What's new in obstetric antiphospholipid syndrome

D. Ware Branch

Department of Obstetrics and Gynecology, Division of Maternal-Fetal Medicine, University of Utah Health, Salt Lake City, UT

Antiphospholipid syndrome (APS) is a rare systemic autoimmune disease, the obstetric features of which include recurrent early miscarriage, fetal death at or beyond 10 weeks of gestation, and early delivery for severe preeclampsia or placental insufficiency. Controversies regarding the specificity of these obstetric clinical features, as well as the laboratory diagnostic criteria, are the subject of current debate and reanalysis. Clinical and laboratory features can be used to stratify women with APS in terms of risk of adverse second and third trimester pregnancy outcomes. Numerous "treatments" have been used in high-risk and refractory patients, but rigorously designed clinical trials are needed. APS is a rare disease that requires innovative investigative approaches to provide credible results.

Learning Objectives

- Describe the obstetric clinical features of antiphospholipid syndrome (APS)
- Understand the controversies in obstetric APS
- Understand the issues related to treatment trials and novel approaches to APS in pregnancy

Introduction

Antiphospholipid syndrome (APS) is a rare systemic autoimmune disease with thrombotic or obstetric clinical features and the presence of persistently positive antiphospholipid antibodies (aPL antibodies). The condition may occur alone or in patients with other autoimmune diseases, most commonly systemic lupus erythematosus. Diagnostic criteria for APS (developed in the late 1990s and revised in 2006) include clinical features consisting of thrombosis and/or 1 of several obstetric morbidities and hold that the pertinent aPL antibodies are lupus anticoagulant (LA), anticardiolipin (aCL) (immunoglobulin G [IgG] and IgM), and anti–β2-glycoprotein I (aβ2-GP-I) (IgG and IgM).[1] Concerns about the sensitivity and specificity of both the clinical and autoantibody criteria are the subject of current debate among experts. A rigorous, structured process consisting of multiple rounds of questionnaires is underway to derive new international diagnostic criteria that will better distinguish APS from other conditions.[2]

By way of background, readers must recognize that the annual incidence of APS is quite low, probably about 2 persons per 100 000 population aged 18 years old or greater; the estimated prevalence is 50 per 100 000.[3] Thus, high-quality studies related to diagnosis and treatment are difficult to perform and will necessarily require "rare disease" approaches.

Selected aspects regarding the diagnosis of obstetric APS

Current guidelines state that the diagnosis of definite APS requires the presence of 1 or more clinical criteria and repeatedly positive tests for aPL antibodies within 5 years of the clinical event.[1] The obstetric clinical criteria include the 3 follow presentations:

- Recurrent (3 or more consecutive) pre-embryonic or embryonic miscarriage <10 weeks n (recurrent early miscarriage [REM]),
- One or more otherwise unexplained fetal deaths ≥10 weeks of gestation, or
- Delivery before 34 weeks for preeclampsia or placental insufficiency.

These obstetric clinical criteria are now 20 years old and historically, have been little challenged. The obstetric features of APS are somewhat nonspecific in nature—they are, unfortunately, relatively common adverse reproductive outcomes, and each one has numerous contributing or etiologic factors. Thus, the specificity of the diagnosis of obstetric APS rests heavily on laboratory confirmation of repeatedly positive aPL antibody results. Existing publications describing the association of aPL antibodies with the obstetric features shown above are limited by their study designs and associated variation in findings as well as issues pertaining to the variety and number of aPL antibody tests used, the definition of positive results, the methods of establishing thresholds for positive results, and the lack of confirmatory testing in many studies.[4-6] To further complicate this, experts regard LA as the most specific autoantibody for the diagnosis of APS, and testing for LA requires properly collected fresh plasma, with testing ideally performed in an experienced laboratory.

REM

In the author's referral practice, REM is the most common obstetric clinical criterion for which the diagnosis of APS is entertained. One systematic review concluded that 2% to 6% of women with REM have positive aPL antibody results,[4] but the authors emphasized that studies are limited as discussed in the preceding paragraph. Also, early miscarriage is often owing to conceptus aneuploidy, and it is more likely to be so in women of advance maternal age. Ideally, evaluation for conceptus aneuploidy will be done in the evaluation of women having repeated early miscarriages. REM may be owing to other maternal or parental abnormalities, including uterine malformations,

Conflict-of-interest disclosure: D.W.B. receives research funding from UCB Pharmaceuticals and the National Institutes of Health related to a trial of certolizumab in the treatment of antiphospholipid syndrome in pregnancy.

