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## **ASSIGNMENT**

### **IMPLANTATION**

Implantation is the attachment of a fertilized egg to the wall of the uterus and typically occurs between 6 and 12 days after ovulation, with most cases happening around day 9. At the point where the fertilized egg enters the uterus, it's known as a *blastocyst* – a round collection of stem cells in a fluid with an outer layer that eventually forms the placenta. This outer layer is essential in this process because it is what adheres to and merges with the endometrium or uterine lining. The sperm and ovum unite through fertilization, creating a conceptus that (over the course of 8-9 days) will implant in the uterine wall, where it will reside over the course of nine months. In humans, implantation is the stage of pregnancy at which the embryo adheres to the wall of the uterus. At this stage of prenatal development, the conceptus is called a blastocyst. It is by this adhesion that the embryo receives oxygen and nutrients from the mother to be able to grow.

The reception-ready phase of the endometrium 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 luteinizing 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 postovulation. On average, it occurs during the 20th to the 23rd day after the last 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 and bring the blastocyst 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.

**What is the endometrium, and what does the endometrium do?**

The uterine lining-- also known as the endometrium -- is composed of two layers:

- The *basal layer* never sheds. It is the part of the endometrium that helps form the other layer.
- The *functional layer* builds up after the previous menstrual cycle ends, forming a perfect environment for a fertilized egg. If the egg is not fertilized, the functional layer will shed during the next menstrual cycle.

When an egg *is* fertilized, it implants in the uterine lining. This usually occurs between 6 and 12 days after ovulations and about 5 to 6 days after fertilization.

Once implanted, the embryo secretes hormones, including human chorionic gonadotropin (hCG), which signals to the mother's body that she is pregnant. This halts the menstrual cycle and prevents the functional layer of the endometrium from being shed.

From this point on, the uterine lining will turn into the placenta, which provides oxygen and nutrients to the baby.

Even when there's no implanted egg to sustain, the uterine lining serves a critical function. The endometrium prevents adhesions of the underlying myometrium layer, which contains the muscle tissue that causes contractions. If adhesions form, it is possible for the uterus to collapse, preventing normal menstruation and pregnancy.

## What role does the endometrium play in implantation?

Studies show that cycles with thicker uterine lining result in successful pregnancies more often. In most successful implantations, the arrival of the egg coincides with peak levels of luteinizing hormone (LH), which primes the endometrium to accept the embryo.

In addition to LH, a chemical called trypsin, produced by the embryo signals the uterine lining to prepare for implantation. A favorable endometrium is thick and exhibits a triple-line pattern under ultrasound imaging.

Unfortunately, even if an egg is successfully fertilized, it is possible for the embryo to fail to implant in the uterine lining. In two out of three cases, this is due to inadequate uterine receptivity. Many factors can contribute to uterine receptivity, including hormones and a type of proteins called cytokines, which allow cells to send and receive signals. Some medications, including progestins and progesterone, can increase the chances of successful implantation after repeated failure.

## Predecidualization

The endometrium increases thickness, becomes vascularized and its glands grow to be tortuous and boosted in their secretions. These changes reach their maximum about 7

days after ovulation. Furthermore, the surface of the endometrium produces a kind of rounded cells, which cover the whole area toward the uterine cavity. This happens about 9 to 10 days after ovulation. These cells are called decidual cells, which emphasises that the whole layer of them is shed off in every menstruation if no pregnancy occurs, just as leaves of deciduous trees. The uterine glands, on the other hand, decrease in activity and degenerate around 8 to 9 days after ovulation in absence of pregnancy. The decidual cells originate from the stromal cells that are always present in the endometrium. However, the decidual cells make up a new layer, the decidua. The rest of the endometrium, in addition, expresses differences between the luminal and the basal sides. The luminal cells form the zona compacta of the endometrium, in contrast to the basalolateral zona spongiosa, which consists of the rather spongy stromal cells.

## 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 nonconception cycles. Furthermore, similar changes are observed when giving stimuli mimicking the natural invasion of the embryo. The embryo releases serine proteases which causes the epithelial cell membrane to depolarize and activates the epithelial Na<sup>+</sup> channel. This triggers a Ca<sup>2+</sup> influx and phosphorylation of CREB. Phosphorylation of CREB upregulates the expression of COX-2, which leads to the release of prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) from epithelial cells. PGE<sub>2</sub> acts on the stroma cells activating cAMP-related pathways in stromal cell leading to decidualization.

## Parts of decidua

The decidua can be organized into separate sections, although they have the same composition. Decidua basalis - This is the part of the decidua which is located basalolateral to the embryo after implantation. Decidua capsularis - Decidua capsularis grows over the embryo on the luminal side, enclosing it into the endometrium. It surrounds the embryo together with decidua basalis. Decidua parietalis - All other decidua on the uterine surface belongs to decidua parietalis. Decidua throughout pregnancy. After implantation the decidua remains, at least through the first trimester. However, its most prominent time is during the early stages of pregnancy, during implantation. Its function as a surrounding tissue is replaced by the definitive placenta. However, some elements of the decidualization remain throughout pregnancy. The compacta and spongiosa layers are still observable beneath the decidua in pregnancy.

The glands of the spongiosa layer continue to secrete during the first trimester, when they degenerate. However, before that disappearance, some glands secrete unequally much. This phenomenon of hypersecretion is called the Arias-Stella phenomenon, after the pathologist Javier Arias-Stella.

## Pinopodes

Pinopodes are small, finger-like protrusions from the endometrium. They appear between day 19 and day 21 of gestational age. This corresponds to a fertilization 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 but inhibited by estrogens.

## Function in implantation

Pinopodes endocytose uterine fluid and macromolecules in it. By doing so, the volume of the uterus decreases, taking the walls closer to the embryoblast floating in it. Thus, the period of active pinocytes might also limit the implantation window.

Function during implantation

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

## 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. Thus, MUC16 inhibits cell-cell adhesion. "Removal of this mucin during formation of uterodomes (bulbous projections from the apical surface of the epithelium that are often found during the implantation period) facilitates trophoblast adhesion in vitro".

## 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. The prefix syn- refers to the transformation that occurs as the boundaries between these cells disappear to form a single mass of many cell nuclei (a syncytium). The rest of the

trophoblasts, surrounding the inner cell mass, are hereafter called cytotrophoblasts. Syncytiotrophoblast is not determined as a cell type, rather is a multinucleated 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. This is the initiation of forming the placenta.

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. The blastocyst secretes factors for a multitude of purposes during invasion. It secretes several autocrine 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.

## Signs of Successful Implantation

If the embryo successfully implants, you can expect to experience a number of signs or symptoms. Unfortunately, the earliest signs of success can appear like the normal signs of a period: cramps, headaches, fatigue, and bloating. In 20% to 30% of women, implantation bleeding occurs, similar to what they experience during a period.

However, if it's implantation and not your period, additional symptoms will follow:

- Your breasts may feel sore, tight, or tender.
- If you continue tracking your basal body temperature after ovulation, you may notice that your average temperature has increased.
- This rise in temperature, combined with fatigue and other symptoms, may make you think you have the flu.
- Within a week, you may feel more frequent urges to urinate. This is because increased blood flow to the uterus has put pressure on your bladder.