THE ROLE OF IMMUNE REGULATION AND IMMUNOMODULATION OF THE ENDOMETRIUM IN THE PREVENTION OF RECURRENT IMPLANTATION DISORDERS AND MISCARRIAGES

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Infertility affects 8 to 12% of couples in the world who are of reproductive age; of these, half seek medical help, and the other 22% undergo fertility treatments. An annual total of ART cycles are conducted because to the rising prevalence of infertility; 15% of patients have repeated implantation failures. As reported by ESHRE in 2018, the live birth rate (LBR) at the third attempt was 20.3% and 17.2% at the fourth attempt [1,2].

Human implantation is a three-stage process, including apposition, adhesion, and invasion. During the apposition phase, the blastocyst contacts the endometrium, mediated by adhesion molecules. The endometrium undergoes changes to prepare for implantation, providing nutrients and support. The apposition and adhesion phase is crucial for successful implantation.

Invasion occurs during the adhesion phase of implantation, where the blastocyst interacts with the endometrial surface, triggering inflammatory-like responses. This interaction triggers a cascade of events, including cytokines and chemokines, leading to the attachment of the blastocyst to the endometrium. This inflammatory response prepares for human invasion, involving the formation of endovascular extravillous trophoblasts (EVTs).

Understanding the pathophysiological mechanisms of infertility requires a comprehensive diagnostic approach that considers the complex nature of immune cells. Current diagnostic tests are simplistic and have limited clinical utility. To fully realize the promise of therapies targeting the uterine immune response, personalized approaches and specific diagnostic criteria are needed. A well-known individual in Europe named R. G. Edwards referred to the low implantation rate of transferred embryos as "the last barrier" in reproductive health [1-3].

The immune response is an important mediator in uterine receptivity, with transcriptional changes occurring in the midsecretory phase. Studies show that immune cells undergo dynamic changes, with immune cell and regulatory genes accounting for most transcriptional changes between prereceptive and receptive phases.

Predominantly uterine natural killer (uNK) cellsT cells, macrophages, and (DCs) dendritic cells play a crucial role in the uterine immune response, mediating quality control at implantation. Their interaction with nonimmune cells and trophoblast cells influences the implantation cascade, establishing receptivity and initiating pregnancy through modulating epithelial-embryo attachment, decidual transformation, and vascular adaptation [2-4].

Ingenuity pathway analysis (IPA) revealed molecular networks and pathways associated with genes differentially expressed in pregnant versus cyclic animals. The four most statistically significant canonical pathways identified by IPA were interferon signalling, complement system, role of pattern recognition receptors in the recognition of bacteria and viruses, and antigen presentation. These pathways contribute to the ability of embryos to survive in the maternal environment, highlighting the importance of innate immunity [5].

The pre-implantation period in Holstein-Friesian dairy cattle revealed a significant proportion of pregnancy losses due to the rapid elongation of embryos. Genome-wide transcriptional profiles of reproductive day 17 endometrial tissue were determined to understand the molecular mechanisms preventing luteolysis and embryo survival [3,4]

The ability of the embryo to survive in the maternal environment has been attributed to a number of mechanisms, including maternal immunological inertness to the conceptus or localized immune tolerance and antigenic immaturity of the conceptus (the bovine trophoblast, like other mammalian species, does not express classical polymorphic

major histocompatibility complex (MHC) class 1 proteins in areas in contact with the maternal endometrium during early pregnancy [5,6].

Genes related with pathways and biological networks that were differentially expressed in pregnant animals compared to cyclic animals were identified by Ingenuity Pathway Analysis (IPA).

Interferon stimulated genes (ISG) were found to be highly up-regulated in pregnant animals, indicating the production of the pregnancy recognition signal interferon tau (IFNτ). These genes may provide localized immune system suppression, allowing the embryo to survive within the uterus. IFITM1 and TAP-1, along with MHC I A and MHC I G, were also found to be up-regulated in pregnant animals. TAP proteins may be involved in local immune suppression, as they have been associated with the capacity of natural killer cells to be non-cytotoxic [7].

