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Review

Refractory obstetrical antiphospholipid syndrome: Features, treatment and outcome in a European multicenter retrospective study☆

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ABSTRACT

Aim: To describe the consecutive pregnancy outcome and treatment in refractory obstetrical antiphospholipid syndrome (APS).
Methods: Retrospective multicenter open-labelled study from December 2015 to June 2016. We analyzed the outcome of pregnancies in patients with obstetrical APS (Sydney criteria) and previous adverse obstetrical event despite low-dose aspirin and low-molecular weight heparin LMWH (LMWH) conventional treatment who experienced at least one subsequent pregnancy.
Results: Forty nine patients with median age 27 years (23 − 32) were included from 8 European centers. Obstetrical APS was present in 71%, while 26% had obstetrical and thrombotic APS. Lupus anticoagulant was present in 76% and triple antiphospholipid antibody (APL) positivity in 45% of patients. Pregnancy loss was noted in 71% with a median age of gestation of 11 (8–21) weeks. The presence of APS non-criteria features (35% vs 17% in pregnancies without adverse obstetrical event; p = 0.09), previous intrauterine death (65% vs 38%; p = 0.06), of LA (90% vs 65%; p = 0.05) were more frequent in pregnancies with adverse pregnancy outcome, whereas isolated recurrent miscarriage profile was more frequent in pregnancies without any adverse pregnancy outcome (15% vs 41%; p = 0.04). In univariate analysis considering all pregnancies (index and subsequent ones), an history of previous intrauterine death was associated with pregnancy loss (odds-ratio 2.51 (95% CI 1.274.96); p = 0.008), whereas previous history of prematurity related to APS (odds-ratio 0.13 95%CI 0.04 0.41, P = 0.006), steroids use during the pregnancy (odds-ratio 0.30 95% CI 0.11–0.82, p = 0.019) and anticardiolipids isolated profile (odds-ratio 0.51 95% CI 0.26–1.03, p = 0.0588) were associated with favorable outcome. In multivariate analysis, only previous history of prematurity, steroids use and anticardiolipids isolated profiles were associated with live-birth pregnancy.

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Conclusion: The main features of refractory obstetrical APS were the high rates of LA and triple APL positivity. Steroids could be effective in this APS profile, but prospective studies are necessary.

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Contents

1. Introduction

Antiphospholipid syndrome (APS) is an autoimmune disease characterized by obstetrical complications and thrombotic events associated to antiphospholipid antibodies (aPL) [1–4]. The pregnancy outcome dramatically improved using the combination of aspirin and low-molecular weight heparin (LMWH). Despite this regimen, 10–15% of APS patients experience pregnancy losses and can be defined as refractory obstetrical APS [5–8,9]. Up to date, there is no large series of refractory APS, with the description of disease characteristics, outcome and subsequent pregnancy treatments. Only limited data are available about the value of additional treatments to aspirin-LMWH combination in obstetrical APS [10,11]. Several studies reported no benefit of steroids which have been associated with foeto-maternal adverse events, but used at high dose. One recent report using a low dose prednisone until 14 weeks of gestation showed increased live birth rate in refractory obstetrical APS [12]. Several retrospective studies analyzed the benefit of hydroxychloroquine in APS patients, mostly with associated SLE and thrombosis, reporting benefit in addition to conventional therapy [13–15].

In this European multicenter study, we aimed to [1] describe patients' characteristics, outcomes in index pregnancies of refractory obstetrical APS; [2] determine factors associated with poor obstetrical outcome in index and subsequent pregnancies; [3] describe treatments use for subsequent pregnancies and try to determine the best regimen to improve obstetrical outcome.

2. Patients and methods

2.1. Patients

We retrospectively analyzed the outcome of pregnancies in women with obstetrical APS [2] and previous adverse obstetrical events despite aspirin-LMWH treatment. All members of European Forum of Antiphospholipid Antibodies and Société National Francaise de Médecine Interne (SNFMI) were asked to fulfill a standardized form during the period from September 2015 to June 2016. These patients are usually attended by the rheumatology, internal medicine, haematology and obstetrics departments. All recruited cases and participating hospitals received a numeric code to ensure privacy and personal data protection.

2.2. Inclusion criteria

The inclusion criteria were: [1] confirmed obstetrical APS (Sydney criteria); [2] history of pregnancy APL-related adverse obstetrical events, particularly: pregnancy loss (early miscarriages, intrauterine deaths), pre-eclampsia or HELLP syndrome, prematurity <34 weeks of gestation despite aspirin and LMWH combination [3] the next subsequent pregnancy after the previously pregnancy failure (only one subsequent pregnancy was considered for each patient).

2.3. Exclusion criteria

Women with pregnancy losses explained by infectious, metabolic, anatomic or hormonal factors or maternal and paternal chromosomal causes were excluded. Women with a history of HBV, HCV, HIV infection, as well as those with non-organ systemic autoimmune diseases, especially Systemic Lupus Erythematosus (ACR criteria), were also excluded.

Patients with purely thrombotic APS, and those who tested positive for non-standard aPL and isotypes other than IgG/IgM were not included in this analysis.

For each patient, APS clinical characteristics (previous thrombosis, obstetrical events, APS non-criteria features), APL class, isotype and titers, previous maternal APS-related complaints (thrombosis, pre-eclampsia, HELLP syndrome, gestational hypertension), and fetal adverse events (miscarriage, intrauterine deaths, stillbirth, intrauterine growth retardation (5e percentile), were collected. Data about pregnancy outcome, date of beginning and characteristics of treatments, delivery, birth weight, Apgar and neonatal complications were collected for the pregnancy with adverse obstetrical event under aspirin and LMWH and for the subsequent pregnancy. Among treatments, aspirin and LMWH (prophylactic and curative doses), steroids, hydroxychloroquine, intravenous immunoglobulins and other immunomodulatory or immunosuppressive drugs were taken into account. In the case of several pregnancies after the index pregnancy only the subsequent one was considered for the analysis.

2.4. Laboratory data

APL positivity was considered using the thresholds of each laboratory for European center, according to the standard laboratory

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