Review

Management of maternal antiphospholipid syndrome

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ABSTRACT

Antiphospholipid syndrome (APS) is a systemic autoimmune disease which manifests as thrombotic and/or obstetric adverse events, mediated by persistent circulating antiphospholipid antibodies (aPL) detected by means of three tests: lupus anticoagulant, anticardiolipin and anti β2-glycoprotein I antibodies. It can be isolated or associated with other autoimmune rheumatic diseases. During pregnancy, patients with APS have a higher risk of obstetric complications and a higher thrombotic risk due to the pregnancy itself. Therefore, a preconception counselling is crucial to assist the patient and her family in planning the pregnancy and to optimise the management by implementing preventive measures that can allow the best outcomes for both the mother and the baby. In clinical practice, we can distinguish between different subsets of patients that require alternative approaches: patients with obstetric APS, patients with thrombotic APS, patients with APS associated with other autoimmune diseases, and asymptomatic individuals (aPL carriers). Pregnancy and foetal outcomes have greatly improved in the past 2 decades as a result of a therapeutic implementation based on individual risk stratification and a combination of low dose aspirin and heparin. Additional strategies have been suggested for women with pregnancy failure despite this management.

Introduction

After more than three decades of study, antiphospholipid antibody syndrome (APS), originally described in patients with and without systemic lupus erythematosus (SLE) (1, 2), remains a systemic autoimmune disease of unknown aetiology characterised by thrombotic and/or obstetric complications, mediated by persistent antiphospholipid antibodies (aPL) namely anticardiolipin (aCL), and anti β2-glycoprotein I (aβ2-GPI) and and or or a positive lupus anticoagulant (LAC) assay (3, 4).

APS may occur in isolation but in approximately 30% of patients it is associated to another systemic autoimmune disease (secondary), mainly SLE (5). The incidence and prevalence of primary APS is uncertain, but a recent study showed that APS occurrs in about 2 persons per 100,000 per year and the prevelance is 50 per 100,000 (6).

Obstetric APS (ob-APS) and thrombotic APS (t-APS) are distinct disorders. Patients may present with vascular thrombosis and no pregnancy complications or, alternatively, display obstetric manifestations in isolation (7, 8). It should be noted that the coexistence of both thrombosis and miscarriages affects only about 2.5–5% of APS pregnancies (9, 10). More recently, a different subset of patients, the so-called "aPL carriers", has been described: these are aPL-positive individuals without any related clinical manifestations (11). However, there are at high risk of prematurity, pre-eclampsia, eclampsia or HELLP (Haemolysis, Elevated Liver enzyme levels, Low Platelet count) syndrome (12).

A healthy pregnancy, by itself, contributes to an increased thrombosis risk due to the physiological induction of a thrombophilic state. In APS, the risk of a thrombotic event is actually raised 50 to 100 times (13, 14). The management of maternal APS should therefore include preventive strategies to reduce the thrombotic risk and to minimise adverse pregnancy outcomes (APOs).

Adequate preconception counselling of aPL-positive, primary or secondary APS includes assessment of risk factors for adverse maternal and foetal outcomes (14). Counselling delivered by a multidisciplinary team including rheumatologists, doctors of internal medicine, and/or haematologists, together

with obstetricians and neonatologists is thought to be maximally effective (15). The aim of this practical review is to describe the clinical management of maternal APS according to the different patient subsets that a physician is likely to encounter in routine clinical practice.

Management of APS in different clinical scenarios

Preconception counselling: assessment of risk factors and pregnancy monitoring plan

Most importantly risk stratification should be performed according to the aPL outline. Taking into account the type, titre and persistence of aPL, patients can be divided into 'high-risk' (LA positivity, or 'triple positivity' - LA+aCL+anti-β2GPI - or medium-high titres of IgG aCL or anti-β2GPI) or 'low-risk' (patients with isolated, intermittently positive aCL or anti-β2GPI at low-medium titres) profiles (11). The pre-conception risk assessment should also include prior pregnancy complications and/or thrombotic events including "APS non-criteria manifestations" (12, 16), genetic risk factors for thrombophilia, major organ involvement, other comorbidities, life style risk factors such as smoking and alcohol consumption and concomitant medications that may compromise foetal development. If APS is associated with other autoimmune diseases or even with only minimal autoimmunity features, autoantibodies and complement levels should be also evaluated together with specific disease activity, when needed (see Table I).

