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Original article

Obstetric antiphospholipid syndrome is not associated with an increased risk of subclinical atherosclerosis

Alessandra Bettiol[1,*], Giacomo Emmi[2,*], Martina Finocchi[2], Elena Silvestri[2], Maria Letizia Urban[2], Irene Mattioli[2], Antonella Scalera[3], Roberta Lupoli[4], Alfredo Vannacci[1], Matteo Nicola Dario Di Minno [4,*] and Domenico Prisco[1,*]

Abstract

Objectives. The persistent positivity of aPLs, either isolated or associated with thrombotic and/or obstetric events (APS), has been associated with the increase of intima-media thickness (IMT) and carotid plaques. Despite the fact that aPLs can promote both thrombotic and obstetric complications, some pathogenic differences have been documented between the two entities. This study aimed to evaluate whether the atherosclerotic risk differs between subjects with obstetric and thrombotic APS.

Methods. A total of 167 APS women (36 obstetric and 131 thrombotic) were compared with 250 aPLs negative controls. IMT of the common carotid artery (CCA) and of the bulb and the prevalence of carotid plaques were assessed.

Results. CCA- and bulb-IMT were significantly higher in women with thrombotic APS, while being similar between the obstetric APS and the controls [CCA-IMT: mean (S.D.) 0.97 (0.49), 0.78 (0.22) and 0.81 (0.12) mm for the thrombotic, obstetric and control groups, respectively, $P < 0.001$ between thrombotic and controls, $P = 0.002$ between thrombotic and obstetric; bulb-IMT: mean (S.D.) 1.38 (0.79), 0.96 (0.27) and 0.96 (0.51) mm for the thrombotic, obstetric and control groups, $P < 0.001$]. Women with thrombotic APS had significantly increased risk of presenting carotid plaques. This risk was significantly lower in obstetric APS.

Conclusion. Unlike thrombotic APS, obstetric APS is not associated with an increase of markers of subclinical atherosclerosis. If confirmed on wider populations, these results could suggest different pathogenetic role of aPLs in promoting atherosclerosis in vascular and obstetric APS, and raise questions on the risk–benefit profile of thromboprophylaxis in obstetric APS outside pregnancy periods.

Key words: antiphospholipid syndrome, lupus anticoagulant, pregnancy, thrombosis, atherosclerosis

Rheumatology key messages

- We compared for the first time subclinical atherosclerosis in obstetric *vs* thrombotic APS.
- Markers of subclinical atherosclerosis are significantly increased in thrombotic APS, but not in obstetric APS.
- aPLs might play different pro-atherosclerotic roles in vascular and obstetric APS.

Introduction

The APS is defined by the occurrence of venous and/or arterial thromboses (thrombotic APS) and/or of adverse recurrent pregnancy outcomes (obstetric APS), in the presence of persistent positivity of aPLs [1].

Venous thromboses are one of the hallmarks of this syndrome [2, 3] and conversely, APS is listed among the most common acquired thrombophilic conditions [4]. However, arterial involvement and accelerated

[1]Department of Neurosciences, Psychology, Drug Research and Child Health (NEUROFARBA), [2]Department of Experimental and Clinical Medicine, University of Firenze, Firenze, [3]Department of Clinical Medicine and Surgery, Federico II University, Naples, Italy, and [4]Department of Translational Medical Sciences, Federico II University, Naples, Italy

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Correspondence to: Giacomo Emmi, Dipartimento di Medicina Sperimentale e Clinica, Università degli Studi di Firenze, Largo Giovanni Brambilla 3, 50134 Firenze, Italy. E-mail: giacomo.emmi@unifi.it

*Alessandra Bettiol, Giacomo Emmi, Matteo Nicola Dario Di Minno and Domenico Prisco contributed equally to this manuscript.

