Autoimmunity Reviews 17 (2018) 956–966

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Antiphospholipid syndrome: An update on risk factors for pregnancy outcome

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ARTICLE INFO

Keywords:
Antiphospholipid syndrome
Risk factors
Pregnancy outcome
Triple aPL positivity
Hypocomplementemia
CMV IgM false positivity
Hydroxychloroquine

ABSTRACT

Background: The optimal treatment of women with primary antiphospholipid syndrome (APS) is still debated. About 20–30% of women with APS remain unable to give birth to healthy neonates despite conventional treatment, consisting of prophylactic-dose heparin and low-dose aspirin. These cases are defined "refractory obstetric APS". The early identification of risk factors associated with poor pregnancy outcome could be the optimal strategy to establish criteria for additional therapies, such as hydroxychloroquine, steroids, intravenous immunoglobulin, and plasma exchange.

Purpose: The aim of the present study was to review current literature about risk factors for poor pregnancy outcome.

Search methods: The PubMed database was used to search for peer-reviewed original and review articles concerning risk factors for pregnancy outcome in APS from 1st January 1990 to 15th January 2018.

Outcomes: History of pregnancy morbidity and/or thrombosis, the association with SLE and/or other autoimmune diseases are well known history-based predictive factors for obstetrical complications, such as miscarriage, maternal venous thromboembolism, intrauterine foetal demise, preeclampsia, and neonatal death. Moreover, laboratory findings associated with poor pregnancy outcome are:triple antiphospholipid antibodies aPL positivity, double aPL positivity, single aPL positivity, false-positive IgM for CMV, and hypocomplementemia. Triple positivity is confirmed as the most significant risk factor by a large body of evidence.

Furthermore, the abnormal uterine arteries Doppler velocimetry results are confirmed to be strongly associated with poor pregnancy outcomes in APS. The good performance of the uterine arteries velocimetry, as a negative predictive factor, was reported by different studies. On the contrary, in case of abnormal uterine arteries results, the relevance of a careful surveillance is highlighted for the high risk of maternal-foetal complications. Nevertheless, this tool is a late indicator to suggest any additional treatments.

Conclusions: In order to prevent obstetrical complications and establish the optimal combination therapy, the knowledge at preconception or at the beginning of pregnancy of risk factors associated with poor pregnancy outcome could be a crucial step for management and treatment of APS. In addition, in the preconception assessment a regimen with low-dose aspirin, folic acid, and vitamin D supplementation should be offered, and a treatment strategy has to be established (conventional vs additional therapy). In fact, additional treatment has to be tailored for each patient.

1. Introduction

The prognosis of pregnancies in women with antiphospholipid syndrome (APS) has greatly improved over the past two decades. However, about 20–30% of APS women remains unable to give birth to healthy neonates despite conventional treatment, based on prophylactic-dose heparin plus low-dose aspirin (LDA) [1,2]. Miscarriage, foetal loss and stillbirth represent some features that can occur at any

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https://doi.org/10.1016/j.autrev.2018.03.018
Received 23 March 2018; Accepted 28 March 2018
Available online 15 August 2018

Table 1
Studies included for the analysis: authors, purpose, study design and methods.