The second step in counselling involves setting up preventive strategies and a personalised monitoring plan. The pharmacological treatment should be tailored on the disease profile, as well as, on the specific risk factors (see below). All women are recommended to take folic acid preconceptionally together with calcium and vitamin D throughtout pregnancy (12).

For high-risk profile patients, visits and blood tests should ideally be performed monthly, a less tight schedule allowed for low risk patients. The prospective evaluation of complement levels can be of help, since in the normal obstetrical population C3 and C4 levels are shown to progressively increase during gestation. Ultrasonography screening during the first (at 11–14 weeks of gestation) and second trimesters (with Doppler at 20–24 weeks of gestation) which is part of routine management should be supplemented by monthly biometric and Doppler findings in the third trimester. This programme allows for the detection of intrauterine growth restriction (IUGR) and it tailors the time of delivery (12). Extra-vigilance with blood pressure monitoring and 24-h urine protein analysis is required in patients with history of renal involvement.

In some conditions, such as recent thrombosis (especially in arterial thrombosis) or active rheumatic disease, the pregnancy needs to be postponed for at least 6 months. In the presence of pulmonary arterial hypertension patients should be discouraged from pregnancy because of a high risk of maternal mortality (17).

Primary APS - Obstetric APS

The most frequent obstetric complication is foetal loss (>10 weeks) and recurrent miscarriage (<10 weeks) (18). Of note, the presence of aPL is thought to contribute to 6% of pregnancy morbidity in the general population (19).

Prophylactic or therapeutic dose of heparin (unfractioned heparin-UFH- or low-molecular weight heparin-LMWH) together with low dose of aspirin (LDA) (75–100mg/day) are recommended (12, 20, 21). The combination of UFH and LDA resulted as the best option to reduce pregnancy loss by 54% in patients with recurrent abortions (22). As LMWH plus LDA has been shown to be as successful as as UFH plus LDA (23-25). LMWH is the preferred option, not only for its pratical reasons but also because there is no need for monitoring and it has a lower risk of osteoporosis (26).

For pregnant APS patients with no history of thrombosis, even though there is a lack of robust data, most physicians use a fixed once daily dosage of LMWH, instead of a weight-adjusted regimen (27).

LDA should be preferably started preconceptionally and LMWH or UFH begin as soon as pregnancy is confirmed. Treatment discontinuation is more controversial and depends on local protocols, use of epidural and the type of delivery. For example, in France, LDA is discontinued 5 to 6 weeks before delivery due to possible effects on epidural anaesthesia (28); LMWH should be switched to UFH at week 36-37 and stopped 4–6 hours prior to elective induction of delivery, caesarean section, or neuraxial anaesthesia; if maintained, LMWH should be suspended 24 hours prior to elective induction of delivery, caesarean section, or neuraxial anaesthesia (28).

Some patients with ob-APS can have higher risk to develop a first thrombotic event due to the high-risk aPL profile plus concomitant risk factors and/or additional "APS non-criteria manifestations". In these women, adjusted prophylactic dose or *therapeutic* dose of heparin should be used throughout the pregnancy (12).

In ob-APS refractory to the combination therapy with LDA and heparin, treatment options to improve pregnancy outcomes include prednisolone (10mg/day) in the first trimester (0–14 weeks) and/or intravenous immunoglobulin (IVIG) and/or plasmapheresis (29). Table II shows the detailed pharmacological treatment.

