Review Article

Female Unexplained Infertility: A Disease with Imbalanced Adaptive Immunity

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Abstract

Unexplained infertility (UI) among women consists of only 10-17% of infertile females. Unexplained or idiopathic infertility is a condition, in which couples are not able to conceive without any definite causes. The presence of the decidual immune system (innate or adaptive) is essential for a successful pregnancy and fertility that is mediated by T helper (Th) 1, Th2, Th17, T follicular helper, $CD8^+$ $CD28^-$ T, and regulatory T cells, as well as autoantibodies such as antiphospholipid antibody, antithyroid antibody, antiovarian antibody, cytokines, and chemokines. Therefore, altered proportions or levels of the mentioned compartments of the adaptive immune system may cause pregnancy failure and infertility, especially in UI. Consequently, a deep understanding of immunological compartments in females with UI may help us to define the causes of this disease with regard to immunology. This review will discuss immunological factors, including cellular, molecular components, and transcription factors that are involved in the etiology of UI.

Keywords: *Autoantibody, cellular immunity, cytokine, molecular immunity, unexplained infertility*

Introduction

The embryo implantation is vital for a successful pregnancy, in which molecular and cellular events (e.g, growth factors and cytokine expression) lead to the development of decidua, adhesion and invasion of trophoblast, and also formation of the placenta. This process takes place in the receptive endometrium during the midsecretory phase or from 19th to 23rd day of the menstrual cycle.[1] In fact, during pregnancy, the expression level of Vitamin D receptor (VDR) is changed. In more detail, VDR expression level in the decidua increases significantly in midstages.[2,3] More than one in every six couples with implantation failure are not able to conceive and are known as infertile. Both genders, whether men or women, equally suffer from infertility.

Definite causes of female infertility range from endometriosis, ovulation, and fallopian tube disorders. In addition to these causes, there are some indefinite causes, which lead to unexplained or idiopathic infertility. Approximately 16% of infertility is reported as unexplained infertility (UI). In addition, women with UI consist of only 10%–17% of infertile females.[4] It was reported that the occurrence of UI depends on the age and selection criteria in the study population. The diagnosis of UI includes hysterosalpingography or laparoscopy to evaluate tubal patency and serum progesterone for detection of ovulation.[5] Many couples with a provisional UI might have spontaneous fertility in the future with the rate of 2%–4% per menstruation in couples.[6]

Aside from complex collaborations between the developing embryo and decidualized endometrium, recognition of the fetus as a semiallogeneic antigen is also crucial for the successful implantation, leading to the maternal immune tolerance against the fetus. The maternal immune tolerance needs alterations in cellular

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and humoral immune responses which is mediated via the immune cells, cytokines, and chemokine in the decidua.[1,7] As the decidual immune system (innate or adaptive) is vital for acceptance (fertility) and rejection of the fetus (infertility), altered proportions or levels of immune compartments could break the maternal immune tolerance and result in infertility, and especially UI [Table 1 and Figure 1].[8] The decidual adaptive immune system includes cellular and humoral immune systems. In more details, decidual cellular immune system includes T helper (Th) subsets such as Th1, Th2, Th17, T follicular helper (Tfh), $CD8^+$ $CD28^-$ T, and regulatory T (Treg) cells and decidual humoral immune system includes autoantibodies and cytokines such as pro-inflammatory and anti-inflammatory cytokines which could play a key role in the female fertility and infertility. Thus, in this paper, we will discuss adaptive immunity and its role in the rejection of the fetus in females with UI.

Table 1: Component level/proportion in females with unexplained infertility

Component	Level/proportion in females with UI	Reference
Cellular		
Th subsets		
Th1/Th2	Increase (increased numbers of Th1 cells and decreased numbers of Th2 cells)	[8]
Th17	Increase in number	[8]
Tfh/CD4 T cell	Increase (increased numbers of Tfh cells and decreased numbers of CD4 T cells)	[10]
Suppressor T cells	Decrease in number of $CD8^+$ $CD28^-$ T cells	[9]
Treg	Decrease in number	[25]
Molecular		
Autoantibody		
APA		
APA-LA b. ACA	Increase in level	[33,39]
ATA		
Anti-TPO	Increase in level	[31,43,44]
Anti-TG		
AOA	Increase in level	[50,51]
Cytokines		
Pro-inflammatory		
IFN-γ	Increase in level	[8,10]
IL-2		
TNF		
IL-17		

