Embryology

3rd lecture
Alaa Hachem (DPhil)

First Week of Development:

❖ Ovulation to Implantation

At puberty, the female begins to undergo regular monthly cycles. These **sexual cycles** are controlled by the hypothalamus. **Gonadotropin-releasing hormone (GnRH)** produced by the hypothalamus acts on cells of the anterior part of pituitary gland, which in turn secrete **gonadotropins.** These hormones, **follicle-stimulating hormone (FSH)** and **luteinizing hormone (LH)** stimulate and control cyclic changes in the ovary.

At the beginning of each ovarian cycle, 15 to 20 primary (preantral) stage follicles are stimulated to grow under the influence of FSH. Under normal conditions, only one of these follicles reaches full maturity. FSH also stimulates maturation of **follicular (granulosa)** cells surrounding the oocyte. Granulosa and thecal cells produce estrogens that:

a) cause the uterine endometrium to enter the follicular or **proliferative phase;**
b) cause thinning of the cervical mucus to allow passage of sperm; and
c) stimulate the pituitary gland to secrete LH.

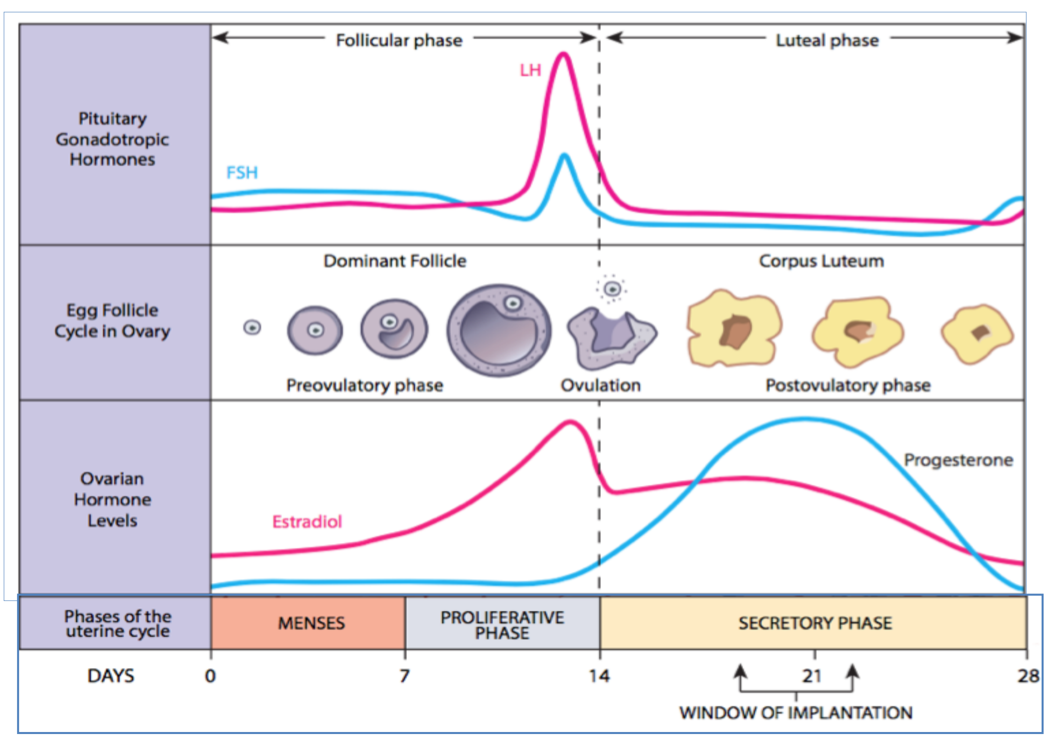
At mid-cycle, there is an **LH surge** that:

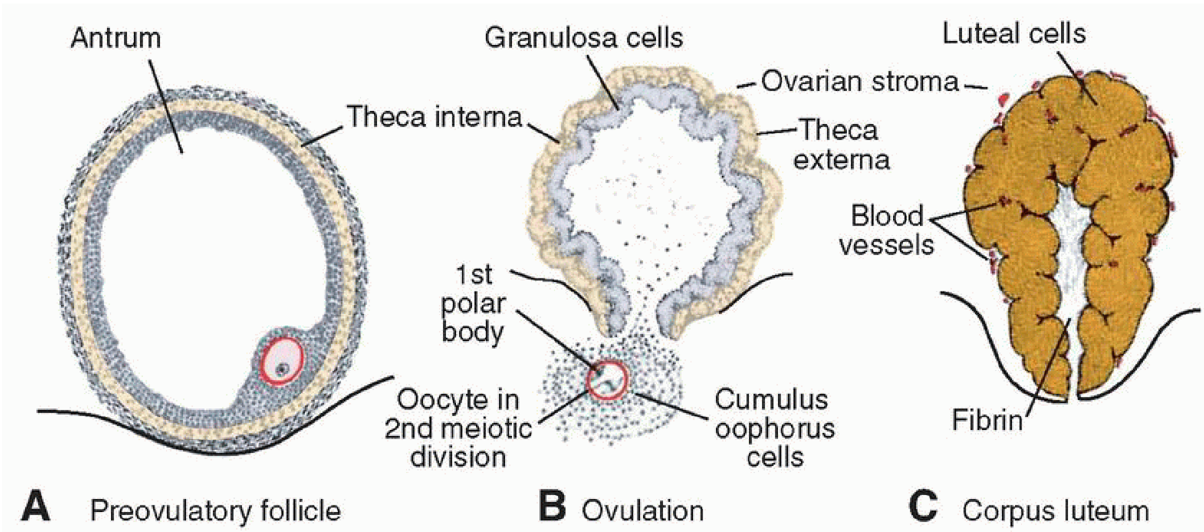
a) elevates concentrations of maturation-promoting factor, causing oocytes to complete meiosis I and initiate meiosis II;
b) stimulates production of progesterone by follicular stromal cells **(luteinization);**
c) causes follicular rupture and ovulation.

The high concentration of LH increases **collagenase activity**, resulting in digestion of collagen fibers surrounding the follicle. **Prostaglandin levels** also increase in response to the LH surge and cause local muscular contractions in the ovarian wall. Those contractions extrude the oocyte, which together with its surrounding granulosa cells from the region of the cumulus oophorus, breaks free (**ovulation**) and floats out of the ovary. Some of the cumulus oophorus cells then rearrange themselves around the zona pellucida to form the **corona radiata**.

Hormonal regulation of the ovarian cycle:

1. Hypothalamus secretes **Gonadotropin-releasing hormone (GnRH)** that stimulates the anterior part of pituitary gland, to produce **follicle-stimulating hormone (FSH)** and **luteinizing hormone (LH).**
2. FSH stimulates follicular growth from day 1 to day 10 of the cycle.
3. The follicular cells of the growing follicle produce Estrogen, and the level of Estrogen reaches the highest at the days 10 to 11 of the cycle.
4. The increased level of estrogen stimulates the anterior part of the pituitary gland to secrete LH (the LH surge) at day 12 of the cycle.
5. LH triggers resumption of the first meiosis (MI), and induce ovulation at day 14 of the cycle.
6. LH also stimulates the development of the granulosa cells and theca cells to form the corpus luteum (the yellow body) in the ovary.
7. Corpus luteum secretes progesterone from day 14 to day 28 of the cycle to maintain pregnancy during the early stages.
8. If a sperm fertilizes the oocyte, second meiotic (MII) will be completed, and implanted embryo will stimulate production of **human chorionic gonadotropin** (hCG), that will prevent the degeneration of the corpus luteum.
9. If the oocyte failed to fertilized, the yellow body will be degenerated at day 28 of the cycle, progesterone production will be decrease, precipitating menstrual bleeding, and stimulate pituitary gland to produce FSH for the next cycle.





☒ CORPUS LUTEUM

After ovulation, granulosa cells remaining in the wall of the ruptured follicle, together with cells from the theca interna, and under the influence of LH, form the **corpus luteum** and secrete the hormone **progesterone**. Progesterone, together with estrogenic hormones, causes the uterine mucosa to enter the **progestational** or **secretory stage** in preparation for implantation of the embryo.