Hydroxychloroquine (HCQ) is an established therapy for SLE due to its anti-inflammatory and immunomodulatory effects. It has been reported that HCQ reduces binding of aPL and restores annexin V expression by cultured human syncytiotrophoblasts and it impairs the aPL related placental damage (30, 31). Two retrospective studies have suggested the benefits of HCQ in improving APOs in APS in addition to conventional treatment (32, 33). In a recent study, high HCQ (400mg/day) *versus* low HCQ (200mg/day) and its administration before *versus* during pregnancy was associated with a significantly higher live birth rate in APS patients without previous thrombosis (29). The HYPATIA study, a multicentre randomised clinical trial (RCT), will start in the near future. This will evaluate the efficacy of HCQ *versus* placebo in addition to standard of care

Table I. Preconception checklist for the risk stratification of a patient with APS planning a pregnancy or currently pregnant.

Maternal risk factors		
•	Previous pregnancy complications:	miscarriages, foetal loss, pre-eclampsia/eclampsia, HELLP syndrome, prematurity, IUGR and SGA infants
•	Previous thrombotic events:	number, site, venous or arterial
•	aPL profile:	Type and titres of LA, aCL , aβ2GPI High-risk profile: LA positivity, 'triple positivity' -LA+aCL+anti-β2GPI - or medium-high titres of IgG aCL or IgG anti-β2GPI Low-risk profile: isolated, intermittently positive aCL or anti-β2GPI at low-medium titres
•	Non-criteria manifestations:	Thrombocytopenia, autoimmune anemia
•	Inherited thrombotic risk factors:	protein C, protein S and anti-thrombin deficiency; factor V Leiden, PT 20210 gene and MTHFR mutation; hyperhomocysteinemia
•	Major organ involvement:	cardiac, pulmonary, renal, CNS involvement (*e.g.* severe pulmonary hypertension, severe renal failure, severe stroke)
•	Maternal comorbidities:	advanced age, arterial hypertension, diabetes, thyroid disease, overweight/obesity
•	Harmful lifestyle habits:	nicotine, alcohol, and recreational drugs
If associated to other autoimmune diseases:		
•	Disease activity:	patient in remission or stable disease in the last 6-12 months and at conception
•	Autoantibodies:	anti-Ro/SSA and anti-La/SS-B antibodies
•	Serological activity:	serum C3/C4, anti-dsDNA titres
•	Teratogenic drugs:	methotrexate, mycophenolate, cyclophosphamide

aPL: anti-phospholipid antibodies; HELLP Syndrome: Haemolysis, Elevated Liver enzyme levels, Low Platelet count Syndrome; IUGR: intrauterine growth restriction; SGA: small-for-gestational-age; LA: lupus anticoagulant; aCL: anticardiolipin antibodies; aβ2GPI: anti-β2-GPI antibodies; PT: prothrombin; MTHFR: methylenetetrahydrofolate reductase; CNS: central nervous system.

in women with persistent aPL planning for pregnancy (34).

Lastly, a recent small case-control study highlighted the potential role of pravastatin (20mg/day) in improving APOs in women with APS complicated by PE/IUGR despite the use of LDA plus LMWH. This drug taken at the onset of PE and/or IUGR until the end of pregnancy seems to increase placental blood flow and improve PE features (35). The protective effects of pravastatin on the endothelium together with its effect in restoring angiogenic balance might explain the amelioration of placental and maternal preeclamptic signs. The Improve Pregnancy in APS with Certolizumab Therapy (IMPACT) is evaluating if the drug, a TNF inhibitor that does not cross the placenta (36), reduces the risk of APOs in APS (37).

Primary APS - Thrombotic APS

Women with previous thrombosis with or without obstetric complications (t-APS) have a high risk of recurrent thrombotic event during the pregnancy (13, 38, 39). Therefore, the treatment of t-APS in pregnant women relies on secondary prevention of recurrence by using anti-thrombotic drugs and on preventive strategies to minimise possible aPL related APOs.

