SCIENTIFIC Publishing Limited

**Trends in Immunotherapy**

https://ojs.ukscip.com/index.php/ti

*Review*

# Immunological Consequences of Infertility: From Immune Basis to Immunotherapy for Miscarriage and Infertility

**Roman Kalmatov [1], Fakher Rahim [2,*], Abdirasulova Zhainagul Abdirasulovna [3], Shamim Gozin [4], Azhimamatova Rakhima Momunovna [5] and Omorova Aizhan Nurlanovna [5]**

[1] International Medical Faculty, Osh State University, Osh City 723500, Kyrgyzstan

[2] Department of Medical Biotechnology, Internal Medicine Faculty, Osh state University, Osh City 723500, Kyrgyzstan

[3] Department of Medical Sciences, International Medical Faculty, Osh State University, Osh City 723500, Kyrgyzstan

[4] Department of General Medicine, Faculty of Medicine, Istanbul Atlas University, Istanbul, Turkey

[5] Department of Clinical Disciplines 1, International Medical Faculty, Osh State University, Osh City 723500, Kyrgyzstan

[*] Correspondence: Bioinfo2003@gmail.com

**Received:** 8 February 2025; **Revised:** 24 February 2025; **Accepted:** 27 February 2025; **Published:** 7 May 2025

**Abstract:** One of the causes of infertility and recurrent miscarriage is immunological factors or factors related to the immune system. Several immunological issues, for instance autoantibodies and alterations in the level of uterine immune cells, play a crucial role in immune-related infertility. This review evaluated all available immunological bases in female reproductive disorders, especially infertility and miscarriage to provide optimal diagnostic strategies for patients. NK cells are considered important elements of the innate immune system, ensuring that there is tolerance between the mother and child's immune systems. Touching on the adaptive immune system, Th cells not only are able to impart directional structure on incoming lymphocytes draining from the periphery but also categorize into different subsets depending on where they are located within peripheral blood. During pregnancy, the immune system is skewed toward a type 2 T helper response, while fetal rejection is associated with a type 1 response The rules of organ transplantation require that the host's immunological mechanisms, based on the incompatibility of antigens of the histocompatibility system, recognize the transplanted piece and ultimately reject it. Among the various therapeutic options, lymphocyte immunotherapy (LIT) stands out as a promising solution based on immunological principles. Some studies have shown that the success rate of LIT is 69%, but other studies have shown that the success rate has increased to 80%. On the other hand, controlled clinical trials are needed to further investigate immunomodulatory therapeutic strategies to help treat this disorder. Therefore, further studies are needed to achieve standardized diagnostic and immunological therapeutic approaches to increase the effectiveness of therapeutic interventions and increase the success rate of assisted reproductive technology (ART) cycles in these women.

**Keywords:** Recurrent Spontaneous Abortion; Lymphocyte Transfusion; Lymphocyte Immunotherapy (LIT); Infertility; Miscarriage

## 1. Introduction

One of the causes of infertility and recurrent miscarriage is immunological factors or factors related to the immune system [1]. The immune system has the task of defending the body against the attack of foreign agents such as viruses and bacteria. But sometimes the immune system identifies the body's tissues as invaders and attacks them, which is called an autoimmune disease [2]. Immune system disorder does not mean a weak immune system, but rather a dysfunction in various organs of the body [3]. Immune system disorders do not have a single, specific cause, and a combination of factors, including genetic background, environmental factors, and lifestyle, can play a role in the occurrence of these disorders [4]. Also, mental state and stress can play a role in this regard. Some autoimmune diseases, such as lupus and rheumatoid arthritis (inflammation of the joints), Crohn's and celiac disease (inflammatory diseases of the digestive system), and Hashimoto's disease (related to the thyroid), prevent pregnancy and lead to infertility [5].

The embryo is formed from the combination of a female egg and a male sperm, and therefore half of the embryo belongs to the father, which is considered foreign and unfamiliar to the mother's body, and the mother's immune system may react to it [6]. In a successful pregnancy, the mother's immune system makes the embryo receptive and adaptable to it; however, if the mother's immune system cannot adapt to the embryo for any reason, it rejects it [7]. This rejection may occur from the very beginning and prevent implantation of the embryo, or it may occur after pregnancy and lead to miscarriage. This can cause infertility and unsuccessful in vitro *fertilization* (IVF), and even if a quality embryo is transferred to the uterus, the result will be negative [8]. Immune system disorders are considered one of the causes of miscarriage. Although miscarriage due to immunological factors is not very common, it usually causes first-trimester miscarriage. In some cases, it may also lead to second-trimester miscarriage [9].

When the embryo is formed, it must produce substances to help with implantation, which produces these substances and proteins; consequently, the mother responds by producing substances to allow implantation to occur [10]. In fact, pregnancy is the result of a conversation and interaction between the mother and the embryo. In some cases, implantation failure is due to the embryo not producing those substances or the mother not responding. In infertility treatment, unsuccessful IVF is one of the cases where immunological examinations and tests should also be requested [11]. Miscarriage is the most common complication of pregnancy, often occurring unexpectedly and can have devastating psychological and physical effects [12].

According to research, about 10 to 20 percent of all pregnancies end in miscarriage. A miscarriage is the sudden loss of an egg or fetus before the 20th week of pregnancy. In many cases, especially very early miscarriages, it is difficult to determine exactly what caused the miscarriage [13]. Potential causes of recurrent spontaneous abortion (RSA) are multifactorial but can be divided into two major categories: fetal (chromosomal abnormalities) and maternal [14]. Also, genetic-chromosomal causes (about 4% of mothers with RSA have a chromosomal abnormality, or single-gene mutations in the interleukin, gamma interferon, TNF genes, etc.). In total, about half of recurrent miscarriages are unexplained, with immunological causes playing a greater role than other causes. Despite all the reasons mentioned, the cause of 10–50% of recurrent miscarriages is still unknown [15].

Several immunological issues, for instance, autoantibodies and alterations in the level of uterine immune cells, play a crucial role in immune-related infertility. This review evaluated all available immunological bases in female reproductive disorders, especially infertility and miscarriage to provide optimal diagnostic strategies for patients.

## 2. Immune Basis of Unsuccessful Pregnancy

### 2.1. Mother-Fetus Relation in Normal Pregnancy

Microchimerism is cell migration from the fetus to the mother during pregnancy, which probably occurs in all pregnancies [16]. Growing evidence suggests that fetal cells can persist in many women of childbearing age for decades after pregnancy, and even for life [16, 17]. Pregnancy, as another source of chimeric cells, is a very common and natural cause of chimerism. Although there are many unanswered questions, chimerism is thought to play an important role in human health [18]. Microchimerism is increased in dizygotic twins with connected placental vessels after blood transfusion, stem cell transplantation, or organ transplantation [19]. The presence of fetal cells in the maternal tissue and circulation is referred to as fetal microchimerism (FMc), and the presence of maternal cells in the fetal circulation is referred to as maternal microchimerism (MMc). Microchimeric fetal cells are found not

only in the peripheral blood, but also in various maternal tissues and organs, including bone marrow, skin, kidney, heart, and liver [20]. The fetus is semi-allogeneic, meaning it inherits half of its antigens from the mother and half from the father [21]. As we know, an incompatible organ transplant is easily rejected without immunosuppression. But normally, during a successful human pregnancy, the semi-allogeneic fetus is spared from attack by the mother's immune system [22]. It is likely that the suppression of the placental immune system, which is necessary to maintain the allogeneic embryo, contributes to the development of microchimerism. This immunosuppression may persist for several months after delivery, allowing the persistence of fetal cells in the mother. Therefore, all mothers are chimeras [23].