Off-label drug use: None disclosed.

parental karyotype abnormalities, and maternal endocrinopathies. Current guidelines call for these causes of REM to be ruled out when considering the diagnosis of APS based on REM.

Some experts,[7-9] including our group at the University of Utah,[10] have found that <5% of women with REM and no other obvious autoimmune or thrombotic disease features have aPL results meeting international consensus criteria.[1] Because several percent of otherwise healthy subjects have positive aPL antibody results,[11,12] further study to determine the exact relationship between REM and aPL antibodies would seem in order.

Fetal death and early delivery for preeclampsia or placental insufficiency

Most experts believe that fetal death and early delivery for severe preeclampsia and/or placental insufficiency are more specific clinical features of APS.[13] Regarding otherwise unexplained fetal death, 1 case-control study of >100 women with fetal death after 22 weeks of gestation found that the odds ratio (OR) was 4.3 (95% confidence interval = 1.0-18.4) for LA, but the OR was not significant for a single positive immunoassay result.[14] Perhaps the best work comes from the Stillbirth Collaborative Research Network, a multicenter, population-based, case-control study of stillbirths.[15] The investigators found positive tests for aPL (aCL or aβ2-GP-I antibodies) in nearly 10% of fetal death cases ≥20 weeks of gestation. After excluding cases that were otherwise explicable, positive results for IgG aCL and IgM aCL antibodies were associated with 5- and 2-fold odds of stillbirth, respectively, whereas IgG aβ2-GP-I antibodies were associated with a 3-fold odds of stillbirth. Two prospective observational studies of women with well-characterized APS noted fetal deaths in >10% of cases in spite of treatment with a heparin agent and low-dose aspirin (LDA).[16,17]

Regarding delivery before 34 weeks for preeclampsia or placental insufficiency, a recent prospective, case-control study of otherwise unselected women delivered for severe preeclampsia or placental insufficiency found that just >10% of cases were positive for aPL antibodies compared with <2% of controls.[18] Two prospective, observational studies of women with well-characterized APS found that 9% to 10% of women with well-characterized APS develop severe preeclampsia in their observed pregnancy in spite of treatment with a heparin agent and LDA.[16,17] Although placental insufficiency (a condition evidenced by fetal growth restriction, oligohydramnios, or fetal surveillance indicating poor placental vascularization/perfusion) typically accompanies preeclampsia in APS, it may occur in the absence of preeclampsia, but it is less well studied in this circumstance.

In summary, the clinical criteria for obstetric APS are relatively nonspecific. Most experts hold that second- and third-trimester features (ie, otherwise unexplained fetal death or early delivery for severe preeclampsia or placental insufficiency) are more specific than REM. The certainty of APS requires proper laboratory confirmation. The author looks forward to expected revisions in the new international diagnostic criteria that will refine the "probability" of a diagnosis of APS in the context of each of the obstetric clinical features.

Possible APS and equivocal cases: example case

A 38-year-old woman is referred, because she has had 2 pregnancy losses within the last 18 months, and an infertility specialist has tested her to autoantibodies, including antinuclear antibodies (ANA), LA, aCL, and aβ2-GP-I. The ANA, LA, aCL IgG, and aβ2-GP-I IgG are negative, but the aCL IgM result is 23 MPL (IgM phospholipid binding) units, and the aβ2-GP-I IgM result is 30 SMU (standard IgM binding units). Her pregnancy losses were identified by obstetrical ultrasound imaging to have occurred at 6 and 7 weeks of gestation, respectively. The patient has no history of autoimmune disease. She has had 2 previously normal pregnancies delivered of live infants at term when she was in her 20s. She is now pregnant at 5 weeks of gestation.

