EXTENDED REPORT

Risk of thromboembolic events after recurrent spontaneous abortion in antiphospholipid syndrome: a case–control study

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ABSTRACT
Objective To investigate whether patients having antiphospholipid syndrome (APS) as the only aetiological factor for recurrent spontaneous abortion (RSA) are at increased risk of thrombosis later in life.

Methods A case–control study at a tertiary university referral centre. The study group consisted of 57 primary APS and RSA women (APS–RSA group). Control groups included: 86 patients with RSA of unknown aetiology (uRSA group), 42 patients with RSA and thrombophilic genetic defects as the only aetiological factor for RSA (tRSA group) and 30 antiphospholipid antibody (aPL) positive but otherwise healthy women (aPL group). The main measurement was the thrombosis rate after long-term follow-up.

Results APS–RSA patients had a significantly higher 12-year cumulative thrombotic incidence rate compared with the three comparator groups (19.3% vs 4.8%, 0.0% and 0.0%, respectively (log rank), p<0.001). Patients in the APS–RSA group had 25.6 thrombotic events per 1000 patient-years (95% CI 12.8 to 45.9). The OR of thrombosis in relation to the presence (APS–RSA group) or absence (uRSA and tRSA groups) of aPL in patients with RSA was 15.06 (95% CI 3.2 to 70.5).

Conclusions Our data indicate that a history of RSA associated with aPL is a risk factor for subsequent thrombosis in the long term.

The antiphospholipid syndrome (APS) is an autoimmune, multisystemic disorder associated with vascular thrombosis and/or pregnancy morbidity in the presence of antiphospholipid antibodies (aPL), namely the lupus anticoagulant (LA) and anticardiolipin antibodies (aCL).1 Women with aPL are considered at increased risk of both recurrent spontaneous abortion (RSA) and thrombotic events.2 Remarkably, while pregnancy loss may be the sole manifestation of disease in such women and autoimmune disease is subclinical mainly in association with fetal wastage,1 it has been reported that outside of pregnancy, women with a history of RSA are considered to be in a prothrombotic state.3

However, aPL frequently persists for many years, without apparent harm. In addition, aPL can be detected in the sera of asymptomatic individuals years before developing a full-blown disease. Therefore, an unresolved critical question is what additional factors lead to the sudden development of thrombosis, occurring in only a minority of patients with these antibodies.4–7

A ‘two-hit hypothesis’ has been proposed to explain why thrombotic events occur only occasionally, despite the persistent presence of aPL. The first hit (aPL) would increase the thrombophilic risk and a second hit is required to trigger the clotting.6–7 Interestingly, two short communications suggested, for the first time, a high incidence of non-pregnancy-related vascular thrombosis in APS patients who present with pregnancy loss (ie, the second hit) as their only manifestation of APS.8–9 Both reports, however, were retrospective including 65 and 52 women, respectively, treated with aspirin and, are in contrast with a retrospective case–control study using questionnaires and concluding that both idiopathic and APS-associated RSA were associated with a similar long-term risk of thrombosis.10

This study was undertaken to investigate whether patients with APS as the only aetiological factor for RSA are at increased risk of thrombosis later in life. This was done using appropriate case patients and three comparator groups.

MATERIALS AND METHODS

Study population and design

This case–control study involved a total of 215 women attending the Hospital Clinic of Barcelona identified from a list of patients who underwent thrombophilia testing in our laboratory from 1996 to 2005. Thirty-eight eligible individuals could not be contacted and appropriate information obtained and they were therefore not included. Therefore, 185 patients with a history of RSA who underwent all the diagnostic tests reported below and 30 healthy women fulfilling the inclusion criteria reported below were included. The survey was performed 4–12 years after the patients had attended our hospital for RSA work-up or after diagnosis with circulating positive aPL, being otherwise healthy women. All the women gave informed consent to participate in the present study, which was approved by the ethics committee of our hospital.

