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Review on antiphospholipid syndrome using low molecular weight heparin

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ABSTRACT

Antiphospholipid syndrome is an immunological condition that causes a recurrent venous or arterial thrombosis as well as foetal loss. APS is defined by persistently elevated levels of antibodies directed against membrane anionic phospholipids or their associated plasma proteins, primarily beta-2 glycoprotein I, or an evidence of a circulating anticoagulant. Women are five times more likely than men to be affected by APS. It's also linked to pregnancy difficulties because it typically affects women in their 30s. Women with APS may have difficulty conceiving and blood clots in the placenta can lead to miscarriage, early birth, and development problems in newborns. Warfarin crosses the placenta and affects foetal coagulation, which increases the risk of bleeding complications in the foetus and during birth. Heparin is a mucopolysaccharide with a molecular weight ranging from 6,000 to 20,000 Daltons that is composed of numerous repeating units of glucuronic acid and sulphated glucosamine. Low molecular weight heparin is injected subcutaneously or intravenously and it works by activating antithrombin III, which then inactivates thrombin and factor Xa to generate its action. So treatment with anticoagulant drugs such as low molecular heparin is administered in combination with low dose aspirin which helps to prevent blood clots and miscarriages.

Keywords: Antiphospholipid, low molecular weight heparin, miscarriage.

INTRODUCTION

In the presence of antiphospholipid antibodies, antiphospholipid syndrome (APS) is an autoimmune thrombophilic illness characterized by recurrent venous, arterial, or small vessel thrombosis and pregnancy morbidity. APS can develop in conjunction with other autoimmune conditions, known as secondary APS, or it can occur without any underlying illness[1]. Recurrent thrombosis and pregnancy problems, as well as thrombocytopenia and hemolytic anemia, are all clinical symptoms[2].

ETIOLOGY

APS, like other autoimmune illnesses, has an unknown cause. There are several potential causes, including[3]

• Autoimmune disease in the foetus and infant is mediated by passive transmission of maternal antibodies.
• There has been a report of PL incidence in families, with possible genetic links[4].
• PL molecules can be found in nature, as well as on the inside of cells and in microbes. Antibodies to PLs are released and stimulated by PLs[5].

CLASSIFICATION FOR APS

Based on criteria of APS

1. Vascular thrombosis criteria
   a. Arterial thrombosis
   b. Venous thrombosis
   c. Small vessel thrombosis

2. Pregnancy criteria
   a. Three or more unexplained consecutive spontaneous abortions before week 10 of gestation.
   b. One or more unexplained death of a morphologically normal foetus at or beyond week 10 of gestation.
   c. One or more premature births of a morphologically normal foetus before week 34 of gestation because of preeclampsia, eclampsia or placental insufficiency.

3. Serological criteria
   a. Elevated IgG anticardiolipin antibody (>40 GPLU or 99th percentile of healthy controls).
   b. Elevated IgM anticardiolipin antibody (>40 MPLU or 99th percentile of healthy controls).
   c. Elevated IgG anti- β2GPI antibody (99th percentile of healthy controls).
   d. Elevated IgM anti – β2GPI antibody (99th percentile of healthy controls).
   e. Positive lupus anticoagulant assay[6].

If a patient fits at least one of the serological req uirements, as well as at least one vascular thrombosis criterion and/or one pregnancy criterion, APS can be d iagnosed [7].
NOTE: β2GPI- Beta-2 glycoprotein I.

