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Antiphospholipid syndrome in pregnancy: a comprehensive literature review

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Abstract

Background Antiphospholipid syndrome (APS) is an autoimmune disorder associated with thrombotic events and adverse obstetric outcomes, particularly in its obstetric form (OAPS). Affecting approximately 0.5% of the population, APS is a leading contributor to recurrent pregnancy loss (RPL), preeclampsia (PE), and fetal growth restriction ((FGR). Despite advancements in understanding its pathophysiology and management, optimal treatment strategies for APS in pregnancy remain challenging and require systematic evaluation. This review synthesizes current evidence on APS mechanisms, diagnostic criteria, and therapeutic interventions, with a focus on maternal and fetal outcomes in OAPS.

Methods A comprehensive search of PubMed, was conducted to identify studies exploring APS pathogenesis, diagnostic standards, and treatment efficacy in obstetric settings. Inclusion criteria prioritized randomized controlled trials, cohort studies, and systematic reviews with a clear focus on APS and pregnancy.

Results The review confirmed that APS current accepted pathogenesis is governed by a "two-hit" model, where antiphospholipid antibodies (aPLs) initiate endothelial damage, culminating in thrombosis and placental insufficiency. Epidemiological analysis underscores the prevalence and severity of APS in obstetric contexts, with lupus anticoagulant (LA) emerging as a significant predictor of adverse outcomes. Evidence supports the use of low-dose aspirin (LDA) and heparin to reduce miscarriage rates, while adjunctive treatments, such as hydroxychloroquine (HCQ), have shown promise in improving live birth rates and reducing preterm delivery in high-risk cases. Emerging therapies, including tumoral necrosis factor (TNF-alpha) inhibitors and nitric oxide modulators, may offer additional benefits in refractory cases.

Conclusion APS remains a critical determinant of adverse pregnancy outcomes, necessitating precise diagnostic criteria and tailored management approaches. This systematic review emphasizes the importance of individualized therapeutic regimens to optimize maternal and fetal health in OAPS and highlights areas for future research, particularly regarding novel pharmacological approaches. Further studies are essential to refine treatment protocols and improve clinical guidelines for managing APS in pregnancy.

Keywords Antiphospholipid syndrome (APS), Obstetric APS (OAPS), Pregnancy complications, Low-dose aspirin (LDA), Fetal growth restriction (FGR), Hydroxychloroquine (HCQ)

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Introduction

In 1983, it was described for the very first time as an acquired type of thrombophilia, a new pathology mediated by autoantibodies, the so-called antiphospholipid syndrome [1]. APS may manifest as a primary, isolated condition or as a secondary disorder in conjunction with other autoimmune diseases, notably systemic lupus erythematosus (SLE) [2]. Besides the dysfunction of the immune system which is one of its main causes, by producing pathogenic antibodies, the dysregulation of the complement also appears to be involved [3].

Later, a less common and extremely severe form of this pathology was described, known as catastrophic antiphospholipid syndrome (CAPS). In these critical cases, the dysfunction of small vessels supplying vital organs leads to widespread organ damage and potentially multiorgan failure [4]. However, this form is very rare, affecting less than 1% of the patients with antiphospholipid syndrome, but one of its possible triggers is pregnancy [4]. Recent research shows that rare mutations in complement regulatory genes may play an important role in driving CAPS. These genetic changes seem to trigger excessive complement activation, which, together with antiphospholipid antibodies (aPL), creates a vulnerability to the sudden, widespread clotting events that define CAPS [5].

The syndrome presents in two primary forms: thrombotic APS, marked by blood clots in both venous and arterial vessels, and obstetric APS (OAPS) [6, 7]. Obstetric APS affects pregnancy outcomes at different stages. Santacruz et al. describe early complications, such as recurrent miscarriage in the first trimester, due to antiphospholipid antibodies disrupting trophoblast function. In later stages, placental dysfunction leads to risks like preeclampsia and fetal growth restriction, premature birth, and perinatal mortality may also occur [8–10].

The underlying pathophysiology of APS is commonly explained through the "two-hit" model, in which antiphospholipid antibodies initially cause endothelial dysfunction, while a secondary environmental factor precipitates clinical symptoms [11]. While the criteria for APS diagnosis emphasize specific clinical and laboratory findings, recent research highlights the variability in antibody profiles and the potential for seronegative APS cases, complicating both diagnosis and management [12]. This underscores the need to investigate non-traditional antibodies to improve the diagnosis and management of complex APS cases [13].

Managing APS in pregnancy remains challenging due to the variability in presentation and the potential severity of outcomes. Conventional treatments, such as low-dose aspirin and heparin, are used to improve pregnancy success rates in affected women [7]. While additional therapies like hydroxychloroquine show promise in cases that are unresponsive to standard care.

The EUROAPS registry, launched in June 2010 as a collaborative web-based platform, enables experts to contribute retrospectively and prospectively with cases of obstetric antiphospholipid syndrome. With data from 1000 cases, this extensive registry provides crucial insights into the clinical features, antibody profiles, and management of OAPS, underscoring the need for standardized protocols to improve maternal and fetal outcomes [14].

This review synthesizes recent findings on APS in pregnancy, addressing its pathogenesis, diagnostic criteria, and treatment options. By exploring these areas, the review aims to provide insights into the unique challenges posed by APS in pregnancy and the latest approaches to improve outcomes for affected women and their children.

Methods

Search and data collection strategy

A systematic review of the literature was undertaken to evaluate the diagnosis, management, and maternal-fetal outcomes associated with Antiphospholipid Syndrome in pregnant women. The electronic database PubMed was searched from January 2018 to October 2024. The search strategy incorporated keywords and MeSH terms such as "Antiphospholipid Syndrome," "pregnancy," "APS management," "thrombosis in pregnancy," and "fetal outcomes." Filters for English language and free full-text articles were applied to optimize relevance.

Eligibility criteria

Articles were selected based on the following criteria: (1) studies involving pregnant women diagnosed with APS based on international criteria (2); studies reporting maternal and/or fetal outcomes in APS pregnancies (3); reviews or clinical trials discussing APS treatments specific to pregnancy, such as low-molecular-weight heparin, aspirin, or corticosteroids. Excluded studies included non-human research, non-English articles, duplicate publications, studies with unvalidated APS diagnoses, studies lacking relevant maternal, fetal, or neonatal outcomes, unpublished or non-peer-reviewed sources, studies with small sample sizes or significant methodological limitations, and studies primarily addressing conditions other than APS.

Screening and selection process

The initial search yielded 847 articles, which were screened by title and abstract, and 120 studies were selected for full-text review. Any discrepancies in article selection were discussed and resolved.

Quality and risk of bias assessment

The quality of the included studies was assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach. For observational studies, the Newcastle-Ottawa Scale was applied, and for randomized controlled trials, the Cochrane Risk of Bias tool was used. Each study was scored based on methodological rigor, sample size, and relevance to APS in pregnancy.

Data synthesis and analysis

The data were synthesized narratively, focusing on three core areas: (1) diagnostic criteria and challenges of APS in pregnancy (2), obstetric outcomes and complications associated with APS, and (3) therapeutic approaches, including anticoagulants and immunosuppressive agents. A descriptive analysis was performed to identify common findings, and summary tables were developed to illustrate treatment outcomes and pregnancy complications. The implications of findings for clinical practice and research were also discussed. Tables were developed to highlight diagnostic criteria and summarize treatment protocols and outcomes for APS in pregnancy.

Results

Key findings from the literature: outcomes, interventions, and guidelines for APS in pregnancy

The comprehensive literature review on antiphospholipid syndrome in pregnancy elucidates several pivotal findings across key thematic areas: clinical management, therapeutic interventions, risk stratification, and pregnancy outcomes. These findings provide a basis for optimizing clinical practices in this high-risk population.

