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Characteristics of Endometrial Cells and the Factors that Influence the Implantation Process

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Abstract

Infertility is a global health problem faced by 8 - 10% of couples in the world. It means 50 - 80 million couples have infertility problem. Knowledge about comprehensive and profound reproductive system is main asset for managing infertility. When look at various factors those contribute to women infertility, so the role of endometrium is very important. The optimal endometrial environment for receiving blastocyst is a major factor in the process of implantation and pregnancy. This study attempts to review and compare sources from research article, case report, and reviews from reputable international journals. Research by Germeyer et al (2010) shows that optimal growth and development of endometrium are factors those greatly contributes for successful implantation which is continued to pregnancy. The same thing is revealed by Neykova review (2020) which states the success implantation process is determined by the quality of the embryo, the readiness of the endometrium to accept the result of conception and interaction, and communication of molecular cells. Currently, various studies are being developed for evaluating endometrium condition through genetic improvement, the use of new biomarkers, non-invasive method even sophisticated method such as proteomic technique Endometrial Receptivity Assay (ERA) in order to solve women infertility problem.

Keyword: Endometrium, Infertility, Implantation, Pregnancy.

Introduction

Infertility is a source of complaints and anxiety for married couples. Infertility affects about 50 - 80 million couples in the world [1]. In Indonesia there are approximately 12% of infertile couples [2]. Infertility is defined as the inability of a married couple to become pregnant for a period of six months to one year without using contraceptives and having active intercourse [1].

WHO Scientific Group classifies infertility into two types, namely primary infertility if a husband and wife have not had children for two years even though the couple does not use contraceptives.

Secondary infertility is when a married couple who had previously had children cannot have children again for two years even though the couple is not using contraceptives and is not breastfeeding [3].

The cause of infertility can come from the husband or wife, or both. According to statistics, 40% of infertility occurs in the female reproductive system, 40% occurs in the male reproductive system, and 20% has no known cause [3]. Infertility in the female reproductive system can be caused by several things, including menstrual abnormalities, abnormalities in the fallopian tubes, ovaries, and endometrial lining of the uterus [1].

Various methods have been used to overcome the problem of infertility, one of which is an engineering technique called in vitro fertilization (FIV). Fertilization technique which was performed in the laboratory was successfully performed for the first time in 1978. This success gave new hope to couples who have difficulty having children [1]. However, in vitro fertilization techniques cannot guarantee 100% success for a couple to have offspring. The success rate for this technique averages only about 35%. The failure of in vitro fertilization techniques is thought to be caused by failure of follicle formation, too low estradiol levels, and less than ideal endometrial conditions [2].

The endometrium is an organ that plays an important role in the process of implantation and pregnancy. Research by Germeyer et al in 2010 showed that impaired endometrial growth, such as a decrease in the rate of cell proliferation, is one of the causes of failure in implantation and pregnancy [4]. In addition, several studies have shown that one of the causes of the low pregnancy rate in humans is an overly thin endometrial lining [5]. The same thing was expressed by Neykova et al in 2020 which stated that the success of the implantation process was determined by the quality of the embryo, the readiness of the endometrium to accept the results of conception and molecular interactions and communication between cells [6].

Based on the results of the study, Cohen et al stated that patients with In Vitro Fertilization who experienced repeated implantation failure need to consider endometrial histology during the secretion phase [7]. In fact, various studies are currently being developed to evaluate the condition of the endometrium through genetic improvement, the use of new

biomarkers, non-invasive methods and even sophisticated methods such as the Endometrial Receptivity Assay (ERA) proteomic technique in order to overcome infertility problems in women [6].

Due to the close relationship between endometrial disorders and infertility, therefore, it is important to carry out in-depth studies and discussions about the nature or characteristics of endometrial cells and what factors influence their development during the implantation process.

Method

This article is a literature review compiled by discussing a number of research articles, case reports, review articles obtained from reputable international journals. There are around 389 articles from a number of reputable journals such as Elsevier, Lancet, Scimedirect and a number of other publishers. Based on the inclusion criteria, 20 articles were reviewed in this review.

