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The European Registry on Obstetric Antiphospholipid Syndrome (EUROAPS): A survey of 1000 consecutive cases

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ABSTRACT

Aim: To analyse the clinical features, laboratory data and foetal-maternal outcomes, and follow them up on a cohort of 1000 women with obstetric antiphospholipid syndrome (OAPS).

Methods: The European Registry of OAPS became a registry within the framework of the European Forum on Antiphospholipid Antibody projects and was placed on a website in June 2010. Thirty hospitals throughout Europe have collaborated to carry out this registry. Cases with obstetric complaints related to antiphospholipid antibodies (aPL) who tested positive for aPL at least twice were included prospectively and retrospectively. The seven-year survey results are reported.

Results: 1000 women with 3553 episodes were included of which 2553 were historical and 1000 were latest episodes. All cases fulfilled the Sydney classification criteria. According to the laboratory categories, 292 (29.2%) were in category I, 357 (35.7%) in IIa, 224 (22.4%) in IIb and 127 (12.7%) in IIc. Miscarriages were the most prevalent clinical manifestation in 386 cases (38.6%). Moreover, the presence of early preeclampsia (PE) and early foetal growth restriction (FGR) appeared in 181 (18.1%) and 161 (16.1%), respectively. In this series, 448 (44.8%) women received the recommended OAPS treatment. Patients with recommended treatment had a good live-birth rate (85%), but worse results (72.4%) were obtained in patients with any treatment (low-dose aspirin (LDA) or low-molecular-weight heparin (LMWH) not on recommended schedule, while patients with no treatment showed a poor birth rate (49.6%).

Conclusion: In this series, recurrent miscarriage is the most frequent poor outcome. To avoid false-negative diagnoses, all laboratory category subsets were needed. OAPS cases have very good foetal-maternal outcomes when treated. Results suggest that we were able to improve our clinical practice to offer better treatment and outcomes to OAPS patients.

1. Introduction

The antiphospholipid syndrome (APS) is an autoimmune disease defined by the presence of vascular thrombosis and/or obstetric complications related to antiphospholipid antibodies (aPL) [1]. The International consensus conducted in Sydney in 2006 summarises obstetric complications in recurrent first trimester miscarriage, foetal losses, stillbirth, early and severe preeclampsia or prematurity (< 34 weeks) due to placental dysfunction [2]. However, there are cases known to have obstetric antiphospholipid syndrome (OAPS) [3] without a previous thrombotic history. Placental insufficiency plays a pivotal role in the pathogenesis of pregnancy complications partly due to the detrimental effects of aPL, from implantation and placenta genesis to delivery [4]. Levy et al. [5] demonstrated that decidual or placental thrombosis could not be confirmed in almost 50% of cases, suggesting an apparent silent inflammatory mechanism [6]. This theory has been demonstrated in subsequent research [7]. It has been postulated that complement activation and secondary endothelial disruption may impair invasion and trophoblast function [8]. Other pathways of inflammation could involve tissue factor over-expression in neutrophils and monocyte cells [9]. They can also involve the release of neutrophil extracellular trap and interleukin-8 [10], the upregulation of the mechanistic target of the rapamycin (mTOR) complex on endothelial cells [11] and the reduced activity of activated C protein [12], despite a negative imbalance of angiogenic factors [13], still in the absence of thrombosis.

There is evidence that APS is the most frequently treatable acquired cause during pregnancy [14], although it is known that the classic form and the obstetric one have different rates of thrombosis [15], response to treatment [16] or follow-up [17]. Those incomplete forms (by meeting neither the clinical nor the laboratory criteria) represent a special challenge for the clinician [18], as there is increasing evidence that patients with low aPL titers can experience poor pregnancy outcomes similarly to high-titer patients [19]. In the same way, women with incomplete clinical forms benefit from treatment, having better prognosis than women without treatment [20]. Thus, at the recent 14th International Congress on Antiphospholipid Antibodies Task Force Report on Obstetric APS and the Update on Antiphospholipid Syndrome in 2017, ten papers concluded that new information should be obtained mainly through randomised clinical trials and large series of patients recruited from multicenter registries [21,22]. In an attempt to confirm the hypothesis that OAPS cases are different from “classical” APS, we assessed the clinical features, laboratory data, treatment, foetal and maternal outcomes, as well as the long-term follow-up of 1000 women with pure OAPS.

2. Patients and methods

2.1. Patients

In order to collect as much information as possible about a heterogeneous entity such as the obstetric antiphospholipid syndrome (OAPS), a simple and accessible web register was set up where all experts could introduce their cases, allowing future knowledge on this disease. The website and database have been accessible ever since June 2010. Since then, patients have been included retrospectively and prospectively on the website www.euroaps.wordpress.com.

2.2. Study design

Thirty tertiary referral centres in twelve European countries and two centres in Argentina are participating in the registry. The members in charge of treating these patients are experts in the management of the APS. To date, the cohort has consisted of 1640 cases, 640 of which were excluded after a thorough revision and 1000 met the proposed Sydney classification criteria. Obstetrics, hematology, internal medicine, autoimmune diseases and rheumatology are the departments involved.

