Name: Adebiyi Oluwatosin Nurat

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Department: Medicine and Surgery

Course: Embryology

Assignment: Discuss the second week of embryonic development

Answer:

Following all the excitement associated with the first gestational week, the newly formed blastocyst is ready to settle into a supportive environment and continue the growth process. Week 2 is often referred to as the week of twos. It’s the week when the embryoblast, extraembryonic mesoderm and trophoblast each separate into two distinct layers. Additionally, there are two cavities that develop within the embryonic unit at this time as well.

While every step is integral for adequate foetal development, one of the most important features of the second week is the completion of implantation and establishment of fetomaternal interactions. This article will follow the developing embryo through the completion of implantation and development of the non-embryonic components of the conceptus. It will also discuss some complications associated with implantation.

Implantation of the blastocyst

Implantation is a complex biochemical and mechanical process that begins in the first week of gestation and extends into the second week. There are many influencing factors that affect the process. These can be grouped into maternal and embryonal factors. However, both entities work synchronously in order to effectively achieve implantation. The process of implantation can be subdivided

into three phases:

There is a period of apposition where the blastocyst establishes weak interactions with the uterine wall.

The attachment phase occurs when definitive binding of the blastocyst to the uterine epithelium is more established, such that the blastocyst cannot be flushed from the uterine cavity.

Finally invasion occurs when the blastocyst begins to burrow into the endometrium.

This period usually occurs between the 19th and 24th day of the menstrual cycle. This coincides roughly with the 6th to 10th day following ovulation.

Maternal factors affecting implantation

In anticipation for successful fertilization each month, the inner uterine wall (endometrium) undergoes a series of changes in order to facilitate the blastocyst. Recall that there are three layers of the endometrium – the strata basalis, spongiosum and compactum.

The deepest layer is the stratum basalis, which functions as the regenerative layer and proliferates to form the stratum spongiosum and stratum compactum. Stratum compactum is the most superficial and the stratum spongiosum resides between the two. Together, the strata compactum and spongiosum form the stratum functionalis; which is the functional layer of the endometrium that facilitates implantation.

The development of the stratum functionalis is mitigated by surges in estrogen (which are released from the maturing ovarian follicle, under the influence of follicle stimulating hormone). If fertilization did not occur during the previous menstrual cycle, the fall in reproductive hormones result in the degeneration of the stratum functionalis. The shedding of this layer during the menstrual phase of the cycle accounts for the vaginal bleeding known as menstruation.

In the subsequent cycle, as follicle stimulating hormone levels rise and stimulate maturation of another ovarian follicle, the resultant increase in estrogen levels leads to proliferation of the stratum basalis. This is known as the proliferative phase, during which time there is thickening of the endometrium. Following an increase in luteinizing hormone and the release of a secondary oocyte, the remaining corpus luteum continues to release estrogen and progesterone to maintain the stratum functionalis. The spiral arteries of the uterus become longer and more tortuous under the influence of the sex hormones.

Following successful fertilization the uterine epithelia, which is characterized by ciliated columnar cells with microvilli, undergoes morphological changes to accommodate the growing embryo. The expression of these cilia (extended processes located at the apical aspect of the cells) is regulated by both progesterone and estrogen. The underlying motile microtubules allow the cilia to move the developing embryo toward a favourable site on the uterine wall. This process usually starts around the end of the first gestational week, when the conceptus is classified as a blastocyst.

The process of bringing the conceptus close to the uterine wall is referred to as adplantation (apposition). As the blastocyst rolls along the surface of the uterus, the pole of the blastocyst with the inner cell mass is adjacent to the uterine wall. Early attachments to the microvilli (short, non- motile, apical epithelial processes) also facilitate the initiation of implantation.

Once the uterine lining is receptive for implantation, the endometrium is said to be in the implantation window. However, this is a complex process that depends on the presence of numerous cytokines, immunomodulators, and increased binding capacity of the epithelium in order for implantation to work. Recall from the first week of gestation that the resulting conceptus is genetically unique when compared with its parents. Therefore, the mother’s

immune system should identify the blastocyst as a parasitic entity that should be destroyed.

A key element in the implantation phase that is thought to modify this anticipated immune response (and other parts of implantation) is known as leukaemia inhibitory factor (LIF). This is a member of the interleukin – 6 (IL-6) family that has the ability to influence several unrelated gene expressions (i.e. it's a pleiotropic entity). Within the reproductive system, it is produced by both the endometrial epithelium as well as the developing blastocyst. Leukaemia inhibitory factor has the following functions with regards to endometrial receptivity:

The decidualization of the stromal cells (discussed below) is by LIF. This response is generated by way of a cyclic adenosine monophosphate (cAMP) pathway that activates a biochemical cascade involving estrogen and progesterone, IL-5, IL-6, prostaglandins, and cyclooxygenase 2 (COX- 2). The resultant cellular morphological change creates a more favourable implantation environment. This particular reaction is important because it plays a significant role in immunomodulation. It is particularly difficult for thymocytes (T-cells) to invade decidual tissue; similarly, decidual cells have a hard time recruiting T-cells from the percolating blood. Therefore, the probability of the maternal immune system mounting a cytotoxic T-lymphocyte (CTL) response against the allogeneic conceptus is markedly reduced.

