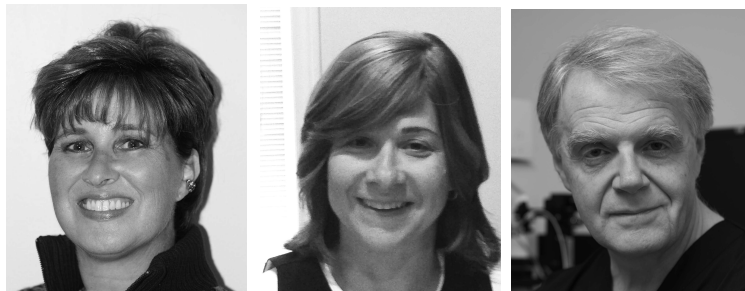


Obstetric Antiphospholipid Syndrome: Has the Black Swan Swallowed a Red Herring?



Several years after the first description of the antiphospholipid syndrome (APS) in 1983¹, Nigel Harris warned that, although they do exist, patients with APS are as rare as black swans — and predicted that “the value of studying antiphospholipid antibodies (aPL) [might] easily be lost in a sea of overinterpreted and over-reported laboratory and clinical findings².” Twenty-seven years later, the Obstetric Task Force of the 14th International Congress on Antiphospholipid Antibodies has confirmed the continuing lack of evidence supporting an association between aPL and recurrent early miscarriage (REM)³. They noted the absence of consistent, predictable clinical outcomes from therapeutic trials and suggested potential causes. Despite apparent adherence to the 1999 initial Sapporo⁴ and 2006 revised Sydney⁵ criteria, studies have used heterogeneous patient selection protocols, variable laboratory inclusion criteria, and small sample sizes. In addition, there has been a lack of pathological or genetic evaluation to determine the nature of pregnancy losses when they occurred. The Task Force expressed concern regarding what they termed the “considerable enthusiasm” for “diagnosing APS and treating as yet unrecognized obstetric morbidities in the setting of positive aPL results.” Given the absence of critical studies of association and therapeutic benefit, they felt that such diagnostic fervor would serve only to further obscure the search for genuine associations and proven treatments.

After 30 years of APS investigations, it would be reasonable to expect increased understanding of the obstetric complications related to aPL, but unfortunately, despite or perhaps because of the “considerable enthusiasm” noted above, there is less clarity, particularly with regard to how or even whether REM fits into the puzzle^{3,6,7,8}. At the Treatment and Evaluation of Recurrent Miscarriage (TERM) program in Toronto, we have been involved in therapeutic and observational studies involving aPL and REM over the same 30-year period.

The early ASA/P study [prednisone and acetylsalicylic acid (ASA) vs placebo (1988-94)] included patients with, among other autoantibodies, variable levels of anticardiolipin antibodies (aCL) and the lupus anticoagulant (LAC), which would not have met current APS criteria⁹. Likewise, the Hep/ASA study [low molecular weight heparin (LMWH) and ASA vs ASA alone, 2000-2004]¹⁰ also included patients with autoantibodies other than aPL, although we did include a subgroup analysis for that category (fulfilling Sapporo criteria). We also included patients with ≥ 2 early losses, as well as ≥ 3 , which engendered considerable criticism at the time we reported our results¹¹. Our practical rationale for our inclusion criteria was 3-fold: (1) it was becoming apparent that there was no etiological difference between women with 2 versus 3 early losses^{12,13}; (2) if aPL were associated with REM, then the presence of the antibody, and not the number of losses, should be the determinant; and finally (3) we expanded the inclusion criteria to address extremely slow patient accrual, a universal issue in investigation of women with aPL and pregnancy morbidity, as evidenced by the similar small sample sizes in other therapeutic trials of this population^{3,10,14}.

Our observational studies over the decades have all added evidence to support the following conclusions regarding aPL and REM: (1) patients with persistent moderate to high levels of aPL are rarely seen: we found 2.7% of 2257 patients with persistent confirmed LAC over 6 years¹⁵; Wahl, *et al* found 0.8% of 6321 patients with ≥ 2 moderate to high aCL IgG or IgM over about 4 years¹⁶; and Pengo, *et al* found confirmed triple positive aPL in 3.6% of 1520 patients over 4 years¹⁷; (2) the vast majority of women with REM have low levels or no aCL or LAC^{15,17,18,19}; (3) regardless of aPL positivity, women with REM have a good prognosis for subsequent live birth, independent of treatment with ASA alone, LMWH/ASA, or unfractionated heparin/ASA^{3,10,14,19}.