NK cells play a crucial role in the upregulation of OAS, a protein involved in the immune response during early pregnancy. This upregulation is linked to the production of osteopontin (SPP1), a gene that regulates the TH1/TH2 balance and apoptosis. Quantitative trait (QTL) analyses in pigs have identified SPP1 as a candidate gene for reproductive performance.

Several interleukins, such as IL-15 and IL-7, are upregulated in pregnant animals to increase the presence of immune tolerance-promoting T-reg cells in the uterus and shift the inflammatory balance towards an anti-inflammatory response. T-reg cells require low levels of some cytokines to differentiate from naive CD4+ T cell precursors, with high levels blocking suppression. Interleukin1β (IL-1β) and interleukin 18 (IL-18) are pro-inflammatory cytokines that were upregulated in pregnant animals, with inhibitors like IL-1RN and IL-18BP also up-regulated [8].

Genes involved in antimicrobial response Bacterial endotoxins are bound by proteins encoded by LBP and BPI. The antimicrobial gene LYZ1 was also up-regulated in pregnant animals, up 2.4 fold, and both were up-regulated 19 and 6 fold, respecttively. During a period of local immune suppression, which happens during pregnancy, increased expression of these genes in pregnant animals may provide innate immunological protection against possible bacterial infection [6].

Human fetuses are semi-allogeneic transplants, and maternal-fetal immune tolerance is crucial for successful pregnancy. CD4+ T cells, divided into Th1 cells, Th2 cells, regulatory T cells (Treg), and Th17 cells, play a significant role in this process. Th1 cytokines, such as interferon-γ, tumor necrosis factor (TNF) α, and interleukins (IL), are considered proinflammatory, while Th2 cytokines like IL4, IL6, IL-10, and granulocyte-macrophage colony stimulating factor control the proinflammatory action of Th1 cytokines. A dominant Th2 state is essential for establishing pregnancy.

The switch from Th1 to Th2 is more pronounced at the maternal-fetal interface, with Th2 cells accumulating in the decidua and uDCs driving naive T cells to become Th2 cells. Elevated progesterone concentrations cause Th2 dominance in early pregnancy. Increases in Th2 cytokines IL-4, IL-10, and monocyte colony stimulating factor in the peripheral blood and at the maternal-fetal interface are associated with successful pregnancy. Th2 cytokines are produced by trophoblast, decidua, amnion, macrophages, Tregs, and the placenta. Women with recurrent pregnancy losses have lower CRTH2+ cell expressions than those undergoing selective pregnancy terminations. Anti-inflammatory cytokines IL-4 and IL-10 inhibit Th1 cells and macrophages, preventing fetal allograft rejection [7].

Monocytes and macrophages play crucial roles in the menstrual cycle and pregnancy, regulating trophoblast activity and endometrial tissue remodeling. Pregnancy hormones indirectly modulate the recruitment of monocytes in the uterus, promoting their differentiation into functional macrophages. Intrauterine administration of PBMCs can also activate hCG--activated macrophages, regulating the uterine environment at the embryo implantation site. Immune events at implantation affect placental morphogenesis, influencing pregnancy viability and fetal development.

Studies show immune cell differences in women with recurrent implantation failure or miscarriage, suggesting analyzing immune cells in the uterus or peripheral blood could aid in infertility diagnosis. However, current evidence is insufficient to justify unproven interventions, and corticosteroids are inappropriate for women with autoimmune or autoinflammatory conditions.

Intravenous iG and targeted biologicals (e.g., [TNF] inhibitors) are examples of other treatments that modulate particular compartments of the immune response and may be helpful in some subsets of infertile women, but they do not show efficacy in other study cohorts.

Immune cells play a crucial role in uterine receptivity during the midsecretory stage of a viable cycle. During implantation, the blastocyst-stage embryo attaches to the epithelial lining, leading to trophoblast

cells entering the uterine stroma and stimulating decidual transformation. This process results in a mature placenta supporting the fetus until birth.

The early phase of placental development requires a transformation to support maternal blood flow and fetal growth. Infiltrating trophoblasts express HLA-C, a paternally inherited alloantigen. Maternal immune cells interact with these antigens, allowing trophoblasts to persist and develop in healthy pregnancy, promoting placental development [1,9].

