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Factors associated with first thrombosis in patients presenting with obstetric antiphospholipid syndrome (APS) in the APS Alliance for Clinical Trials and International Networking Clinical Database and Repository: a retrospective study

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Objective To evaluate the subsequent rate of thrombosis among women with obstetric antiphospholipid syndrome (Ob-APS) in a multicentre database of antiphospholipid antibody (aPL)-positive patients, and the clinical utility of the adjusted Global Antiphospholipid Syndrome Score (aGAPSS), a validated tool to assess the likelihood of developing new thrombosis, in this group of patients.

Design Retrospective study.

Setting The Antiphospholipid Syndrome Alliance for Clinical Trials and International Networking Clinical Database and Repository.

Population Women with Ob-APS.

Methods Comparison of clinical and laboratory characteristics and measurement of aGAPSS in women with Ob-APS, with or without thrombosis, after initial pregnancy morbidity (PM).

Main outcome measures Risk factors for thrombosis and aGAPSS.

Results Of 550 patients, 126 had Ob-APS; 74/126 (59%) presented with thrombosis, and 47 (63%) of these women developed thrombosis after initial PM, in a mean time of 7.6 ± 8.2 years (4.9/100 patient years). Younger age at diagnosis of Ob-APS, additional cardiovascular risk factors, superficial vein thrombosis, heart valve disease, and multiple aPL positivity increased the risk of first thrombosis after PM. Women with thrombosis after PM had a higher aGAPSS compared with women with Ob-APS alone [median 11.5 (4–16) versus 9 (4–13); $P = 0.0089$].

Conclusion Based on a retrospective analysis of our multicentre aPL database, 63% of women with Ob-APS developed thrombosis after initial obstetric morbidity; additional thrombosis risk factors, selected clinical manifestations, and high-risk aPL profile increased the risk. Women with subsequent thrombosis after Ob-APS had a higher aGAPSS at entry to the registry. We believe that aGAPSS is a valid tool to improve risk stratification in aPL-positive women.

Keywords Antiphospholipid antibodies, antiphospholipid syndrome, fetal death, miscarriage, pre-eclampsia, thrombosis.

Tweetable abstract More than 60% of women with obstetric antiphospholipid syndrome had thrombosis after initial pregnancy morbidity.

Linked article This article is commented on by M Spaanderman and C Ghossein-Doha, p. 662 in this issue. To view this mini commentary visit https://doi.org/10.1111/1471-0528.15595.

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Introduction

Antiphospholipid syndrome (APS) is a multisystem disease that can present with thrombosis and/or obstetric complications in patients with persistently positive antiphospholipid antibodies (aPL).[1] Based on the updated Sapporo APS classification criteria, obstetric APS (Ob-APS) is defined as: one or more unexplained deaths of a morphologically normal fetus at or beyond the 10 weeks of gestation (fetal loss); one or more premature births of a morphologically normal neonate before 34 weeks of gestation as a result of eclampsia or severe pre-eclampsia; or three or more unexplained consecutive spontaneous miscarriages before 10 weeks of gestation.[1]

Although recent studies suggest that women with pure Ob-APS are at increased risk of future thrombosis compared with women without APS,[2–5] identifying the subgroup of these patients who are at higher risk of future thrombosis is an unmet clinical need. Concomitant systemic lupus erythematosus diagnosis, cardiovascular disease risk factors, or high-risk aPL profile may increase the risk of thrombosis after aPL-related pregnancy morbidity.[3,6–8] In this context, the use of a thrombosis scoring system, such as the Global Antiphospholipid Syndrome Score (GAPSS), may help to stratify the risk of future thrombosis in women with Ob-APS by subgroups based on traditional cardiovascular risk factors and aPL profile.

