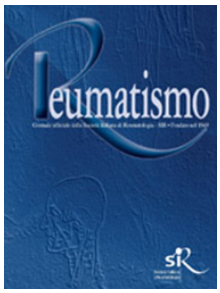

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The use of tumor necrosis factor inhibitors during high-risk pregnancies in antiphospholipid syndrome: a clinical report of a patient with concomitant Takayasu arteritis and case-based review

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Summary
In the field of obstetric antiphospholipid syndrome (APS), studies in mouse models and case reports support the potential benefit of tumor necrosis factor-α inhibitors (TNF-i) in preventing pregnancy loss associated with APS.
We present the case of a 36-year-old woman with a diagnosis of Takayasu arteritis who suffered from antiphospholipid antibody (aPL)-related thrombotic microangiopathy/probable catastrophic APS during her first pregnancy and who had a subsequent successful pregnancy while on treatment with certolizumab pegol (CZP), heparin, and low-dose aspirin. The report is followed by the literature review of published cases of APS or aPL-positive pregnancies treated with CZP or other TNF-i.
A total of 20 pregnancies, including the one here presented, were reported in high-risk APS patients exposed to TNF-i, showing a favorable outcome in most pregnancies (80% live births, 69% absence of adverse pregnancy outcomes).
Despite the limited available evidence, TNF-i could represent a promising option for high-risk patients in obstetric APS.

Introduction

Antiphospholipid antibodies (aPL) are a heterogeneous group of antibodies generally directed against phospholipid-binding proteins that can be responsible for antiphospholipid syndrome (APS) by causing otherwise unexplained macro- or micro-thrombotic events (venous or arterial) disease and/or pregnancy morbidity, especially severe preeclampsia (PE) and/or placental insufficiency (PI). Takayasu arteritis (TAK) is a large vessel vasculitis usually affecting young women of childbearing age, being probably the most common systemic vasculitis in this population (1).

APS and TAK are two distinct clinical entities, although both diseases can coexist. These conditions can be associated with adverse pregnancy outcomes (APOs): APOs were observed in up to half pregnancies in TAK patients, ranging from arterial hypertension with PE to fetal growth restriction (2); in APS obstetric events, which can occur in up to 80% of patients without treatment, include recurrent miscarriages, fetal deaths of a morphologically normal fetus, PE/eclampsia, PI, and severe premature births (3-5).

Few studies have investigated the prevalence of aPL in TAK patients (6-8), reporting rates between 0% and 45%. However, the clinical significance of the presence of aPL during TAK is controversial, with an uncertain pathophysiological role of aPL in disease manifestations. Moreover, very few data on pregnancy outcomes in TAK patients with aPL are available (9).

TNF-α is recognized as a crucial cytokine in the pathogenesis of TAK, and TNF-α inhibitors (TNF-i) are among the therapeutic options for TAK management (10). In the context of APS, studies in pregnant mouse models have linked elevated TNF-α levels in placental tissues with abnormal placentation and pregnancy loss, supporting the potential benefit of TNF-i in preventing pregnancy losses associated with APS through biological mechanisms such as TNF-driven inflammation reduction and prevention of complement activation (11).

Here, we present the case of a 36-year-old female patient with TAK, who suffered from aPL-related thrombotic microangiopathy (TMA)/probable catastrophic APS (CAPS) during her first pregnancy. A subsequent pregnancy was treated with certolizumab pegol (CZP), low molecular weight heparin (LMWH), and low-dose aspirin (LDA) with a good outcome. Additionally, we aim to review previously published cases of APS pregnancies treated with CZP or other TNF-i.

Case Report

In 2008, a 23-year-old woman was admitted to the emergency room because of intense left flank colicky pain with vomiting episodes, severe headache non-responsive to non-steroidal anti-inflammatory drugs, and sudden arterial hypertension (up to 220/130 mmHg). Laboratory testing revealed elevated inflammatory parameters with a C-reactive protein (CRP) value of 89 mg/L. A slight increase of serum creatinine (sCr: 1.25 mg/dL) with estimated glomerular filtration rate of 70 mL/min and 24-hour proteinuria of 370 mg were also recorded. Immunological tests showed lupus anticoagulant (LA) positivity, while other assays [anti-β2glycoprotein I antibodies (aβ2GPI), anti-cardiolipin antibodies (aCL), antinuclear antibodies, anti-double-stranded DNA antibodies, anti-extractable nuclear antigens antibodies, proteinase-3-anti-neutrophil cytoplasmic antibodies, myeloperoxidase-anti-neutrophil cytoplasmic antibodies, cryoglobulins], including C3 and C4 fractions of complement, were all negative or within normal limits. Imaging studies (ultrasound and magnetic resonance angiography) showed serrated ostium stenosis of the right renal artery, left renal artery occlusion with marked impairment of homolateral kidney perfusion, and hypoplastic right vertebral artery (Figure 1).