Four groups of patients were included. The study group consisted of 57 women previously diagnosed with primary APS who had had three or more consecutive spontaneous abortions before 10 weeks’ gestation (APS–RSA group). The diagnosis...
of APS was based on the international consensus statement of the updated classification criteria for definite APS.11 Patients who had been diagnosed before the consensus had been published fulfilled all the later updated international consensus criteria. As the current investigation is a long-term follow-up study, all patients tested positive for aPL on three or more occasions at least 12 weeks apart. Patients with LA, medium to high levels of immunoglobulin (Ig)G and/or IgM aCL, or both, were included. Those with only low IgG and/or IgM aCL were excluded. No other aetiological factor was identified in the fertility studies including routine screening for systemic diseases, diabetes mellitus, thyroid dysfunction, polycystic ovary disease, a chromosome assessment of the woman and her partner, uterine abnormalities, endometrial and hormonal luteal phase defects, endometrial and cervical infection and thrombophilia other than aPL (plasma levels of protein S and C, antithrombin III, factor V Leiden and prothrombin G20210A mutations, acquired protein C resistance).

The first control group included 86 patients with three or more consecutive spontaneous abortions of unknown aetiology before 10 weeks' gestation (uRSA group). All tested negative for the above-mentioned investigations. The second control group included 42 patients with three or more consecutive spontaneous abortions before 10 weeks' gestation with thrombophilic losses (tRSA group). Thrombophilia in this group was defined as factor V Leiden (heterozygote) mutation (n=12), protein C deficiency (n=17), factor V Leiden and prothrombin G20210A mutations, acquired protein C resistance).

Patient follow-up and outcome assessment
Detailed medical histories for the periods before and after the initial laboratory testing, laboratory data, results of imaging studies and medications during the study period were obtained for all patients. In addition, patients or their surrogates were contacted by a doctor involved in the current study in person or by telephone and information was collected using a standardised data sheet. The structured questionnaire designed to elicit any thrombotic event and cardiovascular risk factors used in this study is also used in our institution, and was obtained after achieving consensus between gynaecologists, rheumatologists, internists and haematologists. The study period was defined as the interval from initial laboratory testing to the time of patient interview (minimum follow-up 4 years).

All patients and controls answered a structured questionnaire designed to elicit any thrombotic episode. The following factors were examined to determine their influence on thrombosis risk: ethnicity, hypertension, diabetes mellitus, cancer, family history of thrombosis, smoking, weight, height, high cholesterol, high triglycerides, oral contraceptive use. No woman had received hormone replacement therapy. Current oral contraceptive use was defined as use within the 3 months before the date of the survey. Current smoking was defined as smoking five or more cigarettes a day in the year before the date of the survey.19 20 Current smoking was defined as smoking five or more cigarettes a day in the year before the date of the survey.21 Patients who had not been previously diagnosed with hypertension, hypercholesterolaemia and diabetes were given an appointment at our hospital to check all these parameters by means of non-fasting blood tests and blood pressure measurement. Women were classified as having hypertension, diabetes or hypercholesterolaemia according to criteria previously reported.22 23 Some patients in the APS–RSA and aPL groups had taken low-dose aspirin since the time of testing positive for aPL and were still on treatment at the time of being contacted for the specific purpose of this study.

The primary outcome was incident vascular thrombotic events verified by checking hospital records and confirmed by accepted imaging, Doppler and laboratory studies, as previously reported.23 Deep vein thrombosis was confirmed by Doppler studies and/or phlebography. Pulmonary embolism was confirmed by ventilation/perfusion pulmonary scintigraphy or spiral CT. Peripheral arterial thrombosis was confirmed by arteriography. Cerebrovascular accident and cerebral venous thrombosis were defined by CT and/or brain MRI. Myocardial infarction was confirmed by raised cardiac enzymes and appropriate electrocardiographic changes.
open source epidemiological statistics for public health, version 2.3.1. www.OpenEpi.com, updated 19 September 2010. OR were calculated with the Woolf–Haldane modification, which adds 0.5 to all cells to accommodate possible zero counts when appropriate. Comparison of quantitative variables was performed using analysis of variance with Bonferroni’s post-hoc analysis. Comparison of qualitative variables was undertaken using the χ² test. Cumulative event curves were generated with the Kaplan–Meier method and compared with the log-rank test of significance. All statistical tests were two-sided, and differences were considered statistically significant at p<0.05. Results are presented as mean±SD (and range when appropriate) or n (%).