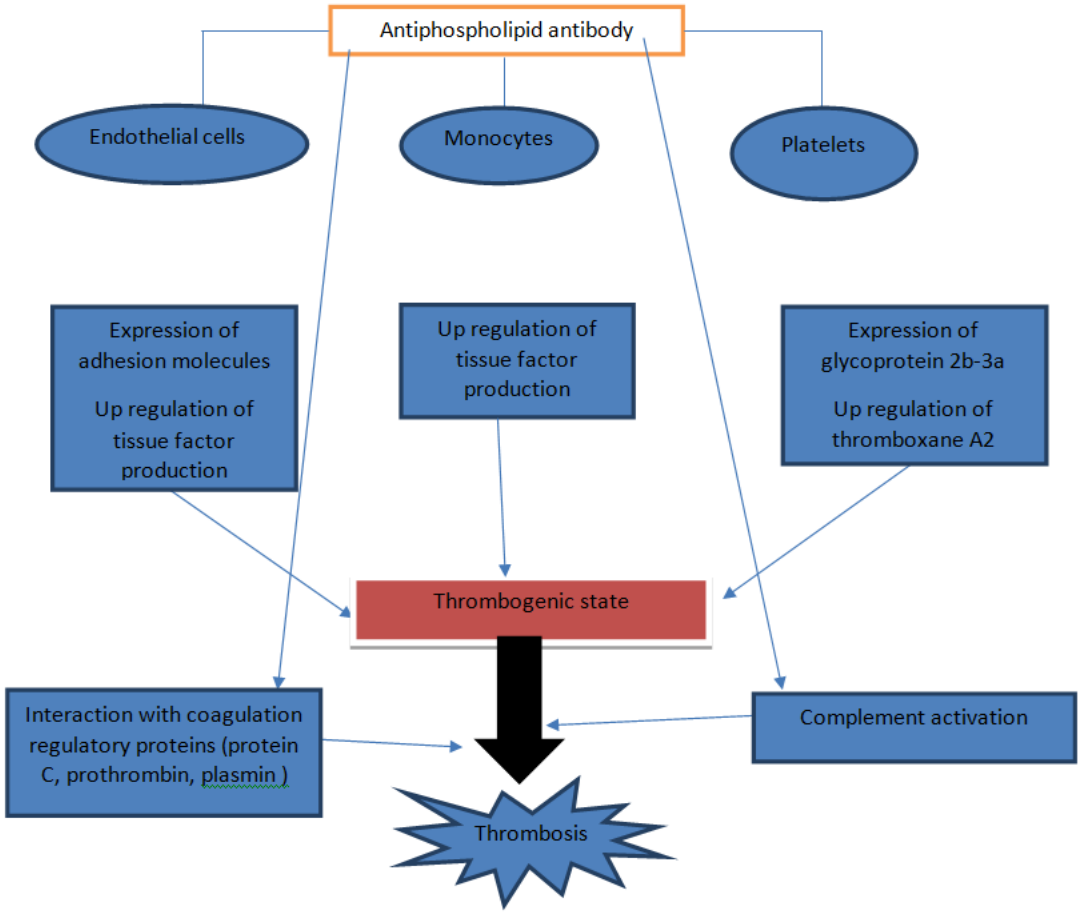
Endothelial cells, monocytes, platelets, and complement have a key role in the production of thrombosis and foetal death in antiphospholipid syndrome, according to research[8]. Platelets that have been activated boost the expression of glycoprotein 2b-3a and the production of thromboxane A2[9].

Although inflammation plays no role in the etiology of antiphospholipid syndrome, findings from mouse research reveal that complement activation plays a critical role in thrombosis[10] and foetal loss caused by antiphospholipid syndrome[11].

FOETAL LOSS

For a long time, it was considered that miscarriage in APS was caused primarily by a reduction in foetal blood supply due by placental thrombosis and infarction. In cases of fortal loss owing to APS, placental infarcts have been observed[12]. Spiral arteries of the placenta are known to grow abnormally in APS[13]. It's possible that this has something to do with endothelial function. Antiphospholipid antibodies bind to placental antigens selectively[14], suggesting a possible mechanism for thrombotic placental injury and reduced foetal blood flow. aPL and antibodies to 2GPI have also been discovered to affect trophoblast proliferation and differentiation[15].Through exposed anionic phospholipid and adherent 2GPI, aPL may bind directly to trophoblast cell membranes. This could lead to a change in gonadotropin secretion[16]. The ability of aPL to fix complement has been linked to the loss of a foetus (and indeed thrombosis) [17].

