Science Letters ISSN 2345-5463 – An International Triannually Journal

Review Article
August 2017 | Volume 5 | Issue 2 |Pages 146-155

ARTICLE INFO

Received
March 06, 2017
Accepted
April 16, 2017
Published
August 15, 2017

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Keywords
Antiphospholipid syndrome
Antiphospholipid antibodies
Autoantibodies
Pregnancy
Autoimmune disease

How to Cite
Lamichhane RKC, Sun LZ, Yousef NR. A brief insight into antiphospholipid syndrome during pregnancy. Sci Lett 2017; 5(2):146-155.

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A Brief Insight into Antiphospholipid Syndrome during Pregnancy

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Abstract

The occurrence of antiphospholipid syndrome (APS) during pregnancy has come to marked attention in the recent years. The APS is primarily a multisystem disorder which also imposes a serious impact on pregnancy. Its association with pregnancy outcome varies from normal delivery to a wide range of complications. APS is an autoimmune disease wherein autoantibodies are produced against the phospholipids of the cell membrane. It causes thrombosis in the arteries and veins to result in pregnancy-associated complications like pre-eclampsia, miscarriage, stillbirth, pregnancy induced hypertension, recurrent thrombotic event, fetal retardation, and sterility. Besides these, gravid women are also at the risk of complications like haemolysis elevated liver enzyme and low platelet (HELLP) syndrome. Diagnosis of APS is difficult due to its various clinical manifestations but detection of an antibody such as antiphospholipid antibody (APLA) in blood is helpful in its diagnosis. APS has different presentation and outcomes among pregnant women. Many cases of fetal loss are in early period. Although, many complications can occur due to APS, but there are only a few numbers of pregnancies that end in a fetal loss. Nevertheless, if detection of APLA is done earlier in pregnancy then with the proper treatment, the successful outcome of the pregnancy can be achieved. This review briefly focuses on APS during pregnancy from its pathogenesis, diagnosis, associated antibodies treatment and recent advances made for better understanding of the disease.

Introduction

Antiphospholipid syndrome (APS) has the ability to form antiphospholipid antibodies (APLA), which are often found during the disease and have clinical manifestations, like pregnancy associated morbidity. The pregnancy associated morbidity might be recurrent early loss of pregnancy, stillbirth, and pre-term birth due to placental insufficiency and/or thrombosis. It is also termed as Hughes syndrome in some countries like United Kingdom [1]. The antibodies which are accountable for this syndrome are lupus anticoagulant (LA), anti-β2-glycoprotein 1 antibodies (anti-β2-GP1 Abs) and anti-cardiolipin antibodies (aCL). These autoantibodies are found prevalent in around 5% of the normal population [2, 3], and there are up to around 40% of women who suffer from recurrent miscarriage or still-birth [4-8]. The prevalence of APLA, even in low risk obstetrical population, ranges from 1-9% [5, 8, 9-11]. These outcomes have been attributed to placental thrombosis and /or infarcts. However, in around 50% of cases decidual or placental thrombosis cannot be confirmed [12, 13].

The disease pathophysiology is mainly due to the action of numerous autoantibodies on their various antigenic targets that are found in APS patients [14]. Despite the inscrutable cause of origin, these autoantibodies are thought to be caused by several environmental factors in the individuals that interact with genetic markers, rendering them susceptible to the disease [15, 16]. Though, the exact pathogenesis of the disease is unclear, many researchers have focused on interactions between antiphospholipid antibodies and target cells like endothelial cells, lymphocyte and trophoblast cells which cause enhanced platelet aggregation, release of inflammatory cytokines, coagulation abnormalities and trophoblast cell damage [17]. The antibodies of APS bind to the receptor of target cells, resulting in its activation and thrombosis of large vessels [18]. There are few other mechanisms which have been considered to play a pivotal role in APS such as inhibition of protein C and S, shield on cell surface of annexin A5 disruption [19] leading to hypercoagulable state, complement activation, neutrophils generating DNA nets [20, 21] and activation of monocyte protease receptor [22]. The probable cause of fetal loss can be due to inflammatory process through the activation of complement pathway [23-26], over-expression of tissue factor in monocytes and neutrophils [26], or via angiogenic factors negative imbalance [27]; even though thrombosis would not be present. The study on placental anatomy of miscarriage patients with APS done by Wang et al. [28] found diffuse thrombosis in uterine spiral artery and other small vessels. This review was an attempt to explore the diagnostic criteria, antibodies, thrombotic events, common outcomes and recent advances of antiphospholipid syndrome.

Diagnostic criteria of antiphospholipid syndrome

According to revised Sapporo criteria done in 2006 [1], the diagnosis of APS should be considered positive if at least one of the clinical criteria and one of the laboratory criteria are met (Table 1)

Clinical criteria

Clinical criteria comprises of the presence of vascular thrombosis (arterial, venous, small vessel) without inflammation of vessel wall in histopathology. A second criterion is pregnancy morbidity inclusive of one of the following: (1) ≥1 unexplained loss of morphologically normal fetus at or ≥10 weeks gestation, which is determined by direct examination or ultrasound; (2) ≥1 premature birth of morphologically normal neonate before 34 weeks gestation precipitated by eclampsia or severe pre-eclampsia or manifestations of placental insufficiency that includes unsatisfactory fetus surveillance test, aberrant Doppler flow velocimetry suggesting fetal hypoxemia, intra-uterine growth restriction (IUGR) and oligohydramnios and (3) ≥3 inexplicable consecutive spontaneous abortions at or before 10 weeks of gestation with the exclusion of hormonal or anatomic abnormalities in mother and chromosome abnormalities on both mother and father side.