ACA=Anticardiolipin antibodies, ATP=Anti-thyroid peroxidase, LA=Lupus anticoagulant, Anti-TG=Anti-thyroglobulin, UI=Unexplained infertility, IFN-γ=Interferon-gamma, TNF=Tumor necrosis factor, IL=Interleukin, Th=T helper, AOA=Anti-ovarian antibody, ATA=Antithyroid antibody, APA=Antiphospholipid antibody

Cellular Immunity

$CD4^+$ T cells and $CD8^+$ T cells as T-lymphocytes populations have a vital role in fertility and infertility, especially in UI.[9,10] Naïve $CD4^+$ T cells are activated and are differentiated following the interaction with antigen-major histocompatibility (MHC) expressed on dendritic cell (DC) as a professional antigen presenting cell (APC). The $CD4^+$ T cells possess several functions, including stimulation of the innate immune cells, cytotoxic T cells, B-lymphocytes, and nonimmune cells.

Furthermore, these $CD4^+$ T cells could play a potential role in the inhibition of the immune response like regulatory $CD4^+$ T cells. There are different subsets of $CD4^+$ T cells such as T helpers: Th1, Th2, Th17 and Treg cells, which have a distinct role in immune responses. The differentiation of these subsets of T cells from naive T cells to different mentioned subsets occurs after the engagement of T cell receptor, receiving DC signals, and an expression of distinct transcription factors, including T-box transcription Factor (T-bet), GATA Binding Protein 3 (GATA3), Retinoic acid receptor-related orphan-receptor-C (RORγt), and forkhead box protein P3 (Foxp3), respectively.[11]

T helper subsets

T helper 1/T helper 2 ratio

The Th1/Th2 ratio has a crucial role in the success of fertility and infertility. While in the pregnancy, Th1 cells inhibit the invasion of a trophoblastic cell, Th2 cells modulate a Th1 response, promote the trophoblast invasion, and maintain the fetus; so, the balance is strongly shifted toward Th2 response.[8] Th1 cells are responsible for the immune response against intracellular pathogens; also, they could trigger autoimmunity and inflammation in which mononuclear phagocytes, including M1 (Classical) macrophages, involve and produce toxic nitric oxide. On the other hand, Th2 cells are responsible for the immune response against extracellular pathogens in which M2 (Alternative) macrophage is involved and produces trophic polyamines. The second macrophage phenotypes (M2) are capable of decreasing the activation of the first macrophage phenotypes (M1) and play a significant role in terminating inflammation. In fact, Th1 cells suppress the development of other subsets of Th cells such as Th2 and Th17. T-bet, the main transcription factor could either promote the development of Th1 cells or suppress the development of Th2 cells by inhibiting the interleukin (IL)-4 gene expression and impairing the GATA3 function, as IL-4 and GATA3 are the essential differentiating cytokines and transcription factors of Th2 cells, respectively. T-bet also inhibits