1. Impact of APS on Pregnancy Outcomes and Key Risk Factors APS is significantly associated with adverse pregnancy outcomes, including recurrent early pregnancy loss, pre-eclampsia, fetal growth restriction, and stillbirth. Quantitative analyses consistently reveal a correlation between high titers of antiphospholipid antibodies (aPL), such as IgG anticardiolipin and anti-beta-2 glycoprotein I, and the increased risk of these outcomes. Patients presenting with multiple aPL positivity or persistently elevated antibody levels demonstrate a notably higher incidence of complications. Early identification of high-risk profiles through repeated antibody titers and structured fetal monitoring has been shown to enhance the timing of interventions and potentially mitigate morbidity.
2. Therapeutic Interventions: Efficacy and Emerging Options Studies assessing the efficacy of therapeutic strategies report that combined anticoagulant therapy, particularly the concurrent administration of LMWH and low-dose aspirin, significantly improves live birth rates in APS patients. New pharmacologic options, including hydroxychloroquine and complement inhibitors, have demonstrated efficacy in refractory APS cases and are associated with reduced obstetric complications, especially in APS cases complicated by concurrent autoimmune conditions such as systemic lupus erythematosus (SLE). Systematic reviews and meta-analyses reveal a statistically significant improvement in obstetric outcomes with these adjunctive therapies, underscoring the necessity for individualized treatment plans and ongoing evaluation of novel pharmacologic agents in APS management. Adopting a multidisciplinary approach—encompassing expertise from obstetrics, rheumatology, and hematology—is essential for managing the complex clinical presentation of APS in pregnant patients, and current guidelines advocate for this integrated model of care.
3. APS and Concomitant Autoimmune Disorders: Compounded Risks The coexistence of APS with autoimmune conditions, most commonly SLE, amplifies pregnancy risk. Data consistently indicate that pregnancies in patients with APS-SLE overlap exhibit higher rates of thrombotic events, pre-eclampsia, and fetal growth restriction. Management of these cases often requires intensified anticoagulation and immunosuppressive regimens, as standard APS protocols may be insufficient to control disease activity and prevent obstetric complications. This subgroup of patients benefits from an escalated treatment protocol, involving immunosuppressive agents and targeted biologics, to address the compounded immunologic and thrombotic risks.
4. Evidence Synthesis and Guidelines Systematic reviews and meta-analyses provide comprehensive insights into the effectiveness of various management strategies, particularly anticoagulant combinations, in APS-affected pregnancies. These studies substantiate that integrated, evidence-based interventions significantly reduce pregnancy morbidity and improve live birth rates. Consensus guidelines from the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) offer robust, evidence-based recommendations that guide clinical decision-making and promote standardized care across clinical settings. Such guidelines underscore the importance of personalized risk stratification and reinforce the utility of combined anticoagulation therapy as a cornerstone of APS management in pregnancy.

Pathogenesis

APS appears as a result of an abnormality in the immune system, which produces pathogenic antibodies known as aPLs [4]. APS is increasingly understood through the lens of the "two-hit" model [15]. Antiphospholipid antibodies lead to endothelial dysfunction, necessitating a secondary environmental trigger to manifest clinical symptoms. Environmental factors, particularly infections, are identified as key triggers that may exacerbate APS symptoms by stimulating abnormal antibody production [16]. Mendoza-Pinto et al. report that nearly half of CAPS cases are precipitated by infections, with bacterial pathogens such as Escherichia coli and Staphylococcus aureus and viral agents like cytomegalovirus and Epstein-Barr virus frequently implicated as triggers. These infections are thought to exacerbate the inflammatory and thrombotic pathways in APS, leading to the severe, multi-system involvement characteristic of CAPS [17].

The predictive model study by Baños et al. highlights that demographic factors like ethnicity and lifestyle choices, such as smoking, increase the risk of adverse pregnancy outcomes in APS. These findings emphasize the importance of early, targeted risk assessments to improve outcomes [18]. Additional factors involved are outlined in Fig. 1.

The two-hit model in APS pathogenesis

This heterogeneous group of antiphospholipid antibodies is situated in the endothelium of certain cells involved in the coagulation cascade, such as platelets [1]. Firstly, aPLs produce endothelial lesions, and with a second hit, the vascular integrity is disrupted, which leads to the appearance of a thrombus [19]. Following this 'two-hit' pattern, aPLs lead to placental insufficiency by inducing a pro-inflammatory state in the vascular wall of the trophoblastic tissues which leads to a prothrombotic state [20]. Because of the direct interaction with the placental tissue, antiphospholipid antibodies are compromising the trophoblast function and placental development [21]. This interaction can lead to impaired trophoblast invasion and reduced chorionic gonadotropin secretion, essential for placental health. These effects contribute to common APS-associated pregnancy complications, such as preeclampsia and fetal growth restriction [22].

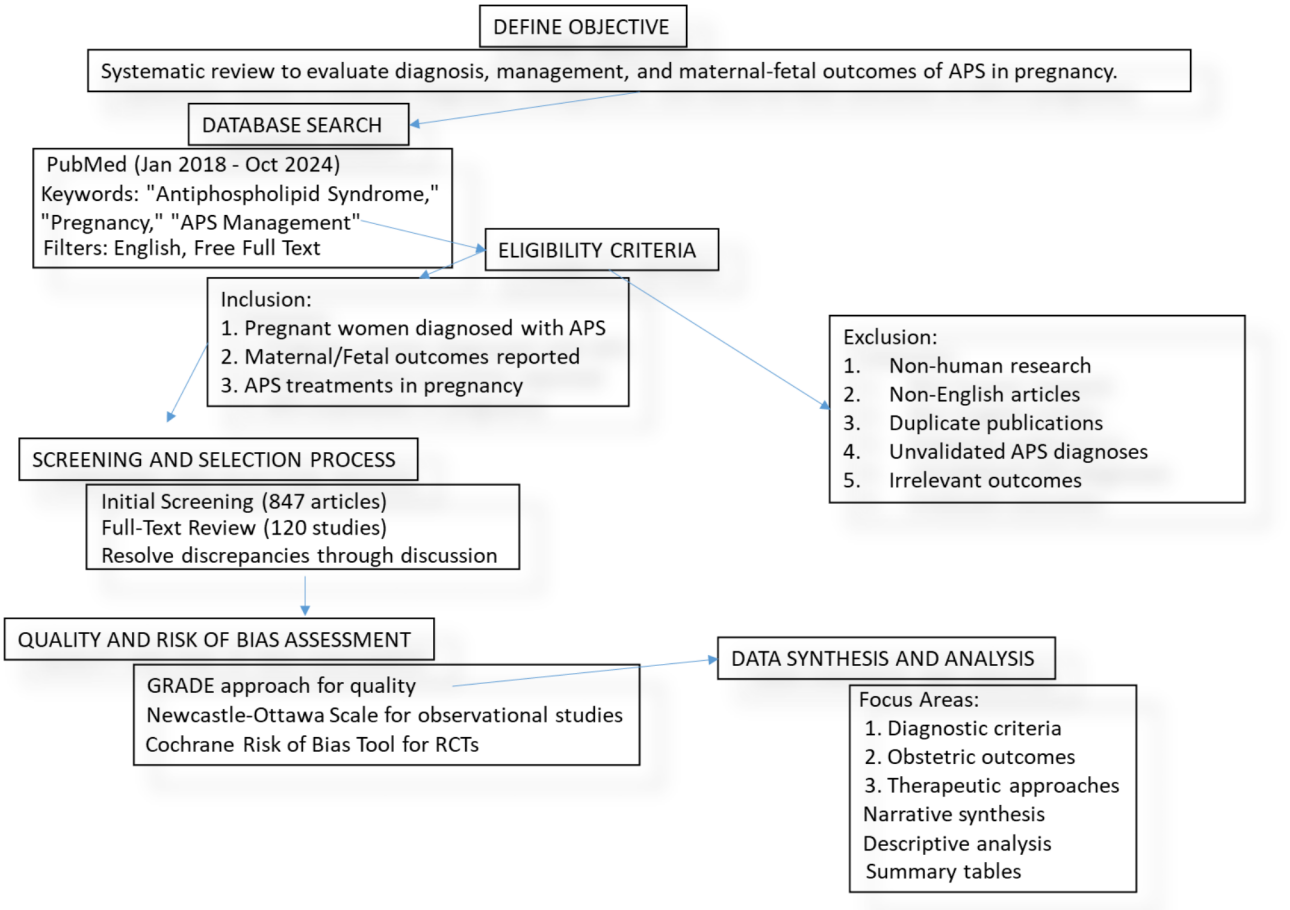

Fig. 1 Flowchart

A recent study supports the 'second hit' hypothesis in APS. Differences in recurrence rates and presentations between isolated thrombotic APS (ItAPS) and isolated obstetric APS (IoAPS) suggest that each subtype may require distinct secondary triggers. In ItAPS, cardiovascular stressors may precipitate thrombotic events, while in IoAPS, elevated β2GPI expression in placental tissues likely contributes to vascular dysfunction during pregnancy [23].