Laboratory criteria

Below listed criteria required to be at least positive twice with twelve weeks of separation and should not exceed five years of the clinical manifestation, so as

Table 1 Diagnostic criteria of antiphospholipid syndrome according to the revised Sapporo criteria.

Clinical criteria	Laboratory criteria
1. Presence of vascular thrombosis (arterial, venous or small vessel) 2. Pregnancy morbidity that may include one of the following: a) ≥1 unexplained deaths of morphologically normal fetus at ≥10 weeks gestation. b) ≥1 premature birth of morphologically normal neonate in <34 weeks gestation due to eclampsia or severe preeclampsia or features of placental insufficiency. c) ≥3 consecutive spontaneous abortions in <10 weeks gestation excluding maternal anatomic or hormonal abnormalities and chromosomal abnormalities on maternal or paternal side.	1. Presence of plasma LA, on ≥2 occasions at ≥12 weeks apart detected according to the guidelines of the International Society of Thrombosis and Hemostasis. 2. Presence of plasma or serum aCL (IgG and/or IgM) in medium or high titer (>40 GPL or MPL, or >99th percentile), on ≥2 occasions, at ≥12 weeks apart, measured by a standardized ELISA‡ 3. Presence of plasma or serum antiß2GP1antibody (IgG and/or IgM) with a titer >99th percentile, on ≥2 occasions, measured by standardized ELISA.

LA = lupus anticoagulant; aCL = anti-cardiolipin antibodies; ELISA = enzyme linked immunosorbent assay; ntiß2GP1 = anti-beta2-glycoprotein 1.

to be considered positive for APS [1]. (1) Presence of plasma lupus anticoagulant (LA), twice or more with at least 12 weeks of separation and should be discerned as per the guidelines set by the International Society of Thrombosis and Haemostasis; (2) presence of plasma/serum anticardiolipin antibody (aCL) of IgG and/or IgM isotype, in medium/high titer (>40 GPL/MPL, or >99th percentile), occurring two or more times, separated by at least 12 weeks, when calculated by standard ELISA (Enzyme-linked immunosorbent assay) and (3) presence of plasma or serum anti-ß2-glycoprotein I (anti-ß2-GP1) antibody of IgG and/or IgM isotype in serum/plasma, with a titer of >99th percentile, occurring two or more times, calculated by standard ELISA.

Antibodies in antiphospholipid syndrome

Antiphospholipid syndrome (APS) is characterized by the existence of antiphospholipid antibodies (APLA) like anti-ß2-glycoprotein I (Anti-β_2GPI), anticardiolipin antibodies (aCL), and lupus anticoagulant (LA), which are associated with arterial, venous or micro-circulation thrombosis and play a substantial role in obstetrical phenomenon. The assay performed in different labs of APLA has been taken into consideration for the correlation between APS and pregnancy outcome. Severity in outcome of complication in mother and fetus varies with the presence of APLA in APS during pregnancy [29]. Ruffatti et al. [30] have shown that, even with proper treatment, high titers and triple positivity for APLA were associated with both mother and fetal complications. Premature birth, fetal loss, and pre-eclampsia were the most common manifestations found to occur in 10–20% of APS associated pregnancies [31].

One of the multi-centered, prospective observational study of pregnancies with systemic lupus erythematosus (SLE) and/or APS called PROMISSE study (Predictors of pRegnancy Outcome: biomarkers In antiphospholipid antibody syndrome and systemic lupus erythematosus), was designed to identify the clinical features, laboratory tests and biomarkers that can be useful in predicting the adverse pregnancy outcomes (APOs) after first trimester. Adverse pregnancy outcomes (APOs) are characterized as fetal loss post 12 weeks gestation, neonatal loss, delivery pre 36 weeks gestation caused by placental insufficiency, and pre-eclampsia or small for gestational age (birth weight <5th percentile). The early data analysis done by PROMISSE stated that strong predictor of adverse pregnancy outcomes in APLA-positive patients was due to lupus anticoagulant [32].

Recurrent miscarriage, stillbirth and presence of associated antibodies

APS was found prevalent in about 15% of recurrent fetal losses, implying that it is among the main non-inherited causes for recurrent miscarriages, although, fetal chromosomal abnormalities were found to be main cause. Recurrent miscarriage is considered if there is a loss of two or more pregnancies with same partner before week 24 of the gestation period [33]. The percentage of unexplained recurrent miscarriages was 7% and 25%, because of the presence of APLA.

Loss of fetus post twenty weeks goes up to 30% [34]. Cervera et al. [35] in their study with 1580 cases of pregnancies concluded that the proportion of early fetal loss (<10 weeks) was 35.4%, whereas that of late fetal loss (≥10 weeks) was 16.9%. The proportion of live birth was 47.67% and ratio of premature to live birth was 10.6%. This cohort [36] did another study that showed early fetal loss as the most common fetal complication (17.1%) followed by late fetal loss (6.7%). Premature births (35% of live births) as well as intrauterine growth restriction (13.7% of live births) were also noteworthy in the report. Still birth is also seen in APS patients and it affected up to 7% of the pregnancies, as seen in the "Euro-Phospholipid" project on 1000 patients. These cases have declined in developed countries [36].