In my consultation practice, referrals for possible APS or equivocal cases, particularly for REM without other clinical concerns (eg, history of thrombosis), are more common than for bona fide APS meeting accepted clinical and laboratory criteria. Typical issues of concern include the following:

- False positive tests for LA, usually owing to poor specimen acquisition or handling or delay in testing;
- Low positive anticardiolipin or anti–β2-glycoprotein I results; or
- Absence of repeat/confirmatory testing 12 weeks after initial tests.

Good clinical practice calls for detailed review of the woman's clinical and laboratory features and repeat testing in an acceptable, qualified laboratory. In most cases, a diagnosis of APS is ruled out. However, because the patient and her partner may feel that a diagnosis of APS provides a treatable "cause" for their obstetric complications, a sympathetic and professional approach to counseling is required. Not infrequent in such cases, a physician has already prescribed a heparin agent, a treatment that the patient is unwilling to discontinue when her APS is not confirmed. It is my practice to explain that (1) several trials show that a heparin agent does not improve the live birth rate in women with unexplained REM and that (2) heparin agents are not without potential complications. I emphasize that bleeding in pregnancy, which might be worsened by use of anticoagulant medication, poses risks for the fetus and mother, particularly after the middle of the second trimester.

On the other end of the spectrum are new-onset and high-risk cases with features strongly suggestive of APS but in whom the diagnosis of APS is not yet established. One such case was a suspected catastrophic antiphospholipid syndrome (CAPS) in a pregnant woman presenting with stroke and evidence of small vessel occlusion in the hepatic and renal vascular beds and in whom initial testing finds a positive LA or medium- to high-titer aCL antibodies. Given the high mortality rate associated with CAPS, medical prudence should prompt consideration of aggressive treatments before confirmatory laboratory testing.

Pathogenesis of obstetric APS

It is currently thought that the pathologic aPL antibodies per se cause the autoimmune manifestations of obstetric APS and that they react against domain 1 of β_2-glycoprotein I, a ubiquitous glycoprotein involved in the clearance of apoptotic cells and microparticles as well as the innate immune response.[19] In mice, passive transfer of aPLs results in clinical manifestations of APS, including fetal loss and reduced fetal weight.[20] The local action of aPLs bound to β_2-glycoprotein I is thought to be instrumental in causing APS-related disease, ultimately via activation of inflammatory cascades. Complement activation is required for fetal loss in a murine model.[21] aPL antibodies target placenta and activate complement via the classical pathway, leading to generation of potent anaphylatoxins, recruitment of neutrophils, and release of proinflammatory mediators, such as tumor necrosis factor-α (TNF-α).[21,22] Inactivation and inhibition of the complement cascade prevent fetal loss and growth restriction that are

associated with addition of aPLs.[21,22] TNF-α, a proinflammatory cytokine associated with complement activation, has likewise been implicated in the signaling pathways by T cells that are essential to the pathogenesis of aPL, and pregnant mice lacking TNF-α are protected from pregnancy loss induced by injections of aPLs.[23] APS-associated pregnancy complications are related to abnormal placental function, probably secondary to inflammation and/or thrombosis, leading to poor vascularization of the developing placenta. Abnormal histologic findings in the spiral arteries have included narrowing, intimal thickening, acute atherosis, and fibrinoid necrosis.[24,25] In addition, placental histopathology demonstrates extensive necrosis, infarction, and thrombosis.

Management of APS in pregnancy

Example case

A 27-year-old woman with APS is now 26 weeks of gestation in her first pregnancy. Her diagnosis of APS was made at the time of a spontaneous deep vein thrombosis 5 years ago when she was found to be repeatedly positive for LA as well as have moderate to high titers of aCL IgG and aβ2-GP-I IgG antibodies. A hematologist has been treating her with long-term anticoagulation, and she was switched to full anticoagulation doses of a low-molecular weight heparin (LMWH) in very early pregnancy. She is also taking LDA. The patient now presents to labor and delivery with an initial blood pressure of 163/102 mm Hg. Her aspartate aminotransferase and alanine aminotransferase are 2- to 3-fold normal, and her platelet count is 74 000 × 109/L. A spot urine protein-to-creatinine ratio is 1.7.

