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**1. Write a short note on implantation.**

**Definition:**

 **implantation** is the stage of [pregnancy](file:///C%3A%5Cwiki%5CPregnancy) at which the embryo adheres to the wall of the [uterus](file:///C%3A%5Cwiki%5CUterus). At this stage of [prenatal development](file:///C%3A%5Cwiki%5CPrenatal_development), the [conceptus](file:///C%3A%5Cwiki%5CConceptus) is called a [blastocyst](file:///C%3A%5Cwiki%5CBlastocyst). It is by this adhesion that the embryo receives oxygen and nutrients from the mother to be able to grow.

In humans, implantation of a [fertilized](file:///C%3A%5Cwiki%5CHuman_fertilization) [ovum](file:///C%3A%5Cwiki%5COvum) is most likely to occur around nine days after [ovulation](file:///C%3A%5Cwiki%5COvulation); however, this can range between six and 12 days.

The reception-ready phase of the [endometrium](file:///C%3A%5Cwiki%5CEndometrium) of the uterus is usually termed the "implantation window" and lasts about 4 days. The implantation window occurs around 6 days after the peak in hormone levels. With some disparity between sources, it has been stated to occur from 7 days after ovulation until 9 days after ovulation, or days 6-10 post ovulation ion. On average, it occurs during the 20th to the 23rd day after the [last menstrual period](file:///C%3A%5Cwiki%5CLast_menstrual_period).

The implantation window is characterized by changes to the endometrium cells, which aid in the absorption of the uterine fluid. These changes are collectively known as [the plasma membrane transformation](file:///C%3A%5Cwiki%5CThe_plasma_membrane_transformation) and bring the [blastocyst](file:///C%3A%5Cwiki%5CBlastocyst) nearer to the endometrium and immobilize it. During this stage the blastocyst can still be eliminated by being flushed out of the uterus. Scientists have hypothesized that the hormones cause a swelling that fills the flattened out uterine cavity just prior to this stage, which may also help press the blastocyst against the endometrium. The implantation window may also be initiated by other preparations in the endometrium of the uterus, both structurally and in the composition of its secretions.

**Fertilization in human**

**Also,** Implantation is when a fertilized egg, or blastocyst, has attached to the lining of the uterine wall. It marks the beginning of pregnancy.

Implantation, in reproduction physiology, the adherence of a fertilized egg to a surface in the reproductive tract, usually to the uterine wall (see uterus), so that the egg may have a suitable environment for growth and development into a new offspring. Fertilization of the egg usually occurs after the egg has left the ovary and is being transported through the fallopian tubes. Male sperm cells deposited in the female reproductive tract travel up to the fallopian tubes to unite with the egg. Once fertilized, the egg begins to undergo a series of cell divisions. The egg takes up to seven days to reach the uterus; by this time the single-celled egg has divided numerous times, so that it is a ball of approximately 200 cells.

The uterus has thick walls suitable for egg attachment and growth. A female hormone known as progesterone, secreted by the corpus luteum in the ovary, influences the readiness of the uterine wall for egg implantation. It increases the blood supply in the wall, water content, and secretion of glycogen, a nutrient for the surrounding tissue and developing egg. If the uterus is not first prepared by progesterone, the egg will not attach itself. Progesterone also inhibits muscular contractions in the uterine wall that would tend to reject the adhering egg.

When the egg reaches the uterus, it usually remains free in the uterine cavity for about a day. It then attaches to the uterine lining (the endometrium). Cells in the outer surface of the egg grow rapidly once contact is made with the uterine wall. The egg disrupts the surface of the endometrium and actively burrows into the deeper tissue. By the 11th day after fertilization, the egg has completely embedded itself into the endometrium. The product of conception—first the fertilized egg and then the developing child and the placenta—normally remains implanted in the human uterus for nine months

**Adaptation of uterus**

To enable implantation, the uterus goes through changes in order to be able to receive the conceptus.

### Predecidualization :The endometrium increases thickness, becomes [vascularized](file:///C%3A%5Cwiki%5CAngiogenesis) and its glands grow to be tortuous and boosted in their secretions. These changes reach their maximum about 7 days after [ovulation](file:///C%3A%5Cwiki%5COvulation).

Furthermore, the surface of the endometrium produces a kind of rounded cells, which cover the whole area toward the uterine cavity.

### Decidualization

Decidualization succeeds predecidualization if pregnancy occurs. This is an expansion of it, further developing the uterine glands, the zona compacta and the epithelium of decidual cells lining it. The decidual cells become filled with lipids and glycogen and take the polyhedral shape characteristic for decidual cells.

