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Functions of uNK cells in endometrium of subfertile and infertile women

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Abstract

Infertility is defined as the lack of ability to get pregnant 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. Most of the lymphoid cells found in the endometrium are uterine natural killer (uNK) cells. This 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 act 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. Although peripheral NK cells fight tumor and virus-infected cells, it has been shown that uNK cells do not fight with trophoblasts, they take part a role in the invasion and vascularization process, and their number increases in early pregnancy.

1. 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. Continuation of pregnancy depends on successful implantation of the blastocyst into the endometrium. During implantation, adhesion molecules, various cytokines, growth factors and hormones are secreted. When these events are out of sync, implantation may fail [1,2]. Low reproductive capacity, delayed conception, and inability to conceive within one year despite unprotected sexual intercourse are associated with subfertility and infertility.

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. Uterine Natural Killer (uNK) cells are immune system cells. The presence of these cells in the endometrium indicates a relationship between reproduction and the immune system. Natural Killer cells, members of the innate immune system, fight virus infected cells and tumor 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. Throughout pregnancy, uNK cells are involved in important events like immune tolerance, formation of placental vasculature, and association with trophoblast cells [5-7]. The density of uNK cells during the menstrual cycle may vary depending on the type of hormone secreted. In a study, it was noticed that the density 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 antigens NK 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 uterine NK cells transmigrate 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]. The increasing density of uNK cells in the early period of pregnancy and the proximity of these cells to trophoblasts are important in terms of not recognizing the fetus as foreign and preventing miscarriage [16]. uNK cells adjacent to fetal trophoblasts during early pregnancy express receptors that can recognize particular 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 LIF (Leukemia Inhibitory Factor), TGFβ (Transforming Growth Factor Beta) and TNF-α (Tumor Necrosis Factor-alpha) are released. These cytokines act on placental development and angiogenesis and show activation or inhibition properties. uNK cells regulate vessel formation and oxygen tension in this region during decidualization [17]. It is thought that the endometrium is as effective as the blastocyst in implantation. uNK cells were first identified in the uterine stroma of pregnant rodents. These cells, which were subsequently shown in the human endometrium, were named endometrial stromal granulocytes. 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 may cause dysfunction in the endometrium and a disordered environment of the stroma.

2. Material and Method

In this study, uNK Cells in the endometrium of infertile women were investigated. Previous studies have been examined by conducting a literature review between 1999 to February 2023. infertility, subfertility, Natural killer cell, uterine natural killer cell, IVF, intracytoplasmic sperm injection (ICSI), embryo implantation, implantation failure, recurrent implantation failures and recurrent pregnancy loss. There was no language restriction when searching for articles. All collected research and review articles formed the reference list.

3. 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 uterine NK cells, one of the immune system elements in the endometrium, has recently attracted attention in reproductive physiology uterine NK cells are unlike peripheral NK cells. Peripheral NK cells fight tumor cells and virus-infected cells, while uNK cells play a role in embryo implantation and vascular shaping during trophoblast invasion in the desudialyzed endometrium. In some studies, examining implantation failure, an increase in the presence of uNK cells in the endometrium was observed before pregnancy. The presence of uNK 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 [20-22]. 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]. The relationship between the density of uNK cells and the menstrual phase varies depending on the type of hormones secreted. Until now, it was known that uNK cells do not carry steroid hormone receptors. In a study, it was shown that these cells synthesize the estrogen receptor (ER) variant, ER-b. Although they express the ER, they do not express the progesterone receptor (PR). Despite the absence of expression of PR, the effect of progesterone on uNK cells suggests that this hormone indirectly affects cells. It has been shown that stromal cells affected by progesterone hormone in the decidualized endometrium secrete cytokines and that the secreted cytokines affect uNK cells [30].

