Immunological Diagnostics for Infertility: Cellular, Molecular, and Genetic Comprehensive Review

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ABSTRACT

Pregnancy represents a unique immunological state where pregnant women develop tolerance mechanisms to avoid fetal rejection. Various mechanisms modulate the maternal immune system to prevent this rejection. Despite these mechanisms, infertility affects approximately 8-12% of reproductive-age couples, particularly those experiencing recurrent implantation failure and recurrent pregnancy loss. Assisted reproductive techniques have significantly advanced in recent decades, yet success rates remain relatively low. Endometrial immune profiling is crucial in understanding infertility and constitutes a distinct microenvironment during pregnancy. Consequently, research has focused on analyzing specific biomarkers, cytokines, and identifying immune system disorders within this context. This approach aims to provide insights for developing personalized treatments. This review examines cellular immune markers, molecular/genetic markers in endometrial studies, and autoantibodies involved in infertility.

Keywords: Immunological Diagnostics, Infertility, Genetic

1. Introduction

Miscarriage, the most common pregnancy complication, often occurs unexpectedly and can have devastating psychological and physical effects (1). It is reported that about 10-20% of clinically confirmed pregnancies end in miscarriage (3-5). Potential causes of spontaneous pregnancy loss include metabolic/endocrinological abnormalities, genetic factors, anatomical issues, immune disorders, thrombophilia, male factors, and psychological factors (2, 6). While some couples' miscarriages can be managed, about 50% of cases have no clearly defined clinical etiology (7). Given that the fetus is genetically distinct from the mother, specific immunological events must occur to enable the mother to carry the fetus to term. Disruptions in these immunological mechanisms can lead to recurrent miscarriages. Reduced maternal immune tolerance toward the fetus may contribute to recurrent pregnancy losses (4). Immunology offers potential solutions to common reproductive medicine problems, including implantation issues, infertility, miscarriage, and complications later in pregnancy (8). Various immunological factors, such as autoantibodies and changes in uterine immune cell levels, are implicated in immune-related infertility. This review explores available immunological tests in reproductive disorders and miscarriage to provide optimal diagnostic strategies for patients.

2. Cellular Immune Markers:

2.1. NK Cells

Natural killer (NK) cells, a fundamental component of the innate immune system, play a pivotal role in maintaining maternal-fetal tolerance (9). These cells are instrumental in warding off infections during pregnancy (10). Within the unique uterine environment, NK cells are crucial in fostering a conducive setting for pregnancy. They produce various factors that are essential for the regulation of placental invasion and the development of maternal vasculature. Uterine NK cells are characterized by their CD56^superbright, CD16^- phenotype (11, 12), distinguishing them from peripheral blood NK (pbNK) cells, which predominantly consist of two subsets: CD56^dim (95%) and CD56^bright (5%) (14). The resemblance of decidual NK (dNK) cells to the CD56^bright subset of pbNK cells suggests a shared lineage, likely originating from CD56^bright pbNK cells that migrate to the uterus and undergo differentiation within the uterine microenvironment (15). During implantation and placentation, uterine NK (uNK) cells constitute approximately 70% of the leukocyte population and interact with trophoblast ligands via specific receptors (16).

Aberrant activity of uNK cells can disrupt vascular patterns, lead to ischemic conditions, and elevate oxidative stress, all of which are particularly detrimental during early trophoblast invasion (11, 17). uNK cells are pivotal for the establishment of normal early placentation and facilitate vascular remodeling at the conclusion of the implantation process. Insufficient trophoblast invasion and altered vascular remodeling are primary pathological features in conditions such as preeclampsia and are thought to contribute to recurrent pregnancy loss (RPL) (18). Furthermore, uNK cells support trophoblast invasion and promote vascular remodeling by inducing extravillous trophoblast (EVT) cells (19) and T regulatory (Treg) cells (FoxP3^+Treg), enhancing feto-maternal tolerance.

The interaction between maternal killer-cell immunoglobulin-like receptors (KIRs) expressed on uNK cells and fetal human leukocyte antigen-C (HLA-C) on EVT cells regulates placentation (20). The KIR/HLA interface is complex and highly polymorphic, influencing susceptibility to various diseases, including infectious diseases, autoimmune conditions, malignancies, and transplant rejection (21-24). KIR genes modulate the immune response at the feto-maternal interface, with KIR A lacking stimulatory receptors, while KIR B encompasses both stimulatory and inhibitory receptors. The KIR AA genotype is predominantly inhibitory, whereas KIR AB and BB genotypes express a mix of activating and inhibitory receptors. Studies indicate that both activating and inhibitory KIR-HLA combinations are implicated in pregnancy loss (25, 26).