Risk stratification

The risk of obstetric morbidity in pregnancies treated with a heparin agent and LDA varies depending on clinical history and laboratory features. With regard to clinical features for which a diagnosis of APS has been made, women with a history of thrombosis, fetal death, or early delivery for severe preeclampsia or placental insufficiency are at increased risk of second- or third-trimester adverse pregnancy outcomes in spite of standard treatments with a heparin agent and LDA.[16,17,26] Among otherwise healthy women diagnosed with APS because of REM, trials using heparin and LDA or LDA alone have found very low risks of second- or third-trimester adverse outcomes, such as fetal death, preeclampsia, and placental insufficiency. One prospective, observational study[16] found that severe preeclampsia occurred in 5% of women diagnosed with APS because of REM (compared with 1.6% of controls). In contrast, 14% of women with prior fetal loss had severe preeclampsia in the study pregnancy.

With regard to risks associated with laboratory features, women with LA or "triple" positivity for the 3 aPL antibodies experience adverse pregnancy outcomes, including fetal death and early delivery for severe preeclampsia or placental insufficiency, in at least one-third of cases in spite of standard treatments with a heparin agent and LDA.[17,26-28] In the PROMISSE study, the 64 women with repeatedly positive LA results had a 39% rate of fetal death, preterm delivery before 34 weeks because of gestational hypertension or placental insufficiency, small for gestational age infant, or neonatal death linked to early delivery.[17] The retrospective PREGNANTS study of 750 women with aPL antibodies and at least 1 clinical feature of APS found that women who were triple positive for aPL antibodies had only a 30% rate of successful pregnancy in spite of treatment with a heparin agent and LDA.[29] Women who are negative for LA but "double" positive for aCL and aβ2-GP-I, particularly of the IgG isotype, have a lower risk of second- or third-trimester adverse pregnancy outcomes when treated with a heparin agent and LDA. Finally, women negative for LA and with a single positive aCL or aβ2-GP-I antibody result leading to their diagnosis of APS have a low risk of adverse pregnancy outcome as do those with low antibody titers and IgM isotype results.[17,27-32]

Treatment in pregnancy

The goals of optimal management of APS during pregnancy are to minimize the risks of adverse maternal and fetal/neonatal outcomes. The maternal risks include APS-associated thromboembolism, CAPS, and risks associated with gestational hypertensive disease. Fetal/neonatal risks include miscarriage, fetal death, and risks associated with early delivery. The current standard treatment of APS in pregnancy is a heparin agent and LDA. This regimen certainly provides maternal thromboprophylaxis and may improve pregnancy outcomes. Women without a history of thrombosis are typically managed on a thromboprophylactic dose of a heparin agent. Those with a history of thrombosis are typically prescribed a full anticoagulation dose. The heparin agent, usually an LMWH, is started in the early first trimester after demonstrating either an appropriately rising human chorionic gonadotropin or an ultrasound-proven intrauterine, live embryo.

Some experts have criticized existing evidence regarding the treatment of APS in pregnancy with a heparin agent and LDA, in particular with regard to proof of efficacy in terms of embryonic/fetal outcomes and avoidance of second- and third-trimester complications. Heparin agent treatment trials have involved patients with predominantly REM.[33-38] Four of these trials found that the addition of a heparin agent to LDA resulted in a higher live birth rate,[33,35,37,38] although the range of live births in the treatment arms of these studies varied considerably. Two of these trials[34,36] proved negative, finding no benefit to the addition of LMWH to LDA—in these studies, the live birth rates in the LDA-only patients were quite good (70%-75%). Successful pregnancy outcomes in excess of 70% also have been reported among APS patients predominantly with REM who were treated with LDA alone.[39,40] These various trials are heterogeneous with regards to clinical events (eg, number of previous pregnancy losses and gestational ages of pregnancy losses) and laboratory criteria (eg, different thresholds for positive test results, inclusion of patients with low titers, and lack of confirmatory testing).[6] Moreover, several of the trials were completed before the publication of the current international consensus criteria, and many of the subjects included in each of these trials would not meet the current consensus criteria for definite APS. Properly designed treatment trials of pregnancies in women with APS diagnosed because of middle-trimester fetal death, early delivery for preeclampsia or placental insufficiency, or thrombosis are lacking.