A study conducted by Yelnik et al. [37] established the relationship between LA and APS with small group of patients that showed 9 out of 17 (53%) had APOs which included fetal death in 29%, while in LA negative patients, 4 out of 24 (17%) had APOs without fetal death. The aCL IgG frequency between patients with and without APOs (69% and 55%, respectively) showed no difference. In addition to that six out of nine patients, who had aCL IgG positive displayed APOs, also had LA. Similarly, β2-GPI IgG positive (61% vs 50%) having APOs, also had LA which was found in five of eight patients. They were able to confirm that LA was only APLA to be associated with APOs after the first trimester and it was the only predictor which was sufficient for poor outcome of pregnancy post first trimester [37]. There was an analogous study done retrospectively by Helgadottir et al. [38], who compared 105 patients with 262 control live-births and reported positive association of LA with a history of fetal death post 26 weeks of gestation, but not β2GPI nor aCL. Another study, done with 247 patients, who had obstetrical APS, was through prospective and retrospective method using a data from European Registry of Antiphospholipid syndrome. It reported that LA as well as triple-positive APLA were found to be in association with early and late pregnancy complications [39].

Recently, a study was conducted that stated anti-β2-GP1 Ig-M antibodies were the predominant form of antiphospholipid antibody in patients with recurrent miscarriage and APS, inferring that β2-GP1 is the main antigen in the disease pathology [40]. Out of 123 patients in this study, all were positive for anti -β2-GP1 IgM, while 13 of the 123 patients (10.6%) were also positive for anticardiolipin IgM. Among those, 99 had successful pregnancies, of which 87 resulted in live births, and the overall success rate was 87.9% (87/99). Miscarriage occurred in 12 cases and 24 patients had not become pregnant by the time they collected the data. The miscarriage group had one case of biochemical pregnancy (1%) and 11 cases of embryo damage (11.1%) while the live birth group included four cases of preterm labor (4%) and 83 cases of full-term birth (83.8%). There was no case of stillbirth [40]. There is a conformational change that occurs when β2-GP1 bind to phospholipids on a cell membrane exposing the key sites for antiphospholipid antibodies to bind. Another study has even showed that β2-GP1 may be the main antigen for anticardiolipin antibodies [41]. β2-GP1 combines with phospholipids on the trophocyte membrane during the process of zygote implantation damaging the trophocyte to cause loss of pregnancy [42, 43]. Another analysis was done with 152 healthy women, out of whom, 141 women had recurrent spontaneous abortion without APS, 58 women had a history of fetal death and 73 women had APS. This analysis reported that there was a marked elevation in antibody titers of anti-β2-GP1 in the APS patients compared to the other three groups [44].

Thrombotic events and associated antiphospholipid antibodies

The other pathology linked with APS along with obstetrical pathologies is recurrent thrombotic events (RTE). The co-occurrence of both miscarriage and thrombosis is gauged to be in the range of 2.5–5% of the APS pregnancies [36]. The indication for the management and the risk present for complications like pulmonary embolism (PE)

renders RTEs as one major problem. Nevertheless, the chances of encountering a thrombotic event in APS patient are usually low if the ongoing pregnancy is undergoing adequate medications. The best prognosticator for thrombosis is LA in comparison to other APLA. The study done on 753 cases and 234 controls revealed a strong relationship between LA and thrombosis having an odds ratio of 5.7-9.4; whereas, all did not have the same kind of association [45]. In contrast to the above finding, another study showed that LA alone was not that significantly attributable to the danger of foremost deep vein thrombosis (DVT) (odds ratio 1.3, and 95 % CI = 0.3 to 6.0), but if the patient had positive anti-β2-GPI antibodies (or anti-prothrombin) and LA, the OR of a foremost DVT escalated to 10.1 with 95 % CI ranging from 1.3 to 79.8 [46]. A retrospective research conducted with 160 APS cases having positive aCL, anti- β_2GPI and LA- so called "triple positive" patients, revealed that 123/160 patients were under long-period anticoagulation therapy. The follow up was done after 1, 5 and 10 years, where-in the occurrence of recurrent thrombosis was evidently 12.2%, 26.1%, and 44.2%, respectively [47]. The rate of the foremost thrombotic incidence in individuals with double or triple-positivity (1.27%) was twice high than that in women with the single-positivity (0.65%), as shown by recent study of 119 female with APLA carriers [48].

There was a new development to give substitute scoring for the diagnosis of APS called global APS score (GAPSS), which is based on risk factors like loss of pregnancy and independent thrombosis [49]. According to the GAPSS, IgG/IgM aCL carries five points; IgG/IgM anti-β2GP1 and LA carry four points; IgG/IgM anti-phosphatidylserine-prothrombin complex antibodies and hyperlipidaemia carry three points; and arterial hypertension carries 1 point [50]. Developed primarily in patients suffering with systemic lupus erythematosus (SLE), it was observed that the higher value of GAPSS scores pertained in patients displaying pregnancy loss and/or thrombosis when compared to the cases without any clinical events. It was used to evaluate two separate groups for incidence of thrombosis and the result was the one with higher GAPSS value experienced higher incidence of thrombosis [51].