☒ CORPUS ALBICANS

If fertilization does not occur, the corpus luteum reaches maximum development approximately 9 days after ovulation. It can easily be recognized as a yellowish projection on the surface of the ovary. Subsequently, the corpus luteum shrinks because of degeneration of lutean cells and forms a mass of fibrotic scar tissue, the **corpus albicans.** Simultaneously, progesterone production decreases, precipitating menstrual bleeding. If the oocyte is fertilized, degeneration of the corpus luteum is prevented by **human chorionic gonadotropin** (hCG), a hormone secreted by the syncytiotrophoblast of the developing embryo. The corpus luteum continues to grow and forms the **corpus luteum of pregnancy.**

☒ Fertilization

Fertilization, the process by which male and female gametes fuse, occurs in the **ampullary region of the uterine tube.** This is the widest part of the tube and is close to the ovary. Spermatozoa are not able to fertilize the oocyte immediately upon arrival in the female genital tract but must undergo (*a*) **capacitation** and (*b*) the **acrosome reaction** to acquire this capability.

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 and undergo the acrosome reaction.

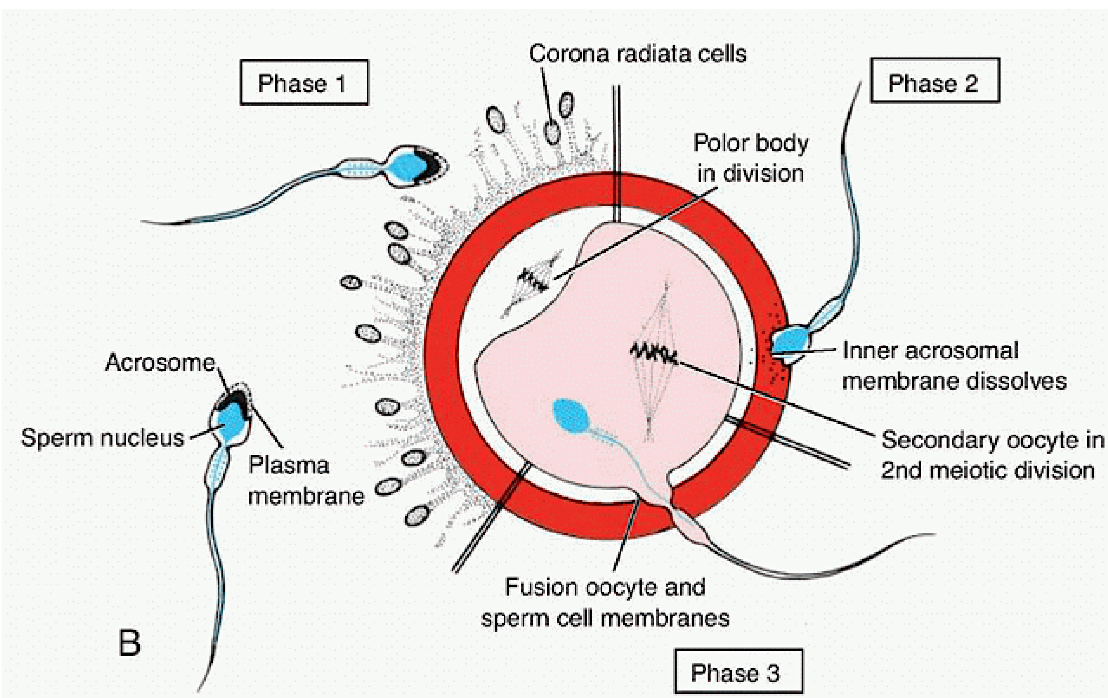
The **acrosome reaction,** which occurs after binding to the zona pellucida, is induced by zona proteins. This reaction culminates in the release of enzymes needed to penetrate the zona pellucida, including acrosin and trypsin-like substances.

The phases of fertilization include:

Phase 1, penetration of the corona radiata;

Phase 2, penetration of the zona pellucida; and

Phase 3, fusion of the oocyte and sperm cell membranes.



PHASE 1: PENETRATION OF THE CORONA RADIATA

Of the 200 to 300 million spermatozoa deposited in the female genital tract, only 300 to 500 reach the site of fertilization. However, only one sperm fertilizes the egg, only capacitated sperm pass freely through corona cells.

