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Management of Women with Antiphospholipid Antibodies or Antiphospholipid Syndrome during Pregnancy

Eunyoung Emily Lee [1], **Jong Kwan Jun** [2] **and Eun Bong Lee** [1,3]

[1]Division of Rheumatology, Department of Internal Medicine, Seoul National University Hospital, Seoul, Korea
[2]Department of Obstetrics and Gynecology, Seoul National University College of Medicine, Seoul, Korea
[3]Department of Molecular Medicine and Biopharmaceutical Sciences, Graduate School of Convergence Science and Technology, Seoul National University, Seoul, Korea

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Address for Correspondence:
Eun Bong Lee, MD, PhD
Department of Internal Medicine, Seoul National University Hospital, 101 Daehak-ro, Jongno-gu, Seoul 03080, Korea.
E-mail: leb7616@snu.ac.kr

ORCID iDs
Eunyoung Emily Lee
https://orcid.org/0000-0002-1575-9007
Jong Kwan Jun
https://orcid.org/0000-0002-0242-1736
Eun Bong Lee
https://orcid.org/0000-0003-0703-1208

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ABSTRACT

Antiphospholipid syndrome (APS), which is characterized by the presence of antiphospholipid antibodies (aPL), is associated with increased risk of thrombosis and obstetric complications, including preterm delivery and recurrent pregnancy losses. APS shows diverse clinical manifestations and the risk of complications varies among clinical subtypes. Although these patients are usually treated with aspirin and anticoagulants, the optimal treatment in various clinical settings is unclear, as the risk of complications vary among clinical subtypes and the management strategy depends on whether the patient is pregnant or not. Also, there are unmet needs for the evidence-based, pregnancy-related treatment of asymptomatic women positive for aPL. This review focuses on the management of positive aPL or APS in pregnant and postpartum women, and in women attempting to become pregnant. For asymptomatic aPL positive women, no treatment, low dose aspirin (LDA) or LDA plus anticoagulants can be considered during antepartum and postpartum. In obstetric APS patients, preconceptional LDA is recommended. LDA plus low molecular weight heparin is administered after confirmation of pregnancy. Vascular APS patients should take frequent pregnancy test and receive heparin instead of warfarin after confirmation of pregnancy. During pregnancy, heparin plus LDA is recommended. Warfarin can be restarted 4 to 6 hours after vaginal delivery and 6 to 12 hours after cesarean delivery. Most importantly, a tailored approach and patient-oriented treatment are mandatory.

Keywords: Antiphospholipid Antibodies; Antiphospholipid Syndrome; Aspirin; Pregnancy

INTRODUCTION

Antiphospholipid syndrome (APS) is clinically defined by the presence of antiphospholipid antibodies (aPL) coupled with thrombosis and/or pregnancy-related morbidities.[1] Patients with APS have increased risk of thrombosis, preterm delivery, and unexplained fetal loss.[2] In a multicenter prospective study of 1,000 APS patients, the survival probability at 10 years was 90.7%, with the most frequent cause of death being severe thrombosis. Of these women, 15.5% became pregnant, but only 72.9% of pregnancies resulted in live births. The most common obstetric complication in women with APS was early fetal loss.[3] Treatment with oral

anticoagulants is generally recommended for patients who have experienced thrombosis, with low dose aspirin (LDA, 75–100 mg/day), with or without heparin, administered to prevent obstetric complications.

Few randomized controlled studies, however, have been performed in pregnant women with APS, making their management uncertain. In addition, the clinical manifestations of APS can differ, with the risk of complications varying according to clinical subtypes and whether or not a patient is pregnant. For example, a retrospective observational study showing that the incidence of pre-eclampsia was high in women with APS found that the rate of pre-eclampsia was higher in women with a history of thrombotic events than in women with a history of only obstetric complications.[4] Furthermore, some patients are persistently positive for aPL but show no clinical signs of APS.

The classification criteria for APS were originally designed to standardize clinical studies on APS, not as diagnostic criteria for clinical practice. Also, it may be more difficult to diagnose obstetric than vascular APS owing to the diversity of clinical presentations of the former. The pathogenesis of APS involves the development of new autoantibodies and antibody complexes. In addition, because decidual cells and syncytiotrophoblasts express high basal levels of β2 glycoprotein I (β2GPI), even low aPL titers may increase the risk of adverse pregnancy outcomes.[5] Because pregnancy-related morbidity and mortality, including fetal loss, often results in psychological sequelae for the patient and her family members,[6] medical decisions in APS positive women must be made carefully, depending on each patient's individual clinical circumstances. This review focuses on the management of women with aPL or APS who are pregnant or attempting to become pregnant. The recommendations of this review are mainly based on the report of the International Congress on aPL Task Force of the American College of Chest Physicians (ACCP) Evidence-Based Clinical Practice Guidelines and The American College of Obstetricians and Gynecologists practice bulletin.

SEARCH STRATEGY

We used the MEDLINE/PubMed and KoreaMed using the key words “antiphospholipid syndrome” or “antiphospholipid antibodies” and “pregnancy” or “anticoagulation” or “aspirin”; no time limit was imposed. Papers written in languages other than English or Korean, duplicates and irrelevant articles were excluded.

