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REVIEW

Immune biomarkers in cases of recurrent pregnancy loss and recurrent implantation failure

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ABSTRACT

Reproductive failures, such as recurrent pregnancy loss (RPL) and recurrent implantation failures (RIF) are a major challenge for reproductive medicine. The current management of RPL and RIF cases identifies some causes for unsuccessful pregnancy in up to half of patients. Several studies have suggested that immune disorders are responsible for an important portion of unexplained cases of RPL and RIF. Moreover, the immune abnormalities responsible for reproductive failures can be classified into disorders related to autoimmunity and changes in cellular immunity. Antiphospholipid syndrome (APS), testing for antiphospholipid (aPL) antibodies, antinuclear antibodies, and antithyroid antibodies are identified as biomarkers of autoimmunity that can predict reproductive failure. The cellular immune response in cases of RPL and RIF can be investigated through the study of natural killer (NK) cells (uterine and peripheral blood) and T lymphocytes (T helper [Th]-1, Th-2, regulatory T and Th-17 cells). Several types of laboratory assays have been used to evaluate the endometrial immune microenvironment, such as the endometrial immune profile and decidualization score. However, the effectiveness of the treatment of RPL and RIF with immunomodulatory drugs has not yet been confirmed. Recently, a group of experts from the International Federation of Gynecology and Obstetrics and the European Society of Human Reproduction and Embryology recommended the investigation of some immune factors and treatment with immunosuppressants in women with RPL. In conclusion, it is important to consider immune abnormalities when managing women with RPL and RIF. The use of immunotherapies must be personalized and based on a specific diagnosis to obtain favorable outcomes.

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The occurrence of reproductive failures, such as RPL and RIF, is still a major challenge for reproductive medicine. Currently, RPL is defined as the occurrence of two or more consecutive spontaneous abortions.[1] It is estimated that up to 3% of couples of childbearing age may have this reproductive condition.[2] Recent studies have reported that the number of couples with RPL is slowly increasing due to several risk factors, such as obesity and the postponement of motherhood by modern women.[3]

The definition for RIF has not been fully established[4] and must be based on the cumulative pregnancy rate, considering the number of euploid embryos previously transferred. Moreover, RIF should be considered when a couple has not had a successful implantation after a certain number of embryo transfers and the predicted cumulative probability of implantation associated with that number is greater than 60%.[4]

Routinely, the management of women with RPL is restricted to the investigation and treat-

ment of a limited number of causes, such as genetic, anatomical, endocrinopathies, and antiphospholipid syndrome (APS).[2, 5, 6] Based on the recommendations from the main international guidelines, the cause of RPL is determined in only half of the patients. Similarly, research on couples with RIF is limited to lifestyle-related risk factors, endometrial thickness, and testing for antiphospholipid (aPL) antibodies or APS.[4]

Physiologically, the inflammatory status of pregnancy is characterized by three distinct moments, two of which are eminently inflammatory (first and third trimester) and one anti-inflammatory (second trimester).[7, 8] The immunology of pregnancy is a complex field of reproductive medicine, with numerous local (in the uterine environment) and systemic (maternal allotolerance) events. From the implantation period onward, an inadequate maternal immune response to the embryonic/fetal allograft contributes to unfavorable obstetric outcomes, such as pregnancy loss and preeclampsia.[7, 8] Furthermore, prepregnancy maternal immune status also interferes with fertility and pregnancy success.[7, 8] Based on the literature, it was suggested that several autoimmune diseases have a negative impact on female reproductive capacity.[9]

The association of immune disorders with RPL and RIF has been studied in the past few decades. Some researchers suggest that immune disorders may be responsible for up to 20% of RPL and RIF cases.[10] Numerous studies have already proven an increased risk of reproductive failure in women carrying autoantibodies, such as aPL antibodies, antinuclear antibodies (ANA), and antithyroid antibodies (ATA), even in the absence of autoimmune diseases. Other studies have also observed a higher frequency of abnormalities in systemic and uterine cellular immunity in women with RPL and RIF.[10, 11] Moreover, RPL and RIF women with autoimmune disorders often have cellular immune disorders, such as increased levels and cytotoxicity of natural killer (NK) cells, an imbalance in the T helper (Th) 1/Th2 immune response, and abnormalities in regulatory T (Treg) cells.[10]

However, the immune biomarkers in cases of reproductive failure have not been discussed and determined by reproductive medicine specialists. Currently, only a consensus on the investigation of APS, ANA, and thyroid peroxidase antibodies (TPO-Ab) in women with RPL has been established.[2] Recently, a group of International Federation of Gynecology and Obstetrics researchers have suggested that immune factors, including autoantibodies, such as ANA, TPO-Ab, and gliadin antibodies, NK cells, and cytokine tests, should be considered in RPL workup when the reproductive medicine center has a specialist with experience in reproductive immunology.[12]

Autoimmunity

The relationship between autoimmune diseases and reproductive failure has already been investigated in the literature. Patients with positive autoantibodies, associated or not with some autoimmune disease, have a high risk of pregnancy loss due to numerous pathophysiological mechanisms, such as: 1) alterations in the cellular immune response, with loss of maternal-fetal tolerance, 2) activation of inflammatory responses in the endometrium and placenta, 3) formation of microthrombi that reduce blood flow to the fetus, and 4) interference in fetal nutrition and development due to deficiency of essential nutrients.[2, 10] APS is the main autoimmune disorder associated with reproductive failure, especially RPL.[2] Furthermore, studies have suggested that women with positive autoantibodies and without a diagnosis of autoimmune disease have an increased risk of RPL and RIF.[10] ANA, ATA, anti-gliadin, anti-transglutaminase, and anti-endomysial antibodies are the most studied autoantibodies.[13-16]

Although there is a strong association between autoimmune disorders and increased risk of reproductive failure, studies investigating targeted immunomodulatory therapies that may help restore maternal-fetal immune tolerance and reduce the risk of pregnancy loss are needed. These integrated approaches offer a promising avenue for reducing autoimmune-related pregnancy loss and improving reproductive outcomes in affected women.[10, 13-16]

Antiphospholipid syndrome and antiphospholipid antibodies

APS was first described in 1983 by Graham Hughes.[17] APS is an autoimmune thrombophilia

that increases the risk of obstetric complications (*e.g.*, RPL, fetal death, and preeclampsia) due to impaired placental microcirculation secondary to thrombus formation.[18] The inhibition of trophoblastic proliferation and, consequently, inadequate placentation is another pathophysiological mechanism of the relationship between APS and obstetric complications.[18-20] Moreover, aPL antibodies promote the activation of the complement system, which has a strong association with reproductive failure.[20, 21]