Management of high-risk APS and refractory cases

As noted in the preceding sections, women with APS can be stratified according to adverse pregnancy outcome risk on the basis of certain laboratory and clinical features. It is not surprising that clinicians have sought and tried alternative "treatments" in high-risk obstetric APS cases and cases that have "failed" the usual recommended treatment with a heparin agent and LDA. These alternative treatments are nearly always in addition to a heparin agent and LDA. Investigators have reported modestly improved pregnancy outcomes when adding low-dose prednisolone[41] or hydroxychloroquine (HCQ)[42] to a heparin agent and LDA. A more recent, retrospective, international, multicenter study of high-risk APS pregnancies concluded that the addition of HCQ treatment was associated with a

significantly higher live birth rate in women with a history of 1 or more pregnancies refractory to conventional therapy.[43] Varying degrees of successful pregnancy outcomes have been reported in retrospective case series of high-risk or refractory obstetric APS using intravenous immunoglobulin infusions and/or aphaeresis.[44-51] Most recently, a retrospective, multicenter study found that triple-positive APS patients with previous thrombosis treated with additional therapies had a significantly higher live birth rate compared with those receiving conventional therapy alone.[52] Finally, improved outcomes in APS pregnancies treated with pravastatin have been reported by one group.[53] Cautious interpretation of these reports is in order, because they are anecdotal or retrospective in nature, and they have not included proper comparison with patients matched for confounders known to be associated with adverse pregnancy outcomes of interest. Notably, comparing current obstetric outcomes with past obstetric outcomes in the same patients is not a legitimate study design. A novel approach is being trialed using anti-TNF blockade in addition to standard treatment with a heparin agent and LDA (NCT03152058).

Future directions

Refining the criteria for the diagnosis of definite APS is underway and will be a welcome tool for future research in the field. For obstetric APS, current understanding of patient risk profiles should be incorporated into ongoing and future trials and must be accounted for in data analyses. Further work to determine which autoantibodies best make the diagnosis of APS are key.

Future studies of the management of obstetric APS must recognize 2 overriding issues. First, properly designed, adequately powered, controlled, randomized treatment trials will not likely be done in women with high-risk or "refractory" obstetric APS given the implications of adverse obstetric outcomes, particularly in the second and third trimesters. This may not be true, however, of REM patients who are at lower risk of adverse outcomes, particularly those with low titers of aPL antibodies.

Second, another major issue is that definite APS is a rare disease, and the study of rare diseases is hampered by funding and methodological challenges for numerous reasons, not the least of which are the small number of patients available in a given geographical region and the frequent lack of an appropriate group of patients for comparison. Innovative, functional approaches will require genuine collaboration among experts, creative institutional review and approval and enrollment mechanisms, study designs that minimize trial sample size, and alternative approaches to statistical analysis of data. Obstetric management should be standardized to the greatest possible extent. Future clinical treatment trials in women with APS should be prospective, registered trials. We strongly recommend the confirmation of aPL antibodies in central laboratories. Collection of appropriate control populations in ongoing, well-structured, prospective, observational studies and registries is likely to be critical to successful future treatment trials.

Correspondence

D. Ware Branch, University of Utah Health, 30 N 1900 E, Room 2B200 SOM, Salt Lake City, UT 84124; e-mail: dwbranch@gmail.com.