Progesterone level drops when pregnancy does not occur. Since progesterone will no longer affect the stromal cells, the number of secreted cytokines will decrease and cause the loss of uNK cells. It has been shown in some studies that stromal cells secrete interleukin-15 (IL15) and this molecule stimulates uNK cells to initiate vascular remodelling (Figure1). uNK cells persist for 8 weeks in the endometrium of pregnancy. uNK cells are thought to regulate the vasculature during the invasion of trophoblast [31,32]. In another study, it was observed that women with heavy menstrual bleeding had an increase in CD56b uNK cells in their endometrial mucosa compared to healthy women [33]. Vascular formation and development during trophoblast invasion are very important in preventing the development of preeclampsia. If vascular development and placentation are insufficient, preeclampsia is likely to develop. For this reason, it is thought that there is a relationship between uNK cells and preeclampsia [34,35]. When an ectopic pregnancy occurs, uNK cells interact with trophoblasts and inhibit vascularization to reduce placentation. The invasion of trophoblast into the decidualized endometrium is one of the most important processes. In this process, uNK cells secrete certain growth factors [36]. These secreted factors are regulated to sustain or inhibit tarophoblast invasion. However, there are studies showing that there is a relationship between vascular development and pregnancy loss [37,38].

uNK cells produce growth factors and cytokines. These cells regulate vessel formation and trophoblast invasion. In order to regulate these functions, a large number of cytokines and growth factors are secreted from trophoblast cells, decidua endometrium cells and uNK cells [39]. LIF (Leukemia Inhibitory Factor), TNF-α (Tumor Necrosis Factor-alpha), VEGF (Vascular Endothelial Growth Factor), G-CSF (Granulocyte Colony Stimulating Factor) secreted in this process. Interferon-c, AngI, AngII are important molecules for vascularization and maintenance of pregnancy. Levels of factors secreted by uNK cells vary throughout pregnancy. AngI and AngII factors and VEGF were observed at higher levels in the first weeks of pregnancy because they are involved in vascularization. It was observed that their levels decreased in the following periods. Trophoblast cells invade the endometrium as invading cells such as tumor cells. But uNK cells do not fight this invasion. On the contrary, they interact with trophoblast cells [40]. Some studies have shown that uNK cells can be derived from precursors of CD34(+) cells located in the endometrium. The roles of uNK cells in recurrent miscarriages and recurrent implantation failures have not yet been fully elucidated. Some studies have indicated that uNK cells have physiologically active roles in the initiation and maintenance of pregnancy. Therefore, corticosteroids that suppress NK cell activity may increase implantation and pregnancy failure. In addition, the evaluation of uNK cells in the menstrual blood of women with important diseases such as preeclampsia is an important factor. It is thought that the transfer of uNK cells may be important in the future to treat reproductive diseases [41].