HLA, along with trophoblast-derived signals, plays a crucial role in facilitating the immune response to fetal alloantigens, ensuring permissive and sustaining pregnancy.

This guarantees that when implantation starts, there will be enough immune cells living in the decidualized endometrium. During the proliferative and periovulatory stages, innate immune cells, in particular macrophages, DCs, and a distinct population of NK cells with a CD56hiCD57l° phenotype (uNK cells) increase in the endometrium.

Erlebacher and Guerin's reviews highlight the role of cells in endometrial receptivity, trophoblast invasion, and immune regulation. The adaptive immune response is crucial for pregnancy tolerance, with regulatory T cells (Treg cells) essential for implantation success. An imbalance between permissive Treg cells and inhibitory effector T cells can lead to implantation failure. Regulatory T cells exert anti-inflammatory, immune suppressive, and vasoregulatory functions.

Through the secretion of cytokines such as transforming growth factor β (TGFβ) and interleukin (IL)-10, they possess a strong ability to control and mitigate inflammation and preserve tissue homeostasis. Proinflammatory cytokines such TNF, IL-6, and IL-17 are released, Teff cell activity is suppressed, and the phenotypes of uNK cells, macrophages, DCs, and other innate immune cells are altered.

Decidual response, triggered by endometrial stromal fibroblasts, is important for successful implantation, occurring after every proliferative phase in ovulatory menstrual cycles, regardless of embryo presence. Decidual immune cells play a crucial role in implantation, influencing cell transformation and vascular bed remodeling. They interact with DCs, uNK cells, and trophoblasts, responding to hormonal triggers, particularly in invasive hemochorial placentation.

Treg cells play a crucial role in controlling inflammation in the decidual process, a process regulated by a sequence of immune cell recruitment. Their potent anti-inflammatory actions are essential for establishing a receptive decidual environment and facilitating endometrial receptivity in the days after conception.

Seminal fluid from the male partner most likely plays a role in the immunological response in females that underlies endometrial receptivity. Seminal fluid induces the production of cytokines that enhance immunological tolerance and advance embryo development when it contracts with the epithelial cells lining the female reproductive canal. These cells then express male alloantigens, which are subsequently produced by trophoblasts. Through a mechanism dependent on IL-11, seminal fluid factors also encourage decidual transformation of uterine fibroblasts. This offers a way for the composition of seminal fluid to "prime" the uterine immunological milieu. When a permissive response is elicited, this increases the chance of a successful implantation and a safe pregnancy.

A changed seminal fluid composition can lead to impaired Treg production and a less favorable environment for embryo development. When a sexually transmitted illness raises the amount of the cytokine interferon γ. Some couples experiencing infertility may have poor endometrial receptivity due to insufficient or incorrect seminal fluid priming.

Seminal plasma (SP) accounts for over 90% of semen volume and plays a crucial role in regulating immune tolerance, embryonic development, and implantation. Abnormal alterations in SP due to advanced age or poor diet can interfere with a woman's immune adaptation to pregnancy, negatively affecting embryo implantation and offspring health. Uterine pathologies like endometriosis and endometritis can cause the endometrium to respond negatively to SP. Research on the mechanism of SP in the endometrium can lead to new targets for intervention to improve reproductive outcomes and provide new ideas for semen-assisted treatment of clinical infertility. One thousand and seven hundred thirty-eight infertile patients had an immune profiling on a timed endometrial biopsy between 2012 and 2018. Result(s): After testing, 16.5% of the patients showed no endometrial immune dysregulation, 28% had a local immune under-activation, 45% had a local immune over-activation, and 10.5% had a mixed endometrial immune profile. However, in good prognosis IVF subgroups and patients using donor eggs, this difference was not significant. For patients with immune over-activation, pregnancy rates were significantly higher for those with a test of sensitivity regarding the type of immunotherapy introduced [8].

Control of reproductive quality and immune cells.

Endometrial immune cells are highly versatile and flexible, similar to other mucosal surfaces. Their abundance and phenotypic status determine their ability to acquire proinflammatory or anti-inflammatory functions and perform immune regulatory and tissue-remodeling roles. They respond to local microenvironmental signals, participating in implantation and early placentation stages. Under certain circumstances, they can transition from permissive activities to cytotoxic effects, limiting conceptus survival and placental development. T cells, uNK cells, macrophages, and DCs must acquire immune regulatory and anti-inflammatory phenotypes to support endometrial receptivity.