PATHOGENESIS OF APS [18]



TREATMENT

APS treatment includes aspirin or aspirin with prednisone, unfractioned heparin or low molecular weight heparin (LMWH), intravenous immunoglobin infusion or plasma exchange. Warfarin crosses the placenta and is teratogenicity in the 1st trimester. Women who are in long term Warfarin treatment must switch to Heparin treatment when trying to conceive or when getting pregnant.

As Warfarin crosses the placenta and affects the foetal coagulation, may risk for bleeding complications in the foetus and during birth. A review reported that the combination therapy with heparin and aspirin may reduce pregnancy loss in women with APA by 54%.

Prolonged heparin therapy treatment may induce osteoporosis. So LMWH is used because of the advantage of daily dosing and it may reduce the risk of osteoporosis.

USES OF ANTICOAGULANT IN LACTATING WOMEN

Heparin and LMWHs are not secreted into breast milk and can be safely given to nursing mothers. Warfarin is safe after delivery and for breast feeding, although it requires close monitoring, frequent visits to an anticoagulant clinic and carries an increased risk of postpartum hemorrhage and perineal hematoma compared with LMWH. In a breast-fed infant, warfarin has no anticoagulant effect. Therefore, the use of warfarin in women who require postpartum anticoagulation therapy is safe and these women should be encouraged to breast feed[19].

CASE REPORT OF APS IN PREGNANT WOMEN

A 30-year-old housewife who had four failed pregnancies in the past. The aberrant platelet count, abnormal hemoglobin count, and RBC were found in the lab and it suggests the microcytic hypochromic anemia. It represents typical bleeding, clotting and prothrombin times. Human immunodeficiency virus (HIV) tests were negative, as similar to hepatitis-B surface antigen (HBsAg) and anti-hepatitis-C (HCV) antibodies. In light of her recurrent pregnancy losses, she was tested for antiphospholipid antibody (APLA) syndrome, and IgM anti-cardiolipin antibody was confirmed to be positive. An abdominal ultrasonography (USG) revealed a single 12-week-old viable foetus.

She was given platelet concentrates since she had acute thrombocytopenia. Prednisone and immunosuppression were also administered to her in effort to boost her platelet count. The platelet count increased in three days and then returned to normal after around two months. After 12 weeks, the IgM anti cardiolipin antibody was tested again and found to be positive.

The patient was subsequently started on a once-daily dose of Ecosprin 75mg and twice-daily doses of unfractioned heparin 5000Us/c. She gave birth to a healthy kid by vaginal delivery at the 37th week of pregnancy. Ecosprin is utilized as an antiplatelet agent, while LMWH is used as an anticoagulant[20].

LOW MOLECULAR WEIGHT HEPARIN

Heparin is a mammalian anionic polysaccharide with an irregular sequence. It's mostly made up of alternating iduronate and glucosamine residues, with the majority of them being sulfated. It's a glucosaminoglycan that's been sulfated. Heparin has the unique ability to prevent freshly spilt blood from clotting. It can be made from oxen's lungs or the mucosa of oxen, pigs, or sheep's intestines. To distinguish it from low-molecular-weight heparins, heparin is frequently referred to as standard heparin or unfractionated heparin in the literature. Heparin is a mucopolysaccharide made up of numerous repeating units of glucuronic acid and sulphated glucosamine with a molecular weight varying from 6,000 to 20,000 daltons[21].

When a quick anticoagulant effect is required, heparin and its derivative, low-molecular-weight heparin (LMWH), are the anticoagulants of choice since their beginning of action is immediate when provided by IV injection. For primary prophylaxis, both forms of heparins are used in lower doses than for the treatment of venous thrombosis or acute myocardial ischemia[22].

MECHANISM OF ACTION OF HEPARIN

Only roughly a third of a heparin dose binds to AT, yet this fraction is responsible for the majority of the anticoagulant effect[23, 24].

The remaining two-thirds has minimal anticoagulant activity at therapeutic doses, but both high-affinity and low-affinity heparin catalyze the AT effect of a second plasma protein, heparin cofactor II, at concentrations greater than usually attained clinically[25].