Others commonly seen outcomes of antiphospholipid syndrome

Pregnancy with APS might also have minor symptoms like thrombocytopenia or livedo reticularis in more than 20% of the cases [36]. The manifestation of thrombocytopenia was seen in nearly 30% of the cases in APS [35]. The association of APS to that of preeclampsia has also been well established by various studies [52, 53]. Preeclampsia criteria must be followed for its diagnosis which includes elevated blood pressure (BP) of >140/90 mm of mercury with proteinuria of at least 300 mg in a 24-hour urine, post 20 week of gestation or elevation of systolic BP by ≥30 mm of mercury or diastolic BP by ≥15 mm of mercury post 20 week of gestation, coexisting with proteinuria and/or edema. For diagnosing severe pre-eclampsia at least one of the following must be present with before mentioned criteria. (1) Systolic BP ≥160 mm of Hg or Diastolic BP ≥110 mm of Hg on two incidents separated by at least 6 hours; (2) proteinuria of ≥5 g in 24- hour urine collection separated by at least 4 hours; (3) cyanosis or pulmonary edema; (4) oligura characterized by <400 ml of urine in 24 hours; (5) persistent headache; (6) Impaired liver function and/or epigastric pain; (7) thrombocytopenia and (8) oligohydramnios, reduced fetal growth or abruption of placenta.

Incidence of 'Hemolysis Elevated Liver Enzyme and Low-platelet' (HELLP) syndrome in APS is difficult to determine. However, it seems severe as well as occurs earlier during pregnancy as opposite to patients not affected by APS [54, 55]. The studies of placental insufficiency are limited, but its occurrence has been established with preeclampsia even in treated patient who has APS [56]. There are many cohort studies which have shown the relation of APS with Intra-Uterine Growth Retardation (IUGR). However, there are some limitations due to small number of patient and difference in definition [56]. The proportion of IUGR ranges from 13–33% in pregnancies with APS, and that of prematurity

ranges from 16–50%, with an average gestational age of 31 weeks [57-62].

Catastrophic Antiphospholipid Syndrome (CAPS) that can also affect mothers is prevalent in around one percent of APS cases. This syndrome can be presented in non-pregnant too. CAPS are thrombotic storm which leads to multi-organ failure due to micro-angiopathic diffuse thrombosis. The association of pregnancy and postpartum was 6% [63]. The risk of getting stroke is increased in an infant who are born from the mothers suffering from APS [64]. According to the latest research done on single pregnancies, aCL is most common single APLA present, but anti-β2-GP1 is the one linked with the lowest live birth rate and highest incidence of intrauterine growth restriction, stillbirth and preeclampsia, in comparison to aCL or LA. The risk of obstetric complications and lower birth rate is increased in women with APS if <1 antiphospholipid antibody is present [65].

Laboratory tests for the detection of antiphospholipid syndrome antibodies

An instrument that is getting acceptance clinically and allows quantitative measurement of autoantibody is Automated Coagulation Laboratory (ACL) Acustar Analyzer (BIO-FLASH instrument). It uses a chemiluminescence immunoassay (CIA) [66- 68]. Blood samples are tested in laboratories using enzyme-linked immunosorbent (ELISA) assay kit. In order to detect LA, clotting assays are used that is phospholipids dependent as APLA is proficient to delay it. Due to the heterogeneity of different individual APLA, LA test is challenging to standardize and one test is not sufficient [51]. The International Society on Thrombosis and Haemostasis guidelines recommended two different assay principles: a sensitive activated partial thromboplastin time (aPTT) and the diluted Russell viper venom (dRVVT) test [69]. Detection of LA in laboratory done as per the updated guidelines should meet the following criteria: (1) when the content of phospholipids in the test is low, prolonged phospholipids dependent clotting test should be done; (2) when there is lack in rectifying the delayed clotting time, small amount of normal plasma is done; and (3) using reagent that gives poor response to effects of LA or using platelet fragment that will remove all APLA [69]. Either a mixing test-specific cut-off (MTC) or index of circulating anticoagulant (ICA) for mixing test interpretation was recommended by current guidelines for LA detection [70]. Latest finding from a study done by taking 350 LA positive plasma and comparing them with patients who did not have anticoagulant in order to analyze rates of inhibition detection suggested that MTC is superior to detect inhibition of LA *in vitro* than ICA [70].

Radioimmunoassay or ELISA by using solid phase antigen cardiolipin is used to detect aCL. For aCL assay, the use of serum is done. GPL, MPL and IgA units are used as an expression of IgG, IgM and/or IgA isotype, respectively, and activity of binding of 1 mg/ml of affinity purified aCL is represented by 1 unit [50]. Generally for APS, aCL are more sensitive whereas LA positivity is more specific [46, 71]. The detection of β2-GP1 antibody is done by ELISA. Nevertheless, anti-β2-GPI antibodies are seldom to be found alone even in patients who have clinical features of APS [72]. Recent studies have been focusing on the five homologous domains (D1 to D5) of β2-GPI. The region of D1 has been found to be mainly associated with APS [73, 74]. Along with these, many researches are being conducted to study the effect of APS on different receptors.