Result and Discussion

1. Endometrium

The endometrium is a thin layer found in the inferior part of the uterus which is rich in tortuous blood vessels. The most important physiological function of the endometrium is in the process of implantation as a result of fertilization. The endometrium is important in the menstrual cycle as a reproductive period. Most of the endometrium is released during menstruation, which then grows again in the proliferation phase followed by the sectoral phase [8]. Figure 1 shows these structural and functional changes in order to prepare for blastocyst implantation and to support embryonic growth in early pregnancy [6].

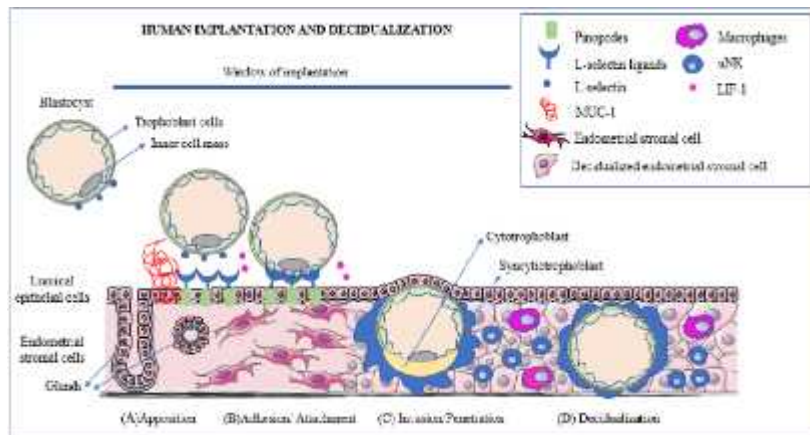


Figure 1. Implantation Process and Decidua Formation.

The implantation process consists of apposition, adhesion or attachment, invasion or penetration and decidualization or formation of decidua. During apposition (A), blastocyst will express L-selectin while expression of Mucin-1 (MUC-1) will block blastocyst and prevent it from implanting. Furthermore, L-selectin will interact with its ligands which are expressed mainly on pinopod during the implantation process. Early in the adhesion phase (B), the blastocyst initiates cleavage of MUC-1 at the implantation site to ensure successful implantation. Cytokines, such as Leukemia Inhibitory Factor (LIF), play an important role during the implantation process by supporting the interaction between embryos and endometrial cells. During the invasion or penetration phase (C), trophoblast cells from the blastocyst penetrate the endometrial epithelium into the stroma. Extra villary trophoblast cells begin to multiply and differentiate into inner cytotrophoblasts and outer syncytiotrophoblasts. After implantation begins and the embryo penetrates the luminal epithelium, the stromal cells

surrounding the embryo turn into decidual (D) cells. Immune cells such as macrophages and Uterine Natural Killer (uNK) cells play an important role during the decidualization process, namely to form an environment conducive to successful implantation. (<http://smart.servier.com>) [9]

The endometrium is composed of stromal cells surrounded by a columnar epithelial layer with glandular cells extending towards the stroma [10] (Figure 2). The lining of the endometrium can be divided histologically and functionally into three. The innermost or basal layer (stratum basale) is attached to the myometrium. The middle layer is characterized by a spongy-looking stroma called the stratum spongiosum. The superficial layer is composed of a compact looking stroma called the stratum compactum. The middle layer is thicker than the superficial layer. The middle and superficial layers are grouped into functional layers, because both layers show marked histological changes throughout the reproductive cycle [11].

