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BIOMEDICAL ENGINEERING

HUMAN PHYSIOLOGY II (PHS212)

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. In humans, implantation of a fertilized ovum is most likely to occur around nine days after ovulation; however, this can range between six and 12 days.

Implantation window

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.

Implantation is a process in which a developing embryo, moving as a blastocyst through a uterus, makes contact with the uterine wall and remains attached to it until birth. The lining of the uterus (endometrium) prepares for the developing blastocyst to attach to it via many internal changes. Without these changes implantation will not occur, and the embryo sloughs off during menstruation. Such implantation is unique to mammals, but not all mammals exhibit it. Furthermore, of those mammals that exhibit implantation, the process differs in many respects between those mammals in which the females have estrous cycles, and those mammals in which the females have menstrual

cycles. Females in the different species of primates, including humans, have menstrual cycles, and thus similar processes of implantation.

Before embryogenesis begins, the ovary releases an unfertilized egg cell, called an oocyte, which then travels down the fallopian tube. The egg is enveloped in an extracellular matrix called the zona pellucida. Sperm can fertilize the egg in the zona pellucida (ZP), which prevents the fertilized egg, called a zygote, from adhering to the wall of the fallopian tube. If the zygote implants in any area besides the uterus, the result is an ectopic pregnancy. This condition prevents the complete development of the embryo, and it can cause fatal hemorrhaging in the pregnant female.

As the zygote moves through the fallopian tube it undergoes several rounds of cell division, a process called cleavage. These cell divisions produce the inner cell mass (ICM), which will become the embryo, and the trophoblast, which surrounds the ICM and interacts with maternal tissues. Together, the ICM and the trophoblast are called the blastocyst. A blastocyst successfully implants in the uterus when, as the ZP exits the fallopian tube, the blastocyst leaves the ZP and binds to the endometrium.

The endometrium is one of the few uterine surfaces to which a blastocyst cannot always implant. The properties of the endometrium change, and only in a brief window can the blastocyst implant on the tissue. In humans, that window includes days six through ten after ovulation. Just prior to ovulation, the endometrium begins to thicken and to expand in response to the release of estrogen from the ovaries. As the embryo moves through the fallopian tubes, the endometrium proliferates, changes in shape, becomes receptive to implantation, and produces a hospitable environment for the embryo. Signaled by the release of progesterone from the ovaries, a series of changes called decidualization occurs. Decidualization includes the gathering of white blood cells around endometrial arterioles, or blood vessels leading from arteries to capillary beds. As that vasculature forms, a molecule that stores energy, called glycogen, accumulates in the expanding connective tissues of the uterus. Furthermore, the endometrium swells as interstitial fluid accumulates in it. The endometrium, swollen with interstitial fluid, vasculature, and nutrients, provides a hospitable environment for embryogenesis.

As the blastocyst moves through the uterus it realigns itself so that the inner cell mass is adjacent to the uterine wall, and the trophoblast contacts the endometrium. The position of the ICM in relation to the endometrium establishes the head to tail, or dorsal-ventral, axis of the embryo, with the dorsal side of the embryo facing the uterine wall. This is the first embryonic event that dictates the organization of the future body.

Successful implantation depends on the blastocyst binding to the endometrium. There are many molecules that are thought to dictate this interaction, but integrins, a type of cell-adhesion molecule, have been identified as a primary component. Integrins extend from the lining of the uterus and from the surface of the blastula. Integrins have many functions in nearly all tissue types, and they have a role in cell adhesion, conveying information about the extracellular environment to the nucleus, and modulating the local immune response. Immediately following implantation, integrins help regulate gene expression in the embryo. Doctors also look for high concentrations of integrins when they look for areas of uterus receptive to implantation in assisted reproductive therapy (ART), and they use the lack of such concentrations to identify women who may be infertile. Despite the contact between the blastocyst and the endometrium, implantation can fail. There are many potential causes of errors. If implantation does not occur, the endometrium breaks down and sheds, along with the blastocyst, as part of the menstrual cycle. However, if a blastocyst does implant, then the endometrium remains in the uterus, and together with uterine tissue, becomes the maternal portion of the placenta, called the deciduas.

Once the blastocyst adheres to the uterine wall, the trophoblast secretes enzymes that digest the extracellular matrix of endometrial tissue. The trophoblast cells then begin to intrude between the endometrial cells, attaching the blastocyst to the uterine surface. Further secretions of enzymes allow the blastocyst to bury itself deeply among the uterine stromal cells that form the structural components of the uterus. Subsequently, trophoblast cells continue to divide and form two extraembryonic membranes. These membranes form the fetal portion of the placenta called the chorion. Additional enzymes and signaling factors secreted by these membranes remodel the uterine vasculature to bathe the fetal or embryonic blood vessels in maternal blood. Chorionic villi are the folds of tissue and blood vessels that connect maternal and fetal blood pools. Maternal blood diffuses into the villi, and it travels through them into the fetus's vasculature. Similarly, fetal blood diffuses from the villi and into the maternal vasculature. Normally fetal and maternal blood do not mix, but the relationship between the two circulatory systems enables the transfer of nutrients and oxygen to the fetus or embryo, and carbon dioxide and urea from the fetus to the mother. While unique to mammals as a reproductive process, implantation is not unique to the uterus and the trophoblast. In the 1980s, researchers found similarities between the invasive abilities of blastocysts and those of cancer cells. The same trophoblast enzymes that digest the endometrium are also used by tumor cells to burrow into tissues throughout body. Tumor cells use the same growth factors as the trophoblast to attract maternal blood vessels, which then interact with the chorion, and to provide nutrients to the expanding mass. In addition, the changes in the endometrium during decidualization such as swelling, the accumulation of white blood cells, and the general activation of the maternal immune system, are consistent with a response to the presence of pathogens or tumors.