RESULTS

Table 1 summarises the demographic variables, risk factors, comorbidities and clinical characteristics in the four groups studied. No differences were observed for any of the parameters considered except aspirin treatment. Twelve and nine patients in the APS–RSA (21%) and aPL (80%) groups, respectively, were given prophylactic daily low-dose aspirin but no woman in the uRSA or tRSA groups received this treatment (p<0.0001). No patient was taking hydroxychloroquine as all patients included had primary APS, as mentioned above.

The mean observation time was similar in the four groups of patients (table 2). Eleven patients in the APS–RSA group (19.3%) and two patients in the tRSA group (4.8%) had a thrombotic event during the study period. No subsequent thrombotic episodes were recorded during the study interval, and there were two thrombotic deaths (due to cerebral arterial infarction and massive pulmonary embolism) in the APS–RSA group. The rate of thrombosis in the APS–RSA group was significantly higher than in the control groups (table 2, figure 1). Patients in the APS–RSA group had 25.6 thrombotic events per 1000 patient-years (95% CI 12.8 to 45.9) while the corresponding figure in the uRSA group was 7.1 thrombotic events per 1000 patient-years (95% CI 0.8 to 25.5). Patients with APS–RSA had a significantly higher 12-year cumulative thrombotic incidence rate compared with the three comparator groups (19.3% vs 4.8%, 0.0% and 0.0%, respectively (log rank), p<0.001) (figure 1).

The OR of thrombosis in relation to the presence (APS–RSA group) or absence (uRSA and tRSA groups) of aPL in patients with RSA was 15.06 (95% CI 3.2 to 70.5, p<0.0001). This was still true when only patients with thrombophilic disorders other than aPL (tRSA group) were considered (OR 4.8, 95% CI 1 to 22.8, p<0.05). Accordingly, the OR was even higher when the APS–RSA group was compared with the uRSA group alone (OR 42.8, 95% CI 2.5 to 742, p<0.0001).

The occurrence of thrombotic events among women with RSA (APS–RSA, uRSA and tRSA groups) treated with aspirin (16% or 2/12 patients) did not differ from patients who did not receive this treatment (6% or 11/173 women, p=0.2) (OR 2.9, 95% CI 0.5 to 15.1). One patient in the APS–RSA group presented with cerebral arterial infarction during the puerperium despite taking low-dose aspirin.

Remarkably, five out of seven (71.4%) patients in the APS–RSA group diagnosed with arterial thrombosis had concomitant thrombosis risk factors (hypertension, one subject; hypertension and hypercholesterolemia, one subject; heavy smoker (≥20 cigarettes/day) and hypercholesterolaemia, one subject; heavy smoker and hypertension, one subject; heavy smoker, one subject) and one out of four (25%) who presented with venous thrombosis had hypertension.

Several patients (6/13, 46%) were diagnosed as having thrombotic events in our hospital. In three cases (23%) it was possible to check medical records in two hospitals located in the metropolitan area of Barcelona, while in the remaining four patients the diagnosis was confirmed by colleagues who provided a copy of diagnostic evidence with pertinent imaging and laboratory studies. Therefore, there were no equivocal cases among the 13 patients diagnosed as having this condition.