A number of coagulation enzymes, including thrombin factor (IIa), factors Xa, IXa, XIa, and XIIa, are inactivated by the heparin-AT complex. The most sensitive to inhibition are thrombin and factor Xa, with human thrombin being roughly 10-fold more sensitive to inhibition by the heparin-AT complex than factor Xa. Heparin must bind to both the coagulation enzyme and AT to inhibit thrombin, although binding to the enzyme is less important for inhibiting activated factor X[26].

Heparin molecules with fewer than 18 saccharides do not bind to thrombin and AT at the same time and hence cannot catalyse thrombin inhibition. Small heparin fragments with the high-affinity pentasaccharide motif, on the other hand, catalyse AT inhibition of factor Xa[27, 28].

Heparin reduces fibrin production as well as thrombin-induced activation of factor V and factor VIII by inactivating thrombin[29].

Unfractionated heparin (UFH) and LMWH can cause vascular endothelial cells to secrete tissue factor pathway inhibitor, which reduces tissue factor22222 VIIa complex procoagulant activity, possibly contributing to heparin and LMWH's antithrombotic effects[30, 31].

CASE REPORT OF HEPARIN

Pregnancy success in a 42-year-old woman with a history of unexplained recurrent miscarriages,

including a sub-septate uterus with free leakage bilaterally, which was rectified by hysteroscopy in October 2009, followed by transcervical septal resection (TCRS) clomiphene citrate administration. From the time she was diagnosed with pregnancy at 5 weeks until her delivery, she was treated with folic acid supplementation, aspirin 75 mg, micronized progesterone 400 mg/d, and low molecular heparin 2500 IU/d.

At 28 weeks, however, a glucose tolerance test with 100g glucose indicated moderate deviations in the first (159mg/dL) and second (164mg/dL) hour results; metformin was prescribed for sugar control. Throughout the prenatal time, the patient received heparin injections on a regular basis.

During pregnancy or delivery, there were no big bleeding episodes. At the conclusion of the treatment, a male kid weighing 3.2 kg was born with a good APGAR score[32].

CONCLUSION

Aspirin combined with LMWH for APS may improve live birth rate and APS pregnant women may predict pregnancy complications and guide the use of anticoagulants. LMWH have been shown to be a safe and effective therapy in conditions to APS, such as hereditary thrombophilia. In patients with recurrent spontaneous abortion who test positive for aPL, the combination of LMWH and aspirin has become standard practice.