Although there are no clinical studies in the management of t-APS during pregnancy, it is currently recommended, as soon as pregnancy is confirmed, to stop vitamin K antagoist (VKA) because of its fetotoxicity and switch to *therapeutic* LMWH with LDA (75–100mg/day) (40, 41). LDA and LMWH should be stopped before the delivery as described in the section above (Table II).

Data suggests that the risk period for development of foetal warfarin syndrome is between the 6th and 12th gestational week (14). In some countries, due to governmental strategies to reduce costs on healthcare (*e.g.* Brazil) (42), in women with positive aPL and history of thrombosis VKA is recommended as a safe option from the 13th week (when teratogenic risk is virtually absent) until the 36th week (because of the high risk of foetal cerebral haemorrhage in the late phase of pregnancy). The authors' recommendation is based on a limited number of published case series or case reports and on their personal experience (42). Women with APS (with history of prior thrombotic event) may benefit from a planned vaginal delivery so LMWH can be switched to therapeutic intravenous UFH, which can be continued through 4 to 6 hours' prior delivery or placement of neuraxial anaesthesia (28).

Special attention should be given to women that develop catastrophic antiphospholipid syndrome (CAPS) during pregnancy. The management of CAPS is challenging to the clinician, early diagnosis and aggressive treatment is essential to save patients from this potentially fatal and rare condition. There are no randomised clinical trials available and management is mainly based on consensus data. A treatment algorithm for management of CAPS in pregnancy has been proposed and it is summarised in Table II.

APS associated to autoimmune diseases

The management of maternal APS associated with autoimmune diseases will focus mainly on SLE, because the

Table II. Maternal management of APS according to different clinical scenarios

Clinical Scenarios		Management
Obstetric APS	*Pregnancy*	**LDA**[a)o] (75-100mg/day) *plus prophylactic* **LMWH**[o] or **UFH**[o] (**HCQ** 5-6mg/kg/day)
Refractory Obstetric		**LDA**[a)o] (75-100mg/day) *plus* therapeutic **LMWH**[o] or **UFH**[o] **AND** **Prednisolone** (10mg/day) in the first trimester (0-14 weeks of gestation) **AND/OR** **IVIG** (2 schemes, before plasmapheresis) 400 mg/kg/day) for 5 consecutive days *or* 1g/kg daily for 2 consecutive days **AND/OR** **Plasmapheresis** (before steroids) three to five consecutive days **AND/OR** (**HCQ** 5-6mg/kg/day) (**Pravastatin** 20mg/day)
	Puerperium	*prophylactic* **LMWH**[o] or **UFH**[o]
Thrombotic APS	*Pregnancy*	stop **VKA**[o] (before the 6th week of gestation) ** start **LDA**[a)o] (75-100mg/day) *plus therapeutic* **UFH**[o] or **LMWH**[o]
	Puerperium	*therapeutic* **UFH** or **LMWH** **OR** **VKA****
CAPS, during pregnancy		First-line Therapy **UFH***[o] (80U/kg IV bolus) *then* continuous infusion of 18U/kg/hr **Plasmapheresis** (before steroids) three to five consecutive days **Glucocorticoids** Methylprednisolone (IV) 500-1000mg/day for 1 to 3 days *and* slowly reduce to 1-0.5mg/kg/day (depending on clinical condition) **IVIG** (2 schemes, before plasmapheresis) 400 mg/kg/day) for 5 consecutive days *or* 1g/kg daily for 2 consecutive days
		Second-line Therapy **RTX** 375mg/m^2 (IV) 1/week during 1 month **OR** **Eculizumab** 900mg (IV)/week for 4 weeks *then* 1,200mg/2 weeks
APS associated to autoimmune diseases (e.g. SLE)	*Pregnancy*	**UFH**[o] or **LMWH**[o] (*Prophylactic/Therapeutic* weight-adjusted dose depending the main clinical manifestation of APS, thrombotic or obstetric) **PLUS** **LDA**[a)o] (75-100mg/day) **PLUS** **HCQ** (5-6mg/kg/day)
	Puerperium	*prophilactic* **UFH** or **LMWH**
aPL carriers	*Pregnancy*	**LDA**[a)o] (75-100mg/day) **OR** **LDA**[a)o] (75-100mg/day) *plus* **UFH**[o] or **LMWH**[o] *(Prophylactic/Therapeutic* weight-adjusted dose depending on aPL profile plus concomitant risk factors and/or additional non-criteria APS manifestations)
	Puerperium	*prophilactic* **UFH**[o] or **LMWH**[o]