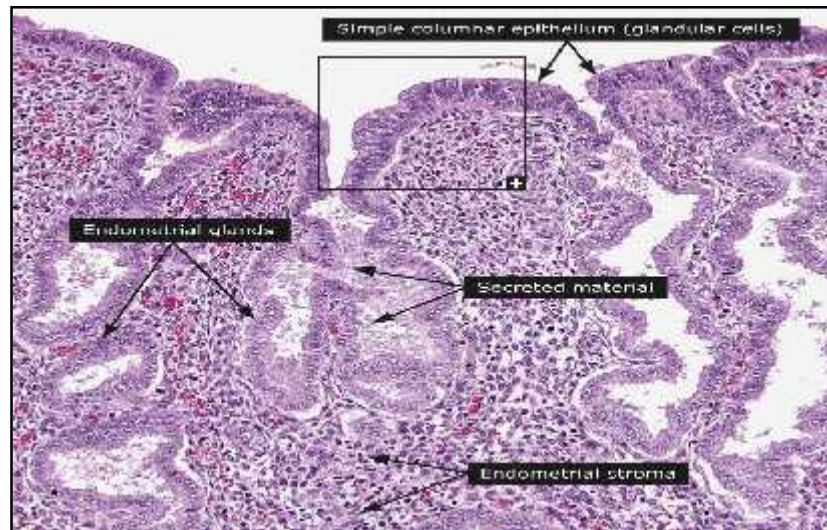


Figure 2. Histological cross section of the endometrium [12]

The lining of the endometrium is a layer that is responsive to changes in reproductive hormones, so changes in this layer vary throughout the reproductive cycle and can be used as an indicator of current hormonal fluctuations. The constituent layer on the endometrial wall of the uterus is a layer of columnar epithelium and lamina propria which consists of connective tissue and glands [10] [11].

2. Endometrial Changes During the Menstrual Cycle

Menstruation is a uterine cycle characterized by the bleeding process. Menstrual cycle length is the distance between the previous cycle and the new cycle. The normal menstrual cycle length is 28 days but variations are wide enough for each individual. The normal menstrual cycle (ovarian cycle) is divided into follicular phase and luteal phase [2].

The follicular phase is aimed at developing follicles in the ovaries due to the influence of the increased FSH. The increase in FSH is caused by regression of the corpus luteum, so that steroid hormones are reduced. The growing follicles cause the production of estrogen to increase, it suppresses the production of FSH.

The production of LH at this time is also increasing, but its role is only to help make estrogen in the follicles. Follicular development ends when the plasma estrogen levels rise. This provides positive feedback to the cyclic center and a sudden peak release

(LH-surge) in the middle of the cycle resulting in ovulation. The increased LH will persist for about 24 hours and decrease in the luteal phase. Within a few hours after the LH increases, the amount of estrogen decreases [2].

The luteal phase is characterized by enlargement of the granulosa cells to form a vacuole and accumulate yellow pigment (lutein) and the follicle will become the corpus luteum. Vascularization in the granulosa layer also increases and reaches a peak on days 8-9 after ovulation. The granulosa cells in the corpus luteum produce large amounts of the hormone progesterone, while theca cells produce the hormone estrogen, so the two hormones will increase in the luteal phase. Starting 10 - 12 days after ovulation the corpus luteum undergoes gradual regression accompanied by a decrease in capillary capillaries followed by a decrease in the secretion of progesterone and estrogen. The endometrium undergoes four phases in the menstrual cycle (Figure 3), namely:

- a. Menstrual or menstrual phase. During this time the endometrium is released from the uterine wall accompanied by bleeding. Only a thin layer remains, called the stratum basale, this stage lasts for about 5 days. The decrease in progesterone and estrogen hormones will stimulate prostaglandins which will cause the spiral arteries in the endometrial functional stratum to

experience vasoconstriction resulting in disruption of blood flow to the functional stratum resulting in temporary ischemia and ultimately leading to cell necrosis in blood vessels in the functional stratum. After vasoconstriction occurs, the spiral arteries will return to vasodilation, which will result in the shedding of the necrotic functional stratum from the remaining part of the endometrium. The endometrium becomes around 2-5 mm because only the basal stratum is permanent. Menstrual blood flows out through the uterus, cervix and vagina [12].

b. The pre-ovulatory phase or the proliferation phase is the time between the end of menstruation and ovulation. The pre-ovulation phase has a long cycle and varies in each phase, which is about 6-13 days for a 28 day cycle. Estrogen will be released into the blood by the growing ovarian follicles to stimulate endometrial repair in the uterus. The cells of the basal stratum undergo mitosis and produce a new functional stratum which causes the endometrium to thicken. The thickness of the endometrium is doubled to about 4-10 mm [12].

