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Anti-phospholipid antibodies in systemic autoimmune diseases: a study among a sub-Saharan population

Anti-phospholipides au cours des connectivites : une étude au sein d'une population sub-sahariennne

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Résumé

Introduction : Les anti phospholipides (APL) peuvent être circulants au cours des connectivites sans traduction clinique. Leur prévalence dans la population générale caucasienne est faible mais peut atteindre 55% au cours du lupus et 57,5% au cours de la sclérodermie systémique. En Afrique subsaharienne, la prévalence de ces anticorps au cours des maladies systémiques est inconnue. Les études antérieurement réalisées ont essentiellement porté sur leurs morbidités au cours d'une forme de connectivite.

Objectifs : Déterminer la fréquence des APL et leurs morbidités au cours des connectivites au sein d'une population subsaharienne.

Patients et méthodes : Il s'agissait d'une étude transversale, multicentrique avec recrutement prospectif au niveau des services de Dermatologie, de Médecine interne de l'hôpital Aristide Le Dantec (HALD) et du service de Dermatologie de l'Institut d'hygiène sociale (IHS) de Dakar. Etaient inclus tous les patients présentant une connectivite et ayant donné leur consentement éclairé pour participer à l'étude. Le prélèvement à la recherche des APL était effectué au Laboratoire d'Hématologie de l'HALD. Un contrôle à 12 semaines était réalisé chez tout patient ayant présenté une positivité d'un ou de plusieurs anticorps. Le diagnostic de syndrome des anticorps antiphospholipides (SAPL) porte sur les critères de Sydney. Les données sociodémographiques, cliniques et paracliniques ont été collectées. L'analyse statistique a été réalisée avec le logiciel Epi-info 7.2. Tout p ≤0,05 était significatif.

Resultats : Nous avons colligé 60 cas de connectivites dont 54 femmes (sexe ratio=0,11). L'âge moyen était de 41,15 ans. La fréquence des APL était de 60% (n=36) au premier test alors que le contrôle n'a été positif que dans 33,3% (n=10). Le lupus anticoagulant (LA) était positif chez 35 patients soit 58,3% et l'anti cardiolipine (ACL) chez 2 patients soit 3,3%. Aucun cas de positivité de l'Ac B2GP1 n'a été trouvé. Cinq cas de SAPL étaient identifiés soit 8,4% de l'échantillon. Une persistance des APL était notée chez 5 patients ne répondant pas aux critères diagnostiques de SAPL (Sydney). Les accidents obstétricaux prédominaient avec un lien statistique significatif p=0,04. Les ulcérations cutanées, digitales n'ont pas été corrélées de façon significative avec les APL (p=0,34 ; p=0,17). Les céphalées étaient associées dans 78 % aux APL sans lien statistique (p=0,298). Il en était de même pour le phénomène de Raynaud (p= 0,306).

Conclusion : Les APL sont fréquemment positifs au cours des connectivites mais ils y sont souvent transitoires. Le LA est l'Ac le plus fréquent et la maladie lupique en constitue la principale cause.

Mots-clés : Connectivites - antiphospholipides - Syndrome des anticorps antiphospholipides - Afrique sub-saharienne.

Summary

Introduction: Anti phospholipids antibodies (aPL) can be circulating during connectivitis without clinical manifestations. Their prevalence in the general caucasian population is low but can reach 55% in lupus and 57.5% in systemic scleroderma. In sub-Saharan Africa, the prevalence of these antibodies during systemic diseases is unknown. Earlier studies conducted have mainly focused on their clinical détails linked to a connectivitis.

Objective: To determine the frequency of aPL and their morbidities when associated with systemic autoimmune diseases among a Sub-Saharan population.

Patients and methods: We conducted a cross-sectional multicenter study with prospective recruitment in Le Dantec Hospital Internal Medicine and Dermatology departments and also dermatology department of the Social Hygiene Institute of Dakar. All patients with a systemic autoimmune disease and who agreed to the informed consent form were included. Test Samples for aPL detection were conducted in the Hematology laboratory of Le Dantec Hospital. A 12-week interval control sample was performed for each patient who presented a positivity for one or more antibodies. The diagnosis of antiphospholipid syndrome (APS) was based on the Sydney classification criteria. Socio-demographic, clinical and paraclinical data were collected. Statistical analysis was performed using Epi-info 7.2 software. A p-value (less than) ≤ 0.05 was statistically significant.