Currently, the Sapporo criteria, initially proposed in 1999 and later updated in 2006, are most commonly used for the diagnosis of APS.[22] The Sapporo criteria emphasize the combination of clinical manifestations with persistent laboratory findings to reduce the risk of false-positive diagnoses. The criteria help differentiate APS from other causes of thrombosis or pregnancy complications, ensuring that only patients with sustained autoantibody presence and associated clinical events are diagnosed with APS. Persistent levels of aPL antibodies, such as lupus anticoagulant (LA), anticardiolipin antibodies (*i.e.*, aCL, IgG, and IgM), and β2 glycoprotein I antibodies (aβ2GPI, IgG, and IgM), and a history of vascular thrombosis and/or obstetric complications are necessary conditions for the diagnosis of APS. Traditionally, APS is confirmed when the patient presents at least one clinical criterion (vascular thrombosis [one or more events of arterial, venous, or small-vessel thrombosis of any organ] or pregnancy morbidity) and one laboratory criterion (LA, aCL IgG/IgM, and/or aβ2GPI IgG/IgM at least two aPL tests performed at least 12 weeks apart).[22]

Three or more consecutive spontaneous abortions before the 10th week of gestation after excluding any anatomic or hormonal abnormalities in the mother and parental chromosomal causes, one or more unexplained fetal deaths of morphologically normal fetus at or beyond 10 weeks of gestation, one or more premature births of morphologically normal neonates before the 34th week of gestation, and prematurity secondary to eclampsia, severe preeclampsia, or placental insufficiency were considered obstetric complications that meet the pregnancy morbidity criteria.[22]

The presence of RIF is not included in the clinical criteria for APS diagnosis.[22] However, numerous studies have observed a higher prevalence of aPL antibodies in women with RIF.[10, 23, 24] Recently, a systematic review and meta-analysis observed that aCL IgG positivity in women with RIF is 5.02 times higher than that in fertile women. Other aPL antibodies, which are not included in the laboratory criteria for APS, were also more prevalent among women with RIF, such as aβ2GPI IgA (OR, 64.8 [95% CI 9.74-431.0]), and antiphosphatidylglycerol-IgG and IgM (OR, 10.74 [95% CI 5.25-22.0] and OR, 4.26 [95% CI 1.76-10.31], respectively).[25]

Antinuclear antibodies

ANA is a class of autoantibodies that bind to cellular components in the nucleus, including proteins, DNA, RNA, and nucleic acid-protein complexes.[26] It was first described in 1948 and, since then, has been considered a marker for autoimmune connective tissue diseases, such as systemic lupus erythematosus, Sjogren's syndrome, and polymyositis/dermatomyositis.[26] Interestingly, up to 20% of the population can have a positive ANA test in the absence of a rheumatological disease. The researchers have suggested that ANA is a biomarker of immune dysregulation that increases the risk of some health disorders in individuals even without the presence of autoimmune diseases.[26]

The mechanisms responsible for reproductive failures associated with positive ANA need to be further investigated. Some researchers have suggested that women with positive ANA have poor oocyte quality, changes in embryonic development, and changes in the pattern of uterine blood flow that impair embryo implantation.[27-29] Furthermore, the presence of ANA can promote an inflammatory profile of the uterine microenvironment and greater activation of the complement system, along with the increased deposition of C3 and immune complexes in the placental tissue.[30]

The indirect immunofluorescence (IIF) test is the gold standard lab test for detecting ANA.[26] The positivity of the test is expressed in titers, which represent the concentration of the autoantibody in the blood. Generally, the presence of high titers is strongly related to autoimmune

diseases. Moreover, IIF also detects the pattern of positivity that correlates with specific ANA subtypes.[26] Anti-dsDNA, anti-histone, and anti-nucleosome antibodies are observed in a homogeneous fluorescence pattern. The membranous pattern is associated with the presence of antibodies against membrane proteins, whereas the speckled pattern occurs in the presence of antibodies directed to other nuclear antigens, and anti-Smith antibodies fluoresce in a course-speckled pattern. Anti-SSA/Ro and anti-SSB/La form a fine-speckled pattern. IIF with discrete speckles suggests anti-centromere antibodies. Moreover, nucleolar speckles are associated with antibodies targeting DNA topoisomerase (Scl-70). The speckled cytoplasmic pattern suggests antibodies to aminoacyl-tRNA synthetase (Jo-1). Furthermore, IIF titers and patterns are used in the diagnosis of a specific immune disease.[26]

Women with RPL and RIF tend to have a higher prevalence of positive ANA than the general population, which can be detected in up to 50% of cases.[14] Women with positive ANA are at high risk for reproductive failure, even when undergoing immunotherapy during pregnancy.[31, 32] ANA positivity was 3.3 times higher in patients with RPL (OR, 3.30; 95% CI 1.41-7.73; I^2 = 87%, P=0.006), including all IIF titers and patterns.[14] A recent systematic review and meta-analysis observed that infertile women with positive ANA undergoing in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI) had a lower pregnancy rate when compared with those with negative ANA (279/908 *vs.* 1136/2347; OR, 0.50, CI 95% 0.38–0.67; P<0.00001; I^2=58%).[13] Positive ANA also increased the miscarriage rate (48/223 *vs.* 109/999; OR, 3.25 95% CI, 1.57–6.76; P=0.002; I^2=61%) and decreased the implantation rate (320/1489 *vs.* 1437/4205; OR, 0.51; 95% CI, 0.36-0.72; P=0.0001; I^2=78%).[13]

Antithyroid antibodies

The relationship between thyroid dysfunction (hyper- or hypothyroidism), especially in the presence of autoimmune thyroiditis (AIT), such as Hashimoto's thyroiditis, and reproductive failure has been discussed in the literature. However, the impact of the presence of ATA in women with normal thyroid function on the risk of RPL and RIF is unclear.[33, 34] TPO-Ab and thyroglobulin antibodies (TgAb) are the two main ATA with a negative impact on female reproduction.[33, 34]

AIT is an immune condition generally associated with other abnormalities of cellular and humoral immunity that increase the risk of reproductive failure, such as an imbalance between the T Helper (Th)-1 and Th-2 immune responses, increased cytotoxicity of NK cells, and the presence of other autoantibodies (aPL and other organ-specific autoantibodies).[10, 35, 36] The theory of cross-reacting antibodies suggests that ATA bind to other tissues (*e.g.*, ovary, endometrium, and trophoblast) and harm the entire female reproductive process.[36-38] Moreover, the highest prevalence of ATA is observed in women with low ovarian reserve, poor oocyte and embryo quality in IVF cycles, and reproductive failure.[39-42]