The diagnosis of TAK with bilateral renal artery involvement was made. The treatment included high-dose oral glucocorticoids (GCs), anti-hypertensive drugs, and LDA. Percutaneous transluminal angioplasty with stenting of the right renal artery was successfully performed. Disease remission was achieved, and GCs were gradually reduced to 2.5 mg prednisone equivalent/day. LDA and antihypertensive drugs were continued.

In 2017, at the age of 32 years, she was referred to our attention because of pregnancy [11+3 gestational weeks (GWs)]. It was unplanned and even its diagnosis was delayed because the patient

used to have irregular menstrual cycles. Because of the known LA positivity and the findings of low titers of both aβ2GPI and aCL, a prophylactic dose of LMWH was added to the treatment already including LDA and anti-hypertensives after multidisciplinary evaluation (rheumatologists, gynecologists, nephrologists).

At 13+2 GWs, the patient was admitted to the intensive care unit because of intense epigastric pain. Laboratory findings were consistent with TMA: 7.3 g/dL of hemoglobin (Hb), 73000/mm^3 platelets (the previous month the values were: 9.0 g/dL of Hb and 123000/mm^3 platelets), elevated CRP (170 mg/L), D-dimer (3642 ng/mL) and liver function tests [glutamic oxaloacetic transaminase (GOT): 64 U/L and glutamic pyruvic transaminase (GPT): 112 U/L], presence of schistocytes, of proteinuria at urinalysis (24-hours proteinuria: 408 mg) with normal renal function (sCr: 0.7 mg/dL). Complement levels were within normal limits (C3: 100 mg/dL and C4: 20 mg/dL). Blood pressure values were found normal (130/85 mmHg). An abdomen-thorax angio-computed tomography scan excluded signs of active TAK and confirmed the previous vascular findings of occluded left renal artery with homolateral wrinkled kidney and of post-ostial vascular stent presence in the right renal artery.

A diagnosis of systemic TMA/probable CAPS and a therapy (12, 13) with high-dose GC pulses, continuous heparin infusion and high-dose intravenous immunoglobulins was started with an initial good clinical and laboratory response (Hb: 8.3, platelets: 187000/mm^3, CRP: 5.2, D-dimer: 563 ng/mL, GOT: 21 U/L, GPT: 33 U/L, sCr: 0.59 mg/dL, schistocytes: absent; proteinuria at urinalysis: 102 mg). However, two weeks later (at 16+2 GWs), she had a clinical and laboratory relapse and was admitted to the nephrology unit. In addition to the high-dose GC pulses and continuous heparin infusions, she underwent five plasma exchange sessions, but, unfortunately, at 18+2 GWs, an intra-uterine fetal death occurred.

The placental histology revealed an area of extensive, recent, full-thickness infarction and villi with changes from chronic hypoxia with syncytial notches.

In the following weeks, clinical and laboratory improvement was observed, and the patient was discharged with the following therapy: medium-dose oral GCs, hydroxychloroquine (HCQ 5 mg/Kg/die, started during the hospitalization), vitamin K antagonist (VKA, which replaced the heparin administered during hospitalization), and anti-hypertensive medications.

An 18F-fluorodeoxyglucose positron emission tomography performed 2 months later, for monitoring purposes, was negative for active vasculitis. To reduce oral GC dose and, at the same time, ensure remission of TAK, an immunosuppressive therapy was proposed. In TAK, TNF-i demonstrated efficacy in inducing and maintaining remission and a GC sparing effect (14). On the other hand, considering that the patient desired a pregnancy and that a pivotal study on CZP, an FC-free TNF-i with minimal placental transfer, was ongoing in high-risk APS pregnancies (NCT03152058), CZP was considered the treatment of choice.