The objectives of this retrospective study were to evaluate the subsequent rate of thrombosis among women with Ob-APS in a multicentre database of aPL-positive patients, and to evaluate the clinical utility of GAPSS as a tool to identify women at higher future thrombosis risk after presenting with Ob-APS. Our hypotheses are that women presenting with an aPL-related pregnancy morbidity are at increased risk of future thrombosis, and that GAPSS is a useful tool to identify subgroups of these high-risk patients.

Methods

APS ACTION Clinical Database and Repository (Registry)

The Antiphospholipid Syndrome Alliance for Clinical Trials and International Networking (APS ACTION) Registry was created to study the natural disease course over at least 10 years in persistently aPL-positive patients, with or without other systemic autoimmune diseases.[9] Each centre had ethics committee approval, and all patients signed informed consent before enrolling on the registry. A web-based data capture system is used to store patient demographics, aPL-related history, and medications. The inclusion criterion was positive aPL based on the updated Sapporo APS classification criteria at least twice, >12 weeks apart, within 1 year prior to enrollment.[1] For the purpose of this retrospective baseline registry analysis we included women with Ob-APS, with or without thrombosis, after the initial diagnosis of pregnancy morbidity. The retrospective study follow-up period is from the first Ob-APS manifestation to thrombosis or registry entry.

The data retrieved were age and type of first pregnancy morbidity (embryonic loss before 10 weeks of gestation, fetal loss after 10 weeks of gestation, premature birth, and pre-eclampsia), age and type of thrombosis (arterial or venous), other autoimmune diseases, cardiovascular risk factors [medication for hypertension, medication for diabetes, medication for hyperlipidaemia, obesity (body mass index, BMI > 30 kg/m^2), and smoking] at the time of entry to the registry, non-criteria manifestations of APS (thrombocytopenia, haemolytic anaemia, livedo reticularis, aPL, nephropathy, and valve disease), aPL data, and medications. There was no funding, and patients were not involved in this study.

Global Antiphospholipid Syndrome Score (GAPSS)

The GAPSS is a validated tool to assess the likelihood of developing new thrombosis that was originally developed

based on patients with lupus,[10] and then validated in patients with primary APS.[11] The GAPSS includes the following points based on a linear transformation derived from beta regression: positive anticardiolipin antibody (IgG/M) scores five points; anti-β_2 glycoprotein-I IgG/M scores four points; lupus anticoagulant test scores four points; anti-phosphatidylserine/prothrombin antibodies (aPS/PT) IgG/IgM scores three points; hyperlipidaemia scores three points; and arterial hypertension scores one point. For the purpose of our analysis, we used the adjusted version of GAPSS (aGAPSS), which excludes aPS/PT, as this test was not available for most of the registry patients.

The primary study outcome was documented thrombosis (venous and/or arterial), confirmed by imaging studies.

Statistical analysis

Although patients included in the APS ACTION registry are followed prospectively, in this retrospective study we analysed the baseline clinical and laboratory characteristics of aPL-positive women presenting with pregnancy morbidity, with a comparison between women with and without subsequent thromboses. We also calculated the mean cumulative adjusted GAPSS (aGAPSS) for each group.[10]

The univariate analysis was performed using the Pearson chi-square and Fisher exact tests to assess the association between thrombosis and risk factors. The demographic, clinical, and serological parameters considered in the univariate analysis are listed in Table 1. Multivariate logistic regression analysis was performed to identify significant

Table 1. Clinical and laboratory characteristics of women with obstetric antiphospholipid syndrome (Ob-APS) listed in the APS ACTION registry, with or without subsequent non-gravid thrombosis