## 2.2. Immunological Termination of Pregnancy

The rules of organ transplantation require that the host's immunological mechanisms, based on the incompatibility of antigens of the histocompatibility system, recognize the transplanted piece and ultimately reject it [24]. On the other hand, in an organ such as the uterus, a fetus whose half of its antigens are foreign to the mother's immunological structure can easily survive for nine months without being rejected by the mother's immunological mechanisms [25]. Such a contradiction, which ultimately leads to the maintenance of a semi-allogeneic fetus in the mother's body, is the most important point to consider in the evolutionary process of reproduction and survival of the human species [26]. Anti-sperm antibodies (ASA) are considered one of the most important causes of fertility issues since the 1970s, and they play a major role in recurrent pregnancy loss (RPL) [27]. There are some antigens on the surface of sperm, which play a role as foreign substances for a pregnant woman [25, 28]. Anti-sperm antibodies and sperm-immobilizing antibodies may impair the movement of spermatozoids in the genital tract of a woman, resulting recurrent miscarriage (RM) [25]. Moreover these substances may affect some stages of sperm-egg interaction [27]. The interleukin receptor also includes two types of receptors, type I and Π, whose antagonists can prevent implantation by combining with these receptors [29]. The type I receptor is found in most cells and is effective in enhancing the action of interleukin. The type Π receptor is also found mostly in lymphocytes, neutrophils, and monocytes [30]. An interleukin receptor antagonist can prevent actions such as the stimulation and secretion of prostaglandins or the secretion of collagenase by combining with its receptor. The immune system comes into action serially at the time of implantation. Immunofluorescence studies have shown that the IL-1 receptor is present in the endometrial epithelium and is significantly increased before implantation [31]. The molecular factors involved in embryo implantation and how to identify these factors could be a key factor in the mechanism of reproductive control. In fact, the factors effective in implantation include two types of interleukin β and α, their receptors, and their receptor antagonists [32].

### 2.2.1. Immunological Barrier

The presence of an immunological barrier at the site of contact between the mother and fetus replaces any pathological presentation of the main antigens of the histocompatibility system or, by masking the paternal alloantigens, inhibits classical graft rejection reactions to the extent possible.

### 2.2.2. Cytokines and T Cells

In normal pregnancy, the ratio of Th2 to Th1 cells is high in the endometrium and decidua [33]. An increase in the ratio of Th1 cells (producing cytokines IL-2, TNF, and INFγ, which are harmful to the fetus) to Th2 cells (producing anti-inflammatory cytokines such as IL-4, IL-5, IL-6, IL-10, IL-15, and LIF - Leukemia Inhibitory Factor, which plays an important role in embryo implantation - which plays a role in facilitating and expanding humoral immune responses and is beneficial to the fetus) causes increased cytotoxicity against the fetus or lack of appropriate stimulation for trophoblast proliferation and differentiation, ultimately leading to non-implantation and miscarriage [34]. In the presence of sufficient progesterone, a factor called PIBF (Progesterone Induces Blocking Factor) is secreted from CD56+ cells of the decidual layer and activated lymphocytes located in the middle of the placental cells, which stimulates the production of protective cytokines from Th2 and reduces the production of cytotoxic cytokines from Th1 [35]. Therefore, progesterone exerts its anti-abortive effects by inducing the production of PIBF. Non-classical HLA antigens, such as HLA-G and its multiple isoforms, are the most important antigens recognized by suppressor T cells [36]. The presence of this antigen can induce leukocytes present in the maternal decidua to produce cytokines with positive and negative functions, both in the direction of growth and in the inhibitory process [37].

### 2.2.3. Allo-Immune Factors

It appears that couples with recurrent unexplained miscarriages have an allo-immune disorder that prevents the mother from developing the necessary immune responses that are beneficial for fetal growth and survival and that are beneficial for the continuation of pregnancy [38]. Therefore, for a successful pregnancy, active antigens must be recognized by maternal cells that have infiltrated the reproductive tract. A common form of these disorders is called decreased or absent maternal blocking antibodies. There are many reasons why the mother produces antibodies against paternal HLA [39]. These antibodies, by binding to the paternal antigen of the fetus, prevent the binding of cytotoxic antibodies to these antigens and also inhibit the maternal immune system against the fetus by reducing the cytotoxic activity of NK cells in the decidua. Therefore, these blocking antibodies, by covering the paternal antigens on the placenta and trophoblasts, prevent the mother from recognizing them as foreign bodies and rejecting them. In conditions where the paternal HLA is very similar to the mother, the production of these protective antibodies is impaired and can be considered one of the causes of recurrent miscarriage. Some studies have specifically linked these genes to recurrent miscarriage and infertility and IVF failure [40, 41]. Studies have also shown their importance in the birth weight of babies who have had successful pregnancies [42]. A percentage of these women have been found to be deficient in various *IgG* subclasses, particularly *IgG3* and *IgG1*, which most likely indicates that the blocking antibody class is of these subtypes [43]. Immunization with paternal mononuclear cells has been proposed as a treatment. The first reports of immunization with paternal leukocyte cells date back to 1981. In that year, researchers used the sharing of HLA antigens between couples as a criterion for immunization [44]. It seems that excessive sharing is increased in couples with recurrent miscarriage, which may be a reason for the low response to paternal antigens and, consequently, miscarriage. The WBC cross-match test is used to detect Anti-Paternal Cytotoxic Antibody (APCA). If the APCA level is more than 30% (highly reactive), it indicates that there is adequate immunization leading to an appropriate response to paternal antigens. In other words, the presence of APCA increases the likelihood of live birth [45]. Another form is the lack of complement regulatory proteins on the surface of fetal cells [46]. These proteins, which include CD46, CD55, and CD59, prevent damage caused by complement system activity at the maternal-fetal level.

## 2.3. Natural Killer Cells (NK Cells)

Crucially, natural killer (NK) cells play a vital role in the innate immune system by supporting mother-fetal immunological tolerance [33]. These cells are essential for creating a conducive uterine environment [35] and effectively protecting against infections during pregnancy [34]. NK cells contribute to successful pregnancies by producing key elements that regulate placental invasion and maternal vascular development [36]. Within the uterus, these unique NK cells (uNK cells) do not express the CD16 protein and exhibit a notably strong CD56 marker, distinguishing them from peripheral blood NK cells (pbNK cells), which mainly consist of CD56dim (95%) and CD56bright (5%) subtypes [37]. The similarity between decidual NK (dNK) cells and the CD56 bright subset of pbNK cells implies a common origin, suggesting that dNK cells likely differentiate in the uterine microenvironment [36]. During implantation and placental growth, uNK cells account for approximately 70% of the leukocyte population in the uterus, engaging with trophoblast ligands through specific receptors [38]. Impaired uNK cell function can disrupt vascular patterns, lead to ischemia, and elevate oxidative stress levels, adversely affecting early trophoblast invasion [39]. These cells are crucial for normal placental development and vascular remodeling at the final stages of implantation [39]. Insufficient trophoblast invasion and abnormal vascular remodeling serve as early indicators of conditions like preeclampsia and recurrent pregnancy loss (RPL) [40]. Furthermore, uNK cells facilitate trophoblast invasion and bolster maternal-fetal tolerance by enhancing extravascular trophoblast (EVT) activity and regulatory T (Treg) cell function, thus aiding vascular adaptation throughout pregnancy [41]. The development of the placenta is regulated by interactions between maternal killer cell immunoglobulin-like receptors (KIRs) on uNK cells and fetal human leukocyte Antigen-C (HLA-C) on EVT cells (extravillous trophoblast) [42]. This KIR/HLA interaction is complex and highly polymorphic, influencing susceptibility to various diseases including infections, autoimmune disorders, cancers, and transplant rejection [43–45]. KIR-A lacks activating receptors while KIR-B contains both stimulatory and inhibitory receptors; together they modulate immune responses at the mother-fetal interface [46]. The BB and KIR-AB genotypes express combinations of activating and inhibitory receptors; in contrast, the KIR-AA

genotype is predominantly inhibitory. Research indicates that miscarriage may be associated with both activating and inhibiting KIR-HLA combinations [47].