Table 1  Demographic features, clinical characteristics and risk factors of the four groups studied

<table>
<thead>
<tr>
<th>Parameter</th>
<th>APS–RSA group (n=57)</th>
<th>uRSA group (n=86)</th>
<th>tRSA group (n=42)</th>
<th>aPL group (n=30)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian*</td>
<td>57 (100)</td>
<td>86 (100)</td>
<td>42 (100)</td>
<td>30 (100)</td>
<td>NS</td>
</tr>
<tr>
<td>Age at RSA diagnosis, years†</td>
<td>32.8±3.5 (26–43)</td>
<td>34.5±4.5 (24–45)</td>
<td>34.3±5.1 (23–42)</td>
<td>31.9±5.6 (24–42)</td>
<td>NS</td>
</tr>
<tr>
<td>Aspirin treatment*</td>
<td>12 (21)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>9 (30)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>First trimester spontaneous abortions†</td>
<td>3.7±1.2 (3–8)</td>
<td>4.3±2.0 (3–15)</td>
<td>3.8±1.1 (3–6)</td>
<td>0±0 (0)</td>
<td>NS</td>
</tr>
<tr>
<td>Second and/or third trimester pregnancy losses†</td>
<td>0.1±0.4 (0–2)</td>
<td>0.03±0.2 (0–1)</td>
<td>0.1±0.4 (0–1)</td>
<td>0±0 (0)</td>
<td>NS</td>
</tr>
<tr>
<td>Uneventful deliveries†</td>
<td>1.0±0.7 (0–2)</td>
<td>0.7±0.6 (0–2)</td>
<td>0.9±0.7 (0–2)</td>
<td>1.3±0.9 (0–3)</td>
<td>NS</td>
</tr>
<tr>
<td>BMI†</td>
<td>24.3±3.9 (17–32)</td>
<td>25.2±4.2 (17–34)</td>
<td>24.7±5.3 (17–34)</td>
<td>25.7±5.8 (18–33)</td>
<td>NS</td>
</tr>
<tr>
<td>Smoker*</td>
<td>48 (84.2)</td>
<td>66 (76.7)</td>
<td>35 (83.3)</td>
<td>20 (67)</td>
<td>NS</td>
</tr>
<tr>
<td>Never†</td>
<td>3 (5.3)</td>
<td>7 (8.2)</td>
<td>2 (4.8)</td>
<td>6 (20)</td>
<td>NS</td>
</tr>
<tr>
<td>Current</td>
<td>6 (10.5)</td>
<td>13 (15.1)</td>
<td>5 (11.9)</td>
<td>4 (13)</td>
<td>NS</td>
</tr>
<tr>
<td>Oral contraceptives*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Never-users</td>
<td>57 (100)</td>
<td>57 (100)</td>
<td>42 (100)</td>
<td>22 (73)</td>
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<tr>
<td>Past-users</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>8 (27)</td>
<td></td>
</tr>
<tr>
<td>Current-users</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Hypercholesterolemia*</td>
<td>2 (3.5)</td>
<td>4 (4.6)</td>
<td>2 (4.7)</td>
<td>4 (13)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension*</td>
<td>4 (7)</td>
<td>3 (3.5)</td>
<td>2 (4.8)</td>
<td>1 (3)</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes*</td>
<td>0 (0)</td>
<td>1 (1.2)</td>
<td>0 (0)</td>
<td>1 (3)</td>
<td>NS</td>
</tr>
<tr>
<td>Malignancy*</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>NS</td>
</tr>
<tr>
<td>Thrombosis family history*</td>
<td>3 (5)</td>
<td>2 (2)</td>
<td>3 (7)</td>
<td>2 (7)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are n (%), if not mean±SD (range). 1 Age at study inclusion. aPL group, patients with positive tests for antiphospholipid antibodies (aPL) without pregnancy or thrombotic morbidity; laboratory testing for aPL was performed at the time of patients attending our hospital. See Materials and methods section for more details; APS–RSA group, antiphospholipid syndrome patients with recurrent spontaneous abortion; BMI, body mass index; NS, not significant; RSA, recurrent spontaneous abortion; tRSA group, patients with recurrent spontaneous abortion without aPL but with other known thrombophilias; uRSA group, patients with recurrent spontaneous abortion without aPL or other known thrombophilias.