CZP was started in 2018, and it was well tolerated and allowed to withdraw GCs in 2021 without any subsequent exacerbation in disease activity.

In 2022, at 36 years of age, a second pregnancy occurred: VKA was replaced with therapeutic dose LWMH, oral calcium was added, and the ongoing therapy with LDA, CZP, HCQ, calcifediol, folic acid, and anti-hypertensives (clonidine and atenolol) was confirmed, according to the plan agreed upon by the multidisciplinary team during preconception counselling. The patient was closely monitored by the multidisciplinary team every 4 weeks. She was asymptomatic and laboratory tests remained within normal ranges throughout pregnancy. At 37+0 GWs, a premature rupture of membranes occurred, and a healthy male baby (2.300 Kg) was born by vaginal delivery. The timeline of events is depicted in Figure 2.

Search Strategy

We retrospectively reviewed the PubMed and Medline, Scopus, and Directory of Open Access Journal databases for the literature published until September 2024 using the following keywords: “TNF-alpha blockers” or “TNF-alpha inhibitors” and “antiphospholipid antibodies” or “antiphospholipid syndrome” and “pregnancy”. An additional search in the list of references of the primary selected

articles was performed, aiming to identify articles not included in the initial search. After the exclusion of articles and abstracts not written in English, we identified four articles (9, 15-17) providing sufficient data regarding cases of APS or aPL-positive female pregnant patients treated with TNF-i, which were included in the review (Table 1).

Discussion and Conclusions

This case shows the diagnostic challenge of different forms of microvascular involvement during pregnancy in the presence of aPL. Based on the CAPS classification criteria (18), definite CAPS is intended as thromboses in three/more organs occurring in ≤1 week, microvascular thrombosis in ≥1 organ, and persistent aPL+. Documentation of all these features is required for definite CAPS classification, but not always possible. When three out of four requirements are met, the patient is classified as probable CAPS. TMA corresponding to small vessels/capillaries occlusion with ischemia due to fibrin formation/platelet aggregation, is usually part of the picture. When TMA is associated with thrombocytopenia, microangiopathic hemolytic anemia, and organ failure, the term systemic TMA is used (19) and results in an umbrella term for several conditions like TTP, infectious HUS, CM-HUS, HELLP syndrome, and sepsis (20, 21). A CAPS subgroup presents with the full clinical picture of CM-HUS; however, both CAPS and CM-HUS confirmation is challenging during the acute management of these patients.

Our patient was initially diagnosed with TAK with bilateral renal artery involvement; 9 years later, she developed signs/symptoms and laboratory findings of TMA during her first pregnancy. TNF-i were proposed to keep TAK under control and to spare GCs. Inspired by the IMPACT trial (11), we felt that CZP was the best choice to also meet the patient's pregnancy desire. Additionally, we leveraged the evidence showing an inflammatory component, especially in patients with microvascular, non-thrombotic domains, and CAPS, and the need for a combined anti-thrombotic and immunomodulatory treatment (12).

We were prompted to review the literature on the use of TNF-i in obstetric APS. Up to September 2024, we identified four articles (9, 16, 17, 22) covering 19 total pregnancies. Table 1 reports on 20 pregnancies (including the one here presented) with a median TNF-i exposure during pregnancy of 9 weeks [interquartile range: 9-28]. In 40% of the pregnancies, a systemic autoimmune, APS-associated disease was present: three TAK, four chronic arthritis, and one systemic lupus erythematosus. The APS subset was mainly obstetric (85%), while two pregnancies (of the same patient) occurred after a thrombotic event (pulmonary embolism) and a probable CAPS/systemic TMA (present clinical case). The aPL profile was as follows: two triple aPL+ (11%), 7 double aPL+ (39%), 7 single aPL+ (39%); three patients presented positivity just for anti-phosphatidylserine/prothrombin antibodies. Most pregnancies were exposed to adalimumab (n=13, 65%), followed by CZP (n=5, 25%) and infliximab (n=2, 10%). The patients with concomitant TAK, RA, or SpA were exposed to TNF-i during pregnancy longer than patients without a concomitant systemic autoimmune disease. Additionally, LDA and LMWH were administered to all the patients, and in three pregnancies (two of the patients with a previous thrombotic event and one of the previous probable CAPS/systemic TMA), LMWH was used at an anticoagulant dose. The use of HCQ was reported in 85% of the pregnancies.