aPL: Anti-phospholipid antibodies; APS: Anti-phospholipid syndrome; CAPS: Catastrophic anti-phospholipid syndrome; IV: Intravenous; IVIG: Intravenous immunoglobulins; RTX: Rituximab; UFH: Unfractionated heparin; U: Units; LMWH: Low molecular weight heparin; kg: kilogram; hr: hour; mg: milligram. *acute phase. **Warfarin: teratogenic, especially between the 6th and 12th week of gestation; risk of foetal bleeding especially after the 36th week of gestation. During puerperium, it can be restarted after bridging therapy with heparin. a) Depending on each countries formulation of the drug.

Note: LDA should be started preconceptionally and stopped before delivery depending on the local protocol. Heparin should be started when pregnancy is confirmed and stopped before delivery depending on the type of heparin and delivery.

[o]In pregnant women with APS and thrombocytopenia, a frequent non-criteria manifestation, the use of heparin, LDA, and VKA should be carefully evaluated due to the increased risk of bleeding. Thrombocytopenia is often mild, usually above 50 x 10^9/L, and does not require any intervention. In this case, antithrombotic prophylaxis should be considered whenever possible. On the other hand, LDA, heparin, and VKA should be avoided when platelet count is below 50 x 10^9/L.

majority of the studies describe these patients only. Disease-related considerations before and during pregnancy, include control of the underlying disease, as active SLE during conception is a strong predictor of APOs and exacerbations of disease can occur during pregnancy (43, 44). Patients with an underlying systemic autoimmune condition suffer from an increased vascular morbidity, not fully ascribable to traditional cardiovascular risk factors. This data should be considered in the preconceptional risk assessment of a patient with APS associated to an autoimmune disease (12).

The treatment in these patients includes LDA, heparin and HCQ. The dose of heparin (*prophylactic* or *therapeutic)* depends on the clinical manifestations (ob-APS or t-APS). LDA and LMWH should be started and stopped as previously mentioned (Table II). In patients with APS associated with SLE, data showed that HCQ 400mg/day is beneficial and recommended before and during pregnancy (12) and immunosuppressive drugs are used to control disease activity in order to improve obstetrical outcomes (12, 32). The therapy with immunosuppressive drugs should be adjusted before conception by stopping teratogenic agents (*e.g.* methotrexate, mycophenolate mofetil) and switching to drugs compatible with pregnancy (*e.g.* azathioprine, calcineurin inhibitors) (Table III).

Table III. APS associated to other autoimmune diseases: drugs compatible during pregnancy.

Withdrawn before conception	Stop at positive pregnancy test	Compatible with pregnancy	Adjunct treatment during pregnancy
Methotrexate[a] Mycophenolate mofetil[a] Cyclophosphamide[a]	Warfarin/Acenocumarol	NSAIDs (avoid after *32w*)	±LDA[d] *(preconceptionally or <16w)*
Leflunomide[b] Tofacitinib[b] Apremilast[b]	selective COX II inhibitors[b]	Prednisone Methylprednisolone	± prophylactic/therapeutic LMWH[e]
Abatacept[c] Tocilizumab[c] Rituximab[c]* Belimumab[c] Ustekinumab[c] Secukinumab[c]	Mepacrine[b]	Chloroquine Sulfasalazine (*2gr/day*) Azathioprine Cyclosporine Tacrolimus Colchicine	Hydroxychloroquine Folic acid *(3 mths before conception)*
		Infliximab (stop 20w)* Adalimumab (stop 20w)* Golimumab (NA)* Etanercept (stop 30-32w)* Certolizumab** Anakinra* Intravenous immunoglobulin	Calcium/Vitamin D