Women with positive ATA tend to have a 3 times higher risk of sporadic pregnancy loss (OR, 3.90; 95% CI 2.48-6.12; P<0.001) and 2 times higher risk of RPL (OR, 2.36; 95% CI 1.71-3.25; P<0.00001).[15, 43] However, research on the negative impact of ATA on IVF/ICSI outcomes is limited. Busnelli *et al.* observed that ATA increased the miscarriage rate (OR, 1.44; 95% CI 1.06–1.95; P=0.02; I^2=35%) and decreased live birth rate (OR, 0.73; 95% CI 0.54-0.99; P=0.04; I^2=41%) in women undergoing IVF/ICSI.[44] Moon *et al.* reported that the presence of ATA alone does not affect the clinical outcomes in IVF/ICSI cycles.[45] However, the association of ATA and subclinical hypothyroidism has been shown to worsen miscarriage and live birth rates in patients undergoing IVF/ICSI.[45] Other researchers have also observed that ATA does not affect the clinical outcomes of IVF/ICSI in euthyroid women.[46]

The international guidelines for managing couples with RPL recommend assessing thyroid function and measuring ATA levels.[2, 12] Moreover, it is recommended that infertile women be screened for serum TSH and ATA levels. Women who desire to become pregnant should monitor their thyroid function. Moreover, the recommendation for hormone therapy is still controversial. It has also been established that thyroid hormone supplementation should be started when TSH levels exceed 4.0 mIU/L.[34]

Cellular immunity

The embryo is considered an allograft for the mother. Since Medawar's first studies, reproductive immunology has sought to understand the uterine and systemic immune mechanisms responsible for maternal allotolerance.[47] Some studies suggest that abnormalities in the systemic cellular immune response and the uterine microenvironment immune response are responsible for obstetric complications.[8, 10] Moreover, NK cells, T lymphocytes, mast cells, macrophages, and dendritic cells are the most important immune effectors involved in the maternal immune response, especially in cases of RPL and RIF.[8, 10]

Natural killer cell

NK cells are the cells responsible for innate immunity. Uterine NK (uNK) cells and peripheral blood NK (pbNK) cells are key cells in embryo implantation. uNK and pbNK cells differ in function and characteristics. uNK cells are abundant in the endometrium and their main characteristic is reduced cytotoxic activity and increased production of cytokines and growth factors. pbNK cellsz are more cytotoxic and act mainly in defense against infections and tumor cells.[48, 49]

They regulate trophoblastic invasion, angiogenesis, and the remodeling of uterine spiral arteries.[48, 49] Interestingly, the concentration of uNK cells varies throughout the menstrual cycle, reaching its maximum concentration in the secretory phase, during the embryo implantation window.[48] This cyclical pattern of endometrial immune cell concentrations has gained interest in the relationship between disorders in the concentration and activity of uNK cells and reproductive failure.[48]

High concentrations of uNK cells, uNK immaturity, and higher cytotoxicity of uNK cells have been shown to increase the risk of reproductive failure. However, the investigation of uNK cells in patients with RPL and RIF has not yet been standardized. The following studies were heterogeneous and used different assays (*e.g.*, immunohistochemistry and flow cytometry) and markers (*e.g.*, CD56, CD57, CD16).[48] Woon *et al.* observed a higher CD56+ (endometrial tissue) uNK level in women with RPL compared with controls (standardized mean difference [SMD], 0.49; CI 0.08–0.90; P=0.02; I^2=88%).[50] The researchers also reported elevated levels of CD56+ uNK cells in the endometrium of women with RIF compared with controls (SMD, 0.49; CI 0.01-0.98; P=0.046; I^2=84%). The endometrial CD56 + CD16-, decidual CD56+, and decidual CD56 + CD16- were similar between the groups (RPL *vs.* control).[50]

The number, concentration, and cytotoxicity of the NK cells were the most studied biomarkers of reproductive failure.[50-52] Elevated concentrations of NK cells have been observed in women with unexplained RPL and RIF.[50, 51] However, these results have not been confirmed by other researchers.[50, 51] Recently, a systematic review and meta-analysis observed increased cytotoxicity of pbNK cells both in the preconception period (mean difference [MD], 7.99; 95% CI 6.40-9.58; P<0.00001; I^2=39%) and during pregnancy in women with RPL (MD, 8.21; 95% CI 6.08-10.34; P<0.00001; I^2=66%).[52]

T helper and regulatory T cells

The balance of the pro- and anti-inflammatory immune response is essential to achieve successful pregnancy. Wegmann *et al.* suggested that the dysregulation of the dichotomy of Th1 and Th2 immune responses increased the risk of reproductive failure.[53] Since then, several researchers have reported that women with RPL and RIF had an abnormal Th1/Th2 cytokine ratio, with a predominantly inflammatory response pattern.[10, 54-57]

The proportion of TNF-α Th cells and Th1/Th2 cell ratios (TNF-α/IL-4 and TNF-α/IL-10) were significantly higher in women with RIF and RPL.[58] The researchers suggest that reestablishing a normal Th1/Th2 ratio improves the gestational outcomes. Lymphocyte immunotherapy (LIT), intravenous human immunoglobulin (IVIG), calcineurin inhibitors, and intravenous lipid emulsions (ILE) are therapeutic options for cases of reproductive failure induced by the dysregulation of the Th1/Th2 immune response.[57, 59-61]

Regulatory T lymphocytes (Treg) are a subpopulation of T lymphocytes (CD4 + FOXP3 + CD25+) that have the ability to regulate the im-

mune response and maintain self-tolerance, limit tissue damage, and prevent the occurrence of autoimmune diseases. Failure in the action of Treg lymphocytes can trigger a breakdown in self-tolerance and consequently result in immune reactions against self-antigens, which is known as autoimmunity.[62] Histopathological analyses have observed that the proportion of decidual Treg cells was significantly lower in induced spontaneous abortion samples compared with abortion samples.[63] Moreover, an animal study suggested that fetal antigens induce an increase in the concentration of Treg cells during pregnancy, which is essential for the maternal allotolerance immune response in the first trimester of pregnancy.[64]

Clinical studies have observed that disorders in Treg cells and Th1/Th2 ratio have a good predictive capacity for pregnancy outcome in patients with RPL and their combined predictive efficacy is higher.[65, 66]