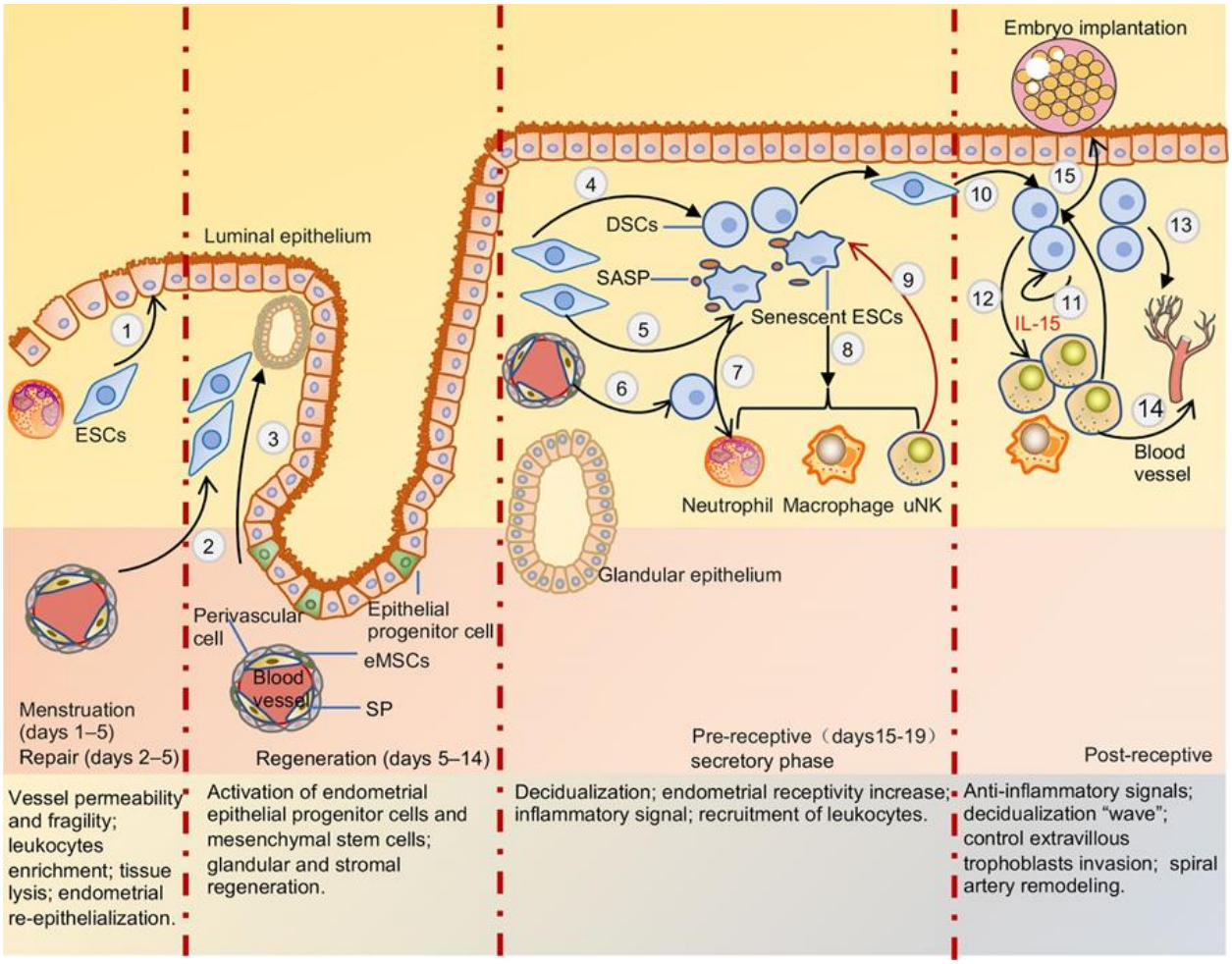

Figure 1. Menstruation, pre-receptive and post-receptive endometrium.

Proteolytic enzymes are produced when blastocyst implantation into the endometrium does not occur. Inflammatory cells proliferate in the medium and tissue destruction occurs (1). After menstruation, stroma and epithelial cells are reshaped from stem cells in the non-shedding basal layer of the endometrium (2,3). Towards the end of the secretory phase endometrial cells differentiate into decidual cells (4,5,6). Some cytokines secreted from decidual cells pull leukocytes towards the environment (7,8). uNK cells can assist in the conversion of endometrial proinflammatory signals into anti-inflammatory signals and facilitate blastocyst adhesion (9,10,11,12,13,14). Cytokines secreted by decidual cells after blastocyst implantation, especially (IL-15), can support the proliferation of uNK cells, interacting with torphoblasts, and remodeling of vessels [42].

4. 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. This review explores the roles of uNK cells in the endometrium and infertility. Although NK cells fight tumor and virus-infected cells, uterine NK cells do not fight trophoblasts, but play a regulatory role. It has been shown that in the late phase of implantation, the density of these cells increases and in the early stages of pregnancy during the invasiveness of trophoblasts. In recent studies, it has been stated that uterine NK cells do not have cytotoxic effects like peripheral NK cells, and they play an important role in vascularization and placentation in the early stages of pregnancy.