PHASE 2: PENETRATION OF THE ZONA PELLUCIDA

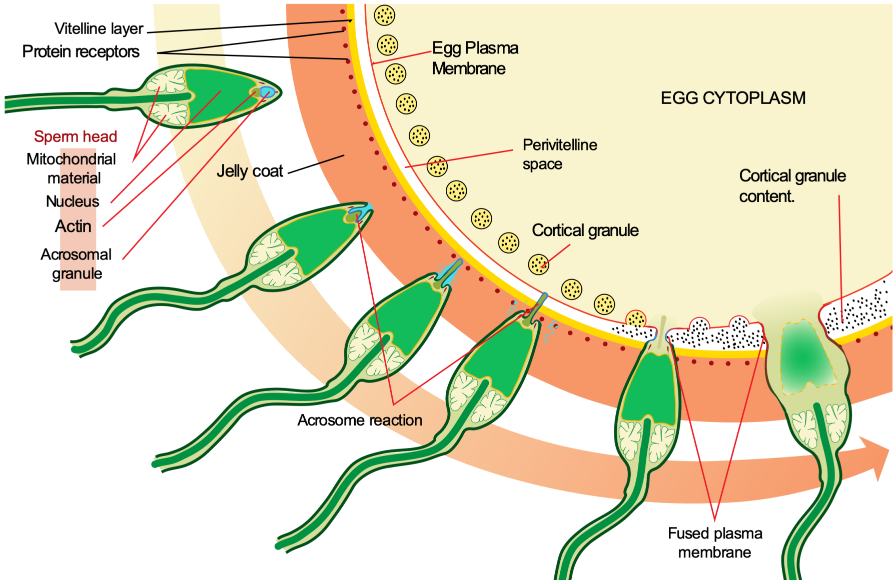
The zona is a glycoprotein shell surrounding the egg that facilitates and **maintains sperm binding and induces the acrosome reaction**. Release of acrosomal enzymes (acrosin) allows sperm to penetrate the zona, thereby coming in contact with the plasma membrane of the oocyte. Permeability of the zona 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.

PHASE 3: FUSION OF THE OOCYTE AND SPERM CELL MEMBRANES

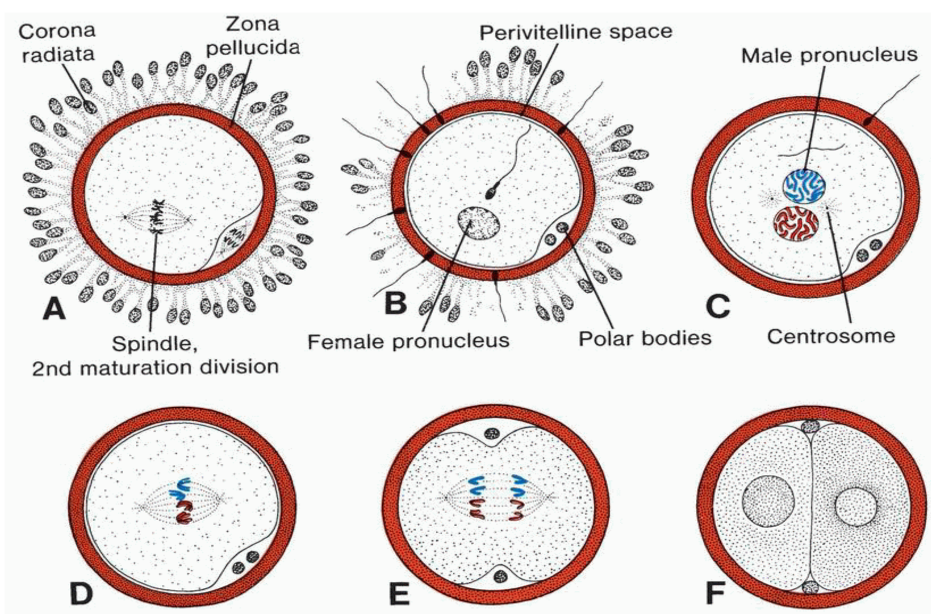
The initial adhesion of sperm to the oocyte is mediated by specific receptors. After adhesion, the plasma membranes of the sperm and egg fuse. In the human, both the head and tail of the spermatozoon enter the cytoplasm of the oocyte, but the plasma membrane is left behind on the oocyte surface. As soon as the spermatozoon has entered the oocyte, the egg responds in three ways:

1. **Cortical and zona reactions.** As a result of the release of cortical oocyte granules, which contain lysosomal enzymes, (*a*) the oocyte membrane becomes impenetrable to other spermatozoa, and (*b*) the zona pellucid alters its structure and composition to prevent sperm binding and penetration. These reactions prevent polyspermy (penetration of more than one spermatozoon into the oocyte).