Apart from those 38 individuals who could not be contacted among all eligible patients initially selected, accurate information was obtained from each subject through a personal or phone interview carried out by a doctor involved in the current study and the structured questionnaire designed to elicit any thrombotic episode. The patients included were thus only those for whom appropriate information was available, thereby avoiding possible missed cases among those not reporting thromboses.

In the whole study population, 43% and 57% of aCL-positive patients had medium and high antibody titres, with no differences in this respect between the three groups presented in table 3 (data not shown). aCL titres were also similar on comparing patients developing thrombosis or not (data not shown). No difference was found regarding aPL and isotype distribution in aPL-positive subjects developing thrombosis or not (table 3).

DISCUSSION
This study shows that patients with RSA associated with the presence of aPL have an increased long-term risk of thrombosis, with an approximately 15-fold greater risk of presenting with a thrombotic event than RSA patients without aPL. Our data also suggest that thrombosis in APS–RSA patients is frequently associated with concomitant cardiovascular risk factors. The most striking feature of the current investigation was the high incidence of non-pregnancy-related vascular thrombosis in APS patients who presented with RSA as their only manifestation of APS. Our study has several strengths. First, retrospective studies cannot exclude the possibility that a thromboembolic event may, in fact, promote the development of aCL. At the time the plasma samples were obtained in our study, participants had no history of thrombotic events. Therefore, the potential confounders of systemic disease or pre-existing vascular injury seem to have been avoided in the current investigation. Second, we included only well-selected case patients according to both international criteria and laboratory guidelines for definite APS. In addition, we used three appropriate control groups including recurrent aborters of unknown aetiology according to a complete diagnostic work-up, patients with RSA associated with inherited thrombophilia, and healthy women testing positive for aPL. Remarkably, the annual incidence of the first episode of venous thromboembolism reported in the tRSA group in
Tables 3. LA and aCL isotype distribution in aPL-positive patients developing thrombosis or not.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>APS–RSA group without thrombosis (n=46)</th>
<th>APS–RSA group and thrombosis (n=11)</th>
<th>aPL group (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>aCL</td>
<td>28 (56%)</td>
<td>5 (46%)</td>
<td>20 (67%)</td>
</tr>
<tr>
<td>aCL IgM</td>
<td>5 (19%)</td>
<td>0 (0%)</td>
<td>4 (13%)</td>
</tr>
<tr>
<td>aCL IgG</td>
<td>15 (58%)</td>
<td>3 (60%)</td>
<td>12 (60%)</td>
</tr>
<tr>
<td>aCL IgM + IgG</td>
<td>6 (23%)</td>
<td>2 (40%)</td>
<td>4 (20%)</td>
</tr>
<tr>
<td>aCL IgM + LAC</td>
<td>3 (33%)</td>
<td>1 (33%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>LA</td>
<td>11 (24%)</td>
<td>3 (27%)</td>
<td>7 (23%)</td>
</tr>
<tr>
<td>aCL + LA</td>
<td>9 (20%)</td>
<td>3 (27%)</td>
<td>3 (10%)</td>
</tr>
<tr>
<td>aCL IgM + LAC</td>
<td>3 (33%)</td>
<td>1 (33%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>aCL IgG + LAC</td>
<td>5 (56%)</td>
<td>2 (67%)</td>
<td>3 (100%)</td>
</tr>
<tr>
<td>aCL IgG + IgM + LAC</td>
<td>1 (11%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

Values are n (%).

*p Value: NS (by $\chi^2$ test).

aCL, antiphospholipid antibodies; aPL group, patients with positive tests for antiphospholipid antibodies (aPL) without pregnancy or thrombotic morbidity; APS–RSA group, antiphospholipid syndrome patients with recurrent spontaneous abortion; IgG, immunoglobulin G; IgM, immunoglobulin M; LA, lupus anticoagulant.

Our study is clearly within the range of estimated risk reported in the literature for patients with inherited thrombophilia.9,10 Finally, this was a long-term study with individual follow-up ranging from 4 to 12 years.