Every pregnancy represents a unique interaction between potentially variable paternal HLA-C groups and maternal KIR genes. Even when originating from the same father, differing HLA-C groups can create a dynamic balance between trophoblasts and uNK cells. Research examining data from women undergoing IVF cycles has indicated a relationship between the inhibitory KIR-AA haplotype, miscarriage rates, and failed implantations after multiple embryo transfers [48]. Additionally, various studies have reported increased uNK cell density in endometrial biopsies from patients experiencing recurrent miscarriage (RM) compared to control subjects [49, 50]. Therefore, understanding KIR and HLA-C genotypes may aid in selecting third-party gametes or gestational carriers to mitigate pregnancy complications such as preeclampsia (PE) [51]. Clinically, it is essential to consider the implications of uNK cell dynamics during reproduction for patients at risk of PE; consequently, these individuals may require more extensive prenatal testing than usual [52].

## 2.4. TH1/TH2 Balance

Comprising a segment of the adaptive immune system, T-helper (Th) cells are classified according to their cytokine production patterns in peripheral blood [53]. Th1 cells, recognized for their pro-inflammatory properties, produce cytokines such as interleukin-2 (IL-2), tumor necrosis factor-alpha (TNF-α), and interferon-gamma (IFN-γ). In contrast, Th2 cells secrete interleukins like IL-10, IL-6, IL-4, IL-5, and IL-13 [54], exhibiting anti-inflammatory effects. While a Th1 response is associated with fetal rejection [55], a Th2-dominant immune response is typically promoted during pregnancy. Excessive Th1 activity can endanger fetal viability and increase the likelihood of recurrent pregnancy loss (RPL) and preeclampsia [24]. Women experiencing implantation failure or RPL tend to have elevated levels of Th1 compared to those with normal pregnancies [56]. Additionally, microarray analyses and intracellular cytokine labelling reveal a prevalence of Th1 cytokines (TNF-α, IFN-γ, IL-2) in individuals facing RPL [57].

Patients experiencing recurrent implantation failure (RIF) exhibit elevated concentrations of the pro-inflammatory cytokine IL-1β and diminished levels of the anti-inflammatory cytokine transforming growth factor beta 1 (TGF-β1) when compared to control groups [58, 59]. Macrophages that are activated by IFN-γ produced from Th1 cells release mediators such as nitric oxide, TNF-α, and neopterin [60]. These substances can induce apoptosis, hinder trophoblast proliferation, and suppress granulocyte-macrophage colony-stimulating factor (GM-CSF) production from the uterine epithelium, leading to toxicity and an increased risk of miscarriage [61]. Neopterin is recognized as a biomarker indicative of pro-inflammatory immune responses. Increased neopterin levels found in various fluids including cerebrospinal fluid, urine, and serum have the potential to activate Th1 cells, stimulate immune responses during pregnancy, and are implicated in recurrent pregnancy loss (RPL) through the generation of reactive oxygen species [62]. While the ELISA method is rarely employed in clinical practices for monitoring neopterin levels, consistent.

### 2.4.1. Interactions between Treg and Non-Th1/2 Cytokines

Although non-Th1/2 cytokines play a vital role in pregnancy, their levels—particularly those produced by regulatory T cells (Treg) and Th17 cells—are not commonly assessed. Th17 cells, which are crucial for immune defense during pregnancy, enhance the synthesis of IL-17, which in turn increases progesterone production and facilitates tissue invasion. Additionally, Th17 cells activate decidual natural killer (dNK) cells and modify the vascular reactivity of uterine arteries, potentially leading to fetal resorption.

### 2.4.2. Role of Autoantibodies in Miscarriage

## 2.5. Antiphospholipid Antibody (APA)

APA causes thrombosis, vasoconstriction, and ultimately placental and decidua insufficiency through various mechanisms, leading to miscarriage. One of the most important immunological causes of miscarriage is antiphospholipid syndrome. For this reason, the American College of Obstetricians and Gynecologists (ACOG) has considered it mandatory to measure antiphospholipid antibodies in patients with recurrent miscarriage; this test should

be repeated every 6 weeks [47]. About 10 to 20 percent of miscarriages occur due to antibodies and at stages less than 10 weeks of pregnancy [47]. Antiphospholipid syndrome manifests itself with specific clinical symptoms such as preeclampsia, abnormal fetal heart rhythm, loss of an apparently normal fetus after 10 weeks without a clear cause, or premature birth before 34 weeks with increased blood pressure and placental insufficiency. Sometimes this syndrome develops in the context of lupus, which is very important to pay attention to [48].

### 2.6. Antinuclear antibody (ANA)

Typically seen in SLE, it causes inflammation in the placenta and ultimately miscarriage. Some studies show that increased antinuclear antibodies, even without immunological symptoms, are associated with increased miscarriage, but many studies have acknowledged the presence of this antibody among normal individuals and downplay the role of this antibody in causing recurrent miscarriage [49].

### 2.7. Increased B Cells

These cells produce antibodies against a series of hormones such as estradiol, progesterone, hCG, thyroid hormones, etc. They can also produce antibodies against a series of neurotransmitters including serotonin, which play an important role in uterine and ovarian activity [50, 51].

### 2.8. Anti-Thyroid Antibodies (ATA)

ATA, such as Anti-TPO antibody and Anti Thyroglobulin antibody, play an important role in the occurrence of recurrent miscarriage, and the prevalence of recurrent miscarriage in the presence of these antibodies was significantly higher compared to the control group [52]. The pathophysiology of miscarriage in these patients is unclear and unrelated to thyroid function, and is more related to the presence of an immune disorder in the body [53].

## 3. Promising Immunotherapies to Reduce the Risk of Miscarriage or Infertility

### 3.1. Lymphocyte Immunotherapy (LIT)

Among the various therapeutic options, lymphocyte immunotherapy (LIT) stands out as a promising solution based on immunological principles [54]. This method, also known as paternal lymphocyte immunization (PLI), involves injecting the father's white blood cells into the mother. The process is designed to help the mother's immune system become more resistant to the father's antigens, potentially reducing the risk of miscarriage by boosting immune acceptance of the pregnancy. While the effectiveness of LIT is still the subject of scientific studies, certain groups of patients have shown promising results, with an 8 to 10 percent increase in live birth rates (**Table 1**). This suggests significant potential for lymphocyte therapy to improve pregnancy success rates among women with a history of miscarriage. LIT is particularly considered when immunological factors or autoimmune factors are suspected of causing implantation failure [55]. The goal of this therapy is to precondition the mother's immune system to recognize and accept paternal antigens present in the developing fetus, thereby reducing immune rejection. Potential benefits of LIT include reduced risk of miscarriage (by modulating the mother's immune response to paternal antigens, LIT lymphocyte therapy may reduce the rate of miscarriage), increased implantation rates (the immune tolerance induced by LIT lymphocyte therapy may improve the likelihood of successful embryo implantation), increased live birth rates (for couples with recurrent implantation failure related to immunological issues, LIT lymphocyte therapy offers a potential increase in live birth rates), and a minimally invasive procedure (this procedure involves a simple blood draw, making it a less invasive option for the woman) [56]. Some studies have shown that the success rate of LIT is 69%, but other studies have shown that the success rate has increased to 80% [57]. In any case, LIT has proven its value not only in the success of assisted reproduction and pregnancy (**Table 1**). The chances of pregnancy are greatly increased with LIT because the immune system can recognize the male lymphocytes, so it does not attack the sperm [58]. LIT should be considered if the mother is immunocompromised and assisted reproductive techniques such as ICSI and IVF are not successful. The patient's mother can get pregnant through ICSI, but as the fetal cells develop, the immune system attacks it, so it does not develop and miscarriage occurs. While LIT is generally safe, potential adverse events include local reactions (mild symptoms, such as redness or swelling at the injection site, are usually transient and manageable), systemic reactions (rare, mild systemic

reactions, such as fever or weakness, may occur), and allergic reactions (although rare, it is important to watch for signs of allergy and seek immediate medical attention if severe symptoms appear).