NSAIDs: non-steroidal anti-inflammatory drugs; w: weeks; NA: not available; mths: months; LDA: low-dose aspirin; LMWH: low molecular weight heparin.
[a]teratogenic; [b]avoid until further evidence is available; [c]limited documentation on safe use in pregnancy and should be replaced before conception by other medication; [d] if risk of pre-eclampsia, *e.g.* patients with lupus nephritis or aPL positive patients; [e]In Anti-phospholipid syndrome, according to clinical phenotype and individual risk profile.
*if maternal disease activity cannot be controlled with different drugs.
**demonstrated lack of transplacental passage (possible use throughout pregnancy if required by maternal disease activity).

Asymptomatic aPL carriers

Antiphopspholipid carriers are frequently identified when aPL testing is performed in the diagnostic work-up of other autoimmune diseases, in subjects with "APS non-criteria manifestations", in women with infertility problems or just by chance in women undergoing coagulation screening for surgical procedures. Even though robust data does not exist, studies have estimated that the prevalence of aPL in the general population ranges between 1% and 5%, but the antibody titre in these individuals is low (45).

It's still unknown the risk of APOs in aPL carriers, but considering the pathogenetic role of the aPL, a stratification risk should be taken into account based on the same risk factors mentioned above for definite APS patients.

Few studies have been conducted on pregnancy outcomes making it difficult to draw conclusions given the heterogeneity of type and number of aPL tested (46-49).

In clinical practice, physicians are used to manage pregnant aPL carriers with LDA, in particular if the patients have already experienced one or two foetal losses or if maternal risk factors coexist (50). LDA is also used in women without aPL for the prevention of PE (51).

The published data are still controversial. A recent systematic review of 5 studies involving 154 pregnancies concluded that primary prophylaxis with LDA did not improve obstetric outcomes in asymptomatic aPL carriers (52). In a large retrospective observational study, the rate of pregnancy losses, gestational weight at delivery and birth weight percentile was not different between aPL positive women treated with LDA and those not treated (46). The same data was confirmed in another large cohort of 73 pregnant aPL carriers (mostly isolated LA) (47).

On the other hand, in a international multicentric study, including 200 women (recruited from 2000 to 2014), with confirmed positive aPL during pregnancy, APOs were experienced by 18% of aPL carriers, similarly to ob-APS (18%) and t-APS (24%); triple aPL positivity was associated to APOs even in aPL carriers treated with LDA plus LMWH (48). This finding prompted a subsequent multicentre study to investigate the treatment approach and pregnancy outcomes in aPL carriers (49). APOs were observed in 9% of women and were associated to acquired traditional risk factors, "APS non-criteria" or "lupus-like" manifestations and triple aPL positivity. APOs occurred despite combination treatment with LDA and *prophylactic* dose of LMWH, suggesting that aPL carriers with multiple

risk factors and a high-risk aPL profile may need additional treatment, for example *therapeutic* dose of LMWH or immunomodulatory treatment (HCQ).
In the first-year analysis of the European Registry on Obstetric Antiphospholipid Syndrome (EUROAPS), women with obstetric morbidity not fulfilling criteria for APS had APOs similar to those with ob-APS and benefit from the combination therapy with LDA and *prophylactic* LMWH (16). Recently, the beneficial role of HCQ in pregnant patients positive for aPL has been hypothesised (53, 54). The RCT HYPATIA will also assess the role HCQ in reducing APOs in aPL carriers (34).

