ⟹ **bony labyrinth** of the temporal bone.

☐ Otic capsule ⟹ **perilymphatic space** (containing perilymph) which in turn develops → the scala vestibuli and scala tympani.

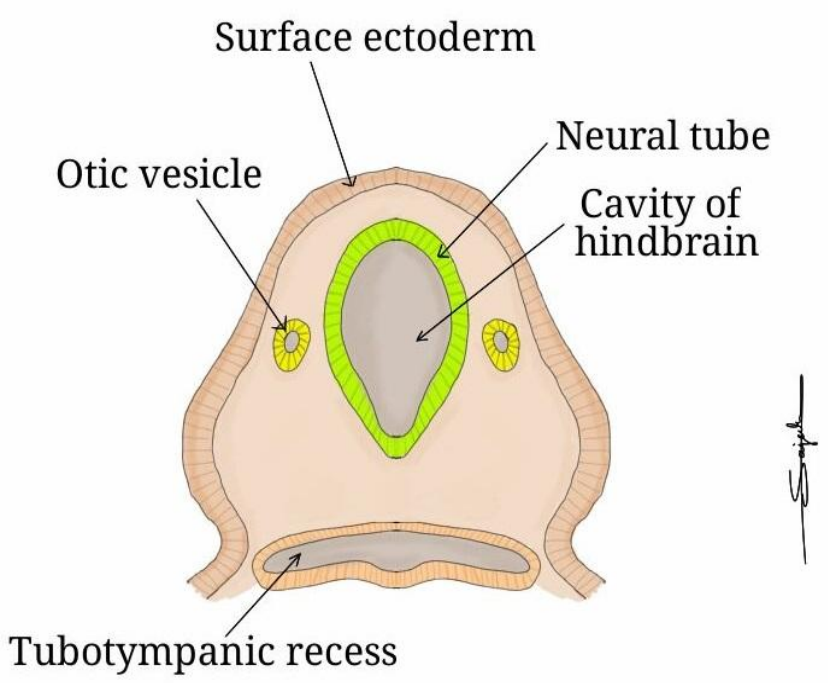


Fig. 17.1 Schematic coronal section illustrating early development of the internal ear, approximately week 5.

Middle Ear

- ☐ First pharyngeal arch → malleus, incus, tensor tympani muscle and CN V.
- ☐ **S**econd pharyngeal arch → the **s**tapes, **s**tapedius muscle and CN VII.
- ☐ First pharyngeal pouch → tubotympanic recess (Fig. 17.1).
  Tubotympanic recess → eustachian (auditory) tube and tympanic or middle ear cavity.
- ☐ First pharyngeal membrane → tympanic membrane.

External Ear

- ☐ First pharyngeal groove → **external auditory meatus**.
- ☐ A temporary, **meatal plug** is a solid epithelial plate appears in the *3rd* month from proliferating ectodermal cells. Later in the *7th* month, this plug begins to disappear.
- ☐ The tympanic membrane or **eardrum** develops from;
  1. An ectodermal epithelium facing the external auditory meatus (pharyngeal groove 1)
  2. An intermediate layer of mesenchyme or connective tissue (pharyngeal arches 1 and 2)
  3. An endoderm epithelium face to the tympanic cavity (pharyngeal pouch 1)
- ☐ The **auricle** or pinna develops from ⟸ fusion of the six auricular hillocks (mesenchymal swellings).

