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Non-Criteria Obstetric Antiphospholipid Syndrome: Myth or Reality?

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Abstract: Women with adverse pregnancy outcomes suggestive of obstetric antiphospholipid syndrome (OAPS) but not fulfilling the clinical and/or laboratory international classification criteria are increasingly recognized both in clinical practice and in literature. This entity is termed non-criteria OAPS (NC-OAPS). It includes clinical scenarios such as two unexplained pregnancy losses, three non-consecutive pregnancy losses, late preeclampsia/eclampsia/signs of placental insufficiency, or recurrent implantation failure, as well as positive low-titers of antiphospholipid antibodies (aPL) and non-classical aPL. Given the heterogeneity of NC-OAPS, an attempt to organize it in subsets was accomplished in the form of a nomenclature proposal. In the last years, retrospective and prospective cohort studies have been designed to clarify the characteristics and outcomes of the different subsets of NC-OAPS. In general, the studies support that NC-OAPS may benefit from treatment, but several considerations must be made on the robustness and nuances of the scientific evidence. In this review we examine the available evidence supporting the diagnosis of NC-OAPS, the features of its different subsets, and the impact of treatment strategies on its outcome, pointing out the questions that are still unanswered.

Keywords: Non-criteria obstetric antiphospholipid syndrome; low-titer aPL; infertility; recurrent implantation failure

1. Introduction

Antiphospholipid syndrome (APS) is a systemic autoimmune disorder characterized by vascular thrombosis and/or pregnancy morbidity, in the presence of antiphospholipid antibodies (aPL) [1]. More recently, aPL-associated "non-criteria" non-thrombotic manifestations (such as livedo racemosa, cardiac valve thickening, cognitive impairment, thrombocytopenia) have been recognized and aggregated to the spectrum of the syndrome [2]. Obstetric antiphospholipid syndrome (OAPS) is a subset of APS characterized by persistently positive aPL and obstetrical complications, which include early pregnancy losses, late fetal losses, and pre-term delivery < 34 weeks of gestation because of severe pre-eclampsia (PE)/eclampsia or placental insufficiency (PI) [1].

APS classification criteria have been created to define homogeneous and well-selected cohorts appropriate for clinical research. The first APS classification criteria were formulated during a post-conference workshop in Sapporo and presented in 1999. These original classification criteria included only moderate-high titers (i.e. >40 GPL or MPL, or >the 99th percentile) of anti-cardiolipin (aCL) IgG/IgM and lupus anticoagulant (LA) as laboratory criteria [3]. In 2006, a revised version of Sapporo criteria was designed at a consensus workshop in Sidney. In these criteria, the anti-β2 glycoprotein-I antibody (aβ2GPI) IgG/IgM antibody was included (in titer > the 99th percentile), and the specificity was enhanced by extending the requirement of persistent presence of aPL to 12 weeks [1]. The more recent American College of Rheumatology (ACR)/European Alliance of Associations for

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Rheumatology (EULAR) APS classification criteria, published in 2023, include a scoring system in which the criteria are differently weighted and organized into six clinical and two laboratory domains [2]. To be classified as APS, patients should accumulate at least 3 points each from the clinical and laboratory domains. The ACR/ EULAR criteria maintain the same definition of aPL persistence, but the maximum time between a clinical event and persistently positive aPL has been shortened from 5 to 3 years. Also, in these new criteria, the presence of only aCL or aβ2GPI IgM isotypes without IgG positivity is attributed a lower weight (1 point). Regarding the obstetrical complications, the various criteria include, in general, the same type of manifestations: ≥ 3 early pregnancy losses, at least one fetal loss >10 weeks of gestation of a morphologically normal fetus, or pre-term delivery <34 weeks gestation because of severe PE/eclampsia or placental insufficiency (PI) [2]. However, the 2023 criteria introduce more stringent details for the pregnancy morbidity, attributing a higher weight to the presence of severe PE/eclampsia and to PI. In the absence of PE/eclampsia/PI, all other obstetric manifestations (≥ 3 pre-fetal [<10w] or ≥ 1 early fetal [10 - 15w 6d] deaths, or an unexplained fetal death at 16w – 33w 6d) are only attributed 1 point (Table 1) [2]. In these new classification criteria, there is a decrease in their sensitivity linked to the obstetric domain, with early and late fetal loss underrepresented, as well as patients carrying only IgM aCL/ aβ2GPI antibodies [4,5]. Until this day, most of the available and recent research cohorts are classified according to the Sydney criteria and this review will reflect that view.

Table 1. 2023 ACR/EULAR OAPS classification criteria.

Clinical domains	**Weight**
>3 Consecutive pre-fetal (<10w) and/or early fetal (10w -15w 6d) deaths	1
Fetal death (16w – 33w 6d) in the absence of PE with severe features or PI with severe features	1
PE with severe features <34w or PI with severe features with/without fetal death	3
PE with severe features <34w and PI with severe features <34w with/without fetal death	4
Laboratory domains	
One-time positive LA	1
Persistent positive LA	5
Moderate or high positive IgM (aCL and/or aβ2GPI)	1
Moderate positive IgG (aCL and/or aβ2GPI)	4
High positive IgG (aCL or aβ2GPI)	5
High positive IgG (aCL and aβ2GPI)	7
At least 3 points from clinical domains plus at least 3 points from laboratory domains is required to classify as OAPS	

Abbreviations: aβ2GPI: anti-β2 glycoprotein-I antibodies; aCL: anticardiolipin antibodies; LA: lupus anticoagulant; OAPS: obstetric antiphospholipid syndrome; PE: preeclampsia; PI: placental insufficiency; w: weeks.

