Obstetric antiphospholipid syndrome: why treatment evidence runs out

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Obstetric antiphospholipid syndrome (APS) presents a formidable challenge in reproductive medicine, marked by recurrent pregnancy loss, pre-eclampsia, and other severe complications. The presence of antiphospholipid antibodies (aPL) drives a prothrombotic and pro-inflammatory state, directly impacting placental function and fetal viability. Despite its clear clinical impact, the therapeutic landscape, meaning the market, for obstetric APS remains surprisingly constrained by a lack of robust evidence for interventions beyond established anticoagulation.

KEY TAKEAWAYS

- The Pivot: Standard-of-care for obstetric APS relies on low-molecular-weight heparin and aspirin, but evidence for additional therapies is largely observational.
- The Data: No specific numeric results are available for novel therapies in obstetric APS, highlighting a significant evidence gap.
- The Action: Clinicians should adhere to current guideline recommendations for anticoagulation and aspirin, while acknowledging the limited data for alternative or adjunctive treatments.

Obstetric antiphospholipid syndrome is an autoimmune condition characterised by the presence of antiphospholipid antibodies and a history of pregnancy morbidity, including recurrent early pregnancy loss, late fetal death, pre-eclampsia, and placental insufficiency. The syndrome is diagnosed based on a combination of clinical criteria, such as vascular thrombosis or specific pregnancy complications, and laboratory criteria, which include persistently positive tests for lupus anticoagulant, anticardiolipin antibodies, or anti-β2-glycoprotein I antibodies. The underlying pathophysiology involves antibody-mediated endothelial activation, complement activation, and impaired trophoblast function, leading to placental damage and adverse pregnancy outcomes.

The primary goal of treatment in obstetric APS is to prevent these adverse outcomes by mitigating the prothrombotic and inflammatory effects of aPL. Current standard-of-care typically involves a combination of low-dose aspirin and prophylactic or therapeutic doses of low-molecular-weight heparin (LMWH). This regimen aims to reduce thrombotic events and improve placental perfusion. But for patients who experience recurrent failures despite this standard approach, the evidence base for further interventions becomes notably thin.

The Current Therapeutic Landscape

For patients with obstetric APS, the established treatment regimen involves daily low-dose aspirin, typically 75-100 mg, initiated before conception or as soon as pregnancy is confirmed. This is combined with prophylactic doses of LMWH,

such as enoxaparin 40 mg once daily, started upon confirmation of pregnancy. The rationale for this dual therapy is rooted in its ability to address both platelet aggregation (aspirin) and coagulation cascade activation (LMWH), thereby reducing the risk of thrombotic events that can compromise placental health. This approach has been incorporated into major international guidelines, meaning the guidelines, for managing obstetric APS, reflecting its consistent, albeit not universally successful, application in clinical practice. For a comprehensive overview of managing complex pregnancies, the Oxford Handbook of Obstetrics and Gynaecology provides a practical reference.

But the efficacy of this standard regimen is not absolute. A significant proportion of patients, particularly those with a history of severe or recurrent pregnancy complications, continue to experience adverse outcomes. This unmet need drives the search for additional or alternative therapies. But the challenge lies in the scarcity of high-quality, randomised controlled trials evaluating these other interventions. Most of the evidence for non-standard treatments comes from small observational studies, case series, or expert opinion, which inherently carry a higher risk of bias and confounding.

Beyond Standard Anticoagulation

When standard LMWH and aspirin fail, clinicians often consider a range of adjunctive therapies, but the data supporting their use are far from conclusive. One such intervention is the use of corticosteroids, often prednisone, particularly in patients with active systemic lupus erythematosus (SLE) or other autoimmune comorbidities. The theoretical benefit stems from their immunosuppressive and anti-inflammatory properties, which might counteract the immune-mediated aspects of APS. But the evidence for corticosteroids specifically in obstetric APS, independent of active SLE, is limited and conflicting. Concerns about maternal and fetal side effects, including gestational diabetes, pre-eclampsia, and fetal growth restriction, further complicate their routine recommendation.

Intravenous immunoglobulin (IVIg) is another therapy sometimes employed in refractory cases of obstetric APS. The proposed mechanism involves immunomodulation, including blocking aPL binding, neutralising circulating antibodies, and modulating complement activation. But, like corticosteroids, the evidence for IVIg in obstetric APS is largely derived from small, uncontrolled studies. Randomised trials have generally failed to demonstrate a clear benefit over standard therapy, and its high cost and potential for adverse reactions, such as aseptic meningitis and renal dysfunction, make its widespread use problematic. The lack of definitive evidence means IVIg remains a last resort for many clinicians, often reserved for patients with repeated failures despite optimal conventional treatment.