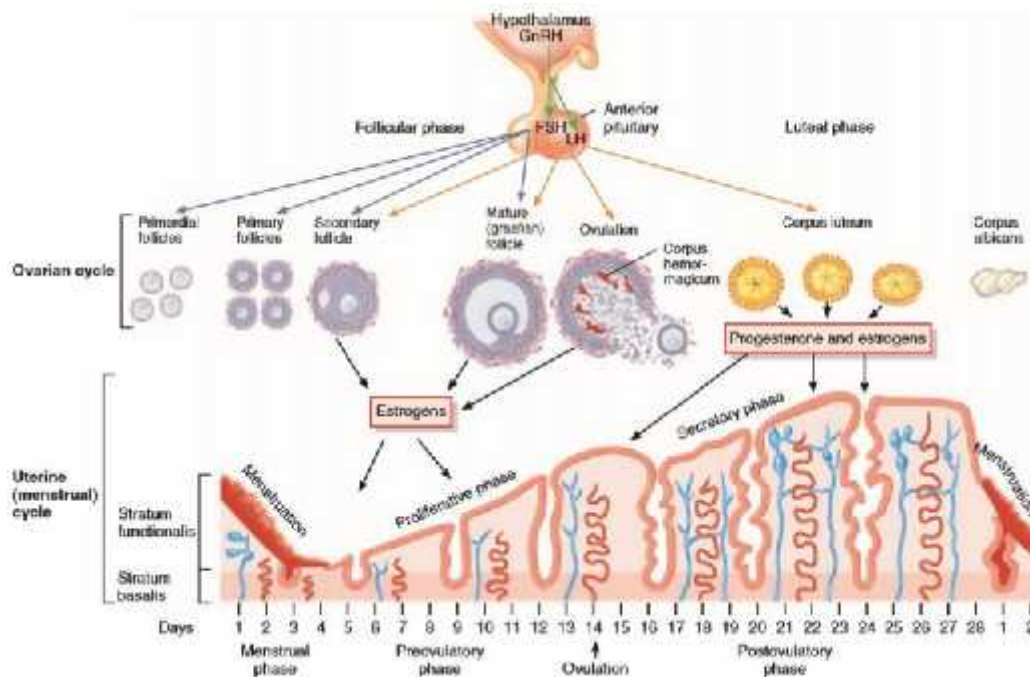


Figure 3. Changes in hormonal regulation in the uterus and ovaries [12]

c. Ovulation phase. This phase occurs when the rupture of the de graff follicle occurs and the secondary oocyte from the ovary to the uterus passes through the uterus. The ovulation phase occurs on day 14 of the 28 day menstrual cycle. The secondary oocyte remains surrounded by the zona pellucida and corona radiata during the ovulation phase [12]. The high estrogen hormone in the pre-ovulation phase provides positive feedback to cells that secrete

Gonadotropin Releasing Hormone (GnRH) and Luteinizing Hormone (LH) which causes the ovulation phase as follows:

- 1) GnRH release from the hypothalamus is caused by stimulation of high estrogen concentrations. Gonadotropins in the anterior pituitary directly stimulate LH secretion.
- 2) The release of FSH and LH from the anterior pituitary is assisted by GnRH.