Classification criteria intentionally include very stringent definitions to accomplish a very high specificity. For this reason, their strict application in routine practice to diagnose individual patients should be avoided, and more emphasis should be given to the broad range of APS features, to the existing complementary tests in any given scenario and in the exclusion of alternative diagnosis. In daily clinical practice, specifically in the obstetric field and more so with the new ACR/EULAR criteria, physicians are frequently faced with patients with clinical features and laboratory manifestations suggestive OAPS, but who do not strictly meet the classification criteria. These patients are globally described as having non-criteria obstetric antiphospholipid syndrome (NC-OAPS) [3]. Evidence is accumulating on the potential clinical significance of NC-OAPS. However, there is much heterogeneity of scenarios and no consensus on the features to include in the definition of NC-OAPS. Consequently, determining the optimal treatment is challenging. Currently, treatment of NC-OAPS requires an individualized strategy according to the patient's risk profile, although the risk factors in NC-OAPS are not completely explored.

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In this review we examine the available evidence supporting the diagnosis of NC-OAPS, the clinical relevance of its different subsets, and the impact of treatment strategies.

2. Definition and Diagnosis of NC-OAPS

The first limitation for the diagnosis of NC-OAPS resides on the diversity of the definitions used in literature. Based on the different scenarios seen on clinical practice and depicted on literature, a nomenclature proposal for "non-criteria" APS subtypes was suggested by our group [6]. According to this proposal, four APS patient profiles are recognized: a) patients with clinical APS criteria, plus the presence of "non-criteria" manifestations, but persistently negative criteria aPL (*Seronegative APS*); b) patients with "non-criteria" manifestations plus aPL positivity fulfilling the APS laboratory criteria (*Clinical non-criteria APS*); c) patients with clinical APS criteria, plus positive aPL, but not fulfilling the laboratory classification criteria because of persistently positive but low titer (between the 95th and 99th percentiles or below 40 GPL or MPL) aPL (*Incomplete laboratory APS*); and d) patients with APS clinical criteria manifestations (thrombotic or obstetric), with persistently negative or low titer criteria aPL, but positive aPL different from LA/aCL/ aβ2GPI IgM or IgG isotypes (*Laboratory non-criteria APS*) (Table 2) [6]. There are other groups of patients frequently present in the literature which were excluded from this nomenclature proposal, although they can have relevance in the spectrum of "non-criteria" APS. These groups include aPL carriers, patients with "non-criteria" manifestations and positivity for "non-criteria" aPL, and patients with clinical manifestations fulfilling APS classification criteria and only one single positive determination of criteria aPL (referred as *Single-positive APS*).

Table 2. Proposed "non-criteria" OAPS subsets.

	Seronegative OAPS	**Clinical non-criteria OAPS**	**Incomplete laboratory OAPS**	**Laboratory non-criteria OAPS**
Clinical features	Criteria + non-criteria manifestations	Non-criteria manifestations	Criteria manifestations	Criteria manifestations
aPL profile	Persistently negative criteria aPL	aPL positivity fulfilling the APS laboratory criteria	Persistently positive but low titer criteria aPL	Persistently negative or low titer criteria aPL, but positive aPL different from LA/aCL/ aβ2GPI IgM or IgG isotypes

Abbreviations: aβ2GPI: anti-β2 glycoprotein-I antibodies; aCL: anticardiolipin antibodies; aPL: antiphospholipid antibodies; APS: antiphospholipid syndrome LA: lupus anticoagulant; OAPS: obstetric antiphospholipid syndrome.

According to this nomenclature proposal, from a laboratory point of view, patients with low titers of aPL or with non-classical aPL may be considered for the diagnosis of NC-OAPS. In the field of NC-OAPS, several pregnancy complications not included within the Sydney criteria were identified. These are the "non-criteria" obstetric manifestations of APS, also designated in literature as "obstetric morbidity associated with APS (OMAPS)". Based on the reports from the multicenter European Registry on Obstetric Antiphospholipid Antibody Syndrome (EUROAPS), the following "non-criteria" obstetric manifestations were recognized: one or two unexplained pregnancy losses before 10 weeks of gestation, three non-consecutive pregnancy losses, late placental vasculopathy (PE after 34 weeks, intrauterine growth restriction after 34 weeks), late premature birth (after 34 weeks and under 37 weeks of pregnancy) with no other apparent cause, placental abruption, placental hematoma, puerperal pre-eclampsia, and recurrent implantation failure (RIF) [7]. These OMAPS are in general less numerous and/or less devastating than those used in the APS classification criteria.

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However, as pregnancies are limited events in the life of a woman, all the obstetric outcomes potentially related to aPL antibodies are viewed as preventable clinical opportunities. For this reason, it is so important to be able to diagnose NC-OAPS with accuracy and understand its relevance in clinical practice.