Classification criteria and APS-defining clinical morbidity

The original criteria for classifying APS, the Sapporo criteria, were published in 1999 and later amended in 2006. APS was defined as the presence of at least one clinical criterion and one laboratory criterion met.[7] Clinical criteria include vascular thromboses and pregnancy-associated morbidity. Patients can be stratified into those with vascular or obstetric APS, depending on whether they have vascular thrombosis or APS-defining pregnancy morbidities alone. Although APS is associated with high rates of pregnancy-related morbidity and mortality, not all obstetric complications are caused by APS. The Sydney criteria[7,8] classify APS-defining morbidity into three groups. The first group includes women with one or more unexplained deaths of a morphologically normal fetus (documented by ultrasound or by direct examination) at or beyond the tenth week of gestation. The second group includes women with one or more premature births of a morphologically normal neonate before the 34th week of gestation because of i) eclampsia or severe pre-eclampsia or ii) recognized features of placental

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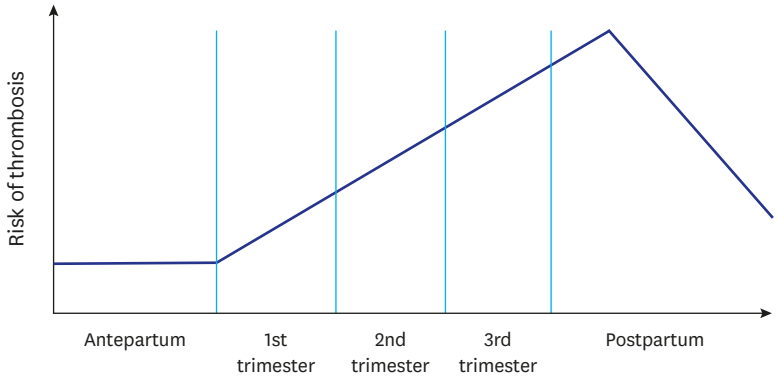

Fig. 1. Risk of venous thromboembolism in pregnant or postpartum women. Postpartum indicates first 6 weeks after delivery.

insufficiency. Generally accepted features of placental insufficiency include abnormal or non-reassuring fetal surveillance tests; abnormal Doppler flow velocimetry waveform analysis suggestive of fetal hypoxemia; oligohydramnios; and a postnatal birth weight below the tenth percentile for gestational age. The third group consists of women who have experienced three or more unexplained consecutive spontaneous abortions before the tenth week of gestation, excluding spontaneous abortions caused by maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes.

Risk factors for thrombosis in pregnant women

The risk of thrombosis increases during pregnancy due to profound hormonal changes and decreased mobility during the period of pregnancy. The risk of thrombosis depends on the stages of pregnancy and delivery methods, being higher during the third than during the first trimester and even higher during the early postpartum period (**Fig. 1**).[9,10] Delivery by cesarean section is associated with a higher risk of thrombosis than vaginal delivery. Other major risk factors include personal history of thrombosis, thrombophilia, systemic lupus erythematosus, APS, heart disease, obesity, diabetes, smoking, sickle cell disease, immobility during the antepartum period, postpartum hemorrhage ≥ 1,000 mL with surgery, pre-eclampsia with fetal growth restriction, blood transfusion, and postpartum infection.[11-13]

Management

aPL-positive women

Primary thrombo-prophylaxis is generally not recommended for patients who are positive for aPL but have no history of thrombosis, as relatively little is known about the risk of the first thromboembolism and the protective effects of LDA or anticoagulants in this population. A review reported that the annual risk of thrombosis in patients with aPL but without lupus was less than 1%.[14] Although one meta-analysis found that LDA had a protective effect in asymptomatic aPL-positive patients, no significant risk reduction was seen when only those studies of good methodological quality were included.[15] A randomized, double-blinded placebo-controlled trial of asymptomatic aPL-positive individuals showed that LDA did not prevent thrombosis[16] and a prospective observational study found that continuous thrombo-prophylaxis with LDA did not reduce the risk of thromboembolism in asymptomatic aPL-positive patients.[17]

In high risk situations, such as during extended immobilization and during post-operation and postpartum periods, thrombo-prophylaxis reduced the risk of thrombosis in aPL

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carriers.[17,18] Thrombo-prophylaxis with LDA has also been recommended for patients with other cardiovascular risk factors, an underlying autoimmune disease such as systemic lupus erythematosus (SLE) with aPL or a high risk aPL profile.[19,20] High risk serological features include positive lupus anticoagulant (LA), triple positivity (LA, anti-cardiolipin [aCL] antibody, anti-β2GPI antibody), and isolated persistently positive aCL antibody at medium to high titers.[21,22] Low molecular weight heparin (LMWH) should be considered for thrombosis prevention in these patients during high risk situations, such as the postpartum period.[21,23]