Most of the pregnancies (16/20, 80%) resulted in a live birth, with 11/16 (69%) reaching full term uneventfully. The reported APOs included three early miscarriages in three patients who underwent assisted reproductive techniques (ARTs) and were older than 40 years.

Other APOs consisted of one severe preterm birth (<34 GW) due to PE, and four preterm births (34<GW<37), one of which was associated with HELLP syndrome [in the patient with RA and obstetric APS, reported by Genest *et al.* 2018 (17)]. It is noteworthy that all the included patients had a history of previous APOs (in 7 cases: intrauterine fetal deaths; in 16 cases: recurrent early miscarriages, in one case: PE) and that just one pregnancy was preceded by a previous uneventful pregnancy. Conception was achieved through ARTs, a known risk factor for APOs, in 75% of cases.

A concern about TNF-i use in patients with autoimmune conditions is the possible induction of additional autoantibodies and eventually a full-blown systemic autoimmune picture. However, no

new autoimmune findings were detected in these women upon TNF-i use in the reported 19 cases. Our patient did not develop any new symptoms, and the child (who is currently nearly 2 years old) did not have any health problems possibly linked to the in-utero exposure to TNF-I, including infections.

In conclusion, the 20 case-reports of use of TNF-i during high-risk pregnancies with aPL reported so far showed its effectiveness in favoring live births and better pregnancy outcomes, while no major safety signals were reported. In consideration of the promising final results from the IMPACT trial (17, 23), even if the overall evidence still remains limited, TNF-i may be considered as an option for selected patients with high-risk pregnancies in the frame of obstetric APS, on top of conventional anti-thrombotic treatment.

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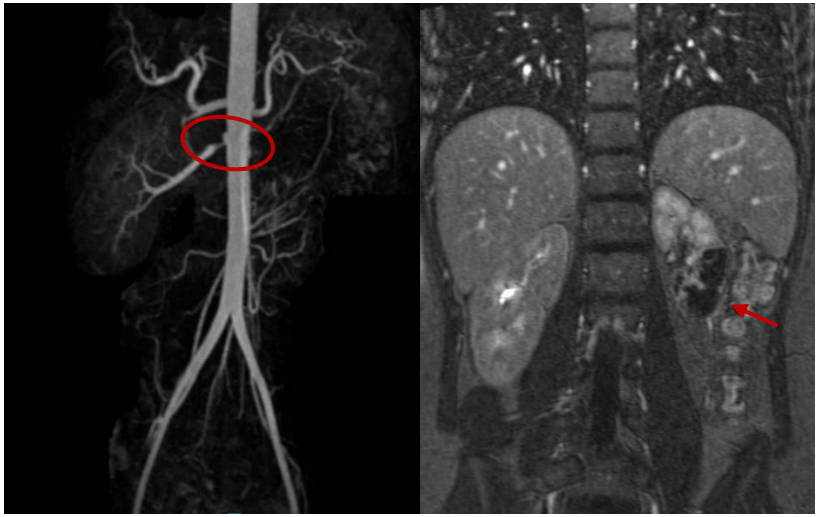

Figure 1. Abdominal magnetic resonance angiography. On the left panel, the abdominal aorta with its branches is depicted; the red circle highlights the renal arteries' origin and shows serrated ostium stenosis of the right renal artery and occlusion of the left renal artery. On the right panel, is it possible to see the kidneys with the ischemic changes of the inferior part of the left kidney (red arrow) due to marked impairment of kidney perfusion.