Variables, *n* (%)	Obstetric APS only (*n* = 52)	Obstetric APS followed by thrombosis (*n* = 47)	*P*
Demographics			
Age of first pregnancy morbidity	28.9 ± 6.77	26.25 ± 5.52	0.03
Associated autoimmune disease			
No other autoimmune disease	28 (53.8%)	29 (61.7%)	0.21
Systemic lupus erythematosus	12 (23.0%)	8 (17.0%)	0.22
Lupus-like disease (three American College of Rheumatology criteria for lupus)	6 (11.5%)	2 (4.2%)	0.09
Other	6 (11.5%)	8 (17.0%)	0.43
Vascular events			
Venous thrombosis	NA	25 (53.1%)	NA
Arterial thrombosis	NA	17 (36.1%)	NA
Venous and arterial thrombosis	NA	5 (10.6%)	NA
Cardiovascular risk factors at entry to registry			
Medication for hypertension	11 (21.1%)	20 (42.5)	0.01
Medication for diabetes	1 (1.9%)	3 (6.3%)	0.13
Medication for hyperlipidaemia	3 (5.7%)	8 (17.0%)	0.03
Obesity (body mass index >30 kg/m^2)	6 (11.5%)	11 (23.4%)	0.06
Smoking (ever)	9 (17.3%)	18 (38.2%)	0.009
First pregnancy morbidity			
Fetal loss	34 (65.3%)	30 (63.8%)	0.43
Premature birth <34 week	14 (26.9%)	12 (25.5%)	0.43
≥Three (pre)-embryonic loss	4 (7.6%)	5 (10.6%)	0.30
Non-criteria manifestations			
Superficial vein thrombosis	1 (1.9%)	6 (12.7%)	0.01
Transient ischemic attack	4 (7.6%)	7 (14.8%)	0.12
Livedo	6 (11.5%)	11 (23.4%)	0.06
Thrombocytopenia	12 (23.0%)	10 (21.2%)	0.41
Haemolytic anaemia	3 (5.7%)	4 (8.5%)	0.29
Heart valve disease	1 (1.9%)	6 (12.7%)	0.01
Skin ulcer	0	4 (8.5%)	NA
aPL-nephropathy	2 (3.8%)	0	NA
Laboratory parameters			
Lupus anticoagulant (alone or with other autoantibodies)	35 (67.3%)	42 (89.3%)	0.004
Triple positivity	17 (32.6%)	13 (27.6%)	0.29

independent factors adjusted for the potential confounding risk factors able to predict thrombosis. The final multivariate logistic regression model included the following variables: age, diagnosis of concomitant autoimmune disease, cardiovascular risk factors, aPL profile, type of pregnancy morbidity, and treatment.

Results

Of 550 patients included in the APS ACTION registry as of May 2015, 419 (76%) were female. We excluded 131 (31%) women with no pregnancy history, and 162 (39%) women with a history of pregnancy but who did not fulfill the updated APS classification criteria for Ob-APS (with or without any morbidity).[1] Of the remaining 126 (30%) women with Ob-APS, 74 (59%) had a history of thrombosis at the time of cohort entry (venous, 43; arterial, 22; and both, 9): 47 (64%) after pregnancy morbidity and 27 (36%) before Ob-APS. For the purpose of this study, only women with vascular thrombosis after the initial pregnancy morbidity ($n = 47$) and women with Ob-APS without thrombosis ($n = 52$) were included.

The clinical and laboratory characteristics of women with Ob-APS with or without thrombosis after pregnancy morbidity are described in Table 1. Fetal loss was the most common pregnancy morbidity in both groups (65 and 64%, respectively). Most of the clinical and laboratory characteristics of the women did not differ, except that in women with thrombosis after Ob-APS compared with women with pure Ob-APS: (1) they had the first pregnancy morbidity at a younger age (26.2 ± 5.5 versus 28.9 ± 6.7 years, $P = 0.03$); (2) they more frequently had superficial vein thrombosis (six versus one, $P = 0.01$) and heart valve disease (six versus one, $P = 0.01$); (3) they more frequently had hypertension (21 versus 11, $P = 0.01$), hyperlipidaemia (eight versus three, $P = 0.03$), and smoking history (18 versus nine, $P = 0.009$) at study entry; and (4) they were more frequently positive for lupus anticoagulant (alone or with other aPL) (42 versus 35, $P = 0.004$). The mean age of inclusion in the registry of women with Ob-APS without thrombosis was 40.8 years (±9.8 years).