CLINICAL SCIENCE

atherosclerosis also represent a consistent burden of the disease [5–7]. Namely, according to a recent meta-analysis of 20 study, common carotid artery intima-media thickness (CCA-IMT), internal carotid artery IMT, carotid bifurcation IMT, prevalence of carotid plaques, and pathologic ankle-brachial index are significantly increased in APS patients as compared with matched controls [8]. Of note, in a recent study we demonstrated that not only APS patients, but also asymptomatic aPLs carriers present an increased subclinical atherosclerosis, with significantly higher levels of IMT and a higher prevalence of carotid plaques as compared with healthy aPL-negative subjects, thus providing further evidence on the role of aPLs *per se* in mediating atherosclerosis [9, 10].

According to the recent EULAR recommendations, primary prophylaxis with low-dose aspirin (LDA) is suggested in carriers of aPLs with a high risk profile [11, 12]. Indeed, according to a meta-analysis of seven observational studies on 460 asymptomatic aPL carriers, LDA was associated with a reduction by half of the risk of thrombosis as compared with non-treatment [13]. On the other hand, the prophylactic treatment with LDA in non-pregnant women with a history of obstetric APS is not mandatory, and should be based on the presence of specific thrombotic/bleeding risk factors [11]. Indeed, according to a meta-analysis of observational studies evaluating the role of LDA as primary prevention of thrombosis in women with a history of obstetric APS without SLE, aspirin was associated with a marked reduction in the risk of a first thrombotic event [13]. However, the results highlighting a beneficial role of aspirin were mainly driven by a single study on 65 patients [14], whereas the other four studies showed no significant role of LDA as primary prophylaxis for thrombotic events in obstetric APS [15–18].

However, questions exist on whether treatment should be tailored according to the specific APS subsets [19, 20]. Thus, considering that growing evidence highlights differences in the pathogenic mechanisms sustaining vascular and obstetric APS [21], concerns regarding differences in the cardiovascular risk in these two conditions exist, and there is a consequent need for a different anti-thrombotic prophylactic management.

Thus, the present study aimed to evaluate subclinical atherosclerosis in thrombotic and in obstetric APS women as compared with a heathy control cohort.

Methods

All women with a persistent positivity for aPLs and diagnosed with APS, attending the Regional Reference Center for Coagulation Disorders of the Federico II University of Naples and the Lupus Clinic of the Department of Experimental and Clinical Medicine of the University of Firenze during the period January 2013 to January 2017, were evaluated for enrolment in this study. The study was conducted in accordance to the declaration of Helsinki, and was approved by our institutional Ethic Committee [Ethics Committee of the University Hospital of Careggi, Florence, Italy (Prot. n. 12097_os; 24 September 2018)]. aPLs was defined as LA, IgG and IgM aCL, or IgG and IgM anti-beta-2-glycoprotein I (aβ2GPI) positivity in two or more determinations, at least 12 weeks apart. In detail, LA was assessed using the DRVVT and the aPTT-based test, according to the International Society on Thrombosis and Haemostasis (ISTH) guidelines [22], whereas IgG and IgM aCL, IgG and IgM aβ2GPI were tested using commercially available kits according to standardized procedures [23]. IgG and/or IgM aCL as well as IgG and/or IgM aβ2GPI were considered as single antibodies. Thus, single aPLs positivity refers to LA or aCL or aβ2GPI, double positivity refers to the positivity of two of the three antibodies types, and triple positivity refers to aCL plus aβ2GPI plus LA positivity. Diagnosis of APS was based on aPLs positivity and previous history of an objectively documented venous or arterial thrombosis (thrombosis group), or of recurrent pregnancy complications (obstetric group), according to the Sydney criteria [24].

Women belonging to either the thrombosis or obstetric groups were matched for age and major thrombotic risk factors (obesity, hypertension, hypercholesterolaemia, hypertriglyceridaemia, impaired fasting glucose) to a cohort of women negative for aPLs, recruited in parallel from the hospital staff during the same period (control group).

For all groups, exclusion criteria were: lack of informed consent, age <18 years, positivity for aPLs documented on only one occasion, malignancy, haematologic diseases, unstable medical conditions or ongoing pregnancy.

