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Full length article

Impact of the 2023 ACR/EULAR antiphospholipid syndrome criteria in 1200 women with prior obstetric antiphospholipid syndrome

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ABSTRACT

Aim: The goal of a high specificity led to a loss of sensitivity in the new 2023 ACR/EULAR APS classification criteria, and mainly affecting obstetric clinical phenotype (OAPS). To reclassify a cohort of 1,200 women diagnosed of OAPS based on the Sydney classification criteria by applying the 2023 ACR/EULAR APS criteria.

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Methods: The European Registry on Obstetric Antiphospholipid Syndrome (EUROAPS) with 1,200 women that fulfil the Sydney classification criteria were reanalysed according to the obstetric (domain 4) and laboratory domain 8 of the new classification criteria.
Results: When our cases were re-classified by applying the clinical criteria of domain 4, 816 cases (68%) would be excluded, leaving 384 cases (32%). The criteria that moderate to high IgM positivity is insufficient to classify patients, it led to a drop of additional 46 women, with a final number of excluded cases of 862 (71.83%), leaving only 338 cases (28.17%). Furthermore, the implementation of 40 units threshold discarded 86 women with an antiphospholipid antibody positivity above the 99th percentile cutoff. Eventually, from the 1,200 cases initially classified by the Sydney criteria, only 256 (21,33%) will remain.
Conclusion: The 2023 ACR/EULAR classification criteria substantially reduce the proportion of women with prior obstetric APS who remain classifiable in our cohort. Although these findings highlight a marked decrease in case identification compared with the Sydney criteria, the potential clinical and research implications of this reduction warrant further evaluation in prospective studies.

Introduction

The antiphospholipid syndrome (APS) is an autoimmune disease defined by the presence of vascular or microvascular thrombosis and/or obstetric complications and/or clinically significant non-thrombotic manifestations occurring in patients with persistently positive antiphospholipid antibodies (aPL) [1]. These autoantibodies primarily target negatively charged phospholipids or phospholipid-protein complexes, with β2-glycoprotein I (β2GPI) and prothrombin acting as key protein cofactors. This binding leads to cellular activation, triggering pro-inflammatory and pro-coagulant signalling pathways, contributing directly to the diverse clinical features of APS[2,3]. There are cases known to have obstetric APS (OAPS) [4] 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 [5].

The International consensus conducted in Sapporo [6] and then revised in Sydney in 2006 [7] summarises obstetric complications in recurrent first trimester miscarriage, foetal losses, stillbirth, early and severe preeclampsia or prematurity (less than 34 weeks) due to placental dysfunction [7].

In 2023, new classification criteria endorsed by ACR/EULAR [8] have been launched, modifying substantially the previous Sydney [7]. Briefly, the updated 2023 ACR/EULAR APS classification criteria include six clinical domains: Domain 1, macrovascular arterial thrombosis; Domain 2, macrovascular venous thrombosis; Domain 3, microvascular manifestations; Domain 4, obstetric morbidity; Domain 5, cardiac valve disease; and Domain 6, thrombocytopenia. In addition, there are two laboratory domains: Domain 7, lupus anticoagulant (LA) positivity; and Domain 8, antiphospholipid antibody (aPL) type, isotype, and titre (anticardiolipin [aCL] and anti-β2-glycoprotein I [aβ2GPI] antibodies) [8]. Specific scores are assigned to each clinical and laboratory feature, and classification as APS requires accumulating of at least 3 points from the clinical domains and at least 3 points from the laboratory domains. Indeed, the 2023 ACR/EULAR criteria achieve high specificity (99%) at the expense of reduced sensitivity (84%) [8,9]. As a result, a considerable number of patients with suspected APS or confirmed aPL-related events could remain unclassified, potentially losing the opportunity for appropriate recognition and targeted clinical management in daily practise[10–12], therefore remaining at increased risk of subsequent thrombotic or obstetric events. Talking about the OAPS, recent papers by Martinez-Taboada et al [13], Tang et al [14], Aiello et al [15] or Vasi et al [16] reported losses ranging from 38% to more than 70%, when both Sydney and ACR/EULAR criteria are compared. However, the number of included patients in this series is not too large, since the pure obstetric form do not reach, approximately, more than 100 women.

The aim is to analyse the differences in a cohort of 1,200 women diagnosed as having OAPS using the Sydney classification criteria, when we apply on the same cohort the 2023 ACR/EULAR criteria.

Materials and methods

Patients.

In order to collect as much information as possible about a heterogeneous entity such as the OAPS, a simple and accessible web-based registry 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. The first 1,200 consecutive women fulfilling the obstetric Sydney criteria and enrolled in the EUROAPS Registry between June 2010 and June 2025 were included in the study. We conducted a comparative study in which we applied the new 2023 ACR/EULAR classification criteria to this series of patients, who had previously been classified as OAPS according to the Sydney criteria.

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 APS. To date, the cohort has consisted of 1200 cases, selected according with previous Sydney classification criteria. Obstetrics, hematology, internal medicine, autoimmune diseases and rheumatology are the departments involved in the process of patient enrolment. The database has been created with all those centers that shared information on the online register. A total amount of 150 items has been introduced to further analysis. Participants have been encouraged to include both complete (pure OAPS) and incomplete cases. These incomplete cases (more than 800 women) will be further analysed elsewhere. All introduced patients automatically received an encryption code to preserve privacy and personal data.