- 3) LH causes the rupture of the de graff follicle and releases the secondary oocyte about 9 hours after the peak of LH. The secondary ovulation remains surrounded by the zona pellucida and corona radiata which will go to the uterus through the fallopian tube [12].
- d. Post ovulation phase or secretion stage. This phase begins after ovulation and lasts from day 14 to 28. Progesterone and estrogen will be produced by lutein cells from the corpus luteum which will help the growth of the endometrium gland, endometrial thickening of about 12-18 mm and increase in endometrial vascularization. The secretory activity of the endometrium starts to secrete glycogen and this period is called the secretion phase. The decrease in the hormones progesterone and estrogen occurs due to degeneration of the corpus luteum due to no fertilization. The decrease in these two hormones causes menstruation in the next cycle [12]. In this phase the endometrium remains approximately still thick, but the shape of the gland changes to a long, twisting and secretion that becomes increasingly visible and obvious. The endometrium has accumulated glycogen and lime which will be needed as food for a fertilized egg. The purpose of these changes is to prepare the endometrium to accept the incoming sperm and the egg to be ready for fertilization [13] [14].

3. Implantation and its Influencing Factors

Implantation is a dynamic process that involves the embryo, starting from hatching, apposition, adhesion, and invasion of the endometrial epithelium. The success of the implantation process depends on the quality of the blastocytes, the receptiveness of the endometrium, and the communication or synchronization between the embryo and the endometrial lining itself. The implantation process

requires coordination and communication in autocrine, paracrine, and endocrine ways [15].

Implantation in humans consists of three stages, namely apposition, adhesion, and invasion. The first step in the implantation process is apposition, which is the initiation of communication between the blastocyst and endometrial receptivity which is influenced by hormones, cytokines, and growth factors. At the time of apposition there is adhesion of the blastocyst to the part of the endometrium called the pinopod. Pinopod is a functional marker of endometrial receptivity.

The next step is adhesion, namely increased physical interaction between blastocytes and the endometrium. The last stage is the invasion process, namely the penetration of the embryo into the epithelial layer and the stroma to form vascularization with the mother's uterus [6] [15].

The process of implantation of trophoblasts in the endometrium is influenced by several factors that play an important role among cytokines and growth factors. The following will briefly describe the role and mechanism of each factor on endometrial growth during the implantation process.

3.1 Hormonal Roles

Ovarian steroid hormones, namely estrogen and progesterone, play an important role in the embryo implantation process. During the implantation process the endometrium undergoes transitions and changes morphologically and functionally under the influence of ovarian hormones. Progesterone and estrogen are the main hormones that affect endometrial growth [2] [15].

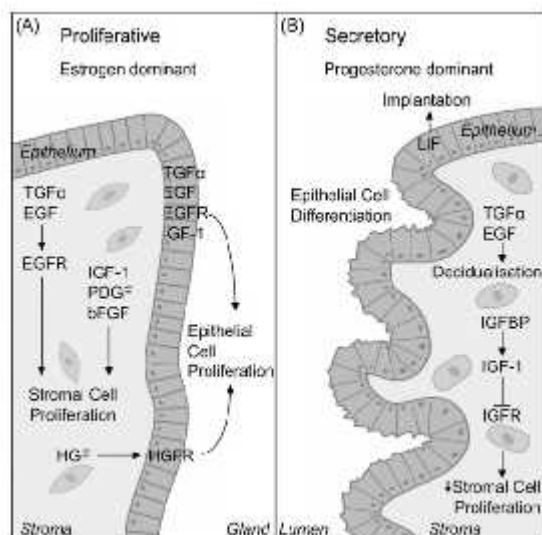


Figure 4 The effect of the hormones estrogen and progesterone on endometrial cell changes (proliferation and secretion phase) [16]

Figure 4 shows that the hormone estrogen plays an important role in the growth, development, and secretory activity of endometrial cells [16]. The estrogen hormone that has been formed will be transported through the blood to its target cells, including endometrial cells. The hormone then binds to the estrogen receptor (RE) to form a hormone complex with RE. The hormone complex with receptors will regulate target gene expression by binding to estrogen response elements (EREs). This binding event causes a specific mRNA transcription and protein translation process. The specific protein formed will induce the proliferation of stromal and epithelial cells as well as thickening of the endometrial lining [16] [17].