Endometrial biomarkers

The endometrium plays a crucial role in the embryo implantation process. The population of immune system cells in the endometrium (periconceptional period) and decidua (site of implantation) is dynamic. In the implantation window, the proportions of immune cells in the endometrium were 40% NK cells, 20% macrophages, 40% Th-1 lymphocytes, and 1.4% Th-2 lymphocytes.[67] Subsequently, in the first trimester of pregnancy, the percentage of immune system cells has changed to 60% NK cells, 25% macrophages, 10% Th-1 lymphocytes, and 15% Th-2 lymphocytes.[67]

The Noyes criterion, which was proposed in 1975, is a valuable tool in evaluating morphological aspects that may influence endometrial receptivity. It is based on the histological analysis of the endometrium, detailing the presence of secretory glands, edematous stroma, and inflammatory cells.[68] These elements indicate the phase of the menstrual cycle and the ability of the endometrium to allow successful embryo implantation.[68] Some specific features within the Noyes criteria appear to have predictive power for successful embryo implantation. Key predictive features include adequate secretory transformation, decidualization and predecidual cell formation, stromal edema, and vascular changes indicating healthy endometrial remodeling.[68] Subsequently, other endometrial biomarkers capable of predicting the success of embryo implantation were investigated, such as uNK cells, plasma cells (CD138), mucin-1 (MUC1), and pro- and anti-inflammatory interleukins.[51, 69-71]

The growth of molecular biology assays has allowed several tools to be proposed to evaluate genes expressed in the endometrial tissue that define the success of endometrial implantation. Dıaz-Gimeno *et al.* observed that approximately half of the genes expressed in the implantation window are involved in immunological mechanisms in the endometrial environment.[72] Endometrial immune profiling (EIP) and the endometrial decidualization score (EDS) are the most promising immune assessment techniques for endometrial receptivity.[73, 74] These tests can help diagnose and treat patients with RPL and RIF.

Endometrial immune profile

EIP, which was proposed in 2016, is used to evaluate the endometrial immune response through the gene expression of five biomarkers, that is, IL-15, IL-18, TNF-like weak inducer of apoptosis (TWEAK), fibroblast growth factor-inducible molecule 14 (Fn14), and NK cells (CD56).[73] The pattern of the endometrial immune response is classified into four categories (*i.e.*, normal activation, local immune overactivation, local immune low activation, and mixed pattern) based on the relationship between the previously mentioned biomarkers, which define three variables as follows: (1) IL-18/TWEAK, (2) IL-15/Fn14, and (3) CD56.[73]

An observational study that evaluated the pattern of EIP in women with reproductive failure has observed that 16.5% of patients did not have endometrial immune dysregulation, 28% had local immune low activation, 45% had local immune overactivation, and 10.5% had a mixed pattern.[75] The researchers suggest that immunotherapy be personalized based on the EIP pattern. Immunosuppressive drugs (*e.g.*, corticosteroids, heparin, and ILE), high concentration of estrogens in the proliferative phase, and the hormonal

adaptation of the luteal phase are indicated in patients with overactivated profiles. Patients with low immune activation should be treated with endometrial scratching, luteal hCG supplementation, and exposure to seminal plasma. The management of patients with RPL and RIF due to immunological causes based on EIP increased the pregnancy rate (57.6% *vs.* 25% [P=0.001] and 38.4% *vs.* 26.9% [P=0.002]).[75]

Endometrial decidualization score

Decidualization is a process that occurs in the endometrial tissue, which involves the preparation of the uterus for embryo implantation and successful pregnancy. The EDS evaluates the expression of six genes involved in this process.[74] The FOXO1 gene promotes progesterone signaling and decidualization; SGK1, SCNN1A, and SLC2A1 are involved in tissue and cellular homeostasis; and IL-15 and GZMB are associated with endometrial immunoregulation and tissue remodeling.[74] Of the women with reproductive failures, 76% had an EDS of <4, and 19% had an EDS of 0, whereas 89% and 11% of the fertile controls had EDS scores of 5 and 4, respectively. Furthermore, the risk of abnormal decidualization occurs when the EDS is less than 4.[74]

Immunotherapies

Immunotherapies for the treatment of couples with reproductive failures have been proposed ever since the early 1980s.[76] No consensus on the routine use of these therapies in the management of couples with RPL and RIF has yet been made. The objective of immunotherapies is to reestablish a maternal immune response that is favorable to embryo implantation. The vast majority of immunotherapies that have been studied tend to have immunosuppressive effects. The mechanisms of action common to immunotherapies are as follows: T-cell suppression, decrease in the level of maternal IL-2 receptor, reduction in the level of IL-6, inhibition in the level of Th1 cytokines, decreased cytotoxicity of pbNK cells, increased levels of progesterone-induced blocking factor, and the balance of the Th1/Th2 and Th17/Treg (CD4+ CD25+) immune response.[77-81]

The first immunotherapy proposed for the treatment of RPL was LIT.[76] In the past decades, most randomized controlled trials and meta-analyses concur with the fact that LIT improves the live birth rate in patients with RPL.[82-84] Although the literature supports the use of LIT in the treatment of couples with RPL, LIT prescription is limited in some countries only being permitted in research protocols. Furthermore, the results of several studies evaluating the use of LIT in cases of RIF are still unclear.[85]

IVIG is a blood derivative that was developed to treat primary immunodeficiency. IVIG was first prescribed in the early 1950s.[86] In 1989, Mueller-Eckhardt *et al.* first proposed the use of IVIG for the treatment of RPL.[87] Studies have suggested that RPL patients with immune disorders (*e.g.*, Th1/Th2 immune response imbalance and elevated pbNK cytotoxicity) are potentially the group of patients who benefit most from this immunotherapy.[84] European Society of Human Reproduction and Embryology recognized that IVIG may improve the live birth rate in females with four or more unexplained RPL.[2] More recent studies have also suggested that IVIG also appears to improve the clinical outcomes in IVF/ICSI cycles for patients with RIF.[88-91]

Lipid emulsion or fat emulsion is a solution composed of fats that was developed for the nutritional support of seriously ill patients. ILE was initially approved for parenteral nutrition in 1962 in Sweden.[92] Subsequently, some immunological effects of ILE were observed, such as the inhibition of pbNK cell cytotoxicity and reestablishment of the Th1/Th2 cytokine balance.[93, 94] Thus, several studies began to observe that the use of ILE increases the birth rate in patients with RPL and RIF.[84] Recently, Khairy *et al.* published a large prospective, quasi-randomized study, with more than 27,000 patients, wherein they observed an increase in live birth rates in patients with RIF undergoing treatment with ILE alone or in combination with corticosteroids and heparin.[95]

Glucocorticoids, heparin, calcineurin inhibitors, vitamin D, recombinant granulocyte colony-stimulating factor, tumor necrosis factor-alpha antagonists, hydroxychloroquine, and human chorionic gonadotropin are drugs with immunomodulatory effects that can improve obstetric outcomes in women with RPL and RIF.