Antepartum: It is unclear whether pregnant women with aPL but no history of the clinical features of APS are at increased risk for obstetric morbidity or thrombosis during pregnancy. A retrospective study of 139 pregnancies in aPL-positive women not fulfilling the classification criteria for APS found that treatment with LDA did not significantly alter pregnancy outcomes, including the rate of pregnancy loss.[24] Thus, there are no strict treatment guidelines for aPL-positive pregnant women with no clinical history of APS. Treatment options can include no treatment, LDA alone, or LDA and a prophylactic dose of LMWH (**Table 1**).[25] However, aPL is highly predictive of pregnancy loss in animal models[26] and human diseases.[27] Moreover, LDA was found to stimulate leukocyte-derived interleukin-3 production, supporting normal trophoblast growth and hormone expression.[28] Based on these findings, the majority of the Advisory Board of the Tenth aPL Antibodies recommended that pregnant women positive for aPL be treated with LDA,[29] and LDA is generally recommended during pregnancy or at the beginning of attempting pregnancy, especially in women at high risk of pre-eclampsia (**Table 1**).[30] More importantly, decisions should be based on discussions with patients and their gynecologists based on individual risk-benefit determinations.

Postpartum: There is at present no high-quality evidence for postpartum care in aPL-positive patients without a clinical history of APS. Decisions should be based on other thrombogenic risk factors, family history of thrombosis, and route of delivery. Thrombo-prophylaxis is recommended in high risk situations, with the puerperium being an established risk factor for venous thromboembolism (VTE) and the risk being highest during the first 6 weeks postpartum.[31] Also, cesarean section increases the risk of VTE.[32,33] The ACCP Evidence-

Table 1. Summary of recommendations for treatment of aPL-positive women and women with APS

Variables	aPL-positive women	Obstetric APS[c]	Vascular APS[d]
Primary prophylaxis for thrombosis	· Not recommended · LDA for patients with other cardiovascular risk factors, systemic lupus erythematosus, or high-risk aPL profile[a] · LMWH in high-risk situations[b]	· Generally not recommended	· Warfarin to target INR 2.0–3.0 for secondary prophylaxis for thrombosis
Antepartum	· Options include - No treatment, LDA alone and LDA plus LMWH · LDA is generally recommended, especially in patients at high risk of preeclampsia	· Preconceptional LDA · LDA plus a prophylactic dose of LMWH after confirmation of intrauterine pregnancy · LDA alone is acceptable in patients with a history of premature birth due to uteroplacental insufficiency and no history of fetal death	· LDA plus a therapeutic dose of LMWH when pregnancy is confirmed · Frequent pregnancy test and switch to heparin from warfarin
Postpartum	· LDA for 6 weeks after vaginal delivery and a prophylactic dose of LMWH and LDA for 6 weeks after cesarean delivery in selected patients	· LDA and a prophylactic dose of LMWH for 6 weeks · LDA alone for 6 weeks in women with preterm vaginal deliveries due to placental insufficiency	· Restart warfarin 4–6 hr after vaginal delivery and 6–12 hr after cesarean delivery

aPL = anti-phospholipid antibody, APS = anti-phospholipid syndrome, LDA = low dose aspirin, LMWH = low molecular weight heparin, INR = international normalized ratio, aCL = anti-cardiolipin.
[a]Positive lupus anticoagulant (LA), triple positivity (LA, aCL antibody, anti-β2 glycoprotein I antibody), and isolated persistently positive aCL at medium to high titers; [b]Surgery, prolonged immobilization, and puerperium; [c]Anti-phospholipid syndrome with obstetric complications only and without vascular complications; [d]APS with history of thromboembolism.

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Based Clinical Practice Guidelines suggested that women with aPL but no personal or family history of thrombosis would not be at increased risk of VTE after delivery, but suggested postpartum anticoagulation in women with traditional risk factors for thrombosis, a personal history of postpartum VTE, or a family history of thrombosis.[11,34] Also, the Korean Society of Thrombosis and Hemostasis Evidence-Based Clinical Practice Guidelines recommend antepartum plus postpartum prophylaxis for pregnant women with positive aPL.[10] Thus, along with intermittent pneumatic compression while in the hospital followed by compression stockings after release, recommendations in selected high risk patients include LDA for 6 weeks after vaginal delivery and prophylactic dose LMWH and LDA for 6 weeks after cesarean delivery (**Table 1**).[35,36]

Obstetric APS

Thrombo-prophylaxis in obstetric APS patients with no history of thrombotic events is generally not recommended in usual daily life settings, although LDA can be considered in patients with some evidence supporting its benefits in reducing the risk of thrombosis.[37,38] However, patients who are attempting to become pregnant should be managed differently.

