Journal Pre-proof

# Are the new 2023 ACR/EULAR classification criteria suitable for advancing the knowledge of obstetric antiphospholipid syndrome?

**Víctor M. Martínez-Taboada[a,e], Ana Micieces Gómez[a], Ana Merino[b], Marcos López-Hoyos[c,f], Sara del Barrio-Longarela[b], Alejandra Comins-Boo[c], Rafael Galvez[a], José L. Hernández[d,e].**

[a]Division of Reumatology. [b]Division of Obstetrics and Gynecology. [c]Immunology Department. [d]Division of Internal Medicine. Hospital Marqués de Valdecilla-IDIVAL. Santander. [e]Department of Medicine and Psychiatry, Universidad de Cantabria. [f]Department of Molecular Biology, University of Cantabria.

**Funding:** Not applicable.

**Conflict of interest:** There is no conflict of interest from any author concerning this paper.

**Running title:** New Classification Criteria and Obstetric Antiphospholipid Syndrome.

**Keywords:** Pregnancy; antiphospholipid syndrome; antiphospholipid antibodies, classification criteria, non-criteria obstetric manifestations

**Correspondence to:**

Prof. Víctor M. Martínez-Taboada

© 2024. This manuscript version is made available under the CC-BY-NC-ND 4.0 license http://creativecommons.org/licenses/by-nc-nd/4.0/

Journal Pre-proof

Departamento de Medicina y Psiquiatría. Universidad de Cantabria

Servicio de Reumatología. Hospital Marqués de Valdecilla. Avda. Valdecilla s/n. 39008, Santander

e-mail: vmartinezt64@gmail.com. Tel: +34 942202510

Journal Pre-proof

*Dear Editor.*

The new classification criteria for Antiphospholipid Syndrome (APS) [**1**], represents a clear update from the initial Sapporo criteria [**2**], later modified in Sydney [**3**], which have been widely used in daily clinical practice. Although it is indisputable that classification criteria should not be used as diagnostic criteria, this aspect is relatively common in everyday clinical practice, and both are often considered part of the same continuum by many clinicians [**4**]. Except for diseases with a "gold standard" for diagnosis, such as gout, the uncertainty in distinguishing between classification and diagnostic criteria in heterogeneous diseases such as APS is significantly greater.

The 2023 ACR/EULAR criteria for APS have several advantages over the previous ones [**1**]. Besides significant methodological advances, their main objective was to develop highly specific criteria intended to identify homogeneous patient groups to advance APS research [**1,5**]. From a practical standpoint, these new criteria aimed to address the limitations of the previous ones [**6**]. Sydney's criteria did not include risk factors for thrombosis. Some less common manifestations such as valvulopathy, thrombocytopenia, or microvascular involvement were not represented, and the definition of obstetric morbidity was perhaps too general. Moreover, from a laboratory perspective, the stratification of antiphospholipid antibodies (aPL) and a clearer definition of their positivity were also lacking in the previous criteria [**6**]. According to the new methodology, the new criteria do not require at least one clinical and one laboratory criterion. Instead, each new manifestation in the different domains has a determined score. A minimum score of 3 is required in both clinical and serological domains to be classified as APS. Furthermore, the interval between the clinical event and the laboratory test has been reduced from 5 to 3 years. **Table 1** shows the time course of clinical and serological criteria from the initial Sapporo criteria to the new ones.