Intravenous immunoglobulin (IVIG) is a biological product and is actually a mixture of gamma globulins found in donated blood from healthy donors [59]. IVIG is used in the treatment of immune and inflammatory disorders, such as children with antibody deficiency, multiple sclerosis (MS), and graft versus host disease (GVHD) [60]. Given that this drug is essentially an antibody and the half-life of most blood antibodies is about three weeks, this product is injected every 3–4 weeks in immunocompromised individuals. In fact, this treatment causes temporary regulation of the immune system in individuals. Adverse reactions following IVIG injection have often been reported in less than 5% of cases with a range of 1 to 15% [61]. In some cases, IVIG injection, due to the presence of bound immunoglobulin molecules, activates the complement system and can lead to inflammation mediated by antibody-antigen complexes. In patients with *IgA* deficiency, IVIG administration can cause severe anaphylactic or allergic reactions due to the production of antibodies against *IgA* [62]. IVIG treatment has been considered as a possible immunological treatment for women with recurrent implantation failure with an increased Th1/Th2 ratio and increased NK cells [63]. Usually, the first IVIG injection is given before or at the onset of pregnancy and may be continued at the physician's discretion until the sixth month of pregnancy. Immunoglobulin protects the fetus from the maternal immune system through various mechanisms such as complement suppression and stimulation of the expansion of suppressor T cells [64]. It can also reduce the adhesion of T cells to major components of the extracellular matrix of the human placenta [65]. IVIG shifts immune responses towards Th2 responses and increases T-reg and decreases Th17 [66]. Several studies have shown that IVIG reduces Th1 cell cytokines and peripheral NK cells [67, 68]. On the other hand, IVIG suppresses the killer activity of NK cells by enhancing the function of CD200 (a molecule that enhances regulatory T cell responses) [56]. IVIG suppresses or modulates antibody production by B lymphocytes [70] and can also neutralize autoantibodies in the maternal circulation [71]. Studies have shown that IVIG infusion can improve implantation and pregnancy outcomes in patients with recurrent implantation failure [72], while another clinical trial study showed that the live birth rate (LBR) was not significantly different between two groups of infertile women with more than two failed embryo transfers who received and placebo [73].

Certain cases of infertility may benefit from intravenous immunoglobulin therapy, especially if there is an underlying immune-related reason. It has demonstrated possible advantages in the following conditions: antiphospholipid syndrome (APS), abnormal natural killer (NK) cell activity, and elevated Th1/Th2 cytokine ratios. On the other hand, its application is still debatable and not always advised.

If recurrent pregnancy loss (RPL) fails in women with antiphospholipid syndrome with low doses of heparin and aspirin, IVIG may be helpful [73, 74]. Live birth rate (LBR) was increased by IVIG [75]. As soon as pregnancy was confirmed, 38 women having a history of three or more consecutive trimester spontaneous miscarriages with antiphospholipid syndrome received 300 mg $kg^{-1}$ intravenous immunoglobulin as a part of pilot research. Infusions were repeated every three weeks up to 16 and 17 weeks of gestation. 81.4% of participants gave birth to healthy babies at 37 ± 42 weeks, while 89.5% of pregnancies proceeded beyond the first trimester [73, 76]. The increase of circulating NK cells, which are essential for maternal tolerance, decidual vasculogenesis, and embryo development, has been linked to recurrent reproductive failure. In an observational study, patients with recurrent miscarriages with NK or NKT-like expansion were administered IVIG and compared outcomes with women not receiving intervention. Increased pregnancy rates were found from 26.2 to 93.8% ($P \leq 0.0001$) and healthy birth rates improved from 17.9 to 80.0% in recurrent reproductive failure ($P \leq 0.0001$) [70, 73]. Another research showed that a total of 44 women with a history of RPL were included in the study. The 1st group, 33 participants, is the intervention group for IVIG therapy and 12 patients were in the control group. Prior to and following IVIG administration, the frequency of Th1 and Th2 lymphocytes was assessed. Th1 lymphocyte frequency was found to be decreased significantly, whereas Th2 increased with a significantly decreased Th1/Th2 ratio (p value < 0.0001) at the end of treatment. The live birth rate difference is 87.5% in the first group and 41.6% in the control group [64]. The aforementioned studies on IVIG therapy had a limited number of participants, making it an unreliable therapeutic approach. More top-quality research is required to obtain additional high-level evidence for IVIG in recurrent pregnancy loss (RPL).

**Table 1.** Available evidence from studies comparing lymphocyte immunotherapy with control groups.

| Study ID | Participants URSA/Control | Age (years) LIT/Control | Method | Findings |
|---|---|---|---|---|
| Ebrahimi et al., 2025, Iran [77] | 63/42 | 28.32 ± 3.73/27.61 ± 3.69 | lymphocyte solution was intradermally injected | Significantly improved the PR: 89.47% vs. 60.1% LBR: 89.47% vs. 56.6% |
| Park et al., 2024, Republic of Korea [78] | 49/75 | ------ | Intravenous immunoglobulin (IVIG) | Significantly improved the LBR: 78.57% vs. 28.57% |
| Liu et al., 2021, China [54] | 444/260 | 29.8 ± 5.0/29.7 ± 5.4 | One mL of lymphocyte solution was intradermally injected | Significantly improved the PR: 65.3% vs. 29.6% LBR: 80.3% vs. 50.6% |
| Lee et al., 2016, Republic of Korea [79] | 111/78 | ------ | Intravenous immunoglobulin (IVIG) | Significantly improved the LBR: 84.8% vs. 58.7% |
| Liang et al., 2015, China [80] | 302/53 | ------ | Immunotherapy with lymphocytes from their partner | Significantly improved the LBR: 87.3% vs. 40.5% And non-significant in PR: 89.7% vs. 79.3% |
| Ramhorst et al., 2000, Argentina [81] | 92/37 | ------ | Paternal alloimmunization | Significantly improved the PR: 58% vs. 46% LBR: 88.3% vs. 52.6% |
| Pfeiffer et al., 1998, Germany [82] | 18/18 | 28.6 ± 6.0/29.5 ± 6.2 | Intramuscular reinjections of autologous blood | Significantly improved the LBR: 86% vs. 64% |
| Gatenby et al., 1993, Australia [83] | 19/22 | 33.3 ± 4.6/32.2 ± 4.4 | Paternal alloimmunization | Significantly improved the LBR: 68% vs. 47% |

Note: LIT, lymphocyte immunotherapy; PR, pregnancy rate; LBR, live birth rate.

## 3.2. Peripheral Blood Mononuclear Cells (PBMC) Therapy

Many meta-analyses examining the effectiveness of PBMCs have produced inconsistent results. However, two meta-analyses conducted in 2019 and 2020, along with a clinical trial from 2020, indicated that PBMC injections could enhance the live birth rate (LBR) in women facing recurrent implantation failure [84–86]. A review published in 2023 suggested that women with repeated implantation failure are likely to benefit from PBMC injection as a treatment option. It also emphasized the importance of performing these injections in labs that adhere to cell culture safety standards. Given that this method has no known adverse effects for patients, it may represent a viable therapeutic option for women experiencing repeated implantation failure [87]. Women with repeated implantation failure had elevated endometrial expression of progesterone (PRs) and estrogen receptors (ERα) during the implantation window. Intrauterine administration of peripheral blood mononuclear cells (PBMC) in patients with repeated implantation failure (RIF) was found effective by enhancing endometrial receptivity and embryo implantation due to decreased mRNA expression of endometrial ERα and PRs isoforms [88].

### 3.2.1. Tumor Necrosis Factor Inhibitor Alpha (Anti-*TNF-α*)

Those experiencing immune system issues may exhibit elevated levels of TNF-α, potentially leading to various complications. Research has established a significant link between increased TNF-α levels and an elevated risk of miscarriage [89]. Furthermore, medications that inhibit TNF-α have been shown to improve pregnancy outcomes by reducing inflammatory cytokines, including TNF-α, throughout the course of pregnancy [90]. By obstructing the activity of TNF-α, these drugs mitigate inflammatory responses by inhibiting fibrinogen-like protein 2 (FGL2), which may alter the Th1/Th2 cell balance [91]. High concentrations of TNF-α can initiate Th1 responses and boost the production of prostaglandin E2 (PGE2), trigger intrauterine contractions, affect the blood coagulation process, and increase oxidative stress. These factors contribute to placental vascular thrombosis and ultimately lead to unsuccessful pregnancies [92]. In treating infertility and miscarriage, FDA-approved TNF-α inhibitors such as Adalimumab (Humira) and Etanercept have been utilized [93]. Investigations into the application of Etanercept during endometrial preparation have demonstrated its ability to improve IVF outcomes for women facing recurrent implantation failure (RIF) [94]. Additionally, studies suggest that Adalimumab can enhance pregnancy success rates in women undergoing IVF by decreasing the TNF-α/IL-10 ratio [95]. Thus, employing TNF-α inhibitors helps lower TNF-α levels and may improve pregnancy outcomes for women with histories of recurrent implantation failure and miscarriage. Therefore, further research is warranted to evaluate the efficacy of TNF-α inhibitor medications in

addressing recurrent implantation failure.