#### Trigger

It is likely that the blastocyst itself makes the main contribution to this additional growing and sustaining of the decidua. An indication of this is that decidualization occurs at a higher degree in conception cycles than in non-conception cycles. Furthermore, similar changes are observed when giving stimuli mimicking the natural invasion of the embryo.

### Pinopodes

Pinopodes are small, finger-like protrusions from the endometrium. They appear between day 19 and day 21 of [gestational age](file:///C%3A%5Cwiki%5CGestational_age). This corresponds to a [fertilization age](file:///C%3A%5Cwiki%5CFertilization_age) of approximately five to seven days, which corresponds well with the time of implantation. They only persist for two to three days. The development of them is enhanced by [progesterone](file:///C%3A%5Cwiki%5CProgesterone) but inhibited by [estrogens](file:///C%3A%5Cwiki%5CEstrogens).

#### Function of the Pinopodes in implantation

Pinopodes [endocytose](file:///C%3A%5Cwiki%5CEndocytosis) uterine fluid and macromolecules in it. By doing so, the volume of the uterus decreases, taking the walls closer to the embryo blast floating in it. Thus, the period of active pinocytes might also limit the implantation window.

#### Function of the Pinopodes during implantation

Pinopodes continue to absorb fluid, and removes most of it during the early stages of implantation.

**Mechanism of implantation**

Implantation is initiated when the blastocyst comes into contact with the uterine wall.

### Zona hatching

To be able to perform implantation, the blastocyst first needs to get rid of its [zona pellucida](file:///C%3A%5Cwiki%5CZona_pellucida). This process can be called "hatching".

#### Factors

Lytic factors in the uterine cavity, as well as factors from the blastocyst itself are essential for this process. Mechanisms in the latter are indicated by that the zona pellucida remains intact if an unfertilized egg is placed in the uterus under the same conditions. A substance probably involved is [plasmin](file:///C%3A%5Cwiki%5CPlasmin). [Plasminogen](file:///C%3A%5Cwiki%5CPlasminogen), the plasmin precursor, is found in the uterine cavity, and blastocyst factors contribute to its conversion to active plasmin. This hypothesis is supported by lytic effects [in vitro](file:///C%3A%5Cwiki%5CIn_vitro) by plasmin. Plasmin inhibitors also inhibit the entire zona hatching in rat experiments.

### Apposition

The very first, albeit loose, connection between the blastocyst and the endometrium is called the apposition.

#### Location

On the endometrium, the apposition is usually made where there is a small crypt in it, perhaps because it increases the area of contact with the rather spherical blastocyst.

On the blastocyst, on the other hand, it occurs at a location where there has been enough lysis of the zona pellucida to have created a rupture to enable direct contact between the underlying [trophoblast](file:///C%3A%5Cwiki%5CTrophoblast) and the decidua of the endometrium. Ultimately, the [inner cell mass](file:///C%3A%5Cwiki%5CInner_cell_mass), inside the [trophoblast](file:///C%3A%5Cwiki%5CTrophoblast) layer, is aligned closest to the decidua. The apposition on the blastocyst is not dependent on if it is on the same side of the blastocyst as the inner cell mass. Rather, the inner cell mass rotates inside the trophoblast to align to the apposition. The entire surface of the blastocyst has a potential to form the apposition to the decidua.

#### Molecular Mechanism

The identity of the molecules on the trophoblast and the endometrial epithelia that mediate the initial interaction between the two remain unidentified. MUC1 is a transmembrane [glycoprotein](file:///C%3A%5Cwiki%5CGlycoprotein) expressed at the apical surface of endometrial epithelial cells during the window of implantation in humans and has been shown to be differentially expressed between fertile and infertile subjects during this time. MUC1 displays carbohydrate moieties on its extracellular domain that are ligands of [L-selectin](file:///C%3A%5Cwiki%5CL-selectin), a protein expressed on the surface of trophoblast cells.

### Adhesion

Adhesion is a much stronger attachment to the endometrium than the loose apposition.

The trophoblasts adhere by penetrating the endometrium, with protrusions of trophoblast cells.

This adhering activity is by microvilli that are on the trophoblast. The trophoblast have binding fiber connections, laminin, collagen type IV, and integrins that assist in this adhesion process

MUC16 is a transmembrane mucin expressed at the apical surface of uterine epithelia. This mucin prevents the blastocyst from implanting in an undesired located on the epithelium. MUC16 inhibits cell-cell adhesion.