The process of proliferation of endometrial cells occurs either directly or indirectly. Endometrial stromal cells have enough RE, so that these cells can proliferate directly. However, this does not occur in endometrial epithelial cells. Endometrial epithelial cells have a little RE so that the process of mitosis in these cells must be assisted by paracrine factors produced by endometrial stromal cells. Endometrial epithelial cell proliferation is induced by the process of stromal cell proliferation. Figure 5 shows that estrogen

which has bind to RE on stromal cells triggers the emergence of epidermal growth factor (EGF) or what is called paracrine factor. These paracrine factors then stimulate the mitotic process in epithelial cells [17].

The action of EGF in inducing the proliferation of epithelial cells is as follows. Paracrine factor (EGF) produced by endometrial stromal cells will bind to its receptors (EGFR) found on the endometrial epithelial cell membrane. This binding event causes the transcription factor to be activated and the transcription and translation processes occur to form specific proteins. Specific proteins that have been formed will induce mitotic events or cell proliferation so that the endometrial epithelial cells thicken [17].

Progesterone, a hormone produced by the ovaries, plays an important role in the preparation of the endometrium for implantation of the product of conception. Progesterone also maintains the viability of the embryo at the pre-implantation stage. Various cellular interactions lead to synchronization between embryonic development and endometrial preparation. In the synchronization process, the role of steroid hormones is needed. Continued progesterone production from the corpus luteum stimulates the differentiation and proliferation of endometrial stromal cells [18].

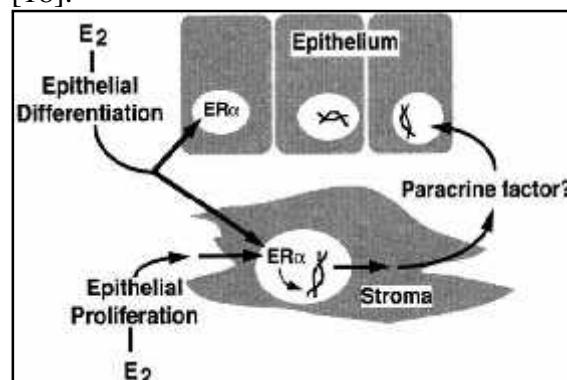


Figure 5. The mechanism of action of the hormone estrogen on endometrial cells [17]

The hormones estrogen and progesterone are known to also regulate HOXA 10 expression and pinopod

formation (Figure 6). HOXA 10 is known to be a gene that is produced by the female reproductive tract, the number increases at the time of the implantation window. Several studies have shown that this gene is closely related to pinopod formation and endometrial receptivity. Good pinopod development is related to one's fertility [19].

Several studies have shown that the chorionic gonadotropin hormone from the embryo is regulated by paracrine factors under the influence of progesterone. The chorionic gonadotropin hormone furthermore regulates endometrial differentiation for blastocyst implantation and increases the synthesis of progesterone in the ovaries. In addition, the hormone progesterone is also known to suppress immunosuppressive effects and plays a role in protecting the fetus from the immune system. Progesterone stimulates NK cells to change the function of NK cells to become more tolerant of the embryo [18].

Apart from estrogen and progesterone, prostaglandins (PGs) also have an important role in reproductive processes such as ovulation, implantation, and menstruation. The biosynthesis of these prostaglandins is regulated by the enzyme cyclooxygenase (COX-1 and COX-2). Several studies have shown that women who have failed implantation have low levels of the enzyme COX-2 [20].

