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Comparative study of obstetric antiphospholipid syndrome (OAPS) and non-criteria obstetric APS (NC-OAPS): report of 1640 cases from the EUROAPS registry

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Abstract

Objectives. To compare clinical features, laboratory data and fetal-maternal outcomes between 1000 women with obstetric APS (OAPS) and 640 with aPL-related obstetric complications not fulfilling Sydney criteria (non-criteria OAPS, NC-OAPS).

Methods. This was a retrospective and prospective multicentre study from the European Registry on Obstetric Antiphospholipid Syndrome.

Results. A total of 1650 women with 5251 episodes, 3601 of which were historical and 1650 latest episodes, were included. Altogether, 1000 cases (OAPS group) fulfilled the Sydney classification criteria and 650 (NC-OAPS group) did not. Ten NC-OAPS cases were excluded for presenting thrombosis during follow-up. All cases were classified as

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category I (triple positivity or double positivity for aPL) or category II (simple positivity). Overall, aPL laboratory categories showed significant differences: 29.20% in OAPS *vs* 17.96% in NC-OAPS ($P < 0.0001$) for category I, and 70.8% in OAPS *vs* 82% in NC-OAPS ($P < 0.0001$) for category II. Significant differences were observed when current obstetric complications were compared ($P < 0.001$). However, major differences between groups were not observed in treatment rates, livebirths and thrombotic complications. In the NC-OAPS group, 176/640 (27.5%) did not fulfil Sydney clinical criteria (subgroup A), 175/640 (27.34%) had a low titre and/or non-persistent aPL positivity but did meet the clinical criteria (subgroup B) and 289/640 (45.15%) had a high aPL titre but did not fulfil Sydney clinical criteria (subgroup C).

Conclusion. Significant clinical and laboratory differences were found between groups. Fetal-maternal outcomes were similar in both groups when treated. These results suggest that we could improve our clinical practice with better understanding of NC-OAPS patients.

Key words: antiphospholipid syndrome, antiphospholipid, antiphospholipid antibodies, non-criteria antiphospholipid syndrome, obstetric antiphospholipid syndrome, treatment, outcomes

Rheumatology key messages

- Obstetric APS is the most frequent treatable autoimmune disease during pregnancy.
- Clinical and laboratory differences between obstetric APS and non-criteria obstetric APS exist, but they have similar fetal-maternal outcomes when treated.
- Non-criteria obstetric APS should be considered as a treatable cause of poor aPL-related obstetric outcomes.

Introduction

Women with APS, an autoimmune systemic disorder related to aPL, are at risk of presenting pregnancy morbidity and/or vascular thrombosis [1]. According to the Sydney classification criteria, pregnancy morbidity includes at least three consecutive miscarriages before 10 weeks of gestation, one or more fetal losses at $\geqslant$10 gestational weeks, stillbirth, and early and severe preeclampsia (PE) or prematurity due to placental insufficiency [2]. Furthermore, laboratory criteria for APS include moderate and/or high IgG or IgM aCL titres (>40 GPL or MPL) and/or >40 arbitrary units (AU) of IgG or IgM anti-β2glycoprotein-1 (aβ2GP1) antibodies. Persistent aPL positivity is defined as two or more consecutive readings at least 12 weeks apart [2]. These criteria define the obstetric APS (OAPS) [3]; however, many patients fail to meet them completely [4]. These cases with incomplete clinical or laboratory data according to the Sydney recommendations could be classified as non-criteria OAPS (NC-OAPS) (Fig. 1) [5], and controversy exists regarding their inclusion within the spectrum of APS in both thrombotic [6] and obstetric forms [7]. Moreover, cases exist in which clinical criteria are fulfilled but fail to reach the laboratory values defining APS or OAPS [8]. Furthermore, cases also exist with low aCL and/or aβ2GP1 titres, intermittent positivity for LA or other non-criteria aPL, e.g. aPS-PT, antiphosphatidylethanolamine or anti-annexin V IgG, IgM or IgA isotypes [9].