The database has been created with all those centers that shared information on the online register. A total amount of 150 items have been introduced, with variables such as “epidemiological data”, “previous pregnancies”, “current pregnancy”, “foetal status”, “puerperium”, “laboratory data” and “treatment schedule” among others, many of which were mandatory to advance in the next register steps. Participants have been encouraged to include both complete (pure OAPS) and incomplete cases. These incomplete cases (640 women) will be further analysed elsewhere. All introduced patients automatically received an encryption code to preserve privacy and personal data.

This registry has the approval and benefit of both the Ethics Committee and Review Board of Vall d'Hebron University Hospital and the University Departments of Medicine and Obstetrics of the Universitat Autònoma de Barcelona.

2.2.1. Inclusion clinical criteria

Women meeting the clinical criteria of the Sydney classification have been introduced in the registry, this is to say, patients with 3 or more consecutive first-trimester miscarriages, foetal losses >11 weeks or prematurity due to presence of placental vasculopathy (less than week 34). These women had not previously presented any major thrombotic event. All previous pregnancies have also been introduced, each one coded as an isolated episode. Subsequently, the current gestation has also been registered. All adverse obstetric events presented have been documented.

2.2.2. Inclusion laboratory criteria

Presence of a positive antiphospholipid antibody: lupus anticoagulant (LA), IgM anticardiolipin (IgM aCL) or IgG anticardiolipin (IgG aCL) and IgM anti-beta2-glycoprotein 1 (IgM anti-β2GPI) or IgG anti-beta2-glycoprotein 1 (IgG anti-β2GPI) is required in two or more blood tests, separated in time by more than twelve weeks. They were divided by laboratory categories as category I (more than one aPL being positive); Category II (only one aPL positivity); IIa: LA+, IIb: IgM aCL or IgG aCL or both positive, IIc: IgM anti-β2GPI or IgG anti-β2GPI or both positive.

2.2.3. Exclusion clinical criteria

Women not meeting the Sydney diagnostic criteria have been excluded, as, for instance, those with <3 consecutive miscarriages or those with establishment of placental pathology appearing beyond week 34. There may have been patients presenting another clinical presentation not included in the Sydney criteria, as long as they have showed other typical clinical criteria. However, patients who have had abortions due to a chromosomal, infectious, hormonal or anatomical cause have also been excluded, as well as those with active infection for HBV, HCV, HIV, syphilis or tuberculosis.

2.2.4. Exclusion laboratory criteria

Following the Sydney recommendations, those patients with medium or low aPL titers as well as those presenting atypical aPL such as antithrombin (aPT) or antiannexin A5 (a-A5) have been excluded.

2.2.5. Other laboratory-analysed parameters

Most of the centres also tested for inherited thrombophilia: protein S, antithrombin, protein C, resistance to activated C protein, homocysteine and gene polymorphisms of methylen-tetrahydropholate reductase (MTHFR), FV Leiden and FII G20210A mutations. Also, a complete panel of autoantibodies has been performed on most of the patients: antinuclear antibodies (ANAs), ds-antiDNA antibodies and antithyroid antibodies. Some patients have also been tested for antibodies to extractable nuclear antigens as Ro/La/RNP/Sm/Scl-70/centromere/Jo-1. Furthermore, almost all patients have been checked for C3 and C4 complement levels, serum protein electrophoresis, vitamin D2 levels or non-criteria aPL.

2.2.6. Miscellaneous

In order to correctly gauge the magnitude of obstetric complications, up to 25 different complications have been categorised: recurrent miscarriage, foetal loss, stillbirth, early-PE, late-PE, early-FGR, late-FGR, early-HELLP, late-HELLP, early-eclampsia, late-eclampsia, other ultrasonographic signs of placental vasculopathy (abnormal uterine blood flow, abnormal foetal placental flow, abruptio placentae, placental haematoma), arterial or venous thrombosis during pregnancy, chorioamnionitis, IVF failure, only one or two miscarriages, perinatal death, prematurity (live birth before 34 weeks), preterm birth (before 37 weeks) and maternal death.

Puerperium follow-up has also been introduced, highlighting the possible shift to an autoimmune disease or thromboembolic event. In addition, three different heparin prophylactic doses have been defined: low, medium and high prophylactic doses, together with therapeutic ones. According to the most common LMWH used (enoxaparin), the doses have been defined as low prophylactic at 20 mg/day, medium at 40 mg/day and high at 1 mg/kg/day. The doses of 1 mg/kg/bid have been labeled as therapeutic.

2.3. Assays

Standard screening assays were used to detect LA according to the Sydney recommendations of the ISTH Subcommittee, and aPL titers have been analysed by the ELISA methods. The results of aCL have been expressed as immunoglobulin G (GPL) or immunoglobulin M (MPL) using international references. The results of anti-β2GPI IgG/IgM assays were calculated arbitrary units using a standard curves obtained from a pool of positive samples accurately calibrates.

In accordance with the Sydney recommendations, all plasmas have been analysed for the four-solid-phase aPL antibody by methods based on calibration curves established by the Sydney standards. The cut-off values used for medium-high titers of aCL antibodies were 40 GPL and/or MPL and low titers between 15 and 39 and/or MPL, before February 2006. From February 2006 on, in accordance with the Sydney classification criteria, the cut-off values used for medium/high titers for both aCL and antiβ2GPI antibodies were calculated using either the Sydney standards or the 99th percentile obtained by testing age-matched healthy women. The aPL positivity had to have been present at least twice, with a minimum interval of 12 weeks. According to the experts' recommendations, investigators are strongly advised to classify APS patients, when studied, into different categories: I, more than one laboratory criteria present, for any combination; IIa, LA present alone; IIb, aCL antibody present alone; IIc, anti-β2glycoprotein-I antibody present alone.