All previous pregnancies have also been introduced, each one coded as an isolated episode. Subsequently, the current gestation has also been registered. All complications and adverse obstetric events presented have been registered.

Inclusion and exclusion criteria

Inclusion clinical criteria: The items defined as obstetric morbidity according to Sydney recommendations [7], were a/ women with history of 3 or more consecutive first-trimester miscarriages, and/or b/ foetal losses > 10 weeks and/or or, c/ prematurity due to presence of early placental vasculopathy (less than week 34).

Inclusion laboratory criteria: The laboratory items defined by Sydney laboratory criteria [7] are: presence of two or more positive LA tests, according to the International Society on Thrombosis and Haemostasis (ISTH) guidelines and guidances [17–19], and/or two or more positive aCL IgG/IgM tests (> 40 GPL/MPL or > 99th percentile), and/or two or more positive aβ2GPI IgG/IgM tests (> 99th percentile). Blood tests

were required to be separated in time by more than twelve weeks.

Exclusion clinical criteria: Women not meeting the Sydney classification criteria were excluded.

Women who had experienced any major thrombotic event preceding the obstetric event. In addition, women who have had miscarriages 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.

Exclusion laboratory criteria: Following the Sydney recommendations, those patients with low aPL titres as well as those presenting non-criteria aPL were excluded for classification. Low titers were defined as aCL IgG/IgM ≤ 40 GPL/MPL or ≤ 99th percentile, and aβ2GPI IgG/IgM ≤ 99th percentile.

Finally, all the 1200 women who meet the obstetric Sydney criteria were analysed according to the new 2023 ACR/EULAR recommendations [8], mainly focusing in obstetrical issues (domain 4) and in aCL and/or aβ2GPI positivity (domain 8) (Table 1). Domains 5 and 6 were not compared because by and large of the 1,200 cases fulfilling the full-blown Sydney criteria lack heart valve studies and thrombocytopenia in the registry.

Statistical analysis

Descriptive statistics was used to present the data. Variables were collected in the EUROAPS as continuous or categorical variables. Mean and standard deviation were used for continuous variables and frequency for the categorical ones.

Results

The most important epidemiologic and demographic data of this cohort of 1200 women diagnosed as OAPS according to Sydney criteria is shown in Table 2. Briefly, the mean age was 35 years; 74% are Caucasian, but other ethnicities were represented. Previous chronic disorders and cardiovascular risk factors have also been depicted, although in a small proportion. Associated autoimmune disorders were low (20%), mostly included systemic lupus erythematosus (SLE, 6.5%) and organ specific. Presence of chronic diseases was recorded in 13.9% of women. Obstetrical background and treatment schedules are also described in Table 2.

We divided the obstetric criteria (domain 4) of the ACR/EULAR APS classification criteria into 3 sub-domains: 4–1: >3 consecutive pre-fetal (<10 weeks) and/or 1 early fetal (10 weeks 0 days – 15 weeks 6 days) deaths; 4–2: fetal death (16 weeks 0 days – 33 weeks 6 days) in the absence of pre-eclampsia (PEC) with severe features, or placental insufficiency (PI) with severe features; and, 4–3: PI with severe features (<34 weeks 0 days) with or without fetal death, and PEC with severe features (<34 weeks 0 days) with or without fetal death. Table 3 present the aPL distribution in this series of 1,200 according to Sydney criteria. In addition, Fig. 1a depicts the distribution of 1,200 cases considering our schematic subdomains. Table 4 shows the numerical distribution of these 1,200 cases based on the 2023 ACR/EULAR recommendations for the new obstetric clinical criteria and also including the observation of isolated aCL/aβ2GPI IgM positivity. Only patients in the domain 4–3 column will be kept classified as OAPS. Of note, by applying the new clinical criteria, 816 cases (68%) would be excluded, leaving 384 cases (32%).

Regarding laboratory classification criteria, Fig. 1b shows the distribution of the EUROAPS patients according to their positivity for lupus anticoagulant and for aCL and/or aβ2GPI IgM and/or IgG in the initial cohort by Sydney criteria. If we apply the restriction that excludes those women who tested positive only for the IgM isotype, then 46 cases will be lost in addition to those who already meet the requirement established by domain 4–3 (46/384 cases; 12%). The final number of excluded cases would be 862 (71.83%), leaving only 338 cases (28.17%) who fulfill the new classification criteria (Table 3). Distribution of the women still classifiable after applying the 2023 ACR/EULAR entry criterion and scoring laboratory criteria thresholds is depicted in Fig. 2a.

EUROAPS patients tested above the 99th percentile threshold for IgG aCL and/or IgG aβ2GPI. Currently, a positive test for the aPL IgG isotype must be above the threshold of 40 units. Eventually, 82 more cases will be lost based on this threshold (Table 5), and the aPL positivity distribution is displayed in Fig. 2b. Overall, if we take all the ACR/EULAR recommendation into account, including the 40-unit threshold, from the 1,200 cases initially included by the Sydney criteria, we finally could only include 256 cases, that is, 21,33%.