Results: Sixty patients with systemic autoimmune diseases were enrolled including 54 women (sex ratio=0.11). The mean age was 41.15 years. The aPL frequency was 60% (n=36) at the first blood test while the control test was positive at 33.3% (n=10). Lupus anticoagulant (LA) was positive in 35 patients corresponding to 58.3% and anticardiolipin (ACL) antibodies in 2 patients representing 3.3%. No β2-glycoprotein antibodies (aβ2-GP1) were detected. Five cases of APS were identified representing 8,4% of the sample. Five patients who didn't meet the diagnosis criteria of APS (Sydney) were persistently aPL positive. Obstetric complications predominated with a statistical significance p=0.04. Cutaneous and digital ulcerations were not significantly correlated with APL (p=0.34 p=0.17). Headaches were observed in 78% of Apl positive cases without any statistical significance (p=0.298). A similar result was observed for Raynaud's phenomenon (p=0.306).

Conclusion: aPL are frequently positive during connectivitis but often transient. LA is the most common antibody and SLE is the main cause.

Key words: connectivitis - antiphospholipid antibodies - antiphospholipid syndrome - sub-saharan africa.

Introduction

If visceral manifestations determine the prognosis during connectivitis, other complications can occur such as Anti-phospholipid Syndrome (APS) highly impairing the quality of life **[1]**. However, the antibodies inducing this phenomenon can be observed without clinical signs and therefore require rigorous monitoring, as the symptoms are both polymorphic and severe, and require early and effective anticoagulation **[2].**

In sub-saharan Africa, studies conducted on the prevalence of antiphospholipid antibodies (aPL) during systemic diseases are scarce, mainly due to the small sample size of 35, 11, and 40 patients respectively **[3, 4, 5]**. Moreover, in daily practice, the research of aPL is only suggested by a medical history of abortion or thrombotic episodes while the clinical pattern of these antibodies features a broad spectrum of clinical presentations. In order to identify risky situations that require preventive management, we considered appropriate to conduct this study mainly aimed to determine frequency and impact of aPL during connectivitis.

Patients and methods: We conducted a cross-sectional multicenter study with prospective recruitment over a 12-month period from August 2017 to August 2018. Patients were recruited from both Le Dantec Hospital in Internal Medicine and Dermatology departments, in addition to the Dermatology department of the Social Hygiene Institute of Dakar. Detection of aPL was carried out in Le Dantec Hospital Haematology department. We included all patient with confirmed connective tissue disease who gave informed consent to participate in the study. Blood samples were performed to look for aPL: lupus anticoagulant (LA), anti cardiolipin (ACL), anti β2-GP1 (a β2-GP1) antibodies and syphilitic serology (TPHA, VDRL). A blood test control at 12 weeks was carried out for any positive aPL at the previous blood test. The APS diagnosis was made according to Sydney criteria, 2006 **[6]**. The statistical analysis was performed using Epi-info 7.2 software. All p ≤0,05 was significant.

Results

Cohort description

We included 60 patients, 54 of whom were women (90%), representing a sex ratio of 0.11. The mean age was 41.15 years with extremes range from 18 to 71 years old and a median of 42.5. Patients aged from 25 to 45 years were the most represented **(Figure 1).**

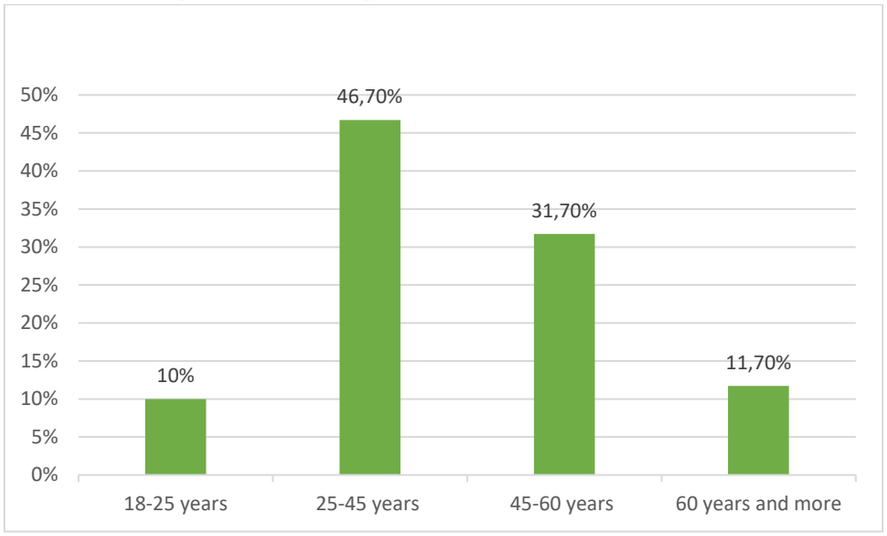

Figure 1: Distribution of patients with connective tissues diseases per age group