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Conflicts of interest

The authors declare no conflicts of interest.

References

1. Mariee, N., Li, T. C., & Laird, S. M. (2012). Expression of leukemia inhibitory factor and interleukin 15 in endometrium of women with recurrent implantation failure after IVF; correlation with the number of endometrial natural killer cells. *Human reproduction*, *27*(7), 1946-1954.
2. Kolanska, K., Suner, L., Cohen, J., Ben Kraiem, Y., Placais, L., Fain, O., ... & Mekinian, A. (2019). Proportion of cytotoxic peripheral blood natural killer cells and T-cell large granular lymphocytes in recurrent miscarriage and repeated implantation failure: case–control study and meta-analysis. *Archivum immunologiae et therapiae experimentalis*, *67*, 225-236.
3. Shaulov, T., Sierra, S., & Sylvestre, C. (2020). Recurrent implantation failure in ivf: A canadian fertility and andrology society clinical practice guideline. *Reproductive biomedicine online*, *41*(5), 819-833.
4. Kolanska, K., Bendifallah, S., Cohen, J., Placais, L., Selleret, L., Johanet, C., ... & Mekinian, A. (2021). Unexplained recurrent implantation failures: Predictive factors of pregnancy and therapeutic management from a French multicentre study. *Journal of Reproductive Immunology*, *145*, 103313.
5. Quenby, S., Nik, H., Innes, B., Lash, G., Turner, M., Drury, J., & Bulmer, J. (2009). Uterine natural killer cells and angiogenesis in recurrent reproductive failure. *Human reproduction*, *24*(1), 45-54.
6. Erbaş, H., & Çetin, T. (2009). Tekrarlayan gebelik kaybı olan olgularda endometriyal CD 56+ Natural Killer hücrelerin araştırılması, Uzmanlık Tezi, Adana, Turkey.
7. Fukui, A., Funamizu, A., Fukuhara, R., & Shibahara, H. (2017). Expression of natural cytotoxicity receptors and cytokine production on endometrial natural killer cells in women with recurrent pregnancy loss or implantation failure, and the expression of natural cytotoxicity receptors on peripheral blood natural killer cells in pregnant women with a history of recurrent pregnancy loss. *Journal of Obstetrics and Gynaecology Research*, *43*(11), 1678-1686.
8. Sfakianoudis, K., Rapani, A., Grigoriadis, S., Pantou, A., Maziotis, E., Kokkini, G., ... & Simopoulou, M. (2021). The role of uterine natural killer cells on recurrent miscarriage and recurrent implantation failure: From pathophysiology to treatment. *Biomedicines*, *9*(10), 1425.
9. Tuckerman, E., Mariee, N., Prakash, A., Li, T. C., & Laird, S. (2010). Uterine natural killer cells in peri-implantation endometrium from women with repeated implantation failure after IVF. *Journal of reproductive immunology*, *87*(1-2), 60-66.
10. Lédée-Bataille, N., Dubanchet, S., Coulomb-L'hermine, A., Durand-Gasselin, I., Frydman, R., & Chaouat, G. (2004). A new role for natural killer cells, interleukin (IL)-12, and IL-18 in repeated implantation failure after *in vitro* fertilization. *Fertility and sterility*, *81*(1), 59-65.
11. Fukui, A., Funamizu, A., Yokota, M., Yamada, K., Nakamua, R., Fukuhara, R., ... & Mizunuma, H. (2011). Uterine and circulating natural killer cells and their roles in women with recurrent pregnancy loss, implantation failure and preeclampsia. *Journal of reproductive immunology*, *90*(1), 105-110.
12. Quenby, S., & Farquharson, R. (2006). Uterine natural killer cells, implantation failure and recurrent miscarriage. *Reproductive biomedicine online*, *13*(1), 24-28.
13. Bulmer, J. N., & Lash, G. E. (2005). Human uterine natural killer cells: a reappraisal. *Molecular immunology*, *42*(4), 511-521.
14. Clifford, K., Flanagan, A. M., & Regan, L. (1999). Endometrial CD56+ natural killer cells in women with recurrent miscarriage: a histomorphometric study. *Human reproduction*, *14*(11), 2727-2730.
15. Amrane, S., Brown, M. B., Lobo, R. A., & Luke, B. (2018). Factors associated with short interpregnancy interval among women treated with *in vitro* fertilization. *Journal of Assisted Reproduction and Genetics*, *35*, 1595-1602.
16. Croy, B. A., He, H., Esadeg, S., Wei, Q., McCartney, D., Zhang, J., ... & Yamada, A. T. (2003). Uterine natural killer cells: Insights to their cellular and molecular biology from mouse modelling. *Reproduction (Cambridge, England)*, *126*(2), 149.