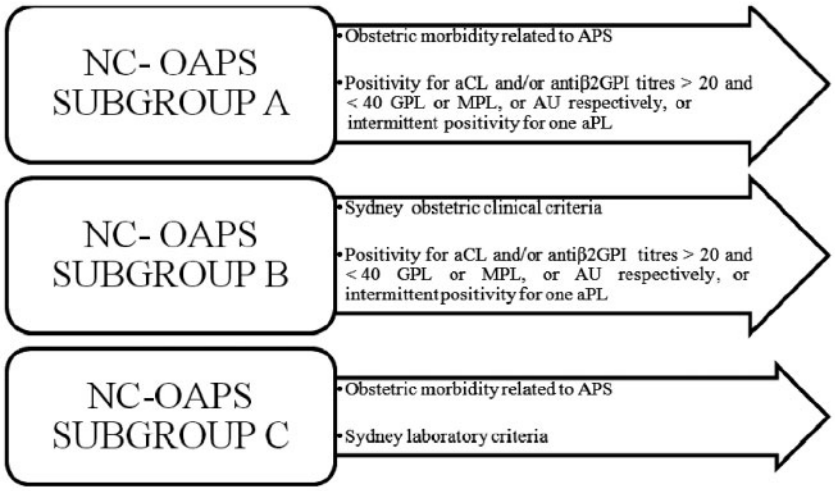
Moreover, evidence shows that cases with persistently negative, classic aPL and clinical complications related to aPL really do exist. Similarly, some of these cases can test positive for non-classic aPL and are known as seronegative APS [10]. Thus, concern arises in clinical practice as to how to classify these women, and what treatment to apply [11]. The fact that classification criteria for OAPS do not include variations in autoantibody profile and titres in different situations, e.g. patients on heparin treatment or who are pregnant, has encouraged some authors to request that the OAPS criteria be redefined [12]. Furthermore, false-positive serology for TORCH [Toxoplasmosis, Other (syphilis, varicella-zoster, parvovirus B19), Rubella, CMV and Herpes] infections has been related to the presence of aPL [13]; in some cases, laboratory techniques were not correctly carried out, yielding false-negative results [14]. However, clinical observations and cohort studies of women with pregnancy morbidity suggested that not considering clinical and/or serological subsets may result in under-diagnosis; consequently, these women might not benefit from the recommended treatment and have poor fetal-maternal outcomes [15]. Thus, within the framework of the European Registry on Obstetric Antiphospholipid Antibody Syndrome project, we collected both OAPS and NC-OAPS in a multicentre registry to analyse their clinical characteristics and follow-up. Herein, we present the results of the comparison between the OAPS (1000 cases) and NC-OAPS (640 cases) groups regarding obstetric morbidity, fetal-maternal outcomes, laboratory results, treatment regimens and live birth rates.

Methods

Patients

Within the European Registry on Obstetric Antiphospholipid Antibody Syndrome project, and with the collaboration of 30 hospitals across Europe, an online registry was created and homogenized to include patients fulfilling the full-blown Sydney classification criteria and those who did so incompletely. Since June 2010, the ad-hoc website and database have been accessible and ongoing (www.euroaps.wordpress.org). On this website or in direct communication with the database administrator, physicians can send or enter patient data to

Fig. 1 Different non-criteria obstetric APS subgroups



NC: non-criteria; OAPS: obstetric antiphospholipid syndrome

facilitate understanding of confusing data associated with aPL-related obstetric syndromes.

Study design

Thirty tertiary referral centres at universities in 10 European countries participate in the Registry. The cohort has 1640 cases: 1000 met the proposed Sydney classification criteria for OAPS and 640 did not (NC-OAPS). Patients were diagnosed and treated at specialized units. Data were obtained from a standardized form containing 150 items registered in the database. All recruited cases and participating hospitals received a numeric code to ensure privacy and personal data protection. In all prospective cases informed patient consent was obtained. The Review Board and Ethics Committee of the Vall d'Hebron University Hospital and the Boards of the University Departments of Medicine and Obstetrics of the Universitat Autònoma of Barcelona approved this centralized Registry.

Clinical inclusion criteria

(i) Women with aPL-related pregnancy morbidity: (a) OAPS group: women fulfilling Sydney classification criteria [2]; and (b) NC-OAPS group: women suffering obstetric complications related to aPL but not fulfilling the full-blown Sydney classification criteria: one or two consecutive miscarriages at $<$10 weeks of pregnancy, late placental vasculopathy (late-onset PE after 34 weeks, late intrauterine growth restriction after 34 weeks) or preterm births ($>$34 to $<$37 weeks of pregnancy) with no other apparent cause. In addition, placental haematoma, abruptio placentae, puerperal PE and recurrent implantation failure were also included.

