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Editorial
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Emphasizing the Diagnostic of Undifferentiated Connective Tissue Disease in Patients with Recurrent Spontaneous Abortions

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Editorial

Connective Tissue Diseases (CTD) are known to be developing in a gradual pattern. First of all, auto-reactive immune cells are stimulated with or without the production of auto-antibodies under the interaction of genetic background and environment factors. Progressively, certain manifestations are induced by the dysfunction of immune system, such as skin rash, arthritis, Raynaud's phenomenon, recurrent spontaneous abortion and etc., In spite of necessity of therapies for specific symptoms, patient's remains in the clinical status of Undifferentiated Connective Disease (UCTD), which have not reached any diagnostic criteria of definite CTD. Eventually, a few patients develop into definite CTD, such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), Sjögren's Syndrome (SS), Antiphospholipid Antibody Syndrome (APS), Systemic Sclerosis (SSc) and etc., which damage organ functions to a deeper extent.

Until now, it still remains controversial for the diagnosis of UCTD by various symptoms of CTD and crossing definitions of different CTD, such as incomplete SLE, latent SLE, overlap syndrome, Mixed Connective Tissue Disease (MCTD) and UTCD. Moreover, as a majority of patients with CTD are of productive age, clinical physicians are facing with more and more patients suffering from unexplained Recurrent Spontaneous Abortions (RSA). Classical symptoms are hardly found in these patients, while, with positive auto-antibodies. Thus, there also exists a controversy in the diagnosis of autoimmune-related RSA or RSA with UCTD. The unclear diagnosis or late recognition of RSA with UCTD with its potential risk of developing into a definite disease, would delay surveillance and prevention, therefore, inducing serious pregnancy complications, developing into definite rheumatic diseases, such as SLE, APS, SS or SSc, and even leading to mortality.

Diagnosis of UCTD

In 1999, Mosca et al. [1] proposed preliminary classification criteria of UTCD which was composed of inclusion and exclusion criteria. The inclusion criteria included clinical symptoms suggestive of connective tissue diseases more than 3 years but not fulfilling any criteria of defined of CTD and with at least twice positive antinuclear antibodies. Clinical manifestations such as malar rash, scleroderma, heliotrope rash, Gottron rash, erosive arthritis and presence of specific antibodies as anti-double strand DNA antibody, anti-Smith antibody, anti-U1 Ribo Nucleo Protein (RNP) antibody, anti Scl-70 antibody, anti-SSB/La antibody, anti-Jo1 antibody and etc. should be excluded [1]. However, the deficit and limit of this diagnosis criterion was so obvious that in 2008, Mosca has committed that this criteria could not cover patients with shorter disease onset, less than 3 years, slow onset pattern or early stage CTD as many specific clinical manifestations and antibodies have been excluded and it could not predict the prognosis of diseases [2].

Moreover, there still remains controversy in diagnosis of UCTD. Dijkstra et al., [3] has suggested that UCTD should be recognized with symptoms and signs of CTD and positive antinuclear antibodies, not fulfilling diagnosis criteria of any CTD. Danieli et al., [4] has proposed the diagnosis with indicative symptoms and signs of autoimmune diseases, not filling any criteria of CTD. Alarcon et al., [5] has considered patients of UCTD with Raynaud's phenomenon, sicca syndrome, unexplained arthritis or other CTD manifestations more than 1 year. Therefore until now a day there still lacks the consensus of UCTD diagnosis criteria. Currently, the diagnosis of UCTD is mainly established with at least one of CTD symptoms or signs, and more than one positive autoimmune antibodies, such as antinuclear antibodies or anti-SSA antibodies, at least one year, not fulfilling any other diagnosis criteria of CTD.

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Association between UCTD and pregnancy

In Spinillo's cohort study of 2458 patients, it has demonstrated that the relation between UCTD and pregnancy was close with significant odds ratios of 2.81. The impact of UCTD on pregnancy and fetal outcomes included abortion or stillbirth (3.23%), eclampsia (11.29%), fetal growth retardation (8.06%), preterm delivery (3.23%), congenital heart block and neonatal lupus. One case-control study of 41 UCTD pregnant patients from Spinillo et al., [6] has shown that UCTD patients had more risks for recurrent spontaneous abortions, defined as at least 2 consecutive spontaneous abortions, with the prevalence of 9.5% compared with control groups of 1.2% (p=0.004) [7]. That is to say, recurrent spontaneous abortions are undoubtedly one of frequent and important clinical manifestations of UCTD.

Meantime, pregnancy tends to be a trigger for UCTD patients to evolve into SLE, APS, SS, DM/PM, SSc and etc [8-9]. Besides, it is possible to develop serious complications during pregnancy in UCTD patients, such as thrombopenia, thrombotic thrombocytopenic purpura, myocarditis, non-specific interstitial lung disease, cardiovascular disease, vasculitis, pericardial tamponade, liver dysfunction and etc.

According to the definition of UCTD, it is necessary to be equipped with at least one clinical manifestation for the diagnosis of UCTD. Recurrent spontaneous abortion accounts for the clinical signs of various autoimmune diseases, such as APS, SLE and SS, and RSA are a common and vital clinical manifestation in UCTD. Therefore, UCTD could be established in patients with history of unexplained RSA and positive antibodies even without any other clinical symptoms. This diagnosis is distinguished from autoimmune associated recurrent spontaneous abortion, which is a much wider concept, composed of autoimmune RSA and alloimmune RSA. The autoimmune RSA is divided into organ non-specific autoantibodies as antiphospholipid antibody, antinuclear antibody and anti-ds DNA antibody and organ specific autoantibodies as Anti-Endothelial Cell Antibody (AECA), Anti-Paternal Cytotoxic Antibody (APCA), Anti-Thyroid Antibody (ATA) and etc. The alloimmune RSA includes innate immune dysfunction with increased quantity and activity of natural killer cells, macrophage dysfunction, dentric cell dysfunction, abnormal complement system and acquired autoimmune imbalance with abnormal T/B lymphocytes and Th1/Th2 cytokine dysfunction [10]. Thus, theoretically, these patients could be diagnosed as UCTD or autoimmune RSA. We prefer the diagnosis of UCTD based on the following two reasons: firstly, pregnancy is one of the most important triggers for 20% to 40% UCTD patients to evolve into a defined CTD in first 3 to 5 years; secondly, it is possible for these patients to develop serious complications so that diagnosis of UCTD is in favor of immunomodulatory therapies in clinical procedures. Briefly, the diagnosis of UCTD could remind obstetricians of emphasizing on surveillance and prevention of abnormal immune systems during pregnancy and vigilant for the development into SLE, APS, SS, DM/PM or SSc and occurrence of serious complications. Only with balanced immune status, could patients prepare for pregnancy. Rheumatologists could also participate in monitoring evolution of UCTD and post-partum follow-up if necessary.

Therefore, clarifying the association between RSA and UCTD plays an important role in understanding UCTD and furthermore, improving the prognosis of UCTD with RSA.

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