Each pregnancy involves a unique interaction between inherited maternal KIR genes and potentially varied paternal HLA-C groups, even from the same father, creating a dynamic balance between trophoblast and uNK cells. A retrospective analysis of 291 women undergoing 1,304 cycles of in vitro fertilization (IVF) revealed a correlation between the inhibitory KIR-AA haplotype, miscarriage, and implantation failure post-double embryo transfer (27).

Additionally, elevated uNK cell density in endometrial biopsies from patients with recurrent miscarriage (RM) compared to controls has been reported in several studies (28-30). Hence, HLA-C and KIR genotyping could be beneficial for selecting third-party gametes or gestational carriers to mitigate pregnancy complications, including preeclampsia (PE). Clinically, the implications of uNK cell dynamics in the reproductive process should be considered for patients at risk of PE, and the frequency

of prenatal examinations for these individuals might need to be increased (31).

2.2. TH1/TH2 Dynamics

T Despite their critical roles in pregnancy, the levels of non-Th1/2 cytokines, such as those produced by regulatory T cells (Treg) and Th17 cells, are less frequently measured. Th17 cells defend against pathogens and are crucial during pregnancy; stimulation of IL-17 production by Th17 cells enhances progesterone secretion and tissue invasiveness (43). Th17 cells also activate decidual natural killer (dNK) cells and impair the vascular reactivity of uterine arteries, potentially leading to embryo resorption (44). Elevated levels of IL-17+ T cells have been detected in women with RPL (45), and Th17 cells show increased expressions of IL-6, IL-17, and IL-23 in cases of unexplained infertility, correlating negatively with fertility outcomes (46). Treg cells (CD4+CD25+Foxp3+), on the other hand, mediate immunosuppression influenced by Th1 and Th17 cells and regulate maternal-fetal immune tolerance. These cells are often diminished in RPL patients (32). Differences in Treg/Th17 immune profiles have been noted between women with RIF and those who are normally fertile. Treatment with Prednisone has been observed to shift the Treg/Th17 balance towards Treg dominance, promoting favorable pregnancy outcomes (48). While promising, clinical data on Treg and TH17 roles in fertility are limited, necessitating further research."

B cells are critical in pregnancy, serving vital roles in humoral immunity and antibody production which support normal pregnancy development. However, B cells can also contribute to adverse obstetric outcomes such as pregnancy loss, preeclampsia, intrauterine growth restriction, stillbirth, and preterm birth, predominantly through autoantibody production (49-51). Despite the known involvement of B cell dysfunction in benign female reproductive pathologies such as endometriosis, research has primarily addressed peripheral B cells rather than those in the endometrial or tissue-specific contexts (52-54).

Evidence indicates that endometrial B cells play a role in the normal development of the endometrium and are also present in endometrial samples from women with reproductive disorders. Conditions like infertility and endometriosis are linked with a broad spectrum of autoimmune diseases, generally resulting from an expanded population of autoreactive B cells (55-58). The presence of endometrial plasma cells is frequently utilized as a diagnostic marker for chronic endometritis (CE), an inflammatory disorder of the endometrium (59-62).

Contrary to the common perception that B cells are scarce or nonexistent in the endometrium, studies demonstrate consistent expression of endometrial B cells in the normal cyclic endometrium. These cells are also found in endometrial tissue from women suffering from endometriosis, infertility, repeated implantation failure (RIF), recurrent pregnancy loss (RPL), endometritis, and other conditions such as abnormal uterine bleeding, endometrial polyps, and uterine fibroids (63, 64).

secretion of granulocyte-macrophage colony-stimulating factor (GM-CSF) from the uterine epithelium, leading to potential abortion and toxicity (39, 40). Neopterin serves as an indicator of pro-inflammatory immune response; elevated levels in fluids such as cerebrospinal fluid, urine, and serum can activate Th1 cells, promoting immunogenic stimulation during pregnancy and contributing to RPL through the associated production of reactive oxygen species (41, 42). Although the ELISA technique is seldom utilized clinically for monitoring Neopterin levels, routine assessment during pregnancy could enhance prognostic outcomes (34) (Figure 1).