Future perspectives

The investigation and treatment of immunological causes in cases of reproductive failure (RPL and RIF) is a matter of debate in reproductive medicine. New laboratory tests have shown the presence of different immune disorders that contribute to reproductive failure. Recently, there has been an advancement in reproductive failure management guidelines that now recommend the investigation of immune biomarkers and the use of immunotherapies (*e.g.*, IVIG in cases of RPL).[2, 12] Previous studies that discussed the effectiveness of some immunotherapies have been questioned with regard to their methodological flaws.[96-101] The indication of any immune intervention must be personalized based on a detailed immune diagnosis. EIP and EDS are examples of laboratory tests that are capable of personalizing the diagnosis of immune abnormalities and directing the best treatment for each subgroup of patients with reproductive failure.[73-75] Furthermore, it is expected that new biomarkers will be studied and randomized clinical trials will be performed to test the effectiveness of immunotherapies.

Conclusions

This review article on immune biomarkers in RPL and RIF highlights the role of immune dysregulation in these reproductive failures. Key findings show that autoantibodies, such as aPL, ANA, and ATA antibodies, are prevalent among patients with RPL and RIF, even without established autoimmune diseases. Cellular immune factors like elevated NK cell activity, Th1/Th2 imbalance, and reduced Treg cells also play significant roles. Identifying these biomarkers can help personalize treatments, such as the use of immunotherapies to improve pregnancy outcomes in affected patients.

The management of RPL and RIF is still considered a challenge in reproductive medicine. Immune disorders are common in women with reproductive failure. New laboratory assays that have been developed for the investigation of immune biomarkers help in the detection of immune abnormalities in patients with RPL and RIF and contribute to the personalization of immunotherapies that can improve the obstetric outcomes of these patients. Despite recent advances in the immune management of reproductive failure cases, such as RPL and RIF, new studies with standardized protocols for immunological investigation and treatment are necessary.

References

1. Kolte AM, Bernardi LA, Christiansen OB, Quenby S, Farquharson RG, Goddijn M, *et al.*; ESHRE Special Interest Group, Early Pregnancy. Terminology for pregnancy loss prior to viability: a consensus statement from the ESHRE early pregnancy special interest group. Hum Reprod 2015;30:495–8.

2. Bender Atik R, Christiansen OB, Elson J, Kolte AM, Lewis S, Middeldorp S, *et al.*; ESHRE Guideline Group on RPL. ESHRE guideline: recurrent pregnancy loss: an update in 2022. Hum Reprod Open 2023;2023:hoad002.

3. Genovese HG, McQueen DB. The prevalence of sporadic and recurrent pregnancy loss. Fertil Steril 2023;120:934–6.

4. Cimadomo D, de Los Santos MJ, Griesinger G, Lainas G, Le Clef N, McLernon DJ, *et al.*; ESHRE Working Group on Recurrent Implantation Failure. ESHRE good practice recommendations on recurrent implantation failure. Hum Reprod Open 2023;2023:hoad023.

5. Toth B, Bohlmann M, Hancke K, Kuon R, Nawroth F, von Otte S, *et al.* Recurrent Miscarriage: Diagnostic and Therapeutic Procedures. Guideline of the DGGG, OEGGG and SGGG (S2k-Level, AWMF Registry No. 015/050, May 2022). Geburtshilfe Frauenheilkd 2022;83:49–78.

6. Practice Committee of the American Society for Reproductive Medicine. Evaluation and treatment of recurrent pregnancy loss: a committee opinion. Fertil Steril 2012;98:1103–11.

7. Mor G. Introduction to the immunology of pregnancy. Immunol Rev 2022;308:5–8.

8. Mor G, Cardenas I. The immune system in pregnancy: a unique complexity. Am J Reprod Immunol 2010;63:425–33.

9. Tincani A, Dall'Ara F, Lazzaroni MG, Reggia R, Andreoli L. Pregnancy in patients with autoimmune disease: A reality in 2016. Autoimmun Rev 2016;15:975–7.

10. Kwak-Kim J, Skariah A, Wu L, Salazar D, Sung N, Ota K. Humoral and cellular autoimmunity in women with recurrent pregnancy losses and repeated implantation failures: A possible role of vitamin D. Autoimmun Rev 2016;15:943–7.

11. Norman RJ. Immunology in reproductive medicine: is current testing and therapy justified by science? Fertil Steril 2022;117:1105–6.

12. Ali A, Elfituri A, Doumouchtsis SK, Zini ME, Jan H, Ganapathy R, *et al.* Managing couples with recurrent miscarriage: A narrative review and practice recommendations. Int J Gynaecol Obstet 2024;164:499–503.

13. Ticconi C, Inversetti A, Logruosso E, Ghio M, Casadei L, Selmi C, *et al.* Antinuclear antibodies positivity in women in reproductive age: from infertility to adverse obstetrical outcomes - A meta-analysis. J Reprod Immunol 2023;155:103794.

14. Cavalcante MB, Cavalcante CT, Sarno M, da Silva AC, Barini R. Antinuclear antibodies and recurrent miscarriage: systematic review and meta-analysis. Am J Reprod Immunol 2020;83:e13215.

15. Xie J, Jiang L, Sadhukhan A, Yang S, Yao Q, Zhou P, *et al.* Effect of antithyroid antibodies on women with recurrent miscarriage: A meta-analysis. Am J Reprod Immunol 2020;83:e13238.

16. Di Simone N, Gratta M, Castellani R, D'Ippolito S, Specchia M, Scambia G, *et al.* Celiac disease and reproductive failures: an update on pathogenic mechanisms. Am J Reprod Immunol 2021;85:e13334.

17. Hughes GR. Thrombosis, abortion, cerebral disease, and the lupus anticoagulant. Br Med J (Clin Res Ed) 1983;287:1088–9.

18. Sammaritano LR. Antiphospholipid syndrome. Best Pract Res Clin Rheumatol 2020;34:101463.

19. Kemp M, Thomas W. Antiphospholipid syndrome in obstetrics. Lupus 2018;27(1_suppl):28–31.

20. de Laat B, Mertens K, de Groot PG. Mechanisms of disease: antiphospholipid antibodies-from clinical association to pathologic mechanism. Nat Clin Pract Rheumatol 2008;4:192–9.