Journal Pre-proof

As shown in **Suppl Table 1** the impact of these criteria was recently analyzed by different authors. Foddai SG et al [**7**], showed that approximately half of the patients diagnosed with APS according to the Sydney criteria would not meet the new ones, with this fact being especially relevant in obstetric manifestations (only 23.2% would meet the new criteria). Although globally, 17.2% of patients developed clinical manifestations during their evolution, allowing for reclassification in up to nearly 66% of cases, it is noteworthy that the clinical manifestations, both thrombotic and especially obstetric, developed during follow-up despite receiving appropriate treatment [**7**]. Another surprising aspect is that most patients with obstetric morbidity developed cutaneous manifestations (suspected livedo racemosa or livedoid vasculopathy), which in our clinical experience are exceptional in OAPS, especially those not associated with autoimmune disease. One of the strengths highlighted by the authors is the inclusion of two validation cohorts with a large number of patients with suspected APS [**1**]. It is evident that in both validation cohorts, there is a clear overestimation of certain clinical characteristics (microvascular involvement or preeclampsia and/or placental insufficiency) and serological characteristics (LA positivity) compared to their prevalence in well-recognized multicenter studies [**8**]. In another study published by Lu Q et al. [**9**], which examines two Asian cohorts, the ACR/EULAR 2023 criteria globally show high specificity but lower sensitivity compared to the Sydney criteria. This decreased sensitivity is particularly due to the impact of the obstetric domain, where it drops to 0.56 (0.4-0.71). In fact, patients who do not meet the new criteria have a higher proportion of obstetric morbidity (52.5% vs 29.4%, p=0.005), especially early fetal death at 10-16 weeks (19% vs 5%, p=0.028). A letter to the editor by Chinese researchers [**10**], recently published as a full article [**11**], analyzing the impact of the new criteria, though less markedly, also highlights the potential impact of the new criteria, especially in OAPS. Additionally, the authors showed concern about potential overdiagnosis caused by the inclusion of thrombocytopenia in the classification domains, especially in patients with SLE. Finally, Zhao Y. et al. [**12**], in another study of Asian

patients, and Vasi I. et al. [**13**], in a study carried out in Turkey, also showed high specificity but lower sensitivity of the new criteria, especially at the expense of the obstetric morbidity and the presence of IgM isotype antibodies.

**Suppl Table 2** shows a PubMed literature search (as of 01/31/2024) including the main terms found in the domains of the new classification criteria and four types of relevant articles. The raw search is sufficiently illustrative to determine that most of the literature on APS refers to thrombotic and obstetric manifestations. There is a notable lack of published evidence regarding microvascular manifestations (possibly except for aPL nephropathy), although a significant number of studies refer to aPL-associated thrombocytopenia. While thrombocytopenia is currently considered an additional thrombotic risk factor, it is unlikely that future clinical trials will be based on a laboratory manifestation that typically does not require treatment *per se* [**14**]. It is obvious that developing well-designed studies, beyond multicenter registries as seen in catastrophic APS [**15**], will be extremely difficult for manifestations such as pulmonary or adrenal hemorrhage, and even for cutaneous manifestations, once livedo reticularis is excluded. When analyzing randomized controlled trials (RCTs) in detail, they are obviously restricted to the most common and relevant manifestations of APS. In thrombotic APS, RCTs focus primarily on different intensities of anticoagulation, direct oral anticoagulants, or hydroxychloroquine [**16,17**]. In OAPS, most RCTs compare different thromboprophylaxis regimens and, to a lesser extent, the impact of corticosteroids, intravenous immunoglobulins, or hydroxychloroquine [**16,18**]. It is noteworthy that all clinical trials, except one conducted in patients with recurrent early-onset preeclampsia [**19**], have predominantly included patients with recurrent early miscarriages [**20**]. Interestingly, the only study that included women with previous preterm birth <34 weeks (secondary to placental disorder) concluded with the enrollment of only 32 patients after 9 years of recruitment across 17 centers [**19**]. It is important to highlight that despite current recommendations in this clinical

context [**21,22**], this study did not demonstrate the superiority of combined treatment over ASA monotherapy [**19**].