2. **Resumption of the second meiotic division.** The oocyte finishes its second meiotic division immediately after entry of the spermatozoon. One of the daughter cells, which receive hardly any cytoplasm, is known as the **second polar body;** the other daughter cell is the **definitive oocyte.** Its chromosomes (22+X) arrange themselves in a vesicular nucleus known as the **female pronucleus.**
3. **Metabolic activation of the egg.** The activating factor is probably carried by the spermatozoon.



The spermatozoon, meanwhile, moves forward until it lies close to the female pronucleus. Its nucleus becomes swollen and forms the **male pronucleus**. Morphologically, the male and female pronuclei are indistinguishable, and eventually, they come into close contact and lose their nuclear envelopes. During growth of male and female pronuclei (both haploid), each pronucleus must replicate its DNA. Immediately after DNA synthesis, chromosomes organize on the spindle in preparation for a normal mitotic division. The 23 maternal and 23 paternal (double) chromosomes split longitudinally at the centromere, and sister chromatids move to opposite poles, providing each cell of the zygote with the normal diploid number of chromosomes and DNA. As sister chromatids move to opposite poles, a deep furrow appears on the surface of the cell, gradually dividing the cytoplasm into two parts, **the two-cell stage embryo**.



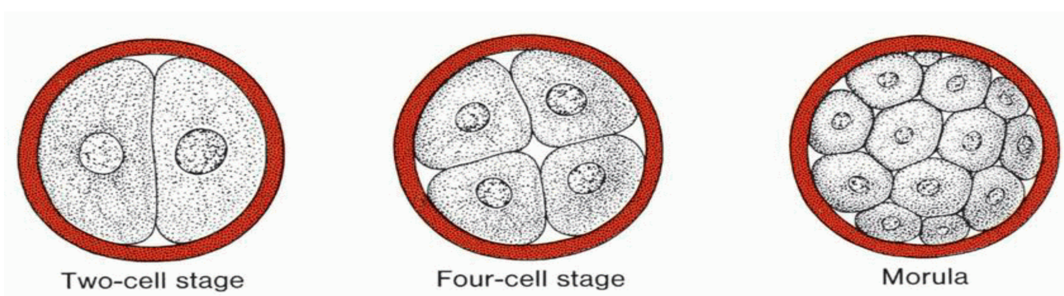
<u>Thus, the main results of fertilization are as follows</u>:

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.** Without fertilization, the oocyte usually degenerates 24 hours after ovulation.

☒ Cleavage

Once the zygote has reached the two-cell stage, it undergoes a series of mitotic divisions, increasing the numbers of cells. These cells, which become smaller with each cleavage division, are known as **blastomeres**. Until the eight-cell stage, they form a loosely arranged clump. However, after the third cleavage, blastomeres maximize their contact with each other, forming a compact ball of cells held together by tight junctions.

This process, **compaction,** segregates inner cells, which communicate extensively by gap junctions, from outer cells. Approximately 3 days after fertilization, cells of the compacted embryo divide again to form a 16-cell **morula**. Inner cells of the morula constitute the **inner cell mass,** and surrounding cells compose the **outer cell mass.** The inner cell mass gives rise to tissues of the **embryo proper,** and the outer cell mass forms the **trophoblast,** which later contributes to the **placenta.**