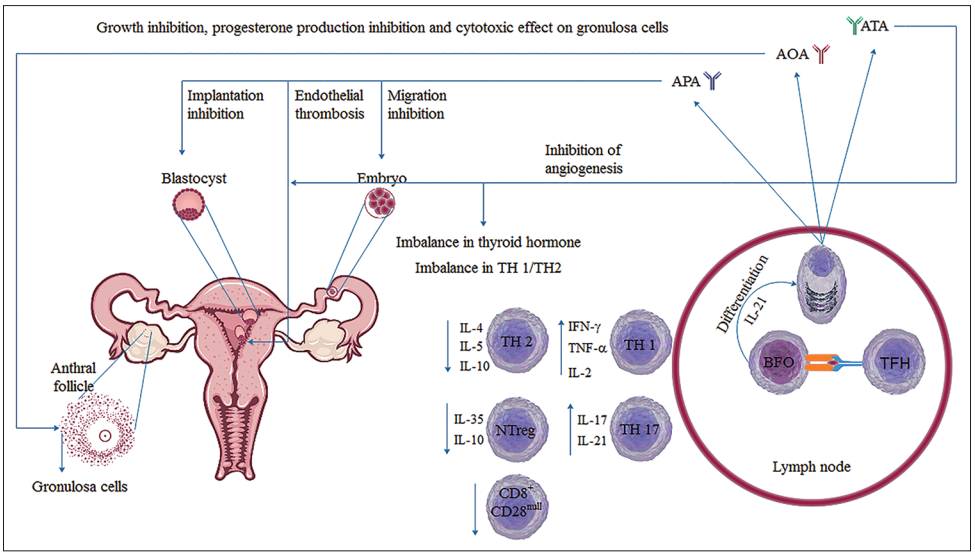

Figure 1: T helper 1/T helper 2 ratio and the number of T helper 17 are increased in females with unexplained infertility that induces pro-inflammatory condition. T follicular helper cells number and production of interleukin-21 are increased. Interleukin-21 production leads to the production of autoantibody. The complications of antiphospholipid antibody production in high levels is thrombosis, inhibition of migration, and implantation of embryo, respectively, antiovarian antibody adversely effects on the growth and progesterone production of granulose cells in antral follicle. Antithyroid antibody adversely effects on thyroid hormone that leads to inhibition of migration and promotion of endothelial thrombosis in females with unexplained infertility

Th17 cells subset by binding to retinoid orphan nuclear receptor (RORC) promoter (encoding the Th17 transcription factor, RORγt). On the other hand, GATA3 inhibits Th1 development by binding to T-bet.[11] With regard to importance of Th1/Th2 balance in pregnancy, inflammation and subsequent changes in the dominance of Th1 or Th2 population determine the chance of fetus survival.

Ozkan *et al.* demonstrated that the Th1/Th2 cell ratio increased in females with UI.[8] Wilczyński *et al*. studied the Th1 and Th2 status before and after immunization in these patients and concluded that the immunization makes changes in the balance of Th1 and Th2 cells causing Th2 dominance and subsequent pregnancy success.[12]

T helper 17

Due to the promotion of inflammatory response and secretion profile of cytokine (IL-17), these cells are named Th17. Because of the interaction with DCs and contribution of IL-6, IL-21, IL-23, and transcription growth factor (TGF-β), naive CD4+T cells are differentiated into the Th17 cells subset. This process is mediated via expression of RORγt that is the main Th17 cells transcription factor. This differentiation has three steps: stimulation step by TGF-β and IL-6, the self-amplification step by IL-21, and the stabilization step by IL-23. Th17 cells are responsible for the immune response against extracellular bacteria and fungi. Moreover, they play a critical role in the pathology of autoimmunity. Some studies suggest that Th17 cells have a fundamental role in the acceptance or rejection of the fetus. Hence, based on this fact that Th17 cells have a critical role in fertility and infertility, the high or low number of these cells may result in fetus rejection or fertility.[11,13]

Some other studies also highlighted the role of Th17 cells in the fetus rejection. Ozkan ZS *et al.* also observed that the level of serum IL-17 increased in females with UI, which is an indicator of increased peripheral blood Th17 cells.[8]

Recent studies have reported that in addition to the vital role of Th17 cells in the occurrence of UI, these cells are vital in the occurrence of unexplained recurrent spontaneous abortion (URSA).

Saifi *et al.* showed that the proportion of Th17 cells in the peripheral blood and decidua was significantly higher in URSA patients compared to normal, early pregnant women. Meanwhile, there was an inverse relationship between Th17 cells and Treg cells in the peripheral blood lymphocytes (PBL) and decidua in URSA. The expression of Th17-related factors, IL-17, IL-23 as well as RORC, in PBL and decidua in URSA patients, was significantly higher than fertile group.[14] Wang *et al*. studied the expression of IL-27 and the role of the IL-27, secreted cytokine by tolerogenic DCs, in the regulation of Th17/Treg cells expression in URSA and found that the expression of IL-27 was lower in decidua of URSA patients compared to fertile females, which result in increased Th17/Treg cells ratio.[15]

Abdolmohammadi *et al*. with the aim of evaluating

the frequency of Th17 cells and their regulating microRNAs (miRNAs) in RSA and control (fertile) women, realized that there is a significant increase in the number of Th17 cells in women with RSA, while there is no significant difference in the expression level of related miRNA, mir-326.[16]