Systemic lupus erythematous (SLE), scleroderma and dermatomyositis (DM) were isolated in 21 patients (31.8%), 15 patients (22.7%) and 8 patients (12%) respectively. Paraneoplastic DM was observed in 3 patients. Rheumatoid arthritis was isolated in 1 patient (1.7%).

Connectivitis was labelled to be mixed in 15 patients including 4 cases of SLE associated with dermatomyositis (6.1%), 3 cases of sclerodermatomyositis (4.5%) and 2 cases of overlap between lupus and scleroderma (3%). The other associations are shown in the graph **(figure 2)**.

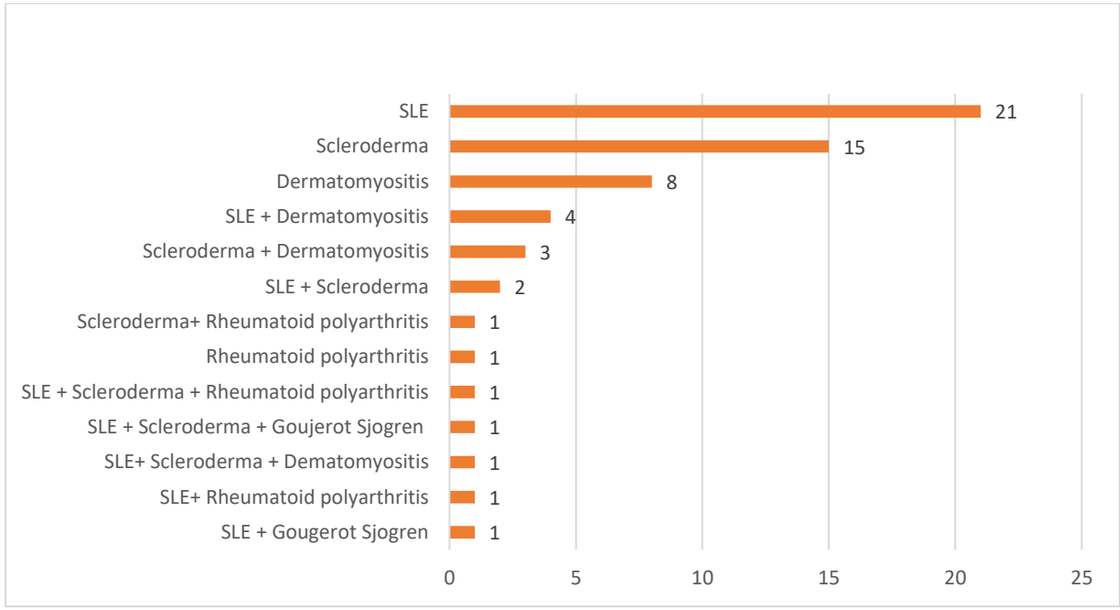

Figure 2: Types of Connective tissue diseases observed in patients

APL frequency

APL antibodies were positive in the first test in 36 patients (60% of the patients). LA was present in 35 patients (58.3%). ACL was noted in 2 patients (3.3%). One of which was associated with LA. No aβ2-GP1 was detected **(Figure 3)**.