Table 1
Comparison between the Sydney criteria and the 2023 ACR/EULAR classification criteria for obstetric antiphospholipid syndrome (APS). The table summarizes clinical and laboratory domains related to pregnancy morbidity, indicating eligibility for classification under each set of criteria. For the 2023 ACR/EULAR criteria, obstetric manifestations are classified within Domain 4 (Obstetric), with assigned weights contributing to overall classification eligibility. Laboratory findings are detailed under Domain 8, with weighted scores based on antiphospholipid antibody type and titre. Differences between criteria highlight the revised weighting system and stricter thresholds for classification in the 2023 ACR/EULAR framework.

Sydney's criteria Clinical criteria		**2023 ACR/EULAR APS classification criteria** Clinical criteria		
Pregnancy morbidity	Eligible for classification	D4. Obstetric	Weight	Eligible for classification
≥ 3 unexplained consecutive spontaneous abortions < 10w	yes	≥ 3 consecutive pre-foetal (<10w) and/or early foetal (10w 0d-15w 6d) deaths	1	no
≥ 1 unexplained deaths ≥ 10w	yes	Foetal death (16w 0d − 33w 6d) in the absence of PEC /PI with severe features	1	no
≥ 1 premature births < 34w because eclampsia or severe PEC	yes	PEC with severe features (<34w 0d) or PI with severe features (<34w 0d) with/ without foetal death	3	yes
≥ 1 premature births < 34w because recognized features of PI	yes	PEC with severe features (<34w 0d) & PI with severe features (<34w 0d) with/ without foetal death	4	yes
Laboratory criteria		Laboratory criteria Domain 8		
aCL IgG/IgM > 40 GPL/MPL or > 99th percentile	yes	aCL IgM and/or aβ2GPI IgM > 40 Units	1	no
aβ2GPI IgG/IgM > 99th percentile	yes	aCL IgG and/or aβ2GPI IgM > 40 Units and < 80 Units	4	yes
		aCL IgG or aβ2GPI IgM > 80 Units	5	yes
		aCL IgG and aβ2GPI IgM > 80 Units	7	yes

Abbreviations.
APS, antiphospholipid syndrome; PEC, pre-eclampsia; PI, placental insufficiency; aCL, anticardiolipin antibodies; aβ2GPI, anti-β2-glycoprotein I antibodies.

Table 2
Demographic, clinic and epidemiologic characteristics of the 1,200 women of EUROAPS registry.

Age at diagnosis, years (mean ± SD)	35.37 ± 5.8
Ethnicity, n (%)	
Caucasian	887 (73.9)
American (Latino)	179 (14.9)
Semitic/Arab	83 (6.9)
African	31 (2.7)
Afro-American/Caribbean	6 (0.5)
Asian	10 (0.8)
Amerindian	4 (0.3)
Smokers, n (%)	173 (14.4)
Chronic diseases, n (%)	
None	696 (58.0)
CVD	
Obesity (≥ 30 BMI)	100 (8.3)
Dyslipidaemia	51 (4.3)
Hypertension	23 (2.4)
Diabetes mellitus	22 (1.8)
Autoimmune diseases, n (%)	
SLE	78 (6.5)
Immune thrombocytopenia	6 (0.5)
Hypothyroidism (Hashimoto's disease)	91 (7.6)
Hyperthyroidism (Grave's disease)	9 (0.8)
Sjögren's syndrome	9 (0.8)
Celiac disease	8 (0.7)
Pernicious anaemia	4 (0.3)
Cryoglobulinemia	1 (0.1)
ANCA-associated vasculitis	1 (0.1)
Rheumatoid arthritis	4 (0.3)
Intestinal inflammatory disease	3 (0.2)
Vitiligo	4 (0.3)
Autoimmune hepatitis	1 (0.1)
Spondyloarthropathy	1 (0.1)
Psoriasis	4 (0.3)
Primary biliary cirrhosis	1 (0.1)
Mixed Connective Tissue Disease	12 (1)
Myasthenia gravis	1 (0.1)
Multiple sclerosis	2 (0.2)
Kidney disease	33 (2.8)
HIV infection	2 (0.2)
HBV infection	1 (0.1)
HCV infection	4 (0.3)
Cardiomyopathy	11 (0.9)
Asthma	30 (2.5)
Alcoholism	12 (1)
Migraine	18 (1.5)
Polycystic ovarian syndrome	18 (1.5)
Irritable bowel syndrome	6 (0.5)
Iron deficiency	16 (1.3)
Endometriosis	11 (0.9)
Neoplasia	0 (0)
Previous DVT	1 (0.1)
Previous arterial ischemia	0 (0)
Others	3 (0.3)
Pregnancy and puerperal complications, n (%)	
Miscarriage x3	470 (39.2)
Fetal loss	320 (26.7)
Stillbirth	261 (21.8)
Pre-eclampsia < 34w	213 (17.8)
Pre-eclampsia > 34w	51 (4.3)
FGR < 34 w	184 (15.3)
FGR > 34 w	50 (4.2)
HELLP < 34 w	41 (3.4)
HELLP > 34 w	5 (0.4)
Eclampsia < 34 w	1 (0.1)
Eclampsia > 34 w	5 (0.4)
Ultrasound signs of placental insufficiency < 34 w	78 (6.5)
Ultrasound signs of placental insufficiency > 34 w	25 (2.1)
Abruptio Placentae	12 (1)
Placental Haematoma	15 (1.3)
Puerperal arterial thrombosis	4 (0.3)
Puerperalvenous thrombosis	7 (0.6)
Chorioamnionitis	3 (0.3)
Maternal death	0 (0)
IVF failure	49 (4.1)
Spontaneous miscarriage x1	176 (14.7)
Spontaneous miscarriage x2	102 (8.5)
Perinatal death	10 (0.8)
Prematurity	306 (25.5)
CAPS	1 (0.1)
Drug treatment, n (%)	
LDA	855 (71.2)
LMWH	842 (70.2)
Steroids	95 (7.9)
HCQ	134 (11.2)
Progesterone	259 (21.7)
anti-TNFa	3 (0.3)
IVIG	6 (0.5)
Metformin	19 (1.6)

