Pregnancy in Antiphospholipid Syndrome: Can we Improve Patient Management?

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Antiphosphlipid syndrome (APS) is characterized by thrombotic events and/or pregnancy morbidity in the presence of antiphospholipid antibodies (aPL). According to the 2006 classification criteria, the tests to detect aPL are: anti-beta2 glycoprotein I antibodies (aβ2GPI), anticardiolipin antibodies (aCL), and lupus anticoagulant (LA) [1]. Pregnancy morbidities included in the APS classification are defined as:

- At least one unexplained fetal death at ≥ 10 weeks of gestation with normal morphology on prenatal ultrasound examination or direct postnatal examination
- At least one preterm delivery of a morphologically normal infant before 34 weeks of gestation due to severe pre-eclampsia, eclampsia, or features consistent with placental insufficiency. Generally accepted features of placental insufficiency include: (i) abnormal or non-reassuring fetal surveillance test (e.g., non-reactive non-stress test), (ii) abnormal Doppler flow velocimetry waveform analysis (e.g., absent end-diastolic flow in the umbilical artery), (iii) oligohydramnios, or (iv) birth weight less than the 10th percentile for gestational age
- At least three unexplained consecutive spontaneous pregnancy losses < 10 weeks of gestation, after exclusion of maternal anatomic and hormonal abnormalities and paternal and maternal chromosomal abnormalities.

After more than 30 years of clinical experience, the treatment milestone of obstetric APS is still low dose aspirin (LDA) in association or not with low molecular weight heparin (LMWH). It is commonly recognized that despite treatment about 25% of APS women still suffer from recurrent pregnancy loss [2].

STRATIFICATION OF RISK

Many efforts have been made to identify patients at high risk of recurrence despite treatment. In terms of aPL profile, patients may have single, double or triple aPL positivity; single or multiple isotypes (IgG, IgM); and low vs. medium–high titers of antibodies. Which aPL profiles, if any, can predict adverse pregnancy outcome in women with APS is still debated; however, it is widely accepted that not all aPL profiles confer the same degree of obstetric risk. Among aPL tests, LA was found to have the highest predictive value according to a multicenter prospective study (PROMISSE: Predictors of PRegnancy Outcome: BioMarkers In Antiphospholipid Syndrome and Systemic Lupus Erythematosus). This was a multicenter observational study on pregnancy outcome of 144 patients with APS and/or systemic lupus erythematosus (SLE) who were aPL-positive. Poor pregnancy outcome was observed mainly in LA-positive women and in women with moderate to high titer IgG aCL; other aPL did not independently predict adverse pregnancy outcome. This study, however, showed some limitations. First, not all patients were tested for aβ2GPI. Second, the study design excluded patients whose pregnancies terminated before 12 weeks; therefore, it does not provide information about the aPL-mediated early miscarriages. Third, the therapeutic strategy was not homogenous among patients, casting some doubt on its possible effects on pregnancy outcome [3].

Another observational multicenter case-control study identified some independent risk factors for pregnancy morbidity. The researchers retrospectively considered 410 pregnancies and found three major independent risk factors for both pregnancy loss and pregnancy complications: (i) history of either thrombosis or previous pregnancy morbidity (without any relation to the type of previous obstetric morbidity), (ii) triple aPL positivity, and (iii) the presence of an underlying SLE or other autoimmune disease [4]. In the same report, patients with single aPL positivity without previous thrombosis seem to have lower risk of poor outcome if managed with conventional treatment [4].

TREATMENT

Identifying risk factors associated with pregnancy failure could be an important step in aiding clinicians to manage APS patients during pregnancy and avoid applying standard therapy to women with a high risk profile. Some patients may in fact require a personalized strategy, in addition to standard protocols, to improve their chances of a successful outcome [Table 1].

Table 1. Proposed management of APS patient with recurrent pregnancy loss despite standard treatment

- Identification of patients at high risk
- Proposed treatments:
  LDA plus LMWH (prophylactic dose) or LDA plus LMWH (therapeutic dose)
  with or without low dose corticosteroids
  with or without HCQ
  with or without plasma exchange
  with or without IVIg

Proposed treatments for women with recurrent pregnancy loss have focused on thromboprophylaxis and immune modulation. The use of LDA and/or prophylactic dose of LMWH to treat women with APS has been guided by the original trials, which included mainly women with recurrent early miscarriage and totally excluded women with previous thrombosis, women with concomitant systemic autoimmune disease and LA-positive patients [5,6]. Therefore, we now understand that the studies conducted in the 1990s totally excluded patients with some of the known major risk factors for pregnancy morbidity in APS.

New pharmacological approaches subsequently explored tried to improve pregnancy outcome in patients refractory to standard therapy. As a first step, experts agreed to administer LMWH at a therapeutic dose, and the results were partially successful [7].

Corticosteroids are known to be associated with significant side effects, especially at a high dose; these include preterm delivery, preeclampsia, gestational diabetes, and hypertension. Despite this, it was demonstrated that women taking low doses of prednisone until 14 weeks of gestation plus standard therapy can experience favorable pregnancy outcome, with a higher live birth rate. [8]

Some controversial findings were seen following therapy with intravenous immunoglobulins G (IVIg). IVIg seem to be safe and effective, but since available data were from small series of patients only, few controlled trials support this approach and the results are therefore inconclusive [9]. With regard to plasma exchange in high risk pregnancies, only case reports have been published, and it is considered as a last-resort treatment.

Hydroxychloroquine (HCQ) should be considered for its antithrombotic and immunomodulatory properties. Its effectiveness was shown in experimental models [10]. A recently published multicenter European retrospective study assessed the effect of non-conventional treatment strategies on pregnancy outcomes in women with APS. A total of 196 pregnancies were evaluated and it was shown that the outcome of high risk pregnancies (previous thrombosis plus triple aPL positivity) significantly improved when additional treatments were applied. These treatments included IVIg and plasmapheresis, IVIg alone, plasmapheresis alone, IVIg and low dose corticosteroids, and IVIg and immunoadsorption. In particular, logistic regression analysis showed that additional treatments were the only independent factors associated with a favorable pregnancy outcome and a significant higher live birth rate.

A possible link between complement activation and pregnancy loss, growth restriction and preeclampsia, through a pro-inflammatory mechanism was recently defined in animal models. These complications could be prevented or reversed by complement inhibition. Those findings are interesting but the real effect of complement inhibition in human pregnancy is still unknown. Hence, this approach is not feasible.

In conclusion, as experts in the field have recently suggested, the use of low dose corticosteroids, LDA, LMWH, IVIg and plasma exchange, either alone or in combination, can improve pregnancy outcome in real life, even if only a few and relatively small randomized controlled trials, with doubtful results, have been published.

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