17. King, A. (2000). Uterine leukocytes and decidualization. *Human reproduction update*, *6*(1), 28-36.
18. Trundley, A., & Moffett, A. (2004). Human uterine leukocytes and pregnancy. *Tissue antigens*, *63*(1), 1-12.
19. Laird, S. M., Tuckerman, E. M., & Li, T. C. (2006). Cytokine expression in the endometrium of women with implantation failure and recurrent miscarriage. *Reproductive biomedicine online*, *13*(1), 13-23.
20. Naruse, K., Lash, G. E., Innes, B. A., Otun, H. A., Searle, R. F., Robson, S. C., & Bulmer, J. N. (2009). Localization of matrix metalloproteinase (MMP)-2, MMP-9 and tissue inhibitors for MMPs (TIMPs) in uterine natural killer cells in early human pregnancy. *Human reproduction*, *24*(3), 553-561.
21. Tang, A. W., Alfirevic, Z., & Quenby, S. (2011). Natural killer cells and pregnancy outcomes in women with recurrent miscarriage and infertility: a systematic review. *Human reproduction*, *26*(8), 1971-1980.
22. King, A., & Loke, Y. W. (1999). The influence of the maternal uterine immune response on placentation in human subjects. *Proceedings of the Nutrition Society*, *58*(1), 69-73.
23. Igarashi, T., Konno, R., Okamoto, S., Moriya, T., Satoh, S., & Yajima, A. (2001). Involvement of granule-mediated apoptosis in the cyclic changes of the normal human endometrium. *The Tohoku Journal of Experimental Medicine*, *193*(1), 13-25.
24. Li, X. F., Charnock-Jones, D. S., Zhang, E. K. O., Hiby, S., Malik, S., Day, K., ... & Smith, S. K. (2001). Angiogenic growth factor messenger ribonucleic acids in uterine natural killer cells. *The Journal of Clinical Endocrinology & Metabolism*, *86*(4), 1823-1834.
25. Craven, C. M., Morgan, T., & Ward, K. (1998). Decidual spiral artery remodelling begins before cellular interaction with cytotrophoblasts. *Placenta*, *19*(4), 241-252.
26. Hanna, J., Goldman-Wohl, D., Hamani, Y., Avraham, I., Greenfield, C., Natanson-Yaron, S., ... & Mandelboim, O. (2006). Decidual NK cells regulate key developmental processes at the human fetal-maternal interface. *Nature medicine*, *12*(9), 1065-1074.
27. Tohma, Y. A., Musabak, U., Gunakan, E., Akilli, H., Onalan, G., & Zeyneloglu, H. B. (2020). The role of analysis of NK cell subsets in peripheral blood and uterine lavage samples in evaluation of patients with recurrent implantation failure. *Journal of Gynecology Obstetrics and Human Reproduction*, *49*(9), 101793.
28. Lash, G. E., Bulmer, J. N., Li, T. C., Innes, B. A., Mariee, N., Patel, G., ... & Laird, S. M. (2016). Standardisation of uterine natural killer (uNK) cell measurements in the endometrium of women with recurrent reproductive failure. *Journal of reproductive immunology*, *116*, 50-59.
29. Miko, E., Manfai, Z., Meggyes, M., Barakonyi, A., Wilhelm, F., Varnagy, A., ... & Szereday, L. (2010). Possible role of natural killer and natural killer T-like cells in implantation failure after IVF. *Reproductive biomedicine online*, *21*(6), 750-756.