T follicular helper/CD4+ T cell

Following $CD4^+$ T cells-B cells interaction, C-X-C chemokine receptor type 5 (CXCR5−) and C-C chemokine receptor type 7 (CCR7+) naive T cells could differentiate to $CXCR5^+$ $CD4^+$ T cells in the presence of IL-6 and 21.[17,18] These differentiated T cells subset are named Tfh cells and involved in the humoral immune system response. Actually, after losing the CCR7 and quitting T cell rich zone of lymph node as a secondary lymphoid organ, the Tfh cells enter the pre-germinal center to interact with antigen-activated B cells and leading to their differentiation into plasma cells. There are different types of Tfh cells based on the pattern of cytokine secretion, including Tfh1, Tfh2, and Tfh10. The Tfh1 is characterized by secreting interferon-gamma (IFN-γ), which triggers immunoglobulin G 2 alpha (IgG2α) production; Tfh2 by secreting IL-4, which triggers IgG 1/E (IgG1/E) production; and Tfh10 by secreting IL10, which triggers IgA production.[11] These antibodies could be named as potential autoantibodies that could induce the immune response to auto-antigen or semialloantigens such as the fetus, leading to the development of the inflammatory process during pregnancy and infertility. An *et al.* confirmed that an increased ratio of the Tfh/$CD4^+$ T cell in peripheral blood could be a contradictory factor that indirectly induces the autoimmune response against the fetus in females with UI.[10]

CD8+CD28− T cell

$CD8^+$ T cells might function as either stimulators or modulators of the immune system response. The modulatory effect is attributed to $CD8^+$ $CD28^-$ cells as the suppressor T cells. After antigenic stimulation, $CD8^+$ T cells downregulate CD28 expression and upregulate CD8 expression and are differentiated to $CD8^+$ $CD28^-$ T cells. It was demonstrated that these MHC-I-restricted suppressor T cells in humans could be differentiated from primed $CD8^+$ T cells with frequent *in vitro* stimulation mediated by APCs and Foxp3 expression. It is confirmed that $CD8^+$ $CD28^-$ T cells suppress the activity of Th cell via IL-10 secretion or cell-to-cell contact pathways.[19] The latter pathway is mediated by acting on APCs and inducing them to express a high level of encoding Ig-like transcript (ILT) 3 and ILT4 genes, converting to tolerogenic ones. Expression of the ILT3 and ILT4 receptors (a family of the immunoglobulin-like inhibitory receptors) inhibit the CD40-CD40 L signaling pathway. As CD40 L (CD154) interacts with CD40 on APC and plays a significant role in inducing them to upregulate B7 molecules to interact with CD80 and CD86 costimulatory molecules and accelerate $CD4^+$ T cell clonal expansion, blockage of this molecule might lead to modulating the action, expansion, and IFN-γ secretion in $CD4^+$ T cells. These tolerogenic $ILT3^{high}ILT4^{high}$ APCs interact with naive $CD4^+$ T cells, which could have the following fates: undergoing anergy, apoptosis or gain constant CD25, FOXP3 expression, and acquire regulatory activity. Furthermore, these APCs are capable of interacting with naive $CD8^+$ T cells, inducing FOXP3 expression, and converting their differentiation to suppressor T cells.[20] Several studies evaluated the role of the subsets of the T cell in the field of the reproductive immunity. The previous study discovered a notably high number of $CD8^+$ $CD28^-$ T cell populations in decidual tissue during pregnancy, which is induced by trophoblast cells in the first trimester at the fetal-maternal interface. These cells are a unique subset of $CD8^+$ T cells that might function in creating tolerogenic and modulatory condition through regulating self-reactive T and NK (natural killer) cells function.[21]

Moreover, a recent study showed that a decreased number of these $CD8^+$ T cells in the maternal-fetal interface might cause the immune cells activity and inflammation, which may lead to infertility. Hill *et al.* reported that the suppressor $CD8^+$ $CD28^-$ T cells/Cytotoxic T cells ratio and the percentage of $CD8^+$ $CD28^-$ T cells decreased in females with UI.[9]

Treg cells and forkhead box protein P3 transcription factor

The $CD4^+$ $CD25^+$ natural thymus-derived Treg (nTreg) and the $CD4^+$ CD25-peripheral-induced Treg (iTreg) are two Treg subsets. The former Treg subset expresses a high level of FOXP3, while the latter does not. The iTreg subset is divided into type 1 regulatory T (Tr1) cells and Th type 3 cells after antigen recognition with the help of cytokines.[11] $CD4^+CD25^+FoxP3^+$ nTreg cells perform their suppressive function mainly through cell–cell contact-dependent mechanisms and largely independent from cytokine. These mechanisms include the transfer of cyclic adenosine monophosphate (cAMP) to target cells through gap junctions[22] as well as the expression of CD39 and CD73 facilitating the local generation of adenosine affecting target cells via adenosine receptors.[23] Both cAMP and adenosine lead to a metabolic disruption in target cells such as $CD4^+$ T cells. It has been shown that regulatory $CD4^+$ $CD25^{high}Foxp3$ T cells consist of 14% of decidual T lymphocytes

