EMBRYOLOGY

gr. ἐμβρυον — «foetus»
Embryology – is a study of formation, embryonic structure, early growth and development of living organisms.
Periods of human development

- Gametogenesis

- Fertilization

- Prenatal period:
  - Conception (0-2 weeks)
  - Embryonic (3-8 weeks)
  - Fetal (9-40 weeks)

- Postnatal period:
  - Newborn (0-28 days)
  - Infancy (29 days - 1 year)
Aristotle
384-322 BC

• Different birth types
  - egg-bearing (birds and fish)
  - live-bearing (mammals)

• Different types of cleavage
  - holoblastic
  - meroblastic

• Placenta and umbilical cord, their function
• *Omne vivum ex ovo* (all life comes from the egg), in 1651 stated against the idea of spontaneous generation
• Identified the blastoderm surrounding the embryo of chick
• Discussed the role of amniotic fluid
• Found islets of blood cells before heart development
M. Malpighi

- Detailed drawings of chick embryo development
- Neurulation
- Somites
- Circulation of blood by arteries and veins to and from the yolk sack
The idea of germ layers in the embryo:
- Lower one – gastrointestinal tube
- Upper one – neural tube
Prenatal Development

Gametes

Gametogenesis

Zygote

Fertilisation

Cleavage

Morula, Blastocyst

Gastrulation

Neurulation

Organogenesis

Histogenesis
Primordial germ cells migrate from the yolk sack into the future gonad (6 week)
Spermatogenesis

- Spermatogonium
  - May divide by mitosis to form more spermatogonia

- Primary spermatocyte
  - Meiosis I
  - Secondary spermatocyte
  - Meiosis II
  - Spermatids
  - Cell differentiation
  - Mature sperm cells
Spermatogenesis

- testis
- epididymis
- seminiferous tubules
- Sertoli cell
- spermatogonium
  - mitotic division
  - primary spermatocyte
  - meiotic division I
    - secondary spermatocyte
    - meiotic division II
    - spermatids
    - mature sperm

- acrosome
- cytoplasm
- lumen

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Spermiogenesis

- Formation of acrosome
- Migration of centrioles backwards and formation of flagella
- Migration of mitochondria to the midpiece of tail
- Discarding the excess of cytoplasm
<table>
<thead>
<tr>
<th>Process</th>
<th>Time</th>
<th>Description</th>
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<tbody>
<tr>
<td>Mitosis of spermatogonia</td>
<td>16 days</td>
<td>Formation of primary spermatocytes</td>
</tr>
<tr>
<td>Meiosis I</td>
<td>22-24 days</td>
<td>Division of primary spermatocytes with formation of secondary spermatocytes</td>
</tr>
<tr>
<td>Meiosis II</td>
<td>Several hours</td>
<td>Division of secondary spermatocytes with formation of spermatids</td>
</tr>
<tr>
<td>Spermiogenesis</td>
<td>24 days</td>
<td>Differentiation of spermatids into the spermatozoa</td>
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<tr>
<td><strong>Total</strong></td>
<td><strong>~64 days</strong></td>
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Spermatozoa

- Haploid nucleus contains male genetic information
- Centriole
- Acrosome contains enzymes
- Axial filament
- Tail for propulsion
- Spiral arrangement of mitochondria provides energy for swimming

Images of spermatozoa and labeled diagram of sperm structure.
• **Kartagener syndrome or immotile ciliary syndrome** - is a rare, genetic disorder that causes defects in the action of cilia lining the respiratory tract and fallopian tube, as well as in the flagella of sperm cells.

• **Symptoms:**
  - Frequent respiratory infections
  - Infertility
Female Reproduction

- Unlike males, who are able to produce sperm cells throughout their reproductive lives, females produce a limited number of egg cells.

- During early fetal development germ cells migrate into the ovaries and differentiate into oogonia.
• The oogonia divide by mitosis for the next few months and some differentiate into primary oocytes.

• By fifth month of development there are about 7 million primary oocytes, but most will degenerate by the birth time.

• Those that remain will be surrounded by a single layer of squamous epithelial cells (follicle cells) called a primordial follicle.

• Degeneration of primary oocytes continues.

