

# Systemic autoimmune diseases and recurrent pregnancy loss: research progress in diagnosis and treatment

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*To the Editor:* Recurrent pregnancy loss (RPL) is defined as the loss of two or more pregnancies before 24 weeks of gestation, and it affects about 1% to 2% of couples.<sup>[1]</sup> The etiology of RPL includes metabolic/endocrinological abnormalities, genetic factors, anatomical factors, immune disorders, thrombophilia, male factors, and psychological factors.<sup>[1,2]</sup> Systemic autoimmune diseases like antiphospholipid syndrome (APS),<sup>[3]</sup> undifferentiated connective tissue disease (UCTD),<sup>[4]</sup> and systemic lupus erythematosus (SLE)<sup>[5]</sup> have been found to be important causes of RPL in recent years. Understanding the associations between different systemic autoimmune diseases and RPL, as well as being able to provide suitable diagnoses and treatments, is of great significance.

APS is a systemic autoimmune disease with a wide range of vascular and obstetric manifestations associated with thrombotic and inflammatory mechanisms orchestrated by antiphospholipid antibodies (aPL).<sup>[3]</sup> APS with adverse pregnancy outcomes as its clinical manifestation is called obstetric antiphospholipid syndrome (OAPS).<sup>[6]</sup> Pregnancy losses including fetal losses at  $\geq 10$  weeks of gestation and spontaneous miscarriages before 10 weeks of gestation are important symptoms of OAPS and have been included in the clinical diagnostic criteria for OAPS.<sup>[7]</sup> In addition, lupus anticoagulant (LA), anticardiolipin antibodies (aCL), or anti-beta-2 glycoprotein I antibodies (a $\beta$ 2GPI) in serum are also necessary for the diagnosis of OAPS.<sup>[7]</sup> The diagnosis of OAPS with pregnancy loss requires the presence of one clinical criterion and one laboratory criterion, as shown in the European Alliance of Associations for Rheumatology (EULAR) recommendations for the management of APS in adults.<sup>[3]</sup>

Some RPL patients, however, might neither be diagnosable as having OAPS nor be able to receive treatment. To solve

this problem, non-criteria obstetric antiphospholipid syndrome (NOAPS) has been put forward. Patients who meet both one non-classical clinical/laboratory criterion and one classical laboratory/clinical criterion can be diagnosed with NOAPS.<sup>[3]</sup> The non-classical criteria related to pregnancy loss are also presented in the EULAR recommendations.<sup>[3]</sup> In addition, a novel nomenclature proposal for non-criteria APS was published in 2020, in which non-criteria APS was divided into seronegative APS, clinical non-criteria APS, incomplete laboratory APS, and laboratory non-criteria APS.<sup>[8]</sup> According to this nomenclature, two or more unexplained *in vitro* fertilization failures and two unexplained spontaneous abortions before 10 weeks are included as non-classical clinical criteria, and non-criteria aPL is included as non-classical laboratory criteria. It is not difficult to see that there are many deficiencies in these NOAPS diagnostic criteria, thus necessitating further improvement.

It is difficult to judge a patient's condition according to these APS or NOAPS diagnostic criteria. Thus, some risk stratification methods have been put forward to guide clinical practice. The presence (in two or more occasions at least 12 weeks apart) of LA, the presence of double (any combination of LA, aCL, or a $\beta$ 2GPI antibodies) or triple (all three sub-types) aPL positivity, or the presence of persistently high aPL titers (titers above the 99th percentile) were regarded as high-risk aPL profiles; isolated aCL or a $\beta$ 2GPI antibodies at low- to mid-level titers (between the 95th and 99th percentiles), particularly if transiently positive, were regarded as a low risk aPL profile.<sup>[3]</sup> A history of SLE, thrombosis, or pathological pregnancy was also regarded as a high-risk factor for adverse pregnancy outcomes.<sup>[9]</sup>

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The treatment of APS and NOAPS is relatively definite. According to EULAR recommendations,<sup>[3]</sup> in women with a high-risk aPL profile but no history of thrombosis or pregnancy complications, treatment with a low-dose of 75 to 100 mg/day of aspirin (LDA) during pregnancy should be considered. In women with a history of OAPS only (no prior thrombotic events), a combined treatment with LDA and low molecular weight heparin (LMWH) at prophylactic dosages during pregnancy is recommended after taking into account the individual's risk profile. In women with NOAPS (no prior thrombotic events), treatment with LDA alone or in combination with LMWH may be considered based on the individual's risk profile. In women with a history of thrombotic APS, a combined treatment of LDA and LMWH at therapeutic dosages during pregnancy is recommended. It should be mentioned that in women with OAPS with recurrent pregnancy complications that occur despite combined treatment with LDA and LMWH at prophylactic dosages, increasing the LMWH dose to a therapeutic dose or the addition of hydroxychloroquine (HCQ) and/or low-dose prednisone during the first trimester may be considered.

There are still many aPL-positive patients who do not meet the NOAPS diagnostic criteria. Evidence from basic scientific studies supports a causative relationship between aPL and RPL, but human studies have not consistently found this relationship.<sup>[10,11]</sup> This does not mean that patients with positive aPL who do not meet the diagnostic criteria for NOAPS do not need to be managed, as they may still develop NOAPS or even OAPS in the future. Unfortunately, the tools for identifying and determining risk in these patients are limited. There is no consensus on whether aPL should be assessed during pregnancy, but it certainly makes sense to detect coagulation indicators during pregnancy.<sup>[12]</sup> More evidence-based medical studies about the management of pregnancy accompanied by positive aPL are needed to guide clinical practice.