(ii) No previous documented thrombotic events. Each patient may have had one or more pregnancy episodes.

Laboratory inclusion criteria

Women with LA positivity and/or aCL, IgG and IgM isotypes and/or aβ2GP1 IgG and IgM isotypes tested positive at least twice on two or more consecutive occasions at least 12 weeks apart were included. In the OAPS cases, titres $>$40 GPL/MPL ($\geqslant$99th centile) and/or $>$40 AU, respectively, are needed. In NC-OAPS cases, low titres 20–39 GPL/MPL or 20–39 AU, respectively (95th–99th centiles), and those with medium-high aPL titres or LA present but not persistently positive are required. We also defined three NC-OAPS subsets: women who fulfilled Sydney laboratory criteria, but not clinical criteria(subgroup A); women with clinical criteria with medium/low aPL titres (tested twice) (subgroup B); and women with no typical clinical criteria and medium/low aPL titres (tested twice) (subgroup C).

Standard laboratory categories according to Sydney recommendations were used and classified for both OAPS and NC-OAPS cases as follows: category I (more than one aPL positivity); category II (only one aPL positivity); IIa: LA positive; IIb: aCL IgG, IgM or both isotypes positive; IIc: aβ2GP1 IgG, IgM or both isotypes positive.

Clinical exclusion criteria

Women with pregnancy losses explained by infectious, metabolic, anatomic or hormonal factors, or maternal and paternal chromosomal causes were excluded. Women with a history of HBV, HCV or HIV active infection were also excluded, as were those with a history of previous thrombosis (its presence defines primary APS).

In the NC-OAPS group, patients with a thrombotic event during pregnancy or follow-up were also excluded (its presence defines primary APS).

Laboratory exclusion criteria

Patients with only one positivity of aPL (not tested twice) or presence of atypical aPL alone, such as aPT, aPS-PT, anti-phosphatidylethanolamine, anti-annexin V, anti-protein C or aPS, with either IgG or IgM isotype positivity, were also excluded.

Other laboratory parameters analysed

Other laboratory items included and analysed in this registry were serum protein electrophoresis, C3 and C4 complement levels, ANAs, anti-dsDNA and antithyroid antibodies. Some women were also analysed for antibodies to extractable nuclear antigens and for inherited thrombophilia.

Miscellaneous

Three different heparin prophylactic doses were defined: low, medium and high, together with therapeutic doses. Since almost all women treated with low molecular weight heparin (LMWH) were put on enoxaparin, prophylactic doses were defined as low: 20 mg/day (2000 U/day); medium: 40 mg/day (4000 U/day); and high: 1 mg/kg/day (100 U/kg/day). Therapeutic doses constituted the administration of 1 mg/kg bid (100 U/kg bid).

Assays

aPL

Screening assays were used to detect LA according to the Sydney recommendations of the International Society on Thrombosis and Haemostasis Subcommittee. Plasma aCL-IgG/IgM and aβ2GP1 IgG/IgM antibody titres were usually determined by commercial ELISA methods. In several cases, an in-house ELISA was used. The results of aCL were expressed as immunoglobulin GPL or immunoglobulin MPL using international reference material. The results of aβ2GP1 IgG/IgM assays were calculated as AU using standard curves obtained from a pool of positive accurately calibrated samples.

All plasmas were analysed for the four-solid-phase aPL by methods based on calibration curves established using the Sapporo standards. The cut-off values used for high titres of aCL antibodies were 40 GPL and/or MPL, and medium-low titres between 20 and 39 GPL and/or MPL prior to February 2006 since when, in accordance with the Sydney classification criteria, the cut-off values used for medium/high titres for both aCL and aβ2GP1 antibodies have been calculated using either the Sapporo standards or the 99th percentile obtained by testing age-matched healthy women.

Other immunological parameters

Serum protein electrophoresis, C3 and C4 complement levels, ANAs, anti-dsDNA and antithyroid antibodies were determined using standard methods.