### 3.3. Tacrolimus (FK-506, Fujimycin)

Often prescribed for autoimmune disorders or to prevent organ transplant rejection, tacrolimus is a potent immunosuppressive medication, especially in liver or kidney transplantation [96]. It functions by inhibiting calcineurin, thereby dampening the immune response and decreasing the production of inflammatory cytokines such as TNF-α, IL-1β, and IL-6 [97]. Tacrolimus also prevents the synthesis and release of key mediators like IL-2, leading to reduced lymphocyte proliferation and decreased generation of cytotoxic T lymphocytes (CTLs) [98]. Its mechanism involves binding to FK506 and FKBP12 proteins to form a complex that hinders IL-2 gene transcription and modifies T cell signaling through calcineurin. Numerous studies indicate that tacrolimus enhances both implantation rates and pregnancy outcomes. Research conducted by Nakagawa et al. demonstrated that in individuals experiencing repeated implantation failures, treatment with tacrolimus notably increased clinical pregnancy and live birth rates by altering the Th1/Th2 cell ratio. This study suggested a dosage of 1–3 mg per day of tacrolimus based on individual Th1/Th2 ratios. Reportedly, the pregnancy rate among women receiving tacrolimus stood at 64%, which was significantly higher compared to those in the control group.

## 4. Discussion

Even though numerous studies have examined various aspects of RIF, this clinical challenge continues to be a significant barrier in infertility treatment. Pregnancy loss attributed to an imbalance in immune responses—such as inadequate inflammatory reactions or excessive endometrial inflammation during the implantation period—underscores the urgent need for innovative and effective therapeutic strategies to address this issue [99]. Currently, emerging immunotherapies aimed at enhancing fertility rates in patients experiencing recurrent implantation failure are concentrating on modulating the maternal immune response during implantation, either by increasing or reducing inflammation. A notable benefit of immunomodulatory therapies is their minimal risk of serious side effects for the fetus [75]. Consequently, these treatments have attracted considerable attention in recent years. Given that RIF is a multifaceted condition, identifying all contributing factors within an individual can be difficult; therefore, it is advisable for infertile women without a history of autoimmune disease and who have undergone high-quality embryo transfers to consult with immunologists after three unsuccessful embryo transfers. In collaboration with these couples, immunologists aim to pinpoint modifiable factors and deliver the most effective interventions to enhance the immune status of women dealing with RIF. However, due to the lack of a conclusive diagnostic test for immune disorders among those experiencing recurrent implantation failure, immunotherapy is frequently initiated based on empirical evidence rather than solid proof of its effectiveness [100]. Personalized medicine is recommended for these women given the complex nature of recurrent implantation failure's underlying causes. This approach involves developing a tailored treatment plan that considers clinical history, test results, and patient background [101]. On the other hand, controlled clinical trials are essential for evaluating immunomodulatory treatment strategies intended to resolve recurrent implantation failure. Ongoing research must establish standardized diagnostic criteria and immunological treatment protocols to enhance success rates in assisted reproductive technology (ART) cycles among these women and thereby improve therapeutic effectiveness.

## 5. Conclusions

Pregnancy is initiated and sustained through complex mechanisms that involve intricate interactions among various subsets of immune cells. Historically, reproductive medicine and fertility management have overlooked the immunological status of the endometrium as a significant factor. However, understanding the uterine immune profile presents a promising opportunity to enhance the effectiveness of ART through personalized treatment approaches. Infertility, affecting 8 to 12% of couples of reproductive age globally, is a growing concern. This highlights the urgent need for advancements in diagnostic tools to assess risks associated with infertility issues, including RPL and RIF. Leukocyte immunotherapy (LIT) represents an innovative and effective method for addressing certain autoimmune diseases and infertility. It provides renewed hope for patients seeking to improve their conditions and strengthens their immune responses. LIT offers potential relief for many couples experiencing repeated miscarriages due to RPL. Increasing attention is being given to LIT as couples aim to navigate immune challenges that

hinder successful pregnancies, particularly because studies indicate higher live birth rates with minimal invasiveness and low adverse effects associated with this treatment. Additionally, IVIG is regarded as a therapeutic option aimed at improving pregnancy outcomes and live birth rates for individuals facing recurrent miscarriage or RIF; it may protect the fetus from maternal immune responses through various mechanisms. Nevertheless, there remains insufficient data to conclusively support an increase in live birth rates following IVIG administration.

## Authors Contributions

F.R. and A.Z.A.: Developed the concept, conducted the data analysis, wrote, and revised the first draft of the manuscript. S.G., O.A.N. and R.K.: Developed the concept, contributed to the draft review, editing, and validation. A.R.M.: Developed the concept, participated in language editing, and conducted the data analysis. All authors have read and agreed to the published version of the manuscript.

## Funding

This work received no external funding.

## Institutional Review Board Statement

The article is comprehensive in its consideration of ethical concepts. The ethics committee gave the study the all-clear.

## Informed Consent Statement

Not applicable.

## Data Availability Statement

No data were used in the present research.

## Acknowledgments

The authors would like to thank all participants of the research and Osh State University for their support.

## Conflicts of Interest

The authors declared no conflict of interest.

## References

1. Kirovakov, Z.; Konova, E.; Hinkova, N.; et al. Immunological Risk Factors in Recurrent Pregnancy Loss in Patients With Hereditary Thrombophilia. *Cureus* **2024**, *16*, e56555.
2. Hara, A.; Iwasa, Y. Autoimmune Diseases Initiated by Pathogen Infection: Mathematical modeling. *J. Theor. Biol.* **2020**, *498*, 110296.
3. Pisetsky, D.S. Pathogenesis of Autoimmune disease. *Nat. Rev. Nephrol.* **2023**, *19*, 509–524.
4. Jörg, S.; Grohme, D.A.; Erzler, M.; et al. Environmental Factors in Autoimmune Diseases and Their role in Multiple Sclerosis. *Cell. Mol. Life Sci.* **2016**, *73*, 4611–4622.
5. Gratiela Gradisteanu, P.; Octavian, S.; Grigore, M.; et al. Dysbiosis, Tolerance, and Development of Autoimmune Diseases. In: *Immunology of the GI Tract - Recent Advances*; Rijeka, L., Eds.; IntechOpen: Rijeka, Licko - Senjska, Croatia, 2022; Volume 4, pp. 2–23.
6. Siu, K.K.; Serrão, V.H.B.; Ziyyat, A.; et al. The Cell Biology of Fertilization: Gamete Attachment and fusion. *J. Cell Biol.* **2021**, *220*, e202102146
7. Wu, H.M.; Chen, L.H.; Hsu, L.T.; et al. Immune Tolerance of Embryo Implantation and Pregnancy: The Role of Human Decidual Stromal Cell- and Embryonic-Derived Extracellular Vesicles. *Int. J. Mol. Sci.* **2022**, *23*, 13382.
8. Ma, J.; Gao, W.; Li, D. Recurrent Implantation Failure: A Comprehensive Summary From Etiology to Treatment. *Front. Endocrinol.* **2022**, *13*, 1061766.
9. Hamadi, G.M.; Lafta, S.F. Immunological Parameters of Recurrent Miscarriages Among Women in Thi-Qar