21. Chaturvedi S, Brodsky RA, McCrae KR. Complement in the Pathophysiology of the Antiphospholipid Syndrome. Front Immunol 2019;10:449.

22. Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, Cervera R, *et al.* International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost 2006;4:295–306.

23. McIntyre JA. Antiphospholipid antibodies in implantation failures. Am J Reprod Immunol 2003;49:221–9.

24. Wu L, Fang X, Lu F, Zhang Y, Wang Y, Kwak-Kim J. Anticardiolipin and/or anti-β2-glycoprotein-I antibodies are associated with adverse IVF outcomes. Front Immunol 2022;13:986893.

25. Jarne-Borràs M, Miró-Mur F, Anunciación-Llunell A, Alijotas-Reig J. Antiphospholipid antibodies in women with recurrent embryo implantation failure: A systematic review and meta-analysis. Autoimmun Rev 2022;21:103101.

26. Ling M, Murali M. Antinuclear Antibody Tests. Clin Lab Med 2019;39:513–24.

27. Fan J, Zhong Y, Chen C. Impacts of Anti-dsDNA Antibody on In Vitro Fertilization-Embryo Transfer and Frozen-Thawed Embryo Transfer. J Immunol Res 2017;2017:8596181.

28. Li Y, Wang Y, Lan Y, Zhang J, Liang Y, Wang S. Antinuclear antibodies in follicular fluid may reduce efficacy of in vitro fertilization and embryo transfer by invading endometrium and granular cells. Am J Reprod Immunol 2020;84:e13289.

29. Pietropolli A, Bruno V, Capogna MV, Bernardini S, Piccione E, Ticconi C. Uterine blood flow indices, antinuclear autoantibodies and unexplained recurrent miscarriage. Obstet Gynecol Sci 2015;58:453–60.

30. Veglia M, D'Ippolito S, Marana R, Di Nicuolo F, Castellani R, Bruno V, *et al.* Human IgG Antinuclear Antibodies Induce Pregnancy Loss in Mice by Increasing Immune Complex Deposition in Placental Tissue: In Vivo Study. Am J Reprod Immunol 2015;74:542–52.

31. Cavalcante MB, Costa FS, Araujo Júnior E, Barini R. Risk factors associated with a new pregnancy loss and perinatal outcomes in cases of recurrent miscarriage treated with lymphocyte immunotherapy. J Matern Fetal Neonatal Med 2015;28:1082–6.

32. Cavalcante MB, Sarno M, Niag M, Pimentel K, Luz I, Figueiredo B, *et al.* Lymphocyte immunotherapy for recurrent miscarriages: predictors of therapeutic success. Am J Reprod Immunol 2018;79:e12833.

33. Poppe K. MANAGEMENT OF ENDOCRINE DISEASE: Thyroid and female infertility: more questions than answers?! Eur J Endocrinol 2021;184:R123–35.

34. Poppe K, Bisschop P, Fugazzola L, Minziori G, Unuane D, Weghofer A. 2021 European Thyroid Association Guideline on Thyroid Disorders prior to and during Assisted Reproduction. Eur Thyroid J 2021;9:281–95.

35. Kim NY, Cho HJ, Kim HY, Yang KM, Ahn HK, Thornton S, *et al.* Thyroid autoimmunity and its association with cellular and humoral immunity in women with reproductive failures. Am J Reprod Immunol 2011;65:78–87.

36. Twig G, Shina A, Amital H, Shoenfeld Y. Pathogenesis of infertility and recurrent pregnancy loss in thyroid autoimmunity. J Autoimmun 2012;38:J275–81.

37. Monteleone P, Parrini D, Faviana P, Carletti E, Casarosa E, Uccelli A, *et al.* Female infertility related to thyroid autoimmunity: the ovarian follicle hypothesis. Am J Reprod Immunol 2011;66:108–14.

38. Rahnama R, Mahmoudi AR, Kazemnejad S, Salehi M, Ghahiri A, Soltanghoraee H, *et al.* Thyroid peroxidase in human endometrium and placenta: a potential target for anti-TPO antibodies. Clin Exp Med 2021;21:79–88.

39. Cevher Akdulum MF, Erdem M, Barut G, Demirdag E, İyidir ÖT, Guler I, *et al.* The relationship between thyroid autoimmunity and poor response to ovarian stimulation in in vitro fertilization women with infertility. Endokrynol Pol 2022;73:699–705.

40. Andrisani A, Sabbadin C, Marin L, Ragazzi E, Dessole F, Armanini D, *et al.* The influence of thyroid autoimmunity on embryo quality in women undergoing assisted reproductive technology. Gynecol Endocrinol 2018;34:752–5.

41. Ali Ghalib HH, Najmaddin Fattah C, Mohammed AK. Association between antithyroid peroxidase antibody and recurrent miscarriage. Eur Rev Med Pharmacol Sci 2023;27:3003–8.

42. Hasegawa Y, Kitahara Y, Osuka S, Tsukui Y, Kobayashi M, Iwase A. Effect of hypothyroidism and thyroid autoimmunity on the ovarian reserve: A systematic review and meta-analysis. Reprod Med Biol 2021;21:e12427.

43. Thangaratinam S, Tan A, Knox E, Kilby MD, Franklyn J, Coomarasamy A. Association between thyroid autoantibodies and miscarriage and preterm birth: meta-analysis of evidence. BMJ 2011;342:d2616.

44. Busnelli A, Paffoni A, Fedele L, Somigliana E. The impact of thyroid autoimmunity on IVF/ICSI outcome: a systematic review and meta-analysis. Hum Reprod Update 2016;22:793–4.

45. Moon KY, Paik H, Jee BC, Kim SH. Impact of thyroid autoantibodies and serum TSH level on clinical IVF outcomes. Taiwan J Obstet Gynecol 2023;62:735–41.

46. Venables A, Wong W, Way M, Homer HA. Thyroid autoimmunity and IVF/ICSI outcomes in euthyroid women: a systematic review and meta-analysis. Reprod Biol Endocrinol 2020;18:120.

47. Billingham RE, Brent L, Medawar PB. Actively acquired tolerance of foreign cells. Nature 1953;172:603–6.

48. Díaz-Hernández I, Alecsandru D, García-Velasco JA, Domínguez F. Uterine natural killer cells: from foe to friend in reproduction. Hum Reprod Update 2021;27:720–46.