2.4. Statistical analysis

Values are expressed as mean, standard deviation, median, 25th and 75th percentiles (Q1 and Q3, respectively), the sum and extreme values (minimum and maximum) for continuous variables, and number and percentages for qualitative variables. A student's *t*-test was used to compare values following normal distribution, while the Mann–Whitney–Wilcoxon's test or the Kruskal–Wallis test was used for data not following a normal distribution. The chi-square test and Fisher's exact test were used to compare categorical variables. The univariate logistic regression analysis was used to estimate the risks of analytical parameters in the presence of the studied morbidities. The statistical software SPSS (ver.22.0.0.0) was used to analyse the datasets (Clinical Research Unit, Althaia Healthcare University Network of Manresa and Barcelona).

3. Results

3.1. Patient baseline clinical characteristics

The patients' demographic data and their baseline characteristics are explained in Table 1. Overall, 5229 pregnancies of 1640 women were analysed. Only 1000 women with 3553 episodes fulfilled the Sydney Criteria, being included for definitive analysis. Most women were Caucasian (72.5%), non-smokers (84.8%) and with a normal body mass index. Interestingly, women's age of diagnosis (35.2 years) was in an interval age in which good fertility is still conserved. However, mean pregnancy failures were 2.19 for each patient. Regarding the widespread belief that obesity is a major risk factor in pregnancy, we have found only 8.6% obese patients in our registry. On the other hand, 76 women (7.6%) had systemic lupus erythematosus (SLE) and 93 (9.3%) clinical or subclinical autoimmune thyroid abnormalities. Concerning their previous obstetric morbidity, 27% women had RM, 17% foetal loss, 18.5% stillbirth, 4.9% early PE and 5.4% early FGR. According to inherited thrombophilic disorders, we have found 15.9% of patients

Table 1
Main demographic characteristics and obstetric background of these 1000 women.

Age (years) mean ± SD	35.20 ± 5.94
Ethnicity n (%)	
African	21 (2.1)
Afro American/Caribbean	6 (0.6)
American (Latino)	159 (15.9)
Asian	5 (0.5)
Caucasian	725 (72.5)
Semitic/Arab	81 (8.1)
Smoking habit n (%)	
Yes	152 (15.2)
No	848 (84.8)
B.M.I. mean ± SD	24.16 (4.68)
Cardiovascular risk factors n (%)	
Obesity	86 (8.6)
High Blood Pressure	48 (4.8)
Dyslipidaemia	22 (2.2)
Diabetes mellitus	18 (1.8)
Previous diseases n (%)	
SLE	76 (7.6)
Thyroid[a]	93 (9.3)
Kidney disease	33 (3.3)
Previous poor obstetric outcome n (%)	
Recurrent miscarriage < 10 weeks	270 (27)
Foetal loss	170 (17)
Stillbirth	185 (18.5)
Early PE (< 34 w)	49 (4.9)
Early FGR (< 34 w)	52 (5.2)
Early HELLP (< 34 w)	12 (1.2)
Total pregnancy failures mean ± SD	2.19 ± 1.59
Previous successful pregnancies mean ± SD	0.6 ± 0.85
Inherited thrombophilia n (%)	
No	841 (0.84)
Yes	159 (0.15)

BMI: Body mass index; SD: Standard deviation; SLE: Systemic lupus erythematosus; PE: Preeclampsia; FGR: Foetal growth restriction.
[a] Includes: hypothyroidism, subclinical hypothyroidism, and antithyroid antibodies.

carrying any of them. Regarding their current obstetric complications, 650 women (65%) had no pregnancy complications, being prematurity (20.7%), early PE (14.3%) and miscarriage (13.2%) the most prevalent ones. All results are depicted in Table 1.

3.2. Laboratory characteristics and obstetric-related morbidities

3.2.1. Laboratory categories and obstetric morbidities

Regarding laboratory categories, we obtained a higher prevalence of category II (708 cases) (70.8%) over category I (292 cases) (29.2%). Within category I, double positivity (184 cases) (18.4%) showed a higher prevalence over triple positivity (110 cases) (11%). Attending to category II we have found that category IIa (single LA positivity) was significantly the most prevalent with 356 cases (50.42% of category II and 35.6% of all cases). The other categories: IIb (single aCL positivity) and IIc (single anti-β2GPI positivity) had 224 (22.4%) and 126 (12.6%) cases, respectively. We can find results deployed in Table 2. Referring to the obstetric-related morbidities, we have found that 651 patients (65.1%) presented no obstetric complications in their current pregnancy. Going on with the current pregnancy complications (latest pregnancy), we can see how prematurity was the most frequent appearing alone in 241 cases (24.1%) or in combination with PE in 128 cases (12.8%) or FGR in 107 cases (10.7%). Full combination (prematurity with PE and FGR) was found in 55 cases (5.5%). We have observed that category I and IIa presented similar percentages in the prematurity obstetric-related complications. Regarding miscarriages, the main laboratory categories were IIa and IIb with 44 and 39 cases each, respectively. In case of foetal loss and stillbirth, we also found similar results in category I and IIa. Otherwise, according to all obstetric complications (all historical pregnancies), we stated that miscarriages, foetal losses and stillbirths were significantly the most prevalent obstetric complications. At this point we found 386 (38.6%) miscarriages, 253 (25.3%) foetal losses and 230 (23%) stillbirths, with similar laboratory category percentages. All data is detailed in Tables 3 and 4.