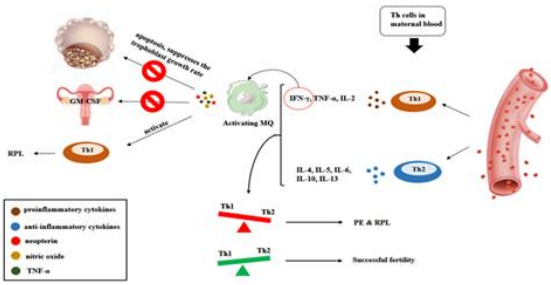

Figure-1. The role of Th1 and Th2 cell responses in fertility and infertility

2.3. Treg/TH17 Interactions

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Table 1. Type of cellular immune markers in infertility

Cellular immune markers	Definition	Mechanism of action
NK cell	one of the innate immune cells that participate in maternal-fetal tolerance while protecting pregnancy from infection	• Regulate placental invasion and maternal vascular development. • Account for the majority of leukocytes in the process of implantation and placentation. • Establishment of normal early placentation through vascular remodeling. • Regulate trophoblast invasion and enhance vascular remodeling induced by EVT cells and Tregs. • Regulated Placentation by interactions between maternal KIRs expressed by uNK cells and fetal HLA-C molecules expressed by EVT cells.
TH1/TH2	An essential component of the adaptive immune system in the peripheral blood can be defined by their cytokine production profile. Th1 cells produce IFN-γ, TNF-α, IL-2. / Th2 cells produce IL-4, IL-5, IL-6, IL-10, IL-13	• Pregnancy is associated with a Th2 response, while a Th1 response lead to embryo rejection. • IFN-γ production leads to the activation of macrophages and production of signaling mediators induces the apoptosis, suppresses the trophoblast growth rate and inhibit the secretion of GM-CSF and Thus, leading to pregnancy termination and toxicity.
Treg/TH17	Tregs and Th17 cells are two $CD4^+$ T Cell subsets with antagonist effects. Th17 cells promote inflammation, whereas Tregs are crucial in maintaining immune homeostasis.	• Their cytokine products play a role in successful implantation. • IL-17 produced by TH17 increased capacities of progesterone secretion and tissue invasion and leading to embryo resorption by induce activation of dNK cells and impair vascular reactivity of uterine arteries. • Treg cells suppress Th1-and Th17-mediated immunity and lead to maternal immune tolerance to the fetus.
B Cell	B cells make antibodies in response to antigens.	Evidence suggests that B cells is important in the normal endometrium and endometrium obtained from women with reproductive pathologies.

3. Autoantibodies:

3.1. Anti-Phospholipid Antibody (APA)

Antiphospholipid syndrome (APS) is an autoimmune disorder characterized by the production of antiphospholipid antibodies (aPLs), which are associated with thrombosis and adverse pregnancy outcomes (65). The primary aPLs identified in APS are anticardiolipin antibodies (aCLs), lupus anticoagulant (LA), and anti-β2-glycoprotein I antibodies (aβ2GPI). These antibodies can disrupt reproductive processes by affecting oocyte development, embryo morphology, uterine receptivity, and decidualization, thereby potentially leading to subfertility (66-68).

Diagnostic criteria for APS are divided into clinical and laboratory categories. Clinically, APS is indicated by vascular thrombosis or specific pregnancy complications, such as fetal death post-10 weeks, preterm delivery before 34 weeks' gestation, or three or more consecutive miscarriages prior to 10 weeks of gestation. Laboratory criteria for APS include the detection of lupus anticoagulant (LA) in plasma, measured twice, 12 weeks apart; anticardiolipin antibody levels in plasma exceeding 40 GPL or MPL, or above the 99th percentile, measured twice, 12 weeks apart; or anti-β2 glycoprotein-I antibody levels in plasma above the 99th percentile, also measured twice, 12 weeks apart. A diagnosis of APS requires meeting at least one clinical and one laboratory criterion (68).