Statistical analysis

Values are expressed as mean (S.D.), median [25th and 75th percentiles (Q1 and Q3, respectively)] and summand extreme values (minimum and maximum) for continuous variables, and number and percentages for qualitative variables. Student's *t*-test was used to compare values following a normal distribution, while Mann–Whitney–Wilcoxon's test or Kruskal–Wallis test were used for data not following a normal distribution. χ^2-test and Fisher's exact test were applied to compare categorical variables. Univariate logistic regression analysis was used to estimate the risks of analytical parameters in the presence of the studied morbidities. The statistical software SPSS (Statistical Package for Social Sciences, https://www.ibm.com/analytics/spss-statistics-software) was used for dataset analyses.

Results

Patient baseline clinical characteristics

A total of 1640 women with 5189 obstetric episodes (pregnancies) were included: 1000 fulfilled Sydney criteria (OAPS) and 640 did not (NC-OAPS). No differences were found between groups in age, ethnicity or comorbidity. All data are summarized in Table 1.

The NC-OAPS group was divided into three subsets: patients who did not meet either the clinical or laboratory Sydney criteria, subgroup A (176/640) (27.5%); those who met the Sydney clinical criteria but not the laboratory criteria, subgroup B (175/640) (27.34%); and finally, those who met the laboratory but not the clinical criteria, subgroup C (289/640) (45.15%). The remaining characteristics are detailed in Table 2.

Laboratory characteristics

Statistical differences were observed when OAPS and NC-OAPS were compared in all laboratory categories.

Table 1 Demographic characteristics

	OAPS *n* = 1000	NC-OAPS *n* = 640	*P*-value
Age, years, mean (S.D.)	35.2 (5.9)	35.1 (5.4)	0.304
Ethnicity, *n* (%)			
Caucasian/Indo Arian	725 (72.5)	505 (78.9)	0.002
American (Latino)	159 (15.9)	57 (8.9)	
Semitic (Arab)	81 (8.1)	57 (8.9)	
African	21 (2.1)	8 (1.3)	
Afro	6 (0.6)	3 (0.5)	
American/Caribbean	5 (0.5)	7 (1.1)	
Asian	3 (0.3)	3 (0.5)	
Amerindian			
Smoker, *n* (%)	152 (15.2)	120 (18.8)	0.059
BMI, *n* (%)	24.2 (4.7)	24.5 (4.5)	0.138
SLE, *n* (%)	77 (7.7)	53 (8.3)	0.671
Presence of other autoimmune diseases, *n* (%)	176 (17.6)	155 (24.2)	0.001
Inherited thrombophilia, *n* (%)	159 (15.9)	111 (17.3)	0.442

OAPS: obstetric APS; NC-OAPS: non-criteria obstetric APS.

Category I (triple or double positivity) had a higher prevalence of OAPS than NC-OAPS (29.2 *vs* 18%) ($P < 0.001$) in both double and triple positivity (18.2 *vs* 13.1% and 11 *vs* 4.8%) ($P = 0.007$ and $P < 0.001$, respectively). Nevertheless, the different isotypes showed differences between groups (see Table 3). Categories IIb (aCL IgG and/or IgM positivity) and IIc (aβ2GP1 IgG and/or IgM positivity) had a higher frequency of NC-OAPS than OAPS ($P < 0.001$), and OAPS was more frequent than NC-OAPS in category IIa (LA positivity alone) ($P < 0.001$) (Table 3). In addition, we have data on the so-called 'atypical' or non-criteria aPL (listed in section 'Laboratory exclusion criteria' in the Methods). In this line, we found that 51 (5.1%) women tested positive for some of these non-criteria aPL in the OAPS group and 72 (11.2%) in the NC-OAPS group ($P < 0.001$) (data not shown).

Table 2 The NC-OAPS subgroups

Subgroup A: NC-OAPS laboratory criteria + NC-OAPS clinical criteria, *n/N* (%)	176/640 (27.5)
Category I	20 cases
Category IIa	25 cases
Category IIb	84 cases
Category IIc	47 cases
Subgroup B: NC-OAPS laboratory criteria + Sydney clinical criteria, *n/N* (%)	175/640 (27.34)
Category I	8 cases
Category IIa	21 cases
Category IIb	85 cases
Category IIc	61 cases
Subgroup C: Sydney laboratory criteria + NC-OAPS clinical criteria, *n/N* (%)	289/640 (45.15)
Category I	87 cases
Category IIa	115 cases
Category IIb	59 cases
Category IIc	28 cases

N: number of cases; NC-OAPS: non-criteria obstetric APS.