3. A glimpse into Pathophysiology

It is now accepted that thrombosis alone cannot explain the pregnancy morbidity associated with aPL antibodies. In OAPS, aPL antibodies target the placenta, with animal models demonstrating the direct aPL-mediated functional damage on placental tissue and/or the inflammatory processes [8]. Multiple aPL-mediated actions on the different cellular components of placental tissue may act together or in different combinations at different times of pregnancy, resulting in defective placentation. The biologic mechanisms potentially implicated in the pathogenesis of aPL-associated obstetric morbidity include trophoblast dysfunction and apoptosis, decidual inflammation, disruption of annexin A5 shield on placental villi surfaces leading to phosphatidylserine exposure, inhibition of endometrial angiogenesis, complement activation, neutrophil infiltration, local tumor necrosis factor secretion, and formation of neutrophil extracellular traps in the intervillous spaces [8,9].

From a placental histopathologic point of view, a systematic review found that the following features were reported more frequently in the placentae of aPL-positive women compared to aPL-negative women: placental infarction, impaired spiral artery remodelling, decidual inflammation, an increase in syncytial knots, decreased vasculosyncytial membranes and the deposition of complement split product C4d (Figure 1) [10].

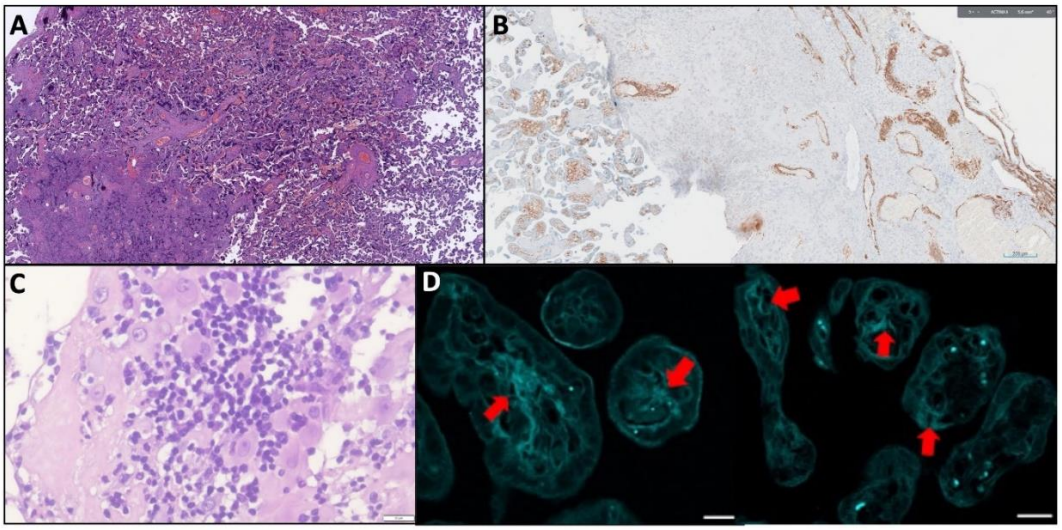

Figure 1. A) Placental infarction and increased syncytial knots. Placental infarction (villous infarction) with intervillous space collapse and coagulative necrosis of chorionic villi in the left lower quadrant and syncytial knot hyperplasia with multiple dark haematoxylin-stained sprouts upon chorionic villi. H&E Staining. Original magnification 2X. B) Impaired spiral artery remodeling with persistence of the muscular wall highlighted by the immunohistochemical detection of smooth-muscle actin (brown structures on the right side). Smooth-muscle actin immunohistochemistry counterstained with haematoxyilin. Original Magnification 4X. C) Decidual inflammation. Chronic deciduitis is characterized by a dense lympho-plasmacytic inflammatory infiltrate dissecting among decidual cells. Plasma cells have a granular excentric nuclei in a basophilic cytoplasm with a characteristic perinuclear clear halo corresponding to the Golgi apparatus. H&E Staining. Original magnification 40X. D) Deposition of complement split product C4d signed with red arrows.

Interestingly, a case-control study including 27 subjects with primary APS, 51 with NC-OAPS, 24 with aPL antibodies associated with other connective tissue disorders (CTD), and 107 healthy controls, found that placental lesions suggesting severe maternal vascular malperfusion were more

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common among primary [odds ratio (OR) 11.7 (95% CI 1.3, 108)] and NC-OAPS [OR 8.5 (95% CI 1.6, 45.9)] compared with controls. The risk of fetal vascular malperfusion was higher in primary APS [OR 4.5 (95% CI 1.2, 16.4)], aPL associated with CTD [OR 3.1 (95% CI 1.5, 6.7)] and NC-OAPS [OR 5.9 (95% CI 1.7, 20.1)] compared with controls. These observations indicate that, although the rates and severity of several types of maternal vascular malperfusion lesions are higher in primary APS, they are also observed in patients with NC-OAPS in a higher frequency than in controls [11].

4. The Relevance of the Different Types of Non-Criteria Obstetric Manifestations

The prevalence of aPL, and hence the role of these antibodies, in specific cohorts of patients with APS-related obstetrical complications not meeting the Sydney criteria was addressed in few studies, and those that exist have several limitations, such as small samples of patients, inclusion of women with criteria obstetrical manifestations or testing only part of the aPL antibodies.

Early recurrent pregnancy loss has been found as the most frequent obstetrical complication in OAPS, described between 35.4% and 38.6% of patients in large cohorts [12,13]. However, the specificity of recurrent early miscarriages is low due to the difficulty in fully excluding other potential causes. It is particularly important to consider this limitation when contemplating the diagnosis of NC-OAPS in the case of ≤ 3 early pregnancy losses. A chromosomal abnormality is the commonest cause of pregnancy losses, and an effort should be made to attain this information, although it is not always feasible.