REFERENCES

1. Hughes GR, Asherson RA, Khamashta MA. Antiphospholipid syndrome: linking many specialties. Ann Rheum Dis. 1989;48(5):355-6. doi: 10.1136/ard.48.5.355, PMID 2658874.
2. Cervera R, Piette JC, Font J, Khamashta MA, Shoenfeld Y, Camps MT, Jacobsen S, Lakos G, Tincani A, Kontopoulou-Griva I, Galeazzi M, Meroni PL, Derksen RH, de Groot PG, Gromnica-Ihle E, Baleva M, Mosca M, Bombardieri S, Houssiau F, Gris JC, Quéré I, Hachulla E, Vasconcelos C, Roch B, Fernández-Nebro A, Boffa MC, Hughes GR, Ingelmo M, 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):1019-27. doi: 10.1002/art.10187, PMID 11953980.
3. Berg TG. Antiphospholipid antibody syndrome and pregnancy. eMedicine; January 2009.
4. Domenico Sebastiani G, Minisola G, Galeazzi M. HLA class II alleles and genetic predisposition to the antiphospholipid syndrome. Autoimmun Rev. 2003;2(6):387-94. doi: 10.1016/s1568-9972(03)00068-5, PMID 14550881.
5. Triplett DA. Antiphospholipid antibodies. Arch Pathol Lab Med. 2002;126(11):1424-9. doi: 10.5858/2002-126-1424-AA, PMID 12421152.
6. Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, Cervera R, Derksen RH, DE Groot PG, Koike T, Meroni PL, Reber G, Shoenfeld Y, Tincani A, Vlachoyiannopoulos PG, Krilis SA. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost. 2006;4(2):295-306. doi: 10.1111/j.1538-7836.2006.01753.x, PMID 16420554.
7. Rahman A. Antiphospholipid syndrome in pregnancy. Indian J Rheumatol. 2016;11(6):S117-21. doi: 10.4103/0973-3698.194543.
8. Pierangeli SS, Chen PP, Raschi E, Scurati S, Grossi C, Borghi MO, Palomo I, Harris EN, Meroni PL. Antiphospholipid antibodies and the antiphospholipid syndrome: pathogenic mechanisms. Semin Thromb Hemost. 2008;34(3):236-50. doi: 10.1055/s-0028-1082267, PMID 18720303.
9. López-Pedrera C, Cuadrado MJ, Herández V, Buendïa P, Aguirre MA, Barbarroja N, Torres LA, Villalba JM, Velasco F, Khamashta M. Proteomic analysis in monocytes of antiphospholipid syndrome patients: deregulation of proteins related to the development of thrombosis. Arthritis Rheum. 2008;58(9):2835-44. doi: 10.1002/art.23756, PMID 18759277.
10. Pierangeli SS, Girardi G, Vega-Ostertag M, Liu X, Espinola RG, Salmon J. Requirement of activation of complement C3 and C5 for antiphospholipid antibody mediated thrombophilia. Arthritis Rheum. 2005;52(7):2120-24. doi: 10.1002/art.21157, PMID 15986360.
11. Girardi G, Redecha P, Salmon JE. Heparin prevents antiphospholipid antibody-induced fetal loss by inhibiting complement activation. Nat Med. 2004;10(11):1222-26. doi: 10.1038/nm1121, PMID 15489858.
12. Mackworth-Young CG, Loizou S, Walport MJ. Antiphospholipid antibodies and disease. Q J Med. 1989;72(269):767-77. PMID 2694208.