After acquisition of informed consent, data about age, gender, height, weight, previous and/or concurrent treatments, and vascular risk factors were collected. In detail, according to the National Cholesterol Education Program criteria, obesity was defined as a waist circumference $\geq$88 cm; hypertriglyceridaemia as triglycerides levels $\geq$150 mg/dl; hypercholesterolaemia as a total cholesterol $\geq$200 mg/dl, with or without high-density lipoprotein cholesterol $<$50 mg/dl; and hypertension as a systolic blood pressure $\geq$130 mmHg and/or diastolic blood pressure $\geq$85 mmHg.

Both for women with APS and for controls, an US assessment of carotid IMT was performed, as already described [25]. IMT was measured in each of the three projections in CCA and bulb. The presence of carotid plaques was defined as an IMT $\geq$1.3 mm. All the US examinations were performed by operators blinded as to the presence/absence of aPLs in each subject. The inter-operator reproducibility of the vascular measurements had been previously evaluated in 25 subjects and the overall Pearson's r value for the IMT measurements was 0.93 ($P < 0.001$).

Statistical analysis

Statistical analysis was performed with the IBM SPSS 22 system (SPSS Inc., Chicago, IL, USA). Continuous data were expressed as mean (S.D.). The *t*-test was

performed to compare continuous variables. In case of values with a skewed distribution, Mann–Whitney *U* test was used to compare means. Categorical variables were expressed as percentages and analysed with the χ^2 test. When the minimum expected value was <5, the Fisher's exact test was used. Logistic regression models were fitted to estimate the risk (expressed as odds ratio and related 95% CI) of carotid plaques presence for women belonging to the thrombosis or obstetric groups as compared with controls. To evaluate potential sources of heterogeneity, sensitivity analyses were performed: (i) after stratifying APS patients according to the number of positive antibodies; (ii) after stratifying APS patients according to combination of positive antibodies; (iii) after excluding subjects with other autoimmune diseases; and (iv) limiting the analysis to non-smokers. All the results are presented as two-tailed values with statistical significance if *P*-values <0.05.

Results

Study population

A total cohort of 167 women diagnosed with APS were included. Of them, 131 had history of arterial or venous thrombosis (thrombosis group) while 36 had history of pregnancy complications (obstetric group). Specifically, 33 women had history of three or more pregnancy losses within the 10th week of gestation, two patients had history of pre-eclampsia with HELLP syndrome (haemolysis, elevated liver enzymes and a low platelet count), and another patient had history of two episodes of intrauterine fetal death complicated by pre-eclampsia. No woman had history of both thrombosis and obstetric complications, therefore groups were totally segregated. Two-hundred and fifty women with negative aPLs were matched to APS cases (control group).

The main demographic and clinical characteristics of the study population are reported in Table 1. The obstetric, thrombosis and control groups were comparable in terms of age and traditional cardiovascular risk factors (hypertension, hypercholesterolaemia, hypertriglyceridaemia, obesity, diabetes). On the other hand, the percentage of current smokers was significantly lower in the obstetric group compared with the other groups (8.30, 32.80 and 38.90% in the obstetric, control and thrombosis group, respectively). Focusing on the antibody profile, no difference in the type, number of positive antibodies and antibody titres was found between the obstetric and thrombosis groups. These two groups were comparable also in terms of disease duration and presence of other autoimmune diseases (either SLE or non-SLE).

As expected, most women in the control group were not treated with any antithrombotic therapy at time of IMT evaluation. On the other hand, a consistent proportion of patients in both the obstetric and the thrombosis groups was on active antithrombotic therapy (86.1 and 93.1%, respectively).

Focusing on the use of drugs that might affect the cardiovascular risk, no significant difference in the proportion of patients treated with CS or with statins was found among the groups.

Assessment of subclinical atherosclerosis

Women in the thrombosis group presented significantly higher levels of CCA-IMT compared with the other two groups [0.97 (0.49) mm for thrombosis groups; 0.78 (0.22) for obstetric group; 0.81 (0.12) for control group; $P < 0.001$ between thrombosis and controls, $P = 0.002$ between thrombosis and obstetric, $P = 1.000$ between obstetric and controls) (Table 2). Similarly, the US assessment of carotid arteries showed a significantly higher bulb-IMT in women with history of thrombosis compared with both obstetric and control groups [1.38 (0.79) mm for thrombosis groups; 0.96 (0.27) for obstetric group; 0.96 (0.51) for control group; $P < 0.001$ between thrombosis and controls and between thrombosis and obstetric, $P = 1.000$ between obstetric and controls].