Taken into account these considerations, several thoughts on the impact of the new ACR/EULAR 2023 criteria on OAPS emerge. First, and awaiting further studies to explore their utility in OAPS, preliminary studies suggest a clear impact on the classification of these patients [**7**]. This is particularly relevant for women with solely obstetric manifestations, recurrent early miscarriages or fetal deaths, which, although nonspecific, are undoubtedly the most frequent in daily clinical practice. From a strictly serological perspective, the lower weight given to IgM antibodies, even double positives, will also pose an additional challenge in classifying patients [**23**]. Second, it is particularly important to emphasize the real differences between classification criteria and diagnostic criteria and, therefore, the therapeutic consequences this consideration should have. Patients with a highly suggestive clinical and serological picture of APS should receive appropriate treatment and monitoring based on experienced clinical judgment, regardless of the new classification criteria [**24**]. Third, basic research in OAPS should not be affected by the new classification criteria, or we risk limiting it to placentation disorders. Fourth, given the frequency of clinically significant OAPS manifestations (severe preeclampsia and/or severe placental insufficiency), included in the current classification criteria (probably below 15-20%), the development of not only new therapeutic alternatives derived from properly designed clinical trials but also a reasonably founded proposal for conventional therapy [**19**], seems unrealistic. Only a multidisciplinary and international multicenter effort will allow for the identification of appropriate treatment for these patients. Fifth, in real clinical practice, the impact of the new clinical manifestations included in the ACR/EULAR classification criteria (especially not associated with another autoimmune disease) appears to be minimal. On the one hand, microvascular involvement is exceptional in young women without associated connective tissue diseases. Furthermore, in most young women with obstetric morbidity, an echocardiogram is neither

Journal Pre-proof

performed nor indicated *a priori* to identify valvular involvement. Although thrombocytopenia can affect approximately a quarter of aPL carriers and qualify them under the classification criteria, its role in OAPS is much more controversial and questionable as a defining feature of a distinct patient subgroup. Finally, the subgroup of patients with suggestive APS clinical manifestations but inconclusive or negative serology poses another frequent challenge for clinicians. While the inclusion of other autoantibodies has not been considered in the current classification criteria, they may have some value in certain patient subgroups [**25**]. Additionally, it has been speculated that in OAPS, persistently low autoantibody titers included in the criteria could play a relevant role [**24**,**26**].

In summary, the new 2023 ACR/EULAR classification criteria for APS represent a commendable effort and a significant advancement in attempting to broaden the clinical spectrum of this disease. Given their impact on some of the most common APS domains, such as the obstetric domain, perhaps the word "provisional" might have conveyed the need to validate these new criteria and determine their true utility. It is evident that as well-designed validation studies become available, the Expert Committee will be able to introduce the necessary changes and improve their applicability, not only in the development of quality research but also in enhancing daily clinical practice.

Journal Pre-proof

**REFERENCES**

1.- Barbhaiya M, Zuily S, Naden R, Hendry A, Manneville F, Amigo MC, et al; ACR/EULAR APS Classification Criteria Collaborators. 2023 ACR/EULAR antiphospholipid syndrome classification criteria. Ann Rheum Dis. 2023 Oct;82(10):1258-1270. doi: 10.1136/ard-2023-224609. Epub 2023 Aug 28. PMID: 37640450.

2.- Wilson WA, Gharavi AE, Koike T, Lockshin MD, Branch DW, Piette JC, et al. International consensus statement on preliminary classification criteria for definite antiphospholipid syndrome: report of an international workshop. Arthritis Rheum. 1999 Jul;42(7):1309-11. doi: 10.1002/1529-0131(199907)42:7<1309::AID-ANR1>3.0.CO;2-F. PMID: 10403256.

3.- Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, Cervera R, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost. 2006 Feb;4(2):295-306. doi: 10.1111/j.1538-7836.2006.01753.x. PMID: 16420554.

4.- Aggarwal R, Ringold S, Khanna D, Neogi T, Johnson SR, Miller A, et al. Distinctions between diagnostic and classification criteria? Arthritis Care Res (Hoboken). 2015 Jul;67(7):891-7. doi: 10.1002/acr.22583. PMID: 25776731; PMCID: PMC4482786.

5.- Knight JS, Erkan D. Rethinking antiphospholipid syndrome to guide future management and research. Nat Rev Rheumatol. 2024 Jun;20(6):377-388. doi: 10.1038/s41584-024-01110-y. Epub 2024 May 3. PMID: 38702511.

6.- Barbhaiya M, Zuily S, Ahmadzadeh Y, Amigo MC, Avcin T, Bertolaccini ML, et al; New APS Classification Criteria Collaborators. Development of a New International Antiphospholipid Syndrome Classification Criteria Phase I/II Report: Generation and Reduction of Candidate Criteria. Arthritis Care Res (Hoboken). 2021 Oct;73(10):1490-1501. doi: 10.1002/acr.24520. Epub 2021 Sep 2. PMID: 33253499; PMCID: PMC8966711.