#### Communication

There is massive communication between the blastocyst and the endometrium at this stage. The blastocyst signals to the endometrium to adapt further to its presence.This, in turn, dislodges the decidual cells from their connection to the underlying [basal lamina](file:///C%3A%5Cwiki%5CBasal_lamina), which enables the blastocyst to perform the succeeding invasion.

This communication is conveyed by [receptor](file:///C%3A%5Cwiki%5CReceptor_%28biochemistry%29) l[igand](file:///C%3A%5Cwiki%5CLigand_%28biochemistry%29) by interactions, both integrin-matrix and proteoglycan ones.

##### Proteoglycan Receptors

Another ligand receptor system involved in adhesion is proteoglycan receptors, found on the surface of the decidua of the uterus. Their counterparts, the proteoglycans, are found around the trophoblast cells of the blastocyst. This ligand receptor system also is present just at the implantation window.

### Invasion

Invasion is an even further establishment of the blastocyst in the endometrium.

#### Syncytiotrophoblasts

The protrusions of trophoblast cells that adhere into the endometrium continue to proliferate and penetrate into the endometrium. As these trophoblast cells penetrate, they differentiate to become a new type of cells, [syncytiotrophoblast](file:///C%3A%5Cwiki%5CSyncytiotrophoblast). The rest of the trophoblasts, surrounding the inner cell mass, are hereafter called [cytotrophoblasts](file:///C%3A%5Cwiki%5CCytotrophoblast). Syncytiotrophoblast is not determined as a cell type, rather is a multi nucleated tissue

Invasion continues with the syncytiotrophoblasts reaching the basal membrane beneath the decidual cells, penetrating it and further invading into the uterine stroma. Finally, the whole embryo is embedded in the endometrium. Eventually, the syncytiotrophoblasts come into contact with maternal blood and form [chorionic villi](file:///C%3A%5Cwiki%5CChorionic_villi). This is the initiation of forming the [placenta](file:///C%3A%5Cwiki%5CPlacenta).

The penetration of the trophoblast to the endometrium is demonstrated through metalloproteinase MMP-2 and MMP-9 Syncytiotrophoblast invade the uterus attempting to reach maternal blood supply, for setting up the foundation for fetal blood flow

#### Extravillous trophoblasts

Extravillous trophoblasts are cells from the invading villi that migrate into the myometrium of the mother’s uterus. These cells remodel the spiral arteries to improve and secure maternal blood flow to the growing embryo. There is also evidence that this process occurs with the uterine veins. Stabilizing them to improve drainage of fetal blood and metabolic wastes. Trophoblasts have also been documented to migrate into the mother and have been found in various tissues. Due to this trophoblasts have been implicated in a phenomenon known as “Fetomaternal Microchimerism” where fetal cells establish cell lines in maternal tissues.

#### Secretions

The blastocyst secretes factors for a multitude of purposes during invasion. It secretes several [autocrine](file:///C%3A%5Cwiki%5CAutocrine) factors, targeting itself and stimulating it to further invade the endometrium. Furthermore, secretions loosen decidual cells from each other, prevent the embryo from being rejected by the mother, trigger the final decidualization and prevent menstruation.

##### Autocrine

[Human chorionic gonadotropin](file:///C%3A%5Cwiki%5CHuman_chorionic_gonadotropin) is an autocrine growth factor for the blastocyst. [Insulin-like growth factor 2](file:///C%3A%5Cwiki%5CInsulin-like_growth_factor_2), on the other hand, stimulates the invasiveness of it.

##### Dislodging

The syncytiotrophoblasts dislodges decidual cells in their way, both by degradation of [cell adhesion molecules](file:///C%3A%5Cwiki%5CCell_adhesion_molecule) linking the decidual cells together as well as degradation of the extracellular matrix between them.

Cell adhesion molecules are degraded by syncytiotrophoblast secretion of [Tumor necrosis factor-alpha](file:///C%3A%5Cwiki%5CTumor_necrosis_factor-alpha). This inhibits the expression of [cadherins](file:///C%3A%5Cwiki%5CCadherins) and [beta-catenin](file:///C%3A%5Cwiki%5CBeta-catenin). Cadherins are cell adhesion molecules, and beta-catenin helps to anchor them to the cell membrane. Inhibited expression of these molecules thus loosens the connection between decidual cells, permitting the syncytotrophoblasts and the whole embryo with them to invade into the endometrium.

The extracellular matrix is degraded by [serine endopeptidases](file:///C%3A%5Cwiki%5CSerine_endopeptidases) and [metalloproteinases](file:///C%3A%5Cwiki%5CMetalloproteinase). The gelatinases exist in two forms; one digesting [Type-IV collagen](file:///C%3A%5Cwiki%5CType-IV_collagen) and one digesting [gelatin](file:///C%3A%5Cwiki%5CGelatin).