The pro-inflammatory state mediated by antiphospholipid antibodies is facilitated by inflammatory factors such as the deposition of IgG and complement, neutrophilic infiltration, but also a local secretion of TNF-alpha [1]. Emerging evidence points to complement activation and endothelial dysfunction as critical mechanisms in APS pathophysiology. Complement activation, often triggered by antiphospholipid antibodies, can lead to endothelial injury and subsequent thrombosis, highlighting the significance of these processes in both thrombotic and obstetric manifestations of APS. Understanding these mechanisms provides a clearer basis for the „two-hit" model [24].

In APS pregnancies, complement activation, driven by antiphospholipid antibodies, disrupts placental function, causing inflammation, thrombosis, and impaired blood flow, leading to fetal growth restriction, preeclampsia, and pregnancy loss [25, 26].

The antiphospholipid antibodies may also have different negative effects on the pregnancy. For example, it is thought that they affect embryo implantation by interfering with endometrial decidualization [1]. They also decrease the trophoblastic viability and invasiveness or even cause trophoblast apoptosis, in both cases, the well-functioning of the placenta is compromised [1]. The consequences of placental dysfunction caused by aPL are several obstetric complications such as stillbirth, defective fetal growth, or preeclampsia [1, 27]. Furthermore, it is recently thought that aPL may prevent the oocyte from developing after being secreted in the follicular fluid [1, 28].

Besides the contribution aPL has in the pathogenesis of antiphospholipid syndrome, pregnancy loss in APS may also be related to the maternal spiral arteries, which may be inadequately invaded by the extravillous cytotrophoblast, a situation that leads to early miscarriages and recurrent pregnancy loss [29–31] On the other hand, the impaired transformation of spiral arteries alongside the coagulation cascade and the complement may cause late pregnancy loss and preeclampsia [30].

Genetic and immunologic distinctions

Recent research has identified distinct genetic markers associated with different subtypes of Antiphospholipid Syndrome, suggesting unique genetic underpinnings for obstetric APS and thrombotic APS [32, 33]. For instance, polymorphisms in genes such as *STAT4*, *TNFAIP3*, and *HIP1* have been linked to an increased risk of OAPS, indicating a genetic predisposition to pregnancy-related complications in APS patients [34–36]. Conversely, genes like *PF4V1*, *SERPINE1*, and *VEGFA* have been associated with TAPS, highlighting a genetic inclination towards thrombotic events [33]. These findings support the notion that OAPS and TAPS may represent distinct clinical subtypes with unique pathophysiological mechanisms.

A study investigating the major autoantibody targets in obstetric antiphospholipid syndrome identifies the β2GPI/HLA-DR complex as a key target in obstetric APS, particularly in recurrent pregnancy loss (RPL). This complex, formed when β2GPI binds to HLA-DR on antigen-presenting cells, exposes unique epitopes that trigger an autoimmune response. Autoantibodies against this complex induce complement-mediated damage to placental tissue, promoting thrombosis and placental insufficiency that compromise fetal survival. Additionally, specific HLA-DR alleles, such as HLA-DR4, HLA-DR7, and HLA-DR13, increase the likelihood of β2GPI binding and autoimmunity, suggesting a genetic predisposition to APS in certain individuals [37].

Neutrophil extracellular traps in APS

Traditionally, antiphospholipid antibodies activate endothelial cells, promoting thrombosis and complement activation, which exacerbates placental inflammation and dysfunction. Recent findings reveal additional pathways, including Neutrophil Extracellular Traps (NETs) and Toll-Like Receptors (TLRs). aPLs trigger NET release, enhancing coagulation, while TLR activation initiates inflammatory responses that compromise pregnancy outcomes. The release of microparticles from activated cells further intensifies coagulation and inflammation, highlighting APS's complex pathology and supporting the need for targeted therapies addressing both thrombosis and inflammation [29, 34, 38].

Epidemiology

APS affects 2–5 per 100,000 Caucasians annually, with a prevalence of 40–50 per 100,000 individuals [39, 40]. While its true prevalence remains unclear, it is estimated to affect 0.5% of the population, predominantly around age 35 and more commonly in women [1, 15]. This gender disparity has drawn focus to pregnancy outcomes, revealing that women with prior thrombotic events face a high risk of complications [8]. Pregnancy complications, including fetal growth restriction (FGR), occur in 2–8% of pregnancies in developed countries but are reported in 12–30% of OAPS cases [41].

As regards pregnancy loss, it is considered that APS contributes to approximately 15% of cases [34]. However, pregnancy loss occurs in 34 up to 76% of APS cases [42]. Also, with a frequency of 54%, recurrent miscarriage in the first trimester is considered to appear in women with APS [9]. There is a recent European survey of 1000 cases of obstetric APS, which claims that the percentage of fetal loss continues to be very high, approximately 27% [43].

Another complication of pregnancy in women with APS is preeclampsia, with a frequency between 10 and 48% [43–45]. Besides, if it were to convert the percentages, it is thought that about 1 in 7 cases of pre-eclampsia may be associated with APS [45]. However, PE occurs in less than 5% of pregnancies, in APS pregnancies its frequency increases up to 17,3%, but only 0,5% of pregnant women are expected to develop a severe form of PE [40].

The most severe form of APS, the so-called catastrophic APS appears in just 1% of APS cases, with an overall mortality rate of approximately 36%, primarily characterized by rapid-onset multiple organ microthromboses [46, 47]. Pregnancy is its CAPS' precipitating factor in approximately 8% of cases [43]. Furthermore, CAPS' appearance de novo in pregnancy compared to non-pregnancy cases has a much higher frequency (48,2 vs. 26,3%) [43].

The prevalence of APS in pregnancy highlights the need for precise diagnostic criteria to enable early intervention and improve outcomes, making this review essential for advancing clinical understanding.

Diagnostic criteria

The American College of Obstetricians and Gynecologists (ACOG), along with the **European Alliance of Associations for Rheumatology** (EULAR) outlines specific diagnostic criteria for Antiphospholipid Syndrome [48]. The diagnosis of antiphospholipid syndrome is based on a combination of clinical manifestations and laboratory findings, with classification criteria serving as standardized tools for research and clinical stratification. Historically, the Sapporo criteria (1999) and their 2006 revision in Sydney provided the framework for APS classification. However, the 2023 ACR/EULAR Classification Criteria have introduced a more refined, weighted approach to APS, enhancing risk stratification and improving clinical applicability. To accurately diagnose antiphospholipid syndrome, both clinical and serological criteria are essential, requiring the presence of at least one clinical and one laboratory feature [49].

The 2023 ACR/EULAR Classification Criteria refine APS classification using a weighted scoring model that integrates clinical and laboratory findings, enhancing specificity and patient care. A key advancement is the recognition of obstetric complications as critical APS indicators. Severe preeclampsia, fetal growth restriction, and late pregnancy loss are now explicitly included, distinguishing obstetric APS from its thrombotic counterpart. The updated classification places greater emphasis on pregnancy-related complications, particularly those linked to placental dysfunction. The recognition of placental dysfunction-related complications as APS-related manifestations underscores the necessity for individualized surveillance and targeted anticoagulation therapy in high-risk pregnancies [50].

While classification criteria are not equivalent to diagnostic criteria, their clinical utility is evident in guiding patient assessment and management. The integration of the 2023 ACR/EULAR Classification Criteria into clinical decision-making enables a more standardized, evidence-based approach to APS diagnosis and risk assessment, ultimately enhancing maternal and fetal outcomes [50].