In a large trial examining the aPL antibodies prevalence in placenta-mediated complications (small for-gestational-age neonate [n=378], PE with severe features [n=30], and placental abruption [n=23]) in patients delivering after >36 gestational weeks, found a prevalence of aPL antibodies of 4.9% in the entire cohort, and comparable between the three subgroups (small for-gestational-age, 3.9%; PE with severe features, 3.3%; and placental abruption, 13%) [14]. This prevalence is similar to the reported prevalence of aPL antibodies in the general obstetric population (ranging between 1.4 and 7%) [14]. A previous study exploring the prevalence of aPL antibodies in late-onset pregnancy complications (>28 gestational weeks) in 100 patients and comparing it with healthy controls with uneventful pregnancies, found a higher prevalence of aPL (31%), resulting in a fourfold risk for any late-onset pregnancy complication. However, this study also included non-classical aPL, as well as stillbirth and placenta-mediated complications occurring under 34 weeks of gestation (which are APS criteria), and these differences could explain the higher aPL antibodies prevalence found [15].

The causal link between aPL with infertility or RIF in those undergoing *in vitro* fertilization (IVF) is a matter of debate. A systematic review estimated positivity rates of criteria and non-criteria aPL tests of 6% and 3% among infertile women, and of 1% and 2% among control subjects, respectively [16]. A significant difference in the positivity rate of patients versus controls emerged for aCL only. However, this study highlighted several limitations of the available studies, including wide heterogeneity in study populations, aPL cutoffs not conforming to international guidelines in more than 75% of studies, aPL positivity not confirmed in 89% of studies, and methodological issues such as inappropriate study design. These limitations precluded more robust statistical analysis and conclusions [16]. Data regarding the association of aPL in IVF outcomes are also conflicting. A metanalysis of only prospective studies addressing the IVF outcomes in infertile patients found no significant association between aPL positivity and IVF outcomes, namely clinical pregnancy, miscarriage and live births [17]. However, two other metanalysis concluded that patients with RIF or at least two implantation failures had higher prevalence of aPL than women with successful implantation or healthy fertile women [18,19]. The strength of association varied according to different aPL subtypes and between the studies, and did not proved causality.

5. The Relevance of the Non-Criteria Laboratory Manifestations

The titers of aPL and their clinical significance have many particularities. For once, it is recognized that aPL levels can fluctuate over time, even becoming undetectable, but evidence on outcomes of patients according to the degree of fluctuation is sparse [20]. The aPL level that is associated with a clinical risk has not been established in practice, but more than 10 years ago authors

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started to report obstetrical complications in patients with low aPL levels [21]. One limitation that should be taken into account is the matter of agreement of test results between different laboratories, which has been shown to be inferior in lower positive titers than in moderate-to-high titers. Also, it is recognized that testing for APS can be affected by pregnancy itself and it should be performed between pregnancies wherever possible [20].

Studies have shown that low levels of IgG/IgM aCL levels and/or IgM aβ2GPI are more frequent in patients with only obstetric morbidity compared to those with thrombosis [22,23]. Other studies reported that the probability of obstetric events without treatment was also similar in women with low titers and women with high titers of aPL, and higher than in aPL negative controls [24–26]. These observations support the concept of incomplete laboratory APS as a subset of NC-OAPS.

Patients with only one positive aPL determination (single positivity) are challenging, because it is difficult to exclude a false-positive aPL elevation due to other causes (e.g., infection, malignancy, or drugs), and previous data indicate that these patients had no increased risk of recurrent events compared with those without aPL [6]. However, it was also noted that a single positive aPL test is more common in purely obstetrical APS than in thrombotic or mixed APS [27]. Therefore, the relevance of a single positive result of aPL remains inconclusive.

In patients with clinical criteria for OAPS but seronegative for conventional aPL antibodies, considerable efforts have been undertaken in the last decades to discover new aPL with clinical relevance. Various antibodies are promising, such as IgA aβ2GPI and aCL antibodies, and those against annexin A5, prothrombin, phosphatidylserine/prothrombin (aPS/PT), phosphatidylethanolamine, phosphatidic acid, phosphatidylserine, phosphatidylinositol, vimentin/cardiolipin complex, β2GPI Domain 1, and β2GPI/HLA-DR complex [6,28,29]. Many patients with seronegative APS could have one or more of these antibodies if they were available in routine clinical practice. Non-conventional aPL were reported in 68% of these patients [30]. In a large Chinese cohort composed of 192 APS patients, 90 seronegative APS patients, 193 autoimmune disease controls, and 120 healthy controls, ten aPL were tested, including 5 non-criteria aPL: aPS/PT IgG/IgM, aCL IgA, aβ2GPI IgA, and anti-β2GPI Domain IgG. At least one non-criteria aPL was detected in 60.9% of seronegative APS and 93.5% of APS patients [28]. The aPS/PT IgG and aPS/PT IgM were the most frequently detected aPL in both APS and seronegative APS patients. The aPS/PT antibodies are indeed amongst the best studied non-criteria aPL, and many groups have showed their association with adverse pregnancy outcomes (APO) [31,32]. A limitation to the use of non-criteria antibodies is the lack of validation of the laboratory assays and respective titers.