13. Parke AL. Placental pathology in antiphospholipid antibody syndrome. In: Khamashta MA, editor Hughes syndrome, antiphospholipid syndrome. London: Springer Verlag; 2000. p. 281-9.
14. Donohoe S, Kingdom JCP, Mackie IJ. Affinity purified human antiphospholipid antibodies bind normal term placenta. Lupus. 1999;8(7):525-31. doi: 10.1191/096120399678840756, PMID 10483030.
15. Chamley LW, Duncalf AM, Mitchell MD, Johnson PM. Action of anticardiolipin and antibodies to beta 2 glycoprotein I on trophoblast proliferation as a mechanism for fetal death. Lancet. 1998;352(9133):1037-8. doi: 10.1016/s0140-6736(05)60080-3, PMID 9759755.
16. Di Simone N, Meroni PL, de Papa N, Raschi E, Caliandro D, De Carolis CS, Khamashta MA, Atsumi T, Hughes GR, Balestrieri G, Tincani A, Casali P, Caruso A. Antiphospholipid antibodies affect trophoblast gonadotrophin secretion and invasiveness by binding directly and through adhered beta 2 glycoprotein I. Arthritis Rheum. 2000;43(1):140-50. doi: 10.1002/1529-0131(200001)43:1<140::AID-ANR18>3.0.CO;2-P, PMID 10643710.
17. Munakata Y, Saito T, Matsuda K, Seino J, Shibata S, Sasaki T. Detection of complement-fixing antiphospholipid antibodies in association with thrombosis. Thromb Haemost. 2000;83(5):728-31. doi: 10.1055/s-0037-1613900, PMID 10823270.
18. Mehdi AA, Uthman I, Khamashta M. Antiphospholipid syndrome: pathogenesis and a window of treatment opportunities in the future. Eur J Clin Investig. 2010;40(5):451-64. doi: 10.1111/j.1365-2362.2010.02281.x, PMID 20345380.
19. Haram K, Jacobsen E-M, Sandset PM. Antiphospholipid syndrome in pregnancy. Antiphospholipid Syndr. 2012;161.
20. Mahajan K, Katyal V, Arya S, Shrama M. Antiphospholipid syndrome in a pregnant female presenting with severe thrombocytopenia and bleeding. Case Rep Med. 2015;2015:234878. doi: 10.1155/2015/234878, PMID 25722728.
21. Ray A. Heparin: powerful and instantaneously acting anticoagulant. Pharmacia*Tutor* 2.11. 2014:30-4.
22. Rosenberg RD, Lam L. Correlation between structure and function of heparin. Proc Natl Acad Sci U S A. 1979;76(3):1218-22. doi: 10.1073/pnas.76.3.1218, PMID 286307.
23. Lam LH, Silbert JE, Rosenberg RD. The separation of active and inactive forms of heparin. Biochem Biophys Res Commun. 1976;69(2):570-7. doi: 10.1016/0006-291x(76)90558-1, PMID 1267803.
24. Andersson LO, Barrowcliffe TW, Holmer E, Johnson EA, Sims GE. Anticoagulant properties of heparin fractionated by affinity chromatography on matrix-bound antithrombin III and by gel filtration. Thromb Res. 1976;9(6):575-83. doi: 10.1016/0049-3848(76)90105-5, PMID 1006626.
25. Tollefsen DM, Majerus DW, Blank MK. Heparin cofactor II: purification and properties of a heparin-dependent inhibitor of thrombin in human plasma. J Biol Chem. 1982;257(5):2162-9. doi: 10.1016/S0021-9258(18)34900-7, PMID 6895893.
26. Casu B, Oreste P, Torri G, Zoppetti G, Choay J, Lormeau JC, Petitou M, Sinäy P. The structure of heparin oligosaccharide fragments with high anti-(factor Xa) activity containing the minimal antithrombin III-binding sequence. Chemical and 13C nuclear-magnetic-resonance studies. Biochem J. 1981;197(3):599-609. doi: 10.1042/bj1970599, PMID 7325974.
27. Lindahl U, Thunberg L, Bäckström G, Riesenfeld J, Nordling K, Björk I. Extension and structural variability of the antithrombin-binding sequence in heparin. J Biol Chem. 1984;259(20):12368-76. doi: 10.1016/S0021-9258(18)90755-6, PMID 6490618.
28. Nesheim ME. A simple rate law that describes the kinetics of the heparin-catalyzed reaction between antithrombin III and thrombin. J Biol Chem. 1983;258(23):14708-17. doi: 10.1016/S0021-9258(17)43920-2, PMID 6643505.
29. Ofosu FA, Hirsh J, Esmon CT, Modi GJ, Smith LM, Anvari N, Buchanan MR, Fenton JW, Blajchman MA. Unfractionated heparin inhibits thrombin-catalyzed amplification reactions of coagulation more efficiently than those catalyzed by factor Xa. Biochem J. 1989;257(1):143-50. doi: 10.1042/bj2570143, PMID 2920007.
30. Altman R, Scazziota A, Rouvier J. Efficacy of unfractionated heparin, low molecular weight heparin, and both combined for releasing total and free tissue factor pathway inhibitor. Haemostasis. 1998;28(5):229-35. doi: 10.1159/000022436, PMID 10420071.
31. Gori AM, Pepe G, Attanasio M, Falciani M, Abbate R, Prisco D, Fedi S, Giusti B, Brunelli T, Giusti B, Brunelli T, Comeglio P, Gensini GF, Neri Serneri GG. Tissue factor reduction and tissue factor pathway inhibitor release after heparin administration. Thromb Haemost. 1999;81(4):589-93. doi: 10.1055/s-0037-1614530, PMID 10235445.
32. Panda B, Das S, Mohapatra L, Sahu MC, Padhy RN. Successful outcome from empirical use of heparin and aspirin in unexplained pregnancy loss. Asian Pac J Reprod. 2012;1(4):323-5. doi: 10.1016/S2305-0500(13)60103-7.