Moreover, compared with controls, a significantly higher prevalence of carotid plaques was found in the thrombosis group (48.90 *vs* 12.80% for thrombosis *vs* control groups; $P = 0.002$). In particular, women in the thrombosis group had an odds ratio of presenting carotid plaques of 6.51 (95% CI: 3.93, 10.78) ($P < 0.001$) compared with control women. On the other hand, women with obstetric APS had a 74% lower risk of presenting plaques compared with women in the thrombosis group [odds ratio 0.26 (0.10–0.62), $P = 0.002$].

To evaluate the impact of the number of positive antibodies on subclinical atherosclerosis, we performed a sensitivity analysis, stratifying women according to the number of positive antibodies (Fig. 1).

In particular, 11 and 29 women in the obstetric and thrombosis group had one positive antibodies, 13 and 53 had two positive antibodies, and 12 and 49 had three positive antibodies.

Focusing on CCA-IMT, IMT in subjects with one positive antibody was similar in the obstetric and thrombosis group, while this latter was significantly higher as compared with the controls. On the other hand, considering women with either two or three positive antibodies, CCA-IMT was significantly higher in the thrombosis group compared with the obstetric and control groups. Independent of the number of positive antibodies, women in the obstetric groups were comparable to controls in terms of CCA-IMT. In addition, levels of CCA-IMT within disease groups were comparable among different strata of positive antibodies.

Measuring bulb-IMT in subjects with one positive antibody, we found that women in the thrombosis group had significantly higher levels of thickness compared with both obstetric and control groups. Similar results were confirmed also focusing on subjects with two and with three positive antibodies. On the other hand, independent of the number of positive antibodies, women in the obstetric groups were comparable to controls in

Table 1 Characteristics of women with history of thrombosis or miscarriage *vs* controls

Characteristics	Control, *N* (%)	Obstetric group, *N* (%)	Thrombosis group, *N* (%)	*P*-value[a]
No. women	250	36	131	
Age [mean (s.d.)]	49.76 (12.69)	51.14 (12.64)	49.44 (13.07)	1.000
Current smokers	82 (32.8)	3 (8.3)	51 (38.9)	0.002[ab]
Antibody positivity				
LA	n.a.	10 (27.8)	40 (30.5)	0.749[c]
aCL IgM	n.a.	16 (44.4)	50 (38.2)	0.495[c]
aCL IgG	n.a.	23 (63.9)	99 (75.6)	0.162[c]
aβ2GPI IgM	n.a.	9 (25.0)	41 (31.3)	0.465[c]
aβ2GPI IgG	n.a.	14 (38.9)	61 (46.6)	0.412[c]
No. antibody types				
1	n.a.	11 (30.6)	29 (22.1)	0.577[c]
2	n.a.	13 (36.1)	53 (40.5)	
3	n.a.	12 (33.3)	49 (37.4)	
Antibody titre (median, IQR)				
aCL IgM	n.a.	80 (58.5–119.0)	89 (70.0–189.0)	0.887[c]
aCL IgG	n.a.	82 (70.0–144.0)	80 (77.0–122.0)	0.341[c]
aβ2GPI IgM	n.a.	99 (63.0–121.4)	80 (65.0–160.0)	0.379[c]
aβ2GPI IgG	n.a.	85.5 (60.7–157.5)	80 (71.0–160.0)	0.341[c]
Months from diagnosis (median, IQR)	n.a.	6 (3.8–15.0)	7 (2.5–60)	0.953[c]
Autoimmune diseases	n.a.	17 (47.2)	68 (51.9)	0.618[c]
SLE	n.a.	13 (36.1)	48 (36.6)	0.953[c]
Others	n.a.	6 (16.7)	26 (19.8)	0.668[c]
Traditional cardiovascular risk factors				
Hypertension	70 (28.0)	7 (19.4)	40 (30.5)	0.423
Hypercholesterolaemia	96 (38.4)	16 (44.4)	52 (39.7)	0.782
Hypertriglyceridaemia	10 (4.0)	1 (2.8)	3 (2.3)	0.665
Obesity	79 (31.6)	7 (19.4)	41 (31.3)	0.323
Diabetes	18 (7.2)	1 (2.8)	17 (13.0)	0.069
Treatments				
Antithrombotic treatment[d]	47 (18.8)	31 (86,1)	122 (93.1)	<0.001[ab]
CS	0 (0)	19 (52.8)	51 (38.9)	0.182
Statin	106 (42.4)	16 (44.4)	76 (58.0)	0.186