6. Comparison between NC-OAPS and OAPS

There are two large comparative studies of the features and pregnancy outcomes in OAPS and NC-OAPS. In the EUROAPS study, a large scale international multi-center registry analysis, patients with OAPS had a higher number of previous miscarriages, fetal losses, stillbirth, early placental vasculopathy (PE <34 weeks and FGR <34 weeks) and prematurity than those included in the NC-OAPS group. Women diagnosed with NC-OAPS had higher rates of RIF and late placental events (PE >34 weeks and FGR >34 weeks) [7]. These observations are, at least in part, the result of the definitions of OAPS and NC-OAPS. Interestingly, the authors of the study also found differences in the outcomes between the two groups. Even though the rate of live births were similar, obstetric complications occurred in 73.4% pregnancies in NC-OAPS and in 65.1% of pregnancies in OAPS ($p<0.001$) [7]. In a large Chinese series including 1006 patients (OAPS n=141, and NC-OAPS n=865), the previous history of >3 spontaneous pregnancy losses was the only significant difference between OAPS and NC-OAPS in terms of previous clinical manifestations (19.9% in OAPS vs 8.3% in NC-OAPS, $p < 0.001$) [33]. Regarding pregnancy outcomes, this study obtained different data than that from the EUROAPS. The authors observed that only the rate of stillbirth was statistically different between groups, being higher in the OAPS group (8.5% vs. 2.0%, $p < 0.001$). Importantly, this study did not include early pregnancy losses as an adverse outcome. After logistic regression analysis, this study found a higher stillbirth risk (OR 2.731, CI 95% 1.104–6.754) but a lower preterm risk (OR 0.486, CI 95% 0.246–0.959) in the OAPS group compared to the NC-OAPS group, but the NC-OAPS group

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has a significantly higher overall risk of APO (OR 0.565, CI 95% 0.336-0.950). Double aPL positivity, triple aPL positivity and gestational hypertension were independently associated with higher odds of APO in the OAPS group, whereas two of the double aPL positivity subtypes, triple aPL positivity and placenta previa were independent risk factors related to APO in the NC-OAPS group [33]. Despite the differences in the results of the mentioned studies, both highlight that NC-OAPS in its general concept may be associated with APO.

On another perspective, in a study of 163 patients (62 subjects with complete APS [38 %], 48 with NC-APS [29.4 %] and 53 [32.5%] asymptomatic aPL carriers) and 785 healthy controls, non-criteria and asymptomatic subjects had increased risks of spontaneous abortion, fetal growth restriction, PE and overall APO compared to negative controls, although the size of the effect was significantly lower than that associated to complete APS [34]. The rates of APO were 5.6% in controls, 41.9% (OR = 6, 95% CI = 2.7-13.5) in APS, 25% (OR = 4.4, 95% CI = 2-9.4) in non-criteria and 28.3 % (OR = 4, 95% CI = 1.8-8.8) in aPL-carriers [34].

7. To Treat or Not to Treat NC-OAPS?

The 2019 EULAR guidelines recommend the combination of low-molecular weight heparin (LMWH) at prophylactic doses and low-dose aspirin (LDA) during pregnancy in women with pure OAPS who have a history of ≥3 early pregnancy losses (< 10 weeks gestation) or ≥1 late loss (≥10 weeks gestation) [35]. This recommendation is supported by a more recent Cochrane review (2020) which included 11 studies (1672 women) and evaluated the efficacy of aspirin or heparin or both to reduce pregnancy complications in women with APS, founding that heparin plus aspirin increased the number of live births in women with APS compared to aspirin alone (RR 1.27, 95% CI 1.09–1.49, 5 studies, 1295 women, low-certainty evidence) [36]. In patients with a history of delivery <34th week of gestation due to eclampsia or severe PE or due to features of PI, EULAR guidelines propose both treatment with LDA or LDA plus heparin at prophylactic dosage considering the individual's risk profile. This recommendation is based on the lack of evidence that in these patients, treatment with LDA plus heparin does not improve the likelihood of live births compared to treatment with LDA alone [35,37].

In the case of NC-OAPS, there is no consensus on the management. The 2019 EULAR guidelines suggest considering the use of either LSA alone or in combination with LMWH, mainly based on expert opinion [35]. In the 2020 ACR guidelines only LDA is recommended as PE prophylaxis, and there is a conditional recommendation against using the combination of prophylactic-dose heparin and LDA for patients with positive aPL who do not meet criteria for OAPS [38].

A systematic review compared the treatment and outcomes of patients with OAPS and NC-OAPS. In 9 studies comparing treatment frequency in obstetric patients, 8 (2762 participants) described similar treatment frequency, and only one reported more frequent treatment in definite OAPS (179 participants) [39]. In the 10 studies reporting a statistical comparison of the pregnancy outcomes of NC-OAPS versus APS, 7 found similar outcomes in terms of successful pregnancies/live births (1171 participants), and the remaining three (1830 participants) even described worse outcomes/increased complications at least in some subset of NC-OAPS in comparison with definite APS. Additionally, 5 studies described improvement of live births in both NC-OAPS and OAPS with treatment [39]. This review only included cohort studies, with heterogeneous study populations, design, and treatment regimens, with a global moderate quality. There are no case–control studies or randomized trials in this area. The Table 3 summarizes the characteristics and main results of the most relevant studies comparing the outcome of NC-OAPS with OAPS. In this setting, the two large cohorts previously described in this review worth another reference. In the European registry EUROAPS, the largest study included in the mentioned systematic review, the percentage of patients treated was similar in OAPS and NC-OAPS groups, with an observed rate of live births similar in both groups (72.8% in OAPS and 73.43% in NC-OAPS), although obstetric complications occurred in 651/ 1000 (65.1%) in OAPS, and in 470/640 (73.4%) in NC-OAPS (p <0.001) [7]. Prematurity was the most frequent complication observed in the OAPS group (24.1%) and miscarriage was the most frequent in NC-OAPS (19.4%) [7]. The other study is a retrospective single-center study with a