Table 2. Laboratory clinical criteria in APS syndrome

1- Lupus anticoagulant (LA) measured in the plasma twice and 12 weeks apart
2- Anticardiolipin antibody in plasma >40GPL or MPL or > 99th percentile, measured twice and 12 weeks apart
3- Anti-β2 glycoprotein-I antibody in plasma >99th percentile measured twice and 12 weeks apart

Antiphospholipid antibodies (aPL) interfere with phospholipids and phospholipid-binding proteins, such as beta-2 glycoprotein 1, protein C, and protein S, impairing the function of these homeostasis regulators and precipitating vascular issues and pregnancy complications (69). Moreover, aPLs activate endothelial cells, escalating the production of arachidonic acid metabolites, adhesion molecules, and cytokines, thereby enhancing the risk of thromboembolism (70). aPL antibodies also impede hormone production by trophoblasts, including hCG, and restrict the invasive capability of extracellular

villous trophoblasts into the maternal decidua (71). Activation of the complement cascade through the classical pathway by aPLs initiates neutrophil recruitment and the subsequent release of proinflammatory cytokines (72).

Miscarriage is a frequent consequence of aPL presence (73-75). During pregnancy, tolerance to fetal alloantigens by the maternal immune system, facilitated by Treg cells, is essential for fetal survival. A reduction in Treg cells may lead to failed embryo implantation and increased production of proinflammatory cytokines (76). Compared to healthy women, those with aPL exhibit fewer Treg cells and more activated T- and pathogenic B-cells (78, 79). Additionally, lower levels of NK and NK T-cells in aPL-positive women contribute to inadequate trophoblast invasion and spiral artery remodeling, emphasizing the altered immune status in these patients (79).

Significantly higher prevalence of autoantibodies against smooth muscle, phospholipids, and nuclear antigens have been observed in women with infertility compared to those with normal pregnancies (80). A notable rise in the prevalence of various autoantibodies, including antinuclear, lupus anticoagulant, anticardiolipin, and anti-double stranded DNA antibodies, is also evident in patients with unexplained infertility versus those with ovulatory infertility (20.5% versus 3.3%) (81). Furthermore, all tested aPLs (IgG, IgM, and IgA anticardiolipin, antiphosphatidyl ethanolamine, antiphosphatidyl inositol, antiphosphatidic acid, anti-phosphatidyl glycerol, antiphosphatidyl choline, and antiphosphatidyl serine) are more frequently observed in women with implantation failure (82). Despite this, routine aPL testing in infertility patients lacks sufficient supporting data; further research into APS's pathophysiology is necessary to develop new therapeutic strategies targeting the immune system's inflammatory signaling pathways.

3.2. Anti-Thyroid Antibody (ATA)

Thyroid autoimmunity (TAI) represents the most prevalent autoimmune disorder among childbearing women, affecting between 5% and 20% of this demographic (83, 84). TAI is characterized by the presence of circulating antithyroid autoantibodies such as thyroid peroxidase antibodies (TPOAb), thyroglobulin antibodies (TGAb), and thyrotropin receptor antibodies (TRAb), which may or may not impair thyroid function (83, 84).

"Previous studies have established that thyroid autoantibodies are prevalent among women of reproductive age, demonstrating particularly high rates in women with a history of subfertility (with prevalence estimates ranging between 10-31%) (85-87) and recurrent miscarriage (with prevalence estimates between 17-33%) (88, 89).

Thyroid hormone synthesis is critical for the progression and maintenance of pregnancy, with thyroid hormone transporters and receptors present in various reproductive tissues including the ovary, early embryo, endometrium, uterus, and placenta (90). Dysregulation of thyroid hormones impairs the stimulatory effects of gonadotropins on granulosa cells, reducing steroid hormone production and leading to menstrual irregularities and ovulatory dysfunctions (90, 91). Moreover, thyroid dysfunctions detrimentally affect folliculogenesis, fertilization rates, embryo quality, and trophoblast invasion, thereby decreasing the likelihood of a successful pregnancy. Consequently, maintaining euthyroidism is essential during pregnancy (90).

Women with thyroid autoimmunity (TAI) often exhibit insufficient production of thyroid hormones due to antibody interference, potentially culminating in pregnancy loss if unmanaged (92, 93). Thyroid peroxidase antibodies (TPO-Ab) are associated with increased risks of miscarriage, placental abruption, and hypertension induced by pregnancy (94). Furthermore, thyrotropin receptor antibodies (TRAbs) can cross the placental barrier, adversely affecting thyroid function in both the mother and fetus (94).