Antepartum: Preconception LDA increases the likelihood of pregnancy, embryo implantation, and good fetal outcomes in patients with obstetric APS.[39,40] Thus, pre-pregnancy counseling is critical in obstetric APS patients who may benefit from preconception LDA. The management of women with obstetric APS who are pregnant or attempting to become pregnant is dependent on previous APS-defining obstetric morbidities. In general, patients with recurrent fetal losses require more intensive thrombo-prophylaxis than those with preterm deliveries due to preeclampsia. Patients who experienced early fetal loss, defined as three or more spontaneous abortions earlier than the tenth week of gestation, or late fetal loss, defined as fetal death after the tenth week of gestation, should be administered LDA when attempting pregnancy and a prophylactic dose of LMWH pregnancy is achieved (**Tables 1**, **2** and **Fig. 2**). Women who had premature birth before the 34th week of gestation, due to uteroplacental insufficiency (e.g., eclampsia, pre-eclampsia, or other evidence of placental insufficiency) may benefit from LDA alone.[41] Although some clinicians recommend combinations of LDA and LMWH, a recent randomized controlled trial found that, when compared with LDA alone, the combination of LMWH and LDA did not reduce the rate of recurrent early-onset pre-eclampsia in women with aPL compared with LDA alone.[42]

Table 2. Dosages of anticoagulation regimens[11]

Anticoagulation regimen	Anticoagulation dosage
Prophylactic LMWH	· Enoxaparin, 40 mg SC once daily · Dalteparin, 5,000 units SC once daily · Tinzaparin, 4,500 units SC once daily · Nadroparin, 2,850 units SC once daily
Therapeutic LMWH	· Enoxaparin, 1 mg/kg SC every 12 hr · Daleparin, 200 units/kg SC once daily · Dalteparin, 100 units/kg every 12 hours · Tinzaparin, 175 units/kg once daily (target anti-Xa level in a therapeutic range of 0.6–1.0 units/mL 4 hr after last injection for twice-daily regimen)
Prophylactic UFH	· 5,000–7,000 units SC every 12 hr in the first trimester · 7,500–10,000 units SC every 12 hr in the second trimester · 10,000 units SC every 12 hr in the second trimester unless aPTT is elevated
Therapeutic UFH	· 10,000 units or more SC every 12 hr in doses adjusted to target aPTT in the therapeutic range (1.5–2.5 × controls) 6 hr after injection

LMWH = low molecular weight heparin, SC = subcutaneous, UFH = unfractionated heparin, aPTT = activated partial thromboplastin time.

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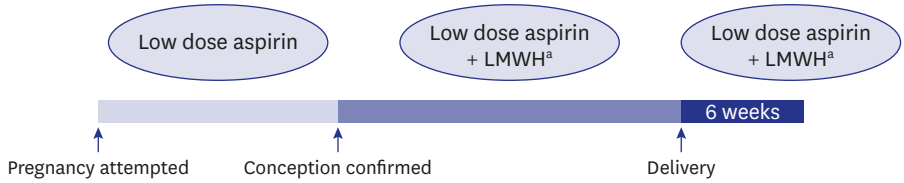

Fig. 2. Management of obstetric antiphospholipid syndrome with recurrent abortion.
LMWH = low molecular weight heparin.
[a]Low molecular weight heparin can be omitted in patients who have only history of placental insufficiency.

Postpartum: Guidelines suggest that patients with a history of three or more consecutive miscarriages before the tenth week of gestation or one or more fetal deaths beyond the tenth week of gestation be treated with LDA and a prophylactic dose of LMWH for 6 weeks after delivery, regardless of the route of delivery. Patients who deliver preterm due to placental insufficiency are recommended to receive LDA for 6 weeks after vaginal delivery and a combination of LDA and a prophylactic dose of LMWH for 6 weeks after cesarean delivery (**Fig. 2**).[35]

Vascular APS

Thrombo-prophylaxis: Non-pregnant APS patients with a history of vascular thrombosis should take lifelong warfarin to target international normalized ratio (INR) 2.0–3.0 for secondary prophylaxis.

Antepartum: During pregnancy, LDA with a therapeutic dose of LMWH or unfractionated heparin is recommended (**Tables 1** and **2**).[34] Because of the teratogenicity of warfarin, the choice of when to substitute warfarin with LMWH is a major clinical issue for women of childbearing age. The 2012 ACCP Evidence-Based Clinical Practice guidelines recommended that these women undergo frequent pregnancy tests and be switched to LMWH as soon as pregnancy is confirmed, rather than switching while preparing for pregnancy (**Fig. 3**).[34]

Postpartum: After delivery, warfarin is recommended indefinitely. To minimize postpartum bleeding, anticoagulation treatment should be started 4–6 hours after vaginal delivery and 6–12 hours after cesarean delivery (**Fig. 3**).[12,43]

Peri-operative management (labor and delivery)

The delivery options in patients receiving anticoagulation include spontaneous labor, induction of labor, and elective cesarean section. The decision should be made in a multidisciplinary team based on obstetric, hematologic, and anesthetic issues.[34] Most guidelines from professional organizations and the United States Food and Drug Administration recommend discontinuing LMWH when spontaneous labor begins or 12–24 hours before scheduled induction of labor, cesarean section, or neuraxial anesthesia (12 hours for prophylactic doses and 24 hours for therapeutic doses).[12,44] In a retrospective study,

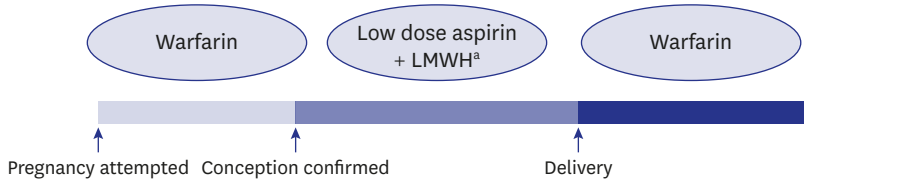

Fig. 3. Management of vascular antiphospholipid syndrome with recurrent abortion.
LMWH = low molecular weight heparin.
[a]Therapeutic dose.