References

1. Miyakis S, Lockshin MD, Atsumi T, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J Thromb Haemost*. 2006;4(2):295-306.
2. Barbhaiva M, Zuily S, Ahmadzadeh Y, Naden RP, Costenbader K, Erkan D. Development of new international classification criteria for antiphospholipid syndrome: phase II item reduction survey [abstract]. *Arthritis Rheumatol*. 2018;70(suppl 10). Abstract 163.
3. Duarte-Garcia A, Pham MM, Crowson CS, et al. The epidemiology of antiphospholipid syndrome. A population-based study. *Arthritis Rheumatol*. 2019;71(9):1545-1552.
4. Andreoli L, Chighizola CB, Banzato A, Pons-Estel GJ, Ramire de Jesus G, Erkan D. Estimated frequency of antiphospholipid antibodies in patients with pregnancy morbidity, stroke, myocardial infarction, and deep vein thrombosis: a critical review of the literature. *Arthritis Care Res (Hoboken)*. 2013;65(11):1869-1873.
5. Clark CA, Laskin CA, Spitzer KA. Anticardiolipin antibodies and recurrent early pregnancy loss: a century of equivocal evidence. *Hum Reprod Update*. 2012;18(5):474-484.
6. de Jesus GR, Agmon-Levin N, Andrade CA, et al. 14th International Congress on Antiphospholipid Antibodies Task Force report on obstetric antiphospholipid syndrome. *Autoimm Rev*. 2014;13:795-813.
7. Pengo V, Ruffatti A, Del Ross T, et al. Confirmation of initial antiphospholipid antibody positivity depends on the antiphospholipid antibody profile. *J Thromb Haemost*. 2013;11(8):1527-1531.
8. Clark CA, Davidovits J, Spitzer KA, Laskin CA. The lupus anticoagulant: results from 2257 patients attending a high-risk pregnancy clinic. *Blood*. 2013;122(3):341-347.
9. Cohn DM, Goddijn M, Middeldorp S, Korevaar JC, Dawood F, Farquharson RG. Recurrent miscarriage and antiphospholipid antibodies: prognosis of subsequent pregnancy. *J Thromb Haemost*. 2010;8(10):2208-2213.
10. Bowman ZS, Wünsche V, Porter TF, Silver RM, Branch DW. Prevalence of antiphospholipid antibodies and risk of subsequent adverse obstetric outcomes in women with prior pregnancy loss. *J Reprod Immunol*. 2015;107:59-63.
11. Shi W, Krilis SA, Chong BH, Gordon S, Chesterman CN. Prevalence of lupus anticoagulant and anticardiolipin antibodies in a healthy population. *Aust N Z J Med*. 1990;20(3):231-236.
12. de Groot PG, Lutters B, Derksen RHWM, Lisman T, Meijers JCM, Rosendaal FR. Lupus anticoagulants and the risk of a first episode of deep venous thrombosis. *J Thromb Haemost*. 2005;3(9):1993-1997.
13. Cervera R, Piette JC, Font J, et al; Euro-Phospholipid Project Group. Antiphospholipid syndrome: clinical and immunologic manifestations and patterns of disease expression in a cohort of 1,000 patients. *Arthritis Rheum*. 2002;46(4):1019-1027.
14. Helgadottir LB, Skjeldestad FE, Jacobsen AF, Sandset PM, Jacobsen E-M. The association of antiphospholipid antibodies with intrauterine fetal death: a case-control study. *Thromb Res*. 2012;130(1):32-37.
15. Silver RM, Parker CB, Reddy UM, et al. Antiphospholipid antibodies in stillbirth. *Obstet Gynecol*. 2013;122(3):641-657.
16. Bouvier S, Cochery-Nouvellon E, Lavigne-Lissalde G, et al. Comparative incidence of pregnancy outcomes in treated obstetric antiphospholipid syndrome: the NOH-APS observational study. *Blood*. 2014;123(3):404-413.
17. Lockshin MD, Kim M, Laskin CA, et al. Prediction of adverse pregnancy outcome by the presence of lupus anticoagulant, but not anticardiolipin antibody, in patients with antiphospholipid antibodies. *Arthritis Rheum*. 2012;64(7):2311-2318.
18. Gibbins KJ, Tebo AE, Nielsen SK, Branch DW. Antiphospholipid antibodies in women with severe preeclampsia and placental insufficiency: a case-control study. *Lupus*. 2018;27(12):1903-1910.
19. Giannakopoulos B, Krilis SA. The pathogenesis of the antiphospholipid syndrome. *N Engl J Med*. 2013;368(11):1033-1044.
20. Abrahams VM, Chamley LW, Salmon JE. Emerging treatment models in rheumatology: antiphospholipid syndrome and pregnancy: pathogenesis to translation. *Arthritis Rheumatol*. 2017;69(9):1710-1721.
21. Holers VM, Girardi G, Mo L, et al. Complement C3 activation is required for antiphospholipid antibody-induced fetal loss. *J Exp Med*. 2002;195(2):211-220.