3.2.2. Associated inherited clot pathway disorders

We have found that inherited thrombophilia was positive in 159 (15.9%) women excluding those who tested positive for heterozygosis C677-MTHFR. Most of those women had activated C-protein resistance/Leyden factor V mutation 44/159 (27.67%), C677-MTHFR mutation in homozygosis 31/159 (19.49%) and protein C deficiency 28/159 (17.61%). In all, 22 women (13.83%) had protein S deficiency, 13 (8.17%) antithrombin III deficiency, 12 (7.54%) prothrombin G20210a mutation, 5 (3.14%) hyperhomocysteinemia, and 4 (2.51%) factor XII deficiency.

3.2.3. Associated connective tissue autoantibodies

ANAs were positive in 295 patients (29.5%), 128 of them had speckled pattern, 106 were homogeneous, 38 nucleolar, 10 centromere, 9 rim and 3 diffuse. Anti-dsDNA was positive in 35 of those patients. Interestingly, the most prevalent extractable nuclear antigens (ENAs) were anti-Ro52 antibody in 42 cases (combined with anti-Ro60 in 30 cases). Anti-Sm was found in 38 cases and RNP in 28 cases.

3.2.4. Other laboratory data

Plasma complement levels were analysed in 850/1000 (85%) cases. Of these, 167/850 (19.64%) had low C3 levels and 148/850 (17.41%) had low C4 levels. Furthermore, 97 women had both C3 and C4 low levels (11.41%). Overall, 218/850 (25.64%) women had low values. Vitamin D2 deficiency was found (< 20 ng/mL) in 279 (27.9%) women.

3.3. Histopathological findings

We have observed that placental biopsy is not a routine way in clinical practice, since those results appear in only 159/1000 cases (15.9%). We would like to highlight that infarcts or thrombus presence was found in 68 (42.76%) and 30 cases (18.86%), respectively, and in contrast, inflammatory findings as fibrin or villitis were found in 37 (29.83%) and 28 (17.61%) cases, respectively. All results are depicted in Table 8.

3.4. Foetal-maternal outcomes

The main outcome studied was the foetal live-birth. Regardless the type of administered treatment, live-birth was achieved in 728/1000 cases (72.8%), while in 272/1000 cases (27.2%) was not. We have observed a lower incidence of maternal thrombosis in all women studied with 25 venous and 6 arterial thromboses, respectively, being puerperal thrombosis the most frequent manifestation. We also encountered an evolution to SLE in 54 (5.4%) cases. All data is summarised in Table 5.

3.5. Treatment schedules related to obstetric complications and maternal-foetal outcomes

We have divided the successful (live-birth patients) and unsuccessful (no live-birth patients) according to whether they were under treatment or not. In brief, successful cases were treated in 614/728 (84.54%) and 114/728 (15.65%) were not. In addition, those treated successfully were under recommended regime (on preconcepcional AAS and LMWH prophylactic dose from the first trimester) in 381/614 (62.05%). Unsuccessful cases were under treatment in 156/272 (57.35%) and 116/272 (42.64%) were not. In closer detail, we found an *in crescendo* number of live births among patients with no treatment

Table 2
Laboratory categories of the Registry of women with OAPS.

Lab category	Class and isotype of aPL	N	n/N(%)
I		294	29.4%
	Triple positivity	110/294/1000 (37.41)	(11)
	LA + aCL IgG + IgM + anti-β2GPI-IgG + IgM +	21	
	LA + aCL IgG + IgM + anti-β2GPI-IgG + IgM–	2	
	LA + aCL IgG + IgM + anti-β2GPI-IgG – IgM +	4	
	LA + aCL IgG + IgM – anti-β2GPI-IgG + IgM +	5	
	LA + aCL IgG – IgM + anti-β2GPI-IgG + IgM +	1	
	LA + aCL IgG – IgM + anti-β2GPI-IgG – IgM +	21	
	LA + aCL IgG + IgM – anti-β2GPI-IgG + IgM–	51	
	LA + aCL IgG – IgM + anti-β2GPI-IgG + IgM–	5	
	Double positivity	184/294/1000 (62.58)	(18.4)
	LA + aCL IgG + IgM +	14	
	LA + aCL IgG + IgM–	48	
	LA + aCL IgG – IgM +	32	
	LA + anti-β2GPI-IgG + IgM +	2	
	LA + anti-β2GPI-IgG + IgM–	24	
	LA + anti-β2GPI-IgG – IgM +	11	
	aCL IgG + IgM + anti-β2GPI-IgG + IgM +	4	
	aCL IgG + IgM + anti-β2GPI-IgG + IgM–	2	
	aCL IgG + IgM + anti-β2GPI-IgG – IgM +	2	
	aCL IgG – IgM + anti-β2GPI-IgG + IgM +	2	
	aCL IgG + IgM – anti-β2GPI-IgG + IgM–	24	
	aCL IgG + IgM – anti-β2GPI-IgG – IgM +	5	
	aCL IgG – IgM + anti-β2GPI-IgG – IgM +	13	
	aCL IgG – IgM + anti-β2GPI-IgG + IgM–	1	
Lab Category	Class and isotype of aPL	N	N (%)
II		706	70.6%
IIa	Lupus Anticoagulant	356/706/1000 (50.42)	(35.6)
IIb	Anticardiolipin antibodies	224/706/1000 (31.72)	(22.4)
	IgG Isotype	116	
	IgM Isotype	75	
	IgG/IgM	33	
IIb	Anti-β2GPI antibodies	126/706/1000 (17.84)	(12.6)
	IgG Isotype	63	
	IgM Isotype	45	
	IgG/IgM	18	