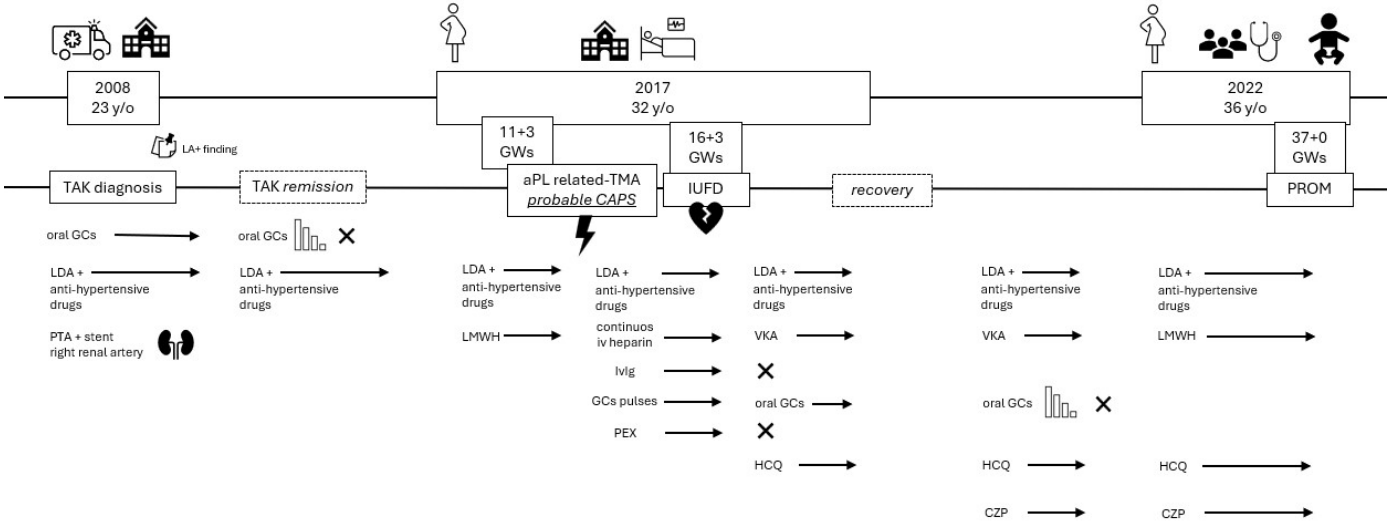

Figure 2. Timeline of the case report. aPL, antiphospholipid antibodies; CAPS, catastrophic antiphospholipid syndrome; CZP, certolizumab; GCs, glucocorticoids; GWs, gestational weeks; HCQ, hydroxychloroquine; IUFD, intrauterine fetal death; IvIg, intravenous immunoglobulin; LA, lupus anticoagulant; LDA, low dose aspirin; LMWH, low molecular weight heparin; PEX, plasma exchange; PROM, premature rupture of membranes; PTA, percutaneous angioplasty; TAK, Takayasu arteritis; TMA, thrombotic microangiopathy; VKA, vitamin K antagonist; y/o, years old.

Table 1. Summary of case reports and case series on tumor necrosis factor inhibitors use in antiphospholipid antibody pregnancies.