Recent advances in the treatment of antiphospholipid syndrome

Recently, some improvement has been seen in dealing with the APS. The main aim is to cultivate positive result in mother, fetus and neonates along with minimizing the complications related to APS. Use of prednisone prior to conception lowers the antibody titer by inhibiting the formation of antibody. Due to this property, it has been used in the treatment of recurrent miscarriage and APS. But it is not used more than 30 weeks after pregnancy to avoid its side effect like obesity and liver dysfunction [40]. Combined therapy had emerged to be more efficient currently in comparison to single therapy that was being used in the past. Contemporary understanding

puts a light on the use of prednisone along with LMWH (low molecular heparin) and aspirin resulting in 87.9% successful pregnancies (87/99) [40]. The administration of LMWH and aspirin is due to their role in coagulation cascade. Another role of heparin is to block the hyper-activated complement system evident in APS [75]. Despite treating patients with prophylactic LMWH and aspirin in lower dose, the chance of a live born neonate is only 30% for triple-positive women [65]. Aspirin has also been used in the treatment of APS due to its role in inhibition of platelet aggregation and lowering prostaglandin syntheses activity which in turn decreases the chances of thrombosis. The rate of live birth was improved from 10% before the treatment to 88% after the use of aspirin [76].

Hydroxychloroquine (HCQ) is also used as a second line of treatment [77]. It is anti-inflammatory and anti-aggregate that prevents cardiac congenital abnormalities and lupus flares. It also averts recurrent loss of fetus. There has been no report on side-effect to babies in mother treated with HCQ [78-80]. The effective therapeutic approach used for CAPS consists of anticoagulation, corticosteroids, and plasma exchange. The first-line treatments used in CAPS are high-dose steroids, i.e., 1000 mg methylprednisolone daily for 3 days or longer and heparin. There has been improvement in fatality rate with plasma exchange as seen by the observational studies and the CAPS registry [77].

Conclusions

Antiphospholipid syndrome is a disease that has high complication in pregnancy for both mother and fetus. Although, there has been some progress in diagnosis and treatment of the disease, but it is still challenging. Preconception counseling and treatments are required for the successful pregnancy outcome. Despite some studies implying no need of screening healthy pregnant women [81], screening of high-risk APS patient will definitely improve their pregnancy outcome. As the risk of maternal death is anticipated in APS, pregnancy should be avoided in patient with pulmonary hypertension and delayed in patient with uncontrolled hypertension or recent thrombotic event such as stroke [82]. Combination therapy has emerged as an efficient method to alleviate the complication of APS. Furthermore, supplementary studies are recommended to apprehend the pathological mechanisms, diagnosis and management so as to enhance the successful pregnancy result.

Conflict of interest

The authors declare no conflict of interest.

References

[1] 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; 4:295–306.

[2] D'Cruz DP. Antiphospholipid (Hughes) syndrome: an overview. In: Khamashta MA, editor. Hughes syndrome, London: Springer-Verlag; 2006, p 9-21.

[3] Pattison NS, Chamley LW, McKay EJ, Liggins GC, Butler WS. Antiphospholipid antibodies in pregnancy: prevalence and clinical associations.Br J Obstet Gynaecol 1993; 100:909-13.

[4] Birdsall M, Pattison N, Chamley l. Antiphospholipid antibodies in pregnancy. Aust N Z J Obstet Gynaecol 1992; 32: 328-30.

[5] Lockwood CJ, Romero R, Feinberg RF, Clyne LP, Coster B,Hobbins JC. The prevalence and biologic significance of lupus anticoagulant and anticardiolipin antibodies in a general obstetric population. Am J Obstet Gynaecol 1989; 161:369-73.

[6] Petri M. Epidemiology of antiphospholipid antibodiesn syndrome. In: Khamashta MA, (ed). Hughes syndrome. London: Springer-Verlag; 2006. P.22-8.

[7] Rai RS, Clifford K, Cohen H, Regan L. High prospective fetal loss rate in untreated pregnancies of women with recurrent miscarriage and antiphospholipid antibodies. Hum Reprod 1995; 10:3301-4.

[8] Yasuda M, Takakuwa K, Tokunaga A, Tanaka K. Prospective studies of association between anticardiolipin antibody and outcome of pregnancy. Obstet Gynecol 1995; 86:555-9.

[9] 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; 120:470-5.

[10] Tsapanos V, Kanellopoulos N, Cardamakis E, Fotopoulos A, Schinas V, Kondakis X, et al. Anticardiolipin antibodies levels in healthy pregnant and non-pregnant woman. Arch Gynecol Obstet 2000; 263(3):111-5.

[11] Matthiesen LS, Berg G, Ernerudh J, Skogh T.A prospective study on the occurrence of autoantibodies in low-risk pregnancies. Eur J Obstet Gynecol Reprod Biol 1993; 83(1);21-6.

[12] Out HJ, Kooijman CD, Bruinse HW, Derksen RH, Histopathological findings in placentae from patients with intra-uterine fetal death and antiphospholipid antibodies. Eur J Obstet Gynaecol Rep Biol 1991; 195:211-20.

[13] Girardi G, Redecha P, Salmon JE, Heparin prevents antiphospholipid-induced fetal loss by inhibiting complement activation. Nat Med 2004; 10:1222-6.