and play a critical role in suppressing the maternal immune system response against the fetus, induction of tolerance, and survival of the fetus during pregnancy. This function is mediated via inhibiting the proliferation of decidual $CD4^+CD25^-$ and $CD8^+$ T cells (self-reactive T cells). As $CD4^+CD25^+$ T cells induce expression and activation of indolamine 2, 3-dioxygenase (IDO) in DCs, they can affect tryptophan metabolism in DCs, which is mediated via the interaction of B7-cytotoxic T lymphocyte-associated antigen 4 (CTLA-4). The IDO catalyzes the tryptophan degradation that results in tryptophan deficiency. As tryptophan is known as a vital stimulus for effector T cells clonal expansion, these cells undergo apoptosis without tryptophan.[24]

Yamamoto *et al*. demonstrated that the expression of Foxp3 (Treg cells transcription factor) is reduced in females with UI. This finding represents that endometrial Treg cell population is decreased in females with UI.[25]

In addition to the critical role of Treg cells in etiology of UI, it is approved that this cell population has a critical role in etiology of RSA. Abdolmohammadi *et al*. assessed the frequency of Treg cells, expression of related transcription factors and their regulating miRNAs in RSA and control (fertile) women. The finding showed that the number of Treg cells decreased in these patients along with related transcription factors including GATA3 and glucocorticoid-induced TNFR family-related gene, while the expression level of the related miRNAs, miR-106b-25–93 in these patients is increased.[16]

Mei *et al*. evaluated the proportions of $CD4^+CD25^{high}$ T cells and FOXP3 expression in peripheral blood and decidua in patients with URSA and discovered that statistically significantly lower proportions of $CD4^+CD25^{high}$ T cells and FOXP3 expression were observed in the peripheral blood of URSA women compared to fertile females.[26]

Jafarzadeh *et al.* with regard to the fact that intravenous IgG (IVIG) treatment have a modulatory effect on immune system cells, particularly Treg cells, evaluated the treatment impact on the frequency of Treg cells in URSA women. He stated that IVIG treatment lead to the increase in the frequency of Treg cells subset and a successful pregnancy subsequently.[27]

As Inhibitor of DNA-binding protein 3 (Id3) and CTLA-4 (Cytotoxic T-Lymphocyte Associated Protein 4) is required for Treg-cell generation, Ding *et al*. identified the endometrial Id3 and CTLA-4 unexplained repeated implantation failure (RIF) and concluded that the presence of $Id3^+$ and $CTLA\text{-}4^+$ Treg cells in the pre-implantation endometrium is increased in women with RIF.[28]

Humoral Immunity

Autoantibodies

As immunological factors could result in fetal loss, infertility, and autoimmunity; immunity against antigens expressed on the genital system and its secretion could play a possible role in the rejection of the semiallogeneic fetus and infertility in females. Basically, autoantibodies such as antiphospholipid antibodies (APAs), antithyroid antibodies (ATAs), and antiovarian antibodies (AOAs) also account for this autoimmunity and infertility, especially UI.[29-31] Production of these autoantibodies is positively correlated with the number of Tfh cells and its secreted cytokine, IL-21.[10]

Antiphospholipid antibodies

Based on researches, APAs could impact directly and indirectly on fertility and infertility. Two types of APAs, not particularly organ-specific antibodies, are APA lupus anticoagulant (LA) and anticardiolipin antibodies (ACA).[32] Aggregation of a heterogeneous population of named antibodies against phospholipids, particularly the antiphosphatidyl choline, anticardiolipin, antiphosphatidyl serine, LAs, and antinuclear antibodies could lead to the development of the antiphospholipid syndrome (APS). The APS is an autoimmune and hypercoagulable state caused by APAs. Increased levels of APAs are assumed to cause an unfavorable maternal immune response against implanting of the embryo and in turn pregnancy failure.[33] APAs have three targets: endothelial cells,[34] trophoblast,[35] and preimplantation embryos.[36] In the endothelial cells, APAs interrupt the generation of prostacyclin that assists vasodilatation and oppressing platelet accumulation, which result in thrombosis.[34] Thrombosis is the formation of an occlusive clot within a blood vessel that reduces blood flow to distal tissue and organs. Thrombosis also restricts the delivery of nutrients and oxygen, resulting in localized tissue and organ necrosis. Blood clot not only is formed under injured conditions but also under certain conditions, including APS. The efficient coagulation system of blood is so important during the development of the thrombosis. Large occlusive clots (thrombi) can break off and embolize to form secondary thrombi in distal locations.[37] Thrombosis in veins and arteries could be one of APS complication, which leads to pregnancy loss and infertility, but its occurrence is still unclear. Complement activation is also involved in the pathogenesis of the APS, this means that complement system (especially complement component 5a) and subsequent leukocyte activation could contribute to thrombotic APS and obstetric APS. Further, the latter one is considered as an activator of platelets, endothelial cells, and also mononuclear leukocytes especially