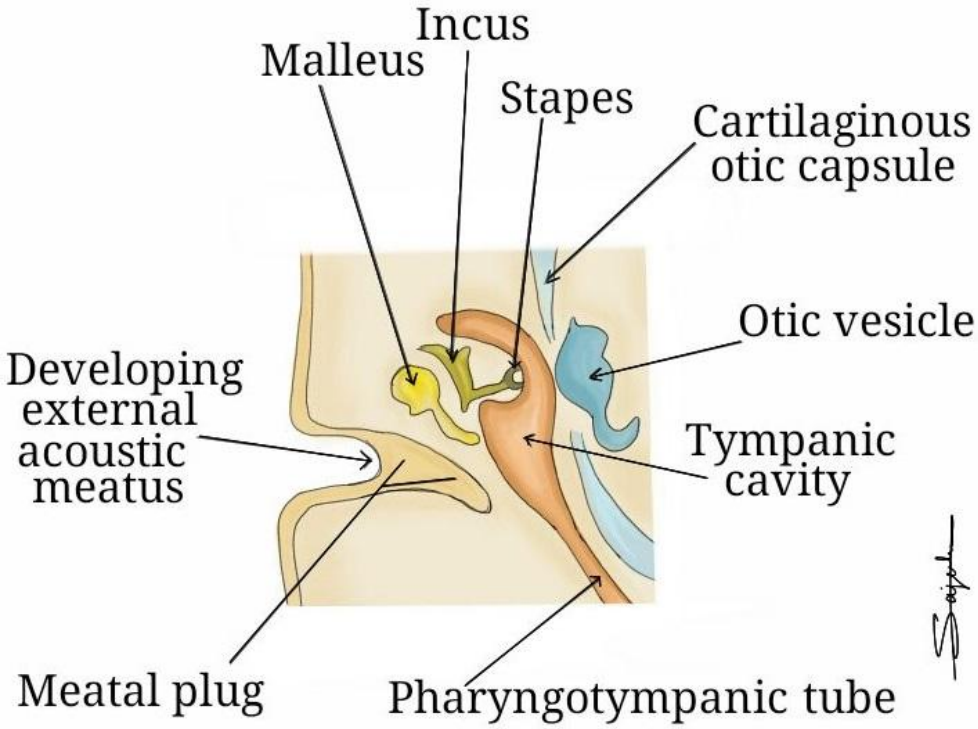


Fig. 17.2 Schematic drawing illustrating development of the middle and external ear.

Related with neuroanatomy;

The pinna of the ear is innervated by;

Cranial n. = CN V_3 (mandibular branch), CN VII, CN IX, and CN X. To summarize it, remember "1975".

Spinal n. = cervical nerves (C2) and (C3).

Ear Anomalies

A. **Congenital deafness**: Failure/maldevelopment of the ossicles or eardrum or body labyrinth. It may be caused by genetic or environmental factors.
A *rubella virus* infection can damage the organ of Corti resulting in hearing loss.

B. **Auricular appendages** (skin tags):
Appear in front of the auricle. It indicates the development of the accessory auricle hillocks.

C. **Microtia**: Rudimentary or small auricle.

D. **Anotia**: Complete absence of the auricle.

E. **Atresia of the external auditory meatus**:
May be complete or partial due to failure of canalization of the meatal plug.

F. **Absence of the external auditory meatus**: Persistence of the meatal plug until birth.

Chapter 18 || Integumentary System

Objectives :

- Identify, understand and explain the development of the skin and its accessory structures.
- Describe the important stages in formation of the teeth.
- List the common anomalies related to the integumentary system.

☐ The integumentary system (Integument = covering) =
skin (epidermis and dermis) + its appendages (hair, nails and surface glands).

SKIN

☐ The skin is the largest organ in your body.
It is composed of: superficial layer **{epidermis}** and a deep layer **{dermis}**.

Epidermis

☐ Firstly, the epidermis is originated as a single layer from the *surface ectodermal* cells.
At the 2nd month, these cells proliferate and divide into (1) periderm and (2) basal layer.
Cells of the later undergo further proliferation and form the third or intermediate layer.