Province. *J. Med. Life* **2022**, *15*, 635–639.
10. Zhang, S.; Lin, H.; Kong, S.; et al. Physiological and Molecular Determinants of Embryo Implantation. *Mol. Aspects Med.* **2013**, *34*, 939–980.
11. Simon, A.; Laufer, N. Assessment and Treatment of Repeated Implantation Failure (RIF). *J. Assist. Reprod. Genet.* **2012**, *29*, 1227–1239.
12. Quenby, S.; Gallos, I.D.; Dhillon-Smith, R.K.; et al. Miscarriage Matters: The Epidemiological, Physical, Psychological, and Economic Costs of Early Pregnancy loss. *Lancet* **2021**, *397*, 1658–1667.
13. Genovese, H.G.; McQueen, D.B. The Prevalence of Sporadic and Recurrent Pregnancy Loss. *Fertil. Steril.* **2023**, *120*(5), 934–936.
14. Turesheva, A.; Aimagambetova, G.; Ukybassova, T.; et al. Recurrent Pregnancy Loss Etiology, Risk Factors, Diagnosis, and Management. Fresh Look into a Full Box. *J. Clin. Med.* **2023**, *12*, 4074.
15. Mendes, D.C.G.; Fonseca, A.; Cameirão, M.S. The Relationship Between Healthcare Satisfaction After Miscarriage and Perinatal Grief Symptoms: A Cross-Sectional Study on Portugal Residents. *Soc. Sci. Med.* **2024**, *353*, 117037.
16. Dawe, G.S.; Tan, X.W.; Xiao, Z.C. Cell Migration From Baby to Mother. *Cell Adhes. Migrat.* **2007**, *1*, 19–27.
17. O'Donoghue, K. Fetal Microchimerism and Maternal Health During and After Pregnancy. *Obstet. Med.* **2008**, *1*, 56–64.
18. Shrivastava, S.; Naik, R.; Suryawanshi, H.; et al. Microchimerism: A New Concept. *J. Oral Maxillofac. Pathol.* **2019**, *23*, 311.
19. Gammill, H.S.; Nelson, J.L. Naturally Acquired Microchimerism. *Inter. J. Dev. Biol.* **2010**, *54*, 531–543.
20. Kammala, A.K.; Lintao, R.C.V.; Hoy, R.; et al. Fetal Microchimeric Cells Influence Maternal Lung Health Following Term and Preterm births. *Sci. Rep.* **2024**, *14*, 28417.
21. Pandey, M.K. Immunological harmony: the dynamic influence of cellular and humoral immunity on pregnancy success. *Discov. Immun.* **2024**, *1*, 2.
22. Davies, C. Why is the fetal allograft not rejected? *J. Anim. Sci.* **2007**, *85*, E32–E35.
23. Kinder, J.M.; Stelzer, I.A.; Arck, P.C.; et al. Immunological implications of pregnancy-induced microchimerism. *Nat. Rev. Immunol.* **2017**, *17*, 483–494.
24. Nakamura, T.; Shirouzu, T.; Nakata, K.; et al. The Role of Major Histocompatibility Complex in Organ Transplantation- Donor Specific Anti-Major Histocompatibility Complex Antibodies Analysis Goes to the Next Stage. *Int. J. Mol. Sci.* **2019**, *20*, 4544.
25. Szekeres-Bartho, J. Immunological Relationship Between the Mother and the Fetus. *Int. Rev. Immunol.* **2002**, *21*, 471–495.
26. Grunstra, N.D.S.; Betti, L.; Fischer, B.; et al. There is an Obstetrical Dilemma: Misconceptions About the Evolution of Human Childbirth and Pelvic Form. *Am. J. Biol. Anthropol.* **2023**, *181*, 535–544.
27. Shibahara, H.; Wakimoto, Y.; Fukui, A.; et al. Anti-sperm Antibodies and Reproductive Failures. *Am. J. Reprod. Immunol.* **2021**, *85*, e13337.
28. Mettler, L.; Skrabei, H. Isolation of Human Spermatozoa Membrane Antigens Binding Sperm-Immobilizing and Sperm-Agglutinating Antibodies. *Int. J. Fertil.* **1979**, *24*, 44–48.
29. Burger, D.; Chicheportiche, R.; Giri, J.G.; et al. The Inhibitory Activity of Human Interleukin-1 Receptor Antagonist is Enhanced by Type II Interleukin-1 Soluble Receptor and Hindered by Type I Interleukin-1 Soluble Receptor. *J. Clin. Investig.* **1995**, *96*, 38–41.
30. Prince, L.R.; Allen, L.; Jones, E.C.; et al. The Role of Interleukin-1beta in Direct and Toll-Like Receptor 4-Mediated Neutrophil Activation and Survival. *Am. J. Pathol.* **2004**, *165*, 1819–1826.
31. Lindhard, A.; Bentin-Ley, U.; Ravn, V.; et al. Biochemical Evaluation of Endometrial Function at the Time of Implantation. *Fertil. Steril.* **2002**, *78*, 221–233.
32. Boraschi, D. What Is IL-1 for? The Functions of Interleukin-1 Across Evolution. *Front. Immunol.* **2022**, *13*, 872155.
33. Saito, S.; Tsukaguchi, N.; Hasegawa, T.; et al. Distribution of Th1, Th2, and Th0 and the Th1/Th2 Cell Ratios in Human Peripheral and Endometrial T Cells. *Am. J. Reprod. Immunol.* **1999**, *42*(4), 240–245.
34. Sykes, L.; MacIntyre, D.A.; Yap, X.J.; et al. Changes in the Th1:Th2 Cytokine bias in Pregnancy and the Effects of the Anti-Inflammatory Cyclopentenone Prostaglandin 15-Deoxy-Δ(12,14)-Prostaglandin J2. *Mediat. Inflamm.* **2012**, *2012*, 416739.
35. Raghupathy, R.; Al-Mutawa, E.; Al-Azemi, M.; et al. Progesterone-Induced Blocking Factor (PIBF) Modulates Cytokine Production by Lymphocytes From Women with Recurrent Miscarriage or Preterm Delivery. *J. Reprod. Immunol.* **2009**, *80*, 91–99.