22. Girardi G, Berman J, Redecha P, et al. Complement C5a receptors and neutrophils mediate fetal injury in the antiphospholipid syndrome. *J Clin Invest*. 2003;112(11):1644-1654.
23. Berman J, Girardi G, Salmon JE. TNF-alpha is a critical effector and a target for therapy in antiphospholipid antibody-induced pregnancy loss. *J Immunol*. 2005;174(1):485-490.
24. Stone S, Pijnenborg R, Vercruysse L, et al. The placental bed in pregnancies complicated by primary antiphospholipid syndrome. *Placenta*. 2006;27(4-5):457-467.
25. Erlendsson K, Steinsson K, Jóhannsson JH, Geirsson RT. Relation of antiphospholipid antibody and placental bed inflammatory vascular changes to the outcome of pregnancy in successive pregnancies of 2 women with systemic lupus erythematosus. *J Rheumatol*. 1993;20(10): 1779-1785.
26. Ruffatti A, Tonello M, Visentin MS, et al. Risk factors for pregnancy failure in patients with anti-phospholipid syndrome treated with conventional therapies: a multicentre, case-control study. *Rheumatology (Oxford)*. 2011;50(9):1684-1689.
27. Ruffatti A, Tonello M, Del Ross T, et al. Antibody profile and clinical course in primary antiphospholipid syndrome with pregnancy morbidity. *Thromb Haemost*. 2006;96(3):337-341.
28. Ruffatti A, Tonello M, Cavazzana A, Bagatella P, Pengo V. Laboratory classification categories and pregnancy outcome in patients with primary antiphospholipid syndrome prescribed antithrombotic therapy. *Thromb Res*. 2009;123(3):482-487.
29. Saccone G, Berghella V, Maruotti GM, et al. Antiphospholipid antibody profile based obstetric outcomes of primary antiphospholipid syndrome: the PREGNANTS study. *Am J Obstet Gynecol*. 2017;216(5): 525.e1-525.e12.
30. Simchen MJ, Dulitzki M, Rofe G, et al. High positive antibody titers and adverse pregnancy outcome in women with antiphospholipid syndrome. *Acta Obstet Gynecol Scand*. 2011;90(12):1428-1433.
31. Ruffatti A, Olivieri S, Tonello M, et al. Influence of different IgG anticardiolipin antibody cut-off values on antiphospholipid syndrome classification. *J Thromb Haemost*. 2008;6(10):1693-1696.
32. Li R, Daguzan M, Vandermijnsbrugge F, Gyling M, Cantinieaux B. Both IgG and IgM anti-beta2 glycoprotein I antibodies assays are clinically useful to the antiphospholipid syndrome diagnosis. *Acta Clin Belg*. 2014; 69(6):433-438.
33. Kutteh WH. Antiphospholipid antibody-associated recurrent pregnancy loss: treatment with heparin and low-dose aspirin is superior to low-dose aspirin alone. *Am J Obstet Gynecol*. 1996;174(5):1584-1589.
34. Farquharson RG, Quenby S, Greaves M. Antiphospholipid syndrome in pregnancy: a randomized, controlled trial of treatment. *Obstet Gynecol*. 2002;100(3):408-413.
35. Rai R, Cohen H, Dave M, Regan L. Randomised controlled trial of aspirin and aspirin plus heparin in pregnant women with recurrent miscarriage associated with phospholipid antibodies (or antiphospholipid antibodies). *BMJ*. 1997;314(7076):253-257.
36. Laskin CA, Spitzer KA, Clark CA, et al. Low molecular weight heparin and aspirin for recurrent pregnancy loss: results from the randomized, controlled HepASA Trial. *J Rheumatol*. 2009;36(2):279-287.
37. Goel N, Tuli A, Choudhry R. The role of aspirin versus aspirin and heparin in cases of recurrent abortions with raised anticardiolipin antibodies. *Med Sci Monit*. 2006;12(3):CR132-CR136.
38. Alalaf S. Bemiparin versus low dose aspirin for management of recurrent early pregnancy losses due to antiphospholipd antibody syndrome. *Arch Gynecol Obstet*. 2012;285(3):641-647.