The criteria also reinforce the importance of confirming persistent antiphospholipid antibody (aPL) positivity through repeat testing at least 12 weeks apart. Lupus anticoagulant remains the most predictive marker, followed by anticardiolipin and anti-β2GPI antibodies, ensuring accurate classification. By offering a structured and evidence-based framework, the updated criteria enhance APS identification, support targeted treatment approaches, and advance research efforts while maintaining a clear distinction between classification and diagnosis.

Sciascia et al. emphasize that precise antiphospholipid antibody testing is essential in APS diagnosis and risk stratification. Key assays include lupus anticoagulant, anticardiolipin, and anti-beta-2 glycoprotein I antibodies, which together provide a comprehensive aPL profile. Advances like thrombin generation assays (TGAs) have refined risk assessment by capturing both procoagulant and anticoagulant dynamics [51].

Lupus anticoagulant is considered the major predictor of thrombosis in non-pregnant patients. In pregnant women is it known that LA is the main predictor of poor pregnancy outcomes [52]. A recent study identified a notably high prevalence of lupus anticoagulant positivity (82.5%) and triple-positive antiphospholipid antibodies (52.5%) among APS patients with severe preeclampsia [53]. When it is found at the beginning of pregnancy, it is associated with thrombotic events on the placenta on the maternal side [54]. Identification of LA may be associated with the detection of a medium or high titer (>40 GPL/MPL or >99th percentile) of anticardiolipin antibodies, both IgG and IgM isotypes, but also IgG/IgM antiB2-GPI antibodies [55, 56]. Either criterion must be confirmed with a 2nd test, 12 weeks after the first one to be considered positive [43]. The strongest predictors of APS are considered to be this triple positivity mentioned above accompanied by a history of thrombotic events [8, 57].

A laboratory marker that may help in identifying high-risk APS pregnancies is represented by the complement [58]. In these cases, low levels of circulating components of the complement may indicate that there is a higher chance of obstetric complications [59]. Saleh et al. also observed an association between hypocomplementemia and increased adverse pregnancy outcomes, particularly pre-eclampsia and intrauterine growth restriction. This suggests that low complement levels might serve as a biomarker for assessing pregnancy risks in patients with APS and SLE. However, there is limited evidence supporting complement consumption as a reliable high-risk marker, with few studies and a small patient population [60].

Another useful biomarker is aPS/PT antibodies; their presence can also predict IUGR or preeclampsia in APS pregnancies and their importance consists in identifying patients who need supplementary treatment, as the processes they are involved in do not respond to regular medication [61].

However, some patients don't present a serological profile that meets the classification criteria; these cases constituted a so-called "non-criteria APS" group [62]. Patients from this group present APS-related clinical manifestations, at least one of the following: superficial venous thrombosis, thrombocytopenia, microangiopathy, heart valve disease, livedo reticularis, migraine, chorea, seizures, myelitis or "lupus-like" manifestations [63, 64]. This group of patients often experiences obstetric complications, such as miscarriage and preeclampsia, even without traditional APS antibodies [65].

Diagnosing APS can be difficult, particularly for „APS-like patients". The expansion of testing to include non-criteria antibodies, such as anti-phosphatidylethanolamine, has been proposed to enhance diagnostic accuracy and identify NC-APS patients who might otherwise remain undiagnosed. While this broader approach aims to facilitate early intervention and potentially reduce thrombotic and obstetric risks, its practical utility remains uncertain, as many of these antibodies lack sufficient specificity and are not consistently associated with clinical manifestations [66].

Distinct antiphospholipid antibody profiles have been observed between patients with obstetric APS and those with thrombotic APS (TAPS), as highlighted by Anunciación-Llunell et al. Specifically, OAPS patients often exhibit elevated IgM levels of antibodies like antiphosphatidic acid (aPA) and anti-β2GPI, while TAPS patients display higher IgG levels of anticardiolipin and anti-annexin 5 (aA5). These variations underscore how antibody profiling can guide personalized APS treatment in pregnancy, where risks of preeclampsia, fetal growth restriction, and preterm birth are elevated [32, 67].

Ripoll et al. identified biomolecular markers distinguishing thrombotic from obstetric APS, revealing subtype-specific pathways. In obstetric APS (VT-/PM+), markers such as Protein tyrosine kinase 2 beta (PTK2B), Glycoprotein V (platelet) (GP5), TIMP metallopeptidase inhibitor 2 (TIMP2), and Fibronectin 1 (FN1) are upregulated, indicating roles in cell adhesion and extracellular matrix remodeling critical for placental function. These findings underscore the mechanistic divergence within APS, supporting the development of tailored therapeutic approaches for each clinical manifestation [68].

The EUREKA model by Pregnolato et al. applies artificial intelligence to analyze individual antibody profiles and clinical factors, enabling risk-adjusted management strategies. This AI-driven precision approach allows for tailored treatment intensity, potentially improving outcomes for both mother and child [69].

Pregnancy outcomes and clinical manifestations in APS

Pregnancy has been associated with an increased likelihood of progression from preclinical autoimmune conditions to fully developed autoimmune diseases in predisposed women [70].

Maternal outcomes in obstetric APS

Obstetrical antiphospholipid syndrome has several manifestations, both maternal and fetal. Maternal outcomes include abdominal pain, general malaise, and chest pain [4]. Gestational hypertensive disease is another maternal outcome with associated risks including placental abruption, and proteinuria, but thrombosis, dyspnea, or pulmonary embolism may also occur [71].

Cutaneous diseases such as *livedo racemosa* are some atypical clinical manifestations of APS [72], Pulmonary injuries such as pulmonary arterial hypertension or alveolar hemorrhage, or even cardiac diseases like nonbacterial Libman-Sacks endocarditis, along with neurological manifestations such as altered mental status, migraine, seizure, or chorea can also occur [73]. Regarding the liver, it may appear to be both a thrombotic and a nonthrombotic disease. From the thrombotic ones we mention Budd-Chiari syndrome and hepatic veno-occlusive disease, and from the other category we remember cirrhosis, autoimmune hepatitis, and portal hypertension [73].

A study evaluating fetal thymus size in maternal autoimmune diseases explores its variations in systemic lupus erythematosus, Sjögren's syndrome, and antiphospholipid antibody syndrome identified an association between maternal autoimmune inflammation and alterations in fetal immune organ development, particularly affecting thymic growth. This research found a significantly reduced fetal thymus-thoracic ratio (TTR) in pregnancies complicated by antiphospholipid syndrome, systemic lupus erythematosus, and Sjögren's syndrome

relative to healthy pregnancies. The reduction in TTR observed in affected pregnancies suggests that inflammatory processes associated with these autoimmune conditions may impair fetal thymus development, potentially leading to compromised neonatal immune function. Furthermore, additional studies are warranted to confirm these findings and to explore the long-term impacts of reduced thymic growth on neonatal and pediatric immune outcomes in this patient population [74].

Fetal outcomes in obstetric APS

Fetal/neonatal outcomes include abortion, intrauterine fetal death or pregnancy loss after 10 weeks of gestation, neonatal morbidity and mortality, intrauterine growth restriction, prematurity, or stillbirth [1]. The major negative outcomes, such as preterm birth, intrauterine growth restriction, and fetal death, are often caused by insufficiency of the placenta, frequently associated with preeclampsia. Especially in preterm births before 34 weeks, OAPS cases show a marked increase in neonatal risks [40, 75].

These complex fetal and neonatal outcomes underscore the critical challenges posed by APS in pregnancy. Figure 2 visually synthesizes these risks, offering a clear depiction of the range of adverse maternal-fetal outcomes linked to placental insufficiency and preeclampsia (See Fig. 3).

It is thought that there is a certain pathophysiological mechanism that induces different pregnancy outcomes related to the gestational age. Therefore, trophoblastic cell proliferation is reduced in the first trimester which leads to early miscarriage (known as the most sensitive clinical symptom), whereas placental dysfunction has a negative impact on pregnancy during the second and third trimesters [9]. However, it is believed that the most specific clinical manifestations of APS are early delivery and fetal death [76]. Because both of these signs are caused by preeclampsia or placental insufficiency, a Doppler ultrasound is required in order to detect if there is a reduced flow in the uterine arteries. An abnormal end-diastolic flow in the uterine artery at 20–24 weeks of gestation is a good predictor of late obstetric complications in women with APS [9]. Furthermore, a very important role have the laboratory and clinical criteria for APS; if fulfilled, there is a higher risk of developing PE/HELLP syndrome, IUGR, or stillbirth, which increases the negative obstetrical outcomes [40].