Additionally, thyroid-stimulating hormone (TSH) enhances the activation of natural killer (NK) cells, promoting their proliferation and cytotoxic activity (95, 96). Thyroid autoantibodies also disrupt the Research indicates that the proportion of peripheral NKT-like cells escalates in women with autoimmune thyroiditis (AIT), contributing to miscarriage and implantation failure (99, 100). Notably, serum levels of interleukin-2 (IL-2) and interleukin-17 (IL-17) are elevated in early pregnancy among patients with AIT compared to controls (101). Th1 cells, through IL-2 and interferon-gamma (INF-γ) production, are crucial in mediating implantation failure and abortion. IL-17, a pro-inflammatory cytokine produced by Th17 cells, plays a significant role in the pathogenesis of abortion (32).

Collective findings from various studies indicate:

- Increased rates of miscarriage and poorer delivery outcomes are observed in the TPOAb-positive group compared to the TPOAb-negative group (102).
- The co-presence of TPOAb and elevated TSH levels in early pregnancy correlates with a heightened risk of gestational diabetes (103).
- TPOAb positivity is associated with placental abruption (104).
- A correlation exists between TPOAb positivity and maternal anemia (105).
- Associations between TPOAb and preterm delivery have shown more consistent findings (106).
- The presence of thyroid autoantibodies significantly elevates the risk of miscarriage across various populations compared to women without these autoantibodies (107).

Consequently, screening for thyroid autoimmunity is recommended as part of the diagnostic workup for women experiencing infertility or early miscarriage to facilitate timely evaluation, diagnosis, and potentially, initial treatment to enhance pregnancy outcomes.

3.3 Anti-Nuclear Antibody (ANA)

Antinuclear antibodies (ANA) target cytoplasmic and nuclear antigens present in all nucleated cells and comprise a broad group that recognizes various cellular components such as double-stranded DNA (ds- DNA), RNA molecules, mitochondrial antigens, and various proteins within the cytoplasm and nucleus, as well as their complexes (108-110). Elevated ANA titers serve as biomarkers for several autoimmune diseases, including systemic lupus erythematosus (SLE) and rheumatoid arthritis. There is also evidence linking high ANA levels to immunologically induced infertility (111). Significant differences in ANA serum positivity, titer, and pattern have been observed between women with and without recurrent pregnancy loss (RPL), with ANA levels being threefold higher in the RPL group compared to controls (112).

"The involvement of antinuclear antibodies (ANA) in recurrent pregnancy loss (RPL) is a subject of ongoing debate, with numerous studies striving to elucidate their influence on this reproductive issue. Research indicates that ANAs negatively impact pregnancy and implantation rates while also potentially degrading oocyte quality and embryo development (113). Moreover, ANAs can initiate the activation of plasmacytoid dendritic cells via Toll-like receptor-9, which enhances the production of inflammatory cytokines such as interferon α. This cascade stimulates the humoral immune response and leads to further ANA production (114, 115). Additionally, evidence demonstrates that ANA-positive groups exhibit significantly lower rates of Miosis II oocytes, normal fertilization, and pregnancy and implantation rates, coupled with increased rates of abnormal fertilization and early miscarriage (116). The presence of anti-dsDNA antibodies is linked to immunological inflammation in the placenta, adversely affecting pregnancy outcomes (117). High levels of ANAs are associated with detrimental effects on oocyte and embryo development, correlating with repeated implantation failure (RIF) and recurrent miscarriage (118). Given the established roles of ANAs in various infertility-related disorders, measuring ANA titers is advised. Continued research and trials are imperative to explore potential roles and immunotherapeutic strategies in affected individuals.

3.4. Antisperm antibody (ASA)

Antisperm antibodies (ASA) were identified in infertile males as early as 1954 by Rumke and Wilson (119). ASAs are immunoglobulins that target sperm antigens and are present in reproductive tract secretions and blood in both genders. Typically, mature sperm are shielded from immune recognition by the blood-testis barrier, which maintains tight intercellular junctions. However, damage to the testis, epididymis, or vas deferens, exposing sperm to the immune system, can prompt an autoimmune response against sperm. Conditions such as testicular carcinoma (120), testicular torsion (121), epididymal and bilateral orchitis (122), varicocele (123), seminal infections, sexually transmitted diseases (125), prostate inflammation (126), and seminal vesicle inflammation can elevate ASA levels. Similarly, structural disruptions in the male reproductive tract, vasectomy, or erectile dysfunction (128) are associated with higher ASA levels. Chronic bacterial infections, such as chronic prostatitis, increase the likelihood of ASA development threefold compared to controls (129, 130). A recent study also linked human papillomavirus (HPV) infection in men with an increased risk of ASA development (131). The reason for variability in ASA production among females, with some developing ASAs while others do not, remains elusive. Sperm cells introduced into the lower female reproductive tract are recognized as allogeneic antigens, triggering an inflammatory or allergic response leading to ASA production (133, 134). Despite some cases of idiopathic ASA presence (135), ASAs impair sperm capacitation, the acrosome reaction, sperm traversal through female reproductive tract secretions, gamete fusion, and early embryo development (136, 137). While ASAs do not affect sperm volume, viability, progressive motility, or morphology, they significantly reduce sperm liquefaction and motility (120)."

