NNAM PRECIOUS CHINONYE

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PHS212

NURSING 200 LEVEL

IMPLANTATION

Implantation is defined as the process of embryo hatching, adhesion and invasion into the endometrium

Series of events that occur before implantation

Cleavage and blastocyte formation

Cleavage:

Cleavage can be defined as a series of repeated mitotic divisions of the zygote resulting in a rapid increase in the number of cells(embryonic cells)these embryonic cells are called blastomeres.Blastomeres become smaller with each successive cleavage division, Cleavage normally occurs as the zygote passes along the uterine tube toward the uterus

Division of the zygote into blastomeres begins approximately 30 hours after fertilization (day 2)

the 1st cleavage is the division of the zygote into a two-cell stage

the 2nd cleavage is from the two -cell stage into a four-cell stage

the 3rd cleavage is from the four -cell stage into an eight-cell stage

After the eight-cell stage, the blastomeres change their shape and tightly align themselves against each other to form a compact ball of cells

This process is refered to as compaction

This phenomenon, compaction, is probably mediated by cell surface adhesion glycoproteins

Approximately 3 days after fertilization, cells of the compacted embryo divide again to form a 16-cell stage called morula stage. When there is 16-32 blastomeres the developing human is called a “morula”

BLASTOCYST FORMATION

After the morula enters the uterus (approx. 4 days after fertilization), a fluid-filled space called the blastocystic cavity appears inside the morula.The fluid passes from the uterine cavity through the zona pellucida to form this space As fluid increases in the blastocystic cavity, it separates the blastomeres into two parts:

*An inner cell mass of cells called the embryoblast, which is surrounded by

*an outer cell mass of cells called the trophoblast

Note; the zona pellucida must degenerate for implantation to occur.

IMPLANTATION

The wall of the uterus consists of 3 layers:

(a) endometrium or mucosa lining the inside wall

(b) myometrium, a thick layer of smooth muscle

(c) perimetrium, the peritoneal covering lining the outside wall

Approximately 6 days after fertilization (day 20 of a 28-day menstrual cycle), the blastocyst attaches to the endometrial epithelium as soon as it attaches to the endometrial epithelium, the trophoblast starts to proliferate rapidly and gradually differentiates into 2 layers :

*An inner layer of cytotrophoblast

*An outer layer of syncytiotrophoblast

Implantation of the blastocyst is completed during the second week of embryonic development. As this crucial process occurs, morphological changes occur in the inner cell mass of embryoblast that produce a bilaminar embryonic disc composed of two layers; epiblast and hypoblast.

Implantation consists 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 (invasion)

(1) Apposition and adhesion

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 midsagittal 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”.

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. The 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 . In mice, E(epithelial)- cadherin was detected in embryonic cells during the peri-implantation period, and it is also detected in the uterine epithelium . The presence of E-cadherin in both the trophoblasts and endometrial epithelium indicates that E-cadherin may play an important role in the initial attachment process .

Selectins are a group of carbohydrate-binding proteins. Although L-selectin was previously thought to be expressed only in hematopoietic cells, human trophoblasts also express L-selectin and its oligosaccharides are expressed in pinopodes . Interaction between L-selectin on human blastocysts and oligosaccharide ligands on the endometrial epithelium has been proposed as an initial step in implantation . Blocking L-selectin with specific antibodies leads to impaired adhesion of trophoblasts to the endometrial epithelium.

2) 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 catalyse 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 (PAI-1) which is the major inhibitor of uPA . The tissue inhibitors of MMPs (TIMPs) 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 antiproliferative signals to differentiate from invasive and proliferative cytotrophoblasts into non-invasive and multinucleated 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

CLINICAL ANATOMY

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 and hormonal signaling as well as epigenetic alterations.Recurrent implantation failure is a cause of female infertility. Therefore, pregnancy rates 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 is the administration of medication, generally progestins, for the purpose of increasing the success rate of implantation and early embryogenesis, thereby complementing the function of the corpus luteum.

In women with more than 3 implantation failures in assisted reproduction, a review of several small randomized controlled studies estimated that the use of adjunct low molecular weight heparin (LMWH) improves live birth rate by approximately 80%.