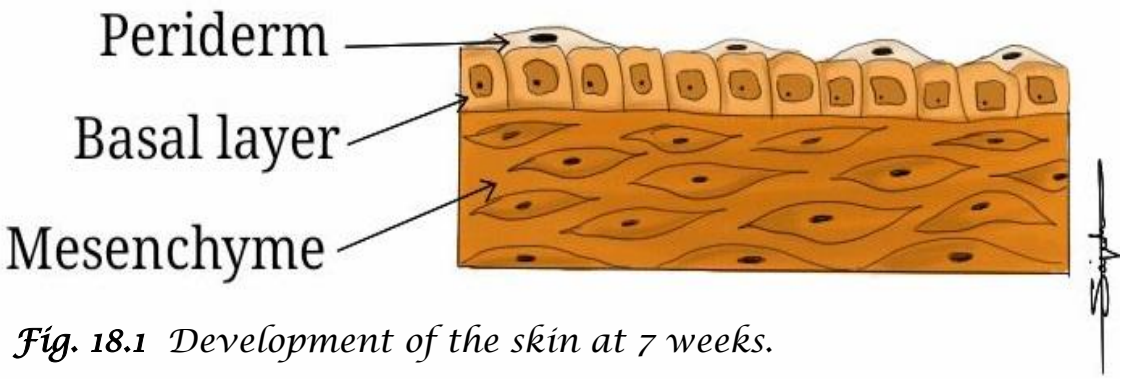


Fig. 18.1 Development of the skin at 7 weeks.

☐ Finally, the epidermis reaches its *four* definitive layers by the end of the *4th* month;

1. Basal or germinative layer (production of new cells)
2. Spinous layer
3. Granular layer
4. Horny layer

- ☐ During the *1st* trimester, neural crest cells migrate, invade the basal layer → **melanoblasts**. Melanoblasts differentiate into → melanocytes → produce the melanin pigment (determining the color of the skin).
- ☐ Langerhans cells arise from ⟸ bone marrow (mesoderm) and invade the epidermis.
- ☐ Generalized **albinism**: Is an inherited condition occurs when there is a lack of the melanin pigment.
- ☐ **Piebaldism** (localized albinism): A lack of melanin appears in isolated patches of skin and/or hair.

Dermis

- ☐ The dermis (corium) is derived from ⟸ lateral plate mesoderm, paraxial mesoderm and neural crest cells.
  The corium gives rise to → irregular projections into the epidermis, the **dermal papillae**, it may contain sensory nerves or small capillary.
- ☐ The mesodermal cells have begun to produce → large amounts of elastic and collagen fibers.
- ☐ Deeper to the dermis, subcorium, or **hypodermis** is a layer of fatty tissue.
- ☐ The degenerated peridermal cells and sebum from sebaceous glands → **vernix caseosa** (a greasy white substance covering the fetal skin at birth).
- ☐ **Ichthyosis** (ichthys=fish) is a group of cutaneous hereditary disorders resulting from excessive or aberrant keratinization of the skin. The latter is characterized by dryness and fish-like skin. Most severe form of ichthyosis may result in a harlequin fetus.

SKIN APPENDAGES

Hair

- ☐ Hair follicle is developed as a proliferation from the germinative layer of the epidermis that grows into the underlying dermis. Soon, the hair buds become club shaped, called **hair bulbs**. The hair bulb is invaginated by mesenchyme, forming → **hair papillae**, which is rapidly filled by blood vessels and nerve endings.
- ☐ Epithelial cells within the hair bulb → **germinal matrix**, which later constitutes the hair.

- Central cells of the buds become keratinized → **hair shaft**.
  Peripheral cells → **epithelial hair sheath**.
  Mesoderm surrounding Hair follicles → **dermal root sheath** and **arrector pili muscle**.

- By week 20, lanugo hairs are the first, fine and soft hairs that appear.
  At birth, these hairs are sloughed off.

- **Hypertrichosis:** An excessive hairiness caused by an overgrowth of the hair follicles.
  It is may be associated with spina bifida.

- Atrichia: A congenital absence of the hair.

- Alopecia: Loss of scalp hair.