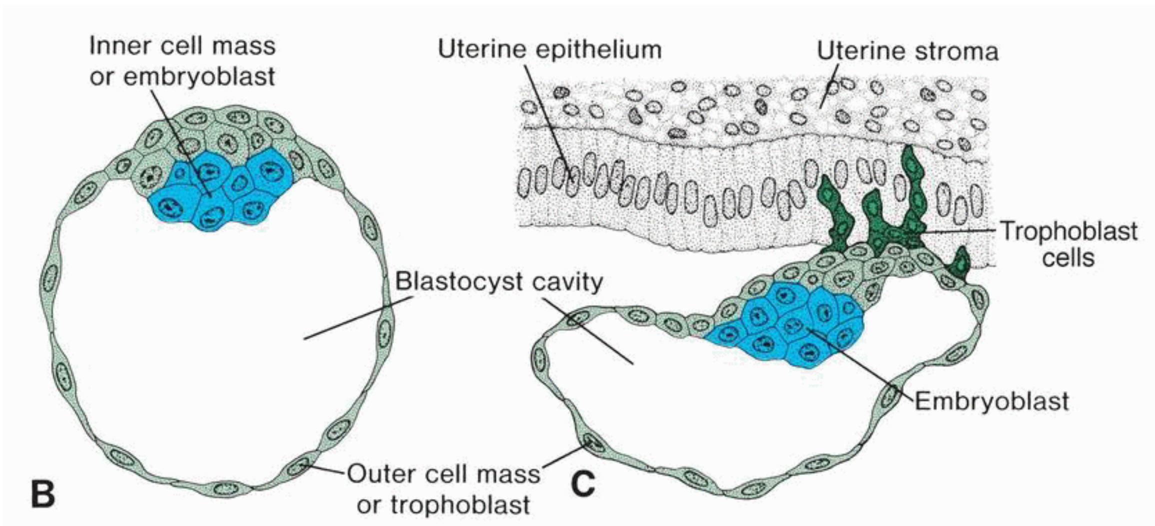


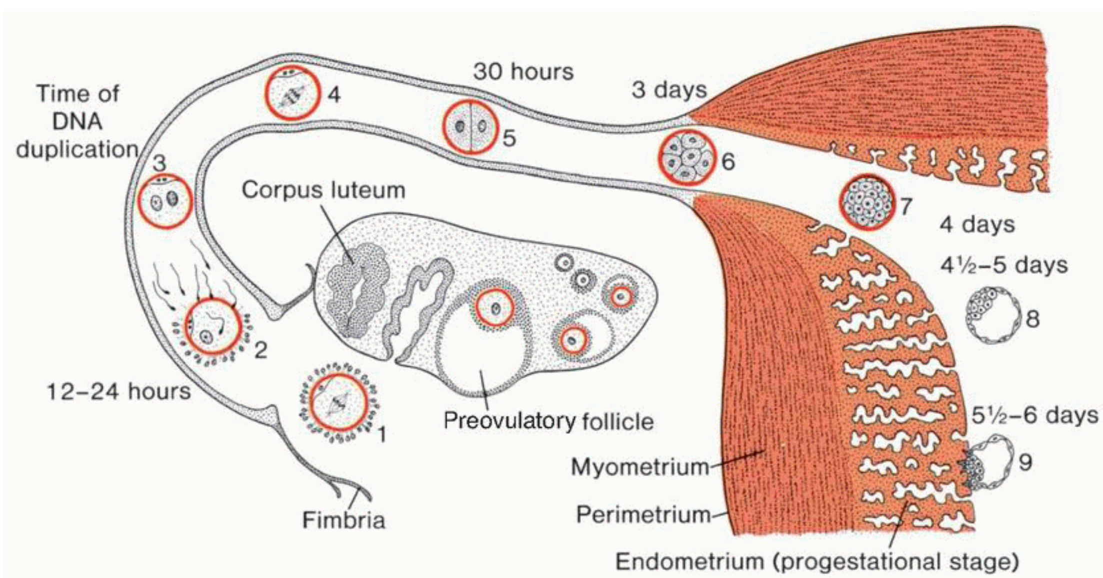
☒ Blastocyst Formation

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. At this time, the embryo is a **blastocyst.** 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 zona pellucid has disappeared, allowing implantation to begin.

In the human, trophoblastic cells over the embryoblast pole begin to penetrate between the epithelial cells of the uterine mucosa about the sixth day. By the end of the first week of development, the human zygote has passed through the morula and blastocyst stages and has begun implantation in the uterine mucosa.





Summary of fertilization in figures