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Our center is one of several across North America that has participated in the PROMISSE study (Predictors of pRegnancy Outcome: bioMarkers In antiphospholipid antibody Syndrome and Systemic lupus Erythematosus), a prospective, observational investigation of aPL and pregnancy outcome (regardless of the presence or absence of clinical criteria of APS, but excluding pregnancies that end before the first trimester). Interim analysis of 144 aPL-positive pregnancies found that the absence of LAC appeared to be a strong predictor of uncomplicated pregnancies in women, regardless of the presence of aCL or anti- β 2-glycoprotein I antibody²⁰. We have also noted an association between persistent LAC and sporadic stillbirth¹⁵, intrauterine growth restriction and HELLP (hemolysis, elevated liver enzymes and low platelet count), and persistent aPL with preterm delivery²¹. It is informative that although PROMISSE is a longterm multicenter international study that includes only stringently evaluated, high-risk patients who fulfill (core-laboratory determined) APS laboratory criteria, there were only 144 aPL-positive pregnancies with 14 (9.7%) late losses between 2003 and 2011²⁰. This low rate of late obstetric mortality in a high-risk population highlights the rarity and complexity of this clinical entity and the difficulties in acquiring an accurately identified sample sufficiently large to study^{14,20,22}.

If we take a moment to broaden rather than narrow our focus after 30 years' collective experience, we can see that "Obstetric APS" appears to have 2 general presentations: the most common includes women with low levels of aCL (but not LAC) and a history of exclusively early losses but no thrombosis (in the absence of any concomitant risk factors such as surgery, oral contraception, or the postpartum period). These patients have a high likelihood of live birth in a pregnancy subsequent to presentation regardless of therapeutic protocol, negligible risk of postpartum thrombosis, and a good longterm prognosis²². The less frequent presentation involves women with persistently high levels of aPL including LAC, a history of second or third trimester loss(es), and possibly a history of thrombotic events. These patients often have an unpredictable pregnancy course regardless of therapeutic protocol. Their longterm prognosis has been reported to include a potentially higher risk of thrombotic events despite continuous anticoagulation^{3,22,23}.

There are no data in the literature regarding remission rates for APS. Cervera, *et al* recently reported 85% of 1000 patients had no thrombotic events over a 10-year observation period²³. During the second 5-year followup period, 24.8% of patients taking antithrombotic treatment versus 5.2% of patients without any antithrombotic treatment developed thrombosis, and 8.1% versus 1.5%, respectively, developed APS-related obstetric complications. Of the 135 patients who received no antithrombotic treatment, 93.3% and 97.0%, respectively, had no thrombotic or adverse obstetric events. In addition, investigators were unable to

identify any clinical or laboratory prognostic factors for this syndrome and neither individual aPL nor any combination of them was associated with an increased incidence of any specific clinical manifestation. While a confirmed moderate to high aPL was an inclusion criterion for this cohort, there was no mention of whether aPL levels were measured or varied throughout the 10-year followup.

The current classification of APS is a permanent designation. The immutability of this label should therefore necessitate compelling laboratory and clinical evidence before it is applied. The expert panel that recommended revisions to the Sapporo criteria recognized this when they called for an extension of the laboratory criteria for repeated aPL measurements from not less than 6 to not less than 12 weeks apart³. This revision was intended to eliminate the risk of transient, infection-related aCL and artificially prolonged LAC due to anticoagulation following an acute thrombotic event. Perhaps even this period of aPL positivity is still too brief.

It is our contention that the current classification thresholds are too broad, and that patients with lower levels of aPL, no LAC, and REM only should not be given the APS designation at all. Only those patients who have a history of thrombotic events and/or late obstetric morbidity with consistently high aPL with or without a LAC should be classified as APS. This would eliminate the somewhat specious designations "obstetric APS" and "thrombotic APS" altogether and clarify the syndrome as simply "APS."

Many APS-related articles over the last 30 years have been inconclusive, ending with the authors calling for more multicenter studies to confirm their results¹. As it currently stands, the APS classification system functions "like a fishing trawler [capturing] many more innocent subjects than it should"²⁴. The resultant overdiagnosis caused by inclusion of women with REM and low or transient levels of aPL is hampering our understanding of this syndrome. We suggest that useful and conclusive data already exist in our collective studies, particularly with regard to therapeutic approaches to aPL-associated pregnancy, but it will be necessary to separate the intended catch from the bycatch.

We propose a collegial challenge: a collective, multicenter, retrospective analysis of results from all pregnancy-related observational and therapeutic trials³. Subgroup analysis should be restricted to include only patients with a history of late adverse obstetric events (with or without thrombosis) and persistently high levels of aPL. Collated results would add to those recently reported by Ruffatti, *et al* and would provide aPL-specific, treatment-associated pregnancy outcome data that refute, support, or advance the current standard of care²⁵. Regardless of the findings, this proposed retrospective collaborative study would clarify and inform clinical decision making for physicians with pregnant patients and clearly defined APS.

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