N: number of cases; OAPS: obstetric antiphospholipid syndrome.

(114 live births), non-standard treatment regime (233 live births), and standard treatment regime (381 live births). In the same way, we obtained similar progression regarding newborn weight (2203 g in untreated patients, 2431 g in non-standard treated patients and 2907 g in standard-treated patients). According to the weeks of delivery, the higher prevalence of prematurity appeared in untreated patients with 59.6% of the cases in the whole group. There were more frequent births after 24 weeks in patients with a recommended regime (86.8%) than in patients with a non-standard treatment (77.6%) and untreated patients (62.6%). On the other hand, if we study obstetric complications, the

Table 3
Detailed current[a] obstetric complications in this OAPS series (N = 1000). A general view and related to laboratory categories.

	All	Cat. I	Cat. IIa	Cat. IIb	Cat. IIc	*p*-Value
	N = 1000	n = 294	n = 356	n = 224	n = 126	
Complications	651 (65.1)	207 (70.4)	230 (64.6)	135 (60.3)	79 (62.7)	0.098
Prematurity	241 (24.1)	79 (26.9)	92 (25.8)	40 (17.9)	30 (23.8)	0.086
Miscarriage (latest)	118 (11.8)	23 (7.8)	44 (12.4)	39 (17.4)	12 (9.5)	0.007
Foetal loss	84 (8.4)	31 (10.5)	24 (6.7)	15 (6.7)	14 (11.1)	0.166
Stillbirth	56 (5.6)	22 (7.5)	26 (7.3)	4 (1.8)	4 (3.2)	0.009
PE (< 34 w)	143 (14.3)	46 (15.6)	59 (16.6)	23 (10.3)	15 (11.9)	0.139
PE (> 34 w)	36 (3.6)	14 (4.8)	14 (3.9)	6 (2.7)	2 (1.6)	0.349
FGR (< 34 w)	116 (11.6)	41 (13.9)	45 (12.6)	13 (5.8)	17 (13.5)	0.021
FGR (> 34 w)	39 (3.9)	14 (4.8)	12 (3.4)	11 (4.9)	2 (1.6)	0.353
HELLP (< 34 w)	27 (2.7)	7 (2.4)	17 (4.8)	1 (0.4)	2 (1.6)	0.013
HELLP (> 34 w)	2 (0.2)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.8)	0.283
Prematurity + PE	128 (12.8)	36 (12.2)	54 (15.2)	22 (9.8)	16 (12.7)	0.302
Prematurity + FGR	107 (10.7)	34 (11.6)	43 (12.1)	14 (6.3)	16 (12.7)	0.107
Prematurity + PE + FGR	55 (5.5)	15 (5.1)	23 (6.5)	7 (3.1)	10 (7.9)	0.204
Abnormal uterine blood flow	78 (7.8)	21 (7.1)	26 (7.3)	21 (9.4)	10 (7.9)	0.783
Abnormal fetoplacentary flow	17 (1.7)	5 (1.7)	7 (2.0)	3 (1.3)	2 (1.6)	0.985
Placental haematoma	13 (1.3)	3 (1.0)	5 (1.4)	0 (0)	5 (4.0)	0.015
Abruptio placentae	10 (1.0)	1 (0.3)	4 (1.1)	2 (0.9)	3 (2.4)	0.254

OAPS: Obstetric Antiphospholipid Syndrome; Prematurity: Born alive < 34 weeks; FGR: Foetal Growth Restriction; PE: Pre- eclampsia; Cat: Laboratory category.
[a] Latest pregnancy.

Table 4
Detailed all obstetric complications in this OAPS series (N = 1000). A general view and related to laboratory categories.