[a]Calculated using the Pearson χ^2 test for proportions and the Mann–Whitney *U* test for continuous variables. [b]Statistically significant for $P < 0.05$. [c]Comparison only between miscarriage and thrombosis groups. [d]Antiplatelet and/or anticoagulant agents.
aβ2GPI: anti-beta-2-glycoprotein I antibodies; IQR: interquartile range; n.a.: not applicable.

terms of bulb-IMT. Of note, levels of bulb-IMT within disease groups were comparable among different strata of positive antibodies.

When stratifying APS patients according the combination of positive antibodies, levels of bulb-IMT and CCA-IMT were higher in the thrombosis group as compared with the obstetric group in all subgroups, although without statistical significance, probably as a result of the small sample size of the subgroups (supplementary Table S1, available at *Rheumatology* online).

In an attempt to limit the effects of additional immune-mediated disorders with known pro-thrombotic potential on IMT, we performed a sensitivity analysis including only women with no additional immune disorders. Results confirmed higher CCA-IMT and bulb-IMT [1.00 (0.54) and 1.43 (0.88), respectively] for women with history of thrombosis compared with both obstetric [0.74 (0.14) and 0.89 (0.25) for CCA- and bulb-IMT, respectively] and control groups [0.81 (0.12) and 0.96 (0.19), respectively]; however, these differences did not reach statistical significance.

To further control for the potential confounding effected related to the smoking habit, we performed an additional sensitivity analysis, excluding current smokers. Results confirmed higher CCA-IMT and bulb-IMT for patients with thrombotic APS, as compared with both the obstetric and control groups (data not shown).

Discussion

This is the first study specifically evaluating and comparing subclinical atherosclerosis in obstetric *vs* thrombotic APS. Our findings highlight that IMT, either CCA or at bulb, is significantly increased only in APS patients with history of thrombosis, while being comparable to that of a healthy control group in patients with obstetric APS.

TABLE 2 Intima-media thickness and carotid plaques in women with obstetric APS and thrombotic APS, and in controls

	Control ($n = 250$)	Obstetric group ($n = 36$)	Thrombosis group ($n = 131$)	Difference between obstetric and control	*P*-value (obstetric *vs* control)	Difference between thrombosis and control	*P*-value (thrombosis *vs* control)	Difference between obstetric and thrombosis	*P*-value (obstetric *vs* thrombosis)
CCA-IMT[a]	0.81 (0.12)	0.78 (0.22)	0.97 (0.49)	−0.03 (0.5)	1.000	0.16 (0.03)	<0.001[c]	−0.19 (0.06)	0.002[c]
Bulb-IMT[a]	0.96 (0.51)	0.96 (0.27)	1.38 (0.79)	0.00 (0.08)	1.000	0.43 (0.5)	<0.001[c]	−0.42 (0.09)	<0.001[c]
Presence of plaques[b]	32 (12.80)	7 (19.40)	64 (48.90)	1.64 (0.67–4.06)	0.281	6.51 (3.93–10.78)	<0.001[c]	0.26 (0.10–0.62)	0.002[c]

[a]Reported as mean thickness in mm S.D. [b]Reported as numbers (percentages) or as OR (95% CI). [c]Statistically significant for $P < 0.05$.
CCA: common carotid artery; IMT: intima-media thickness; OR: odds ratio.