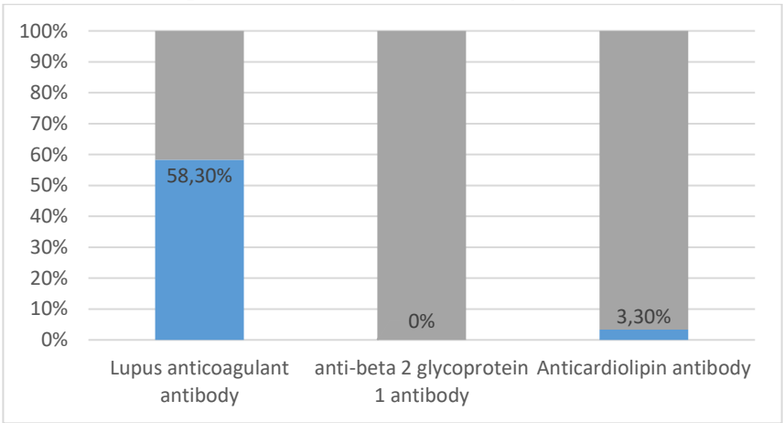

Figure 3: Frequency of antiphospholipid antibodies in the first test

LA was present in 21 cases of lupus, 14 cases of scleroderma (58.3%) and 7 cases of dermatomyositis (43.8%). It was also positive in 2 patients with rheumatoid arthritis and 1 with Sjögren's syndrome.

The positive ACL was IgM type in 2 patients with scleroderma and lupus **(figure 3)**.

APL antibodies persistence was noted in 10 cases (33.4%). It consisted of LA in 9 patients and ACL in 1 patient corresponding to the patient undergoing a double positivity. The underlying connective tissue disease was SLE in 7 cases, scleroderma in 4 cases in addition to 2 cases of dermatomyositis and 1 case of Gougerot Sjogren syndrome **(Figure 4)**.

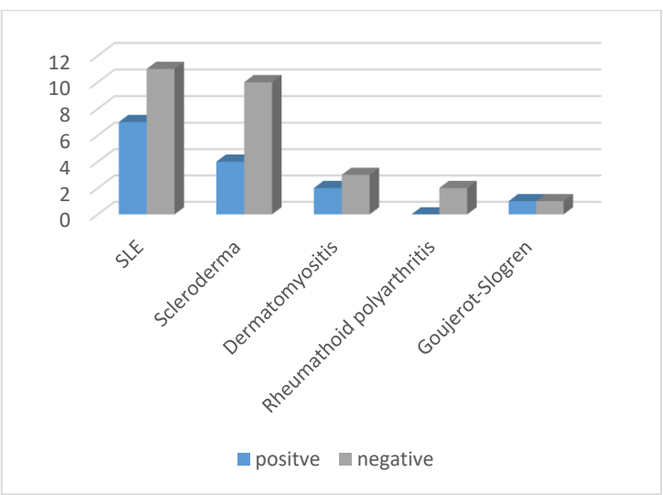

Figure 4: Underlying systemic autoimmune diseases at 12 weeks later aPL control

APL IMPACT:

- **Correlation between antiphospholipid antibodies and the various connective tissue diseases**

Among the 10 positive controls, SLE was noted in 7 cases and scleroderma in 4 cases. There was no significant association between the different connective tissue disease and APL antibodies **(Table I).**

Table 1: Link between APL antibodies and Connective tissue diseases

		positive	Negative	total	p
SLE	yes	7	11	18	0,233
	no	3	9	12	
Scleroderma	yes	4	10	14	0,267
	no	6	10	16	
Dermatomyositis	yes	2	3	5	0,360
	no	8	17	25	
Rheumatoid Polyarthritis	yes	0	2	2	0,437
	no	10	18	28	
Goujerot Sjogren	yes	1	0	1	0,333
	no	9	20	29	

- Gynaecological-obstétrical manifestations and aPL

APL antibodies were positive in 8 patients with gynecological-obstetrical manifestations (abortion, stillbirth, prematurity, pre-eclampsia). The control was positive in only 4 patients.
Obstetrical events correlated to persistence of aPL (p=0.04) rather than with the first test (p=0.22) **(table II)**.

Table II: Link between Obstetrical Accidents and APL antibody

	APL antibody		Control	
Obstetrical Accidents	Positive	Negative	Positive	Negative
Yes	8	9	4	2
No	24	13	4	17
Total	32	22	8	19
P	0,22		0,04	

- Association between Pulmonary arterial hypertension (PAH), Raynaud's phenomenon and APL

We noticed 13 patients who initially tested positive to APL also presented Raynaud's phenomenon. Among them, 4 were controlled positive. There was no statistical link between Raynaud's phenomenon and aPL (p=0.306).
All patients with PAH (n=10) had Raynaud's phenomenon. Seven of them were positive, 3 of which were also positive at the control.
Six patients who had Raynaud's phenomenon without PAH were initially positive, with only one being persistent at control. APL antibodies were not correlated.