49. Guerrero B, Hassouneh F, Delgado E, Casado JG, Tarazona R. Natural killer cells in recurrent miscarriage: an overview. J Reprod Immunol 2020;142:103209.

50. Von Woon E, Greer O, Shah N, Nikolaou D, Johnson M, Male V. Number and function of uterine natural killer cells in recurrent miscarriage and implantation failure: a systematic review and meta-analysis. Hum Reprod Update 2022;28:548–82.

51. Seshadri S, Sunkara SK. Natural killer cells in female in-

fertility and recurrent miscarriage: a systematic review and meta-analysis. Hum Reprod Update 2014;20:429–38.

52. Cavalcante MB, da Silva PH, Carvalho TR, Sampaio OG, Câmara FE, Cavalcante CT, *et al.* Peripheral blood natural killer cell cytotoxicity in recurrent miscarriage: a systematic review and meta-analysis. J Reprod Immunol 2023;158:103956.

53. Wegmann TG, Lin H, Guilbert L, Mosmann TR. Bidirectional cytokine interactions in the maternal-fetal relationship: is successful pregnancy a TH2 phenomenon? Immunol Today 1993;14:353–6.

54. Lee SK, Na BJ, Kim JY, Hur SE, Lee M, Gilman-Sachs A, *et al.* Determination of clinical cellular immune markers in women with recurrent pregnancy loss. Am J Reprod Immunol 2013;70:398–411.

55. Kwak-Kim J, AlSubki L, Luu T, Ganieva U, Thees A, Dambaeva S, *et al.* The role of immunologic tests for subfertility in the clinical environment. Fertil Steril 2022;117:1132–43.

56. Ebrahimi F, Omidvar-Mehrabadi A, Shahbazi M, Mohammadnia-Afrouzi M. Innate and adaptive immune dysregulation in women with recurrent implantation failure. J Reprod Immunol 2024;164:104262.

57. Nakagawa K, Sugiyama R. Tacrolimus treatment in women with repeated implantation failures. Reprod Med Biol 2024;23:e12558.

58. Yin B, Zeng Y, Wu T, Yu S, Xu J, Liu S, *et al.* Functional properties of peripheral CD8+ T cells in patients with repeated implantation failure. Am J Reprod Immunol 2017;78.

59. Ahmadi M, Abdolmohammadi-Vahid S, Ghaebi M, Aghebati-Maleki L, Afkham A, Danaii S, *et al.* Effect of Intravenous immunoglobulin on Th1 and Th2 lymphocytes and improvement of pregnancy outcome in recurrent pregnancy loss (RPL). Biomed Pharmacother 2017;92:1095–102.

60. Yokoo T, Takakuwa K, Ooki I, Kikuchi A, Tamura M, Tanaka K. Alteration of TH1 and TH2 cells by intracellular cytokine detection in patients with unexplained recurrent abortion before and after immunotherapy with the husband's mononuclear cells. Fertil Steril 2006;85:1452–8.

61. Liu J, Li M, Fu J, Yuan G, Li N, Fu Y, *et al.* Tacrolimus improved the pregnancy outcomes of patients with refractory recurrent spontaneous abortion and immune bias disorders: a randomized controlled trial. Eur J Clin Pharmacol 2023;79:627–34.

62. Kumar P, Marron K, Harrity C. Intralipid therapy and adverse reproductive outcome: is there any evidence? Reprod Fertil 2021;2:173–86.

63. Hardtke-Wolenski M, Landwehr-Kenzel S. Tipping the balance in autoimmunity: are regulatory t cells the cause, the cure, or both? Mol Cell Pediatr 2024;11:3.

64. Sasaki Y, Sakai M, Miyazaki S, Higuma S, Shiozaki A, Saito S. Decidual and peripheral blood CD4+CD25+ regulatory T cells in early pregnancy subjects and spontaneous abortion cases. Mol Hum Reprod 2004;10:347–53.

65. Wang Q, Zhang J, Wang F. A Study of the Predictive Value of Treg and Th1/Th2 Cytokines on Pregnancy Outcome in Patients with Recurrent Pregnancy Loss. Altern Ther Health Med 2023;29:400–3.

66. Wang W, Sung N, Gilman-Sachs A, Kwak-Kim J. T Helper (Th) Cell Profiles in Pregnancy and Recurrent Pregnancy Losses: Th1/Th2/Th9/Th17/Th22/Tfh Cells. Front Immunol 2020;11:2025.

67. Norwitz ER, Schust DJ, Fisher SJ. Implantation and the survival of early pregnancy. N Engl J Med 2001;345:1400–8.

68. Noyes RW, Hertig AT, Rock J. Dating the endometrial biopsy. Am J Obstet Gynecol 1975;122:262–3.

69. Horne AW, Lalani EN, Margara RA, Ryder TA, Mobberley MA, White JO. The expression pattern of MUC1 glycoforms and other biomarkers of endometrial receptivity in fertile and infertile women. Mol Reprod Dev 2005;72:216–29.

70. Goto T, Goto S, Ozawa F, Yoshihara H, Kitaori T, Komura M, *et al.* The association between chronic deciduitis and recurrent pregnancy loss. J Reprod Immunol 2023;156:103824.

71. Tuckerman E, Laird SM, Stewart R, Wells M, Li TC. Markers of endometrial function in women with unexplained recurrent pregnancy loss: a comparison between morphologically normal and retarded endometrium. Hum Reprod 2004;19:196–205.

72. Díaz-Gimeno P, Horcajadas JA, Martínez-Conejero JA, Esteban FJ, Alamá P, Pellicer A, *et al.* A genomic diagnostic tool for human endometrial receptivity based on the transcriptomic signature. Fertil Steril 2011;95:50–60, 60.e1–15.

73. Lédée N, Petitbarat M, Chevrier L, Vitoux D, Vezmar K, Rahmati M, *et al.* The Uterine Immune Profile May Help Women With Repeated Unexplained Embryo Implantation Failure After In Vitro Fertilization. Am J Reprod Immunol 2016;75:388–401.

74. Dambaeva S, Bilal M, Schneiderman S, Germain A, Fernandez E, Kwak-Kim J, *et al.* Decidualization score identifies an endometrial dysregulation in samples from women with recurrent pregnancy losses and unexplained infertility. F S Rep 2020;2:95–103.

75. Lédée N, Petitbarat M, Prat-Ellenberg L, Dray G, Cassuto GN, Chevrier L, *et al.* Endometrial Immune Profiling: A Method to Design Personalized Care in Assisted Reproductive Medicine. Front Immunol 2020;11:1032.