Sperm agglutination serves as a crucial parameter in the Anti-Sperm Antibody (ASA) assay, as evidenced by reference 138. Although there is a weak correlation between sperm agglutination and the presence of ASA, factors other than sperm antibodies can also induce agglutination (139-141). The World Health Organization's 2010 laboratory manual for human semen analysis categorizes sperm agglutinates as indicative of ASA presence (139). Furthermore, the presence of ASA correlates significantly with reductions in sperm count, vitality, and motility (141, 142), and studies suggest that asthenozoospermia may warrant ASA testing (143).

ASA in semen predominantly comprises two classes of immunoglobulins: IgA and IgG (139). Clinically, IgA is more significant, though over 95% of individuals with IgA also possess IgG (reference 139). The detection of ASA on spermatozoa can be accomplished through two direct assays: the Mixed Antiglobulin Reaction (MAR) test, using fresh semen, and the Immunobead (IB) test, employing washed spermatozoa (139). These tests involve incubating the sample with latex beads coated with anti-human antibodies (139). If ASA are present, these antibodies

bind to the sperm surface antibodies, and under microscopic observation, motile spermatozoa coated with beads are identified, with the percentages of coated motile sperm counted (139). Insufficient counts of motile spermatozoa (fewer than 100) necessitate the use of indirect assays (139).

Direct assays yield information confirming the presence and type of immunoglobulins (IgG or IgA) and their specific localization on the sperm's head, midsection, tail, or entire length (139). Conversely, indirect assays assess sperm-specific immunoglobulins in sperm-free fluids such as heat-inactivated serum, seminal plasma, and dissolved cervical mucus, which are incubated with ASA-free donor sperm previously washed from the original seminal fluid, considering the interaction time between sperm and potential antibodies (139).

Indirect testing is advisable in cases of oligozoospermia or stenospermia, either alone or in combination, and in scenarios of obstructive azoospermia or when a sample is unavailable for testing, allowing for semen to be frozen and stored until analysis (139). Despite thorough research into immunological infertility, substantial ambiguity remains regarding the application of ASA testing and treatment strategies for men with ASA, underscoring the need for further investigation.

4. Molecular and Genetic Markers for Endometrial Analysis

4.1. Endometrial Immune Profile Test (EIP):

The Endometrial Immune Profile (EIP) test, which utilizes reverse transcription-quantitative polymerase chain reaction (RT-qPCR), quantitatively assesses gene expressions related to immune modulation in the endometrium. This includes the evaluation of interleukin-15 (IL-15), interleukin-18 (IL-18), tumor necrosis factor-like weak inducer of apoptosis (TWEAK), fibroblast growth factor-inducible molecule 14 (Fn14), and CD56 (144).

It is well-documented that a balanced immune cell profile, particularly the equilibrium between TH1 and TH2 cells, along with the activity and cytotoxicity levels of uNK cells, are critical for fostering feto-maternal tolerance. Any imbalance can precipitate reproductive issues, such as compromised implantation processes.

The interaction between TWEAK and its receptor, Fn14, mitigates local cytotoxicity and regulates uNK cell functions, influencing various physiological and pathological outcomes like embryonic development, angiogenesis, inflammation, and apoptosis (145-148). Furthermore, TWEAK modulates the expression of other cytokines such as IL-18 and IL-15, thereby playing a crucial role in controlling uNK cell cytotoxicity and promoting maternal tolerance towards the fetus.

Research indicates that IL-18 is actively expressed in the endometrium during the implantation window (WOI) and is instrumental in managing trophoblast invasion, migration, and uNK cell activity, as well as promoting angiogenesis and placental vascularization essential for maternal-fetal nutrient and oxygen exchange (149).