30. Okada, H., Nakajima, T., Sanezumi, M., Ikuta, A., Yasuda, K., & Kanzaki, H. (2000). Progesterone enhances interleukin-15 production in human endometrial stromal cells in vitro. *The Journal of Clinical Endocrinology & Metabolism*, *85*(12), 4765-4770.
31. Moffett, A., & Colucci, F. (2014). Uterine NK cells: active regulators at the maternal-fetal interface. *The Journal of clinical investigation*, *124*(5), 1872-1879.
32. Robson, A., Harris, L. K., Innes, B. A., Lash, G. E., Aljunaidy, M. M., Aplin, J. D., ... & Bulmer, J. N. (2012). Uterine natural killer cells initiate spiral artery remodeling in human pregnancy. *The FASEB Journal*, *26*(12), 4876-4885.
33. Shivhare, S. B., Bulmer, J. N., Innes, B. A., Hapangama, D. K., & Lash, G. E. (2015). Menstrual cycle distribution of uterine natural killer cells is altered in heavy menstrual bleeding. *Journal of reproductive immunology*, *112*, 88-94.
34. Wallace, A. E., Whitley, G. S., Thilaganathan, B., & Cartwright, J. E. (2015). Decidual natural killer cell receptor expression is altered in pregnancies with impaired vascular remodeling and a higher risk of pre-eclampsia. *Journal of Leukocyte Biology*, *97*(1), 79-86.
35. Burton, G. J., Woods, A. W., Jauniaux, E., & Kingdom, J. C. P. (2009). Rheological and physiological consequences of conversion of the maternal spiral arteries for uteroplacental blood flow during human pregnancy. *Placenta*, *30*(6), 473-482.
36. Robson, A., Lash, G. E., Innes, B. A., Zhang, J. Y., Robson, S. C., & Bulmer, J. N. (2019). Uterine spiral artery muscle dedifferentiation. *Human Reproduction*, *34*(8), 1428-1438.
37. Ball, E., Bulmer, J. N., Ayis, S., Lyall, F., & Robson, S. C. (2006). Late sporadic miscarriage is associated with abnormalities in spiral artery transformation and trophoblast invasion. *The Journal of Pathology: A Journal of the Pathological Society of Great Britain and Ireland*, *208*(4), 535-542.
38. Chen, X., Liu, Y., Cheung, W. C., Zhao, Y., Huang, J., Chung, J. P. W., ... & Li, T. C. (2018). Increased expression of angiogenic cytokines in CD56+ uterine natural killer cells from women with recurrent miscarriage. *Cytokine*, *110*, 272-276.
39. Lala, P. K., & Chakraborty, C. (2003). Factors regulating trophoblast migration and invasiveness: possible derangements contributing to pre-eclampsia and fetal injury. *Placenta*, *24*(6), 575-587.
40. Colucci, F. (2017). The role of KIR and HLA interactions in pregnancy complications. *Immunogenetics*, *69*(8-9), 557-565.

41. Díaz-Hernández, I., Alecsandru, D., García-Velasco, J. A., & Domínguez, F. (2021). Uterine natural killer cells: from foe to friend in reproduction. *Human Reproduction Update*, *27*(4), 720-746.
42. Xie, M., Li, Y., Meng, Y., Xu, P., Yang, Y., Dong, S., ... & Hu, Z. (2022). Uterine natural killer cells: A rising star in human pregnancy regulation. *Frontiers in Immunology*, 2733.
43. Aksak, T. (2023). The role of uterine natural killer (uNK) cells in the endometrium of infertile women. *Advanced Engineering Days (AED)*, *6*, 38-41.