Author	Purpose	Study design and methods
Alijotas-Reig [1]	To analyse the clinical features, laboratory data, foetal-maternal outcome and follow-up in woman with OAPS	Retrospective multicentre
Bats [9]	To evaluate the efficacy of a uniform management protocol in OAPS patients with at least one 2nd- or 3rd-trimester intra-uterine foetal death	Prospective observational single-centre
Bouvier [10]	To assess the incidence of pregnancy outcome for women with OAPS	Prospective observational single-centre
Bramham [11]	To evaluate pregnancy outcome in women with APS according to their clinical phenotype, obstetric APS recurrent miscarriage (Group 1), with late foetal loss or early delivery due to placental dysfunction (Group 2) and thrombotic APS (Group 3)	Retrospective observational single-centre
Carmona[2]	To analyse risk factors and evaluate foetal outcome in treated APS pregnancies	Prospective observational single-centre
Caruso [12]	To determine whether uterine artery velocimetry is a useful tool for identifying pregnancies with APS	Prospective observational single-centre
Cervera[13]	To assess the prevalence of morbidity and mortality during a 10-year period	Prospective multicentre
De Carolis[14]	To investigate the predictive value of low complementemia in relation to pregnancy outcome in APS	Prospective observational single-centre
De Carolis [15]	To investigate the relationship between TORCH complex false positivity and obstetric outcome in APS	Prospective observational single-centre
Deguchi [16]	To understand the clinical features of APS-complicated pregnancies and evaluate risk factors for the adverse pregnancy outcomes	Retrospective multicentre
Jeremic [17]	To evaluate pregnancy outcomes and to determine which clinical parameters are risk factors for adverse pregnancy outcomes	Prospective observational single-centre
Latino [18]	To identify risk factors that are associated with treatment failures	Retrospective observational single-centre
Le Thi Huong [19]	To examine the predictive value of clinical examination, laboratory tests and Doppler ultrasound examination in SLE and/or APS pregnancies	Prospective observational single-centre
Liu [20]	To identify the relation between pregnancy outcome and single- or double-positivity of aCL and anti-β_2GPI in APS	Retrospective observational single-centre
Lockshin [21]	To investigate which serologic and clinical findings predict adverse pregnancy outcome in patients with antiphospholipid antibody	Prospective observational multicentre
Reggia [22]	To evaluate the association between C3 and C4 and obstetric complications	Retrospective multicentre
Rezk [23]	To assess prospectively the maternal and foetal outcome and to find out predictors of poor pregnancies outcome	Prospective observational single-centre
Ruffatti [24]	To document the relationship between antibody profile and pregnancy outcome in patients with APS	Retrospective observational single-centre
Ruffatti [25]	To evaluate the relationship between the aPL profile and clinical characteristics of pregnant women with APS and neonatal outcome	Retrospective observational single-centre
Ruffatti [26]	To identify the risk factors associated with pregnancy failure in patients with APS treated with conventional therapy	Retrospective multicentre case-control
Saccone [27]	To assess the risk of obstetric complications in association with specific antibody profile	Retrospective multicentre cohort
Sailer [28]	To investigate whether increased anti-β_2GPI predict pregnancy loss in women positive for LA	Prospective observational single centre
Silver 1994	To determine if maternal mid-trimester serum alpha-fetoprotein are associated with adverse pregnancy outcomes	Retrospective single centre cohort
Simchen [29]	To investigate whether in patients with APS high positive aPL titre are associated with adverse pregnancy outcome	Retrospective single centre cohrt
Stone [30]	To introduce a standard protocol for the treatment of refractory APS	Prospective observational single-centre
Venkat-Raman [31]	To assess 2nd trimester uterine artery Doppler in the prediction of preeclampsia and SGA infants in women with PAPS	Prospective observational single-centre
Yelnik [32]	To confirm that Lupus anticoagulant is the main predictor of adverse pregnancy outcomes in aPL-positive patients	Prospective observational multicentre

OAPS = Obstetric Antiphospholipid Syndrome; APS = Antiphospholipid Syndrome; TORCH = Toxoplasma, Others, Rubella, Cytomegalovirus and Herpes Simplex Virus tests; SLE = Systemic Lupus Erythematosus; aCL = anti-Cardiolipin antibodies; anti-β_2GPI = anti-β_2 Glycoprotein I antibodies; aPL = Antiphospholipid antibodies; LA = Lupus Anticoagulant; SGA = Small for Gestational Age; PAPS = Primary Antiphospholipid Syndrome.

stage of pregnancy. Moreover, some pregnancies are complicated by the occurrence of preeclampsia, intrauterine growth restriction (IUGR), and pre-term delivery.

Infants born to such complicated pregnancies generally could have a childhood and adulthood more likely associated with several diseases, such as obesity, diabetes, hypertension and cardiovascular disorders [3–6].

The early identification of risk factors associated with poor pregnancy outcome could be the optimal strategy to establish management, counselling and criteria for additional therapies, such as hydroxychloroquine (HCQ), steroids, intravenous-immunoglobulins (IVIG), plasma exchange, in combination with conventional treatment.

Recently, a comprehensive study on EULAR recommendations for women's health and the management of family planning,assisted reproduction, pregnancy and menopause in patients withsystemic lupus erythematosus (SLE) and/or APS was published by a multidisciplinary panel of experts [7]. It provides a useful guide for the physicians involved in the care of these cases. These authors underlined the importance of some issues, to facilitate physician-patient communication, preconception counselling, and risk stratification for pregnancy outcome.

In the past years, several studies have been performed in order to identify variables or risk factors predictive of complications despite conventional treatment, sometimes with contrasting and not-conclusive results.

The aim of the present study was to review current literature about risk factors of poor pregnancy outcome in women with antiphospholipid syndrome (APS), and to indicate which factors can be used in order to identify the best treatment in pregnancy.