• At birth = 1 million primordial follicles

• At puberty 400,000 remain
The primordial follicle is the earliest stage of follicular development

- In the mature ovary, primordial follicles are found in the stroma of the cortex
- The primary oocytes within the primordial follicles begin the first meiotic division in the embryo, but the process is arrested at the prophase of I meiotic division
- One layer of squamous follicular cells

A long period of meiotic arrest exposes the primary oocyte to adverse environmental influences and may contribute to errors in meiosis. Such errors result in anomalies such as trisomy of chromosome 21 (Down syndrome).
Primary follicles

- Primary oocyte
- One layer of cuboidal follicle cells
- Zona pellucida is formed between follicle cells and oocyte
Secondary follicles

- Follicle cells undergo stratification

- Connective tissue cells form the theca layers of the secondary follicle:
  - The **theca interna** is the inner, highly vascularized layer of cuboidal secretory cells. They synthesize and secrete the androgens that are the precursors of estrogen.
  - The **theca externa** is the outer layer of connective tissue cells. It contains mainly smooth muscle cells and bundles of collagen fibers.
Tertiary follicles

- Follicular cells form the granulosa layer of the follicle
- Formation of fluid-containing cavities
Tertiary Follicle

* Developing Antral Cavity

* Thecas
Mature Graafian follicle

- The mature or Graafian follicle contains a large cavity (antrum)
- Before ovulation first meiotic division is over, forming secondary oocyte
- The secondary oocyte is arrested at metaphase in the second meiotic division.
Fertilization: The process in which the spermatozoon penetrates into the ovum to form fertilized ovum. In the ampulla of oviduct.
• Spermatozoa “founds” the ovum by chemotaxis

• They follow a concentration gradient of a chemoattractant secreted from the oocyte and thereby reach the oocyte in the uterine tube

• The chemoreceptors are located on the tail of spermatozoa
**Capacitation**

Capacitation - removal of glycoproteins (decapacitation factor) which cover the sperms.

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The plasma membrane of epididymal spermatozoa contains a complement of surface molecules (proteins and carbohydrates) illustrated here as yellow T's.

The surface molecules in epididymal sperm become coated with seminal plasma proteins (orange halos) that mask portions of the membrane molecules.

When sperm are exposed to the female tract environment, these seminal plasma coatings, along with some of the surface molecules, are removed, thus exposing portions of the molecules that can bind to the zona pellucida of the oocyte.
Process of fertilization

Sperm bind to sperm receptor ZP-3 induces Acrosome reaction: release of acrosomal enzyme
Process of fertilization

1. Fusion of the membrane of sperm and ovum
2. The nucleus of sperm penetrate into ovum
3. Formation of pronuclei
4. Fusion of pronuclei

Alteration of ovum

24 h
**Cortical reaction:** Cortical granules $\rightarrow$ perivitelline space $\rightarrow$ degrade ZP-3, alteration of zona pellucida $\rightarrow$ barrier for sperm penetration
Zygote

1 – father’s pronucleus
2 – mother’s pronucleus
3 – centrioles
Prenatal Development

Fertilization
Gametes
Zygote
Morula, Blastocyst
Gastrulating
Cleavage
Organogenesis
Histogenesis
Neurulation
Histogenesis
Formation of blastocyst and implantation

Cleavage and formation of blastocyst

1. **Cleavage**: early division of fertilized egg
2. **Blastomere**: daughter cells from cleavage
3. **Morula**: 12 to 16-cell stage, enclosed in the zona pellucida, like morus
4. **Blastocyst**: about 100 blastomeres, blastocoele, inner cell mass and trophoblast
Phase of cleavage

Fertilized egg

2-cell stage
18~36h

4-cell stage
36~48h

8-cell stage
48~60h
First days of development.
As the zygote travels down the oviduct it undergoes cleavage without increasing its size. This subdivides the large zygote into many smaller daughter cells called **blastomeres**. 24 Hours: First cleavage. 48 Hours: Second cleavage.

3 Days: Embryo consists of 6 to 12 cells, reorganization (compaction: *Uvomorulin*, a glycoprotein is involved in compaction) of the blastomeres, starts at the 8 cell stage. The centrally placed blastomeres are now called **the inner cell mass** (they give rise to most of the embryo proper, which is also called the **embryoblast**). The blastomeres at the periphery constitute the outer cell mass, they are the primary source for the membranes of the placenta. It is also referred to as the **trophoblast**

4 Days: Embryo consists of 16 to 32 cells **called morula**.
Morula
5 Days: The embryo is now called a **blastocyst**.

A large cavity called the **blastocyst cavity** forms due to the hydrostatic pressure. The **embryoblast** cells form a compact mass at one side of the cavity (**embryonic pole**), while the **trophoblast** is organized into a thin, single-layered epithelium.
Appearance and inner structure of blastocyst

Appearance

Inner structure
Before Implantation

Hatching of zona pellucida under the influence of uterine secretion
Day 7

Bilaminar germ disc

Inner cell mass

2 layers of cells in disc (7th day)

**Epiblast**: columnar cells adjacent to trophoblast

**Hypoblast**: cuboidal cells adjacent to blastocoel

Amniotic cavity

Primary yolk sac
Implantation (imbeding)

The process by which the blastocyst settles into the endometrium.