##### Immunosuppressive

The embryo differs from the cells of the mother, and would be rejected as a parasite by the [immune system](file:///C%3A%5Cwiki%5CImmune_system) of the mother if it didn't secrete [immunosuppressive](file:///C%3A%5Cwiki%5CImmunosuppressive) agents. Such agents are [Platelet-activating factor](file:///C%3A%5Cwiki%5CPlatelet-activating_factor), [human chorionic gonadotropin](file:///C%3A%5Cwiki%5CHuman_chorionic_gonadotropin), [early pregnancy factor](file:///C%3A%5Cwiki%5CEarly_pregnancy_factor), [immunosuppressive factor](file:///C%3A%5Cw%5Cindex.php%3Ftitle%3DImmunosuppressive_factor%26action%3Dedit%26redlink%3D1), [Prostaglandin E](file:///C%3A%5Cwiki%5CProstaglandin_E)2, [Interleukin 1](file:///C%3A%5Cwiki%5CInterleukin_1)-alpha, [Interleukin 6](file:///C%3A%5Cwiki%5CInterleukin_6), [interferon](file:///C%3A%5Cwiki%5CInterferon)-alpha, [leukemia inhibitory factor](file:///C%3A%5Cwiki%5CLeukemia_inhibitory_factor) and [Colony-Stimulating Factor](file:///C%3A%5Cwiki%5CColony-Stimulating_Factor).

##### Decidualization

Factors from the blastocyst also trigger the final formation of decidual cells into their proper form. In contrast, some decidual cells in the proximity of the blastocyst degenerate, providing nutrients for it.

##### Prevention of menstruation

[Human chorionic gonadotropin](file:///C%3A%5Cwiki%5CHuman_chorionic_gonadotropin) (hCG) not only acts as an immunosuppressive, but also notifies the mother's body that she is [pregnant](file:///C%3A%5Cwiki%5CPregnant), preventing menstruation by sustaining the function of the [corpus luteum](file:///C%3A%5Cwiki%5CCorpus_luteum).

  **Implantation failure**

Implantation failure is considered to be caused by inadequate uterine receptivity in two thirds of cases, and by problems with the embryo itself in the other third.

Inadequate uterine receptivity may be caused by abnormal [cytokine](file:///C%3A%5Cwiki%5CCytokine) and hormonal signaling as well as [epigenetic alterations](file:///C%3A%5Cwiki%5CEpigenetic_alteration). Recurrent implantation failure is a cause of [female infertility](file:///C%3A%5Cwiki%5CFemale_infertility). Therefore, [pregnancy rates](file:///C%3A%5Cwiki%5CPregnancy_rate) can be improved by optimizing endometrial receptivity for implantation. Evaluation of implantation markers may help to predict pregnancy outcome and detect occult implantation deficiency.

[Luteal support](file:///C%3A%5Cwiki%5CLuteal_support) is the administration of medication, generally [progestins](file:///C%3A%5Cwiki%5CProgestin), for the purpose of increasing the success rate of implantation and early [embryogenesis](file:///C%3A%5Cwiki%5CHuman_embryogenesis), thereby complementing the function of the [corpus luteum](file:///C%3A%5Cwiki%5CCorpus_luteum).

In women with more than 3 implantation failures in [assisted reproduction](file:///C%3A%5Cwiki%5CAssisted_reproduction), a review of several small [randomized controlled studies](file:///C%3A%5Cwiki%5CRandomized_controlled_studies)estimated that the use of adjunct [low molecular weight heparin](file:///C%3A%5Cwiki%5CLow_molecular_weight_heparin) improves [live birth rate](file:///C%3A%5Cwiki%5CLive_birth_rate) by approximately 80%.

**Stages of implantation:**

Implantation consist of three stages:
(a) the blastocyst contacts the implantation site of the endometrium (apposition)

(b) trophoblast cells of the blastocyst attach to the receptive endometrial epithelium (adhesion)

(c) invasive trophoblast cells cross the endometrial epithelial basement membrane and invade the endometrial stroma

**1.**  Implantation begins with apposition of the blastocyst at the uterine epithelium, generally about 2-4 days after the morula enters the uterine cavity. The implantation site in the human uterus is usually in the upper and posterior wall in the mid sagittal plane. Implantation is considered a pro-inflammatory reaction in which endometrial vascular permeability is markedly increased at the attachment site, mediated by Cyclooxygenase (Cox)-derived prostaglandins. Prostaglandin E2 is increased in the luminal epithelium and the underlying stroma at the both of mice and human implantation site, thus indicating its role in attachment and localized endometrial vascular permeability. Prostaglandin E2 is considered as one of the important regulators of human trophoblast invasion, which activates other signaling proteins . During apposition process, the blastocyst differentiates into an inner cell mass (embryo) and trophectoderm (placenta). Stromal cells surrounding the implanting blastocyst differentiate into a specialized cell type called decidual cells, via a process known as decidualization.