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therapeutic dose of enoxaparin with the last dose 24 hours before the surgery, no patients had thromboembolic complications through 30 days after the procedure.[45] Patients receiving therapeutic doses of LMWH should be switched to unfractionated heparin, which has a shorter half-life, at weeks 36–37 of gestation. However, LMWH can be continued until 38 or 39 weeks in patients regarded as being at very low risk of unpredictable preterm delivery.[46] Women can safely take LDA during the second and third trimesters without adverse effects on fetal hemodynamics or premature closure of the ductus arteriosus.[47,48] LDA can be stopped at any time beyond 36 weeks of gestation in patients with no history of thrombosis.[35] Moreover, stopping LDA 7 days before delivery can minimize the risks of even minor bleeding.[49] Regarding epidural analgesia or neuraxial anesthesia, single agent of LDA can be continued safely according to the 2018 American Society of Regional Anesthesia and Pain Medicine guidelines, but the combination LDA with other anti-platelets of anticoagulants may cause bleeding complications, such as spinal hematoma and caution is warranted.[50]

Management of APS with SLE

APS often presents as secondary APS related to other autoimmune disease, especially SLE.[51] It is reported that up to 40% of SLE patients have aPL[52] and aPL is associated with not only obstetric complications but chronic damage in SLE.[53] Since there are no studies focused on APS patients with SLE, management of APS in SLE should be in line with the treatment of primary APS.[19] All patients with rheumatic and musculoskeletal disease including SLE should be screened for aPL at diagnosis or before or early in pregnancy.[19,54]. In a recent meta-analysis, subgroup analysis of aPL positive patients with the background of SLE revealed a significant protective effect of LDA.[15] However, considering the risk-benefit of LDA, it is unclear whether this should be applied to all aPL positive SLE patients. In current guidelines, SLE patients who are aPL positive, LDA is recommended[54] especially in patients with high-risk aPL profile (persistently positive medium/high titers or multiple positivity) and/or with other atherosclerotic/thrombophilic factors.[19]

Future investigations

There are still many uncertainties in the diagnosis and treatment of APS. For example, the classification and management of patients with extra-criteria clinical manifestations or non-criteria aPL[41] should be considered in future investigations. Also, as there are studies reporting of the lower risk of VTE in Asian patients than in Caucasians,[10,55-57] despite the increasing incidence of APS in Korea,[58] it could be necessary to establish individualized anticoagulation strategies for different ethnic backgrounds.

CONCLUSION

In summary, primary prevention of thrombosis is generally not recommended in asymptomatic aPL-positive women, although anticoagulation should be considered in high-risk conditions. LDA is recommended before conception and during pregnancy to improve pregnancy outcomes. For selected high risk patients, 6 weeks of LDA is recommended for vaginal delivery, and LDA plus a prophylactic dose of LMWH are recommended for cesarean section during the postpartum period. In patients with obstetric APS, LDA is recommend before pregnancy and LDA plus a prophylactic dose of LMWH during pregnancy and for 6 weeks after delivery. In patients with a history of premature birth due to uteroplacental insufficiency but no history of fetal loss, LDA alone is acceptable. Women of childbearing age with vascular APS should be treated with warfarin with frequent pregnancy tests. These

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patients should be switched immediately to LDA and a therapeutic dose of LMWH when pregnancy is confirmed. The treatment of APS in women of childbearing age depends on the types of prior obstetric and/or vascular complications. In addition, traditional risk factors for thrombosis should also be considered before deciding medical treatment. Current review has limitations. First, it did not address extra criteria clinical manifestations in the diagnosis of APS. Second, the study suggested a general approach in all races, despite the varying risk of thrombosis among different races. Lastly, the options of direct-acting oral anticoagulants (DOACs) in the selection of anticoagulants were not addressed. However, there are not enough data to judge the safety of DOACs during pregnancy. Although this review outlines treatment guidelines, a tailored approach and patient-oriented treatment are mandatory.

