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LETTERS TO THE EDITOR

Impact of the 2023 ACR/EULAR classification criteria in pregnant women with primary antiphospholipid syndrome: insights from a Portuguese cohort

Lopes AR[1,2], Martins C[1,2], Barreira SC[1,2], Martins P[1,2], Pulido-Valente M[3], Pinto L[2,3], Capela S[1,2], Cruz-Machado AR[1,2]

Dear Editor,

Antiphospholipid syndrome (APS) remains a major cause of pregnancy morbidity. The 2023 ACR/EULAR criteria introduced stricter definitions of obstetric morbidity and differential weighting of antibody isotypes and titres to improve specificity[1]. However, concerns persist regarding reduced sensitivity for obstetric-only phenotypes and their clinical implications[2-5].

This study was a retrospective review and reclassification of pregnancies in women fulfilling the 2006 Sydney criteria for APS, applying the 2023 ACR/EULAR criteria to compare clinical characteristics and outcomes after reclassification. Women with primary APS were prospectively followed at our multidisciplinary rheumatology–obstetrics clinic between 2009 and 2024. All eligible pregnancies were identified through the institutional clinical database and patient records, and reclassified according to the 2023 ACR/EULAR criteria. To ensure completeness and accuracy, serological and obstetric variables were independently verified by rheumatologists and obstetricians with expertise in the field of reproductive rheumatology. Only pregnancies with full documentation meeting the required obstetric definitions of the 2023 criteria were included. Each pregnancy was considered one observation. Some women contributed more than one pregnancy; therefore, observations are not statistically independent, and this should be taken into account when interpreting group comparisons. Pregnancies with secondary APS or incomplete follow-up were excluded. Given the exploratory nature of the study and the limited sample size, no correction for multiple comparisons was applied; therefore, p-values should be interpreted as descriptive rather than confirmatory.

Overall, thirty pregnancies meeting the Sydney criteria were analysed. There were 24 live births (80.0%) and 6 losses (20.0%); pregnancy losses included 4 early miscarriages, 1 late miscarriage and 1 medical termination. Adverse pregnancy outcomes (APOs) also comprised 2 small-for-gestational-age newborns, 1 fetal growth restriction (FGR) and 1 preterm birth. Twenty-one pregnancies (70.0%) fulfilled the 2023 ACR/EULAR criteria. Thrombotic APS cases decreased from 22 to 19 due to reclassification of women with a high-risk thrombotic profile (n = 1) or isolated IgM positivity (n = 2). Likewise, obstetric APS declined from 8 to 2, due to lower weighting assigned to early pregnancy losses (n = 4) and isolated IgM positivity (n = 2).

Women fulfilling the new 2023 ACR/EULAR criteria (n = 21) were younger at diagnosis (23.7 ± 6.7 vs. 32.3 ± 4.6 years, p = 0.002) and more often had high-risk serological profiles (lupus anticoagulant: 95.2% vs. 44.4%, p = 0.005; triple antiphospholipid (aPL) positivity: 42.9% vs. 0%, p = 0.029).

In contrast, women who did not meet 2023 ACR/EULAR criteria had higher prevalence of IgM anticardiolipin antibodies (aCL) (55.6% vs. 14.3%, p = 0.032), particularly high titre (>80 units; 44.4% vs. 9.5%, p = 0.049) and IgM anti-β2 glycoprotein I antibodies (aβ2GPI) (55.6% vs. 14.3%, p = 0.032), particularly at low titre (<40 units; 44.4% vs. 4.8%, p = 0.019). Low-titre IgG β2GPI (<40 units) was found exclusively in pregnancies excluded from 2023 ACR/EULAR criteria. Group differences are shown in Table 1.

Despite a significantly lower birth weight in neonates from mothers meeting the 2023 ACR/EULAR criteria (2880 g vs. 3355 g, p = 0.002), the incidence of APOs was comparable (Table I).

The 2023 ACR/EULAR criteria appear to undervalue recurrent early pregnancy losses, low titre and isolated IgM antibodies, potentially excluding women with clinically significant obstetric APS. Observational studies have shown that even low titre aPL and/or IgM isotypes can be deleterious in early phases of implantation[6,7]. Almost half of obstetric APS, some with severe fetal morbidity, are identified by a single antibody, in-

1. Rheumatology Department, ULS Santa Maria, Lisbon Academic Medical Center, Lisbon, Portugal.
2. Faculdade de Medicina, Universidade de Lisboa, Lisbon Academic Medical Center Lisbon, Portugal.
3. Obstetrics, Gynecology, and Reproductive Medicine Department, ULS Santa Maria, Lisbon Academic Medical Center, Lisbon, Portugal.

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Correspondence to: Ana Rita Ribeiro Lopes
E-mail: anaritarlopes22@gmail.com

TABLE I. Demographic, clinical, and serological characteristics of pregnant women with APS and comparison between women meeting or not meeting the 2023 ACR/EULAR criteria.