Author	Age	Maternal diagnosis	Previous pregnancy outcomes	Laboratory findings	TNF-i and duration of exposure	Other treatments	Pregnancy outcomes
Genest *et al.,* 2018 (17)	39 y/o	RA, o-APS	4 IUFD >10 GWs	na	CZP sc/2w (duration of exposure not known)	LDA, LWMH prophylactic dose	Cesarean delivery at 36 GWs (HELLP syndrome)
Alijotas-Reig *et al.,* 2019 (16)	41 y/o	o-APS	2 IUFD >10 GWs	aβ2GPI IgG+	ADA sc/2w up to 8w	HCQ, LDA, LWMH prophylactic dose	Miscarriage at 8 GWs
	41 y/o	o-APS	3 miscarriages <10 GWs, 1 IUFD >10 GWs	LA+, aCL IgG+	ADA sc/2w up to 9w	HCQ, LDA, LWMH prophylactic dose	Miscarriage at 9 GWs
	41 y/o	o-APS	8 miscarriages <10 GWs	aCL IgG/M+, aPT/PH IgM+	ADA sc/2w up to 8w	HCQ, LDA, LWMH prophylactic dose	Miscarriage at 8 GWs
	35 y/o	o-APS	3 miscarriages <10 GWs, 1 IUFD >10 GWs	aCL IgG/M+, aβ2GPI IgG/M+	ADA sc/2w up to 9w	HCQ, LDA, LWMH prophylactic dose	Delivery at 34 GWs
	38 y/o	o-APS	5 miscarriages <10 GWs	LA+, aβ2GPI IgG/M+	ADA sc/2w up to 9w	HCQ, LDA, LWMH prophylactic dose	Delivery at 36 GWs
	37 y/o	o-APS	3 miscarriages <10 GWs	aCL IgG/M+, aβ2GPI IgG/M+, aPT/PS IgM+	ADA sc/2w up to 9w	HCQ, LDA, LWMH prophylactic dose	Delivery at 38 GWs
	34 y/o	PsA, o-APS	2 miscarriages <10 GWs, 1 IUFD >10 GWs	LA+, aCL IgG+, aPT/PS IgM+	CTZ sc/2w up to 36w	HCQ, LDA, LWMH prophylactic dose	Delivery at 37 GWs
	34 y/o	o-APS	5 miscarriages <10 GWs	LA+	CTZ sc/2w up to 9w	HCQ, LDA, LWMH prophylactic dose	Delivery at 37 GWs
	38 y/o	o-APS	4 miscarriages <10 GWs	LA+, aCL IgG/M+, aβ2GPI IgG/M+	ADA sc/2w up to 9w	HCQ, LDA, LWMH prophylactic dose	Delivery at 37 GWs
	40 y/o	o-APS	4 miscarriages <10 GWs	aPT/PS IgM+	ADA sc/2w up to 9w	HCQ, LDA, LWMH prophylactic dose	Delivery at 38 GWs
	40 y/o	o-APS	4 miscarriages <10 GWs	aCL IgM+	ADA sc/2w up to 9w	HCQ, LDA, LWMH prophylactic dose	Delivery at 36 GWs
	37 y/o	o-APS	3 miscarriages <10 GWs	aCL IgG+	ADA sc/2w up to 9w	HCQ, LDA, LWMH prophylactic dose	Delivery at 40 GWs
	41 y/o	o-APS	1 IUFD >10 GWs	aPT/PS IgM+	ADA sc/2w up to 9w	HCQ, LDA, LWMH prophylactic dose	Delivery at 38 GWs
	40 y/o	RA, o-APS	4 miscarriages <10 GWs	aβ2GPI IgG+	ADA sc/2w up to 28w	HCQ, LDA, LWMH prophylactic dose	Delivery at 39 GWs
	39 y/o	SpA, o-APS	8 miscarriages <10 GWs	aPT/PS IgM+	ADA sc/2w up to 28w	HCQ, LDA, LWMH prophylactic dose	Delivery at 40 GWs
Jovicic *et al.,* 2023 (9)	29 y/o	TAK, t+oAPS, Chron disease	3 miscarriages <10 GWs	LA+, aCL IgM+	IFX iv/4w (duration of exposure not known)	AZA 2 mg/Kg, LDA, LMWH therapeutic dose	Vaginal delivery at 37.5 GW
	33 y/o	TAK, t+oAPS, Chron disease	3 miscarriages <10 GWs, 1 live birth 37.5 GW	LA+, aCL IgM+	IFX iv/4w (duration of exposure not known)	AZA 2 mg/Kg, LDA, LMWH therapeutic dose	Vaginal delivery at 38 GW
Madenidou *et al.,* 2023 (15)	30 y/o	o-APS	5 miscarriages <16 GWs; 1 PE	LA+	CZP sc/2w up to 28w	HCQ, LDA, LWMH therapeutic dose, PDN 10 mg/day	Cesarean delivery at 32 GWs (PE)
Present case	36 y/o	TAK, CAPS+o-APS	1 IUFD 18 GWs (during CAPS/TMA)	LA+, aCL IgM+, aβ2GPI IgM/G+	CZP sc/2w up to 37w	HCQ, LDA, LMWH therapeutic dose	Vaginal delivery at 37 GW (premature rupture of membranes)

a-β2GPI, anti-beta2glycoprotein; a-CL, anticardiolipin antibodies; ADA, adalimumab; APO, adverse pregnancy outcome; aPT/PS, anti-prothrombin/phosphatidylserine antibodies; AZA, azathioprine; CAPS, catastrophic antiphospholipid syndrome; CZP, certolizumab; GW, gestational week; HCQ, hydroxychloroquine; HELLP, hemolysis, elevated liver enzymes, low platelets; IUFD, intrauterine fetal death; IFX, infliximab; LA, lupus anticoagulant; LDA, low-dose aspirin; o-APS, obstetric antiphospholipid syndrome; PDN, prednisone; PE, preeclampsia; PsA, psoriatic arthritis; SpA, spondyloarthropathy; TAK, Takayasu arteritis; t-APS, thrombotic antiphospholipid syndrome; TMA, thrombotic microangiopathy; w, week; y/o, years old.