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Chinese cohort comprising 1006 patients, published after the systematic review [33]. In this study, all patients had some form of treatment, although a smaller proportion of women with OAPS received LDA alone compared with the NC-OAPS group, and a higher proportion of patients received LDA combined with LWMH plus hydroxychloroquine (HCQ) or glucocorticoids [33]. The OAPS patients had a significantly higher risk for stillbirths compared to the NC-OAPS patients, while the NC-OAPS group had a significantly higher risk for preterm birth and overall APO [33].

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Table 3. Main studies comparing outcomes of pregnancies in women with OAPS and NC-OAPS.

Authors (Ref)	Year	Design and setting	Study population	Number of patients	Objective	Main results
Liu H *et al* [33]	2024	Retrospective Single-center	Includes: 1) OAPS 2) NC-OAPS (aPL-related pregnancy morbidity [two unexplained miscarriages, ≥3 non-consecutive miscarriages, late PE, placental abruption, late premature birth, and two or more unexplained IVF failure), low-titer and/or non-persistent aPL) Excludes other SAD No inclusion of non-classical aPL	OAPS: 141 NC-OAPS: 865	-To compare clinical characteristics and obstetric outcomes between primary OAPS and NC-OAPS -To explore the risk factors for APO in both groups	- OAPS patients had a significantly higher risk for stillbirths compared to the NC-OAPS patients, while the NC-OAPS group had a significantly higher risk for preterm birth and overall APO - Double aPL positivity, triple aPL positivity, and gestational hypertension were the independent risk factors for APO in OAPS patients - Two of the double aPL positivity subtypes, triple aPL positivity and placenta previa were independent risk factors for APO in NC-OAPS patients
Chen J *et al* [40]	2024	Retrospective Single-center	Includes: Patients with ≥2 pregnancy losses with: 1) Medium-high titer aPL 2) Low-titer APL Excludes other SAD No inclusion of non-classical aPL	Medium-high titre aPL: 32 Low-titre aPL: 92	-To investigate the impact of low−titer aPL in patients with recurrent pregnancy loss -To compare pregnancy outcomes between patients with low and medium–high aPL levels.	-Appropriately treated patients in both low-titer and medium high-titer aPL positivity achieved higher live birth rates (33.3% vs 67.6% in low titers, and 66.7% vs 79.3% in medium-high titer group)
Martínez - Taboada, VM *et al* [41]	2022	Retrospective Single-center	Includes: 1) OAPS 2) NC-OAPS (aPL-related pregnancy morbidity, low-titer or intermittent positive aPL) 3) Seronegative APS group Excludes other SAD No inclusion of non-classical aPL	OAPS: 66 NC-OAPS: 140 Seronegative APS: 57	- To compare characteristics and fetal-maternal outcomes between women with OAPS, NC-OAPS and seronegative APS	-Patients with OAPS received more intensive treatment with LMWH+LDA (75.8% in OAPS and 45.7% in NC-OAPS patients). -Live birth rate was similar between groups, with and without treatment, but APO are more frequent in OAPS after treatment. -SoC treatment increased the live birth rates in both groups (75.4% in OAPS and 70.7% in NC-OAPS).
Spinillo *et al* [34]	2021	Prospective Single-center	Includes: 1) APS	APS: 62 NC-APS: 48	-Evaluate the rate of obstetric complications and the	-All the categories of women with aPL have increased incidence of APO

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			2) NC-APS (aPL-related pregnancy morbidity, low-titer or intermittent positive aPL) 3) aPL carriers (asymptomatic) 4) Control group (healthy pregnant women) Includes patients with SAD and thrombotic APS. No inclusion of non-classical aPL.	aPL carriers: 53 Control: 785	burden of obstetric outcomes in APS, NC-APS and asymptomatic aPL carriers	-LMWH plus LDA was carried out in 85.5% of subjects with complete APS, 4.2% of NC-APS and none of aPL carriers -The rate of APO were 5.6% in controls, 41.9% (adj.OR = 6, 95 %CI = 2.7-13.5) in APS, 25% (adj.OR = 4.4, 95 %CI = 2-9.4) in NC-APS and 28.3% (OR = 4, 95 %CI = 1.8-8.8) in aPL-carriers -SAD were independently associated with an increased risk of adverse obstetric outcomes
Li X *et al* [42]	2021	Prospective Single-center	Includes: 1) OAPS group 2) NC-OAPS group (aPL-related pregnancy morbidity, low-titer and/or non-persistent aPL) Includes patients with SAD No inclusion of non-classical aPL positivity	APS: 34 NC-OAPS: 94	-To assess possible factors related to the pregnancy outcomes of patients with positive aPL and APO histories -To compare criteria OAPS and NC-OAPS patients	- Similar live births in OAPS and NC-OAPS (76.5% and 74.5%, respectively) when treated -Preeclampsia or eclampsia before the 37th gestational week was significantly higher in the OAPS group - In NC-OAPS, LMWH was a protective factor for APO. The percentage of APOs in the LDA + LMWH group was lower than that in the LDA only group.
Pregnolato F *et al* [25]	2021	Retrospective Single-center	Includes: 1) Criteria aPL group 2) Low-titer aPL group 3) Control group (patients with SAD and negative aPL) No inclusion of non-classical aPL	Criteria aPL: 100 Low-titer aPL: 55 Control: 226	- To evaluate the impact of aPL positivity fulfilling classification criteria ('criteria aPL') and at titers lower than thresholds considered by classification criteria ('low-titer aPL')	-An association between every single aPL test and also low-titer aPL and pregnancy morbidity. -LA and aβ2GPI IgG are the strongest predictors of pregnancy morbidity -Women with low-titer aPL benefited from SoC treatment and its effectiveness was greater than for criteria aPL.
Alijotas-Reig *et al* [7]	2020	Partially retrospective Multicentric (30)	Includes: 1) OAPS group 2) NC-OAPS group (aPL-related pregnancy morbidity, low-titer and/or non-persistent aPL) Includes patients with SAD No inclusion of isolated non-classical aPL positivity	OAPS: 1000 NC-OAPS: 640	-To compare features and fetal-maternal outcomes between women with OAPS and NC-OAPS.	-Similar percentages of treatment in OAPS (77%) and NC-OAPS groups (76.09%) -Similar fetal-maternal outcomes in both groups after SoC treatment: live birth rate of 85% in OAPS and 89.6% in NC-OAPS

