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Review

# 14th International Congress on Antiphospholipid Antibodies Task Force Report on Obstetric Antiphospholipid Syndrome☆

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ABSTRACT

Pregnancy morbidity is one of the clinical manifestations used for classification criteria of antiphospholipid syndrome (APS). During the 14th International Congress on Antiphospholipid Antibodies (aPL), a Task Force with internationally-known experts was created to carry out a critical appraisal of the literature available regarding the association of aPL with obstetric manifestations present in actual classification criteria (recurrent early miscarriage, fetal death, preeclampsia and placental insufficiency) and the quality of the evidence that treatment(s) provide benefit in terms of avoiding recurrent adverse obstetric outcomes. The association of infertility with aPL and the effectiveness of the treatment of patients with infertility and positive aPL was also investigated. This report presents current knowledge and limitations of published studies regarding pregnancy morbidity, infertility and aPL, identifying areas that need better investigative efforts and proposing how critical flaws could be avoided in future studies, as suggested by participants of the Task Force. Except for fetal death, there are limitations in the quality of the data supporting the association of aPL with obstetric complications included in the current APS classification criteria. Recommended treatments for all pregnancy morbidity associated to APS also lack well-designed studies to confirm its efficacy. APL does not seem to be associated with infertility and treatment does not improve the outcomes in infertile patients with aPL. In another section of the Task Force, Dr. Jane Salmon reviewed complement-mediated inflammation in reproductive failure in APS, considering new therapeutic targets to obstetric APS (Ob APS).



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☆ Dedicated to the memory of Silvia Pierangeli, PhD.

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## 1. Introduction

The Obstetric Task Force of the 14th International Congress on Antiphospholipid Antibodies met on the 18 September 2013 in Rio de Janeiro, Brazil. The Task Force was charge with reviewing obstetric diagnostics and treatments as they pertain to our current understanding of obstetric antiphospholipid syndrome (Ob APS). In preparation for the meeting, the Task Force chairman, Guilherme R. de Jesus, MD, and associate director, Ware Branch, MD, engaged internationally-known experts in the field to present critical, evidence-based updates on Ob APS. The three current criteria for Ob APS [1] were identified as key components of meeting, and members of the APS international community also felt that a review of the possible association of infertility and antiphospholipid antibodies (aPL) should be included. Drs. de Jesus and Branch also asked Jane Salmon, MD, an expert in the role of complement-mediated inflammation in reproductive failure in antiphospholipid syndrome (APS), to review this topic, especially as findings might point to new therapeutic targets. As a general guideline for each area of Ob APS, presenters and participants were asked to consider the following questions. Drs. de Jesus and Branch stressed a critical, evidence-based analysis of each area.

- What is our current understanding of association of the clinical feature with antiphospholipid antibodies and antiphospholipid syndrome, and what needs to be done to improve our understanding of the association?
- What is the current status of the treatment for each clinical feature of Ob APS, and what needs to be done to clarify the evidence for or against currently used treatments?
- Are there intriguing, new ideas regarding prevention or treatment of Ob APS, and how might these be studied?

Of course, underlying these questions is the larger issue of whether or not the current clinical criteria for Ob APS deserve modification.

The issue of testing for antiphospholipid antibodies came up several times, though it was not the mission of this Task Force to make specific comments or recommendations about such testing. There seems little doubt, however, that crystalizing the relationship between alleged clinical associations and antiphospholipid antibodies fundamentally depends upon improvements in antiphospholipid testing.

Registered attendees were encouraged to offer comments and criticisms during the meeting, though time was somewhat limited, and via email after the meeting. Not surprisingly, several participants voiced their opinions about the current status of the clinical associations with antiphospholipid antibodies and the treatments currently used or recommended. Given the frustrating and emotionally-charged nature of reproductive failure, it came as no surprise that strong opinions emerged. Dr. Nancy Agmon-Levin and her colleagues were enthusiastic participants in this aspect of the Task Force and have offered their unpublished survey results regarding the management of "non-criteria Ob APS" for consideration by the group. We have included an abbreviated version of their observations in the section covering recurrent early miscarriage. Thus, the summary of this Task Force's findings is presented in 5 sections: (1) Recurrent early miscarriage (<10 weeks gestation), (2) fetal death (≥10 weeks gestation), (3) preeclampsia and placental insufficiency, (4) infertility, and (5) complement-mediated inflammation in pathogenesis of APS-related adverse obstetric outcomes.

## 2. Recurrent early miscarriage (REM)

### *2.1. Association of aPL and REM [summary prepared by Guilherme R. de Jesus, MD, and Cecilia Chighizola, MD, with comments of Nancy Agmon-Levin, MD, and colleagues included]*

The main objective of this review was to analyze the association of REM (<10 weeks gestation) with aPL, as listed in the revised Sapporo criteria [1].

Dr. de Jesus reviewed the rationale for the association of REM and aPL, based on in vitro and animal studies. Besides classical thrombotic mechanism of aPL, these antibodies have been associated to complement activation, reduction of annexin-V, and placental tissue damage, ultimately resulting in abortion [2–4]. APL also induce trophoblast injury and apoptosis, inhibit syncitia proliferation and formation, decrease production of human chorionic gonadotrophin, and impair trophoblast invasion and adequate secretion of growth factors [5]. Therefore, it seems reasonable, according to basic science studies, that patients with circulating aPL could have a higher frequency of early pregnancy losses.

One meta-analysis evaluated the aforementioned association. Opatrny et al. [6] reported a positive association between anticardiolipin (aCL) IgG antibodies (OR 3.56, 95% CI 1.48–8.59; low and moderate to high titers included) and recurrent miscarriage occurring at less than 13 weeks gestational age, but only 2 studies (total of 907 patients) could be included in this analysis. The authors did not find any study examining the association between lupus anticoagulant (LA) and aCL IgM with pregnancy loss before 13 weeks, while the relationship between anti-β2 glycoprotein-I (aβ2GPI) antibodies and recurrent abortion before 13 weeks was not statistically significant (OR 2.12, 95% CI 0.69–6.53). Notably, comparison between studies was difficult