6th day to 11th day

Fundus and body of uterus
• **6 Days**: Blastocyst implants into the uterine wall.

• The blastocyst hatches from the zona pellucida before implanting.

• The trophoblast at the embryonic pole differentiates to produce the *syncytiotrophoblast*, and begins to implant the blastocyst into the uterine endometrium.

• Some of the proliferating trophoblast cells lose their membranes and form a syncytium. The trophoblast cells, which form the wall of the blastocyst, retain their cell membranes and constitute the *cytotrophoblast*.

• Secretion of hCG (maintaining of corpus luteum)
Implantation

Days 6 – 12
Adhesion, blastocyst to endometrium
Trophoblast proliferation
Syncytiotrophoblast
Secretion of hydrolytic enzymes
Breakdown of endometrium
Implantation
Day 6-12 after fertilization
Ectopic pregnancy - when a blastocyst implants in the peritoneal cavity on the surface of the ovary, within the oviduct, or at an abnormal site in the uterus. Ectopic pregnancy is often revealed by symptoms of abdominal pain and/or vaginal bleeding.
Prenatal Development

Gametes → Zygote → Morula, Blastocyst → Cleavage → Gastrulation

Fertilization → Zygote → Gametes

Organogenesis → Neurulation → Histogenesis

Gametogenesis
GASTRULATION

• Gastrulation - process of three germ layers formation:
  – external *(ectoderm)*
  – middle *(mesoderm)*
  – internal *(endoderm)*

2 stages:
  – *Delamination* – 7th day,
  – *Immigration* - 14-15th day
**Delamination** – Dividing of the inner cell mass into two layers:

- External layer – *epiblast*
- Internal layer – *hypoblast*

Part of epiblast cells will form the wall of amniotic vesicle

*Another part of epiblast cells close to the hypoblast will give rise to the embryo*

Hypoblast cells will form the wall of the yolk sac
Second stage of gastrulation – immigration of cells

1. Formation of the **PRIMITIVE SREAK** – longitudinal thickening of the epiblast

2. Formation of the **PRIMITIVE NODE** at the anterior (cranial) end of the primitive streak, through which cells will migrate and form mesoderm, endoderm and notochord
1 Primitive sreak
2 primitive pit
3 primitive node
4 oropharyngeal membrane
5 cardiac plate
6 amniotic membrane
7 mesoderm
8 endoderm
9 cloacal membrane

NB 1+2+3 primitive sreak
Determine the direction of the embryo

Significance of primitive streak

- Determine the direction of the embryo
- notochord
Notochord as Inducer

Induces overlying ectoderm → Neural Tissue (Neural Induction)
Specifies cell type in the Floor Plate of the Neural Tube
Transforms para-axial mesoderm (somite) into vertebral bodies
Stimulated early development of the dorsal pancreas
notochord
• Induction of the neural plate.
• The axial mesoderm & notochord induce the overlying ectoderm to form the neural plate.
Neural Plate ➔ Neural Tube

Four Stages of Neural Tube formation:

1) Thickening of the Neural Plate

2) Establishing the contours of the Neural Plate: Cell shape changes and rearrangement of cells

3) Lateral Neural Folds elevate to form the Neural Groove – medial hinge acts as an anchor, Cell shape changes apically, expanding lateral epidermis forces elevation

4) Apposition and fusion of the Neural Folds to form the Neural Tube
• **Neural Crest.**
• During neurulation neural crest cells begin to migrate in a craniocaudal wave
• Neural crest cells are an extremely important population of cells that migrate into the embryo to form a variety of structures
Prenatal Development

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- Histogenesis
Ectoderm

- Neural tube – nervous system
- Epidermis of skin, glands, hair, nails and etc.
Endoderm

- Epithelium of GI tract and respiratory tract
Mesoderm

• Connective tissue
  – Specialized (cartilage, bone, bone marrow, blood, adipose tissue)
  – Nonspecialized (ligaments, tendons, fascia)

• Heart and vessels

• All muscle

• Immune system
Mesoderm

- Dorsal (Paraxial)
- Intermediate
- Lateral:
  - Somatic
  - Splanchnic
Dorsal mesoderm - Somite
• **Somites**

  subdivide into:

  1. **Dermatomes:**  
     form the **dermis**  
     of the skin

  2. **Myotomes:**  
     skeletal muscles

  3. **Sclerotomes:**  
     bones of axial skeleton
Mesoderm
(formation of somites)

Formation of somites take place from the cranial to the caudal end of the embryo.