Dendritic cells, macrophages, and T cells are crucial immune cells for endometrial receptivity. They regulate immunological tolerance, affect uterine vascular adaptation, and regulate inflammatory activation. Maintaining endometrial receptivity requires a balance of phenotypes, with T cells, tolerogenic DCs, M2 macrophages, and M1 macrophages being essential. The immune system's role in quality control is supported by immune cell phenotypic plasticity, but persistent changes in immune cell morphologies can lead to infertility and repeated implantation failure [1,9].

Alloantigens (and other antigens) linked to seminal fluid, male and female gametes, and the conceptus are recognized by T cells and uNK cells, which then get activated and create memory in response. This characteristic may allow the immune system of the female to distinguish between various male partners and conception occurrences and react to them differently. This is probably going to play a big part in the "biosensor" function that the decidua are said to have, which allows the decidual cells to support or stop supporting distinct embryos based on the immunologic compatibility and chromosomal integrity of those embryos.

Immune cells play a crucial role in detecting and eliminating embryos during the peri-implantation phase. This mechanism ensures viable pregnancy under favorable conditions with compatible embryos. The complexity of immune response signaling netwoTreg cells, uNK cells, and stromal cell decidualization are critical immune cells for endometrial receptivity, influencing uterine epithelial attachment competence, trophoblast differentiation, and vascular adaptation. Depletion of these immune cells can lead to severe consequences for implantation and placental development complicates defining endometrial receptivity genes [1,10].

By interacting with other uterine immune cell subsets to alter the perivascular microenvironment and releasing cytokines—such as IL-8, TNF, vascular endothelial growth factor, IL-8, interferon γ, and placental growth factor—they are able to facilitate vascular development and remodeling. Moreover, they play crucial roles in the control of endometrial bleeding and the elimination of senescent decidual cells at the end of each menstrual cycle.

Measurement of these cells in women who have miscarried or experienced implantation failure has generated a great deal of attention as a diagnostic tool. An increased risk of repeat miscarriage and poor IVF outcomes was first believed to be associated with higher numbers of uNK cells and/or lower percentages of the distinctive CD56bright CD16– phenotype, with increasing CD56dim CD16+ cells. Following IVF, repeated implantation failure was not found to be associated with uNK cells, and the typical variation in luteal phase numbers was found to be a factor accounting for the variations in results between studies. uNK cells, which are crucial for cytokine secretion and fertility, are often overlooked in tests for fertility. Despite their importance, their relationship to fertility remains unclear. Examining peripheral blood NK cells in women with subfertility or recurrent implantation failure is concerning due to their phenotypic differences and the varying percentage of CD56+ NK cells in peripheral blood. Recent meta-analyses confirm the lack of robust evidence to support measuring uNK cells in peripheral blood or the uterus as clinically useful in predicting infertility or miscarriage [1,11].

The Luteal Phase's Hormonal Adaptation. For over-activated and mixed profiles, a modification of luteal support was advised. A healthy pregnancy depends on the local immunological tolerance that progesterone mediates. This is in addition to its endocrine function. There are several ways in which progesterone affects the mother's immune system: - By means of progesterone-induced blocking factor (PIBF) synthesis, which suppresses NK cell function and causes maternal lymphocytes to produce Th-2-dominant cytokines. By stimulating galectin-1, a progesterone-induced protein necessary for generating tolerogenic dendritic cells, which in turn encourages the in vivo proliferation of Treg cells that secrete IL-10.

Because progesterone suppresses the immune system, it is advised large daily vaginal dosages (1,200

mg) when a local immunological over-activation was identified. Also suggested oral estradiol supplementation (4 mg) to reduce the local expression of IL-18 when it was increased. For women who are pregnant, the therapy would start on the day of oocyte retrieval and last for eight weeks following ET [1,12].