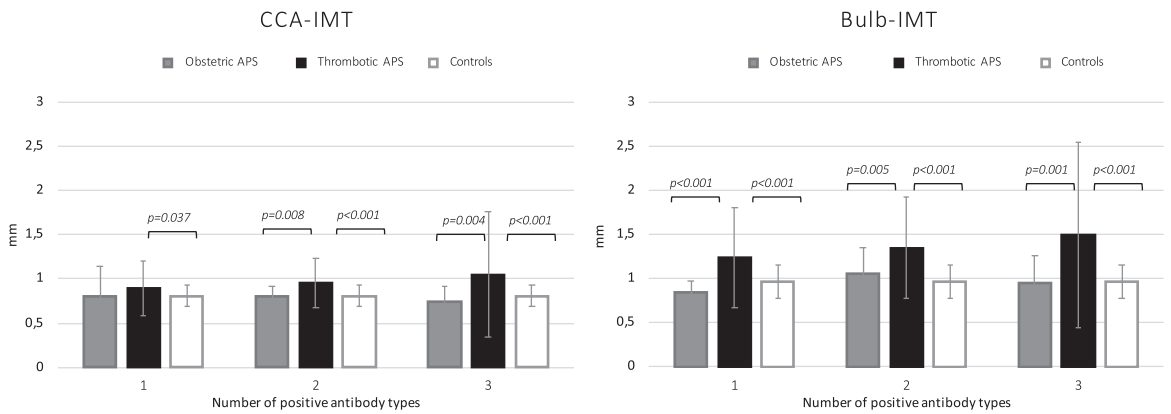
The link between APS and premature atherosclerosis has already been described in the literature, indicating a higher cardiovascular risk in these patients. According to a study by Kravvariti and colleagues [26], patients with APS, either primary or SLE-related, carry a 2.5-fold risk of atherosclerotic carotid and femoral plaques compared with healthy controls, i.e. similar to that of diabetic patients. Risk of atherosclerosis seems to be particularly increased in primary APS patients with plasma fibrin clot permeability and susceptibility to clot lysis [27]. In another study by Padjas and colleagues on 26 young primary APS patients without clinical symptoms of heart disease, a high incidence of subclinical cardiovascular damage was described, with SPECT indicating myocardial perfusion defects and coronary calcifications in around one sixth of cases, and with right ventricle systolic pressure being elevated in around 25% of patients [28]. Notably, the presence of these cardiovascular risk markers was significantly higher in patients with high titre of aCL and aβ2GPI antibodies [28].

In a recent study, we demonstrated the role of aPLs in mediating the atherosclerotic process and the cardiovascular risk by comparing IMT in APS patients, in asymptomatic carriers with persistent aPLs positivity (APP patients), and in healthy controls [9]. The 104 evaluated APP patients had a significantly higher CCA-IMT and bulb-IMT as compared with the matched healthy controls, comparable to those observed for symptomatic APS patients. Similarly, the presence of carotid plaques was significantly more frequent among APS and APP patients as compared with healthy controls. Notably, the number of positive antibodies and the high antibody titre were significantly associated with increased levels of CCA-IMT, bulb-IMT and the prevalence of carotid plaques, thus reinforcing the concept that the antibodies, rather than the disease manifestations, mediate the cardiovascular damage [9]. In line with these considerations, the EULAR recommendations indicate that LDA should be prescribed as primary thromboprophylaxis in APP patients [11].

The procoagulant state mediated by aPLs seems to be directly involved both in the pathogenesis of venous and/or arterial thrombotic events and obstetric complications, i.e. the two main manifestations of APS [1, 6]. However, although aβ2GPI antibodies are present in both the APS phenotypes, differences in their tissue distribution have been described. Specifically, levels of aβ2GPI antibodies in endothelial districts are significantly higher in patients with thrombotic APS as compared with patients with obstetric manifestations, the latter group presenting higher aβ2GPI levels in the decidual and placental tissues [21]. Indeed, in our previous studies we found that patients with aβ2GPI positivity, either alone or with concomitant aCL and/or LA positivity, had significantly higher CCA-IMT, bulb-IMT and prevalence of carotid plaques as compared with controls [5, 9].