Hydroxychloroquine, an antimalarial drug with immunomodulatory properties, has gained attention in the context of autoimmune diseases, including SLE. Its potential benefits in APS include anti-thrombotic effects, reduction of aPL titres, and anti-inflammatory actions. Some observational studies suggest a positive impact on pregnancy outcomes in APS patients, particularly those with concomitant SLE. But dedicated, adequately powered trials specifically investigating hydroxychloroquine as an adjunctive therapy in obstetric APS are still lacking. Its use is often extrapolated from its known benefits in SLE, rather than direct evidence in APS pregnancy.

Statins, primarily known for their lipid-lowering effects, also possess pleiotropic properties, including anti-inflammatory and immunomodulatory actions. Preclinical studies have shown that statins can reduce aPL-mediated endothelial activation and improve placental function in animal models of APS. This has led to interest in their potential therapeutic role in obstetric APS. But clinical data in pregnant women are sparse, and concerns regarding fetal safety, particularly teratogenicity, have historically limited their use during pregnancy. Newer evidence suggests some statins might be safer in pregnancy, but robust clinical trials are needed before they can be routinely recommended for obstetric APS. This

is a complex area, and clinicians often refer to detailed guidelines, such as those found in the Oxford Handbook of Rheumatology, for managing autoimmune conditions in pregnancy.

The Unmet Need and Future Directions

The persistent challenge in obstetric APS is the absence of clear, evidence-based guidance for patients who do not respond to standard LMWH and aspirin. This leaves clinicians in a difficult position, often resorting to therapies with limited data or relying on individualised approaches based on expert consensus rather than robust trial evidence. The heterogeneity of obstetric APS, with varying antibody profiles and clinical presentations, further complicates trial design and interpretation. Some patients may have isolated obstetric APS, while others have it in the context of systemic lupus erythematosus, which can influence treatment response and prognosis. Our previous coverage on myasthenia gravis in pregnancy highlights similar complexities in managing autoimmune conditions during gestation.

The lack of large, multicentre, randomised controlled trials for these adjunctive therapies represents a significant gap in the literature. Such trials are difficult to conduct in rare conditions like obstetric APS, particularly given the ethical considerations of withholding potentially beneficial treatments in pregnant women. But without them, the field will continue to rely on anecdotal evidence and small studies, perpetuating the uncertainty surrounding optimal management for refractory cases. The need for better diagnostic tools to identify high-risk patients more precisely, and for biomarkers to monitor treatment response, is also critical. Improved understanding of the specific pathways involved in aPL-mediated placental injury could also pave the way for targeted therapies, enabling the development of treatments that move beyond broad immunosuppression or anticoagulation.

The open-label nature of many studies in this area is an obvious caveat. It is challenging to blind patients and clinicians to interventions like IVIg or corticosteroids, which can introduce bias. The trial populations are often small and heterogeneous, making it difficult to draw generalisable conclusions. The primary endpoints in many studies are often composite outcomes, which can mask differential effects on individual pregnancy complications. The absence of a clear consensus on what constitutes 'refractory' obstetric APS also complicates the comparison of study results and the development of standardised treatment algorithms. This is a field where the evidence for treatment often runs out precisely when clinicians need it most, leaving them to navigate complex decisions with insufficient data.

> **CLINICAL IMPLICATIONS**
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> For clinicians managing obstetric APS, the message is clear: stick to low-dose aspirin and LMWH. That is where the evidence is, however imperfect. Deviating into corticosteroids, IVIg, or other immunomodulators for refractory cases means stepping into a therapeutic grey zone, where the data are observational at best, and often conflicting. The potential for maternal and fetal side effects with these unproven therapies should always weigh heavily in the decision-making process.
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> The industry has shown limited appetite for large-scale trials in this relatively small patient population, which is understandable from a commercial perspective but leaves a significant unmet need. Developing novel agents specifically targeting the unique pathophysiology of obstetric APS, rather than repurposing drugs from other autoimmune conditions, would be ideal. But the investment required for such development, coupled with the challenges of conducting trials in pregnancy, makes this a distant prospect.
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> Patients with obstetric APS, particularly those with a history of recurrent losses, face immense emotional

> and physical burdens. They are often desperate for any intervention that might improve their chances of a successful pregnancy. This vulnerability can lead to the adoption of unproven therapies based on limited evidence or anecdotal success. It is incumbent upon clinicians to provide clear, evidence-based counselling, managing expectations about the efficacy of adjunctive treatments and transparently discussing the limitations of the current data.
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> The field needs dedicated research funding and collaborative efforts to conduct adequately powered, randomised controlled trials for novel and adjunctive therapies in obstetric APS. Until then, clinicians must continue to manage these complex pregnancies with the best available evidence, acknowledging its significant limitations, and prioritising patient safety above all else.

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