[14] Harris EN, Asherson RA, Hughes GR. Antiphospholipid antibodies–autoantibodies with a difference. Annu Rev Med. 1988; 39:261–271.
[15] Gharavi AE, Pierangeli SS. Origin of antiphospholipid antibodies: induction of aPL by viral peptides. Lupus 1998; 7(2):S52–S54.
[16] Sherer Y, Blank M, Shoenfeld Y. Antiphospholipid syndrome (APS): where does it come from? Best Pract Res Clin Rheumatol 2007; 21(6):1071–1078.
[17] Ruiz-Irastorza G, Crowther M, Branch W, Khamashta MA. Antiphospholipid syndrome. Lancet 2010; 376:1498–509.
[18] Du VX, Kelchtermans H, de Groot PG, de Laat B. From antibody to clinical phenotype, the black box of the antiphospholipid syndrome: pathogenic mechanisms of the antiphospholipid syndrome. Thromb Res 2013; 132(3):319–26.
[19] Rand JH, Wu XX, Lapinski R, van Heerde WL, Reutelingsperger CP, Chen PP, Ortel TL, et al. Detection of antibody-mediated reduction of annexin A5 anticoagulant activity in plasmas of patients with the antiphospholipid syndrome. Blood 2004; 104(9):2783–2790.
[20] Proulle V, Furie RA, Merrill-Skoloff G, Furie BC, Furie B. Platelets are required for enhanced activation of the endothelium and fibrinogen in a mouse thrombosis model of APS. Blood 2014; 124(4):611–22. 10.
[21] Yalavarthi S, Gould TJ, Rao AN, Mazza LF, Morris AE, Nunez-Alvarez C et al. Release of neutrophil extracellular traps by neutrophils stimulated with antiphospholipid antibodies: a newly identified mechanism of thrombosis in the antiphospholipid syndrome. Arthritis Rheumatol 2015; 67(11):2990–3003.
[22] López-Pedrera C, Aguirre MA, Buendía P, Barbarroja N, Ruiz-Limon P, Collantes-Estevez E et al. Differential expression of protease-activated receptors in monocytes from patients with primary antiphospholipid syndrome. Arthritis Rheum 2010; 62(3):869–77.
[23] Girardi G, Redecha P, Salmon JE, Heparin prevents antiphospholipid-induced fetal loss by inhibiting complement activation. Nat Med 2004; 10:1222-6.
[24] Carbone J, Sarmiento E, Rodriguez-Molina J, Fernandez-Cruz, Hipocomplementemia C3 y C4 en el syndrome antifosfolipido obstetric. Rev Clin Esp 2008; 208:168-71.
[25] Salmon JE, Girardi G. Antiphospholipid syndrome revisited: a disorder initiated by inflammation. Lupus 2007; 16:1-2.
[26] 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; 174:1222-6.
[27] Girardi G, Yarilin D, Thurman JM, Holers VM, Salmon JE. Complement activation induces dysregulation of angiogenic factors and causes fetal rejection and growth restriction. J Exp Med 2006; 203:2165-75.
[28] [28] Wang YQ, Niu JH, Wang JL, Ye RH, Zhao YY. Patient with antiphospholipid syndrome accompanied by pre-eclampsia who developed HELLP syndrome and eclampsia after abortion. Chin Med J. 2012; 125:4142–4.
[29] Pengo V, Banzato A, Bison E, Bracco A, Denas G, Ruffatti A. What have we learned about antiphospholipid syndrome from patients and antiphospholipid carrier cohorts? Seminars Thromb Hemost 2012; 38(4):322–327.
[30] Ruffatti A, Calligaro A, Hoxha A, et al. Laboratory and clinical features of pregnant women with antiphospholipid syndrome and neonatal outcome. Arthritis Care Res 2010; 62(3):302–307.
[31] 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; 74:1011–8.
[32] 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; 64:2311–8.
[33] Rai RS, Regan L, Clifford K, et al. Antiphospholipid antibodies and β2-glycoprotein-I in 500 women with recurrent miscarriage: results of a comprehensive screening approach. Hum Reprod 1995; 10(8):2001–2005.
[34] Drakeley AJ, Quenby S, Farquharson R. Mid-trimester loss-appraisal of a screening protocol. Hum Reprod 1998; 13:1975-80.
[35] Cervera R, Piette J-C, Font J, Khamashta MA, Shoenfeld Y, Camps MT. Antiphospholipid syndrome : clinical and immunologic manifestations and patterns of disease expression in a cohort of 1,000 patients. Arthr Rheum 2002; 46:1019-27.
[36] Cervera R, Khamashta MA, Shoenfeld Y, Camps MT, Jacobsen S, kiss E, Zeher MM,et al. et al. Morbidity and mortality in the antiphospholipid syndrome during a 5-year period: a multicentre prospective study of 1000 patients. Ann Rheum Dis 2009; 68(9):1428–1432.
[37] Yelnik CM, Laskin CA, Porter TF, Branch DW, Buyon J P, Guerra M M, Salmon J E. Lupus anticoagulant is the main predictor of adverse pregnancy outcomes in aPL-positive patients: validation of PROMISSE study results. Lupus Sci Med 2016; 3(1):e000131.
[38] Helgadottir LB, Skjeldestad FE, Jacobsen AF, Sandset PM, Jacobsen EM. The association of antiphospholipid antibodies with intrauterine fetal death: a case-control study. Thromb Res 2012; 130:32–7.
[39] Alijotas-Reig J, Ferrer-Oliveras R, Ruffatti A, Tincani A, LEfkou E, Bertero MT, et al. The European Registry on Obstetric Antiphospholipid Syndrome (EUROAPS): a survey of 247 consecutive cases. Autoimmun Rev 2015; 14:387–95.
[40] Song Y, Wang H-Y, Qiao J, Liu P, Chi H-B. Antiphospholipid Antibody Titers and Clinical Outcomes in Patients with Recurrent Miscarriage and Antiphospholipid Antibody Syndrome: A Prospective Study. Chin Med J 2017; 130(3):267-272.
[41] Flint J, Panchal S, Hurrell A, Van de Venne M, Gayed M, Schreiber K, et al. BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding. Rheumatol 2016; 2:269–99.
[42] Agostinis C, Biffi S, Garrovo C, Durigutto P, Lorenzon A, Bek A, et al. In vivo distribution of ß2 glycoprotein I under various pathophysiologic conditions. Blood 2011; 118:4231–8.
[43] La Rosa L, Meroni PL, Tincani A, Balestrieri G, Faden D, Lojacono A, et al. Beta 2 glycoprotein I and placental anticoagulant protein I in placentae from patients with antiphospholipid syndrome. J Rheumatol 1994; 21:1684–93.
[44] Lee RM, Emlen W, Scott JR, Branch DW, Silver RM. Anti-beta2-glycoprotein I antibodies in women with recurrent spontaneous abortion, unexplained fetal death, and antiphospholipid syndrome. Am J Obstet Gynecol 1999; 181:642–8.

