Human Embryo Development & Placental Development

Steps of human embryo development:

1. Fertilization
2. Cleavage
3. Implantation
4. Differentiation

Fertilization

Is process by which female & male gametes (mature egg & mature sperm) fuse to form zygote, it occurs in the ampullary region of fallopian tube. Without fertilization, the ova will die after 24 hour of ovulation. Fertilization in human is completed within 20 hours. Of the 200 to 300 million spermatozoa deposited in the female genital tract, only 300 to 500 reach the site of fertilization. Only one of these fertilizes the egg. The phases of fertilization are:

- phase 1, penetration of the corona radiata;
- phase 2, penetration of the zona pellucida;
- phase 3, fusion of the oocyte and sperm cell membranes

PHASE 1: PENETRATION OF THE CORONA RADIATA:

Only capacitated sperm can pass freely through corona cells. Capacitation is a period of conditioning in the female reproductive tract that in the human lasts approximately 7 hours. During this time a glycoprotein coat and seminal plasma proteins are removed from the plasma membrane that overlies the acrosomal region of the spermatozoa. Only capacitated sperm can pass through the corona cells.
PHASE 2: PENETRATION OF THE ZONA PELLUCIDA:

The zona is a glycoprotein shell surrounding the egg that facilitates and maintains sperm binding and induces the acrosome reaction. Both binding and the acrosome reaction are mediated by the ligand ZP3, a zona protein. The acrosome reaction, which occurs after binding to the zona pellucida, is induced by zona proteins. During this reaction, multiple points of fusion between plasma membrane and outer acrosomal membrane permitting release of acrosomal content that need to penetrate the zona pellucida and exposes the inner membrane of sperm that will fuse with membrane of ovum. Release of acrosomal enzymes (acrosin) allows sperm to penetrate the zona, thereby coming in contact with the plasma membrane of the oocyte. Permeability of the zona pellucida changes when the head of the sperm comes in contact with the oocyte surface. This contact results in release of lysosomal enzymes from cortical granules lining the plasma membrane of the oocyte. In turn, these enzymes alter properties of the zona pellucida (zona reaction) to prevent sperm penetration and inactivate species-specific receptor sites for spermatozoa on the zona surface. Other spermatozoa have been found embedded in the zona pellucida, but only one seems to be able to penetrate the oocyte.

PHASE 3: FUSION OF THE OOCYTE AND SPERM CELL MEMBRANES

The initial adhesion of sperm to the oocyte is mediated in part by the interaction of integrins on the oocyte and their ligands, disintegrins, on sperm. After adhesion, the plasma membranes of the sperm and egg fuse.
In the human, both the head and tail of the spermatozoon enter the cytoplasm of the oocyte, but the plasma membrane is left behind on the oocyte surface.

**As soon as the spermatozoon has entered the oocyte:**

**1- the egg responds in two ways:**

1. Cortical and zona reactions:
   
   (a) *the oocyte membrane* becomes impenetrable to other spermatozoa.
   
   (b) *the zona pellucida* alters its structure and composition to prevent sperm binding and penetration. These reactions prevent polyspermy.

2. Resumption of the second meiotic division. The oocyte finishes its second meiotic division immediately after entry of the spermatozoon and form female pronucleus.

**2- The spermatozoon,** meanwhile, moves forward until it lies close to the female pronucleus & undergo the following to form the **male pronucleus** by:

1. decondensation of sperm chromosomes by releasing protamines process known as chromosome remolding, the nuclear envelope & new cytoplasmic organells assemble around remodelled chromosome.

2. the tail detaches and degenerates.

**3-Finally, male and female pronuclei** fused to form single cell called **zygote** and tow haploid set of chromosomes come togerther. Soon after , anaphase and telophase are completed, one-cell zygote becomes a tow cell embryo. The main results of fertilization are as follows:
1. Restoration of the diploid number of chromosomes, half from the father and half from the mother. Hence, the zygote contains a new combination of chromosomes different from both parents.

2. Determination of the sex of the new individual. An X-carrying sperm produces a female (XX) embryo, and a Y-carrying sperm produces a male (XY) embryo. Hence, the chromosomal sex of the embryo is determined at fertilization.