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Xi F *et al* [43]	2020	Prospective Single-center	Includes: 1) APS group 2) NC-APS group (not defined) 3) Control group (healthy pregnant women) Includes patients with SAD No inclusion of non-classical aPL.	APS: 44 NC-APS: 91 Control: 135	- To investigate pregnancy outcomes of women with aPL positivity - To assess risk factors associated with APO	-Live birth rate was 95.5% in APS and 97.8% in NC-APS -Total use of LMWH in APS group was significantly more than in NC-APS and the number of patients who took HCQ in APS group was significantly lower than in NC-APS. -After treatment, the incidence of IUGR was higher in APS group than in NC-APS group, and both were higher than in the control group.
Ofer-Shiber S *et al* [44]	2015	Retrospective Single-center	Includes: 1) APS: Criteria aPL with vascular thrombosis and/or pregnancy morbidity 2) NC-APS: Low-titer aPL with vascular thrombosis and/or pregnancy morbidity	APS: 126 NC-APS: 117	- To determine the clinical manifestations and outcome of patients with persistently low (20-40 U) aCL or aβ2GPI IgG/IgM titers compared with those with persistent moderate-high titers and/or positive LA	-Low titer of ACL/ aβ2GPI IgG/IgM was significantly associated with an increased risk of thrombotic and obstetrical manifestations of APS similar to the risk found in patients with moderate- to high titer
Mekinian A *et al* [21]	2012	Retrospective Single-center	Includes: 1) APS 2) NC-APS (low-titer aPL) 3) Control (seronegative APS group) Excludes other SAD No inclusion of non-classical aPL or LA	APS: 25 NC-APS: 32 Control: 21	- To assess whether the presence of low-titer aPL might be associated with APS-like obstetrical events - To analyze the impact of treatment with LDA and/or LMWH in patients with low-titer aPL levels.	-Pregnancy outcomes in untreated patients with NC-APS are poor and similar to those in obstetrical patients with confirmed APS. -Conventional APS treatment substantially improved pregnancy and neonatal outcomes in both groups of patients. -The total number of obstetrical events per patient decreased significantly in both groups after treatment to reach an identical median value (from 3 [1–8] to 0 [0–2] in group 1 ($p < 0.05$) and from 3 [1–6] to 0 [0–2] in group 2 [$p < 0.05$]).

Abbreviations: aβ2GPI: anti-β2 glycoprotein-I antibodies; aCL: anticardiolipin antibodies; aPL: antiphospholipid antibodies; APO: adverse pregnancy outcomes; APS: antiphospholipid syndrome; LA: lupus anticoagulant; LDA: low-dose aspirin; LMWH: low molecular weight heparin; NC-OAPS: non-criteria antiphospholipid syndrome; OAPS: obstetric antiphospholipid syndrome; SAD: systemic autoimmune diseases; SoC: standard of care; IUGR: intrauterine growth restriction.

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There are some studies that approach the management of one particular subset of NC-OAPS. The EUREKA algorithm was specifically designed to stratify the probability of obstetric complications in patients with different aPL titers (medium–high titers, as required for classification criteria for APS, and low titers, lower than the threshold considered by classification criteria), and the effectiveness of the therapy based on the aPL profile [25]. All women with low-titer aPL benefited from treatment with LDA+LMWH±HCQ, and its effectiveness was even greater for low-titer than for criteria aPL antibodies [25]. Other studies also reported that the appropriate treatment of patients with low aPL levels led to better pregnancy outcomes (Table 3) [21,40]. Some studies found that patients with aPS/PT also had a reduction of pregnancy losses if they received treatment during their pregnancy [30,31,45]. Furthermore, recent retrospective studies found that treatment with LDA plus LMWH +/- HCQ improved IVF outcomes in patients with aPL, increasing the clinical pregnancy rate, implantation rate, and take-home baby rate [46,47].