7.- Foddai SG, Radin M, Cecchi I, Rubini E, Barinotti A, Alba P, et al. 2023 ACR/EULAR classification criteria in existing research cohorts: an international study. Rheumatology (Oxford). 2024 Jan 30:keae058. doi: 10.1093/rheumatology/keae058. Epub ahead of print. PMID: 38290789.

Journal Pre-proof

8.- Cervera R, Piette JC, Font J, Khamashta MA, Shoenfeld Y, Camps MT, et al. Antiphospholipid syndrome: clinical and immunologic manifestations and patterns of disease expression in a cohort of 1,000 patients. Arthritis Rheum. 2002 Apr;46(4):1019-27. doi: 10.1002/art.10187. PMID: 11953980.

9.- Lu Q, Gan Y, Yao Z, Li C. A diagnostic performance study of the 2023 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria for patients with antiphospholipid syndrome from the Antiphospholipid Syndrome Chinese Collaborative cohort presenting with suspected antiphospholipid syndrome. Arthritis Rheumatol. 2024 Feb 25. doi: 10.1002/art.42835. Epub ahead of print. PMID: 38403457.

10.- Tang Z, Shi H, Liu HL, Cheng X, Ye J, Su Y, et al. Correspondence on '2023 ACR/EULAR antiphospholipid syndrome classification criteria'. Ann Rheum Dis. 2024 Feb 15;83(3):e4. doi: 10.1136/ard-2023-225013. PMID: 37989549.

11.- Yang Y, Jiang H, Tang Z, Pan H, Liu H, Cheng X, et al. Assessment of the 2023 ACR/EULAR antiphospholipid syndrome classification criteria in a Chinese cohort: Impact on clinical practice. J Autoimmun. 2024 Jun;146:103237. doi: 10.1016/j.jaut.2024.103237. Epub 2024 May 14. PMID: 38749076.

12.- Zhao Y, Huang C, Zhou Y, Qi W, Cai B, Hu C, et al. Performance validation of the 2023 American College of Rheumatology/European League Against Rheumatism antiphospholipid syndrome classification criteria in an antiphospholipid syndrome cohort. J Thromb Haemost. 2024 Jun;22(6):1660-1674. doi: 10.1016/j.jtha.2024.02.019. Epub 2024 Mar 9. PMID: 38462219.

13.- Vasi İ, Kardaş RC, Ekici M, Yıldırım D, Kaya B, Duran R, et al. Assessment and comparison of the 2023 ACR/EULAR APS criteria with the revised Sapporo criteria. Int J Rheum Dis. 2024 May;27(5):e15175. doi: 10.1111/1756-185X.15175. PMID: 38720575.

Journal Pre-proof

14.- Zuily S, Cervera R, Foret T, Bertocchi S, Tincani A. Thrombocytopenia in antiphospholipid syndrome: Is anticoagulation and/or antiaggregation always required? Autoimmun Rev. 2023 Aug 22:103417. doi: 10.1016/j.autrev.2023.103417. Epub ahead of print. PMID: 37619905.

15.- Rodriguez-Pintó I, Espinosa G, Cervera R. What we know and what we don't know about catastrophic antiphospholipid syndrome. Rheumatology (Oxford). 2024 Feb 6;63(SI):SI46-SI53. doi: 10.1093/rheumatology/kead556. PMID: 38320593.

16.- Tektonidou MG, Andreoli L, Limper M, Tincani A, Ward MM. Management of thrombotic and obstetric antiphospholipid syndrome: a systematic literature review informing the EULAR recommendations for the management of antiphospholipid syndrome in adults. RMD Open. 2019 Apr 28;5(1):e000924. doi: 10.1136/rmdopen-2019-000924. PMID: 31168416; PMCID: PMC6525610.