Obstetric outcomes

Many clinical presentations in previous pregnancies were found between groups. Miscarriage, fetal loss and early placental vasculopathy were the most significant differences found. One miscarriage occurred in 14.5% of OAPS cases ($P < 0.001$) and two in 9.5% ($P < 0.001$). Furthermore, one or two miscarriages occurred in 24% of NC-OAPS cases ($P < 0.001$); fetal loss (25.3%) and stillbirth (23%) were more frequent in the OAPS group than in the NC-OAPS group (6.7% and 5.8%, respectively) ($P < 0.001$). Early placental vasculopathy (<34 weeks) was more prevalent in OAPS [18.1% PE, 16.1% fetal growth restriction (FGR)] than in NC-OAPS cases (2.8% PE, 3% FGR) ($P < 0.001$). Furthermore, late PE presentations (>34 weeks) were more frequent in NC-OAPS (15.5%) than in OAPS cases (4.6%) ($P < 0.001$), as was FGR (12.5% in the NC-OAPS group *vs* 4.7% in the OAPS group) ($P < 0.001$). All previous obstetric complications are detailed in Table 4.

The current obstetric complications appeared in 651/1000 (65.1%) in OAPS and 470/640 (73.4%) in NC-OAPS ($P < 0.001$). The most frequent complications observed in the OAPS group were prematurity [241/1000 (24.1%)] and miscarriage [124/640 (19.4%)] in the NC-OAPS group. The chronology of placental vasculopathy

Table 3 Laboratory results of these series

	OAPS *n* = 1000	NC-OAPS *n* = 640	*P*-value	A *n* = 176	B *n* = 175	C *n* = 289	*P*-value
Category I	292 (29.2)	115 (17.9)	<0.001	20 (11.4)	8 (4.6)	87 (30.1)	<0.001
Double+	182 (18.2)	84 (13.1)	0.007	17 (9.7)	7 (4.0)	60 (20.8)	<0.001
LA and aCL	92 (9.2)	29 (4.5)	<0.001	2 (1.1)	0 (0)	27 (9.3)	<0.001
LA and aCL IgM+	48 (4.8)	14 (2.2)	<0.001	1 (0.6)	0 (0)	13 (4.5)	0.001
LA and aCL IgG+	32 (3.2)	8 (1.3)	0.226	0 (0)	0 (0)	8 (2.8)	0.007
LA and aCL IgG+ and aCL IgM+	12 (6.6)	7 (8.3)	0.609	1 (0.6)	0 (0)	6 (2.1)	0.084
LA and aβ2GP1	37 (3.7)	8 (1.3)	0.003	1 (0.6)	0 (0)	7 (2.4)	0.047
aCL and aβ2GP1	53 (5.3)	47 (7.3)	0.092	14 (8.0)	7 (4.0)	26 (9.0)	0.127
Triple+	110 (11.0)	31 (4.8)	<0.001	3 (1.7)	1 (0.6)	27 (9.3)	<0.001
Category II	708 (70.8)	525 (82.0)	<0.001	156 (88.6)	167 (95.4)	202 (69.9)	<0.001
Category IIa (LA)	357 (35.7)	161 (25.2)	<0.001	25 (14.2)	21 (12.0)	115 (39.8)	<0.001
Category IIb (aCL)	224 (22.4)	228 (35.6)	<0.001	84 (47.7)	85 (48.6)	59 (20.4)	<0.001
IgG+	116 (11.6)	93 (14.5)	0.082	38 (21.6)	37 (21.1)	18 (6.2)	<0.001
IgM+	75 (7.5)	108 (16.9)	<0.001	38 (21.6)	42 (24.0)	28 (9.7)	<0.001
IgG+ and IgM+	33 (3.3)	26 (4.1)	0.419	7 (4.0)	6 (3.4)	13 (4.5)	0.850
Category IIc (aβ2GP1)	127 (12.7)	136 (21.3)	<0.001	47 (26.7)	61 (34.9)	28 (9.7)	<0.001
IgG+	63 (6.3)	66 (10.3)	0.003	22 (12.5)	29 (16.6)	15 (5.2)	<0.001
IgM+	45 (4.5)	46 (7.2)	0.020	17 (9.7)	24 (13.7)	5 (1.7)	<0.001
IgG+ and IgM+	19 (1.9)	24 (3.8)	<0.001	8 (4.5)	8 (4.6)	8 (2.8)	0.495

Data are presented as *n* (%). OAPS: obstetric APS; NC-OAPS: non-criteria obstetric APS. aβ2GP1: anti-β2glycoprotein-1.