Excessive or imbalanced IL-18 expression has been linked to reproductive disorders like preterm birth, preeclampsia, and fetal growth restriction (150). IL-18 also influences the TH1/TH2 balance; it can stimulate TH1 immune responses, triggering cytotoxic T cell activation and pro-inflammatory cytokine production (e.g., TNF and INF) (151). Conversely, IL-18 can exhibit TH2-like activity, enhancing eosinophil responses and IL-5 and IL-13 production, thus supporting TH2 responses in synergy with IL-4 (152).

IL-15, another crucial immune system cytokine, supports the survival, proliferation, and maturation of immune cells, including uNK cells (153).

In the EIP test, the IL-18/TWEAK mRNA ratio serves as a biomarker for angiogenesis and the TH1/TH2 balance. High IL-18 expression, which typically benefits the immune response, can become deleterious by promoting local cytotoxicity if not balanced by TWEAK expression (146). Elevated TWEAK levels can counteract excessive IL-18 expression, preventing the transformation of uNK cells into cytotoxic entities (146).

IL-15/Fn-14 mRNA serves as a biomarker to assess the activation and maturation of uterine natural killer (uNK) cells by evaluating the presence of uNK-CD56+ cells. The activation and maturation status of NK cells during pregnancy is critical. As uterine NK cells are typically immature, they undergo a process of maturation, where IL-15 plays a pivotal role in their recruitment and development.

In a study examining the endometrial immunity of 104 patients with recurrent pregnancy loss (RPL), 75% exhibited signs of endometrial immune dysregulation. Among these, 31% displayed an underactive uterine immune profile, 50% an overactive profile, and 19% a mixed pattern. Notably, uterine immune profiling was significantly correlated with higher live birth rates (LBR) when dysregulation was identified (154).

Another investigation on the endometrial immunity of 394 patients with recurrent implantation failure (RIF) identified overactivation in 56.6% of cases and low activation in 25%. The LBR among these dysregulated/treated patients at their subsequent embryo transfer was 39.8% (155). These findings underscore the need for further research to verify the efficacy of these assessments.

4.2. Endometrial Decidualization Score (EDS)

Decidualization involves the extensive proliferation, secretion, and regression of the endometrium's inner lining in preparation for pregnancy. This process

transforms human endometrial stromal cells into decidual cells, creating a tissue receptive to embryo implantation (156). Decidualization primarily relies on the action of progesterone on estradiol-primed progesterone receptors in endometrial stromal cells (157).

A key progesterone signaling mediator, Forkhead box O1 (FOXO1), induces senescence in a subset of decidualized stromal cells, crucial for tissue remodeling essential for embryo implantation (158). Additionally, decidualization involves increased expression of homeostatic tissue and cellular factors (159), as well as glucose transport molecules like Glut1 and Glut3 in the human endometrium, peaking during the mid-luteal phase to support embryo implantation and growth (160).

Concomitant with these metabolic enhancements, there is a notable increase in uterine natural killer (NK) cells in the endometrium during this phase (161). These uNK cells, secreting growth-promoting, angiogenic, chemotactic, and immunoregulatory factors, play significant roles in angiogenesis, placental growth, and trophoblast invasion regulation (162, 163). Moreover, interleukin 15 levels in the endometrium, which bolster the proliferation and survival of NK cells, also rise during the luteal phase (164, 165).

Molecular diagnostics utilizing targeted RNA sequencing has been employed to detect endometrial gene expressions crucial for progesterone signaling and decidualization (FOXO1) (166, 167), tissue and cellular homeostasis (SGK1, SCNN1A, and SLC2A1) (168-170), and immunoregulatory and tissue remodeling factors (IL-15 and GZMB) (158). This gene expression profile evaluation is referred to as the decidualization score.

Research indicates that among women with reproductive failures, 76% had EDS scores ≤ 4, and 19% had scores of 0, whereas 89% and 11% of fertile controls had EDS scores ≥ 5 and 4, respectively (171). However, additional studies are necessary to confirm the utility and effectiveness of this score.