Abbreviations: CVD, cardiovascular disease; BMI, body mass index; HIV, Human immunodeficiency virus; HBV Hepatitis B virus; HCV, Hepatitis C virus; DVP, deep vein thrombosis; SLE, systemic lupus erythematosus; ANCA, anti-neutrophil cytoplasmic antibodies; FGR, fetal growth restriction; HELLP, Haemolysis, Elevated Liver enzymes, and Low Platelets counts; w, weeks; IVF, in vitro fertilization; CAPS, catastrophic antiphospholipid syndrome; LDA, low dose aspirin; LMWH, low molecular weight heparin; HCQ, hydroxychloroquine; TNF, tumor necrosis factor; IVIG, intravenous immunoglobulins.

Table 3
Antiphospholipid laboratory category and combined antibody positivity of the 1,200 women in EUROAPS registry.

Lab Category, n (%)	
Cat I (Triple positivity OR Double positivity)	345 (28.4)
Cat II a (LA +)	426 (35.8)
Cat II b (IgM and/or IgG aCL)	285 (23.8)
Cat II c (IgM and/or IgG aβ2GPI)	144 (12)
triple positivty, n (%)	
LA + aCL IgG + aβ2GPI IgG	89 (7.4)
LA + aCL IgM + aβ2GPI IgG	8 (0.7)
LA + aCL IgG + aβ2GPI IgM	4 (0.3)
LA + aCL IgM + aβ2GPI IgM	22 (1.8)
Double positivty, n (%)	
LA + aCL IgG	72 (6)
LA + aCL IgM	34 (2.8)
LA + aβ2GPI IgG	29 (2.4)
LA + aβ2GPI IgM	15 (1.2)
aCL IgG + aβ2GPI IgG	37 (3.1)
aCL IgM + aβ2GPI IgG	3 (0.2)
aCL IgG + aβ2GPI IgM	10 (0.8)
aCL IgM + aβ2GPI IgM	22 (1.8)
Single positivity, n (%)	
LA	426 (35.5)
aCL IgG	194 (16.2)
aCL IgM	91 (7.6)
aβ2GPI IgG	91 (7.6)
aβ2GPI IgM	53 (4.4)

Abbreviations: LA, lupus anticoagulant; aCL, anticardiolipin; aβ2GPI, anti-β2 Glycoprotein I; IgG, immunoglobulin G; IgM, immunoglobulin M.

Discussion

When applying the new ACR/EULAR classification criteria to a cohort of 1,200 cases who met the previous full-blown 2006 Sydney classification criteria for obstetric phenotype (OAPS), we are only able to reclassify 256 cases, which corresponds to 21.33%. The loss of cases is attributable to both the clinical and laboratory inclusion criteria; however, the changes introduced in the clinical morbidity domain have a substantially greater impact, accounting for the exclusion of 816 cases (68%). The difficulties in classify patients is especially evident in the obstetric phenotype, referred to as obstetric morbidity in the Sydney criteria [7] or domain 4 in the new 2023 classification criteria [8]. The fact that two obstetrical issues such as prefetal death and fetal death (subdomains 4–1 and 4–2 in our study, respectively) weigh only 1 point