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REFERENCES

1. Banzato A, Pengo V. Clinical relevance of β_2-glycoprotein-I plasma levels in antiphospholipid syndrome (APS). *Curr Rheumatol Rep* 2014;16(6):424.
PUBMED | CROSSREF
2. Yelnik CM, Lambert M, Drumez E, Le Guern V, Bacri JL, Guerra MM, et al. Bleeding complications and antithrombotic treatment in 264 pregnancies in antiphospholipid syndrome. *Lupus* 2018;27(10):1679-86.
PUBMED | CROSSREF
3. Cervera R, Serrano R, Pons-Estel GJ, Ceberio-Hualde L, Shoenfeld Y, de Ramón E, et al. Morbidity and mortality in the antiphospholipid syndrome during a 10-year period: a multicentre prospective study of 1000 patients. *Ann Rheum Dis* 2015;74(6):1011-8.
PUBMED | CROSSREF
4. Bramham K, Hunt BJ, Germain S, Calatayud I, Khamashta M, Bewley S, et al. Pregnancy outcome in different clinical phenotypes of antiphospholipid syndrome. *Lupus* 2010;19(1):58-64.
PUBMED | CROSSREF
5. Meroni PL, Borghi MO, Grossi C, Chighizola CB, Durigutto P, Tedesco F. Obstetric and vascular antiphospholipid syndrome: same antibodies but different diseases? *Nat Rev Rheumatol* 2018;14(7):433-40.
PUBMED | CROSSREF
6. Arachchillage DR, Machin SJ, Mackie IJ, Cohen H. Diagnosis and management of non-criteria obstetric antiphospholipid syndrome. *Thromb Haemost* 2015;113(1):13-9.
PUBMED | CROSSREF
7. Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, Cervera R, 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.
PUBMED | CROSSREF
8. Atanassova PA. Antiphospholipid syndrome and vascular ischemic (occlusive) diseases: an overview. *Yonsei Med J* 2007;48(6):901-26.
PUBMED | CROSSREF
9. Heit JA, Kobbervig CE, James AH, Petterson TM, Bailey KR, Melton LJ 3rd. Trends in the incidence of venous thromboembolism during pregnancy or postpartum: a 30-year population-based study. *Ann Intern Med* 2005;143(10):697-706.
PUBMED | CROSSREF
10. Bang SM, Jang MJ, Kim KH, Yhim HY, Kim YK, Nam SH, et al. Prevention of venous thromboembolism, 2nd Edition: Korean Society of Thrombosis and Hemostasis evidence-based clinical practice guidelines. *J Korean Med Sci* 2014;29(2):164-71.
PUBMED | CROSSREF
11. Bates SM, Greer IA, Hirsh J, Ginsberg JS. Use of antithrombotic agents during pregnancy: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004;126(3 Suppl):627S-644S.
PUBMED | CROSSREF

12. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics. 196: Thromboembolism in pregnancy. *Obstet Gynecol* 2018;132(1):e1-17.
PUBMED | CROSSREF

13. James AH, Jamison MG, Brancazio LR, Myers ER. Venous thromboembolism during pregnancy and the postpartum period: incidence, risk factors, and mortality. *Am J Obstet Gynecol* 2006;194(5):1311-5.
PUBMED | CROSSREF

14. Barbhaiya M, Erkan D. Primary thrombosis prophylaxis in antiphospholipid antibody-positive patients: where do we stand? *Curr Rheumatol Rep* 2011;13(1):59-69.
PUBMED | CROSSREF

15. Arnaud L, Mathian A, Ruffatti A, Erkan D, Tektonidou M, Cervera R, et al. Efficacy of aspirin for the primary prevention of thrombosis in patients with antiphospholipid antibodies: an international and collaborative meta-analysis. *Autoimmun Rev* 2014;13(3):281-91.
PUBMED | CROSSREF

16. Erkan D, Harrison MJ, Levy R, Peterson M, Petri M, Sammaritano L, et al. Aspirin for primary thrombosis prevention in the antiphospholipid syndrome: a randomized, double-blind, placebo-controlled trial in asymptomatic antiphospholipid antibody-positive individuals. *Arthritis Rheum* 2007;56(7):2382-91.
PUBMED | CROSSREF

17. Ruffatti A, Del Ross T, Ciprian M, Bertero MT, Sciascia S, Scarpato S, et al. Risk factors for a first thrombotic event in antiphospholipid antibody carriers: a prospective multicentre follow-up study. *Ann Rheum Dis* 2011;70(6):1083-6.
PUBMED | CROSSREF

18. Girón-González JA, García del Río E, Rodríguez C, Rodríguez-Martorell J, Serrano A. Antiphospholipid syndrome and asymptomatic carriers of antiphospholipid antibody: prospective analysis of 404 individuals. *J Rheumatol* 2004;31(8):1560-7.
PUBMED

19. Fanouriakis A, Kostopoulou M, Alunno A, Aringer M, Bajema I, Boletis JN, et al. 2019 update of the EULAR recommendations for the management of systemic lupus erythematosus. *Ann Rheum Dis* 2019;78(6):736-45.
PUBMED | CROSSREF

20. Wahl DG, Bounameaux H, de Moerloose P, Sarasin FP. Prophylactic antithrombotic therapy for patients with systemic lupus erythematosus with or without antiphospholipid antibodies: do the benefits outweigh the risks? A decision analysis. *Arch Intern Med* 2000;160(13):2042-8.
PUBMED | CROSSREF

21. Ruiz-Irastorza G, Cuadrado MJ, Ruiz-Arruza I, Brey R, Crowther M, Derksen R, et al. Evidence-based recommendations for the prevention and long-term management of thrombosis in antiphospholipid antibody-positive patients: report of a task force at the 13th International Congress on Antiphospholipid Antibodies. *Lupus* 2011;20(2):206-18.
PUBMED | CROSSREF