[45] Galli M, Luciani D, Bertolini G, Barbui T. Lupus anticoagulants are stronger risk factors for thrombosis than anticardiolipin antibodies in the antiphospholipid syndrome: a systematic review of the literature. Blood 2003; 101:1827–32.
[46] 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; 3:1993–7.
[47] Pengo V, Ruffatti A, Legnani C, et al. Clinical course of high-risk patients diagnosed with antiphospholipid syndrome. J Thromb Haemost 2010; 8(2):237–242.
[48] Mustonen P, Lehtonen KV, Javela K, Puurunen M. Persistent antiphospholipid antibody (aPL) in asymptomatic carriers as a risk factor for future thrombotic events: a nationwide prospective study. Lupus 2014; 23(14):1468–1476.
[49] Sciascia S, Sanna G, Murru V, Roccatello D, Khamashta MA, Bertolaccini ML. GAPSS: the global anti-phospholipid syndrome score. Rheumatology 2013; 52:1397–403.
[50] Sciascia S, Baldovino S, Schreiber K, Solfietti L, Radin M, Cuadrado M. J, et al. Thrombotic risk assessment in antiphospholipid syndrome: the role of new antibody specificities and thrombin generation assay. Clini Molr Allerry 2016; 14:6.
[51] Zuily S, Ait Aissa K, Membre A, Regnault V, Lecompte T, Wahl D. Thrombin generation in antiphospholipid syndrome. Lupus 2012; 21:758–60.
[52] Abou-Nassar K, Carrier M, Ramsay T, Rodger MA. The association between antiphospholipid antibodies and placenta mediated complications: a systematic review and meta-analysis. Thromb Res 2011; 28(1):77–85
[53] do Prado AD, Piovesan DM, Staub HL, Horta BL. Association of anticardiolipin antibodies with preeclampsia: a systematic review and meta-analysis. Obstet Gynecol 2010; 116(6):1433–43.
[54] Costedoat-Chalumeau N, Guettrot-Imbert G, Leguern V, Leroux G, Le Thi Huong D,Wechsler B et al. Pregnancy and antiphospholipid syndrome. Revue de Medecine Interne 2012; 33(4):209–216.
[55] Le Thi Thuong D, Tieulié N, Costedoat N, Andreu MR, Wechsler B, Vauthier-Brouzes D, et al. The HELLP syndrome in the antiphospholipid syndrome: retrospective study of 16 in 15 women. Ann Rheum Dis 2005; 64(2):273–278.
[56] Levy RA, dos Santos FC, de Jesús GR, de Jesús NR. Antiphospholipid Antibodies and Antiphospholipid Syndrome during Pregnancy: Diagnostic Concepts. Front Immunol 2015; 6:205.
[57] Canti V, Castiglioni MT, Rosa S, Franchini S, Sabbadini MG, Manfredi AA et al. Pregnancy outcomes in patients with systemic autoimmunity. Autoimmunity 2012; 45: 169–175.
[58] De CS, Botta A, Santucci S, Garofalo S, Martino C, Perrelli A, et al. Predictors of pregnancy outcome in antiphospholipid syndrome: a review. Clin Rev Allergy Immunol 2010; 38: 116–124.
[59] Geis W, Branch DW. Obstetric implications of antiphospholipid antibodies: pregnancy loss and other complications. Clin Obstet Gynecol 2001; 44: 2–10.
[60] Motta M, Boffa MC, Tincani A, Avcin T, De CS, Lachassinne E. Follow-up of babies born to mothers with antiphospholipid syndrome: preliminary data from the European neonatal registry. Lupus 2012; 21:761–763.
[61] Ruffatti A, Tonello M, Visentin MS, Bontadi A, Hoxha A, De CS et al. Risk factors for pregnancy failure in patients with anti-phospholipid syndrome treated with conventional therapies: a multicentre, case-control study. Rheumatol Oxf Engl 2011; 50: 1684–1689.
[62] Venkat-Raman N, Backos M, Teoh TG, Lo WT, Regan L. Uterine artery Doppler in predicting pregnancy outcome in women with antiphospholipid syndrome. Obstet Gynecol 2001; 98: 235–242.
[63] Gómez-Puerta JA, Sanin-Blair J, Galarza-Maldonado C. Pregnancy and catastrophic antiphospholipid syndrome. Clin Rev Allergy Immunol 2009; 36(2-3):85–90.