Demographic characteristics	Sydney Criteria (n = 30)	2023 ACR/EULAR Criteria		*p*-value$^{\phi}$
		Classified (n = 21)	Not classified (n = 9)	
Age at APS diagnosis (years), mean ± SD	26.3 ± 7.3	23.7 ± 6.7	32.3 ± 4.6	**$p = 0.002$**
Age at conception (years), mean ± SD	32.3 ± 4.2	31.5 ± 4.3	34.0 ± 3.7	$p = 0.144$
Time from diagnosis to conception (years), median [IQR]	5.0 [9.0]	8.5 [7.5]	7.0 [7.5]	**$p < 0.001$**
Time from last thrombotic event to conception (years), median [IQR]	6.0 [10.0]	1.0 [4.0]	8.5 [8.0]	**$p < 0.001$**
Classification, n (%)				
Thrombotic APS	22 (73.3)	19 (90.5)	3 (33.3)	**$p = 0.003$**
Obstetric-only APS	8 (26.7)	2 (9.5)	6 (66.7)	N/A
Antiphospholipid antibody profile, n (%)				
Persistent LA	24 (80)	20 (95.2)	4 (44.4)	**p = 0.005**
Anticardiolipin antibodies				
IgM positivity (total)	8 (26.7)	3 (14.3)	5 (55.6)	**p = 0.032**
IgM <40	0	0	0	N/A
IgM 40-80	2 (6.7)	1 (4.8)	1 (11.1)	p = 0.517
IgM >80	6 (20)	2 (9.5)	4 (44.4)	**p = 0.049**
IgG positivity (total)	14 (46.7)	11 (52.4)	3 (33.3)	p = 0.440
IgG <40	2 (6.7)	2 (9.5)	0	p = 1.000
IgG 40-80	5 (16.7)	3 (14.3)	2 (22.2)	p = 0.622
IgG >80	7 (23.3)	6 (28.6)	1 (11.1)	p = 0.393
Combined IgG and IgM positivity	3 (10.0)	3 (14.3)	0	p = 0.534
aB2GPI				
IgM positivity (total)	8 (26.7)	3 (14.3)	5 (55.6)	**p = 0.032**
IgM <40	5 (16.7)	1 (4.8)	4 (44.4)	**p = 0.019**
IgM 40-80	1 (3.3)	1 (4.8)	0	p = 1.000
IgM >80	3 (10.0)	2 (9.5)	1 (11.1)	p = 1.000
IgG positivity (total)	13 (43.3)	9 (42.9)	4 (44.4)	p = 1.000
IgG <40	4 (13.3)	0	4 (44.4)	**p = 0.005**
IgG 40-80	5 (16.7)	5 (23.8)	0	p = 0.286
IgG >80	6 (20.0)	6 (28.6)	0	p = 0.141
Combined IgG and IgM positivity	6 (20.0)	3 (14.3)	3 (33.3)	p = 0.329
Double positivity (LA and aCL or aB2GPI)	19 (63.3)	12 (57.1)	7 (77.8)	p = 0.419
Triple positivity (LA, aCL, and aB2GPI)	9 (30.0)	9 (42.9)	0	**p = 0.029**
Cardiovascular risk factors and main comorbidities				
High blood pressure, n (%)	2 (6.7)	1 (4.8)	1 (11.1)	p = 0.517
Obesity, n (%)	5 (16.7)	1 (4.8)	4 (44.4)	**p = 0.019**
Diabetes, n (%)	0	0	0	N/A
Dyslipidemia, n (%)	4 (13.3)	3 (14.3)	1 (11.1)	p = 1.000
Smoking, n (%)	2 (6.9)	1 (5.0)	1 (11.1)	p = 0.532
Thyroid disease, n (%)	4 (13.3)	2 (9.5)	2 (22.2)	p = 0.563
Gynecologic adverse condition*, n (%)	2 (6.7)	0	2 (22.2)	p = 0.083