It was observed that OAPS has an impact not only on the pregnancy-related morbidities mentioned above, but can also appear combined with other vascular clinical manifestations. An example of this common ground is fetal loss before 10 weeks of gestation in patients with deep vein thrombosis [77].

A meta-analysis by Xu et al. (2022) found a strong link between antiphospholipid antibodies and fetal growth restriction in APS pregnancies, specifically implicating anticardiolipin antibodies and anti-beta2 glycoprotein 1 antibodies. Among the 11,000 pregnancies analyzed, elevated ACA and β2GP1 levels were associated with significantly increased FGR risk, with odds ratios of 2.25 and 1.31, respectively. These findings suggest that APS, via these antibodies, can impair placental function and restrict fetal growth. Notably, lupus anticoagulant showed no significant impact on FGR, underscoring the importance of monitoring ACA and β2GP1 levels to better manage fetal risks in APS pregnancies [78].

The most severe form of APS, known as CAPS, can also be triggered by pregnancy. It is a very rare manifestation and it consists of multiorgan thrombosis, implying, especially small vessels, but it can also present non-specific symptoms similar to those in sepsis, acute fatty liver, infective endocarditis, vasculitis, and other autoinflammatory conditions [45, 79, 80]. It is thought that 80% of CAPS cases are precipitated by pregnancy, half of the cases occurring during pregnancy, and the other half after the termination of pregnancy [45]. Recognizing the diverse clinical manifestations of APS is critical for early diagnosis and timely intervention, especially in preventing severe outcomes such as CAPS [81].

Treatment and management of obstetric antiphospholipid syndrome

The most important thing one must avoid in APS is the appearance of first or recurrent thrombotic complications, alongside negative obstetric outcomes. To do so, there must be a rigorous observation of signs and specific criteria that lead to an early administration of proper treatment [82]. Given the heterogeneity of APS manifestations, individualized treatment plans that consider each patient's specific subtype, antibody profile, and pregnancy history are crucial. Recent literature, including the 2020 American College of Rheumatology (ACR) guidelines for reproductive health in rheumatic and musculoskeletal diseases supports the move toward personalized treatment protocols in APS, where factors such as monotherapy versus combination therapy are tailored based on patient risk and clinical history. This personalized approach is especially beneficial in managing obstetric APS, as individualized care may significantly reduce the likelihood of miscarriage, preeclampsia, and intrauterine growth restriction [83].

Primary prophylaxis for high-risk APS patients

The management of obstetric APS depends mostly on whether there are previous APS-related obstetric morbidities or not [84]. If there is a patient with no history of thrombotic events, thrombi-prophylaxis is not needed,

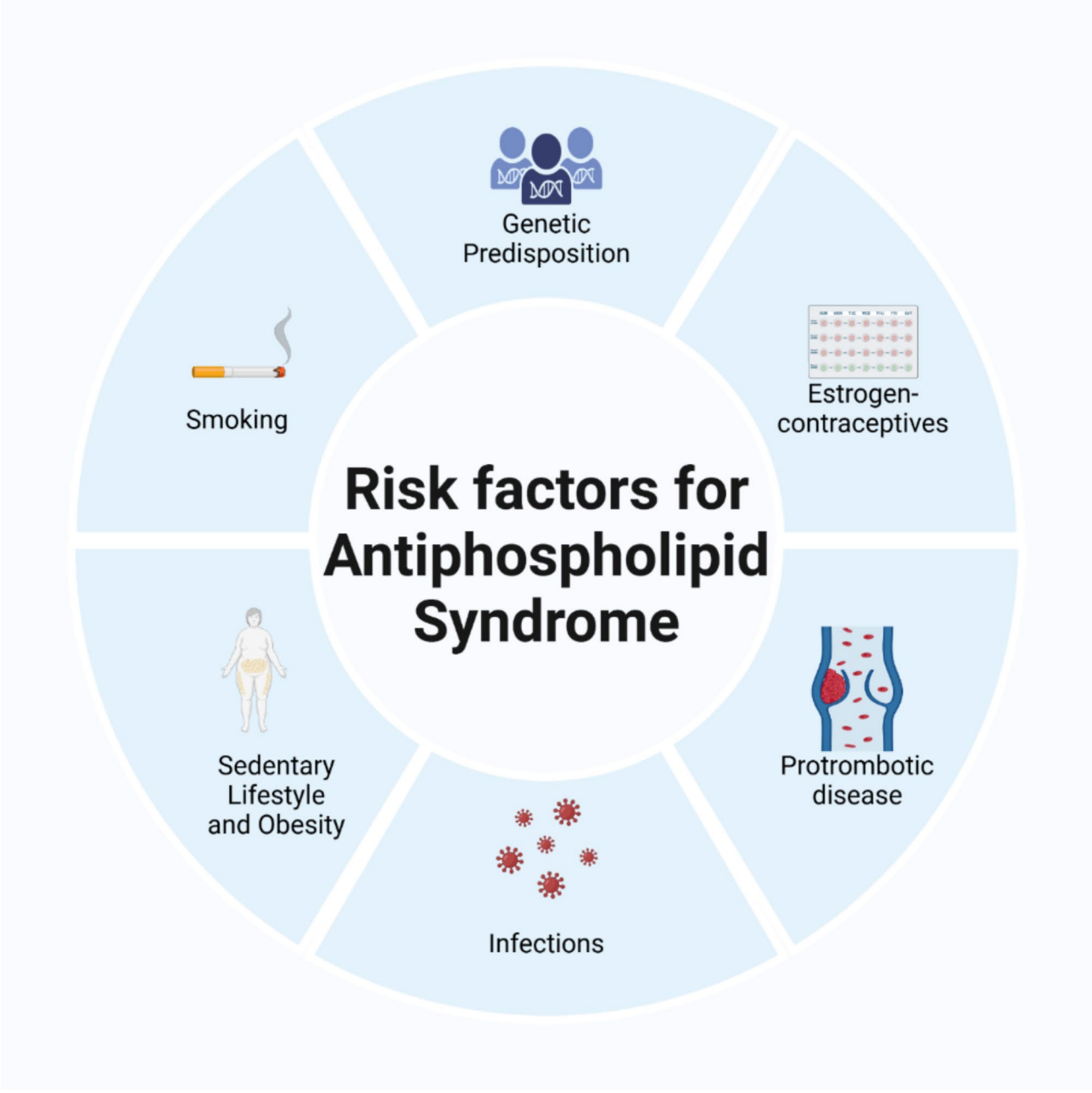

Fig. 2 Risk Factors for Antiphospholipid Syndrome.Created in BioRender. Murvai, R. (2024) https://BioRender.com/b13h832

but if the patient had recurrent early miscarriages or late fetal losses, thrombi-prophylaxis should be taken into consideration [84].

In pregnant women with antiphospholipid syndrome, antithrombotic therapy should be integrated with a thorough evaluation of additional prothrombotic risk factors, including advanced maternal age, smoking, obesity, hypertension, diabetes, pre-eclampsia, postpartum hemorrhage, and prolonged immobility. A comprehensive risk assessment is essential to inform individualized prophylactic strategies, mitigate thrombotic complications, and optimize maternal and fetal outcomes.