Table 4 Detailed all obstetric complications in OAPS and NC-OAPS groups

	OAPS *n* = 1000	NC-OAPS *n* = 640	*P*-value	Subgroup A *n* = 176	Subgroup B *n* = 175	Subgroup C *n* = 289	*P*-value
Prematurity	285 (28.5)	35 (5.5)	<0.001	0 (0)	35 (20.0)	0 (0)	<0.001
Abortion ×1	145 (14.5)	158 (24.7)	<0.001	54 (30.7)	18 (10.3)	86 (29.8)	<0.001
Abortion ×2	95 (9.5)	156 (24.4)	<0.001	61 (34.7)	9 (5.1)	86 (29.8)	<0.001
Miscarriage (×3)	386 (38.6)	96 (15.0)	<0.001	0 (0)	96 (54.8)	0 (0)	<0.001
Fetal loss	253 (25.3)	43 (6.7)	<0.001	0 (0)	43 (24.5)	0 (0)	<0.001
Stillbirth	230 (23.0)	37 (5.8)	<0.001	0 (0)	37 (21.1)	0 (0)	<0.001
PE (<34 weeks)	181 (18.1)	18 (2.8)	<0.001	0 (0)	18 (10.2)	0 (0)	<0.001
PE (>34 weeks)	46 (4.6)	99 (15.5)	<0.001	26 (14.8)	14 (8.0)	59 (20.4)	0.002
FGR (<34 weeks)	161 (16.1)	19 (3.0)	<0.001	0 (0)	19 (10.9)	0 (0)	<0.001
FGR (>34 weeks)	47 (4.7)	80 (12.5)	<0.001	27 (15.3)	16 (9.1)	37 (12.8)	0.209
HELLP (<34 weeks)	35 (3.5)	6 (0.9)	0.001	0 (0)	6 (3.4)	0 (0)	0.009
HELLP (>34 weeks)	3 (0.3)	11 (1.7)	0.002	4 (2.3)	1 (0.6)	6 (2.1)	0.428
Prematurity + PE	160 (16.0)	15 (2.3)	<0.001	0 (0)	15 (8.6)	0 (0)	<0.001
Prematurity + FGR	139 (13.9)	13 (2.0)	<0.001	0 (0)	13 (7.4)	0 (0)	<0.001
Prematurity + PE + FGR	69 (6.9)	8 (1.3)	<0.001	0 (0)	8 (4.6)	0 (0)	<0.001
Ecographic signs of placental insufficiency (<34 weeks)	77 (7.7)	11 (1.7)	<0.001	0 (0)	11 (6.2)	0 (0)	0.001
Ecographic signs of placental insufficiency (>34 weeks)	25 (2.5)	73 (11.4)	<0.001	14 (8.0)	11 (6.3)	48 (16.6)	0.001
Placental haematoma	13 (1.3)	13 (2.0)	0.247	3 (1.7)	3 (1.7)	7 (2.4)	0.825
Abruptio placentae	10 (1.0)	5 (0.8)	0.650	0 (0)	3 (1.7)	2 (0.7)	0.136

Data are presented as *n* (%). Prematurity: born alive <34 weeks. OAPS: obstetric APS; NC-OAPS: non-criteria obstetric APS; FGR: fetal growth restriction; HELLP: hemolysis, elevated liver enzymes and low platelet count; PE: pre-eclampsia.

Table 5 Treatment regimes in OAPS and NC-OAPS groups

	OAPS *n* = 1000	NC-OAPS *n* = 640	*P*-value
No treatment	230 (23.0)	153 (23.9)	0.672
LDA alone	97 (9.7)	85 (13.3)	0.024
LDA alone preconceptional	46 (4.6)	45 (7.0)	0.036
LDA alone gestation	51 (5.1)	40 (6.3)	0.321
LMWH alone	39 (3.9)	27 (4.2)	0.749
LMWH alone preconceptional	5 (0.5)	4 (0.6)	0.743
LMWH alone gestation	34 (3.4)	23 (3.6)	0.834
LDA and LMWH	634 (63.4)	375 (58.6)	0.051
Recommended regime	448 (44.8)	300 (46.9)	0.411

Data are presented as *n* (%). OAPS: obstetric APS; NC-OAPS: non-criteria obstetric APS; LDA: low-dose aspirin; LMWH: low molecular weight heparin.