	All	Cat. I	Cat. IIa	Cat. IIb	Cat. IIc	*p*-Value
	N = 1000	n = 294	n = 356	n = 224	n = 126	
Prematurity	285 (28.5)	89 (30.3)	112 (31.5)	47 (21.0)	37 (29.4)	0.041
Miscarriage × 3	386 (38.6)	102 (34.7)	136 (38.2)	105 (46.9)	43 (34.1)	0.024
Foetal loss	253 (25.3)	84 (28.6)	79 (22.2)	57 (25.4)	33 (26.2)	0.315
Stillbirth	230 (23.0)	65 (22.1)	87 (24.4)	49 (21.9)	29 (23.0)	0.871
PE (<34 w)	181 (18.1)	59 (20.1)	74 (20.8)	26 (11.6)	22 (17.5)	0.031
PE (>34 w)	46 (4.6)	16 (5.4)	16 (4.5)	8 (3.6)	6 (4.8)	0.794
FGR (<34 w)	161 (16.1)	50 (17.0)	61 (17.1)	22 (9.8)	28 (22.2)	0.015
FGR (>34 w)	47 (4.7)	15 (5.1)	15 (4.2)	14 (6.3)	3 (2.4)	0.390
HELLP (<34 w)	35 (3.5)	8 (2.7)	19 (5.3)	6 (2.7)	2 (1.6)	0.109
HELLP (>34 w)	3 (0.3)	2 (0.7)	0 (0.0)	0 (0.0)	1 (0.8)	0.172
Prematurity + PE	160 (16.0)	47 (16.0)	70 (19.7)	23 (10.3)	20 (15.9)	0.029
Prematurity + FGR	139 (13.9)	40 (13.6)	55 (15.4)	21 (9.4)	23 (18.3)	0.087
Prematurity + PE + FGR	69 (6.9)	18 (6.1)	31 (8.7)	8 (3.6)	12 (9.5)	0.063
Ecographic signs of placental insufficiency (<34 w)	77 (7.7)	24 (8.2)	25 (7.0)	21 (9.4)	7 (5.6)	0.569
Ecographic signs of placental insufficiency (>34 w)	25 (2.5)	6 (2.0)	10 (2.8)	5 (2.2)	4 (3.2)	0.886
Placental haematoma	13 (1.3)	3 (1.0)	5 (1.4)	0 (0.0)	5 (4.0)	0.013
Abruptio placentae	10 (1.0)	1 (0.3)	4 (1.1)	2 (0.9)	3 (2.4)	0.256

Cat: laboratory aPL category; Prematurity: Born alive <34 weeks; FGR: Foetal Growth Restriction; PE: Pre-eclampsia.

Table 5
Foetal and maternal outcomes related to this cohort of women.

	n/N (%)
Live births	728/1000 (72.8)
No live births	272/1000 (27.2)
Maternal outcomes	
Pregnancy thrombosis	
Venous	6/1000 (0.6)
Arterial	0/1000 (0)
Puerperal thrombosis	
Venous	19/1000 (1.9)
Arterial	6/1000 (0.6)
Evolvement into systemic diseases	
SLE	54/1000 (5.4)
ITP	10/1000 (1.0)

PE: Preeclampsia; FGR: Foetal growth restriction; SLE: Systemic lupus erythematosus; ITP: idiopathic thrombocytopenic purpura.

Table 6
Treatment regimes in this cohort of women.

	Cases
	n/N/N (%)
No treatment	230/1000 (23)
Treatment	770/1000 (77)
LDA alone	97/770 (12.59)
LDA alone preconceptional	46/97/770 (47.42) (5.97)
LMWH alone	39/770 (5.06)
LDA + LMWH	/770/1000 (82.33) (63.4)
Recommended schedule	448/770/1000 (58.18) (44.8)
Other drugs	
Progesterone during first trimester	/770/1000 (18.18) (14)
Hydroxychloroquine	93/770/1000 (12.07) (9.3)
Prednisone	70/770/1000 (9.09) (7)
IVIGs	11/770/1000 (1.42) (1.1)
Anti-TNF	3/770/1000 (0.38) (0.30)

LDA: Low-dose aspirin; LMWH: Low molecular weight heparin; IVIGs: intravenous immunoglobulin; Recommended schedule: LDA preconceptional + LMWH started preconceptional or in first trimester.

correlation is clearly opposed. Untreated patients presented a higher prevalence of early PE (41.2%) and FGR (27.2%) than correctly treated patients (6.6% and 4.2% of PE and FGR, respectively). Moreover, there were more miscarriages (22.6%), foetal losses (14.8%) and stillbirths (14.2%) in untreated patients than in patients with a recommended regime (9.2% miscarriages, 4% foetal losses and 1.8% stillbirths). All data is detailed in Tables 6 and 7.

Table 7
Detailed current[a] obstetric complications in this OAPS series (N = 1000) according to treatment compliance.

	Treatment and Recommended regime	Treatment but no Recommended regime	No Treatment	*p*-Value
	n = 448	n = 322	n = 230	
Miscarriage (latest)	41 (9.2)	39 (12.1)	52 (22.6)	<0.001
Foetal loss	18 (4.0)	32 (9.9)	34 (14.8)	<0.001
Stillbirth	8 (1.8)	15 (4.7)	33 (14.3)	<0.001
Weeks at delivery				
0–10	41 (9.8)	41 (12.7)	59 (25.7)	<0.001
11–23	18 (4.0)	31 (9.6)	27 (11.7)	
≥24	389 (86.8)	250 (77.6)	144 (62.6)	
Live birth	381 (85.0)	233 (72.4)	114 (49.6)	<0.001
Live birth (yes)	n = 381	n = 233	n = 114	
Preterm	103 (27.0)	121 (51.9)	75 (65.8)	<0.001
Prematurity	67 (17.6)	99 (42.5)	68 (59.6)	<0.001
PE (<34 w)	25 (6.6)	57 (24.5)	47 (41.2)	<0.001
PE (>34 w)	18 (4.7)	10 (4.3)	8 (7.0)	0.524
FGR (<34 w)	16 (4.2)	50 (21.5)	31 (27.2)	<0.001
FGR (>34 w)	25 (6.6)	10 (4.3)	4 (3.5)	0.304
HELLP (<34 w)	6 (1.6)	10 (4.3)	7 (6.1)	0.020
HELLP (>34 w)	0 (0.0)	1 (0.4)	1 (0.9)	0.229
New-borns[b]	n = 392	n = 239	n = 117	
Weight of new-born (g)[c]	2907	2431	2203	<0.001

