

### 3. EMBRYOLOGY AND DEVELOPMENT

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#### INTRODUCTION

Embryology – the field of study that pertains to the developing organism/human

Basic embryology – usually taught in the chronologic sequence of events. These events are the basis for understanding the congenital anomalies that we encounter in the fetus, and help explain the relationships to other organ system concerns. Below is a synopsis of some of the critical steps in embryogenesis from the anatomic rather than molecular basis. These concepts will be more intuitive and evident in conjunction with diagrams and animated sequences. This text is a synopsis of material provided in Langman's Medical Embryology, 9<sup>th</sup> ed.

First week – ovulation to fertilization to implantation

Fertilization restores

- 1) the diploid number of chromosomes,
- 2) determines the chromosomal sex and
- 3) initiates cleavage.

Cleavage of the fertilized ovum results in mitotic divisions generating blastomeres that form a 16-cell morula. The dense morula develops a central cavity and now forms the blastocyst, which restructures into 2 components. The inner cell mass forms the embryoblast and outer cell mass the trophoblast.

*Consequences for fetal management: Variances in cleavage, i.e. splitting of the zygote at various stages/locations - leads to monozygotic twinning with various relationships of the fetal membranes. Cleavage at later weeks will lead to conjoined twinning.*

Second week: the week of twos – marked by bilaminar germ disc formation.

Commences with blastocyst partially embedded in endometrial stroma

Trophoblast forms –

- 1) cytotrophoblast – mitotic cells that coalesce to form
- 2) syncytiotrophoblast – erodes into maternal tissues, forms lacunae which are critical to development of the uteroplacental circulation. Cytotrophoblast then forms primary villi protruding into syncytium.

Embryoblast forms epiblast and hypoblast which constitute the “bilaminar disc”.

- 1) epiblast layers – give rise to the amniotic cavity superior to it
- 2) hypoblast layer gives rise to the primitive yolk sac/ extracoelomic cavity. Cells from the yolk sac will form the extraembryonic mesoderm which forms the chorionic cavity

*Consequences to fetal development: Site of embedding on the anterior or posterior uterine wall may have consequences to fetal accessibility. Ectopic implantation constitutes risk to fetus and mother.*

Third week – trilaminar germ disc stage

Gastrulation: the process that establishes 3 germ cell layers

Event begins with formation of primitive streak on surface of epiblast. This has an orientation with the cephalic end marked by the primitive node and pit

Epiblast cells migrate to the primitive streak, detach and slip underneath in process called invagination, thereby displacing the hypoblast and becoming the endoderm. Another layer of cells forms between this endoderm and the epiblast- these form the mesoderm and the remaining epiblast now is referred to as the ectoderm.

Invaginating cells that migrate cephalad to form the prechordal plate which will become important in the induction of the forebrain. It is located close to the buccopharyngeal membrane (tightly adherent ectoderm and endoderm cells) that will form the opening of the oral cavity.

Migrating cells then form the notochord extending from the prechordal plate cranially to the primitive pit caudally. Where the pit forms the indentation in the epiblast – the neurenteric canal temporarily connects the amniotic and yolk sac cavities.

The Cloacal membrane is formed at the caudal end of the embryonic disk- formed by tightly adherent ecto- and endoderm.

Establishment of body axes, laterality and fate map concept - see chapter 3 (Genetics and embryology).

*Clinical consequences of errors at this stage of development*

*Anterior midline of germ disc subject to necrosis from high dose alcohol – explains midline craniofacial features and holoprosencephaly.*

*Insufficient mesoderm formation in caudal aspect of embryo - caudal dysgenesis – evident in utero as hypoplasia lower limbs, vertebral anomalies, GU anomalies*

*Errors in laterality sequences may lead to situs inversus.*

*Remnants of the primitive streak may result in tumors exhibiting all three germ cell layers – i.e. sacrococcygeal tumors*

#### Trophoblast activities

More definitive villi forming by invasion of mesodermal cells which are source of developing capillaries. The tertiary/definitive placental villus has capillaries traversing it and contacting capillaries in chorionic plate and connecting stalk. These same capillaries communicate with the circulatory system forming in the embryo, such that when the heart starts beating in the 4<sup>th</sup> week the villous system can complete the loop.

Cytotrophoblastic cells continues to grow beyond the villi and connect form an outer cytotrophoblast shell, which bonds the chorionic sac to the maternal tissues. The chorionic cavity enlarges and the embryo becomes attached to the trophoblastic shell by the connecting stalk that will become the umbilical cord.

*These terms are important in the fetal evaluation later as these vascular spaces /structures become a source for sampling of cells/blood.*

#### Third to eighth week – the embryonic period

Period of organogenesis - derived from 3 germ layers – ecto-, meso- and endoderm. This is the period in which the embryo is most susceptible to disturbances in organ development.

Ectoderm – gives rise to the organs and structures that maintain contact to the outside world.

- 1) the CNS
- 2) the peripheral nervous system
- 3) the sensory epithelium of the ear, nose and eye
- 4) the epidermis, hair and nails
- 5) subcutaneous glands, mammary glands, pituitary gland and enamel of the teeth.