neutrophil that is a leading factor of the fetal wound and pregnancy failure.[38] *In vitro* assessment also showed that APS prevents the extravillous trophoblast development and migration by binding to β2-glycoprotein I that is an indicator of pregnancy failure.[35]

Moreover, Radojcić *et al.* with the aim of measuring nonorgan-specific anticardiolipin level as one of APAs found that it is elevated in females with infertility, confirming the fact that these autoantibodies participate in the pathology of the UI and infertility.[39]

Sauer *et al.* measured the levels of APAs, including ACA, antiphosphatidylethanolamine, antiphosphatidylinositol, antiphosphatidic acid, antiphosphatidylglycerol, antiphosphatidylcholine, and antiphosphatidylserine and demonstrated that these antibodies increased in females with UI.[33] Patients with URSA also showed high levels of ACA (IgG and IgM) and LA compared to the normal subject.[40]

Antithyroid antibodies

Thyroid autoimmunity (TAI) is a condition in which autoantibodies against thyroid peroxidase (TPO) and / or thyroglobulin (TG) are secreted that affects 5%–20% of healthy pregnancies.[41] The cause of TAI disease is still unknown; it is assumed to be a bifactorial disease (genetic and environmental factors). Two types of TAI disease include autoimmune thyroiditis and autoimmune hyperthyroidism that are called Hashimoto's (lymphocytic) thyroiditis (HT) and Graves' disease (GD), respectively. The impaired $CD4^{+}CD25^{+}$T regulatory cell populations cause failure in the tolerance of the immune system response and imbalancement in cytokines network, which contribute to the stabilization of apoptosis. Induced apoptosis seems to have a key role in the etiology of the HT and GD. However, different mechanisms are involved in this process. In the HT, the induction of apoptosis leads to the damage of thyrocytes; whereas, in the GD, it leads to damage of thyroid-infiltrating lymphocytes. The differences in the apoptotic mechanisms produce two very different forms of thyroid autoimmune responses, eventually developing into HT and GD, respectively. With regard to the role of thyroid hormones in balancing of immune system, the Th1 cell populations and secreted tumor necrosis factor alpha (TNF-α) is higher than Th2 cells population and secreted IL-10 in women with TAI. So the correlation of TAI with impaired cellular and humoral immune responses along with the rejection of the fetus is evident.[42] Aside from this, as thyroid hormones are vital for the development of a fetus, especially its brain, somatic tissues, and also the progression of its metabolism in early gestation, the TAI disease could influence adversely on pregnancy that is accompanied with infertility, including UI.

Bellver *et al*. discovered that the prevalence of TAI with anti-TPO (aTPO), anti-TG (aTG), and aTPO plus aTG antibodies in females with UI was enhanced.[43] Geva *et al*. supported the Bellver J discoveries. They evaluated the presence of ATAs in females with UI and concluded that there is a high level of these antibodies in mentioned patients.[44] Habib Zade and Faghih confirmed the results of these previous studies represented that an increase in serum aTPO antibodies is related to the occurrence of UI.[31]

Antiovarian antibodies

AOAs are a heterogeneous group of antibodies and include antibodies against the zona pellucida, granulosa membrane, and theca interna that consist of follicle containing ovum.[45] There is little knowledge about the role of female genital tract-specific antibodies. In the past, AOAs were known to be correlated with premature menopause, adrenal defect, and polyglandular autoimmunity.[46,47] Recently, it has been proved that these antibodies could be involved in either infertility or unsuccessful *in vitro* fertilization (IVF) treatment. Frequent IVF treatments make ovarian antigens to be released in a considerable amount. These antigens might be capable of stimulating the production of AOAs.[45] In more detail, antibodies against granulosa cells with the cooperation of the complement system have a cytotoxic effect. This effect is along with inhibiting the production of progesterone by these cells.[48] In addition, AOA prevents DNA synthesis and the growth of granulosa cells.[49] Thus, these antibodies play an essential role in reproductive functions of the human ovary, and they can influence it negatively which lead to infertility.

