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Mini Review

Implantation: A Multifactorial Process that Affects IVF Success Rates

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Abstract

The success rate after treatment by *in vitro* fertilization (IVF) is greatly depended upon cooperation of a suitably primed endometrium and the fertilized oocyte, which is at the blastocyst stage. Low pregnancy rates after *in vitro* fertilization are attributed to a failed implantation procedure. In this review article the various parameters which play a fundamental role in implantation are described.

Keywords: *Implantation; Blastocyst; Endometrium*

Introduction

The embryo implantation stage is a complex process that requires the mutual interaction of a suitably primed endometrium and the penetration of the blastocyst. Low pregnancy rates after *in vitro* fertilization are attributed to a failed implantation procedure. On the contrary, the implantation is called successful when the blastocyst arrives at the suitable time frame implantation window when the endometrium is properly adapted and developed to become receptive to the blastocyst developmental processes [1]. The assessment of endometrial function in terms of receptivity *in vitro* Fertilization (IVF) cycles is, however, a highly controversial issue as to date no explicit marker of receptivity has been defined. This review depicts the cellular and molecular events that coordinate this complex process and highlight recent advances in this area of reproductive medicine.

Process of Implantation

Regarding the implantation stage in particular, steroid hormones play an important role in the coordination of the blastocyst and the endometrium. A necessary requirement for the implantation is the increased secretion of estradiol before ovulation, as at the given time the high concentration thereof contributes to the division and differentiation of the epithelial cells of the uterus. At the same time, the constantly increasing progesterone promotes the division and differentiation of stromal cells whose results in the transition of the endometrium to secretory and therefore able to achieve implantation [2].

The implantation process in humans can be presented as a gradual progress including the phase of apposition, attachment and finally of guided interaction between trophoblast and epithelial endometrial cells. Implantation can be divided in distinct stages related to the development of the hatching embryo and its interaction with the endometrial cells. In the human species, the embryo enters the endometrial cavity 72-96 hours after fertilization. The escape from the transparent zone is performed on the fifth day (approximately 110-120 hours after ovulation). The apposition, as well as, the attachment process is followed by the epithelial penetration process, thus signalling the beginning of stage 5 of implantation. Even though the mechanism of blastocyst penetration to the surface of the epithelium has not been fully investigated, it is certain that the determinant factor is the presence of endometrial receptors, as well as of necessary enzymes, cytokines, chemokines, other gene products and the presence of adhesion molecules [3,4].

The acquisition of special proteins on the endometrial surface and the embryonic epithelium is of vital importance for the promotion of the placentation process. The nature of the specific bio-indicators of endometrial receptivity proves that the processes of apposition-attachment are promoted through the interaction between attachment molecules and the components of the extracellular matrix (ECM). As soon as the embryo acquires an expanded trophoblast layer, the cells of the syncytiotrophoblast penetrate through the basic membrane in the lower layer and continue to multiply. As soon as the process of attachment and penetration of the embryo are achieved, access to the endometrial vascular system is the first priority [5].

By the time, the increase in size and metabolism of syncytiotrophoblast require increased quantities of oxygen and nutrients in relation to a better management of cell waste, thus achieving a longer term survival. Finally, the cells of syncytiotrophoblast begin their penetration to the vascular system of the woman so achieving their integration to the vascular system wall, while at the same time they ensure access to the endometrial feeding sources.

The cooperation between the activated blastocyst with the now receptive endometrium depends on many factors. To begin with, catechol estrogens (4-hydroxyestadial-17B) as well as the increasing secretion of chorionic gonadotropin play an important role in the production of steroid hormones thus maintaining the secretion of progesterone and facilitating the penetration of the blastocyst. Platelet-activating factor (PAF), heparin binding EGF - like growth factor (HB-EGF) and HSPG heparin sulfate proteoglycan (HSPG) are of great importance, since through their connection to the EGF promote the division and maturation of the blastocyst [6].

The production of prostaglandins is a necessary requirement for a successful implantation. More specifically, the COX enzyme is responsible for the transformation of the arachidonic acid to prostaglandins and it appears in two forms COX-1 and COX-2. The latter is directly related to the implantation process as well as to the presence of blastocyst. The genes of this enzyme, which is so necessary for the implantation are promoted through interleukin-1, while metalloproteinase-9 holds an assisting part as well. With the penetration of the blastocyst, the attachment receptors significantly decrease, while the receptors of the vascular cells increase, so facilitating the contact of embryonic cells with those of the mother and transformation of these cells to vascular with the higher aim of penetrating the uterus [6].

Finally, proteinases, catapsinases B and C integrins and growth factors IGF-1, IGF-2, play a determinant role, while the most important metalloproteinase-3 contributes mostly to diminish negative issues such as hemorrhage and placental abruption, as it promotes and postpones at the same time the penetration of the blastocyst, thus indicating the proper position in the endometrium and deterring the aforementioned negative results [6].

A further vital factor for the success of the implantation is the immunological factor. In particular, the fertilized oocyte constitutes a foreign body due to the genetic differentiation by half from the woman. The crucial point for the smooth outcome of the implantation is that the embryo when implanted is not identified by the mother's immunological mechanisms and therefore is not rejected.

The main cause for this condition is the trophoblast, which contributes to the deactivation of immunological mechanisms, due to the direct contact with the uterine tissue and the uterine immune system. This deactivation is achieved because of the expression of the HLA-G molecules, which protect the trophoblast cells from the dissolution that the uterine NK (natural killer) cells would cause under different conditions.

A second possible explanation is the lack of immunological elaboration by the anatomic part of the decidua of the uterus. This is the result of the presence of the NK CD56+ lymphocytes. These lymphocytes are characterized by decreased cytotoxicity compared to those of the peripheral blood. The suspended cytotoxicity is the result of the action of cytokines (produced by the blastocyst) as well as of the steroid hormones and progesterone. Finally, the corticotropin releasing hormone (CRH), which is expressed by the epithelial and stromal cells of the endometrium plays an important role and participates in the suspension of immunological processes so as to achieve a successful implantation stage [5,6].

Conclusion

Synchronization between blastocyst development and the acquisition of endometrial receptivity is a prerequisite for the success of IVF. Human embryo implantation should be considered a three-stage process, which includes apposition, adhesion and invasion. Although the recent discovery of molecules crucial for successful embryo implantation has offered new insights into this issue, focus on functional rather than the morphological characteristics of endometrial receptivity may give the answer for a successful embryo implantation, thus improving the ability of specialists to treat infertility.

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