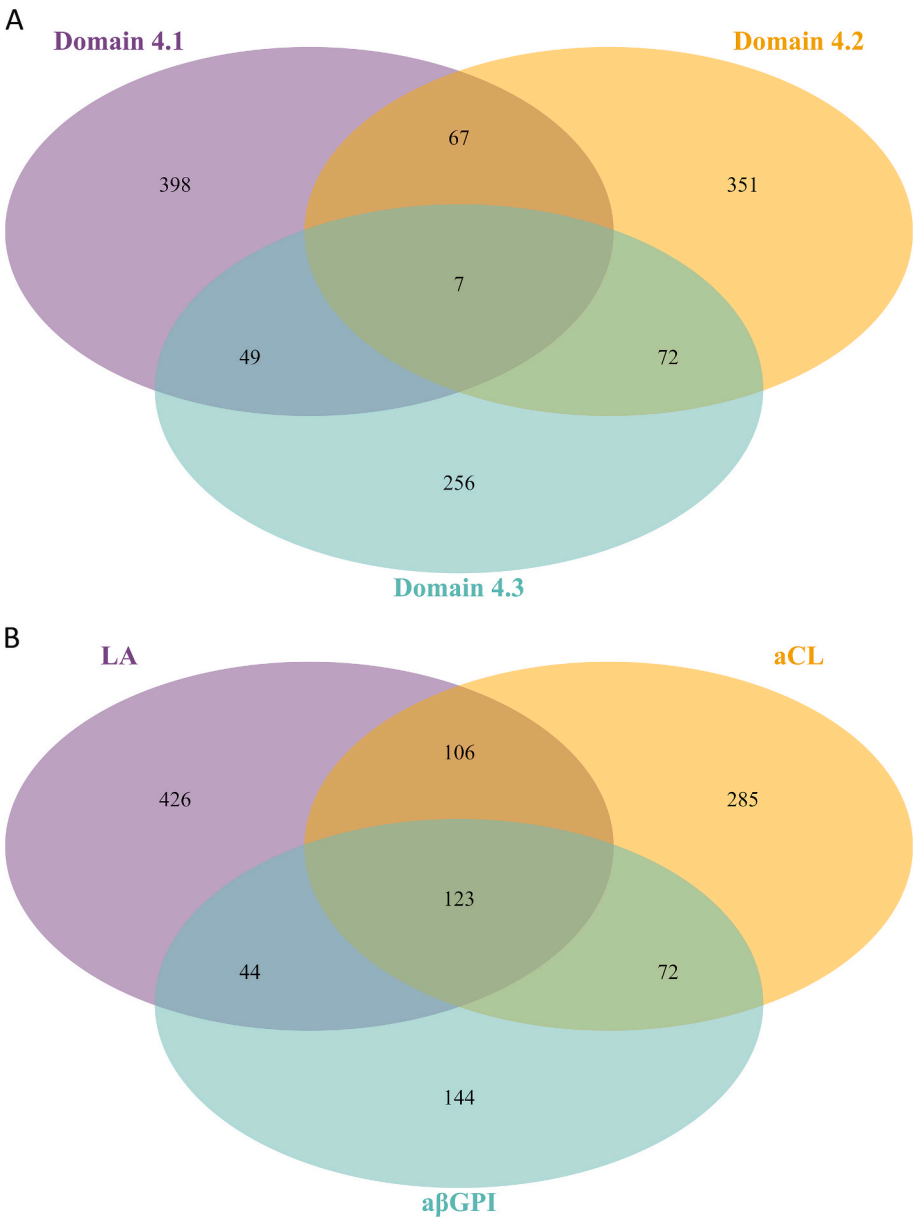

Fig. 1. Reclassification of 1,200 EUROAPS patients according to the new ACR/EULAR APS classification criteria. Venn diagrams showing **(A)** distribution of OAPS patients based on clinical obstetric criteria (Domain 4). Patients are subdivided into: Domain 4.1, including 3 or more consecutive miscarriages before 10 weeks of gestation and/or fetal losses before 16 weeks; Domain 4.2, comprising fetal deaths occurring at the interval of 16–34 weeks of gestation; and Domain 4.3, including cases of preeclampsia and/or placental insufficiency with severe features before 34 weeks of gestation, irrespective of fetal demise. Overlap represents women fulfilling more than one obstetric item across different pregnancies. **(B)** Distribution of OAPS patients based on laboratory criteria, showing positivity for lupus anticoagulant (LA), anticardiolipin antibodies (aCL) of IgG and/or IgM isotype, and anti-β2 glycoprotein I antibodies (aβ2GPI) of IgG and/or IgM isotype.

each one, and that these are not cumulative, means it is impossible to reach the minimum of 3 points required for this domain [8]. Moreover, without an embryological basis or support from any institutional or scientific society recommendations or guideline [20], it was decided to group early miscarriages and fetal losses up to week 16 into a single category. The exclusion of women presenting with recurrent pregnancy loss and markedly elevated aPL titres raises concerns, as these features are strongly suggestive of clinically significant APS. The lack of classification becomes even more concerning in the current context, in which women who are positive for autoantibodies are increasingly observed to experience recurrent implantation failure of healthy, euploid embryos [21,22]. This reinforces the idea that the loss of euploid embryos should be properly considered and scored in further classification criteria. Overall, from the all poor obstetric outcomes the only one classified as APS are those related to early placental vasculopathy, as it is the only one that allows us to reach the required 3 points.

Another point that deserves special consideration is the reduced weight given to the IgM isotype. As previously commented, when we applied this new criterion to our series, 46 more cases drop. Persistently moderate to high aCL and aβ2GPI IgM titres over time, weighs only 1 point, insufficient for APS classification. However, large cohort studies indicate that over 15% of patients present with recurrent, isolated aPL-IgM positivity, associated with both thrombotic and obstetric events [4,23–27]. Furthermore, IgM isotypes are included in risk-based scoring systems such as aGAPSS [28], or the EUREKA algorithm [29]—yet they are not deemed sufficient to classify APS patients. The last point related to laboratory criteria that has been analysed, refers to fixed ELISA units for measuring the aPL positivity. Under the current 2023 ACR/EULAR classification, which defines moderate antibody positivity as titres of 40–79 units and high positivity as $\geq$ 80 units [8], the use of a fixed cutoff

Table 4
Distribution of the EUROAPS registry cases according to the obstetric clinical phenotypes of ACR/EULAR criteria.