In vicinity of neural plate these become neuroectoderm and participate in neurolation, which results in configurational changes that lead to creation of neural tube with a narrow caudal aspect – the spinal cord and the broader cephalic portion – the brain vesicles. Until fusion is complete, the tube communicates with amniotic cavity by way of neuropores. A subpopulation of these cells, the neural crest cells migrate. Those from the trunk region migrate to either the skin to form melanocytes or via another pathway to form the sensory ganglia, sympathetic and enteric neurons, Schwann cells and cells of the adrenal medulla.

Implications for fetal medicine – tumors derived from the neural crest cells in the vicinity of the adrenal may be picked up. Defects in neural tube development - persistent connection with amniotic cavity and basis for elevated AFP in amniotic fluid..

### Derivatives of the mesodermal layer

Proliferation of the mesodermal germ layer results

- 1) paraxial mesoderm – close to midline
- 2) intermediate mesoderm and
- 3) lateral mesoderm which divides into
  - a) splanchnic/visceral mesoderm continuous with mesoderm of yolk sac or
  - b) somatic/parietal mesoderm along amnion mesoderm

1) Paraxial mesoderm – organizes into segments in craniocaudal sequence forming somites, each of which has its own sclerotome (cartilage and bone), myotome ( muscle) and dermatome(skin) and nerve component.

2) Intermediate mesoderm forms segmental and unsegmented masses that ultimately generate components of the urogenital system.

3) lateral plate mesoderm – splits into parietal and visceral layers. The parietal mesoderm along with overlying ectoderm will form the lateral and ventral abdominal wall, while that surrounding the intraembryonic cavity form the mesothelial membranes lining the peritoneal, pleural and pericardial cavities. The visceral layer with the underlying endoderm will form the wall of the gut, or form the serous membranes around the organs.

Vasculogenesis originates in the mesoderm, which is the source for both the precursors to the vessels as well as the hematopoietic stem cells. Once a primary vascular bed is established angiogenesis describes the process of sprouting new vessels from existing ones.

### Derivatives of the endodermal layer

This cell population covers the ventral surface of the embryo and forms the roof of the yolk sac. As the craniocaudal folding occurs, more of this lining gets folded into the embryo and 3 regions of the primitive gut are described.

- 1) The foregut – from the buccopharyngeal membrane to the liver bud
- 2) The hindgut which terminates in the cloacal membrane
- 3) The midgut in between which remains connected to the yolk sac via the vitelline duct

As development progresses the endoderm will give rise to the

- a) epithelial lining of the respiratory tract
- b) the parenchyma of thyroid, parathyroid, liver and pancreas
- c) reticular stroma of tonsils and thymus
- d) epithelial lining of bladder and urethra
- e) epithelial lining of tympanic cavity and auditory tube

### Third month to Birth – the fetal period

Maturation of tissues and organs. In contrast to preceding months in which the head presented the region of greatest growth, the remainder of the body accelerates its growth. At three months:

- 1) The face becomes more human as the eyes move to the ventral aspect and the ears come to lie laterally.
- 2) Limbs attain relative lengths as compared to rest of body.
- 3) Ossification centers appear and
- 4) External genitalia are such that the gender can be identified.
- 5) The intestine, which had herniated into the umbilical cord has returned to the abdominal cavity after the 12<sup>th</sup> week.

During the 4<sup>th</sup> and 5<sup>th</sup> months the fetus lengthens but does not increase its weight substantially, attaining 500gm by the end of the 5<sup>th</sup> month, at which time fetal movements are perceived by the mother.

During the 2<sup>nd</sup> half, fetal weight increases with the majority of weight gain during the last 2.5 months when the fetus gains 50% of its full-term weight. Several congenital anomalies are associated with intrauterine growth restriction and the tendency to preterm delivery. Preterm delivery of an infant with congenital anomalies is further complicated by the immature respiratory and nervous systems, which have not yet established coordination.

At the end of the 9<sup>th</sup> month the skull has the largest circumference of all body parts, a fact taken into account when considering the delivery of infants with tumors, or those with abdominal wall defects.

### Fetal membranes and placenta

The trophoblast has villi anchored in the mesoderm of the chorionic plate and that are attached peripherally to the maternal deciduas via the outer cytotrophoblast shell. These villous stems branch and ultimately the fetal and maternal circulations come in close proximity as cytotrophoblastic cells and connective tissue cells disappear.

As the pregnancy advances the villi on the embryonic pole proliferate forming the chorion frondosum while those at the opposite pole deteriorate and form the chorion laeve (smooth). The decidua is the functional layer of the endometrium which is shed during parturition. The decidua over the chorion frondosum, the decidua basalis is rich in lipid and glycogen containing cells whereas the deciduas capsularis at the abembryonic pole degenerates allowing the chorion laeve to come in contact and to fuse with the uterine wall (decidua parietalis) on the opposite side of the uterus, thereby obliterating the uterine lumen.

Therefore the functional components of the placenta are the chorion frondosum and the decidua basalis. Fusion of the amnion and chorion to form the amnio-chorionic membrane obliterates the chorionic cavity. It is this membrane that ruptures during labor releasing the amniotic fluid.