New pair of somites is formed to the back of already formed somite every 6-7 hours.
Intermediate mesoderm

- Urinary system
- Genital system
Lateral mesoderm

- **Somatic:**
  - limbs
  - Body walls, including parietal serous membrane

- **Splanchnic:**
  - All layers of the intestines' wall (except the epithelium), including visceral serous membrane
The embryo at 4 weeks
Provisional organs are formed at early stages of embryonic development:

- Yolk sac
- Allantois
- Amnion
- Chorion

They form fetal membranes, connect the embryo with mothers organism and perform other special functions.
1 Primitive streak
2 Primitive pit
3 Primitive node
4 Oropharyngeal membrane
5 Cardiac plate
6 amniotic membrane
7 mesoderm
8 endoderm
9 cloacal membrane

NB 1+2+3 Primitive streak
• Extraembryonic mesoderm divides into internal and external layers:
  • **Internal layer** takes part in the formation of external layer of amnion, yolk sac and allantois
  • **External layer** lines trophoblast from inside and together they form chorion
Yolk sac

Wall of the yolk sac:
- Internal layer – extraembryonic endoderm,
- External layer - extraembryonic mesoderm.

Yolk sac takes part in the formation of the primitive gut.

Yolk sac gives rise to:
- **Primitive blood cells** (differentiate to blood cells and endothelial cells of vessels)
- **Primordial germ cells** (migrate to the future gonads)
• Allantois – an outpocketing of the primary gut into the connecting stalk (future umbilical cord)

• Well developed vessels, that will further guide the vessels of the umbilical cord

• Degenerates during 2\textsuperscript{nd} month of development and forms first urachus - a canal that connects the urinary bladder of the fetus with the umbilical cord, and then median umbilical cord
amniotic cavity - The amniotic fluid-filled cavity surrounding the developing embryo/fetus within the uterus.

amniotic membrane: 0.2-0.5mm
extraembryonic ectoderm + extraembryonic mesoderm

amniotic fluid: 500-1000ml
Amniotic cavity

Umbilical cord

Chorion

Umbilical (allantoic) vessels

Yolk sac

Amnion

Extraembryonic coelom

2 months
Amnion Function

Mechanical protection: hydrostatic pressure

Allows free movement - which aids in neuromuscular development

Antibacterial

Allow for fetal growth

Protection from adhesions
Placenta

Chorion

Decidua

Amniotic cavity
Umbilical cord
Chorion
Umbilical (allantoic) vessels
Yolk sac
Amnion
Extraembryonic coelom

Chorionic sac
Amniotic sac
Eye
Rib
Spleen

2 months
Chorion consists of cytotrophoblast and syncytiotrophoblast. Invaginates the wall of the uterus, forming the fetal part of placenta.
9-13 days:

- Fusion (5) of trophoblastic lacunae (3) and mothers capillaries (4).

- Evagination of cytотrophoblast (1) into syntyiotrophoblast (2) – formation of primary chorionic villi (A).
• After Day 16 extraembryonic mesoderm invaginates into the primary villi (1).
• Formation of secondary chorionic villi (A), consisting of mesenchyme (1), cytotrophoblast (2) and syncytiotrophoblast (3).
• At the end of week 3 cells of mesenchyme (1) differentiate into the capillaries (4) and cells of connective tissue
• Now chorionic villi have capillaries (4), surrounded by loose connective tissue (1), cytotrophoblast (2) and syncytiotrophoblast (3), and become **tertiary chorionic villi** (A).
After 4th month cytотrophobласт gradually disappears.
A – chorionic villi
1 – connective tissue and capillaries
2 – remnants of cytотrophobласт
3 – syncytотrophobласт
Umbilical artery

Umbilical vein

Spiral artery

Uterus vein

Decidua basalis

Placenta septa
Decidua - endometrium *implantation* decidua

**Decidua capsularis:** between the implantation site and the uterine lumen

**Decidua parietalis:** remaining endometrium

**Decidua basalis:** under the implantation site
Barrier between mother’s blood and baby's blood:

- Syncytiotrophoblast (3)
- Cytotrophoblast (2)
- Basal membrane of the trophoblast
- Connective tissue (1)
- Basal membrane of the capillary (4)
- Endothelium of fetal capillary (4)
Functions:

- Gas and metabolic exchange
- Endocrine (pregnancy hormones)
  - hCG
  - Estrogen
  - Progesterone
  - Relaxin
  - Prolactin
- Immune protection
Monozygotic twins
Siamese twins