Domain 4.1	Domain 4.2	Isolated IgM +	Domain 4.3	
			no	yes
no	no	no	0	227
		yes	0	29
	yes	no	306	62
		yes	45	10
yes	no	no	333	42
		yes	65	7
	yes	no	57	7
		yes	10	0
		Total, n (%)	816 (68.0)	384 (32.0)
		Total isolated IgM, n (%)		46 (12.0)
		Total losses, n (%)	862 (71.8)	
		Remaining, n (%)		338 (28.2)

The 1,200 women of EUROAPS registry were distributed according to the clinical criteria of the obstetric domain (Domain 4) of the 2023 ACR/EULAR APS classification criteria that were defined as: Domain 4.1, women with 3 or more consecutive miscarriages before 10 weeks of gestation and/or fetal losses before 16 weeks; Domain 4.2, women with fetal deaths occurring at the interval of 16–34 weeks of gestation; and Domain 4.3, cases of preeclampsia and/or placental insufficiency with severe features before 34 weeks of gestation, irrespective of fetal demise. Only women fulfilling the Domain 4.3 criteria will be reclassified as OAPS. Women with isolated IgM positivity will additionally drop.

of 40 units leads to the additional exclusion of 86 cases. This is because enrolment in the EUROAPS cohort was done based on percentiles thresholds rather than the fixed cutoff of 40 arbitrary units, and the above excluded patients met the 99th percentile without reaching 40 ELISA units. This raises a significant concern regarding the laboratory classification criteria.

Significant variability in positivity thresholds across commercially available ELISA kits is also a considerable challenge. Several studies, including those conducted by our group, have highlighted the significant inter-assay and inter-laboratory variability in the quantification of aPL using ELISA, raising concerns about the reliability of absolute cutoff values [30]. To improve such inconsistencies, the International Society on Thrombosis and Haemostasis (ISTH) recommended adopting the 99th percentile from normal control populations as the threshold for positivity [24,31], replacing the arbitrarily defined fixed-unit cut-offs currently recommended by the 2023 ACR/EULAR APS classification criteria. This percentile-based strategy, previously endorsed within the Sydney criteria for aβ2GPI antibodies, has demonstrated improved specificity, reduced variability between methods and better comparability across laboratories and patient cohorts[24,31,32].

The obstetric domain within the 2023 ACR/EULAR APS classification criteria introduces substantial changes aimed at improving classification precision. However, several important concerns emerge that warrant critical evaluation and potential further refinement.

First, the new obstetric domain introduces novel terminology and temporal subdivisions—such as 'pre-foetal loss' (10–15 weeks + 6 days) and 'foetal loss' (16–33 weeks + 6 days)—that differ markedly from long-established definitions endorsed by major obstetric and reproductive medicine organisations. In the obstetric literature, pregnancy losses occurring before approximately 10 weeks of gestation are generally defined as early embryonic losses, whereas losses occurring from around 10 weeks (or up to 12 6/7 weeks, depending on the guideline) through approximately 23–24 weeks are consistently classified as foetal losses [33–37]. These definitions are uniformly supported by leading professional bodies, including the American College of Obstetricians and Gynaecologists (ACOG) [38], the European Society of Human Reproduction and Embryology [39], and others [33,40].

These arbitrary temporal subdivisions lack clear clinical justification and introduce relevant scoring inequalities. Under the new criteria, ≥3 recurrent early losses (before 10 weeks) or pre-foetal losses (10–15 weeks + 6 days) are assigned only 1 point. Similarly, late foetal losses (16–33 weeks + 6 days) also receive only 1 point, regardless of clinical severity or the possible presence of subtle but clinically relevant placental pathology. This approach undervalues recurrent pregnancy loss, dilutes its clinical significance, and further reduces the likelihood of appropriately classifying women with APS based solely on obstetric morbidity, particularly in the absence of clearly documented placental pathology. Moreover, the inability to accumulate points for multiple losses within the same clinical domain further exacerbates this underestimation and limits the classification of patients who previously fulfilled well-established diagnostic thresholds for obstetric APS.

Another important concern relates to the differential weighting between late foetal loss (16–33 weeks + 6 days) and severe early placental insufficiency manifesting as pre-eclampsia before 34 weeks. While severe pre-eclampsia is appropriately recognised with higher scores (3–4 points) because of its well-defined pathogenic mechanisms and prognostic implications, late foetal losses receive disproportionately low weighting. This occurs despite the fact that late foetal death often reflects significant placental dysfunction, underlying vascular pathology, and increased maternal morbidity risk. Consequently, the current scoring system may not fully capture the true clinical severity and adverse outcomes associated with late foetal loss.