Apart from LDA and LMWH, no other treatments have robust evidence of effectiveness in OAPS or NC-OAPS. Glucocorticoids did not appear to improve pregnancy outcomes in early trials [48,49]. However, a more recent small study in women with refractory APS-associated pregnancy loss reestablished the interest in this therapy, reporting that low-dose prednisolone in the first trimester (10 mg daily until 14 weeks of gestation), in addition to aspirin and heparin, was associated with an increase in live birth rates compared with historical self-controls (4% live birth rate prior to use of prednisolone compared to 61% using prednisolone) [50]. There are few data suggesting that HCQ can be useful in refractory primary obstetric APS [51]. The HYPATIA trial is an ongoing prospective randomized controlled trial, currently recruiting, aiming to find if HCQ improves pregnancy outcome in women with aPL antibodies [52]. Intravenous immunoglobulins (IVIG) have also been explored as a treatment option. A metanalysis showed varying levels of success in improving live birth rates and reducing miscarriage rates through IVIG intervention in aPL-positive patients with recurrent miscarriage, being this effect more prominent and statistically significant in aPL-positive patients in combination with systemic lupus erythematosus or other similar autoimmune diseases, but the IVIG-treated group exhibited a higher incidence of preterm labor [53]. In a posterior multicenter clinical trial, an IVIG-only add-on intervention for refractory OAPS did not demonstrate efficacy in improving the proportion of live births after 30 weeks of gestation [54].

Given the scarce and low-quality data concerning treatment of patients with NC-OAPS, no formal recommendations exist. Facing with this conundrum, physicians should personalize treatment according to individual´s risk profile and within a discussion with the woman, weighting potential risks and estimated benefit of treatment in each scenario. Known risk factors for adverse events include poor reproductive history (history of ≥ 4 pregnancy losses), high-risk antibody profile (higher number of positive aPL such as triple or double positivity, or high aPL titers), concomitant systemic lupus erythematosus and/or other autoimmune diseases, hypocomplementemia, and false-positive CMV IgM antibodies [55]. In this equation, physicians may also consider additional risk factors for pregnancy loss or thrombosis, advanced maternal age, or IVF pregnancy [38].

The majority of studies on OAPS focus on the treatment strategies aiming to prevent repeated APO. However, outside the context of pregnancy, patients with pure OAPS have been shown to be at risk of future thrombosis, with a wide range of cumulative risk or incidence rates described in the different articles (from 10.4% to 63% in over 10 years, and a an incidence rate of 3.3-4.9/100 patient-year) [56–59]. A study also found that the risk remains higher than in patients without aPL antibodies even under aspirin treatment [60]. The several studies pointed out diverse predictors of future thrombosis events, such as multiple aPL positivity, presence of antinuclear antibodies, heart valve disease, younger age of OAPS, higher adjusted Global Antiphospholipid Syndrome (aGAPPS) and systemic lupus erythematosus [56,57,59]. The applicability of these observations to long-term outcomes in women with NC-OAPS is not determined, and there is no agreement regarding the benefit of prescribing prophylactic anti-thrombotic treatment to these women.

8. Discussion

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NC-OAPS is a heterogenous condition, that comprises both diverse clinical manifestations and aPL profiles. This characteristic, per se, complicates its investigation, as published studies have very diverse study populations and designs. In this review, we tried to describe the available evidence focusing on each NC-OAPS feature, remarking that the different scenarios are associated with different grades of evidence and diverse clinical impact.

Currently, evidence from observational studies, mostly retrospective, tends to suggest that patients with NC-OAPS are at risk of APO and may benefit from treatment. Given the lack of high-quality evidence there are no formal recommendations on the management of these patients. Regardless, many patients with NC-OAPS are treated similarly to those with OAPS [39]. One possible explanation for this fact is that clinicians tend to offer a safe treatment and patients are eager to take it when faced with APO in the context of aPL presence, although accepting a possible and unknown proportion of overtreatment.

Future studies appropriately designed and with adequate power, should analyze the different subsets of NC-OAPS with well-defined and homogenous NC-OAPS populations in order to clarify discrepancies and similarities among them and suggest management specificities. Especially in what refers to treatment in the different scenarios of NC-OAPS, randomized controlled trials should be conducted before a treatment is generalized. However, these trials are recognizably difficult to achieve, as it was shown by the pilot APPLE (AntiPhospholipid syndrome low-molecular weight heparin Pregnancy Loss Evaluation) trial. This trial was designed to evaluate LMWH/aspirin versus aspirin prophylaxis alone during pregnancy in women with a history of ≥2 early pregnancy losses or ≥1 late pregnancy losses and positive aPLs according to the Sydney criteria. It was not possible to conclude the recruitment of the study because many patients wanted to use LMWH/ASA during pregnancy in hopes of improving pregnancy outcomes [61]. Furthermore, although APS classification criteria were created for inclusion of patients in trials, these should not preclude the conduction of high-quality studies including women not fulfilling these criteria.

Another line of research urgently needed is the impact of NC-OAPS, in its different versions, on long-term outcome and its best management. This is an understudied topic, that will be increasingly relevant as more and more women are getting tested for aPL and getting treated during pregnancy.

9. Conclusions

NC-OAPS is an heterogenous and increasingly recognized condition. Presently, evidence suggests that it may have a significant although variable impact on pregnancy outcomes. There are however many current gaps in the knowledge on this topic that deserve an appropriate and high-quality investigation effort.

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