Among women with Ob-APS with subsequent thrombosis, the mean time between pregnancy morbidity and thrombosis was 7.6 ± 8.2 years (4.9 per 100 patient years) (Figure S1). Based on the registry entry data, at least one cardiovascular risk factor and multiple aPL positivity (defined as positivity for more than one aPL criteria test) were identified using stepwise multivariate logistic regression analysis as independent risk factors for thrombosis (Table S1).[1]

Women with Ob-APS with subsequent thrombosis after pregnancy morbidity had a higher aGAPSS than those with Ob-APS alone [median 11.5 (4–16) versus 9 (4–13), $P = 0.0089$, Figure 1]. Higher aGAPSSs were also noted after a subgroup analysis of the type of thrombosis [12 (4–16) for arterial thrombosis, 11 (4–13) for venous thrombosis, and 9 (4–13) for Ob-APS alone, $P = 0.038$ and $P = 0.044$, respectively].

Discussion

Main findings

This is the first multicentre international large-scale analysis of women with Ob-APS for their risk of first thrombosis after the initial pregnancy morbidity. In addition, our study is the first attempt to quantify the thrombosis risk of these women. In our cohort, we observed that 63% of women with APS presenting with pregnancy morbidity eventually developed thrombosis after a mean time of 7.6 years (4.9 per 100 patient years), which was independently associated with multiple aPL positivity. We also found that pregnancy morbidity at a younger age, concomitant cardiovascular risk factors, and non-criteria manifestations (namely superficial vein thrombosis and heart valve disease) were predictors of new thrombosis.

Strengths and limitations

Our study has several strengths and limitations. Although our study is one of the largest international analyses of the association between Ob-APS and subsequent thrombosis, the study is limited by the retrospective case–control study design. Similarly, the retrospective assessment of cardiovascular disease risk factors at the time of entry to the registry, but not at the time of thrombosis, limits the accuracy of aGAPSS.

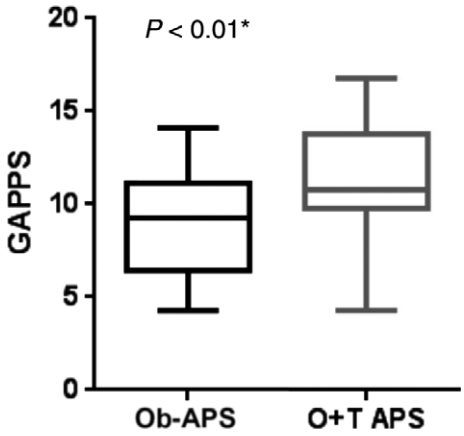

Figure 1. Global Antiphospholipid Syndrome Score (GAPPS) based on obstetric APS (Ob-APS) versus obstetric and thrombotic APS (O+T APS). Data are shown as box plots, where each box represents the 25–75th percentiles: lines inside the box represent the median values. The whiskers represent the 95% CI. *Assessed by Student's *t*-test.

Interpretation

The increased risk of thrombosis following pregnancy morbidity in aPL-positive women, compared with the general population, has been previously described both retrospectively and prospectively,[2,3] although not all studies agree.[4] A 10-year prospective study of 1592 women with three consecutive miscarriages before the 10th week of gestation or one fetal death at or beyond the 10th week of gestation compared the frequencies of thrombosis among women with pregnancy morbidity and positive aPL ($n = 517$), women carrying the coagulation factor polymorphisms F5 6025 or F2 rs1799963 ($n = 279$), and women with negative thrombophilia screening results ($n = 796$).[3] Annual rates of deep vein thrombosis (1.46%; range 1.15–1.82%), pulmonary embolism (0.43%; range 0.26–0.66%), superficial vein thrombosis (0.44%; range 0.28–0.68%), and cerebrovascular events (0.32%; range 0.18–0.53%) were significantly higher in women with aPL than in the other groups, despite treatment with low-dose aspirin. On the other hand, one study described thrombosis rates after fetal loss in women with APS to be of 1.3 and 7.4 per 100 patient-years in aspirin-treated and untreated women, respectively.[5] A retrospective cohort of 32 women with Obs-APS treated with aspirin reported an overall thrombosis rate of 3.3 per 100 patient-years; however, the thrombosis rate with double or triple aPL positivity was 4.6 per patient-year ($n = 7$ and 14, respectively), and 10 per 100 patient-years with SLE-associated Ob-APS.[7]