In addition, LIF upregulates numerous epidermal growth factors such as heparin – binding epidermal growth factor like protein (HB-EGF), epiregulin (EPR), and amphiregulin (AREG). These proteins act as ligands for the epidermal growth factor receptors and subsequently stimulate the proliferation of the endometrial epidermis.

LIF also stimulates the activity of implantation genes, including members of the Wnt family (Wnt 4, 5a, and others) and MutS homolog homebox 1 gene (MSX 1). These and other implantation genes result in differentiation of the luminal and glandular epithelia (decidualization), proliferation of the stromal cells, and decrease in the polarity of the epithelium to foster adhesion.

Uterodomes (also known as pinopods) are micro-protrusions of the luminal surface of the uterine epithelium that interdigitate with the blastocyst during adplantation and attachment. While they are present throughout the luteal phase of the menstrual cycle, they increase in number under the influence of LIF. In lower other mammals, pinopods are thought to play a significant role in pinocytosis (cell drinking). However, this is not its primary role in humans. As a result, they are referred to as uterodomes based on their appearance.

Under normal circumstances, the luminal surface of the uterus is coated with a thick layer of glycocalyx. This is a carbohydrate, glycoprotein rich layer that promotes repulsion of foreign entities from the cell membranes. It also has a large quantity of mucins (MUC-1 and MUC-4). LIF mediates significant local downregulation of MUC-1 in the area of the epithelium adjacent to the hatched blastocyst, which reduces repulsion of the blastocyst. However, relatively high levels of mucins are normally present in unfavourable implantation sites to prevent attachment.

Finally, the presence and activity of a member of the junctional adhesion molecule family (JAM-2)

is also noted to be increased within the uterus during the 1st to 2nd gestational weeks. Junctional adhesion molecules have the ability to interact within the family (i.e. JAM-JAM binding) as well as with other integrins on non-uterine cells. They therefore promote cellular attachment to the epithelial membrane. Both LIF and progesterone have been shown to upregulate the expression of these adhesion molecules.

As mentioned earlier, the luminal uterine stroma undergoes morphological transformation under the influence of LIF, estrogen and progesterone. This process – known as decidualization – involves accumulation of lipids and glycogen at a cellular level. The cells (i.e. decidual cells) subsequently acquire a polyhedral shape (as opposed to their previous columnar appearance). The process begins locally at the site of fetomaternal attachment, but gradually radiates until the entire endometrium has been transformed. On a molecular level, bone morphogenetic protein 2 (BMP-2) is needed for this transformation to occur; its deficiency is a known cause of infertility. The decidua provides an immunologically safe space for the embryo,

in addition to providing nutrition for its development.

Fetal factors affecting implantation

As the blastocyst is hatched from the zona pellucida, it comes into contact with the endometrium. Surface proteins on the trophoblast known as trophinin interact with similar trophinin molecules on the endometrial surface.

Of note, by the end of week 2, the bilaminar disc develops a localized region of thickened cells in the hypoblast. This area is referred to as the prechordal plate. Not only does the prechordal plate help with the organization of the head region during development, but it also indicates the future head region and the location of the mouth.

The syncytiotrophoblast is a highly invasive structure that penetrates the endometrium in order for the blastocyst to become embedded. The trophinin-trophinin binding also induces endometrial epithelial apoptosis in the mother in order to accommodate the invading cell mass. The blastocyst then utilizes the nutrients from the recently destroyed maternal cells as it continues to grow. Furthermore, the syncytiotrophoblast (under the influence of LIF) begins to produce human chorionic gonadotropin hormone (β- hCG). The presence of β-hCG prevents corpus luteum degeneration, resulting in the continued release of estrogen and progesterone. The detection of the glycoprotein in maternal circulation and urine also forms the basis of the pregnancy test.

Another recently discovered element that contributes to implantation is the protein preimplantation factor. It is derived from the embryo and has been shown to aid in maternal immunomodulation, embryo- endometrial adhesion, and endometrial apoptosis.

Review of the initial sequence of implantation

Let’s recap the initial implantation sequence:

Endometrial development occurs each month in anticipation of successful fertilization.

Successful fertilization occurs and the zygote develops into a blastocyst.

The blastocyst roles along the endometrium towards a favourable implantation site.

Concurrently, there is maternal immunomodulation, downregulation of repelling entities and upregulation of adhesion moieties.

The blastocyst hatches from the zona pellucida.

Adplantation occurs when weak carbohydrate binding occurs between the embryo and the glycocalyx.

As the embryo gets closer to the endometrium, stronger bonds are formed. These involve interactions with integrins, L- selectin, osteopontin, cadherins, trophinin, as well as CD44 and CD98.

Attachment stimulates maternal decidualization and embryonal trophoblast differentiation.

Trophoblastic invasion coincides with desmosomal detachment of maternal cells, as well as apoptosis of adjacent decidua.

Amniotic cavity

While implantation ensues, the embryoblast also undergoes differentiation to form a bilaminar disc. The flat, circular disc is comprised of a thicker epiblast with high columnar cells and a thinner hypoblast with small cuboidal cells. A small space develops relative to the epiblast; it is the precursor of the amniotic cavity.

Epiblastic cells forming the floor of the cavity subsequently separate to form amnioblasts that will form the amnion (surrounding the amniotic cavity). The sac and cavity will eventually become filled with amniotic fluid later on in the pregnancy. They provide shock absorption and facilitate movement of the foetus during development.