3. Initiation of cleavage.

**Clinical correlation:**

**In Vitro Fertilization**: During IVF, mature oocytes from stimulated ovaries are retrieved transvaginally with sonographic guidance. Sperm and ova are then combined in vitro (culture medium) to prompt fertilization. If successful, viable embryos are transferred transcervically into the endometrial cavity using sonographic guidance.

**Intracytoplasmic sperm injection**: During the micromanipulation technique of ICSI, cumulus cells surrounding the ova are enzymatically digested, and a single sperm is directly injected through the zona pellucida and oocyte cell membrane.

**Cleavage**

Cleavage is a series of mitotic divisions that results in an increase in cells, blastomeres, which become smaller with each division. The embryo remains in the fallopian tube for 3-4 days until it reaches morula stages. Morula is a ball of cells formed by repeated divisions of zygots. The embryo enters the uterus at the morula stage. The embryo floats free in the uterus temporarily for up 72 hours and uterine secretions are used for nourishment.
**Preimplantation genetic diagnosis** (PGD) is where one or two cells (blastomeres) are removed from the embryo prior to replacement in an IVF cycle. These are tested for specific genetic diseases and only unaffected embryos replaced.

**Implantation**

Is the process by which the embryo itself attaches for endometrium side of the uterine wall and gradually penetrates endometrium to reaches the circulatory system of the mother. Implantation occurs six-seven days after fertilization. This occurs in the three phases:

1. **Apposition**—initial loosely adhesion of the blastocyst to the uterine wall.
2. **Adhesion**—increased physical contact between the blastocyst and uterine epithelium.
3. **Invasion**—penetration and invasion of syncytiotrophoblast and cytotrophoblast into the endometrium and uterine vasculature.

This process is, yet, a poorly understood phenomena, requires preparations of both embryo and endometrium to be successful:

1. **Embryo preparation:**

   a. **Blastocyst formation:** About the time the morula enters the uterine cavity, fluid begins to penetrate through the zona pellucida into the intercellular spaces of the inner cell mass. Gradually, the intercellular spaces become confluent, and finally, a single cavity, the **blastocele**, forms. Cells of the inner cell mass, now called the **embryoblast**, are at one pole, and those of the outer cell mass, or **trophoblast**, flatten and
form the epithelial wall of the blastocyst. The embryo usually reaches this stage by day 5 post fertilization. Embryonic stem cells are derived from inner cell mass of blastocyst. These cells are pluripotent, have ability to form any type of cell and tissue.

b- **blastocyst hatching**: is an escaping of embryo from zona pellucida and outer covering of egg. It is a critical step toward successful pregnancy. It allows association of trophoblasts with endometrial epithelial cells and permits release of trophoblast-produced hormones into the uterine cavity.

2- **Endometrium preperations**

   a) morphological changes: after ovulation, oestrogen and progesterone alter structure of endometrium from proliferative to secretory. The component of endometrium continue to grow, leading to tortuosity of the glands and coiling of the spiral arteriols. Intracytoplasmic glycogen vacuoles appear and transudation of plasma occurs. peak secretory phase is reached 7 days post-ovulation.

   b) Endometerium receptivity: factors other than gonadal steroids influence uterine receptivity for implantation when appropriately conditioning by oestrogen and progesterone. receptivity of endometerium is limited to days 16-19 (of a 28-day cycle), and it’s essential that the hatched blastocyst impacts and adheres to endometrial surface during this implantation windows if pregnancy is to occur.
**Differentiation**

Is differentiation of cells into specialized tissue to form inter related organ system. This period called embryonic period, Starts at second week post fertilization and ends on the last day of the eighth week.

Bilaminar *embryonic disc is formed in 2nd week post fertilization*:

- Inner cell mass divides into epiblast and hypoblast
- 2 fluid filled sacs
  - *Amniotic sac* from epiblast
  - Yolk sac from hypoblast

**Trilaminar embryonic disc** is formed in the third week post fertilization:

- Grastrulation: is an invagination of epiblast cells into primitive streak (groove) on dorsal surface of epiblast & replace hypoblast, becoming *endoderm* on days 14-15:
  - Day 16: *mesoderm* (a new third layer) formed in between.
  - Epiblast cells remaining on surface forming *ectoderm*
- From these three primary “germ” layers, all body tissues develop.