UCTD is a group of heterogeneous autoimmune diseases characterized by the presence of at least one symptom of connective tissue disease accompanied by a positive test for the antinuclear antibody (ANA).<sup>[13]</sup> At present, there is no consensus on the diagnostic criteria of UCTD, and the generally accepted criteria are that both of the following points need to be met: (a) at least one symptom of connective tissue disease must be present and (b) there must be a positive test for ANA (titers  $\geq 1:80$ ).<sup>[13]</sup> UCTD is the most common autoimmune disease in pregnant women, with a prevalence of up to 2.5%,<sup>[14]</sup> and it has been reported that UCTD patients have a 9% to 21% risk of pregnancy loss.<sup>[4,14]</sup> It has also been shown that ANA positivity is significantly associated with RPL in women without defined autoimmune diseases.<sup>[15]</sup> Therefore, we can conclude that both UCTD and ANA positivity are potential etiologies of RPL. RPL is considered to be a symptom of connective tissue diseases, and it is better to manage unexplained RPL combined with positive ANA as a pregnancy loss-associated undifferentiated connective tissue disease (PLUCTD). The concept of PLUCTD is helpful for standardizing the clinical management of this kind of disease. Even though there is no consensus on the diagnostic criteria for PLUCTD at present, the impact of

UCTD and ANA on RPL still needs to be given more attention.

There is no consensus on the treatment of PLUCTD. It is clear that UCTD is not considered a contraindication of pregnancy. According to the opinion of Chinese experts,<sup>[16]</sup> HCQ treatment (0.2–0.4 g/day, bid) starting at 3 to 6 months before planned pregnancy can benefit patients with PLUCTD. Low-dose prednisone ( $\leq 10$  mg/day) should be used throughout pregnancy and up to 3 months postpartum in patients with PLUCTD who are prone to conversion to other autoimmune diseases. Coagulation indicators also need to be monitored during pregnancy, and LDA and LMWH at prophylactic or even therapeutic doses may be used in patients prone to thrombosis based on the individual's risk profile.<sup>[17]</sup> Patients who still developed pregnancy loss after this treatment were said to have had refractory PLUCTD, for which no effective treatment strategy is available at present but for which exploratory therapy for research purposes is encouraged. In addition, the significance of monitoring ANA titers or the autoantibody profile during pregnancy is uncertain. Also, the anti-extractable nuclear antigen antibody profile or other autoantibodies testing positive during pregnancy may be a marker of poor prognosis, but this opinion needs to be confirmed by clinical studies in the future.<sup>[18]</sup>

SLE usually affects women of childbearing age. Pregnancy is considered to be high-risk due to a combination of maternal risks (such as lupus flare ups, diabetes, and preeclampsia) and adverse pregnancy outcomes (such as RPL, intrauterine fetal demise, preterm birth, fetal intrauterine growth restriction, and fetal congenital heart block).<sup>[19]</sup> Disease activity prior to conception, the onset of SLE during pregnancy, and underlying renal disease may be risk factors of RPL in SLE women; however, the most recognized risk factor is the presence of aPL.<sup>[5]</sup> Secondly, OAPS or NOAPS have been observed in many SLE women with RPL, which establishes the relationship between the mechanism by which SLE and OAPS/NOAPS causes RPL. In addition, ANA is also a classical immunological marker of SLE, which may be related to the mechanism by which SLE causes RPL. For RPL patients with SLE, their condition must be stabilized before their next pregnancy, especially when SLE is active or when there is active nephritis or hypertension.<sup>[12]</sup> Teratogenic immunosuppressive drugs should be discontinued for at least 6 months before pregnancy and should be replaced by pregnancy-safe immunosuppressants such as HCQ and cyclosporine A (CsA). During pregnancy, the assessment of disease activity—including renal function parameters and serological markers (such as serum C3/C4 and anti-dsDNA titers)—is recommended to monitor for adverse obstetrical outcomes and disease flare-ups. HCQ (0.2–0.4 g/day, bid) is recommended preconceptionally and throughout pregnancy for RPL patients with SLE,<sup>[12]</sup> and low dose prednisone ( $\leq 10$  mg/day) should be added if disease activity increases. If HCQ and low doses of prednisone fail to control lupus activity, relatively safe immunosuppressants such as acetazolamide (AZA) ( $1.5\text{--}2\text{ mg}\cdot\text{kg}^{-1}\cdot\text{day}^{-1}$ , bid), CsA ( $3\text{--}5\text{ mg}\cdot\text{kg}^{-1}\cdot\text{day}^{-1}$ , bid) or tacrolimus ( $2\text{--}3\text{ mg/day}$ , once every 12 h) may be considered. The obstetrician

should work with a rheumatologist to manage these SLE patients during pregnancy.

In summary, OAPS/NOAPS, UCTD, and SLE are important etiologies of RPL. The diagnosis and treatment of RPL combined with systemic autoimmune diseases is difficult at present because of limited basic and clinical research. RPL caused by systemic autoimmune diseases needs to be further studied. On the one hand, the mechanism by which systemic autoimmune diseases and antibodies cause RPL needs to be further explored; on the other hand, different treatment strategies for these conditions require further examination.

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### Conflicts of interest

None.

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