[64] Berkun y, Padeh S, Barash J, Uziel Y, Harel L, Mukamel M, Revel-Vilk et al. Antiphospholipid syndrome and recurrent thrombosis in children. Arthritis Rheum 2006; 55(6):850–855.
[65] Saccone G, Berghella V, Maruotti GM, Tullio G, Giuseppe R, Giuliana S, et al. Antiphospholipid antibody profile based obstetric outcomes of primary antiphospholipid syndrome: the PREGNANTS study. Am J Obstet Gynecol 2017; 216(5):525e1-e-12.
[66] de Maistre E, Volot F, Mourey G, Aho LS, Ternisien C, Briquel ME et al. Performance of two new automated assays for measuring von Willebrand activity: HemosIL AcuStar and Innovance Thromb. Haemost 2014; 112(4): 825–830.
[67] Lippi G, Ippolito L, Russello T, Ponzo V, Salvagno GL, Guidi GC. Analytical performance of the new ACL AcuStar HemosIL D-Dimer. Blood Coagul 2012; 23(2):164–167.
[68] Minet V, Bailly N, Douxfils J, Osselaer JC, Laloy J, Chatelain C et al. Assessment of the performances of AcuStar HIT and the combination with heparin-induced multiple electrode aggregometry: a retrospective study. Thromb Res 2013; 132 (3):352–359.
[69] Pengo V, Tripodi A, Reber G, Rand JH, Ortel TL, Galli M, et al. Update of the guidelines for lupus anticoagulant detection. J Thromb Haemost 2009; 7:1737–40.
[70] Moore GW, Culhane AP, Daw CR, Noronha CP, Kumano O. Mixing test specific cut-off is more sensitive at detecting lupus anticoagulants than index of circulating anticoagulant. Thromb Res 2016; 139:98–101.
[71] Sciascia S, Cosseddu D, Montaruli B, Kuzenko A, Bertero MT. Risk Scale for the diagnosis of antiphospholipid syndrome. Ann Rheum Dis 2011; 70:1517–8.
[72] Sciascia S, Murru V, Sanna G, Roccatello D, Khamashta MA, Bertolaccini ML. Clinical accuracy for diagnosis of antiphospholipid syndrome in systemic lupus erythematosus: evaluation of 23 possible combinations of antiphospholipid antibody specificities. J Thromb Haemost 2012; 10:2512–8.
[73] Pengo V, Ruffatti A, Tonello M, Hoxha A, Bison E, Denas G, et al. Antibodies to Domain 4/5 (Dm4/5) of β2-Glycoprotein 1 (β2GP1) in different antiphospholipid (aPL) antibody profiles. Thromb Res 2015; 136:161–3.
[74] Pengo V, Ruffatti A, Tonello M, Cuffaro S, Banzato A, Bison E, et al. Antiphospholipid syndrome: antibodies to Domain 1 of β2-glycoprotein 1 correctly classify patients at risk. J Thromb Haemost 2015; 13:782–7.
[75] Di Simone N, Meroni PL, D'Asta M, Di Nicuolo F, D'Alessio MC, Caruso A. Pathogenic role of anti-beta2-glycoprotein I antibodies on human placenta: Functional effects related to implantation and roles of heparin. Hum Reprod Update 2007; 13:189-96.

[76] 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; 174:1584-9.

[77] Cervera R, Espinosa G. Update on the catastrophic antiphospholipid syndrome and the "CAPS Registry" Semin Thromb Hemost 2012; 38(4):333–338.

[78] Briggs GG, Freeman RK, Yaffe SJ. Drugs in pregnancy and lactation. 9th ed. Philadelphia: Lippincott Williams & Wilkins; 2011.

[79] Levy RA, Vilela VS, Cataldo M, et al. Hydroxychloroquine (HCQ) in lupus pregnancy: double-blind and placebo-controlled study. Lupus 2001; 10: 401-404.

[80] Frassi M, Biasini C, Taglietti M, Daneli E, Faden D, Lojacono A, et al. Hydroxychloroquine in pregnant patients with rheumatic disease: a case control observation of 76 treated pregnancies. Lupus 2004; 13:755.

[81] Harris EN, Spinnato JA. Should anticardiolipin tests be performed in otherwise healthy pregnant women? Am J Obstet Gynecol. 1991; 165:1272–1277.

[82] Ruiz-Irastorza G, Khamashta MA. Lupus and pregnancy: ten questions and some answers. Lupus 2008; 17:416–20.