22. Choi H, Ahn SS, Song JJ, Park YB, Song J, Lee SW. Anti-phospholipid antibody syndrome occurrence in patients with persistent anti-phospholipid antibodies. *Rheumatol Int* 2019;39(8):1359-67.
PUBMED | CROSSREF

23. Ceccarelli F, Chighizola C, Finazzi G, Meroni PL, Valesini G. Thromboprophylaxis in carriers of antiphospholipid antibodies (APL) without previous thrombosis: "Pros" and "Cons". *Autoimmun Rev* 2012;11(8):568-71.
PUBMED | CROSSREF

24. Del Ross T, Ruffatti A, Visentin MS, Tonello M, Calligaro A, Favaro M, et al. Treatment of 139 pregnancies in antiphospholipid-positive women not fulfilling criteria for antiphospholipid syndrome: a retrospective study. *J Rheumatol* 2013;40(4):425-9.
PUBMED | CROSSREF

25. Derksen RH, Khamashta MA, Branch DW. Management of the obstetric antiphospholipid syndrome. *Arthritis Rheum* 2004;50(4):1028-39.
PUBMED | CROSSREF

26. Blank M, Cohen J, Toder V, Shoenfeld Y. Induction of anti-phospholipid syndrome in naive mice with mouse lupus monoclonal and human polyclonal anti-cardiolipin antibodies. *Proc Natl Acad Sci U S A* 1991;88(8):3069-73.
PUBMED | CROSSREF

27. Lynch A, Marlar R, Murphy J, Davila G, Santos M, Rutledge J, et al. Antiphospholipid antibodies in predicting adverse pregnancy outcome. A prospective study. *Ann Intern Med* 1994;120(6):470-5.
PUBMED | CROSSREF

28. Fishman P, Falach-Vaknin E, Sredni B, Meroni PL, Rudniki C, Shoenfeld Y. Aspirin modulates interleukin-3 production: additional explanation for the preventive effects of aspirin in antiphospholipid antibody syndrome. *J Rheumatol* 1995;22(6):1086-90.
PUBMED

29. Tincani A, Branch W, Levy RA, Piette JC, Carp H, Rai RS, et al. Treatment of pregnant patients with antiphospholipid syndrome. *Lupus* 2003;12(7):524-9.
PUBMED | CROSSREF

30. Gibbins KJ, Ware Branch D. Pre-eclampsia as a manifestation of antiphospholipid syndrome: assessing the current status. *Lupus* 2014;23(12):1229-31.
PUBMED | CROSSREF

31. Kamel H, Navi BB, Sriram N, Hovsepian DA, Devereux RB, Elkind MS. Risk of a thrombotic event after the 6-week postpartum period. *N Engl J Med* 2014;370(14):1307-15.
PUBMED | CROSSREF

32. Sultan AA, Tata LJ, West J, Fiaschi L, Fleming KM, Nelson-Piercy C, et al. Risk factors for first venous thromboembolism around pregnancy: a population-based cohort study from the United Kingdom. *Blood* 2013;121(19):3953-61.
PUBMED | CROSSREF

33. Blondon M, Casini A, Hoppe KK, Boehlen F, Righini M, Smith NL. Risks of venous thromboembolism after cesarean sections: a meta-analysis. *Chest* 2016;150(3):572-96.
PUBMED | CROSSREF

34. Bates SM, Greer IA, Middeldorp S, Veenstra DL, Prabulos AM, Vandvik PO. VTE, thrombophilia, antithrombotic therapy, and pregnancy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2012;141(2 Suppl):e691S-e736S.
PUBMED | CROSSREF

35. Lockwood CJ, Lockshin MD. Antiphospholipid syndrome: Pregnancy implications and management in pregnant women. https://www.uptodate.com/contents/antiphospholipid-syndrome-pregnancy-implications-and-management-in-pregnant-women. Updated 2020. Accessed December 15, 2018.

36. Berghella V. Cesarean delivery: preoperative planning and patient preparation. https://www.uptodate.com/contents/cesarean-delivery-preoperative-planning-and-patient-preparation. Updated 2020. Accessed March 25, 2019.

37. Danowski A, Rego J, Kakehasi AM, Funke A, Carvalho JF, Lima IV, et al. Guidelines for the treatment of antiphospholipid syndrome. *Rev Bras Reumatol* 2013;53(2):184-92.
PUBMED | CROSSREF

38. Erkan D, Merrill JT, Yazici Y, Sammaritano L, Buyon JP, Lockshin MD. High thrombosis rate after fetal loss in antiphospholipid syndrome: effective prophylaxis with aspirin. *Arthritis Rheum* 2001;44(6):1466-7.
PUBMED

39. Schreiber K, Sciascia S, de Groot PG, Devreese K, Jacobsen S, Ruiz-Irastorza G, et al. Antiphospholipid syndrome. *Nat Rev Dis Primers* 2018;4(1):17103.
PUBMED | CROSSREF