Adding Human Chorionic Gonadotrophin (hCG) to the Luteal Phase Supplementation. According to earlier research, hCG stimulates local angiogenesis and both the maturation and proliferation of uNK cells. The hormone known as hCG, which is physiologically generated by the embryo, has a direct role in the local response by promoting sufficient angiogenesis and regulating the activation of uNK cells at the maternal-fetal interface. In the event of limited CD56 recruitment or immaturity of uNK cells, we advised hCG supplementation during the mid-luteal phase.

Excessive Immune Response and Assessment of Immunotherapy Sensitivity. In order to verify the effectiveness of the selected immunotherapy it is advised a test cycle under therapeutic conditions for patients with dysregulated endometrium who had either an over-activation or a mixed profile. In order to assess the immunotherapy's sensitivity, the prescribed course of treatment was started on a fresh replacement cycle (intralipid IV perfusion on day 8, along with luteal support for the LMWH on day 3 for corticosteroids). As previously mentioned, the mid-luteal phase was used for the routine endometrial immune profiling [1,13].

Women often fail to become pregnant after embryo transfer in IVF programs, a condition known as Recurrent Infertility (RIF). Treatment options include intrauterine administration of HCG, G-CSF, or autologous peripheral blood (PBMCs) mononuclear cells [1].

ESHRE reports that the Endometrial Receptivity Array (ERA, Igenomix) has been used for ten years in IVF, determining the optimal day for embryo transfer. However, its effectiveness is currently debated due to conflicting reports. In 2018, the LBR was 20.3% at the third attempt and 17.2% at the fourth.

IVF, immunotherapy, and personalized medicine have shown limited efficacy in treating women with endometrial overactive or mixed immune profiles. Cochrane reviews and meta-analyses show that immunotherapy, such as glucocorticoids (GC), low-molecular-weight heparin (LMWH), and mechanical procedures, rely on a general context of infertility and are not tailored to precise molecular diagnosis. GC is recommended as first-line treatment, while LMWH is considered an alternative option for cases where corticosteroids are ineffective.[13]

In contrast, the proportions of uterine CD68+ macrophages, CD83+ mature dendritic cells, CD8+ T cells, and Foxp3+ regulatory T cells were significantly higher in CE patients. The proportion and function of the immune cell subsets analyzed in peripheral blood, as well as the percentages of CD56+ NK cells, CD163+ M2 macrophages, and CD1a+ immature dendritic cells in the endometrium, were not significantly changed between non-CE and CE patients. Patients with treated CE showed a substantial decrease in the proportion of CD68+ macrophages, CD83+ mature dendritic cells, CD8+ T cells, and Foxp3+ regulatory T cells in the endometrium following antibiotic therapy.

Chronic endometritis (CE) is a condition where the clinical pregnancy rate is significantly lower in patients with at least one HPF with five or more CD138+ cells per HPF. In contrast, cases with fewer than five CD138+ or no plasma cells per HPF indicate the absence of CE. A study on uterine immune cells in women with recurrent uterine fibroids (RRF) found that after a single course of antibiotics (500 mg levofloxacin orally twice a day plus 400 mg metronidazole orally once a day for 14 days), 17.9% of patients had persistent CE. The study examined the levels of uterine immune cells using immunohistochemistry (IHC) staining in both cured and persistent CE patients. Results showed that the proportions of uterine CD68+ macrophages, CD83+ mature dendritic cells, CD8+ T cells, and Foxp3+ Treg cells significantly decreased in patients with cured CE. However, in patients with persistent CE, there was no significant difference in uterine immune cells [1,14].

This study assessed the peripheral and uterine immune status of women with cervical cancer (CE) and recurrent ovarian failure (RRF). It found CE prevalences of 10.4% and 10.5% in Chinese women with RM and RIF, respectively. There were no significant differences in peripheral blood CD3+ T cells, CD4+ T cells, CD8+ T cells, NK cells, and B cells between women with and without CE. The study revealed that CE may influence the levels of endometrial innate and adaptive immune cells in women with RRF. In the implantation period, patients with RM and RIF have a major change in the proportion of endometrial immune cells, suggesting that CE may have a role in inducing an increase in many uterine immune cell types [11,15].