Moreover, obstetric APS seems to be not exclusively related to thrombotic mechanisms, as decidual and placental inflammation has been detected in obstetric APS

Fig. 1 IMT in obstetric and thrombotic APS and in controls, stratified on the number of positive antibodies



CCA: common carotid artery; IMT: intima-media thickness.

women in addition to infarction, decidual vasculopathy, spiral artery and placental thrombi [29].

These molecular and clinical observations have raised the question of whether obstetric and thrombotic APS are two distinct diseases [21]. However, epidemiological data do not clearly support this hypothesis. In a retrospective study evaluating the long-term outcomes of APS patients [30], 6 out of 31 observed patients (19%) with history of pregnancy complications developed thrombosis, while 6 out of the 49 female patients (12%) with a history of thrombosis developed an adverse pregnancy outcome. In another retrospective study on 126 obstetric APS women, >60% of women had thrombosis after initial pregnancy morbidity, thus indicating a consistent epidemiological and clinical overlap between the two disease complications [31].

In our study, out of a total of 167 APS women, none had history of both thrombotic and obstetric complications. This result could have been influenced by the fact that a consistent proportion of patients with obstetric APS was treated with antithrombotic treatments as primary thromboprophylaxis, as indicated in the EULAR recommendations for patients with high-risk APL profile [11]; thus the role of this therapy on the prevention of thrombotic complications cannot be excluded. Nevertheless, the fact that within our cohort, no woman with thrombotic APS reported obstetric complications during her whole reproductive life suggests the existence of two different pathogenic scenarios.

Based on our results, only thrombotic APS seems to be associated with a subclinical atherosclerotic state, while women with obstetric APS present IMT levels comparable to those of a matched population of healthy controls. These findings were confirmed also when stratifying according to the number of positive aPLs types, and when excluding patients with additional concomitant autoimmune disorders or patients who were currently smokers, thus further reinforcing the concept that thrombotic and obstetric APS present different pathogenetic mechanisms promoting atherosclerosis.

Of note, the proportion of women with obstetric APS that were currently smokers at time of IMT evaluation was significantly lower as compared with those observed in the thrombosis and in the control groups. This might be related to the fact that a consistent proportion of obstetric APS women had quit smoking during the previous pregnancies, without subsequently restarting this habit. In our sensitivity analysis performed only on currently non-smoking women, we confirmed that, differently from thrombotic APS, obstetric APS was not associated with an increased risk of subclinical atherosclerosis.

Some limitations of our study need to be discussed. First, clinical data were retrospectively collected from medical charts at time of IMT evaluation; this might have impaired the accuracy of the collected data and might have accounted for missing information. Second, as already discussed, the presence of active antithrombotic treatments might represent a significant source of bias in the present study. Third, the heterogeneity in the number of patients belonging to the thrombotic and obstetric APS groups might have influenced the statistical power.

However, our results provide new evidence favouring the concept that obstetric and thrombotic APS are two distinct entities, associated with different profiles of atherosclerotic risk. Based on our findings, only patients with thrombotic APS carry an increased risk of subclinical atherosclerosis, while obstetric APS does not seem to be associated with a similar risk of atherosclerosis.

Considering that a consistent literature evidence reports an increased risk of thrombotic events in patients with primary obstetric APS [32, 33], our results might suggest the presence of two different pathogenetic mechanisms mediating thrombotic complications in thrombotic and obstetric APS, the latter being not dependent only on an increase atherosclerotic state.

Indeed, these results not only suggest a different pathogenetic role of aPLs in promoting atherosclerosis in vascular and obstetric APS, but also raise questions

about the optimal prophylactic management for cardiovascular risks in these APS patients. While the benefits of an active anticoagulant and/or antiplatelet treatment in thrombotic APS are well established, further studies are needed to evaluate the risk–benefit profile of these therapies as the only prophylactic treatment in obstetric APS. In this context, the role of additional pharmacological alternatives (i.e. HCQ) for the primary thrombotic prophylaxis of obstetric APS outside pregnancy periods should be evaluated.

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Supplementary data

Supplementary data are available at *Rheumatology* online.

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