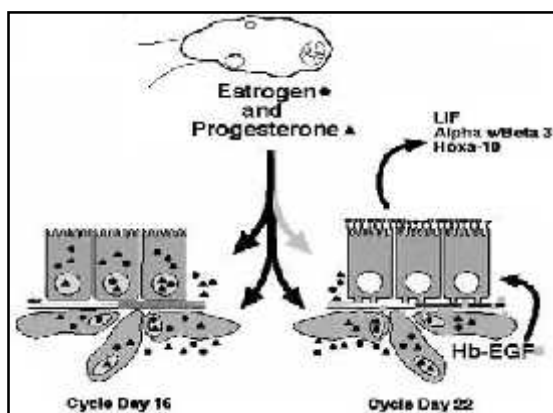


Figure 6. Mechanism of the hormones estrogen and progesterone on pinopod formation [17]

3.2 Role of Cytokines

The endometrium produces cytokines that play a role in the implantation process, namely colony stimulating factor 1 (CSF-1), leukemia inhibitory factor (LIF), and interleukin-1 (IL-1). Expression of CSF-1 and receptors for CSF-1 was found in both the endometrium and the preimplantation embryo. Leukemia inhibitory factor (LIF) is one of the cytokines of the interleukin 6 group (IL6) which is essential for successful implantation, is expressed in embryos and adult tissues, and is secreted by the uterus in high enough levels [15] [21]. Expression of IL6 is found in endometrial glandular epithelial cells during the secretory phase [15].

-receptor LIF On the surface of the cell binds to glycoprotein gp-130, a form of high affinity receptor that stimulates signal formation and induces molecules and contributes to stromal cell expression. LIF plays a role in the endometrial function of humans and domestic species. Furthermore, it has been suggested that LIF mRNA and protein are expressed in glands in the endometrium during the luteal phase of the menstrual cycle when implantation is about to occur [21].

LIF-r and gp-130 expressed throughout the lumen of the endothelium (LE) in women proved fertile. The soluble form of gp-130 is excreted by the endometrium, is formed by proteolytic fractions and excreted in high levels in the middle of the luteal phase. This situation is stimulated by estrogen with progesterone in the culture of endometrial epithelial cells. This suggests that a high likelihood of low levels of potential antagonists regulating activation of the membrane-bound IL-6 family receptors [21].

The misregulation of soluble gp-130 in unexplained infertility patients is additional evidence of the role of the cytokine IL-6 family in normal pregnancy endometrial function. In addition, a correlation has been shown between LIF and LIF-R levels and LE formation in the uterine cavity, primarily as a sign of receptivity. Several studies have shown that LIF expression in

several studies is associated with recurrent miscarriage and some conditions of unexplained infertility according to their role in early pregnancy. Expression of LIF is absolutely necessary in the implantation process, without LIF implantation will not occur [21].

3.3. The Role of Growth Factor

In transfer embryos, the highest implantation rate is obtained when the reproductive cycle of the donor embryo is in sync with the recipient cycle. Synchronization of the uterine endometrium and blastocysts can be achieved through the influence of the ovarian hormones progesterone and estrogen. Progesterone will stimulate a preceptive stage that is responsive to estrogen. In the uterus, estrogen or

estradiol will bind to its receptors and cause uterine receptivity [21].

This will stimulate the uterus to produce growth factors such as epidermal growth factors (EGF), heparin-binding EGF (HB-EGF) and transforming growth factor (TGF) [15]. These proteins will cause the expression of the cyclooxygenase enzymes (COX enzyme), which is the main enzyme that synthesizes prostaglandins. The COX-2 enzyme is important in the implantation process because in mouse experiments if a COX-2 enzyme defect is found, the endometrium cannot accept the embryo so that prostaglandins are very important in supporting the ability of the uterus to accept blastocysts even though the mechanism is not yet clear [21].