Prematurity: Born alive less or equal than 34 weeks; FGR: Foetal Growth Restriction; PE: Pre-eclampsia.
[a] Latest pregnancy.
[b] There are more new-borns than live births due to gemelar pregnancies.
[c] In grams.

4. Discussion

Prior to this publication, we only found case series with <300 reported OAPS cases [23–25]. In our 1.000-patient analysis, 72.5% were

Table 8
Placental histopathological findings n/N/N (%).

Placental biopsy	159/1000 (15.9)
Normal	35/159 (22.01)
Pathological	124/159 (77.98)
Infarcts	68/124/159 (54.83) (42.76)
Fibrin	37/124/159 (29.83) (23.27)
Thrombus	30/124/159 (24.19) (18.86)
Villitis	28/124/159 (22.58) (17.61)
Choriangiosis	15/124/159 (12.09) (9.43)
Calcifications	11/124/159 (8.87) (6.91)

Caucasian, non-smokers (84.8%) and middle-aged (35.2 years). There was no high rate of comorbidities, being thyroid disease and SLE the most prevalent. Certainly, in patients carrying aPL it is possible to stay in a grey zone with other autoimmune diseases [26]. Thus, a genetic predisposition [27] and a trigger that may damage endothelial surface [28] with aPL generation could explain its heterogeneous presentation. Furthermore, we have observed that there were a few cases that presented other clinical manifestations, such as migraine (34 cases) and high blood pressure (48 cases), reinforcing the theory of endothelial damage [29]. All of our patients have been referred from specialized units in different countries throughout Europe. This explains why a high percentage of patients had already been treated (77%), thus obtaining a fair number of patients under the recommended regime (preconceptional LDA and prophylactic dose of LMWH from the first trimester on in 44.8% of cases). We found 15.17% of refractory cases among patients treated under recommended regime, similar to the data published by Ruffatti et al. in their recent review [23]. We would like to highlight that in the last 10 years (the time lapse of this ongoing register); hydroxychloroquine has arrived as a promising new therapy for refractory OAPS [30]. Case-tailored management was found probably because patients with less thrombotic events observed came from these specialized centers. We only found 31 cases (3.1%) in which thrombotic phenomena occurred, in contrast to what was published by Drozidnsky et al., where the thrombosis rate reached 12% [31]. In any case and contrary to what was classically thought, it seems that venous and/or arterial thromboses are not frequent complications among the OAPS patients. In fact, opinion leaders in antiphospholipid antibodies are convinced that most cases will have only obstetric complications with none or few thrombotic events [21], showing a huge difference from primary APS and its thrombosis recurrence [32]. As we can find in our series, placental histology reveals <24.19% of cases with documented thrombosis, which correlates with the previous studies from Out et al. [4]. Furthermore, we can see how neutrophils lead patients into a pro-inflammatory state. In a mouse model of SLE patients, this excessive amount of neutrophil extracellular traps (NET) infiltrate the placenta, leading to vascular damage in patients with SLE [33]. Thus, the data on the registry support the definition that the obstetric antiphospholipid syndrome refers to women with only obstetric aPL-related complaints and no history of past or current thrombotic events at the time of diagnosis [34].

Regarding the most prevalent clinical manifestations, there are different percentages published in the literature. Recurrent miscarriage before 10 weeks is considered the most prevalent obstetric complication (38.6%) in our registry, followed by foetal loss (25.3%) and stillbirth (23%). In fact, there is an average of 2.2 non-evolutive pregnancies per patient with an SD of 1.6 in our study cohort. Analysing current pregnancies, we observed that premature births (20.6%) due to PE and FGR or both are more prevalent that in the previous poor outcomes. This is partly because there is a higher rate of treatment in current pregnancies, observing a delay in the clinical appearance.