Luborsky *et al*. assessed the frequency of AOAs in order to compare these antibody levels in unexplained infertile women and control group (fertile females). The results indicated that the frequency of these antibodies was significantly enhanced in females with UI.[50] Shatavi *et al.* with regard to the fact that polyclonal anti-hormone antibodies such as gonadotropin antibodies aside from AOA are an important biomarker in UI realized that a high frequency of gonadotropin antibodies was observed in females with UI.[51]

Cytokine

Cytokine networks have a significant function in the reproductive system and pregnancy. Cytokines influence the uterine functions through menstruation, implantation, pregnancy, and parturition. The interactions among cytokines are a complicated and dynamic process that is regulated by pregnancy hormones.[52] In addition to their role in regulating biological processes, they possess an immunomodulatory, mitogenic, and proapoptotic role in nonimmune cells.[53] Cytokines also participate

in regulating trophoblast invasiveness. The maternal hormones contribute to the modulatory effect of cytokines on maintaining the fetus. During pregnancy, these hormones could define the differentiation of naive $CD4^+$ T cells into Th1 or Th2 cells. At the fetal-maternal interface, pregnancy hormones such as progesterone induce the IL-3, IL-4, IL-5, and IL-10 production, which suppress Th1 responses and help to create a tolerogenic environment in women, whereas relaxin, which is another hormone produced by the ovary and the placenta, promotes the production of IFN-γ by Th1 cells. Furthermore, Th1-secreted cytokines (such as IFN-γ, IL-2, and TNF) cause the failure in pregnancy, whereas Th2 secreted cytokines (such as IL-4, IL-5 and IL-10, which suppress Th1 responses) cause the tolerance to the fetus and pregnancy. The early pregnancy human decidua provides a pro-inflammatory environment to support placentation and paradoxically harboring anti-inflammatory cytokine. The anti-inflammatory cytokines could modulate the immune cells response. Moreover, IL-35 is capable of inhibiting the Th-17 cells development.[54] Thus, the imbalance in cytokine networks, pro-inflammatory, and anti-inflammatory cytokines may lead to impaired pregnancy and infertility, including UI.

Ozkan *et al.* demonstrated that unexplained infertile females had a high ratio of TNF-α/IL-10, IFN-γ/IL-10, and IFN-γ/IL-4 compared with fertile females, while IL-35/IL-17 was lower in comparison with fertile females, representing that the ratio of pro-inflammatory/anti-inflammatory cytokines is increased in former patients.[8] According to the previous study, the IL-4 level might increases in females with UI as well.[10] Wilczyński *et al*. evaluated the TNF-a, IL-10, IL-5, IL-4, IL-2, and IFN-γ levels in these patients after immunization and realized that only IFN-γ level is decreased.[12]

Wang *et al*. in order to assess the effect of adoptive transfer of trichostatin-induced $CD4^+$ $CD25^+FOXP3^+$ Treg cells on the prevention of RSA in CBA/J mice, injected trichostatin to the mice on first and 4^{th} day of pregnancy and realized that TSA treatment lead to the successful pregnancy and high secretion of TGF-β and IL-10 indicating high number of $CD4^+CD25^+FOXP3^+$ Treg cells in RSA prone mice.[55]

Conclusion

Studies have demonstrated that prominent changes are made to create a maternal immune tolerance to the fetus during pregnancy, whereas imbalance in their status is involved in the initiation of inflammatory process and pathology of infertility, especially UI. How does this maternal immune system imbalance occur? Autoimmunity (the process in which self-reactive immune cells and autoantibodies involve), including APS, thyroid and ovarian autoimmunity preferentially could affect women, almost throughout their reproductive age. In fact, autoimmune conditions probably influence all steps of fertility from ovarian and testicular failures to implantation failure, representing as pregnancy failure and infertility. Based on these findings, more studies are needed to be carried out to recognize the different aspects of the adaptive immune system response and its disordering functions in females with UI.

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Conflicts of interest

There are no conflicts of interest.

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