Editorial paper

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Obstetric antiphospholipid syndrome: evolving classification and implications for clinical practice and research


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Introduction

Antiphospholipid syndrome (APS) is an autoimmune disease characterized by the combination of persistent antiphospholipid antibodies (aPL) and clinical manifestations, including venous or arterial thrombosis and pregnancy complications. The diagnostic and classification criteria of APS have undergone significant changes in recent decades [1–3].

Obstetric APS (oAPS) is a subtype of APS characterized by exclusively pregnancy-related complications – such as early recurrent miscarriage, unexplained fetal death, severe preeclampsia, or preterm delivery due to placental insufficiency – in the absence of thrombotic events [4].

In recent years, oAPS and vascular APS (vAPS) have increasingly been recognized as two distinct clinical entities, suggesting that the underlying pathophysiological changes leading to clinical events also differ [5]. In the vascular form, aPL attack components of the coagulation cascade. While thrombotic events were previously considered the main factor underlying the symptoms of oAPS, recent findings indicate that oAPS involves other mechanisms as well: there is an established direct multifaceted effect of anti-β2-glycoprotein I on trophoblast cells, which can lead to direct placental functional impairment, and it interacts with stromal decidual cells and endometrial endothelial cells. The role of the annexin V protective layer and phosphatidylserine expressed on trophoblast cells, as well as the function of aPL that bind to them, is becoming increasingly understood. In addition, other new players have been recognized in the pathogenesis of oAPS, including extracellular vesicles, microRNAs and the release of neutrophil extracellular traps [6, 7]. The presence of aPL in oAPS may also disrupt the delicate balance of NK cell-mediated immune regulation, leading to alterations in cell activation, cytokine production, and cytotoxic functions [8].

The Sydney criteria (2006) have provided the standard diagnostic framework for a long time. This employed binary logic: at least one clinical (thrombosis or obstetric event) and one laboratory criterion were required for diagnosis [1].

The 2023 American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) classification criteria system implemented a fundamentally new approach. The new system is score-based, includes one clinical and one laboratory entry criterion, and includes 6 clinical (macrovascular thrombosis, microvascular events, pregnancy morbidity, valvular heart disease, hematological abnormalities) and 2 laboratory (LA and ELISA-based aPL tests) domains, with each item having a weighted value. Each domain is assigned a score [1–7]; however, a minimum of 3 points must be collected from both the clinical and laboratory domains. The aim was to achieve higher specificity (99% up from 86%), but this came at the cost of decreased sensitivity (84% down from 99%). This reduction in sensitivity is particularly pronounced in the oAPS population [2].

Thus, oAPS is now considered a separate diagnosis, with pregnancy symptoms appearing as a subset of symptoms, alongside other clinical and laboratory features. The main aim of the scoring system is to reduce false positive cases, but if there are not enough points, some real oAPS cases may be missed from the diagnosis. The "non-criteria obstetric APS" (NC-oAPS) forms do

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not strictly fit the classical definition, but they are still dangerous – they must also be treated in daily clinical practice. This system does not provide an opportunity to verify them either [4].

Comparison of the old and new criteria

Based on the Sydney criteria, the diagnosis of oAPS could also be established in cases where the patient presented with exclusively obstetric complications, such as three or more early miscarriages (< 10 weeks) or one intrauterine fetal death after ≥ 10 weeks. Repeated immunoglobulin M (IgM) antibody positivity was also considered sufficient to meet the laboratory criterion. The system's high sensitivity allowed it to encompass a broad patient demographic; however, its specificity remained relatively low [1].

In contrast, the introduction of the 2023 ACR/EULAR criteria streamlined the entry requirements: patients needed at least one clinical symptom from one of the domains and a reliable aPL test (lupus anticoagulant, or moderate-to-high titer anticardiolipin antibody or anti-β2-glycoprotein I (IgG/IgM). This was then followed by a weighted score from both the clinical and laboratory domains.

The range of obstetric events has been narrowed: for example, early miscarriages or late fetal losses without isolated preeclampsia/placental insufficiency are no longer considered sufficient on their own. Furthermore, the reduced significance attributed to isolated IgM positivity has led to the exclusion of many patients previously identified as oAPS [2] (Table I).

The new classification system has reinforced the long-expressed need among clinicians and researchers to distinguish oAPS as a separate entity [4, 6, 9].