**Major derivatives of the embryonic germ layers**
Placental development

- Trophoblast differentiation:

  By the eighth day postfertilization, after initial implantation, the trophoblast has differentiated into: An outer multinucleated syncytium—primitive syncytiotrophoblast, and an inner layer of primitive mononuclear cells—cytotrophoblast. The latter are germinal cells for the syncytium.

- Lacunae Formation Within the Syncytiotrophoblast: Beginning about 12 days after conception, the syncytiotrophoblast of the trophoblast shell is permeated by a system of intercommunicating channels called trophoblastic lacunae.

  As the embryo enlarges, more maternal decidua basalis is invaded by basal syncytiotrophoblast. After invasion of superficial decidual capillary walls, lacunae become filled with maternal blood.

- Development of Primary Villous Stalks

  With deeper blastocyst invasion into the decidua, the extravillous cytotrophoblasts give rise to solid primary villi composed of a cytotrophoblast core covered by syncytium. These arise from buds of cytotrophoblast that begin to protrude into the primitive syncytium before 12 days postfertilization.

- Chorionic Villi

  Beginning on approximately the 12th day after fertilization, chorionic villi can first be distinguished. Mesenchymal cords derived from extraembryonic mesoderm invade the solid trophoblast columns, These form secondary villi. After angiogenesis begins in the
mesenchymal cores, the resulting villi are termed tertiary. Although maternal venous sinuses are tapped early in implantation, maternal arterial blood does not enter the intervillous space until around day 15. By approximately the 17th day, however, fetal blood vessels are functional, and a placental circulation is established.

Chorionic villi was originally developed around the entire surface of implanted conceptus. Later with the growth of conceptus, villi adjacent to capsular and marginal decidua become rare and shorter up to eventually disappear, while villi adjacent to basal decidua become long and branched. By this way, the chorion is divided into regions of different surface: Villous chorion / chorion frondosum - against the basal decidua & smooth chorion/ chorion laeve - against the marginal and capsular deciduae.

Placenta AT TERM

- Is a discoid, a diameter 15 - 25 cm and 2- 3 cm thick, weighs 500 to 600 g.
- Is hemochorionic - the blood of mother enters the intervillous space and flows slowly around the villi, allowing an exchange of metabolic and gaseous products with fetal blood.
- The fetal part or villous chorion - smooth with insertion of umbilical cord and outlines of umbilical vessels that are seen through the amnion.
- The maternal part or decidua basalis is divided into irregular convex areas - cotyledons separated by placental septa.
- Fetal part: a chorionic plate + chorionic villi
- project into the intervillous space (is deriving from the lacunae developed in the syncytiotrophoblast during the 2nd week).

- chorionic villi may be either free or anchored to the decidua basalis = main stem villi, one main stem villus forms a unit of the fetal part of the placenta known as - the cotyledon, they are separated each other by septa of placenta.

- Maternal part: is decidua basalis that usually forms a compact layer known as the basal plate protrudes between individual cotyledons as placental septa.

**Placental functions**

1-Placental metabolism - placenta, in particular during early pregnancy, synthesizes glycogen, cholesterol, and fatty acids that all serve as a source of nutrients and energy for the embryo.

2-Placental transport - is bidirectionally (between the placenta and maternal blood and vice versa) gases, nutrients, hormones, electrolytes, antibodies, wastes, and also several drugs are transported across the placental membrane. 4 main transport mechanisms are utilized: simple cell diffusion, facilitated diffusion, active transport, and pinocytosis.

3-Placental endocrine secretion: the syncytiotrophoblast is endocrine active and produces hormones of 2 categories: protein hormones: human chorionic gonadotropin (hCG), human chorionic somatomammatropin (hCS) or placental lactogen, human chorionic thyrotropin (hCT), and human chorionic corticotropin (hCACTH) steroid hormones: progesterone + estrogens.