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The role of uterine natural killer (uNK) cells in the endometrium of infertile women

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Abstract

Subfertility is defined as delayed conception with low fertility, while infertility is defined as inability to conceive naturally within one year despite unprotected sexual intercourse. The endometrium is the inner layer of the uterus where the blastocyst attaches and grows. The content of the endometrium and the number of immune system cells therein can be associated with infertility. The fact that most of the lymphoid cells in the endometrium are uterine natural killer (uNK) cells has drawn attention to the immune system in infertility. However, the roles of uNK cells have not yet been fully elucidated. Studies suggest that uNK cells, members of the lymphoid system, may play an important role in implantation and pregnancy. Although the high number of these cells, which are important for implantation and the continuation of pregnancy, is associated with infertility, there are also studies suggesting that there is no relationship between them. In our study, it was aimed to investigate studies examining the relationship of uNK cells with subfertility and infertility.

Introduction

Implantation occurs when the blastocyst adheres to and subsequently invades the endometrium during the implantation window that occurs in the late secretory stage of the endometrium. Successful implantation of the blastocyst into the endometrium is important for the continuation of the pregnancy. During implantation, adhesion molecules, various cytokines, growth factors and hormones are secreted. When these events are out of sync, implantation may fail [1,2]. Subfertility is defined as having low reproductive capacity and delay in getting pregnant, while infertility is defined as the inability to conceive naturally within one year despite unprotected sexual intercourse. The most common cause of subfertility is the mother's ovulation problem. At the beginning of ovulation problems are polycystic ovary syndrome (PCOS), advanced maternal age, decreased ovarian reserve due to medical reasons such as chemotherapy and hormonal problems. However, tubal uterine obstruction, endometriosis, inflammatory pelvic disease, gonorrhea, chlamydia infection, problems related to sperm structure and function have been associated with subfertility and infertility. Recent studies have shown that the framework of the endometrium, the adhesion molecules secreted and the number of immune system cells therein may be associated with subfertility and infertility. The presence of uterine Natural Killer cells, one of the immune system cells, in the endometrium shows that there is a relationship between infertility and the immune system. Natural Killer cells, which are members of the innate immune system, destroy tumor cells and virus-infected cells. They constitute 10% of the lymphocytes in the peripheral blood. These cells, which are morphologically characterized by their large cytoplasm containing azurophilic granules, can lyse cells without the need for immunoglobulin molecules. It is thought that increased blood levels of NK cells in women may affect implantation [3,4]. Most of the uNK cells consist of CD16-/CD56+ cells. These cells are called bright cells and they secrete cytokines. During pregnancy, uNK cells are involved in many important events such as the formation of the vascular structure of the placenta and trophoblast cells, as well as immune tolerance [5,6,7]. The number of natural killer cells in the uterus during the menstrual cycle may vary depending on the hormones secreted. In a study, it was observed that the number of uNK cells was highest in the early pregnancy period from the secretory phase to the late luteal phase [8]. These cells are found in areas very close to the implantation site during pregnancy, and studies have shown

that uNK cells are closely associated with trophoblasts. When pregnancy does not occur, uNK cells are destroyed by apoptosis. For a healthy pregnancy development, fetal trophoblasts invade the endometrium, move into the maternal arteries and provide blood flow to meet the needs of the fetus. If the invasion of trophoblasts does not occur adequately, pregnancy results in miscarriage or preeclampsia. In the literature, there are studies examining the functions of uNK cells in recurrent implantation failures. Some studies have found a high rate of abnormal expression of uNK cells and antigens in the endometrium of women with recurrent implantation failure. *In vitro* studies of endometrial specimens from women with recurrent implantation failure have demonstrated an increase in CD56 antigen immunohistochemically [9,10]. However, NK cell receptors and cytokines in peripheral blood and endometrium are very important for the implantation and maintenance of pregnancy [11]. uNK cells are large granular T lymphocytes located in the endometrium. Peripheral blood and uterine NK cells, which are known to have common CD56 antigens on their surfaces, differ according to the antigens they do not have on their surfaces. uNK cells do not have CD16 and CD3 antigens, whereas peripheral blood NK cells have these antigensNK cells are grouped as CD16+CD56d and CD16−CD56b. CD16−CD56b are cells found in the decidual endometrium. And it lacks the bright antigen and its receptors, which are usually found on lymphocytes involved in host defense [12]. Although it is argued that uNK cells migrate from the bone marrow and settle in the endometrium, there is controversy about their excessive proliferation in the endometrium before implantation. In this regard, it is more prevalent that approximately 50% of uNK cells are proliferative and reproduce themselves after migrating from the peripheral blood to the endometrium. These cells are particularly maximized in the mid, late luteal phase and early pregnancy endometrium [13]. In one study, an increase in genes controlling the proliferation of uNK cells was observed in the luteal phase endometrium [14]. uNK cells appear to be located around blood vessels, usually found in the endometrial stroma. Therefore, these cells are thought to be involved in the decidualization of the endometrial stroma or the remodeling of spiral arteries [15]. There is an opinion that the increased number of uNK cells in early pregnancy and their proximity to trophoblasts ensure that the fetus is not perceived as foreign by the mother and does not cause miscarriage [16]. uNK cells adjacent to fetal trophoblasts during early pregnancy express receptors that can recognize specific antigens on the surface of trophoblasts. It was observed that uNK cells in the mid-luteal phase of the endometrial cycle increased under the influence of progesterone and came to the uterus. Although uNK cells do not have progesterone receptors, they do contain prolactin, estrogen β and glucocorticoid receptors. Estrogen attracts cells to the uterus, while prolactin promotes the maturation and differentiation of cells. When uNK cells interact with trophoblasts, important cytokines such as Transforming Growth Factor Beta (TGFβ), Leukemia Inhibitory Factor (LIF) and Tumor Necrosis Factor-alpha (TNF-α) are released. These cytokines act on placental development and angiogenesis and show activation or inhibition properties.