- Headaches and aPL positivity

Headaches occurred without high blood pressure in 11 aPL positive patients on the first test. The control was positive in only 4 of these patients. There was no statistical correlation (p=0.298).

- Psychiatric disorders and aPL positivity

Three patients with psychiatric disorders were all positive at the first testing, 2 of which were persistent. There was no significant association between psychiatric disorders and aPL positivity (p=0.2)

- Cutaneous ulcerations and aPL positivity

An initial aPL positivity was found in 15 patients with skin ulcerations. The control was positive in two patients. Skin ulcerations are not correlated with aPL (p=0.343).

- **Direct coombs test and aPL**

APL antibodies were detected in 80% of patients with a positive direct coombs test (n=9). Their detection was only transient. The control was negative in all of these cases. However, the persistence of aPL was noted in two patients with

a negative coombs test. There was no significant association between a Coombs test and aPL (p=0.143).

- Pulmonary fibrosis and aPL positivity

Six patients developed pulmonary fibrosis. They all had scleroderma condition except one which had dermatomyositis with negative APL antibodies.

Among the 5 patients who presented pulmonary fibrosis on an underlying scleroderma condition, the APL antibodies were positive in 2 cases, with only one persisting case after control.

- Anti-phospholipid Syndrome

We observed 5 cases of APS standing for 8.4% of our cohort. They all involved women with an average age of 45.5 years.

Patient 1: A 49-year-old female patient with medical history of two successive miscarriage and a stillbirth, followed by SLE with cutaneous manifestations of acute and discoid lesions with a notion of headaches without high blood pressure. The LA was positive.

Patient 2: A 52-year-old female patient with story of two stillbirths. She was treated for SLE with skin manifestations of acute, subacute and discoid lupus. There were no headache associated. The LA was positive.

Patient 3: A 35-year-old female patient with a history of fetal death before 12 SA. She had SLE associating psychiatric disorders with visual hallucination. LA were the pathogenic antibodies found.

Patient 4: A 66-year-old female patient was followed for scleroderma with dilated cardiomyopathy and apical intraventricular left thrombus. A PAH course was reported. The antibodies found also included lupus anticoagulant.

Patient 5: A 46-year-old female patient with a history of ischemic stroke 5 years ago without any known cardiovascular risk factor and a history of pre-eclampsia.

She was treated for SLE associated with scleroderma. She developed a PAH and pulmonary fibrosis. The clinical examination revealed digital necrosis. IgM-like ACL antibody was positive.

Discussion

The main limitations of this work were the small sample size and the absence of a case-control population. Notwithstanding, we recruited 60 patients with connective tissue diseases. They mostly involved young women (90%) experiencing mainly lupus disease (53.3%), scleroderma (40%) and dermatomyositis (26.7%).

Despite the size, our sample is more representative than most of the sub-saharan africans series previously reported, particularly in Senegal where the different study populations were 35, 11 and 40 cases of connective tissue diseases **[3, 4, 5].** In addition to this population representativeness, our sample made it possible to determine the broad spectrum profile of APL antibodies during connectivitis tissue diseases because it is made up of different types of systemic diseases, unlike previous studies that have focused solely on one type of connective tissue diseases. In Sub-Saharan Africa we do not have a reference frame of studies considering associations.

Our study reports a high frequency of APL antibodies during connective tissue diseases (60%) but they are transient (present at control in one-third, 33.3%) and are rarely morbid because they induce APS in only 13.4%.

Although a control group has not been studied, the presence of aPL during systemic disease is significant. They are less common in other circumstances. A prevalence of 1.2% **[7]** is reported by Juby et al among a young population of 250 apparently healthy individuals of comparable age to our population.

Among 1200 pregnant women without autoimmune diseases, the presence of APL antibodies were also noted in 1.2% **[8].** Other authors have also estimated the frequency of aPL in pregnancy to be less than 4% **[9].** Comparison with elderly subjects also supports our results because despite a high risk of antibodies in this population, the prevalence observed in our study population (mean age 41.1 years) is much higher. In a study conducted considering APL antibodies in elderly subjects with no detected pathology, Charkravarty didn't report any antibody detection in both a cohort of 100 subjects with a mean age of 75.6 years and a cohort of 63 subjects over 65 years of age **[9, 10].** In Senegal, some authors have studied the presence of APL antibodies in certain situations, particularly during miscarriage, during wich APL antibodies were detected in 21% of women **with this obstetric incident [4]** and 23% of young subjects without sickle cell disease condition **[11]**.