There are plenty of studies made on several groups of patients, from which we can extract ideas such as the following: the protective effect of low-dose aspirin against thrombosis, in patients with high-risk antiphospholipid antibody profile, as primary treatment of thromboprophylaxis [82]. However, the official guideline (EULAR) shows that LDA alone only prevents arterial thrombosis, but not the venous one [40]. Nevertheless, the established standard of care for obstetric APS continues to be

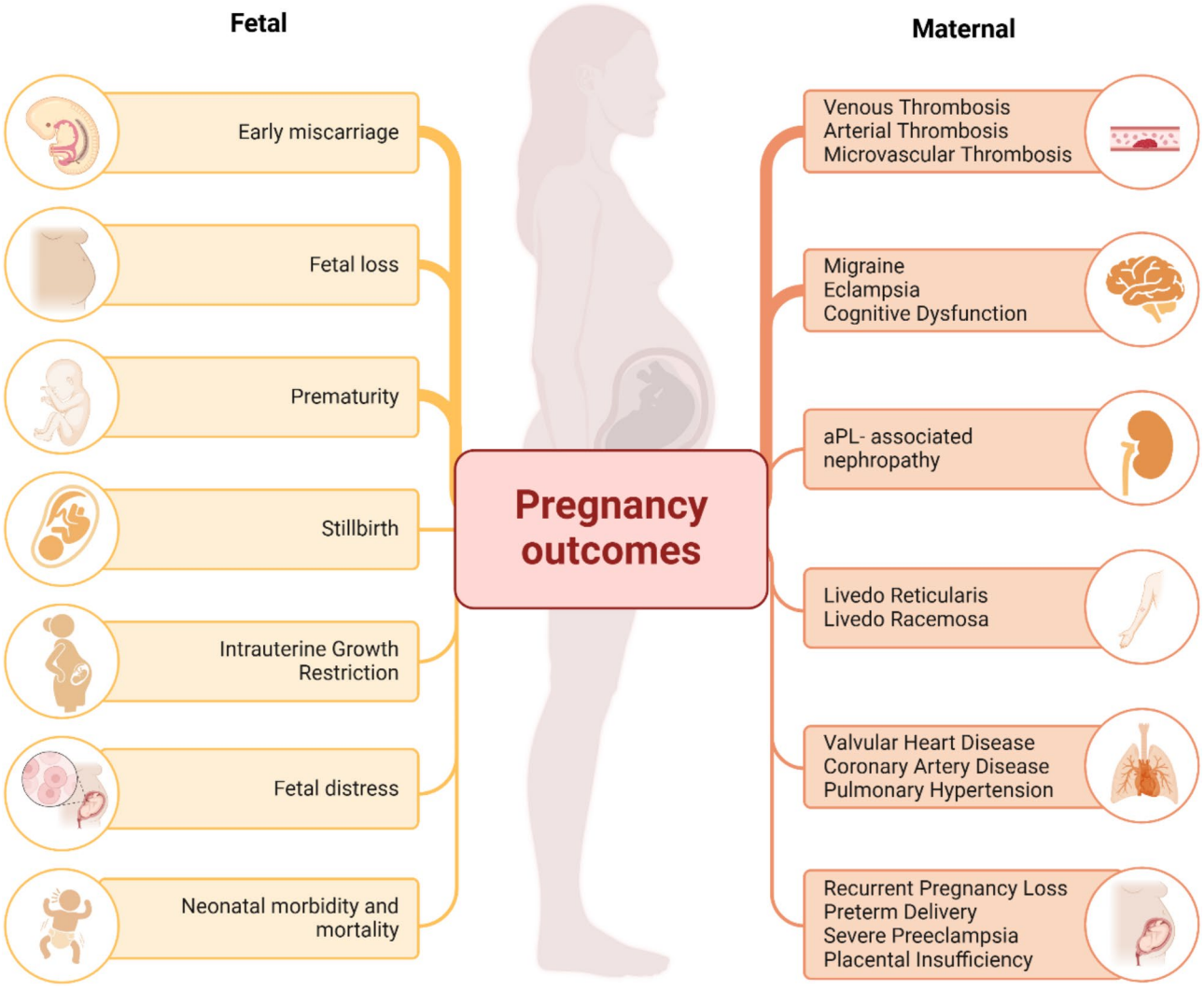

Fig. 3 Maternal-fetal Outcomes in Antiphospholipid Syndrome. Created in BioRender. Murvai, R. (2024) https://BioRender.com/m41w221

the combined administration of low-dose aspirin and low-molecular-weight heparin, a regimen that has demonstrated superior efficacy in optimizing pregnancy outcomes and mitigating thrombotic risk.

LDA and Low-Molecular-Weight heparin (LMWH) In pregnancy, APS management is complicated by the limitations of anticoagulation options. While warfarin is avoided due to fetal risks, low-molecular-weight heparin combined with low-dose aspirin remains the standard [85, 86].

Some cohort studies showed that LDA combined with heparin has a much better effect in obstetrics APS, with a higher rate of live births [82, 87]. According to a Cochrane review, this dual treatment improved outcomes in cases of APS-related RPL [88]. However, they would not notice a difference regarding the risk of pre-term delivery, preeclampsia, or intrauterine growth restriction [82]. Therefore, EULAR guidelines recommend using Hydroxychloroquine, for its immune-modulating properties, or low-dose corticosteroids besides LDA plus Heparin, in refractory cases with pregnancy complications, both of which lead to improved pregnancy outcomes [20].

For asymptomatic patients with antiphospholipid antibodies, the ACR suggests cautious monitoring without routine anticoagulation unless a history of obstetric complications is present, in which case LDA and LMWH may be considered based on individualized risk assessment [89].

Regardless, the treatment for obstetric APS includes the use of LDA even in the preconception stage and low molecular weight heparin at prophylactic doses added when the pregnancy is confirmed [90]. A ten-year follow-up study conducted by Niznik et al. investigates the long-term outcomes of patients with primary obstetric

antiphospholipid syndrome. The findings showed that while low-dose aspirin and low-molecular-weight heparin improved pregnancy outcomes, a significant number of patients still experienced thrombotic events over time, highlighting the need for continued risk management [91].

A long-term observational study spanning 17 years assessed anticoagulant therapy's effectiveness in pregnant women with APS, analyzing 92 pregnancies treated with LMWH or unfractionated heparin (UFH) combined with low-dose aspirin. Interestingly, UFH showed a slightly higher live birth rate (84%) compared to LMWH (79%), suggesting that UFH may offer a viable, cost-effective alternative without compromising safety—a notable finding for settings where resources may limit LMWH use [92, 93].

The optimal dosing regimen for LMWH in pregnant patients with thrombotic APS has yet to be definitively established. Current studies and guidelines, including EULAR, advocate for therapeutic-dose heparin during pregnancy in APS patients, particularly for those with a history of thrombotic events [94]. This recommendation, though based on limited data, is supported by evidence indicating that women with APS and a history of cerebrovascular events are at heightened risk for recurrence during pregnancy, underscoring the necessity for vigilant anticoagulation management [95].

Vitamin K antagonists Vitamin K antagonists can also be used in the treatment of thrombotic APS or as secondary thromboprophylaxis [34]. However, due to its known teratogenicity, current guidelines advise transitioning from warfarin to therapeutic LMWH combined with LDA by the sixth week of gestation [96] (Arslan & Branch, 2019). This regimen reduces the risk of warfarin embryopathy while ensuring adequate thromboprophylaxis throughout pregnancy [96].

According to the British Society for Haematology (BSH) guidelines, women with thrombotic APS previously treated with warfarin should have warfarin reinstated in the postpartum period, as it is deemed safe during lactation and remains the preferred long-term anticoagulant for secondary thrombosis prevention. However, postpartum warfarin should be avoided until at least the fifth day and for a longer period in women at increased risk of postpartum hemorrhage [97].

Hydroxychloroquine (HCQ) Hydroxychloroquine is traditionally used in lupus, but emerging research shows it may also benefit pregnant women with APS. Known for its immunomodulatory properties, HCQ is recommended for use alongside LDA and LMW in pregnancy complications associated with APS. Studies suggest that HCQ not only improves pregnancy outcomes but also aids in endothelial function, potentially minimizing the prothrombotic state induced by antiphospholipid antibodies [98]. Also, HCQ can reduce placental inflammation and improve trophoblast function, thereby decreasing placental insufficiency and enhancing maternal-fetal health in high-risk pregnancies [16]. .

HCQ is typically regarded as safe in pregnancy; however, recent studies suggest a minor teratogenic risk, particularly with first-trimester exposure. In a cohort of 2,045 HCQ-exposed pregnancies, a dose-dependent increase in urinary tract and oral cleft malformations was observed, with a relative risk of 1.33 for daily doses ≥ 400 mg, compared to 0.95 for doses < 400 mg [99].