36. Jasinski-Bergner, S.; Eckstein, M.; Taubert, H.; et al. The Human Leukocyte Antigen G as an Immune Escape Mechanism and Novel Therapeutic Target in Urological Tumors. *Front. Immunol.* **2022**, *13*, 811200.
37. Zhuang, B.; Shang, J.; Yao, Y. HLA-G: An Important Mediator of Maternal-Fetal Immune-Tolerance. *Front. Immunol.* **2021**, *12*, 744324.
38. Uţa, C.; Tîrziu, A.; Zimbru, E.L.; et al. Alloimmune Causes of Recurrent Pregnancy Loss: Cellular Mechanisms and Overview of Therapeutic Approaches. *Medicina* **2024**, *60*, 1896.
39. Meuleman, T.; van Beelen, E.; Kaaja, R.J.; et al. HLA-C Antibodies in Women with Recurrent Miscarriage Suggests that Antibody Mediated Rejection is One of the Mechanisms Leading to Recurrent Miscarriage. *J. Reprod. Immunol.* **2016**, *116*, 28–34.
40. Motlagh Asghari, K.; Novinbahador, T.; Mehdizadeh, A.; et al. Revolutionized Attitude Toward Recurrent Pregnancy Loss and Recurrent Implantation Failure Based on Precision Regenerative Medicine. *Heliyon* **2024**, *10*, e39584.
41. Yatsenko, S.A.; Rajkovic, A. Genetics of Human Female Infertility†. *Biol. Reprod.* **2019**, *101*, 549–566.
42. Bohn, C.; Vogel, M.; Poulain, T.; et al. Birth Weight Increases with Birth Order Despite Decreasing Maternal Pregnancy Weight Gain. *Acta Paediatr.* **2021**, *110*, 1218–1224.
43. Vidarsson, G.; Dekkers, G.; Rispens, T. IgG subclasses and allotypes: from structure to effector functions. *Front. Immunol.* **2014**, *5*, 520.
44. Eidizadeh, A.; Papert, S.; Valk, J.; et al. Adverse Drug Reactions Following Lymphocyte Immunotherapy for the Treatment of Infertility: A Retrospective Study. *J. Obstet. Gynaecol. Res.* **2022**, *48*, 2571–2582.
45. Saremi, A.T.; Sanaye Naderi, M.; Pooladi, A.; et al. Evaluations of WBC Cross-Match Results After Lymphocyte Immunization in Women with Recurrent Spontaneous Abortion in Sarem Women's Hospital %J Sarem. *J. Med. Res.* **2017**, *2*, 19–23.
46. Chighizol, C.B.; Lonati, P.A.; Trespidi, L.; et al. The Complement System in the Pathophysiology of Pregnancy and in Systemic Autoimmune Rheumatic Diseases During Pregnancy. *Front. Immunol.* **2020**, *11*, 2084.
47. Salmon, J.E.; Girardi, G. Antiphospholipid Antibodies and Pregnancy Loss: A Disorder of Inflammation. *J. Reprod. Immunol.* **2008**, *77*, 51–56.
48. Skoura, R.; Andronikidi, P.E.; Anestakis, D.; et al. Antiphospholipid Syndrome and Preeclampsia in Pregnancy: A Case Report. *Cureus* **2022**, *14*, e28458.
49. Liu, T.; Guo, X.; Liao, Y.; et al. Correlation Between the Presence of Antinuclear Antibodies and Recurrent Pregnancy Loss: A Mini Review. *Front. Endocrinol.* **2022**, *13*, 873286.
50. Kolatorova, L.; Vitku, J.; Suchopar, J.; et al. Progesterone: A Steroid with Wide Range of Effects in Physiology as Well as Human Medicine. *Int. J. Mol. Sci.* **2022**, *23*, 7989.
51. Santana-Sánchez, P.; Vaquero-García, R.; Legorreta-Haquet, M.V.; et al. Hormones and B-cell development in health and autoimmunity. *Front. Immunol.* **2024**, *15*, 1385501.
52. Xie, J.; Jiang, L.; Sadhukhan, A.; et al. Effect of Antithyroid Antibodies on Women with Recurrent Miscarriage: A Meta-Analysis. *Am. J. Reprod. Immunol.* **2020**, *83*, e13238.
53. Sarkar, D. Recurrent Pregnancy Loss in Patients with Thyroid Dysfunction. *Indian J. Endocrinol. Metab.* **2012**, *16*, S350–S351.
54. Liu, S.; Gu, X.; Weng, R. Clinical Effect of Lymphocyte Immunotherapy on Patients with Unexplained Recurrent Spontaneous Abortion. *Immun. Inflamm. Dis.* **2021**, *9*, 1272–1278.
55. Seles, L.; Zaha, I.A.; Luncan, M.; et al. Immunomodulatory Treatment Impact on IVF Outcomes in KIR AA Genotype: Personalized Fertility Insights. *Medicina* **2024**, *60*, 948.
56. Aslanian-kalkhoran, L.; Kamrani, A.; Alipourfard, I.; et al. The Effect of Lymphocyte Immunotherapy (LIT) in Modulating Immune Responses in Patients with Recurrent Pregnancy Loss (RPL). *Int. Immunopharmacol.* **2023**, *121*, 110326.
57. Sarno, M.; Cavalcante, M.B.; Niag, M.; et al. Gestational and Perinatal Outcomes in Recurrent Miscarriages Couples Treated with Lymphocyte Immunotherapy. *Eur. J. Obstet. Gynecol. Reprod. Biol.:X* **2019**, *3*, 100036.
58. Wigby, S.; Suarez, S.S.; Lazzaro, B.P.; et al. Sperm Success and Immunity. *Curr. Top. Dev. Biol.* **2019**, *135*, 287–313.
59. Kumar, P.; Philip, C.E.; Eskandar, K.; et al. Effect of Intravenous Immunoglobulin Therapy in Recurrent Implantation Failure: A Systematic Review and Meta-Analysis. *J. Reprod. Immunol.* **2024**, *166*, 104323.
60. Muyayalo, K.P.; Li, Z.H.; Mor, G.; et al. Modulatory Effect of Intravenous Immunoglobulin on Th17/Treg Cell Balance in Women with Unexplained Recurrent Spontaneous Abortion. *Am. J. Reprod. Immunol.* **2018**, *80*, e13018.
61. Aghamohammadi, A.; Farhoudi, A.; Nikzad, M.; et al. Adverse Reactions of Prophylactic Intravenous Im-

munoglobulin Infusions in Iranian Patients with Primary Immunodeficiency. *Ann. Allergy Asthma Immunol.* **2004**, *92*, 60–64.
62. Nydegger, U.E.; Fierz, W.; Risch, L. Benefits and Risks of IgA in Immunoglobulin Preparations. *Transfus. Apher. Sci.* **2012**, *46*, 97–102.
63. Li, J.; Chen, Y.; Liu, C.; et al. Intravenous Immunoglobulin Treatment for Repeated IVF/ICSI Failure and Unexplained Infertility: A Systematic review and a Meta-Analysis. *Am. J. Reprod. Immunol.* **2013**, *70*, 434–447.
64. Ahmadi, M.; Abdolmohammadi-Vahid, S.; Ghaebi, M.; et al. Effect of Intravenous Immunoglobulin on Th1 and Th2 lymphocytes and Improvement of Pregnancy Outcome in Recurrent Pregnancy Loss (RPL). *Biomed. Pharmacother.* **2017**, *92*, 1095–1102.
65. Jerzak, M.; Rechberger, T.; Górski, A. Intravenous Immunoglobulin Therapy Influences T cell Adhesion to Extracellular Matrix in Women with a History of Recurrent Spontaneous Abortions. *Am. J. Reprod. Immunol.* **2000**, *44*, 336–341.
66. Ahmadi, M.; Aghdam, S.A.; Nouri, M.; et al. Intravenous Immunoglobulin (IVIG) Treatment Modulates Peripheral Blood Th17 and Regulatory T Cells in Recurrent Miscarriage Patients: Non Randomized, Open-Label Clinical Trial. *Immunol. Lett.* **2017**, *192*, 12–19.
67. Szereday, L.; Späth, P.; Szekeres-Bartho, J. Natural Killer Cell Activity and Cytokine Production After in Vitro Immunoglobulin Treatment of Lymphocytes Derived from Pregnant Women with or Without Risk for Spontaneous Abortion. *Am. J. Reprod. Immunol.* **1999**, *42*, 282–287.
68. Graphou, O.; Chioti, A.; Pantazi, A.; et al. Effect of Intravenous Immunoglobulin Treatment on the Th1/Th2 Balance in Women with Recurrent Spontaneous Abortions. *Am. J. Reprod. Immunol.* **2003**, *49*, 21–29.
69. Virro, M.R.; Winger, E.E.; Reed, J.L. Intravenous Immunoglobulin for Repeated IVF Failure and Unexplained Infertility. *Am. J. Reprod. Immunol.* **2012**, *68*, 218–225.
70. Ramos-Medina, R.; García-Segovia, A.; Gil, J.; et al. Experience in IVIg Therapy for Selected Women with Recurrent Reproductive Failure and NK Cell Expansion. *Am. J. Reprod. Immunol.* **2014**, *71*, 458–466.
71. Toth, B.; Jeschke, U.; Rogenhofer, N.; et al. Recurrent Miscarriage: Current Concepts in Diagnosis And Treatment. *J. Reprod. Immunol.* **2010**, *85*, 25–32.
72. Abdolmohammadi-Vahid, S.; Pashazadeh, F.; Pourmoghaddam, Z.; et al. The Effectiveness of IVIG Therapy in Pregnancy and Live Birth Rate of Women with Recurrent Implantation failure (RIF): A Systematic Review and Meta-Analysis. *J. Reprod. Immunol.* **2019**, *134–135*, 28–33.
73. Stephenson, M.D.; Fluker, M.R. Treatment of Repeated Unexplained in Vitro Fertilization Failure with Intravenous Immunoglobulin: A Randomized, Placebo-Controlled Canadian trial. *Fertil. Steril.* **2000**, *74*, 1108–1113.
74. Chay, J.; Lust, K.; Kubler, P.; et al. When Conventional Treatment Fails: The Role of Intravenous Immunoglobulin in Recurrent Pregnancy Loss Secondary to Antiphospholipid Syndrome. *Obstet. Med.* **2013**, *6*, 76–79.
75. Melo, P.; Thornton, T.; Coomarasamy, A.; et al. Evidence for the Effectiveness of Immunologic Therapies in Women with Subfertility and/or Undergoing Assisted Reproduction. *Fertil. Steril.* **2022**, *117*, 1144–1159.
76. Marzusch, K.; Dietl, J.; Klein, R.; et al. Recurrent First Trimester Spontaneous Abortion Associated with Antiphospholipid Antibodies: A Pilot Study of Treatment with Intravenous Immunoglobulin. *Acta Obstet. Gynecol. Scand.* **1996**, *75*, 922–926.
77. Ebrahimi, R.; Asghari, K.M.; Alamdary, S.J.; et al. Intradermal lymphocyte Therapy: A Promising Treatment for Recurrent Pregnancy loss in Patients Without Anti-TPO Antibodies. *Hum. Immunol.* **2025**, *86*, 111229.
78. Park, J.S.; Song, A.Y.; Bae, J.Y.; et al. IL-17 Producing T to Foxp3$^{+}$CD4$^{+}$ Regulatory T Cell Ratio as a Diagnostic and Prognostic Marker in Women With Recurrent Pregnancy Loss and Its Implications for Intravenous Immunoglobulin Therapy. *Am. J. Reprod. Immunol.* **2024**, *92*, e70020.
79. Lee, S.K.; Kim, J.Y.; Han, A.R.; et al. Intravenous Immunoglobulin G Improves Pregnancy Outcome in Women with Recurrent Pregnancy Losses with Cellular Immune Abnormalities. *Am. J. Reprod. Immunol.* **2016**, *75*, 59–68.
80. Liang, X.; Qiu, T.; Qiu, L.; et al. Female Third Party Lymphocytes are Effective for Immunotherapy of Patients with Unexplained Primary Recurrent Spontaneous Abortion: A Retrospective Analysis of Outcomes. *Eur. J. Contracept. Reprod. Health Care* **2015**, *20*, 428–437.
81. Ramhorst, R.; Agriello, E.; Zittermann, S.; et al. Is the Paternal Mononuclear Cells' Immunization a Successful Treatment for Recurrent Spontaneous abortion?. *Am. J. Reprod. Immunol.* **2000**, *44*, 129–135.
82. Pfeiffer, K.A.; Sillem, M.; Daniel, V.; et al. Activated Autologous Blood therapy in Recurrent Spontaneous Abortion–Results of a Pilot Study. *Hum. Reprod.* **1998**, *13*, 491–497.
83. Gatenby, P.A.; Cameron, K.; Simes, R.J.; et al. Treatment of Recurrent Spontaneous abortion by Immunization