The clinical utility of aGAPSS in assessing the thrombotic risk in different clinical scenarios has been described and validated previously, as recently summarised in a systematic review.[12] In the first description of patients with SLE, it was observed that GAPSS values of ≥10 had the best diagnostic accuracy for APS. In patients with primary APS, GAPSS values of ≥11 were strongly associated with a higher risk of recurrence (OR 18.27, 95% CI 3.74–114.5), giving the best accuracy in terms of sensitivity and specificity.[13] More recently, in a cohort of patients with autoimmune disease, Fernandez Mosteirin et al.[14] showed that aGAPSS values of ≥5 had the best diagnostic accuracy (AUC = 0.661; $P < 0.001$) for any thrombotic event. Cut-off values may differ for different of cohorts,[13,15] which suggest that baseline characteristics in divergent groups of patients can account for differences in the cut-off values of GAPSS.

Several studies also demonstrated that aGAPSS seems to be a valid tool to assess the likelihood of developing new thrombotic events in patients with APS and may guide pharmacological treatment for high-risk patients. This score has been independently validated in different APS populations,[11,13,16] and also in specific groups, such as young APS patients with acute myocardial infarction.[15]

In a recent study, aGAPSS baseline values were statistically higher in patients with APS and a history of thrombosis compared with patients without.[14] A Chinese cohort reported a higher aGAPSS in patients with thrombosis than in patients with pregnancy morbidity only, but patients with both thrombosis and pregnancy morbidity had no statistical difference in aGAPSS when compared with patients with Ob-APS only.[17] We showed that women with Ob-APS who experience thrombosis after initial pregnancy morbidity have higher aGAPSS values, when compared with those without thrombosis.

Conclusion

Our retrospective analysis of a large-scale aPL registry suggests that: (1) among women with both thrombosis and Ob-APS, more than half developed thrombosis after an initial aPL-related pregnancy morbidity; and (2) a younger age at the time of onset for an Ob-APS-related event, additional cardiovascular risk factors, superficial vein thrombosis, heart valve disease, and multiple aPL positivity increased the risk of the first thrombosis after pregnancy morbidity. In addition, the aGAPSS may be a valid tool for a substantial improvement in risk stratification for thrombosis in women with Ob-APS, and to identify women who might benefit from a tailored management approach.

Disclosure of interests

Roger Abramino Levy is a licensed professor of Rheumatology at Universidade do Estado do Rio de Janeiro, currently working as global medical expert for GlaxoSmithKline in Upper Providence, PA, USA. The other authors declare that they have no conflicts of interest. Completed disclosure of interests forms are available to view online as supporting information.

Contribution to authorship

GRJ, SS, DE, and RAL were involved in data acquisition, study design, writing, the literature review, and statistical analysis. DA, ISN, RR, MB, MT, AB, VP, LJ, PLM, AU, HC, DWB, LA, HMB, PRF, MP, ER, RC, JSK, TA, and RW were involved in data acquisition, writing, and the literature review.

Details of ethics approval

This study was approved by Hospital Universitário Pedro Ernesto's Ethics Committee on 18 October 2012 (approval no. 02190912.6.1001.5259).

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Histogram of interval in years between pregnancy morbidity and thrombosis.

Table S1. Stepwise multivariate logistic regression analysis for independent risk factors for thrombosis. ■

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