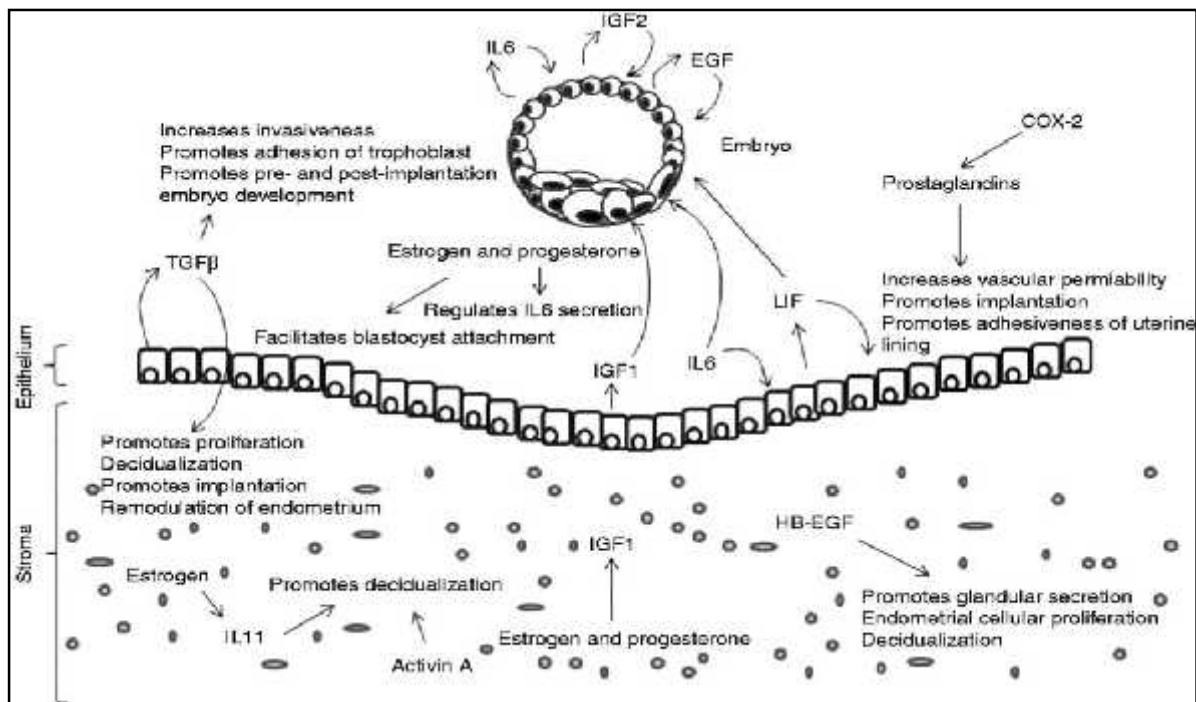


Figure 7. The role of hormones, growth factors, and cytokines in the implantation process [15]

Heparin-binding EGF is thought to play a role in the implantation process because it is only secreted by cells at a potential site for implantation in mice, namely on the epithelial surface of the uterine cavity. In addition, HB-EGF is able to stimulate trophoblast growth and blastocyst attachment sites. Trophoblasts for this growth factor and IL-1 are

required to maintain the uterus in an embryo-receptive stage. If there is no IL-1 receptor or IL-1 receptor is not functioning, there will be no adhesion between the uterus and the trophoblast. It has been suggested that the process of adhesion and subsequent invasion of the endometrium involves adhesion molecules [21].

Another group of growth factors that are known to play an active role in the implantation process is the transforming growth factor (TGF). TGF is a molecule that plays an active role in cellular modulation of endometrial cells to carry out the process of proliferation, decidualization and implantation. TGF 1 group is known to increase the adhesiveness of planting trophoblast cells in the extracellular matrix endometrium. Singh et all suggested that abnormalities in the TGF expression process can lead to implantation failure and pregnancy in humans [21].

Conclusion

The implantation event is a complex process involving many factors. The implaintation process is a very crucial and important stage in the event of pregnancy. Research with human samples is generally limited to tissue and embryo biopsy with the consent of a patient undergoing an in vitro fertilization program. Research on the implantation process, communication between the embryo and the endometrium is mostly carried out using experimental animals because research uses human samples related to more complex ethical issues and techniques.

These studies have found many factors which are responsible for the implantation process and its physiological mechanisms. However, this will develop more over time.

Therefore, molecular studies using high end technology to determine which genes are involved in the implantation process need to be carried out. The results are expected to be able to increase the success of the engineering process in reproduction so that it can become a bright spot for infertile couples to have offspring.

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