This study has several limitations. This is a retrospective analysis of prospectively collected material and only a relatively low number of subjects with unequal distribution in the four groups studied could be included. However, the importance of this study lies in the fact that the presence of aPL was demonstrated before the occurrence of the thrombotic event. In fact, very little is known about the risk of thrombosis in aPL-positive individuals who are still free of thrombosis.4,7 Therefore, our study represents a relevant contribution in this respect. It should be noted that patients were not checked for the presence of B2-glycoprotein-1 antibodies because all were diagnosed and recruited before the 2006 updated classification criteria for APS.11 A review including 28 studies and analysing 60 associations between B2-glycoprotein-1 antibodies and thrombosis concluded that the results were partly controversial, but measurement of these antibodies may still be practical and useful in some situations.27 A recent multicentre follow-up study28 including only aPL carriers, concluded that hypertension and LA (but not B2-glycoprotein-1 antibodies) are independent risk factors for thrombosis. This notwithstanding, by majority, the last consensus paper on the subject agreed that IgG and IgM anti-B2-glycoprotein-1 should be included as part of the modified Sapporo criteria for thrombosis and pregnancy complications.11 The consensus also stressed that testing for anti-B2-glycoprotein-1 can be helpful for APS diagnosis, particularly when aCL and LA are negative and APS is strongly suspected.11

Overall, our results are in line with previous reports suggesting that non-pregnant women with a history of RSA are in a prothrombotic state.3,10,29 In addition, a large retrospective study of 130 000 women reported that a history of first trimester spontaneous abortion was associated with a significantly increased risk of maternal ischaemic heart disease.30 The authors hypothesised that this may reflect common determinants, such as thrombophilic genetic defects and aCL.30 Our study shows that the presence of circulating aPL rather than thrombophilic genetic defects in patients with RSA is the main determinant of thrombotic events in later life. Therefore, we found that patients with RSA and aPL have an approximately fivefold greater risk of presenting with a thrombotic event than RSA patients with thrombophilic genetic defects. Interestingly, only 19.3% of patients in the APS–RSA group and no woman in the aPL group developed a thrombotic event in the long term, despite aPL and aCL and their isotype distribution being similar in aPL-positive patients developing thrombosis or not and irrespective of being recurrent aborters or healthy controls (table 3).

There is currently no way to predict when or which aPL patients will develop thrombosis. The above notwithstanding, in this respect, our study is in agreement with previous reports31–33 suggesting that aPL-positive individuals should be risk-stratified according to traditional cardiovascular risk factors, which can be responsible for triggering acute thrombosis.

The above data have potentially interesting implications. First, our results provide further support to the ‘two-hit hypothesis’6,6 in which aPL (first hit) increases the thrombophilic risk and the clotting takes place in the presence of another thrombophilic condition (ie, RSA associated with traditional cardiovascular risk factors or not, acting as the second hit). This would explain previous epidemiological studies suggesting that a woman’s reproductive history may indicate future cardiovascular risk.30,34 On the other hand, the aetio-pathogenesis of APS is apparently multifactorial involving responses of both adaptive and innate immunity, being supported by a genetic background and triggered by environmental factors. In other words, genetically determined and environmental factors (second hits) may cooperate with aPL (first hit) in favouring thrombotic events.3 Therefore, whether an individual will develop a thrombotic event depends on the concomitant presence of additional factors that may increase the whole thrombotic risk. This would explain why up to 80% of patients with RSA associated with aPL did not develop a thrombotic event.

In conclusion, our data indicate that a history of RSA associated with aPL is a risk factor for subsequent thrombosis in the long term. This may have clinical implications, mainly in those patients with traditional cardiovascular risk factors. If our results are confirmed by others, further studies would be warranted to assess the efficacy and risks of long-term thromboprophylaxis with aspirin and/or heparin in patients with RSA associated with aPL.

Competing interests None.

Patient consent Obtained.

Ethics approval This study was conducted with the approval of the ethics committee of the Hospital Clinic of Barcelona.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

Clinical and epidemiological research


Risk of thromboembolic events after recurrent spontaneous abortion in antiphospholipid syndrome: a case–control study

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