with Paternal Lymphocytes: Results of a Controlled Trial. *Am. J. Reprod. Immunol.* **1993**, *29*, 88–94.
84. Maleki-Hajiagha, A.; Razavi, M.; Rezaeinejad, M.; et al. Intrauterine Administration of Autologous Peripheral Blood Mononuclear Cells in Patients with Recurrent Implantation failure: A Systematic Review and Meta-analysis. *J. Reprod. Immunol.* **2019**, *131*, 50–56.
85. Yang, D.N.; Wu, J.H.; Geng, L.; et al. Efficacy of Intrauterine Perfusion of peripheral Blood Mononuclear Cells (PBMC) for Infertile Women Before Embryo Transfer: Meta-Analysis. *J. Obstet. Gynaecol.* **2020**, *40*, 961–968.
86. Pourmoghadam, Z.; Abdolmohammadi-Vahid, S.; Pashazadeh, F.; et al. Efficacy of Intrauterine Administration of Autologous Peripheral Blood Mononuclear Cells on the Pregnancy Outcomes in Patients with Recurrent Implantation Failure: A Systematic Review and Meta-Analysis. *J. Reprod. Immunol.* **2020**, *137*, 103077.
87. Genest, G.; Banjar, S.; Almasri, W.; et al. Immunomodulation for Unexplained recurrent Implantation Failure: Where Are We Now?. *Reproduction* **2023**, *165*, R39–R60.
88. Farifteh, F.; Fazeli, E.; Zeinab Hosseini, S.; et al. Intrauterine Administration of Autologous Peripheral Blood Mononuclear Cells Regulates the Endometrium Estrogen and Progesterone Receptor Expression: An RCT. *Int. J. Reprod. Biomed.* **2023**, *21*, 343–354.
89. Ohams, M.; Jerzak, M.; Górski, A. Effects of Sildenafil Citrate and Etanercept Treatment on TNF-α Levels in Peripheral Blood of women with Recurrent Miscarriage. *Ginekol. Pol.* **2015**, *86*, 520–524.
90. Berthelot, J.M.; De Bandt, M.; Goupille, P.; et al. Exposition to anti-TNF Drugs During Pregnancy: Outcome of 15 Cases and Review of the Literature. *Jt. Bone Spine* **2009**, *76*, 28–34.
91. Lee, S.K.; Na, B.J.; Kim, J.Y.; et al. Determination of Clinical Cellular Immune Markers in Women with Recurrent Pregnancy Loss. *Am. J. Reprod. Immunol.* **2013**, *70*, 398–411.
92. Zhang, C.; Deng, X.; Zhang, X.; et al. Association Between Serum TNF-α Levels and Recurrent Spontaneous Miscarriage: A Meta-analysis. *Am. J. Reprod. Immunol.* **2016**, *75*, 86–93.
93. Chambers, C.D.; Johnson, D.L. Emerging Data on the use of Anti-Tumor Necrosis Factor-alpha Medications in Pregnancy. *Birth Defects Res. A.* **2012**, *94*, 607–611.
94. Santiago, K.Y.; Porchia, L.M.; López-Bayghen, E. Endometrial Preparation with Etanercept Increased Embryo Implantation and Live Birth Rates in Women Suffering from Recurrent Implantation Failure during IVF. *Reprod. Biol.* **2021**, *21*, 100480.
95. Winger, E.E.; Reed, J.L.; Ashoush, S.; et al. Treatment with Adalimumab (Humira) and Intravenous Immunoglobulin Improves Pregnancy rates in Women Undergoing IVF. *Am. J. Reprod. Immunol.* **2009**, *61*, 113–120.
96. Scalea, J.R.; Levi, S.T.; Ally, W.; et al. Tacrolimus for the Prevention and Treatment of Rejection of Solid Organ Transplants. *Expert Rev. Clin. Immunol.* **2016**, *12*, 333–342.
97. Yu, Y.; Zhong, J.; Peng, L.; et al. Tacrolimus Downregulates Inflammation by Regulating Pro-/Anti-Inflammatory Responses in LPS-Induced keratitis. *Mol. Med. Rep.* **2017**, *16*, 5855–5862.
98. Liu, J.; Farmer, J.D., Jr.; Lane, W.S.; et al. Calcineurin is a Common Target of Cyclophilin-Cyclosporin A and FKBP-FK506 Complexes. *Cell* **1991**, *66*, 807–815.
99. Lédée, N.; Petitbarat, M.; Prat-Ellenberg, L.; et al. Endometrial Immune Profiling: A Method to Design Personalized Care in Assisted Reproductive Medicine. *Front. Immunol.* **2020**, *11*, 1032.
100. Robertson, S.A.; Moldenhauer, L.M.; Green, E.S.; et al. Immune determinants of endometrial receptivity: a biological perspective. *Fertil. Steril.* **2022**, *117*, 1107–1120.
101. Bashiri, A.; Halper, K.I.; Orvieto, R. Recurrent Implantation Failure - Update Overview on Etiology, Diagnosis, Treatment and Future Directions. *Reprod. Biol. Endocrinol.* **2018**, *16*, 121.