The risk of not considering certain obstetric manifestations—e.g., recurrent miscarriages or fetal losses in women with positive aPL under the 2023 ACR/EULAR criteria—or of overlooking prior obstetric morbidity when only isolated but recurrent IgM positivity are present, may entail significant health concerns both during and outside pregnancy. In this context, women with obstetric manifestations classified as OAPS according to Sydney but without receiving treatment showed a lower birth rate and higher bad outcomes than those receiving standard of care [4], and the risk of a first thrombotic event without prophylaxis is above 10% during pregnancy and the puerperium [41,42], with no observed increase in bleeding risk [43]. Although the higher thrombotic risk in untreated OAPS has been demonstrated in general obstetric APS cohorts [44], this evidence may also be relevant for women who are 'missed' by the new criteria, as lack of classification may result in lack of treatment and, consequently, exposure to a similar risk profile. Therefore, when clinical suspicion remains high, further clinical evaluation and additional research are required to guide evidence–based management. The main strength of our study is the number of cases included. Other reported studies, focused in thrombotic, obstetric or mixing clinical APS phenotypes, that included smaller number of pure obstetric cases, had already hinted at the problem [13–16,45,46]. These 1,200 cases reinforce and validate those initial observations.

However, we must mention two weaknesses. The first refers to the inability to include thrombocytopenia, as it is not consistently documented in our dataset. The advantage of having data from 30 hospitals also entails, among others things, this limitation. The impact of do not consider this variable is unknown. In one hand, the current upper platelet count threshold for pregnant women (<100,000/μL) [8] risks inadvertently including patients with gestational thrombocytopenia (<150,000 μL), a benign condition occurring in approximately 7–12% [47,48]. In addition, up to 5% of these healthy pregnant women have platelet counts in the range of 70,000/μL–100,000/μL [49–51]. We could be excluding women with true thrombocytopenia, but according the commented percentage (~5%), its absolute impact appears to be very low. Nevertheless, gestational thrombocytopenia is an exclusion criterion for the haematology domain 6.

The second weakness is the inability to analyse cases with cardiac valvular involvement, since this variable was not systematically recorded in our database. Thus, some EUROAPS cases that were previously excluded under the new obstetric classification criteria may now fulfil the new criteria, potentially allowing their reclassification as APS. In any case, the overall prevalence of cardiac valvular involvement in APS — including valvular thickening, vegetations and dysfunction — is approximately 11%, [52] although this figure may vary due to the high technique-dependence of cardiac imaging findings [53]. In addition,

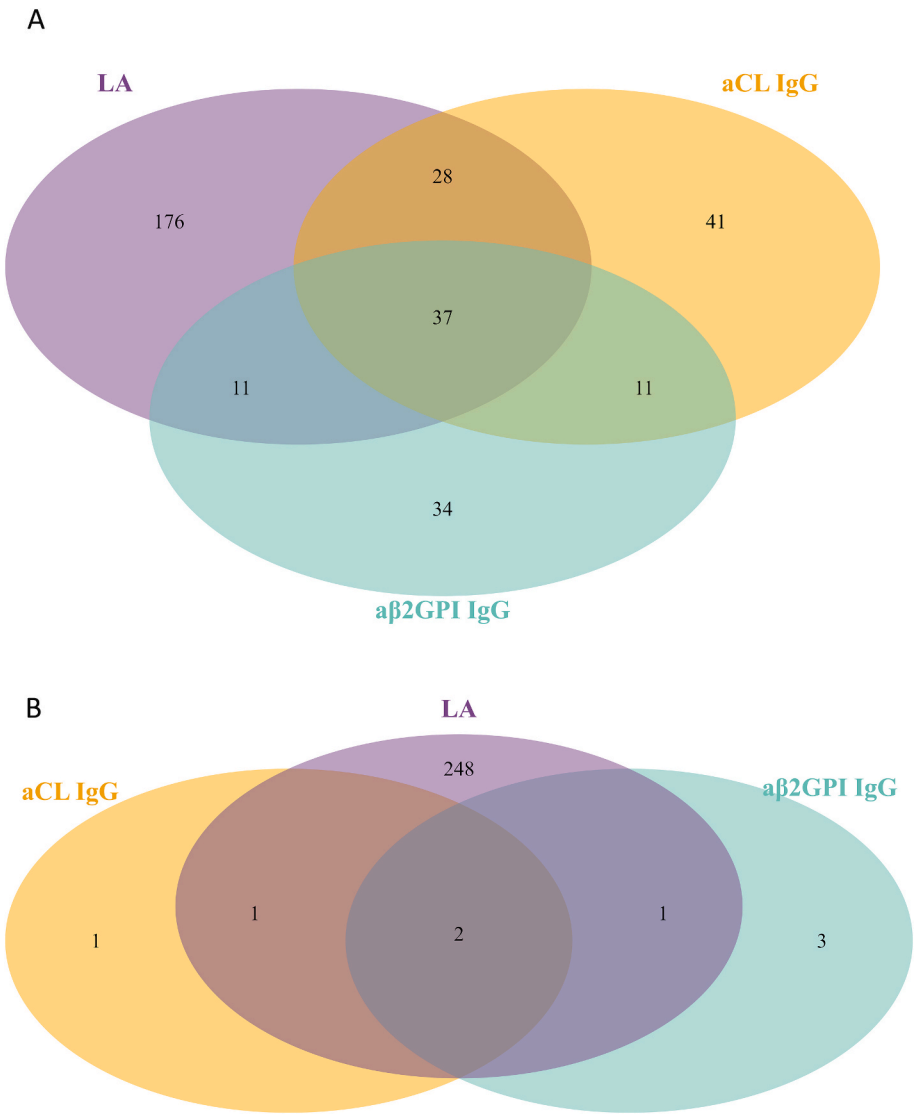

Fig. 2. Antiphospholipid antibody profile of EUROAPS patients fulfilling domain 4.3 of the ACR/EULAR classification criteria. Domain 4.3 includes cases with preeclampsia and/or placental insufficiency with severe features before 34 weeks of gestation, regardless of fetal demise. Venn diagrams show its distribution according to their aPL positivity of (**A**) Domain 4.3 patients after excluding those who were only positive for IgM isotype antibodies, and (**B**) Domain 4.3 patients considering only those with antiphospholipid antibody titres above the threshold of 40 units. aβ2GPI, anti-β2 Glycoprotein I antibodies; aCL, anticardiolipin antibodies; LA, lupus anticoagulant.