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Demographic characteristics	Sydney Criteria (n = 30)	2023 ACR/EULAR Criteria		*p*-value$^{\phi}$
		Classified (n = 21)	Not classified (n = 9)	
APS treatments during pregnancy, n (%)				
Anticoagulation, n (%)	27 (90.0)	19 (90.5)	8 (88.9)	p = 1.000
Prophylactic LMWH, n (%)	11 (36.7)	5 (23.8)	6 (66.7)	**p = 0.042**
Therapeutic LMWH, n (%)	17 (56.7)	15 (71.4)	2 (22.2)	**p = 0.020**
Warfarin**, n (%)	2 (6.7)	2 (9.5)	0	p = 1.000
Low-dose aspirin, n (%)	30 (100.0)	21 (100.0)	9 (100.0)	N/A
Combined therapy (anticoagulant and antiplatelet), n (%)	27 (90.0)	19 (90.5)	8 (88.9)	p = 1.000
Hydroxychloroquine, n (%)	7 (23.3)	7 (33.3)	0	p = 0.071
Maternal and Perinatal Outcomes during follow-up, n (%)				
Early pregnancy loss***, n (%)	4 (13.3)	4 (19.0)	0	p = 0.287
Late pregnancy loss ***, n (%)	1 (3.3)	0	1 (11.1)	p = 0.300
Stillbirth***, n (%)	0	0	0	N/A
Medical termination of pregnancy, n (%)	1 (3.3)	1 (4.8)	0	p = 1.000
Gestational age at delivery (weeks), median [IQR]	39.0 [2.4]	39.3 [2.4]	38.6 [2.7]	p = 0.922
Preterm births, n (%)	1 (4.2)	1 (6.3)	0	p = 1.000
Fetal growth restriction, n (%)	1 (4.2)	1 (6.3)	0	p = 1.000
Small for gestational age, n (%)	2 (10.0)	2 (15.4)	0	p = 0.521
Birth weight at delivery (grams), median [IQR]	3135.0 [506]	2880.0 [498]	3355.0 [600]	**p = 0.002**
Cesarean deliveries, n (%)	17 (73.9)	10 (66.7)	7 (87.5)	p = 0.369
Gestational hypertension, n (%)	1 (3.7)	0	1 (11.1)	p = 0.333
Gestational diabetes mellitus, n (%)	3 (11.1)	2 (11.1)	1 (11.1)	p = 1.000
Pre-eclampsia, n (%)	0	0	0	N/A
Eclampsia, n (%)	0	0	0	N/A
Maternal thrombotic events during pregnancy/postpartum, n (%)	2 (6.7)	2 (9.5)	0	p = 1.000
Occurrence of adverse pregnancy outcomes, n (%)	8 (26.7)	7 (33.3)	1 (11.1)	p = 0.374

APS, antiphospholipid syndrome; LA, lupus anticoagulant; aCL, anticardiolipin antibodies; aB2GPI, anti-β2 glycoprotein I antibodies; IgM, Immunoglobulin M; IgG, immunoglobulin G; LMWH, low-molecular-weight heparin; N/A, not applicable. *Gynecologic adverse condition includes gynecologic or structural conditions that may impair fertility or complicate pregnancy, such as endometriosis, uterine fibroids, uterine anomalies, or polycystic ovary syndrome. **Warfarin exposure was documented in two pregnancies where conception occurred during ongoing anticoagulation therapy, without prior preconception counselling. One pregnancy ended in spontaneous miscarriage and the other in elective termination during the first trimester. ***Early pregnancy loss: before 12 weeks+6 days of gestation; Late pregnancy loss: between 13 weeks+0 days and 19 weeks+6 days of gestation; Stillbirth: after 20 weeks of pregnancy.
ϕ Data are expressed as mean ± standard deviation, median [interquartile range], or number (%), as appropriate. p-values refer to comparisons between women fulfilling and not fulfilling the 2023 ACR/EULAR criteria and are descriptive rather than confirmatory, as no correction for multiple comparisons was applied. Statistical tests used include independent samples t-test, Mann–Whitney U test, and Fisher's exact test, as applicable.

cluding isolated IgM aCL or aβ2GPI[6]. These findings reinforce that obstetric and thrombotic APS represent distinct clinical entities and differ in their serological profiles for pathogenicity.

The biological plausibility of these observations is supported by experimental evidence showing that the placenta and trophoblast are privileged aPL targets. β2GPI, the main autoantigen recognised by aPL, is highly expressed at the maternal–fetal interface.[8] Binding of aPL to β2GPI interferes with trophoblast function and spiral artery remodelling[8], essential to establish adequate uteroplacental blood flow. Failure leads to early losses, or, if pregnancy progresses, hypoperfusion, pre-eclampsia and FGR.[8] This pathogenic mechanism reinforces that low-titre and IgM antibodies may play a more direct role in obstetric APS than in thrombotic APS.

In our cohort, pregnancy outcomes were similar regardless of classification status, suggesting that women failing the 2023 ACR/EULAR criteria may still benefit from standard antithrombotic therapy. These findings, from a Portuguese multidisciplinary obstetric APS cohort, align with international reports and provide valuable local insight into the applicability of the new criteria. While our design quantifies the reclassification impact of applying the 2023 ACR/EULAR criteria to

a cohort fulfilling Sydney 2006, it does not allow assessment of diagnostic accuracy or prognostic performance. The aim of this study was to describe which pregnancies would no longer be classified under the new criteria and to highlight the potential clinical implications of this reclassification. Prospective validation in larger cohorts will be needed to determine diagnostic and prognostic value.

Although the new criteria improve specificity for research, their reduced sensitivity may inadvertently exclude at-risk women from both clinical care and future studies. Clinical judgment must remain central in identifying and managing obstetric APS.

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