In developed countries, women are delaying childbirth, leading to increased difficulties in achieving reproductive success. Women older than 45 years show increased uterine senescence, higher rates of pregnancy loss, and a greater risk of embryo-endometrium asynchrony. The number of CD11c+ endometrial dendritic cells (DCs) declines with age, while endometrial DCs from post-menopausal women have a greater capacity to induce CD103+ expression on CD8+ T cells than DCs from premenopausal women. The number of CD4+ T helper type 17 (Th17) cells and C-C motif chemokine receptor 5 (CCR5)+ CD4+ T cells significantly increases in the post-menopausal endometrium and is more susceptible to human immunodeficiency virus (HIV) infection.

In premenopausal women, the endocrine system maintains tight control of the endometrial immune system through the secretion of hormones and growth factors, particularly the sex hormones estradiol and progesterone. Estradiol suppresses transepithelial resistance of endometrial epithelial cells, leading to decreased blastocyst attachment and implantation. Multiple PRRs, including TLR5, have been implicated in these processes.

Endometrial epithelial cells secrete various cytokines, chemokines, and antimicrobials, which can modulate immune cell function in the endometrium. Aging affects the phenotype and distribution of blood NK cells, with reduced proliferation capacity in older women compared to younger women. In vitro studies have shown that age negatively affects endometrial stromal cell proliferation, with reduced mRNA expression of BMP-2, STAT3, prolactin, and IGFBP-1 [1,15].

So, diagnostic tests are crucial in identifying different types of immune dysfunction in women, aiding in the design of clinical trials for targeted therapies. These tests detect informative immune parameters, defining competency for healthy pregnancy. Future tests should be applied to peripheral blood during before pregnancy planning or early after conception for early intervention. A consensus definition of minimum essential immune markers will facilitate harmonization across studies. The development of immunologic, genetic, or microbiomic diagnostics for uNK cells, Treg cells, DC, and macrophages would enable targeted treatments in specific patient subgroups.

XÜLASƏ

Endometriumun immunrequlyasiyası və immunmodulyasiyası təkrari implantasiya pozulmaları və təkrari düşüklərin profilaktikasında əsas amil kimi

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***Açar sözlər**: interferon, interleykin, hem oksigenaz-1, transformasiya edən böyümə faktoru, şiş nekrozu faktoru, təkrar implantasiya uğursuzluqları, təkrarlanan düşüklər*

Endometriumun immunrequlyasiya sistemi çox mürəkkəbdir və müxtəlif xarici (ətraf mühit, həyat tərzi, infeksion amillər və daxili amillərin (genetika, genetik dəyişiklik, yaş faktorları, hormonal status, sperma, ginekoloji və digər xəstəliklər) təsirinə adaptasiya imkanlarından asılı olaraq çox dəyişkəndir. Təkrari implantasiya və təkrari düşük problemlər

РЕЗЮМЕ

Иммунорегуляция и иммуномодуляция эндометрия как ключевой фактор профилактики рецидивирующих имплантационных нарушений и привычных выкидышей

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***Ключевые слова**: интерферон, интерлейкин, гемоксигеназа-1; трансформирующего фактора роста, фактор некроза опухоли, повторные неудачи имплантации, привычные выкидыши*

Иммунорегуляторная система эндометрия очень сложна и сильно вариабельна, в зависимости от способности адаптироваться к воздействию различных внешних (окружающая среда, образ жизни, инфекционные факторы) и внутренних факторов (генетика, генетические изменения, возрастные факторы, гормональный статус,

olduğu, çoxlu psixoloji və iqtisadi çətinliklər yaratdığı üçün onların qarşısını almaqla məqsədilə çoxsahəli elmi tədqiqatlara ehtiyac vardır.

сперма, гинекологические и другие факторы). Поскольку репродуктивные проблемы вызывают множество психологических и экономических трудностей, для их предотвращения необходимы междисциплинарные научные исследования.