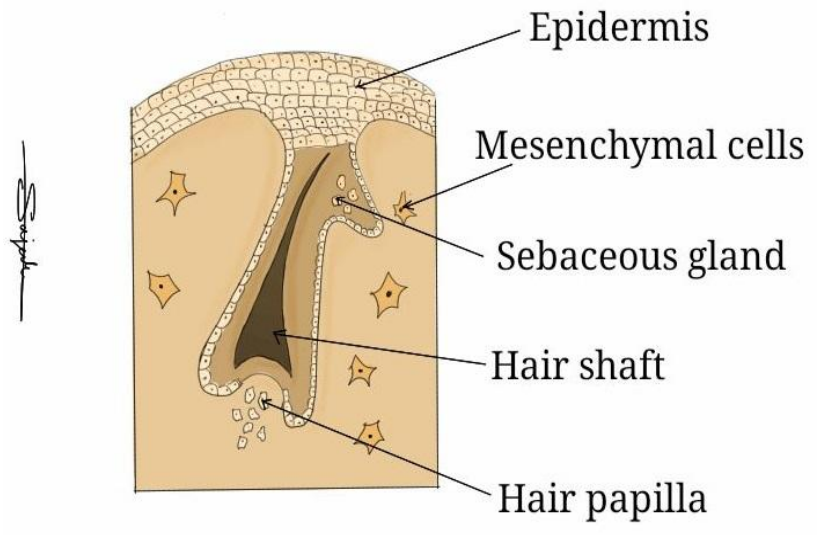


Fig. 18.2 Development of a hair.

Sebaceous Glands

- Sebaceous gland develops as buds from the wall of the epithelial hair sheath of the hair follicle (Fig. 18.2).

- Central cells of this gland will degenerate → a sebum that empties into hair follicle to reach the skin.

Nails

- Nails are derived from ⟸ epidermis as thickened areas or **nail fields**.
  Firstly, the nail field appears at the tip of each digit and then ⟹ migrates to the dorsal surface pulling its innervation with them.

- Nail fields are surrounded by the **nail folds**.
  Cells from the nail fold grow over the nail field and undergo keratinization → **nail plate**.

- **F**ingernails develop **f**irstly at week 10, while the **t**oenails appear at week 14.
  To remember this point; *("F" precedes "T" in alphabetical order).*

- Congenital anonychia: Is the absence of nails due to a failure of the nail plate to form (rare).

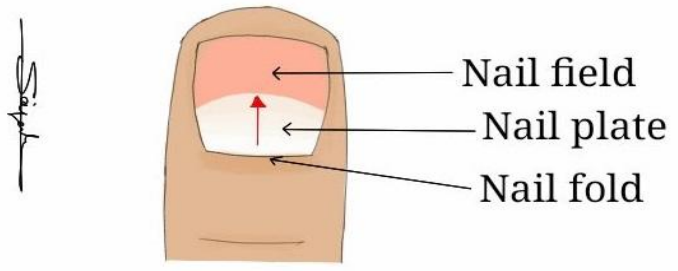


Fig. 18.3 Formation of a fingernail.

Sweat Glands

- ☐ Sweat glands are formed as epidermal bud down-growth into the underlying dermis.
  2 types of sweat glands are found; eccrine and apocrine.
- ☐ **Eccrine** sweat glands: Widely developed and distributed along the body.
  Ducts of these glands open into the skin.
- ☐ **Apocrine** sweat glands: Found wherever there is body hair e.g., face, axillae, pubic region… etc.
  Ducts of these glands open into the hair follicle.

Mammary Glands

- ☐ Mammary gland is a modified sweat gland.
  It begins to develop during the *6th* week, from the mammary ridges as mammary buds that begin to penetrate the underlying mesoderm.
- ☐ Mammary ridge is a thickened line of ectoderm which appears at week 4 and extends bilaterally from the axilla to the inguinal region.
  Shortly, these lines disappear except that of the thoracic or pectoral region.
- ☐ Canalization of the mammary buds → lactiferous ducts and alveoli.
- ☐ Lactiferous ducts open into a mammary pit (depressed area at the site of the gland origin).
  Soon after birth, this pit (by proliferation of the surrounding mesenchyme of the areola) → the nipple.
- ☐ Mammary gland **anomalies** include;