17.- Bala MM, Celinska-Lowenhoff M, Szot W, Padjas A, Kaczmarczyk M, Swierz MJ, et al. Antiplatelet and anticoagulant agents for secondary prevention of stroke and other thromboembolic events in people with antiphospholipid syndrome. Cochrane Database Syst Rev. 2020 Oct 12;10(10):CD012169. doi: 10.1002/14651858.CD012169.pub3. PMID: 33045766; PMCID: PMC8094585.

18.- Riancho-Zarrabeitia L, Lopez-Marin L, Cacho PM, López-Hoyos M, Barrio RD, Haya A, et al. Treatment with low-dose prednisone in refractory obstetric antiphospholipid syndrome: A retrospective cohort study and meta-analysis. Lupus. 2022 Jun;31(7):808-819. doi: 10.1177/09612033221091401. Epub 2022 Apr 11. PMID: 35410552.

19.- van Hoorn ME, Hague WM, van Pampus MG, Bezemer D, de Vries JI; FRUIT Investigators. Low-molecular-weight heparin and aspirin in the prevention of recurrent early-onset pre-eclampsia in women with antiphospholipid antibodies: the FRUIT-RCT. Eur J Obstet Gynecol Reprod Biol. 2016 Feb;197:168-73. doi: 10.1016/j.ejogrb.2015.12.011. Epub 2015 Dec 19. PMID: 26771908.

20.- Guerby P, Fillion A, O'Connor S, Bujold E. Heparin for preventing adverse obstetrical outcomes in pregnant women with antiphospholipid syndrome, a systematic review and meta-analysis. J Gynecol Obstet Hum Reprod. 2021 Feb;50(2):101974. doi: 10.1016/j.jogoh.2020.101974. Epub 2020 Nov 7. PMID: 33171281.

Journal Pre-proof

21.- Tektonidou MG, Andreoli L, Limper M, Amoura Z, Cervera R, Costedoat-Chalumeau N, et al. EULAR recommendations for the management of antiphospholipid syndrome in adults. Ann Rheum Dis. 2019 Oct;78(10):1296-1304. doi: 10.1136/annrheumdis-2019-215213. Epub 2019 May 15. PMID: 31092409.

22.- Cáliz Cáliz R, Díaz Del Campo Fontecha P, Galindo Izquierdo M, López Longo FJ, Martínez Zamora MÁ, et al. Recommendations of the Spanish Rheumatology Society for Primary Antiphospholipid Syndrome. Part I: Diagnosis, Evaluation and Treatment. Reumatol Clin (Engl Ed). 2020 Mar-Apr;16(2 Pt 1):71-86. English, Spanish. doi: 10.1016/j.reuma.2018.11.003. Epub 2019 Feb 1. PMID: 30713012.

23.- Alijotas-Reig J, Marques-Soares J, Esteve-Valverde E, Miró-Mur F, Belizna C, Udry S, et al. Correspondence and comments on American College of Rheumatology and EULAR antiphospholipid syndrome classification criteria: comment on the article by Barbhaiya et al. Arthritis Rheumatol. 2024 May;76(5):816-817. doi: 10.1002/art.42792. Epub 2024 Feb 7. PMID: 38200647.

24.- Tincani A, Andreoli L. Setting the Bar Differently: How to Navigate Old And New Sets of Criteria for the Classification of Antiphospholipid Syndrome. Rheumatology (Oxford). 2024 Apr 5:keae214. doi: 10.1093/rheumatology/keae214. Epub ahead of print. PMID: 38579186.

25.- Vandevelde A, Gris JC, Moore GW, Musiał J, Zuily S, Wahl D, et al. Added value of antiphosphatidylserine/prothrombin antibodies in the workup of obstetric antiphospholipid syndrome: communication from the ISTH SSC Subcommittee on Lupus Anticoagulant/Antiphospholipid Antibodies. J Thromb Haemost. 2023 Jul;21(7):1981-1994. doi: 10.1016/j.jtha.2023.04.001. Epub 2023 Apr 13. PMID: 37061133.