(<34 weeks in OAPS patients and >34 weeks in NC-OAPS patients) was the other main difference between groups. Detailed results are shown in Table 5.

Fetal outcomes

Weeks of delivery, live births and newborn weight were compared with fetal outcomes. Live births were reached in 728/1000 (72.8%) in the OAPS group and 470/640 (73.43%) in the NC-OAPS group. Fetal outcomes related to treatment schedules and main newborn weights are listed in supplementary Table S1, available at *Rheumatology* online.

Maternal outcomes

Gestational venous thrombosis was observed in 6 cases (6/1000; 0.6%) and puerperal venous thrombosis in 19 (19/1000; 1.9%) in the OAPS group (total venous thrombosis: 25 episodes, 2.5%). No arterial thrombosis appeared during pregnancy in either group. Puerperal arterial thrombosis occurred in six cases (6/1000; 0.6%) in the OAPS group. Thus, 31 episodes (31/1000; 3.1%) of thrombotic events were observed in the OAPS group. In addition, 10 cases (10/650; 1.5%) initially included as NC-OAPS subgroup C presented puerperal venous thrombosis and were excluded from the analysis since they finally fulfilled the full-blown Sydney clinical criteria and therefore were reclassified as thrombotic APS. No arterial thrombosis was seen in this group. Forty cases (4%) in the OAPS group evolved to another autoimmune disease during the puerperium (33 to SLE and 7 to idiopathic thrombocytopenic purpura), and 13 cases (2%) in the NC-OAPS group evolved to SLE.

Treatment analysis

The therapeutic regimens are shown in Table 5, and supplementary Tables S1 and S2, available at *Rheumatology* online. Most patients were placed on some type of treatment (1257/1640; 76.64%). In brief, 770/1000 cases (77%) in the OAPS group and 487/640 (76.09%) in the NC-OAPS

group were treated. Interestingly, the percentage of patients treated was similar in both groups despite there not currently being any approved treatment for NC-OAPS. OAPS and NC-OAPS women were put on preconceptional low-dose aspirin (LDA) plus prophylactic LMWH from the first trimester: 448/1000 (44.8%) and 308/640 (48.12%), respectively. All data are shown in Table 6.

Regarding obstetric complications, good obstetric outcomes including live births were observed when patients were treated with the recommended regimen: 381/448 (85%) in the OAPS group and 276/308 (89.6%) in the NC-OAPS group.

Discussion

This largest published series focused on women with OAPS, and women with previous poor obstetric outcomes and aPL positivity but not fulfilling the full-blown Sydney criteria (NC-OAPS). Furthermore, accurate analyses of this series showed that, albeit with different laboratory and clinical characteristics, these women had similar fetal-maternal outcomes after responding equally well to treatment.

Interestingly, patients with OAPS had a higher number of miscarriages, fetal losses, stillbirth, early placental vasculopathy (PE $<$34 weeks and FGR $<$34 weeks) and prematurity than those included in the NC-OAPS group. However, women diagnosed with NC-OAPS presented different clinical behaviour, having higher rates of recurrent implantation failure and late placental events (PE $>$34 weeks and FGR $>$34 weeks). It is also significant that differences in laboratory categories were found between groups, with category I and category IIa being more frequent in the OAPS group. This laboratory difference between groups is supported by other studies, such as the Assessment of the Prevalence of Major Psychiatric Disorders in a Cohort of Women With Clinical Criteria Corresponding to Pure, Abortive-form, Obstetrical, Antiphospholipid Syndrome (NOHA-PSY) observational study [16] showing a high association of LA with pregnancy losses, demonstrating the pathogenic activity of this aPL alone. These characteristics hinted at a differential fact between groups, which led us to speculate that we were dealing with two different entities.

Many authors have described a wide variety of aPL related to obstetric morbidity, including antibodies against 'atypical or non-classical' phospholipids, particularly aPS-PT and phosphatidylethanolamine [17]. These antibodies, combined with low titres of classical aPL, could be useful for the diagnosis of seronegative APS or NC-OAPS [18]. Up to 50% of women with recurrent pregnancy loss may present these non-classical aPL antibodies [19], and patients with APS and early pregnancy loss may have higher aPT IgG positivity [20]. Similar results were observed in the present study, with the NC-OAPS group having double the non-criteria aPL positivity of the OAPS group, with a higher prevalence of consecutive miscarriages and recurrent implantation failure in the former group. These data reinforce the possible role played by these atypical aPL in the pathogensis of or as a markers for NC-OAPS.