39. Silver RK, MacGregor SN, Sholl JS, Hobart JM, Neerhof MG, Ragin A. Comparative trial of prednisone plus aspirin versus aspirin alone in the treatment of anticardiolipin antibody-positive obstetric patients. *Am J Obstet Gynecol*. 1993;169(6):1411-1417.
40. Pattison NS, Chamley LW, Birdsall M, Zanderigo AM, Liddell HS, McDougall J. Does aspirin have a role in improving pregnancy outcome for women with the antiphospholipid syndrome? A randomized controlled trial. *Am J Obstet Gynecol*. 2000;183(4):1008-1012.
41. Bramham K, Thomas M, Nelson-Piercy C, Khamashta M, Hunt BJ. First-trimester low-dose prednisolone in refractory antiphospholipid antibody-related pregnancy loss. *Blood*. 2011;117(25):6948-6951.
42. Mekinian A, Lazzaroni MG, Kuzenko A, et al; SNFMI and the European Forum on Antiphospholipid Antibodies. The efficacy of hydroxychloroquine for obstetrical outcome in anti-phospholipid syndrome: data from a European multicenter retrospective study. *Autoimmun Rev*. 2015;14(6):498-502.
43. Sciascia S, Hunt BJ, Talavera-Garcia E, Lliso G, Khamashta MA, Cuadrado MJ. The impact of hydroxychloroquine treatment on pregnancy outcome in women with antiphospholipid antibodies. *Am J Obstet Gynecol*. 2016;214(2):273.e1-273.e8.
44. Ruffatti A, Favaro M, Hoxha A, et al. Apheresis and intravenous immunoglobulins used in addition to conventional therapy to treat high-risk pregnant antiphospholipid antibody syndrome patients. A prospective study. *J Reprod Immunol*. 2016;115:14-19.
45. Frampton G, Cameron JS, Thom M, Jones S, Raftery M. Successful removal of anti-phospholipid antibody during pregnancy using plasma exchange and low-dose prednisolone. *Lancet*. 1987;2(8566):1023-1024.
46. Kobayashi S, Tamura N, Tsuda H, Mokuno C, Hashimoto H, Hirose S. Immunoadsorbent plasmapheresis for a patient with antiphospholipid syndrome during pregnancy. *Ann Rheum Dis*. 1992;51(3):399-401.
47. Nakamura Y, Yoshida K, Itoh S, et al. Immunoadsorption plasmapheresis as a treatment for pregnancy complicated by systemic lupus erythematosus with positive antiphospholipid antibodies. *Am J Reprod Immunol*. 1999; 41(5):307-311.
48. El-Haieg DO, Zanati MF, El-Foual FM. Plasmapheresis and pregnancy outcome in patients with antiphospholipid syndrome. *Int J Gynaecol Obstet*. 2007;99(3):236-241.
49. Ruffatti A, Marson P, Pengo V, et al. Plasma exchange in the management of high risk pregnant patients with primary antiphospholipid syndrome. A report of 9 cases and a review of the literature. *Autoimmun Rev*. 2007;6(3):196-202.
50. Bortolati M, Marson P, Chiarelli S, et al. Case reports of the use of immunoadsorption or plasma exchange in high-risk pregnancies of women with antiphospholipid syndrome. *Ther Apher Dial*. 2009;13(2): 157-160.
51. Mayer-Pickel K, Horn S, Lang U, Cervar-Zivkovic M. Response to plasmapheresis measured by angiogenic factors in a woman with antiphospholipid syndrome in pregnancy. *Case Rep Obstet Gynecol*. 2015; 2015:123408.
52. Ruffatti A, Tonello M, Hoxha A, et al. Effect of additional treatments combined with conventional therapies in pregnant patients with high-risk antiphospholipid syndrome: a multicentre study. *Thromb Haemost*. 2018; 118(4):639-646.
53. Lefkou E, Mamopoulos A, Fragakis N, et al. Clinical improvement and successful pregnancy in a preeclamptic patient with antiphospholipid syndrome treated with pravastatin. *Hypertension*. 2014;63(5): e118-e119.