Marques-Soares et al. [10] reviewed data from the European Registry on Obstetric Antiphospholipid Syndrome (EUROAPS), established in 2011, to examine how the new 2023 ACR/EULAR criteria would impact the classification of women in the registry and how this would affect future research. The EUROAPS [11] was established with the aim of creating a standardized database of patients with oAPS. By early 2023, data from more than 1,200 women had been collected. Marques-Soares et al. [10] compared clinical data from women in the registry diagnosed using the Sydney criteria with the criteria of the new system. In particular, early fetal losses and late losses without preeclampsia or placental insufficiency (domain 4/2) were examined, which are no longer sufficient in the new system. Overall, 76% of the original patient group in the registry became "ineligible" based on the new criteria (814 had isolated obstetric histories now insufficient alone and 46 had isolated IgM positivity). It was highlighted that the 2023 criteria drastically narrow the group of oAPS patients. The downgrading of IgM positivity and the reduction of the weight of several pathological events in pregnancy result in the exclusion of a significant part of the research population, which may compromise the representativeness of future clinical trials. The authors emphasize that while the gain in specificity is advantageous, the drastic decrease in sensitivity raises serious concerns.

Ruffilli et al. [12] retrospectively analyzed data from 2 Italian centers (2006–2023) and included 121 women with a primary diagnosis of oAPS. Only 26 patients (22%) could be classified according to the new ACR/EULAR criteria, while 91 patients (75%) could be classified according to the Sydney criteria. New events also occurred frequently among patients who met the Sydney criteria but could not be classified according to the new criteria, and early miscarriages were significantly more common in this group. This study also clearly supports that the sensitivity of the new criteria is extremely low (20.4%), and milder but more common oAPS phenotypes are not classified, which may result in a clinically

Table I. Old oAPS vs. new APS criteria

Feature	Old oAPS criteria (Sydney)	New (2023 ACR/EULAR) criteria
Clinical focus	Only obstetric complications (miscarriage, fetal loss, PE/PI, preterm birth)	Multiple clinical domains: thromboembolic, microvascular, obstetric, cardiac, hematologic
Laboratory requirement	Persistent aPL positivity for ≥ 12 weeks, medium–high titer	aPL positivity as entry criterion + laboratory domains scored
Diagnostic approach	Binary (fulfilled/not fulfilled)	Weighted, point-based system
Sensitivity/specificity	High sensitivity, moderate specificity	Lower sensitivity, higher specificity
Intended use (research vs. clinical)	Primarily for research (standardization)	For research and modeled clinical diagnosis
Role of oAPS	Distinct entity (without thrombosis)	Obstetric events considered part of the APS spectrum, evaluated together with other dominant clinical features

ACR – American College of Rheumatology, aPL – antiphospholipid antibody, EULAR – European Alliance of Associations for Rheumatology, oAPS – obstetric antiphospholipid syndrome, PE – preeclampsia, PI – pulsatility index.

Table II. Distribution of patients diagnosed with oAPS according to fulfillment of the Sydney and the new ACR/EULAR classification criteria

Study/registry	Study period	Number of oAPS patients	Met Sydney criteria (%)	Met 2023 ACR/EULAR criteria (%)
EUROAPS Registry (Marques-Soares et al. [10])	2011–2025	1,200	1,200 (100)	338 (28.2)
Ruffilli et al. [12]	2006–2023	121	91 (75)	26 (22)
Own cohort	2021–2025	43	30 (69.8)	6 (14)

ACR – American College of Rheumatology, EULAR – European Alliance of Associations for Rheumatology, oAPS – obstetric antiphospholipid syndrome.

relevant group being excluded from the classification. Consequently, the new system is best utilized for the identification of severe, high-risk patients; however, standard clinical protocols necessitate that the majority of patients still receive treatment [12].

We also examined the data of patients we have cared for. We retrospectively analyzed the data of 92 women with a primary oAPS diagnosis, reviewing their data from 01.06.2021 to 30.08.2025. Of these, 49 cases were diagnosed as NC-oAPS. In this group, aPL antibody positivity was usually detected only once or only noncriteria aPL positivity was detected. Of the additional 43 patients, only 6 patients (14%) could be classified according to the new ACR/EULAR criteria, while 30 patients (69.8%) met the criteria according to the Sydney criteria (Table II).

The message of the studies is consistent: the new criteria are excellent for defining strictly defined, homogeneous research populations, but they are not optimal for classifying cases of oAPS.

Conclusions

The diagnostic criteria for obstetric antiphospholipid syndrome have fundamentally changed between the Sydney and 2023 ACR/EULAR systems. The new system provides high specificity, but significantly reduces sensitivity, and as a result, a large proportion of patients (including clinically relevant oAPS cases) are excluded from the classification.

Based on the presented data, we can draw the following conclusions:

1. The new criteria adversely affect patients with isolated obstetric manifestations.
2. The marginalization of IgM positivity requires reconsideration, as it has clinical significance in some subgroups.
3. The narrowing of research populations threatens the representativeness of future clinical studies.

Based on the above, it is of utmost importance that the new criteria are used for classification purposes only, and that the medical experience and the complete clinical picture of the patient remain primary in establishing the clinical diagnosis.

In the longer term, it may be appropriate to develop oAPS-specific criteria that better reflect the real patient population.

Disclosures

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