The presence of aPL is more common in women. Most patients were female (sex ratio 0.11). This is due to the study population, which consisted only of connective tissue diseases whose predominance in female subjects is usual **[12, 13].**

In etiological approach, SLE is the main cause observed in 68.75% of patients with no statistical link (p=0.233). This does not offer any particularity to our population but would be intrinsically related to the lupus disease which is unanimously the main etiology of secondary APS and constituted in our sample the first connective tissue disease. This finding in a black population is also observed in Caucasians where lupus was predominantly represented, corresponding to 36% of a population of 1000 cases of APS recruited in 13 countries **[14].** In Senegal, different authors confirm our results **reporting an involvement of SLE in 82% and 57% of APS cases [3, 5]**.

Indeed, LA is the main circulating aPL during systemic diseases (58.3%), essentially observed during SLE which equals to 65.6%. ACL was reported in **3.3% of our samples** and no aβ2-GP1 was detected. This finding is compliant with the results of **Sobanski et al reporting the presence of LA in 25% followed by ACL in 18.8% among 16 cases who presented Apl in a sample of 249 patients [15].** Korean authors have also reported the predominance of LA [16]. The scarcity of ACL antibodies outlined in this study confirms the results of American studies reporting a low prevalence of ACL antibodies in dark patients with SLE (3 out of 80) [**17**]. **However**, ACL appears to be related to scleroderma according to Touré et al in Senegal and G. Sanna in Italy [**5, 18**].

This is confirmed by some authors comparing isolated scleroderma with those associated with SLE who noted in the first group higher ACL levels than LA [**20**].

If APL antibodies are common during connective tissue diseases, they are rarely pathogenic. APS was observed only in 13.4% of patients with an aPL. This syndrome is mainly induced by the presence of LA with exclusive female involvement and the lupus being the main underlying connective tissue condition. Our study confirms the findings previously made in Senegal where Diallo et al reported lupus in 80% of cases of APS **[23]** as well as **in Morocco and Europe where it is observed in 80% and 36.2% respectively during secondary APS [14, 20**].

Looking at the symptomatology, obstetrical manifestations are the main morbidities attested by a significant correlation (p=0.04) with positive controls but without any correlation to the first tests (p=0.22). Nevertheless, in practice, the discovery of an aPL during an obstetrical accident may mistakenly induce the interruption of etiological research and the introduction of anticoagulation. This is justified for practical and preventive purposes, but should not lead to stop the etiological research. There is no link between obstetrical symptoms and the presence of aPL on the first test.

Obstetrical accidents are often reported in both Caucasian and black populations [**3, 21**]. However, there is a contradiction with some studies that report the predominance of thrombotic events [**14, 22, 23**] found only in 2 of our patients. One of whom had an intracardiac thrombus that is exceptional during APS with a predilection involvement of right chambers [**24**].

Apart from those patients meeting the criteria for APS, we observed 5 cases of persistent APL antibodies that did not meet the diagnosis criteria for APS. In the literature they are labelled as "probable APS", "pre-APS" or "asymptomatic APS" **[25].** The risk factors leading the transformation to true APS have been established. These would be a history of thrombosis, presence of LA and a high ACL IgG titer [**26].** The real question in these circumstances is to define the appropriateness of initiating preventive anticoagulant treatment. These patients are being monitored and do not show any predictive signs of APS despite a 14-month follow-up.

In absence of larger studies, aPL finding would not be a risk factors for PAH during scleroderma. This lung damage is frequently present during scleroderma and has prompted the search for a link with aPL, which has not been demonstrated. This corroborates several studies both in the West (p=1) [16] and in sub-Saharan Africa (p=0.51) **[5, 27]**. This association is rather described during the course of SLE despite contradictory findings **[26, 27]**.

Conclusion

APL antibodies are common but often transient during connective tissues diseases whose SLE is the most frequent underlying disease. LA is the main circulating antibody and rarely induces APS. In obstetrical accidents, the presence of aPL in a first test should not interrupt the process of etiological research of other causes because there is no significant link.

Authors don’t declare any conflict of interest.

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