  A. **Polythelia** (poly=extra, thelia=nipple): Supernumerary nipples occur along the mammary line.

  B. **Polymastia** (mastia=breast): Supernumerary breasts appear along the mammary line.

  C. **Gynecomastia** (gyne=woman): Enlarged male's mammary gland.
  Usually associated with *Klinefelter syndrome*.

  D. In **inverted nipples**, breast feeding may be difficult.

  E. Athelia or amastia.

TEETH

- ☐ Teeth (=dental, plural) ← oral ectoderm, underlying mesenchyme and neural crest cells.
- ☐ Development of the tooth occurs in 4 major stages;
    1. Initiation stage: weeks 6 - 7
    2. **Bud** stage: week 8
    3. **Cap** stage: weeks 9 - 10
    4. **Bell** stage: weeks 11 - 12
    5. Apposition stage: varies per tooth
    6. Maturation stage: varies per tooth
- ☐ By week 6, these ectodermal cells down-grow and penetrate the underlying neural crest cells → a U - shaped structure, the **dental lamina** → dental buds → enamel organs.
- ☐ Enamel organs consist of 2 layers, outer enamel epithelium and inner enamel epithelium. Enamel organs → ameloblasts → a cup-shaped **enamel**.
- ☐ The underlying neural crest cells (mesenchyme former) incorporate into the concavity of the cup → **dental papilla**.
- ☐ The dental papilla → odontoblasts and dental pulp. Odontoblasts → predentin → calcifies → dentine.
- ☐ Mesenchyme surrounding the dental papilla condenses → **dental sac** → cementoblasts (cementum former) and periodontal ligament.

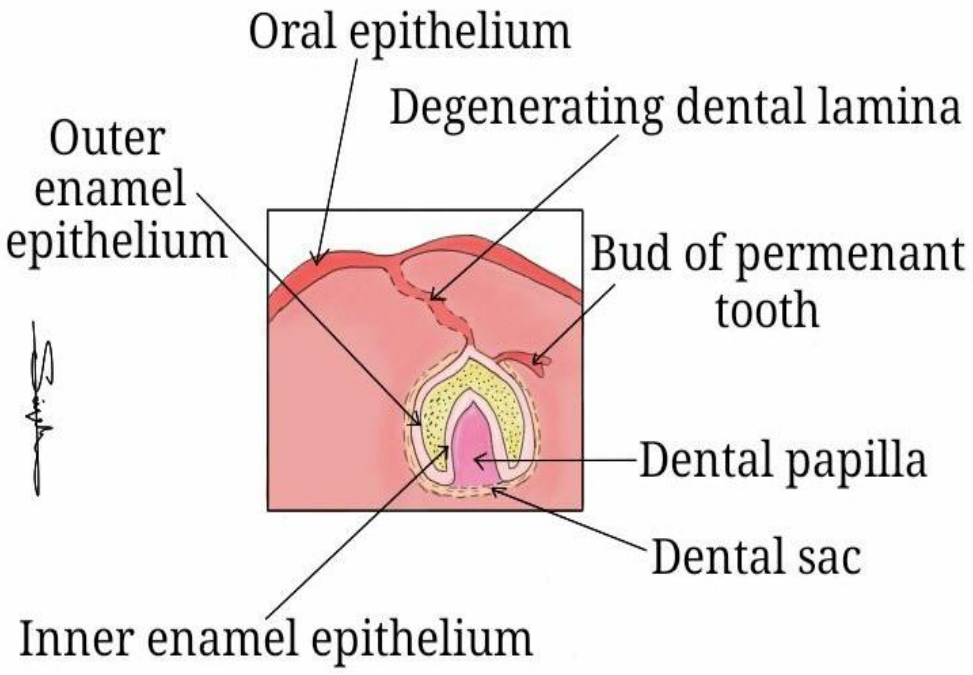


Fig. 18.4 Early bell stage of formation of the tooth, week 10.

- Two groups of teeth are formed;
  1) primary, milk, or deciduous 20 teeth 2) secondary or permanent 32 teeth
  * Both sets are developed in the same way.

- The eruption of the deciduous teeth occurs between 6 and 24 months after birth.
  The permanent teeth erupt from the *6th* year until adulthood.

- Common congenital **anomalies** of the teeth are abnormal in number, size, or shape.
  These may be caused by genetic or environmental factors.
  Other causes may be; vitamin A deficiency, vitamin D deficiency (rickets), and tetracycline.