these figures have been usually obtained from cases of APS associated with systemic lupus erythematosus.

If the primary goal of the new APS classification criteria is to increase specificity in order to elucidate the mechanistic role of aPL in the disease pathogenesis, then combining disparate clinical criteria that are not clearly mechanistically linked may ultimately hinder this objective. Such heterogeneity in clinical phenotypes could dilute the specificity and complicate the interpretation of antibody-pathology relationships.

Conclusion

The 2023 ACR/EULAR APS criteria substantially reduce the classification of patients previously identified as having OAPS under the 2006 Sydney criteria. Differences in domain weighting, the lower consideration of IgM isotypes, and fixed ELISA thresholds contribute to the exclusion of many obstetric APS cases. Given the resulting 78% case loss, these discrepancies may introduce a considerable bias in future research cohorts, potentially limiting the comparability of studies and hindering progress toward a better understanding of obstetric APS.

CRediT authorship contribution statement

Jaume Alijotas-Reig: Writing – review & editing, Writing – original draft, Validation, Supervision, Project administration, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Enrique Esteve-Valverde:** Supervision, Formal analysis, Data curation. **Luis Sáez-Comet:** Investigation, Formal analysis, Data curation. **Ariadna Anunciación-Llunell:** Investigation, Formal analysis. **Raquel Ferrer-Oliveras:** Investigation, Formal analysis, Data curation. **Eleftheria Lefkou:** Investigation, Formal analysis, Data curation. **Arsène Mekinian:** Investigation, Formal analysis, Data curation. **Cristina Belizna:** Investigation, Formal analysis, Data curation. **Ariela Hoxha:** Investigation, Formal analysis, Data curation. **Angela Tincani:** Investigation, Formal analysis, Data curation. **Luca Marozio:** Investigation, Formal analysis, Data curation. **Gerard Espinosa:** Investigation, Formal analysis, Data curation. **Sara de Carolis:** Investigation, Formal analysis, Data curation. **Sebastian Udry:** Investigation, Formal analysis, Data curation. **Jose Omar Latino:** Investigation, Formal analysis, Data curation. **Elisa Llurba:** Investigation, Formal analysis, Data curation.

Table 5
Distribution of obstetric reclassified cases by aPL positivity.

LA	aCL IgG	aβ2GPI IgG neg	99th pos	Moderate pos	High pos
neg	**neg**	46	31	3	0
	99th pos	40	11	0	0
	Moderate pos	1	0	0	0
	High pos	0	0	0	0
pos	**neg**	176	10	1	0
	99th pos	27	35	0	0
	Moderate pos	1	0	0	0
	High pos	0	0	0	2
Domain 4.3 cases, n (%)		384 (32.0)			
Isolated IgM +		46			
LA neg and < 40-units cut-off		82			
Remaining of initial 1,200 cases, n (%)		256 (21.3)			

From the 1,200 EUROAPS registry, only those fulfilling Domain 4.3, defined as cases of preeclampsia and/or placental insufficiency with severe features before 34 weeks of gestation, irrespective of fetal demise, were included. These patients were redistributed according to their antiphospholipid antibody profile: presence of lupus anticoagulant (LA pos) and graded IgG positivity for aCL and/ or aβ2GPI as follows: titres > 80 units threshold (High pos), titres > 40 units threshold (Moderate pos), titres > 99th percentile threshold (99th pos). Women with isolated IgM positivity were classified as triple negative (neg; light grey). Women with LA negative and not reaching the 40-unit threshold (LA neg & <40-units cut-off; dark grey).

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Ethical approval.

The EUROAPS registry was reviewed and approved by the Ethics Committee and Institutional Review Board of the Departments of Medicine and Obstetrics, Universitat Autònoma de Barcelona, and Vall d'Hebron University Hospital (approval number PR(AG)34/2010). All procedures were conducted in accordance with the Declaration of Helsinki.

Research data.

Data of this article in stored in the Vall d'Hebron Research Institut (VHIR) repository data.

Data Availability.

The data underlying this article includes sensitive and confidential information on patient data and will be shared on reasonable request to the corresponding author.

Author contributions.

JA-R and EE-V are the coordinator and manager of the EUROAPS registry, and did the acquisition and curation of clinical data. JA-R did the conception and design of the work and drafted the manuscript. FM-M did analysis of data, interpretation of the data, the design of the work, and drafted and reviewed manuscript critically. AA-L reviewed manuscript critically. The rest of the authors participated in the acquisition of data for the work, and reviewed it critically. All authors approved the final version.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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