Cytokines are regulatory peptides or glycoproteins. Unlike hormones, cytokines usually act as paracrine or autocrine signals in local tissue, and only occasionally, they have more distant effects as endocrine mediators.

**2.**  Cell adhesion of the blastocyst trophectoderm and endometrial luminal epithelial cells of the uterus is mediated by cell adhesion molecules, including integrins, cadherins, selectins, and immunoglobulins. Cell adhesion molecules are expressed on the surface of invasive trophoblast, and these molecules interact with ligands expressed by the extra-cellular matrix of the decidua in a temporal and spatial way . Integrins are a family of transmembrane glycoproteins that act as cell surface receptors formed by various combinations of two different, non-covalently linked α and β subunits. Menstrual cycle-specific integrins are up-regulated in the mid-luteal phase of human endometrium and have been considered as markers of the window of implantation. It has been suggested that a lack of integrin expression during the window of implantation can contribute to unexplained infertile women . HThe trophoblast also expresses integrins at the time of implantation and at a site of outgrowing trophoblast cells . Cadherins are a family of glycoproteins involved in the Ca2+-dependent cell-cell adhesion mechanism .

#### 3. Invasion

The process of implantation allows fetal trophoblast cells to invade and migrate into the maternal decidua. By this time, the trophoblasts at the implantation site have formed masses of cytotrophoblasts and syncytiotrophoblasts. Eventually, trophoblast cells destroy the wall of the maternal spiral arteries, converting them from muscular vessels into flaccid sinusoidal sacs lined with endovascular trophoblast . The aim of invasion is to reconstruct the maternal spiral arteries, which will maintain a high blood flow between the fetus and the mother, replacing small, high-resistance vessels with large, low-resistance vessels. The extent of trophoblastic invasion determines later placental efficiency and fetal viability in late gestation. Deficiencies in trophoblastic invasion give rise to adverse pregnancy outcomes such as intrauterine growth restriction (IUGR) and preeclampsia . Formation of placental villi is associated with remodeling of the extra-cellular matrix through tissue degradation and revision by various proteinases including serine proteases, matrix metalloproteinases (MMPs) and collagenases . Serine proteases, including urokinase-type plasminogen activator (uPA) and tissue-type plasminogen activator (tPA) can catalyze the conversion of plasminogen to plasmin for proteolytic degradation of the ECM. Trophoblast cells express plasminogen activator receptors. Invasion and migration of mouse trophoblastic cells are closely related to their PA activity . The zinc-dependent family of MMPs is a key player in matrix degradation during trophoblastic invasion. The MMP family is classified into three groups, including collagenases, gelatinases, and stromelysins based on the specificity of substrate. Type IV collagen is a fundamental component of the basal membrane and it is one of the major structures of the uterine ECM. The invasive capacity of human trophoblastic cells has been shown to correlate with increased production of type IV collagenase (MMP-2 and MMP-9).

During early pregnancy, fetal trophoblast cells invade the uterus and penetrate the basement membrane, a property that is characteristic of malignant cells. However, unlike tumor invasion, trophoblast invasion of the uterus should be under strict control confining the placenta and within the time constraint of a pregnancy. Limitation of trophoblastic invasion is attributed to the balance of activating and inhibiting growth factors, cytokines, and enzymes. Decidual cells produce plasminogen activator inhibitor-1 which is the major inhibitor of uPA . The tissue inhibitors of MMPs tightly regulate the activities of MMPs. Decidual transforming growth factor (TGF)-β plays a major regulatory role in limitation of human trophoblast invasion by up-regulating both TIMPs and PAI-1 . In addition, TGF-β provides anti proliferative signals to differentiate from invasive and proliferative cytotrophoblasts into non-invasive and multi nucleated syncytiotrophoblasts at the human fetal-maternal interface. Decorin, a decidua-derived TGF-β binding proteoglycan, negatively regulates proliferation, migration, and invasiveness of human extravillous trophoblast cells in a TGFβ-independent manner.



 **Diagram on implantation**