- **Natal teeth**: Teeth that have already erupted at birth.

Review Questions

1. ***Of the following, which pair is incorrect;***

a) Medial umbilical ligament / umbilical arteries

b) Median umbilical ligament / urachus

c) Ligamentum teres / right umbilical vein

d) Fossa ovale / foramen ovale

2. ***The first sign of respiratory system formation is;***

a) Primitive foregut **b)** Tracheoesophageal septum

c) Respiratory diverticulum **d)** Bronchial buds

3. ***The embryonic foregut differentiates into all of the following except;***

a) Lung **b)** Gallbladder **c)** Stomach

d) Ventral pancreas **e)** All of the above are correct

4. ***The most upper part of the inferior vena cava is originated from;***

a) Right umbilical vein **b)** Left umbilical vein

c) Right vitelline vein **d)** Left vitelline vein

5. ***Kupffer cells of the adult liver are derived from;***

a) Neural crest cells **b)** Mesoderm

c) Ectoderm **d)** Endoderm

6. ***Esophageal atresia usually results in;***

a) Polyhydraminos **b)** Oligohydraminos

7. ***The posterior fontanelle is usually closed by;***

a) Birth **b)** Age 6 months

c) Age 1 year **d)** Age 2 years

8. ***The anterior pituitary gland is of which origin;***

a) Ectoderm **b)** Endoderm

c) Mesoderm **d)** Neuroectoderm

9. ***What is the origin of the middle ear cavity;***

a) Pharyngeal arch 1

b) Mesoderm

c) Pharyngeal pouch 1

d) Pharyngeal cleft 1

10. ***The parathyroid glands;***

a) Are 4 in number

b) Develop from pharyngeal pouch 2

c) Secrete calcitonin

d) Anatomically, they lie anterior to the thyroid gland

11. ***Failure of the optic fissure to close results in;***

a) Microphthalmos

b) Detached retina

c) Coloboma iridis

d) Congenital cataracts

12. ***What is the origin of the stapes?***

a) Pharyngeal arch I

b) Pharyngeal arch II

c) Pharyngeal arch III

d) Pharyngeal arch IV

13. ***The transitional epithelium of the urinary bladder is derived from ,,,,,,,,, while that of the ureter is derived from ,,,,,,,,, .***

a) Endoderm – endoderm

b) Mesoderm – endoderm

c) Mesoderm – mesoderm

d) Endoderm – mesoderm

14. ***A urachal cyst represents a remnant of the;***

a) Cloaca

b) Urogenital sinus

c) Allantois

d) Hindgut

15. ***Extrinsic eye muscles are derived from which of the following?***

a) Preotic myotomes

b) Epimere

c) Hypomere

d) Occipital somites

16. ***During week 7, the upper limb bud rotates ,,,,,,, whereas the lower one rotates ,,,,,,, .***

a) Medially – laterally

b) Laterally – medially

c) Medially – medially

d) Laterally – laterally

17. ***Limb musculature;***

a) Is originated from somatic mesoderm
b) Starts as mesenchymal condensations
c) Splits into extensor and flexor compartments
d) Spinal nerves play an important role in differentiation process
e) All of the above

18. ***The pyramidal lobe, appears in the neck of some persons, is remnant from which structure?***

a) Foramen cecum
b) Hyoid bone
c) Thyroglossal duct
d) Body of tongue

19. ***The central nervous system (CNS) originates from:***

a) Ectoderm
b) Mesoderm
b) Endoderm
e) Neural crest cells

20. ***In female embryos, the paramesonephric ducts form the:***

a) Ovarian ligament
b) Broad ligament
b) Lower part of the vagina
d) Uterine tubes

21. ***Give the origin of the upper & lower lips?***

22. ***Sternal plates fuse through the …….. direction.***

23. ***What are the factors affecting the descent of testis?***

24. ***What is the associated anomaly of the kidney?***

25. ***Explain the anomaly ' ectopia cordis'.***

26. ***List the embryological origin of the diaphragm.***

27. ***Describe that how the sphenoid bone was formed.***

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