26.- Meroni PL, Borghi MO, Grossi C, Chighizola CB, Durigutto P, Tedesco F. Obstetric and vascular antiphospholipid syndrome: same antibodies but different diseases? Nat Rev Rheumatol. 2018 Jul;14(7):433-440. doi: 10.1038/s41584-018-0032-6. PMID: 29891914.

Journal Pre-proof

**Table 1.** Comparison of clinical classification criteria for antiphospholipid syndrome (APS).

| | **Sapporo (1999) [2]** | **Sydney (2006) [3]** | **New criteria (2023) [1]** |
|---|---|---|---|
| **Required Criteria** | 1 clinical + 1 laboratory | 1 clinical + 1 laboratory | ≥3 points from clinical domains + ≥3 points from serological domains |
| Time gap between clinical event and laboratory test | 5 years | 5 years | 3 years |
| **Clinical criteria** | | | |
| **Vascular thrombosis** | | | **Domain 1**<br>**Domain 2** |
| High-risk profiles for thrombosis | Not considered | Not considered | Differentiates thrombosis development with/without risk factors<br>- High risk of venous thromboembolic disease<br>- High risk of arterial cardiovascular disease |
| **Microvascular Domain** | Not considered(a) | Not considered(a) | **Domain 3**(b) |
| **Pregnancy morbidity** | - 1 or more unexplained fetal deaths after the 10th week[a]<br>- 1 or more preterm births (<34 weeks) due to eclampsia or severe preeclampsia or severe placental insufficiency<br>- 3 or more miscarriages before the 10th week[a] | - 1 or more unexplained fetal deaths after the 10th week[a]<br>- 1 or more preterm births (<34 weeks) due to eclampsia or severe preeclampsia or severe placental insufficiency<br>- 3 or more miscarriages before the 10th week[a] | **Domain 4**<br><br>- Fetal death and recurrent early miscarriage lose diagnostic value<br>- Distinguishes between early fetal death (10-15+6 weeks) and late fetal death (16-33$^{+6}$ weeks) |
| **Heart valve involvement** | Not considered(a) | Not considered(a) | **Domain 5** |
| **Thrombocytopenia** | Not considered(a) | Not considered(a) | **Domain 6** |
| **Serologic criteria** | | | |
| **Lupus** | Present on | Present on | **Domain 7** |

Journal Pre-proof

| | | | |
|---|---|---|---|
| **anticoagulant (LA)** | two or more occasions, at least 6 weeks apart | two or more occasions, at least 12 weeks apart | - Present on two or more occasions, at least 12 weeks apart<br>- Higher classification value<br>- The single determination of LA is valued when repeated tests are not available. |
| **Anticardiolipin antibodies** | IgG and IgM at medium or high titers, present on two or more occasions, at least 6 weeks apart (ELISA) | IgG and IgM at medium or high titers, present on two or more occasions, at least 12 weeks apart (ELISA) | **Domain 8**<br>- They distinguish between moderate and high titers |
| **Anti-$\beta_2$ glicoproteína-I antibodies** | Not included | IgG and IgM at medium or high titers, present on two or more occasions, at least 12 weeks apart (ELISA) | **Domain 8**<br>- They distinguish between moderate and high titers |
| Antibodies stratification | Equal value is assigned to IgM and IgG isotypes | Equal value is assigned to IgM and IgG isotypes | - Lower classification value for IgM<br>- Higher classification value for IgG<br>- Double positives are given higher classification value than single positives |

Journal Pre-proof

Journal Pre-proof

**Declaration of interests**

☒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.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Journal Pre-proof

**HIGHLIGHTS**

- The new 2023 ACR/EULAR classification criteria represent an overall advance for research in antiphospholipid syndrome (APS).

- To achieve high specificity, in some domains such as obstetric morbidity, the most frequent clinical manifestations such as early and late fetal deaths, have lost significant classification value.

- The lower classification value of antiphospholipid antibodies of the IgM isotype may also have an important impact on patients with obstetric APS.

- Several recent studies unequivocally point out the impact on the sensitivity of the new criteria, especially in the obstetric domain.

- This study underscores the importance of distinguishing between classification and diagnostic criteria and emphasizes the therapeutic implications of this differentiation in obstetric APS.

Journal Pre-proof