4.3. Human Herpesvirus 6A Test (HHV6A)

Human Herpesvirus 6A (HHV-6A) is categorized within the beta-herpesviruses and is recognized as part of the Roseolovirus genus (172-175). It exhibits a broad cellular tropism, infecting numerous cell types across various tissues, including: 1) diverse immune cells—such as CD4+ T cells, CD8+ T cells, and NK cells; 2) various nervous system cells—such as astrocytes, microglial cells, oligodendrocytes, and neuronal cells; 3) and cells from other tissues including liver cells, human fibroblasts, epithelial cells, and endothelial cells (174-176). Moreover, HHV-6A is capable of infecting different cells within the female reproductive tract, being detected in the vaginal canal, uterus, and cervix (177, 178, 179). The viral infection of immune cells leads to an increased production of pro-inflammatory cytokines including IL-1β, TNFα, IFN-α, IFN-γ, and IL-6, while concurrently reducing the levels of the anti-inflammatory cytokine IL-10 (180-186). Furthermore, infection by HHV-6A enhances the toxicity of NK cells in non-pregnant women, particularly when endometrial epithelial cells are involved, resulting in elevated pro-inflammatory cytokine levels that may inhibit implantation (9, 187). This suggests that endometrial NK cell contamination plays a role in the pathogenesis of primary infertility. Conversely, during pregnancy, NK cells exhibit reduced susceptibility to foreign antigens due to interactions with HLA-G and HLA-E on cytotrophoblasts, which inhibit attacks against paternal antigens (188). Theoretically, HHV-6A infection could disrupt this protective interaction, leading to impaired implantation and contributing to primary unexplained infertility and preeclampsia (PE). Research indicates that Human herpesvirus 6A deoxyribonucleic acid was found in 43% of endometrial samples from women with primary unexplained subfertility, in contrast to 0% in fertile controls (177). Additionally, cases of PE show a higher prevalence of inherited chromosomally integrated HHV-6A (iciHHV-6A) and possibly acquired infections, suggesting susceptibility to PE (189, 190). The evidence thus far is compelling and merits further investigation.

4.4. B Cell CLL/Lymphoma 6 Test (BCL6)

B-cell lymphoma 6 (BCL6), a crucial proto-oncogene, plays a predominant role in regulating humoral immunity and lymphoma survival (191, 192) (Figure 2). This transcriptional repressor is involved in cellular differentiation, cell cycle control, and apoptosis inhibition (193). Elevated BCL6 expression correlates with unexplained infertility, endometriosis-associated infertility, and common pregnancy diseases such as preeclampsia (PE) (194-198). Notably, BCL6 is frequently altered in pre-eclamptic placentas as shown through systematic meta-analysis and expression network analysis (199, 200). Its overexpression stimulates ARNT2 (aryl hydrocarbon receptor nuclear translocator 2) production, which partners with hypoxia-inducible factor 1a (HIF-1a) to influence trophoblast invasion and contribute to PE pathogenesis (198, 201-203). A study revealed that 2977 genes, enriched with metabolism-related pathways and transporter functions, were differentially expressed in severe early-onset PE (EO-PE), while 375 genes associated with immune pathways were more prevalent in severe late-onset PE (LO-PE), with BCL6 being upregulated in both conditions (196). Aberrant BCL6 expression exhibits high sensitivity and specificity for diagnosing all stages of endometriosis, indicating its potential as a biomarker (204). The prevalence of elevated

endometrial BCL6 expression in women with unexplained infertility (UI) is reported at 75.3% and 80% (194, 195). Although some progress has been made, further research is necessary to fully elucidate the molecular mechanisms through which BCL6 exerts its diverse functions in the placenta and endometrium.

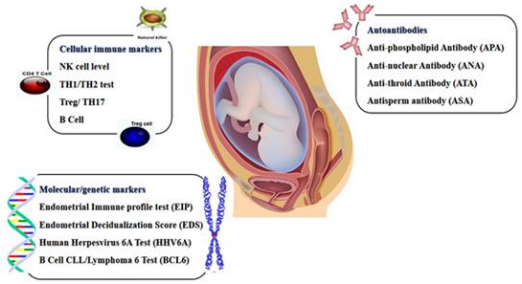

Figure-2. Different methods of identifying immune system disorders in infertility

Conclusion

The establishment of pregnancy and its maintenance, involve complex states, tightly regulated by intricate relationships among the different cell subsets of the immune system. Endometrial immune status has been a neglected factor in reproductive medicine and management. However, the uterine immune profiling represents a clinical innovation which can significantly increase the appropriate assisted reproductive technology (ART) through personalization. Currently, infertility is a growing problem, affecting 8-12% of couples of reproductive age worldwide. Therefore, it is clear that there is a great need in this field for progress in the development of diagnostic tests that provide the possibility of assessing the risk of these infertility, such as RPL and RIF, etc.

Ethical Issue

There was no ethical issue in this review.

Conflict of Interests

There was no conflict of interest in this study.

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Author's ORCID

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