76. Taylor C, Faulk WP. Prevention of recurrent abortion with leucocyte transfusions. Lancet 1981;2:68–70.

77. Aslanian-Kalkhoran L, Kamrani A, Alipourfard I, Chakari-Khiavi F, Chakari-Khiavi A, Aghebati-Maleki L, *et al.* The effect of lymphocyte immunotherapy (LIT) in modulating immune responses in patients with recurrent pregnancy loss (RPL). Int Immunopharmacol 2023;121:110326.

78. Higuchi K, Aoki K, Kimbara T, Hosoi N, Yamamoto T, Okada H. Suppression of natural killer cell activity by monocytes following immunotherapy for recurrent spontaneous aborters. Am J Reprod Immunol 1995;33:221–7.

79. Kheshtchin N, Gharagozloo M, Andalib A, Ghahiri A, Maracy MR, Rezaei A. The expression of Th1- and Th2-related chemokine receptors in women with recurrent miscarriage: the impact of lymphocyte immunotherapy. Am J Reprod Immunol 2010;64:104–12.

80. Kilpatrick DC. Soluble interleukin-2 receptors in recurrent miscarriage and the effect of leukocyte immunotherapy. Immunol Lett 1992;34:201–6.

81. Pandey MK, Thakur S, Agrawal S. Lymphocyte immunotherapy and its probable mechanism in the maintenance of pregnancy in women with recurrent spontaneous abortion. Arch Gynecol Obstet 2004;269:161–72.

82. Mowbray JF, Gibbings C, Liddell H, Reginald PW, Underwood JL, Beard RW. Controlled trial of treatment of recurrent spontaneous abortion by immunisation with paternal cells. Lancet 1985;1:941–3.

83. Beer AE. How did your mother not reject you? Ann Immunol (Paris) 1984;135D:315–8.

84. Cavalcante MB, Alcântara da Silva PH, Sampaio OG, Câmara FE, de Melo Bezerra Cavalcante CT, Barini R. The use of immunotherapies for recurrent miscarriage: an overview of systematic reviews and meta-analysis. J Reprod Immunol 2023;158:103986.

85. Cavalcante MB, Sarno M, Barini R. Lymphocyte immu-

notherapy in recurrent miscarriage and recurrent implantation failure. Am J Reprod Immunol 2021;85:e13408.

86. Eibl MM. History of immunoglobulin replacement. Immunol Allergy Clin North Am 2008;28:737–64, viii.

87. Mueller-Eckhardt G, Heine O, Neppert J, Künzel W, Mueller-Eckhardt C. Prevention of recurrent spontaneous abortion by intravenous immunoglobulin. Vox Sang 1989;56:151–4.

88. Peero EK, Banjar S, Khoudja R, Ton-Leclerc S, Beauchamp C, Benoit J, *et al.* Intravenous immunoglobulin for patients with unexplained recurrent implantation failure: a 6-year single center retrospective review of clinical outcomes. Sci Rep 2024;14:3876.

89. He Y, Tang R, Yu H, Mu H, Jin H, Dong J, *et al.* Comparative effectiveness and safety of 36 therapies or interventions for pregnancy outcomes with recurrent implantation failure: a systematic review and network meta-analysis. J Assist Reprod Genet 2023;40:2343–56.

90. Sung N, Khan SA, Yiu ME, Jubiz G, Salazar MD, Skariah A, *et al.* Reproductive outcomes of women with recurrent pregnancy losses and repeated implantation failures are significantly improved with immunomodulatory treatment. J Reprod Immunol 2021;148:103369.

91. Woon EV, Day A, Bracewell-Milnes T, Male V, Johnson M. Immunotherapy to improve pregnancy outcome in women with abnormal natural killer cell levels/activity and recurrent miscarriage or implantation failure: A systematic review and meta-analysis. J Reprod Immunol 2020;142:103189.

92. Hallberg D, Holm I, Obel AL, Schuberth O, Wretlind A. Fat emulsion for complete intravenous nutrition. Postgrad Med 1967;42:A149–52.

93. Meng L, Lin J, Chen L, Wang Z, Liu M, Liu Y, *et al.* Effectiveness and potential mechanisms of intralipid in treating unexplained recurrent spontaneous abortion. Arch Gynecol Obstet 2016;294:29–39.

94. Abdolmohammadi-Vahid S, Danaii S, Hamdi K, Jadidi-Niaragh F, Ahmadi M, Yousefi M. Novel immunotherapeutic approaches for treatment of infertility. Biomed Pharmacother 2016;84:1449–59.

95. Khairy M, Harb H, Eapen A, Melo P, Kazem R, Rajkhowa M, *et al.* The use of immunomodulation therapy in women with recurrent implantation failure undergoing assisted conception: A multicentre cohort study. Am J Reprod Immunol 2024;91:e13819.

96. Sun Y, Cui L, Lu Y, Tan J, Dong X, Ni T, *et al.* Prednisone vs Placebo and Live Birth in Patients With Recurrent Implantation Failure Undergoing In Vitro Fertilization: A Randomized Clinical Trial. JAMA 2023;329:1460–8.

97. Cavalcante MB, Barini R. Prednisone and Live Birth Rate in Patients With Recurrent Implantation Failure. JAMA 2023;330:970–1.

98. van Hoogenhuijze NE, Mol F, Laven JS, Groenewoud ER, Traas MA, Janssen CA, *et al.* Endometrial scratching in women with one failed IVF/ICSI cycle-outcomes of a randomised controlled trial (SCRaTCH). Hum Reprod 2021;36:87–98.

99. Cavalcante MB, Barini R, Kwak-Kim J. Endometrial scratching for embryo implantation failure-uterine immune biomarkers as a selection criterion. Hum Reprod 2021;36:1446–7.

100. Eapen A, Joing M, Kwon P, Tong J, Maneta E, De Santo C, *et al.*; RESPONSE study group. Recombinant human granulocyte- colony stimulating factor in women with unexplained recurrent pregnancy losses: a randomized clinical trial. Hum Reprod 2019;34:424–32.

101. Cavalcante MB, Sarno M, Ricardo B. Recombinant human granulocyte-colony stimulating factor for all recurrent miscarriage patients or for a select group? Hum Reprod 2019;34:2081–3.

Conflicts of interest

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors' contributions

Marcelo B. Cavalcante conceived the idea of this review and draft of the manuscript; Manoel Sarno and Ricardo Barini revised the manuscript critically for important intellectual content. All authors contributed to the writing of this article and approved the final version of the manuscript.

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