With regard to the miscarriages, we suggest a more accurate definition; to our knowledge, miscarriage could be classified as early miscarriage (or embryonic loss) when it occurs before 10 gestational weeks and fetal loss when it occurs after 10 gestational weeks [35]. It has also been suggested that pre-embryonic and embryonic losses could be early markers of embryo aPL-related injury. However, and attending to the Sapporo and Sydney criteria, the only morphologically well-formed embryo inclusion minimises the probability of chromosomal abnormalities. Ectopic, molar, and biochemical pregnancies were not included [36]. We have found that it is the most prevalent clinical manifestation in our population, in both previous and historical episodes. This is in line with what was published by other authors, in which women with aPL could have a higher rate of early pregnancy loss [37]. Reviewing the different associations according to the laboratory categories, we have a homogeneous distribution and we have observed a strong association between category I and category IIa, with recurrent miscarriages and foetal losses respectively. Interestingly, examining poor obstetric outcomes, there is a significant increase of recurrent miscarriages in the presence of category IIb. Moreover, other studies yielded similar results [38], in spite of both different inclusion criteria and positive laboratory aPL results. Otherwise, when we focus on the manifestations related to placental insufficiency, we observed a strong association between different laboratory categories and PE (around 15–20% with categories I and IIa, and 10–15% with categories IIb and IIc). Also, the correlation is clear in the case of FGR, where 14–20% of the association is with category I, IIa and IIc and a minor association with category IIb (6–10%). This placental dysfunction may also reflect excessive inflammation driven by the activation of complement with the consequent endothelial injury [39], and also by aPL signaling Toll-like receptors 4 (TLR4) on extravillous trophoblast, increasing the secretion of pro-inflammatory cytokines [40]. As we have seen in our registry, several positivity for aPL revealed a strong association with PE in another publication [41]. Moreover, prospective and retrospective studies have observed that the persistent presence of high aPL titer is associated with preterm deliveries and FGR [42].

All laboratory categories are represented in the OAPS registry. Classically, triple and double positivity are related to poor obstetric manifestations, whereas a single positivity is poorly related to them [43]. On the contrary, in our registry we found a strong association between all laboratory categories and obstetric complications regardless the degree of positivity. We found that category I was linked to RM in 34.7% cases, prematurity in 30.3%, foetal loss in 28.6% and stillbirth in 22.1%. According to our registry, we can state that category IIa (the most prevailing in our registry) shows a robust association with RM in 38.2% of cases, prematurity 31.5%, stillbirth 24.4% and foetal loss 22.2%. Among the other categories, despite the smaller number of cases, a high frequency of obstetric complications were also showed (i.e., category IIb had a high rate of RM of 46.9%, while category IIc had the highest rate of early FGR with 22.2% of the affected cases). Nevertheless, some authors argue that there is no clear association with aCL antibodies [44]. In a similar way, Andreoli et al. said that not all the patients carrying anti-β2GPI develop aPL-related clinical events [45], although this might be linked to the fact that several epitopes of β2GPI can be targeted by specific aPL [46]. Nevertheless, the debate on this topic is ongoing [47] and we will probably be in need of massive registries to evaluate one by one the different aPL with their kinetics and clinical implications. At this point, we should add that in usual clinical practice many aPL analyses are done with concurrent treatments. Therefore, it is necessary to standardise assays in order to avoid overdiagnosis, especially in the era of direct anticoagulants [48].

Interestingly, 15.9% of cases had an inherited trombophilic disorder (ITD). Similar results exist in another aPL Caucasian series [49]. Currently, there is a controversy within ITD and OAPS patients. As previously mentioned [15], we have not found any association between these entities and a high rate of thrombosis. In concurrence with our results, Berman el al. [49] did not find an increased risk of developing thrombotic phenomena in these patients either. In contrast, other authors as Diz-Kucukkaya et al. [50] found that the presence of the Leyden Factor V mutation may define a small group of patients who had a high risk of thrombosis. Conversely, over the past few years, a theory

has appeared that shows a link between circulating microparticles (MPs) and thrombosis, especially in APS and inherited trombophilia cases [51]. In this line, there are two studies [52,53] that establish this relationship in both primary and obstetric APS. None of these studies found differences in the number of MPs types in either entity.

Our study has also examined the role played by the complement pathway in the pathogenesis of OAPS. Several authors have demonstrated this relationship, reinforcing the theory that complement activation (that induces a pro inflammatory state) predicts adverse pregnancy outcomes [54,55]. However, in the EUROAPS registry we only found 14–16% of patients with low complement values (less than expected), possibly due to the lack of information in some patients. In the same line, we have observed a high frequency of vitamin D deficit (21.4% of patients), suggesting an involvement in the OAPS generation [56,57].

To conclude, we would like to highlight the good results achieved in the comparative between different treatment schedules (Table 7). Actually, despite the fact that many authors recommend the combination of preconceptional LDA and a prophylactic dose of LMWH from the first trimester on [58,59], other recent publications pose that there still exist many controversies which prevent their use from being standardised [60]. Nonetheless, we can say that the high rate of good foetal maternal outcomes and the fewer obstetric complications observed in the treated group requires clinicians to think about a standardised schedule for all OAPS patients.

5. Conclusion

Recurrent first trimester miscarriage followed by prematurity and foetal loss were the most common obstetric morbidities in this cohort. All laboratory categories and isotypes are represented in our registry, obtaining a strong correlation between all of them and obstetric complications. A high rate of histopathological findings did not contain thrombosis, highlighting antiphospholipid obstetric syndrome as a mixed inflammatory and thrombotic entity. Maternal and foetal outcomes were excellent when the recommended therapy was used.

EUROAPS project is the biggest published European registry on obstetric antiphospholipid syndrome and it is ongoing. We consider that collaboration between specialized centers, sharing information and discussing the established diagnostic criteria could improve the medical prognosis of OAPS patients.

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Conflict of interests

The authors declare that there is no conflict of interests.

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IRB approval

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