For APS patients with a history of recurrent fetal loss unresponsive to conventional therapies, initiating hydroxychloroquine therapy at a dose of 400 mg daily before conception may provide additional benefit. A multicentre study investigated the effect of additional treatments combined with conventional therapies in pregnant patients with high-risk antiphospholipid syndrome suggests that preconception HCQ therapy significantly reduces the risk of fetal death in cases previously refractory to low-dose aspirin and heparin alone, offering a promising strategy for improving pregnancy outcomes in high-risk APS patients [100].

The use of HCQ in pregnancy should be individualized, with informed maternal consent, as teratogenic risks are highest in the first 12 weeks. Initiation after 12 weeks may be advisable. Currently, there is limited data on HCQ's impact on recurrent pregnancy complications in obstetric APS unresponsive to standard treatments. The ongoing prospective randomized controlled trial, "Hydroxychloroquine to Improve Pregnancy Outcome in Women with Antiphospholipid Antibodies" (HYPATIA), is designed to address critical questions about the efficacy and safety of hydroxychloroquine use in pregnancy for APS patients unresponsive to standard therapies [86, 101].

Corticosteroids Recent studies underscore that corticosteroids when administered in conjunction with low-dose aspirin and hydroxychloroquine, are generally effective and pose minimal risk if carefully managed. Diligent dosage monitoring is essential to reduce the likelihood of adverse outcomes, including preterm birth, hypertension, and potential fetal effects. This approach ensures that corticosteroids deliver therapeutic efficacy, safeguarding maternal and fetal health without heightening pregnancy-associated risks [102].

Statins A malfunction that leads to increased resistance in fetoplacental circulation may be due to a vicious activity of nitric oxide synthetase, as its levels were found lower in patients with preeclampsia [103]. Therefore NO is consid-

ered to play an important role in fetoplacental circulation, as increased NO levels were found related to favorable pregnancy outcomes [103]. Statins, such as Pravastatin, increase NO levels alongside placental hemodynamics and support intrauterine fetal growth [103]. However, the use of pravastatin has not yielded the expected results, and current evidence does not support its efficacy at the same level as low-dose aspirin and low-molecular-weight heparin in improving pregnancy outcomes.

Recent research highlights the potential role of Simvastatin in improving pregnancy outcomes for patients with OAPS by targeting glycolysis-related neutrophil extracellular traps (NETs). Simvastatin's inhibition of glycolysis through the PI3K-AKT-PKM2 pathway presents a novel mechanism to manage OAPS, suggesting it could serve as an adjunct therapy in cases where standard treatments fall short [104].

Plasma exchange and High-Dose intravenous immunoglobulin (IVIG) While the majority of obstetric APS cases respond adequately to standard treatment (low-dose aspirin and low-molecular-weight heparin), a subset of patients may require adjunctive therapies such as hydroxychloroquine and prednisone. In rare instances of refractory OAPS unresponsive to conventional management, alternative interventions, including plasma exchange or IVIG may be considered. However, given that recurrent pregnancy loss in some of these patients may stem from factors unrelated to OAPS, further research is warranted to elucidate potential underlying causes. High-dose intravenous immunoglobulin (IVIG) therapy has been evaluated as a treatment option in cases of aspirin–heparin-resistant secondary antiphospholipid syndrome during pregnancy. This approach is particularly considered for managing recurrent adverse pregnancy outcomes associated with APS, where conventional therapies may be insufficient [105].

The addition of intravenous immunoglobulin (IVIG) to standard therapies for APS (LDA, LMWH) has not shown significant improvements in live birth rates or reductions in miscarriage, preterm delivery, or intrauterine growth restriction. However, IVIG is associated with a decreased risk of pre-eclampsia, suggesting it may be valuable in high-risk APS pregnancies. These findings, while promising, highlight the need for further research to confirm IVIG's role in managing APS-related hypertensive complications during pregnancy [106].

The multicenter study by Kaneko et al. (2023) indicates that while intravenous immunoglobulin alone may not reliably enhance live birth rates, its use in combination with therapies such as rituximab or pravastatin has shown improved outcomes. Among patients with obstetric APS who were unresponsive to standard treatments, this combination approach led to better pregnancy outcomes in approximately 62.5% of cases. This evidence suggests that IVIG, as part of a multi-targeted treatment strategy, may effectively address multiple pathways in APS pathophysiology, offering a promising adjunctive option for managing high-risk, refractory OAPS cases [107].

Experimental therapies for refractory cases Beyond standard therapies, novel treatments like eculizumab, a complement inhibitor, are being explored for APS in pregnancy. Eculizumab specifically targets complement activation, potentially mitigating the inflammatory and thrombotic complications associated with the syndrome. Alijotas-Reig et al. suggest that eculizumab holds particular promise for women with refractory APS symptoms, offering a targeted approach for cases unresponsive to conventional therapies [108].

Another alternative treatment may be represented by anti-TNF-alpha agents, as it is thought that TNF-alpha may help in developing obstetric complications [76]. One safe TNF inhibitor that cannot cross the placenta is considered to be Certolizumab, which increases positive pregnancy outcomes in APS patients [76].

Catastrophic APS (CAPS)

Regarding CAPS, even though there are not enough trials to guide a specific treatment for it, anticoagulant therapy should be taken into consideration, as it is an important thrombophilic disorder [4]. Therefore, combined therapy is usually recommended, known as 'triple therapy', which is formed by anticoagulants, corticosteroids, plasmapheresis, or intravenous immunoglobulin [4]. Plasmapheresis removes certain antibodies and some of the proinflammatory and prothrombotic mediators, by removing cca. 2–3 L of plasma for 3–5 days. If the cases are refractory, immunosuppressive treatment is required, such as Hydroxychloroquine, Rituximab, or Eculizumab, to prevent fast deterioration of clinical conditions [109].

Postpartum management

EULAR and the American College of Obstetricians and Gynecologists recommend continuing prophylactic-dose anticoagulation for 6–12 weeks postpartum in women with obstetric APS to mitigate the risk of thrombosis [110].

These strategies underscore the need for a personalized, multidisciplinary approach to optimize maternal and fetal outcomes in OAPS, especially in high-risk or refractory cases.

APS management and assisted reproduction techniques (ART)

According to EULAR guidelines, the efficacy and safety of assisted reproductive techniques, including ovulation

induction and in vitro fertilization, in women with APS are primarily supported by observational studies. Pregnancy rates are comparable to those in the general population, reaching up to 30%. ARTs are generally considered safe when the disease is stable and appropriate antithrombotic therapy is administered in aPL-positive cases.

Although a standardized protocol is lacking, general prophylactic measures can be recommended for aPL-positive women undergoing ovarian stimulation. Antithrombotic management, including low-dose aspirin and low molecular weight heparin, should be individualized based on risk assessment, similar to pregnancy protocols. LDA should be discontinued three days before oocyte retrieval and resumed the following day, while LMWH should be paused at least 12 h before the procedure and restarted the same day if no bleeding occurs. In aPL-positive patients not receiving LDA during stimulation, initiation is recommended on the day of embryo transfer, typically in combination with LMWH, which should be continued throughout pregnancy.

Ovarian hyperstimulation syndrome can be minimized through the use of milder hormonal stimulation or a GnRH antagonist protocol. The natural cycle approach presents an alternative, albeit with lower pregnancy success rates. The ART induction protocol should be individualized, ensuring an optimal balance between procedural safety and therapeutic efficacy.

aPL-positive women in pregnancy

The EULAR guidelines advocate for prophylactic treatment with low-dose aspirin (LDA) (75–100 mg/day) in asymptomatic aPL carriers with a high-risk profile, even in the absence of APS classification criteria or traditional risk factors. Given the association between high-risk aPL profiles and an increased risk of obstetric and thrombotic complications, this recommendation extends to pregnant women with no prior history of thrombosis or pregnancy complications, with or without SLE, for whom LDA should be considered as a preventive strategy to optimize maternal and fetal outcomes.

Currently, there is a lack of high-quality evidence to guide postpartum management in aPL-positive patients without a clinical history of APS. Consequently, clinical decisions should be tailored based on the presence of additional thrombogenic risk factors, familial thrombotic history, and the mode of delivery. In high-risk scenarios, thrombo-prophylaxis is recommended, as the puerperium represents a well-established period of increased susceptibility to venous thromboembolism (VTE), with the highest risk occurring within the first six weeks postpartum [111].