Management of puerperium and breastfeeding

In the general population, the incidence of venous thromboembolism (VTE) during pregnancy and the puerperium has been estimated to be 5.5–6 times higher compared with non-pregnant women (55) and up to ≥20-fold in puerperium until approximately 12 weeks postpartum (28). Women with APS have a major risk factor that increases even more the risk of VTE during puerperium.
In puerperium, both LMWH and UFH can be restarted when haemostasis is achieved (generally around 6 hours after vaginal delivery and 12 hours after a cesarean delivery). Women with ob-APS (with no history of thrombosis) are recommended to take *prophylactic* LMWH or UFH up to 6 weeks after delivery.
Women with t-APS (with history of prior thrombotic event) are at very high risk for recurrent VTE during puerperieum. American College of Chest Physicias recommends LMWH with an adjusted-dose strategy or 75% of therapeutic dose; alternatively, VKA may be resumed (14, 26). LDA, heparin and warfarin can be safely admistered during breastfeeding (56).
If warfarin is the anticoagulation preferred for long-term therapy, a transition from LMWH or UFH to warfarin must be done. The first dose can be administered the day after delivery along with short-term bridging heparin (ideally LMWH) for ≥5 days and until the international normalised ratio (INR) ≥2 on two consecutive days (57).
Asymptomatic aPL carriers should be treated with *prophylactic* LMWH for at least 6 weeks after delivery. Besides pharmacological agents in the management of APS, the importance of avoiding immobility and the use of compression stockings in puerperium play an important role (28).

APS and assisted reproduction techniques

Given the difficulties for successful pregnancies, assisted reproduction techniques (ARTs) could be an option for APS women. These techniques include ovarian stimulation, oocyte retrieval, *in vitro* fertilisation, and transfer of the fertilised embryo into the uterus (58). Observational studies showed that ARTs can be safely and successfully performed in women with APS (59, 60). The efficacy of pregnancy rate is comparable with that in the general population (up to 30%). As with pregnancies that are achieved naturally, candidates for ARTs should have inactive disease and be on appropriate antithrombotic treatment. Although the best protocol is not still well-defined, the thrombophilaxis (LDA and/or *prophilactic vs. therapeutic* LMWH) should be recommended during pregnancy according to the clinical phenotype and individual risk profile. LDA should be stopped three days before egg retrieval and resumed the following day. Patients taking LMWH should be stopped at least 12 hours prior to the procedure and resumed in the same day as long as there is no bleeding (12). Friendly ovarian stimulation, single embryo transfer, use of natural oestrogen or progestin through a nonoral route may be the safest approach to avoid ovarian hyperstimulation syndrome (61).

Conclusion

Pregnancy in APS patients should be considered high-risk. Surveillance and treatment are needed to optimise maternal and foetal outcomes. The current standard of care of maternal APS is based on clinical phenotype and individual risk profile. A heparin-LDA combination therapy constitutes the conventional treatment protocol for pregnant women affected by APS. These strategies are unsuccessfull in approximately 20% of cases, so women refractory to conventional treatment need additional options. New approaches aiming to improve pregnancy outcomes include the first trimester administration of corticosteroids, plasmapheresis and IgIV. However, more "easy to use" strategies, such as the immunomodulator HCQ, seems to have a beneficial effect, particularly if it is administered at therapeutical dose. Further studies are needed to evaluate the role of pravastatin in the care of APS patients developing PE. More data on the best management of aPL carriers and "APS non-criteria manifestations" are needed in order to improve maternal and foetal outcomes. Recently, the few available guidelines based on the systematic review of the literature were analysed within the frame of ERN ReCONNET (European Reference Network on rare and complex connective tissue and muskoloskeletal diseases), an initiative funded by the European Council with the aim to improve patient care through the identification of unmet needs in the diagnosis and management of APS. The management of pregnancy, of non-criteria manifesations, and of the primary phophylaxis are areas of uncertainity that should be taken into account for the development of future clinical guidelines (62).

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