uNK cells act as master regulators of decidual angiogenesis and control oxygen tension at the maternal-fetal interface [17]. It is thought that the endometrium is as effective as the blastocyst in implantation. In some studies, investigating the role of uNK cells in implantation, an increased number of uNK cells was observed in the endometrial stroma of preimplantation women [18,19]. Studies showing that the density of uNK cells can increase the angiogenesis factor suggested that increased and decreased decidual angiogenesis levels are associated with implantation failure and pregnancy loss. Some investigators point out that excessive accumulation and aggregation of uNK cells in the endometrium may cause dysfunction in the endometrium and a disordered environment of the stroma.

Material and Method

Electronic databases, Science Direct, Pubmed, Medline, Embase and Web of Science were searched. All searches were made from 1999 to February 2023. Keywords were infertility, subfertility, Natural killer cell, uterine natural killer cell, IVF, intracytoplasmic sperm injection (ICSI), embryo implantation, implantation failure, recurrent implantation failures (RIF) and recurrent pregnancy loss. There was no language restriction when searching for articles. All collected research and review articles formed the reference list.

Discussion

Infertility can occur depending on female, male and embryo factors. Genetic diseases, endocrine disorders, infectious diseases and immunological disorders can be shown among the reasons for the failure of embryo implantation. Although people diagnosed with infertility can enter the pregnancy process with *in vitro* fertilization (IVF) treatment, recurrent implantation failures in some patients negatively affect couples both financially and psychologically. For this reason, providing early prognostic markers and optimal options can contribute more positively to patients. The presence of uNK cells, one of the immune system elements in the endometrium, has recently attracted attention in reproductive physiology. In some studies examining implantation failure, an increase in the presence of uNK cells in the endometrium was observed before pregnancy. The presence of uterine Natural killer cells at the interface of the endometrium and trophoblast also suggests that trophoblasts may become targets for Natural killer cells during the implantation process. The proximity of uNK cells to trophoblasts

suggested that they could recognize trophoblasts fetally and regulate invasion [20,21,22]. However, a study showed that uNK cells are reduced before menstruation and there is also a decrease in the factors that protect the vasculature, which triggers menstrual disruption [23,24]. uNK cells regulate spiral arteries in the maternal-fetal bed by producing various angiogenic factors [25,26]. In a study, significant immunohistochemical differences were found in NK cells in endometrial samples, and it was stated that it would be important to establish a clinical standard for counting these cells [27,28]. In another study on NK cells, it was stated that immune tolerance is not limited to the decidua, but also affects the innate immune system in the periphery. Accordingly, they observed that T-helper 1 (Th1) cell-directed negative changes, one of the subcomponents of NK cells, were observed in blood samples before *in vitro* fertilization (IVF) and 1 week after IVF [29].

Conclusion

In recent years, there are studies that take attention to the fact that the presence of uterine Natural killer cells in the endometrium may take a role in the implantation process and at the same time, take part in the activity of trophoblasts in the maternal tissue. They stimulate growth in early development by synthesizing cytokines and remodeling maternal spinal arteries and providing trophoblast adhesion. However, an excessive increase in the number of uNK cells may also cause recurrent pregnancy loss. The pathophysiology of uNK cells in infertility and subfertility has not yet been fully elucidated. Therefore, there is a need for more preimplantation studies, especially measuring the levels of uNK cells at the molecular level and investigating them immunohistochemically

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