Preventive and proactive management

Effective management of antiphospholipid syndrome (APS) in pregnancy necessitates a combination of preventive and therapeutic strategies aimed at minimizing the risks to both mother and fetus.

Preconception counseling plays a pivotal role in APS management, as it prepares women for potential challenges associated with pregnancy while offering guidance on necessary precautions and treatments [81].

A critical aspect is the detection of high-risk antiphospholipid antibody (aPL) profiles, characterized by lupus anticoagulant positivity, double or triple aPL positivity, or persistently elevated aPL titers, as reflected in the aPL and Global Anti-Phospholipid Syndrome scores. Additional risk factors include coexisting autoimmune diseases, particularly SLE, a history of thrombotic or obstetric APS, and traditional cardiovascular risk factors. Early identification of these risks enables tailored monitoring and intervention, improving maternal and fetal outcomes [112].

As a general therapeutic measure, folic acid supplementation starting one month prior to conception and continuing throughout pregnancy should be considered [113, 114]. Additionally, calcium and vitamin D supplementation is recommended for patients undergoing treatment with corticosteroids or heparin, due to the osteopenic effects of these medications [112, 115].

Pregnant women with APS should adhere to local protocols for high-risk pregnancies, modifying the frequency and method of fetal surveillance based on maternal and fetal condition [112].

This monitoring is complemented by adjustments in therapy, such as the administration of low-dose aspirin and heparin, which have shown significant efficacy in reducing the incidence of pregnancy complications associated with APS [116].

The Table 1 outlines EULAR recommendations for the treatment of APS in pregnancy.

Discussion

Summary of key findings

This review provides a comprehensive synthesis of current knowledge on the impact of antiphospholipid syndrome in pregnancy, emphasizing its role in adverse obstetric outcomes, such as recurrent pregnancy loss, preeclampsia, and intrauterine growth restriction. Evidence supports that combined therapy with low-dose aspirin and low-molecular-weight heparin significantly improves live birth rates and mitigates some APS-associated risks. Nonetheless, challenges remain, particularly regarding the management of preterm birth, fetal growth restriction, and cases unresponsive to standard therapies. Emerging adjunctive therapies, including hydroxychloroquine and TNF-alpha inhibitors, offer potential

Table 1 Treatment management of APS in pregnancy

Therapy	Dosage/Protocol	Efficacy	Side Effects	References
Low-Dose Aspirin (LDA)	75–100 mg/day preconception and during pregnancy	Reduces risk of thrombosis and improves pregnancy outcomes	Minimal (e.g., gastrointestinal discomfort)	[40, 90, 95]
LMWH	Prophylactic dose during pregnancy	Increases live birth rates, reduces recurrent miscarriage	Injection site reactions, bleeding risk	[94, 96, 98]
Hydroxychloroquine (HCQ)	400 mg daily	Improves endothelial function, reduces placental inflammation	Rare teratogenic risk with first-trimester exposure	[105, 107]
Corticosteroids	Low dose in severe cases	Mitigates inflammation in refractory APS	Hypertension, preterm birth	[109, 110]
Intravenous Immunoglobulin	High dose in refractory cases	May reduce preeclampsia risk in high-risk pregnancies	Expensive, potential allergic reactions	[112, 113]

benefits for these refractory cases, yet robust clinical validation is essential to establish their safety and efficacy in pregnancy.

Clinical implications and treatment insights

The findings underscore the necessity for early, precise diagnosis and tailored treatment approaches in managing APS during pregnancy. The combination of LDA and LMWH has become a fundamental strategy, offering notable improvements in maternal and fetal outcomes. This regimen not only addresses thrombotic risks but also underscores the significance of individualized care, where patient history and aPL profiles inform therapeutic decisions. Adjunctive therapies, such as hydroxychloroquine, have shown promise in enhancing outcomes by modulating the immune response, particularly in high-risk APS cases with persistent adverse events. Additionally, TNF-alpha inhibitors, like certolizumab, present a promising option for APS cases unresponsive to conventional anticoagulation. However, their use necessitates meticulous monitoring to ensure maternal efficacy while minimizing fetal risk. These findings suggest that a layered, multidisciplinary approach that incorporates immunomodulatory agents and tailored anticoagulation protocols is essential in optimizing pregnancy outcomes in APS.

Gaps and constraints in existing evidence

The current research landscape for APS in pregnancy is marked by notable gaps that limit clinical translation. Small sample sizes, reliance on observational data, and inconsistent definitions of aPL positivity complicate efforts to establish universally applicable treatment guidelines. Particularly for severe APS presentations, such as catastrophic APS, limited evidence hinders informed decision-making in clinical settings. These constraints underscore an urgent need for standardized research frameworks that can yield more consistent and actionable findings.

Strategic research priorities

To bridge these gaps, future studies should aim to establish a more robust evidence base through large-scale, randomized trials evaluating both traditional and novel therapeutic options, including hydroxychloroquine and biologics like TNF-alpha inhibitors. Developing optimized protocols for anticoagulant use—balancing efficacy with fetal safety—is equally essential. Research should also expand to assess the long-term health outcomes of mothers and children post-APS pregnancy, providing insights that extend beyond the perinatal period. Additionally, improved risk stratification tools and studies reflecting population diversity are critical to ensuring that APS management becomes more personalized and universally applicable.

Conclusion

In summary, APS presents substantial risks in pregnancy, necessitating an integrated, multidisciplinary approach to management. Evidence supports the benefits of combined anticoagulation therapy, yet individualized risk assessment and the judicious inclusion of adjunct therapies remain pivotal for optimizing maternal and fetal outcomes. As new therapies continue to emerge, ongoing research is imperative to establish safe and effective protocols that address the complexities of APS in pregnancy. Such efforts are essential to advance clinical practice, reduce pregnancy-related morbidity and mortality, and ultimately improve the quality of care for women with APS.

Conclusion

The findings synthesized in this review emphasize the multifaceted challenges and advancements in managing APS during pregnancy. Evidence supports the implementation of combined anticoagulation therapies, alongside potential immunomodulatory adjuncts, as critical to improving maternal and fetal outcomes. Moreover, high-risk APS cases, particularly those overlapping with SLE, necessitate tailored, multidisciplinary approaches and robust fetal monitoring protocols. Future investigations should focus on refining therapeutic strategies, assessing the long-term safety and efficacy of emerging therapies, and enhancing predictive models for adverse outcomes to inform best practices in managing APS in pregnancy.

Abbreviations

ACR	American College of Rheumatology
aPLs	Antiphospholipid antibodies
ART	Assisted reproduction techniques
CAPS	Catastrophic antiphospholipid syndrome
EULAR	European League Against Rheumatism
FGR	Fetal growth restriction
FN1	Fibronectin 1
GP	Glycoprotein
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
HCQ	Hydroxychloroquine
HYPATIA	Hydroxychloroquine to Improve Pregnancy Outcome in Women with Antiphospholipid Antibodies"
IgG	Immunoglobulin G
IoAPS	Isolated obstetric APS
ItAPS	Isolated thrombotic APS
IVIG	Intravenous immunoglobulin
LA	Lupus anticoagulant
LDA	Low-dose aspirin
LMWH	Low-molecular-weight heparin
MeSH	Medical Subject Headings
NETs	Neutrophil Extracellular Traps
OAPS	Particularly in its obstetric form
PE	Preeclampsia
PTK2B	Protein tyrosine kinase 2 beta
RPL	Pregnancy loss
TNF	Alpha tumoral necrosis factor
SLE	Systemic lupus erythematosus
RPL	Recurrent pregnancy loss
TLRs	Toll-Like Receptors
TGAs	Thrombin generation assays
TIMP2	TIMP metallopeptidase inhibitor 2
TTR	Thymus-thoracic ratio

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Data availability
All the data processed in this article are part of the research for a doctoral thesis, being archived in the aesthetic medical office, where the interventions were performed (https://orcid.org/0000-0003-2747-1411).

Declarations

Ethics approval and consent to participate
The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board (or Ethics Committee) of the University of Oradea.

Consent for publication
Informed consent was not required for this study, as it is a systematic review that analyzes data from previously published research rather than involving direct interaction with human participants.

Competing interests
The authors declare no competing interests.

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