REFERENCES

1. Wenhui Wang, Dingqing Feng, Bin Ling. Endometrial microbiome affects endometrial receptivity from the perspective of the endometrial immune microenvironment. J Biologia Futura. Published: 26 September 2022. Volume 73, pages 291–300, (2022) https://link.springer.com/article/10.1007/s42977-022-00134-3
2. Sarah A. Robertson Ph.D. a, Lachlan M. Immune determinants of endometrial receptivity: a biological perspective. Int J Mol Sci. 2022 Nov; 23(21): 12787. https://doi.org/10.1016/j.fertnstert.2022.04.023 Published online 2022 Oct 24.
3. Nathalie Lde,Nathalie Lédée, Marie PetitbaratMarie, Petitbarat1Laura et al. Sec. Immunological Tolerance and Regulation. Endometrial Immune Profiling: A Method to Design Personalized Care in Assisted Reproductive Medicine. Volume 11 - 2020 | https://doi.org/10.3389/fimmu.2020.01032
4. Nathalie Lédée, Marie Petitbarat 1, Laura Prat-Ellenberg et al. The Next Frontier in ART: Harnessing the Uterine Immune Profile for Improved Performance. Int. J. Mol. Sci. 2023, 24(14), 11322; https://doi.org/10.3390/ijms241411322
5. Nathalie Lédée, Marie Petitbarat, Lucie Chevrier et al. The Uterine Immune Profile May Help Women with Repeated Unexplained Embryo Implantation Failure After In Vitro Fertilization. Innate immune defences in the human endometrium. Reproductive Biology and Endocrinology volume 1, Article number: 116 (2003)
6. Carosso A, Revelli A, Gennarelli G et al (2020) Controlled ovarian stimulation and progesterone supplementation affect vaginal and endometrial microbiota in IVF cycles: a pilot study. J Assist Reprod Gen 37(9):2315–2326. https://doi.org/10.1007/s10815-020-01878-4
7. Walker, Caroline G., Meier, Mathew D. et al. Modulation of the maternal immune system by the pre-implantation embryo. (2010). BMC Genomics 11 (1) 474 474-1-474-13. https://doi.org/10.1186/1471-2164-11-474113118199 BMC Genomics volume 11, Article number: 474 (2010)
8. Mustapha Benkhalifa, Fabien Joao, Cynthia Duval et al. Endometrium Immunomodulation to Prevent Recurrent Implantation Failure in Assisted Reproductive Technology. J Mol Sci. 2023 Sep 27;24(19):14639. doi: 10.3390/ijms241914639.
9. Qiuzi Shen, Xiaoyu Wu, Jin Chen et al. Immune Regulation of Seminal Plasma on the Endometrial Microenvironment: Physiological and Pathological Conditions. PMID: 37834087 PMCID: PMC10572377 DOI: 10.3390/ijms241914639
10. Jun Kitazawa, Fuminori Kimura, Akiko Nakamura et al. Endometrial Immunity for Embryo Implantation and Pregnancy Establishment. The Tohoku Journal of Experime, 5 Apr 2024, Vol 9, Issue 94 DOI: 10.1126/sciimmunol.adj7168
11. Sung Ki Lee, Chul Jung Kim, Dong-Jae Kim et al. Immune Cells in the Female Reproductive Tract. Immune Netw. 2015 Feb;15(1):16-26. English. Copyright © 2015 The Korean Association of Immunologists.
12. Yuye Li, Ph.D.a · Shuyi Yu, M.Sc.a · Chunyu Huang et al. Evaluation of peripheral and uterine immune status of chronic endometritis in patients with recurrent reproductive failure. Volume 113, Issue 1p187-196.e1January 2020
13. Mickey V. Patel, Zheng Shen, Charles R. Wira. Do endometrial immune changes with age prior to menopause compromise fertility in women? Explor Immunol. 2022;2:677–692 DOI: https://doi.org/10.37349/ei.2022.00076
14. Jonna Bister, Iva Filipovic, Ylva Crona-Guterstam et al. Tissue-specific nonheritable influences drive endometrial immune system variation. Science Immunology. https://orcid.org/0009-0003-4604-5060, https://orcid.org/0000-0002-8166-5500, https://orcid.org/0000-0003-2147-9308, https://orcid.org/0000-0003-4998-4904
15. Xiaoqing Yang, Meivita Devianti, Yuan H. Yang et al. Endometrial mesenchymal stem/stromal cell modulation of T cell proliferation. Reproduction. 2019 Jan;157(1):43-52. doi: 10.1530/REP-18-0266.