40. Espinosa G, Cervera R. Current treatment of antiphospholipid syndrome: lights and shadows. *Nat Rev Rheumatol* 2015;11(10):586-96.
PUBMED | CROSSREF

41. Uthman I, Noureldine MHA, Ruiz-Irastorza G, Khamashta M. Management of antiphospholipid syndrome. *Ann Rheum Dis* 2019;78(2):155-61.
PUBMED | CROSSREF

42. van Hoorn ME, Hague WM, van Pampus MG, Bezemer D, de Vries JIFRUIT Investigators. Low-molecular-weight heparin and aspirin in the prevention of recurrent early-onset pre-eclampsia in women with antiphospholipid antibodies: the FRUIT-RCT. *Eur J Obstet Gynecol Reprod Biol* 2016;197:168-73.
PUBMED | CROSSREF

43. Arya R. How I manage venous thromboembolism in pregnancy. *Br J Haematol* 2011;153(6):698-708.
PUBMED | CROSSREF

44. US Food and Drug Administration. FDA drug safety communication: updated recommendations to decrease risk of spinal column bleeding and paralysis in patients on low molecular weight heparins. https://www.fda.gov/media/87316/download. Updated 2013. Accessed March 25, 2019.

45. Hwang HG, Koo SM, Uh ST, Kim YK. The perioperative management of antithrombotic therapies using enoxaparin. *J Korean Med Sci* 2017;32(6):942-7.
PUBMED | CROSSREF

46. Bauer KA. Use of anticoagulants during pregnancy and postpartum. https://www.uptodate.com/contents/use-of-anticoagulants-during-pregnancy-and-postpartum?search=use-of-anticoagulants-during-pregnancy-and-&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1. Updated 2020. Accessed May 4, 2020.

47. Grab D, Paulus WE, Erdmann M, Terinde R, Oberhoffer R, Lang D, et al. Effects of low-dose aspirin on uterine and fetal blood flow during pregnancy: results of a randomized, placebo-controlled, double-blind trial. *Ultrasound Obstet Gynecol* 2000;15(1):19-27.
PUBMED | CROSSREF

48. Miyazaki M, Kuwabara Y, Takeshita T. Influence of perinatal low-dose acetylsalicylic acid therapy on fetal hemodynamics evaluated by determining the acceleration-time/ejection-time ratio in the ductus arteriosus. *J Obstet Gynaecol Res* 2018;44(1):87-92.
PUBMED | CROSSREF

49. Hirsh J, Guyatt G, Albers GW, Harrington R, Schunemann HJ. Executive summary: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008;133(6 Suppl):71S-109S.
PUBMED | CROSSREF

50. Horlocker TT, Vandermeuelen E, Kopp SL, Gogarten W, Leffert LR, Benzon HT. Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy: American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines (Fourth Edition). *Reg Anesth Pain Med* 2018;43(3):263-309.
PUBMED | CROSSREF

51. Nam SW, Cho SK, Kim D, Lee KE, Park DJ, Lee SS, et al. Antiphospholipid antibody positivity and the clinical outcomes of patients with systemic lupus erythematosus. *J Rheum Dis* 2018;25(4):239-47.
CROSSREF

52. Mok CC, Tang SS, To CH, Petri M. Incidence and risk factors of thromboembolism in systemic lupus erythematosus: a comparison of three ethnic groups. *Arthritis Rheum* 2005;52(9):2774-82.
PUBMED | CROSSREF

53. Taraborelli M, Leuenberger L, Lazzaroni MG, Martinazzi N, Zhang W, Franceschini F, et al. The contribution of antiphospholipid antibodies to organ damage in systemic lupus erythematosus. *Lupus* 2016;25(12):1365-8.
PUBMED | CROSSREF

54. Sammaritano LR, Bermas BL, Chakravarty EE, Chambers C, Clowse ME, Lockshin MD, et al. 2020 American College of Rheumatology Guideline for the management of reproductive health in rheumatic and musculoskeletal diseases. *Arthritis Rheumatol* 2020;72(4):529-56.
PUBMED | CROSSREF

55. Nicole Tran H, Klatsky AL. Lower risk of venous thromboembolism in multiple Asian ethnic groups. *Prev Med Rep* 2019;13:268-9.
PUBMED | CROSSREF

56. Jang MJ, Bang SM, Oh D. Incidence of venous thromboembolism in Korea: from the Health Insurance Review and Assessment Service database. *J Thromb Haemost* 2011;9(1):85-91.
PUBMED | CROSSREF

57. Lee CH, Lin LJ, Cheng CL, Kao Yang YH, Chen JY, Tsai LM. Incidence and cumulative recurrence rates of venous thromboembolism in the Taiwanese population. *J Thromb Haemost* 2010;8(7):1515-23.
PUBMED | CROSSREF

58. Hwang JJ, Shin SH, Kim YJ, Oh YM, Lee SD, Kim YH, et al. Epidemiology of antiphospholipid syndrome in Korea: a nationwide population-based study. *J Korean Med Sci* 2020;35(5):e35.
PUBMED | CROSSREF