In addition, we also already know how complement and TNF-α pathway activation play a key role in the pathogenesis of aPL-related obstetric morbidity. As our manuscript reported, 268/1640 (16.34%) analysed cases showed low C3/C4 levels. Complement deposition in placental tissue has also been demonstrated in aPL-complicating pregnancies [21, 22]. Furthermore, in a retrospective cross-sectional study, Ohmura *et al.* [23] showed how recurrent pregnancy loss in a murine model had high titres of anti-C1q antibodies that were able to activate the classical complement pathway. Moreover, for those cases they suggest a novel therapy focusing on the C5-C5aR axis, based on the pathogenic role of C5a receptors that recruit neutrophils-releasing TNF-α in the decidua.

The Sydney criteria were intended for multicentre studies and clinical trials on APS, and not for diagnostic purposes in daily clinical practice. Unfortunately, the majority of clinicians in the APS field use these criteria as a definite diagnostic tool and, similarly, the British Committee for Standards in Haematology guidelines also standardized APS management [24]. However, many experts currently recommend overhauling the diagnostic criteria or the management of non-APS criteria, including the obstetric form, owing to evidence of clinical similarities and results with the classical form [25]. At this point, we would like to emphasize the differences found in clinical presentations and outcomes in our two groups, especially when the patients were not treated; however, the most significant result was the good obstetric fetal-maternal outcomes in both groups when these women were treated.

Prospective randomized controlled trials focused on treatment strategies in women with aPL and a history of recurrent miscarriages are scant. Some appear to demonstrate the superiority of the heparin—mainly unfractionated—plus LDA combination over LDA alone [26]. By contrast, Farquharson *et al.* [27] reported that the addition of LMWH to LDA did not significantly improve pregnancy outcome compared with LDA alone. Concurring with most studies and meta-analyses, the British Committee for Standards in Haematology [24] and American College of Chest Physicians guidelines [28] provided recommendations for treating women fulfilling the international consensus criteria for obstetric APS based on the association of heparin plus LDA. Prospective and retrospective cohort studies in women with NC-OAPS suggested that they have similar pregnancy outcomes with standard treatment for OAPS [29–32]. However, since these studies were short case series, interpretation of the results was limited. Interestingly, our series showed a low evolution rate towards autoimmune diseases compared with classical APS. Furthermore, we found few thrombotic events. We should mention that 10 women in the NC-OAPS group evolved to thrombotic APS, since they presented thrombosis during follow-up. All met Sydney laboratory criteria, thereby reinforcing the importance of close monitoring of 'seronegative' or 'non-criteria' APS [33].

The Registry has some weak points. The main weakness lay in the fact that it was a multicentre and partly retrospective study. Not all recruited cases had complete information on embryo-fetal or parental karyotype in recurrent miscarriage, laboratory items such as complement levels or non-classical aPL. Finally, aPL test results were difficult to interpret in certain cases since different commercial and homemade methods were used. Conversely, the inclusion of laboratory data from different centres could also avoid a possible bias attributable to methodology of one or few laboratories.

The strong points were that 1640 patients with >5000 pregnancies were analysed, representing the largest published series to date. The fact that 30 referral hospitals participated in their respective countries minimizes the selection bias that could be attributed to data collection at a single centre.

Conclusion

We are certain that a different nosologic entity exists in the OAPS and that its correct classification must be addressed. Thus, we found clinical and laboratory differences between OAPS and NC-OAPS patients, with similar fetal-maternal outcomes when treated. However, differences in treatment rates, livebirths and thrombotic complications between groups were not observed. We suggest that prospective multicentre studies, appropriately designed and accurately powered, should be conducted to ascertain the diagnostic validity, management and long-term maternal outcomes of NC-OAPS. However, as clinical practice shows, these studies are very difficult to undertake. In the meantime, decisions on the management of these women during pregnancy should be based on an individual risk–benefit ratio assessment. We believe that the benefits of treating these women during pregnancy outweigh those of not treating them.

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Supplementary data

Supplementary data are available at *Rheumatology* online.

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