Diplomarbeit

The Antiphospholipid Syndrome in Pregnancy – Literature Research and Assessment with an Insight into Management

eingereicht von

Stephanie Frohnmayer

zur Erlangung des akademischen Grades

Doktor(in) der gesamten Heilkunde

(Dr. med. univ.)

an der

Medizinischen Universität Graz

ausgeführt am

LKH-Universitätsklinik für Frauenheilkunde und Geburtshilfe

unter der Anleitung von

Ass. Dr. Karoline Mayer-Pickel

und

ao. Univ. Prof. Dr. Mila Cervar-Zivkovic

Graz, 03.05.2015

Eidesstattliche Erklärung

Ich erkläre ehrenwörtlich, dass ich die vorliegende Arbeit selbstständig und ohne fremde Hilfe verfasst habe, andere als die angegebenen Quellen nicht verwendet habe und die den benutzten Quellen wörtlich oder inhaltlich entnommenen Stellen als solche kenntlich gemacht habe.

Graz, am 03.05.2015 *Stephanie Frohnmayer eh*

Danksagungen

An dieser Stelle möchte ich mich bei meinen Diplomarbeitsbetreuerinnen Ass. Dr. Karoline Mayer-Pickel und ao. Univ. Prof. Dr. Mila Cervar-Zivkovic von ganzem Herzen für die Zusammenarbeit und ihren guten Ratschlägen bedanken.

Außerdem danke ich meinen Schwestern, die mir immer mit gutem Beispiel voran gingen und mir den Grundstein für meine Ausbildung gelegt haben.

Schließlich möchte ich mich bei meinen Eltern bedanken, die mir meine Ausbildung ermöglicht haben.

Zusammenfassung

Das Antiphospholipidsyndrom ist eine der häufigsten Autoimmunerkrankungen bei Patienten mit Thrombosen und Schwangerschaftskomplikationen. Viele Jahre lang dachte man, das Antiphospholipidsyndrom sei ein Teil des Systemischen Lupus Erythematodes. Im Jahre 1959 beschrieben die Ärzte Dr. J.P. Hughes und Dr. P.G.I. Stovin das Syndrom erstmals als eigenständiges Krankheitsbild und Dr. G.R.V. Hughes beschrieb 1983 die Erkrankung im Detail und mit einem vom Systemischen Lupus Erythematodes unabhängigen Auftreten, ohne den verpflichtenden Zusammenhang mit dem Systemischen Lupus Erythematodes. Über die Jahre haben Erfahrung und klinisches Know-how das Bild und die Diagnosekriterien des Antiphospholipidsyndrom verändert. Die heute anerkannten Diagnosekriterien sind noch immer die Sydney Kriterien von 2006.

Antiphospholipidantikörper, die für eine Diagnose obligatorisch sind, können in 1-5% der Bevölkerung festgestellt werden und sind somit relativ häufig. Diese Antikörper richten sich einerseits gegen Phospholipide, die auf Zellmembranen lokalisiert sind und andererseits gegen das Komplementsystem und greifen so in die Gerinnung ein. Obwohl APS etwa so häufig vorkommt wie Multiple Sklerose, ist die Bekanntheit und das Wissen um die Erkrankung sehr gering.

Die klinischen Symptome der Erkrankung beinhalten arterielle und/oder venöse Thrombosen und/oder Schwangerschaftskomplikationen. Von diesen muss eines vorherrschen in Kombination mit dem Nachweis von einem der drei anerkannten Antiphospholipidantikörper, um eine sichere Diagnose stellen zu können. Jedes Organ oder Gewebe kann betroffen sein, das heißt alle Fachbereiche der Medizin sind betroffen und alle Fachärzte müssen sich mit diesem Syndrom auseinander setzten. Interdisziplinäre Zusammenarbeit und Austausch unter den Kollegen sind wichtig, um diese Erkrankung effektiv diagnostizieren und behandeln zu können.

Zudem fallen Patienten häufig auf, die einen unerfüllten Kinderwunsch haben. Wegen der hohen Inzidenz von klinischen Symptomen in schwangeren Frauen, werden die meisten Diagnosen von Gynäkologen gestellt, weshalb es umso wichtiger ist, das Augenmerk auf das gynäkologische Antiphospholipidsyndrom zu lenken. Besonders dieser Fachbereich ist

wichtig, da hier Komplikationen fatale Auswirkungen haben können und informierte Fachärzte von großer Bedeutung sind.

Da die Erkrankung noch immer jung und nicht ausreichend erforscht ist, sind eine ständige Verbesserung des Verständnisses der Ätiologie und des Pathomechanismus und die Optimierung der Diagnostik unumgänglich. Die Behandlungsmöglichkeiten müssen ständig überprüft und dementsprechend angepasst werden.

Diese Arbeit beschreibt das Antiphospholipidsyndrom und konzentriert sich auf die Schwangerschaftskomplikationen, die eine interdisziplinäre Diagnostik und Behandlungsplanung erfordern. Neueste Studienergebnisse und Entwicklungen werden einbezogen, angeführt und evaluiert, um die neuesten Standards bezüglich der Behandlung und des Managements zu präsentieren.

Table of Contents

Glossary and Abbreviations

$a\beta_2$-GPI:	anti-β_2-glycoprotein 1
aCL:	anticardiolipin antibody
ANA:	anti-nuclear antibodies
aPL:	antiphospholipid antibodies
APS:	antiphospholipid syndrome
aPTT:	activated partial thromboplastin time
β_2-GP1:	β_2-glycoprotein 1
BS:	Behçet syndrome
CAD:	coronary heart disease
CAPS:	catastrophic antiphospholipid syndrome
dRVVT:	dilute Russell's viper venom time
DVT:	deep vein thrombosis
ELISA:	enzyme-linked immunosorbent assay
FFP:	fresh frozen plasma
hCG:	human chorionic gonadotropin
HEEC:	human endometrial endothelial cells
HIT:	heparin-induced thrombocytopenia
INR:	international normalized ratio
ITP:	idiopathic thrombocytopenic purpura
IUFD:	intrauterine fetal death
IUGR:	intrauterine growth restriction
IVIG:	intravenous immunoglobulin therapy
LA:	lupus anticoagulant antibody
LDA:	low dose aspirin
LMWH:	low molecular weight heparins
MS:	multiple sclerosis
PAPS:	primary antiphospholipid syndrome
PE:	preeclampsia
SAPS:	secondary antiphospholipid syndrome
SGA:	small for gestational age
SLE:	systemic lupus erythematodes
TIAs:	transient ischemic attacks
TNF:	tumor necrosis factor
TTP:	thrombotic thrombocytopenic purpura
UFH:	unfractured heparin
VEGF:	vascular endothelial growth factor

Figure Reference

Table Reference

1 Abstract

The Antiphospholipid Syndrome (APS) is one of the most common systemic autoimmune diseases connected to thrombosis and complications during pregnancy. For many years the disease was unknown and thought to be part of the Systemic Lupus Erythematodes (SLE) disease. Dr. J.P. Hughes and Dr. P.G.I. Stovin described the syndrome initially in 1959. In 1983 Dr. G.R.V Hughes described the syndrome in detail detaching the mandatory connection to SLE. Years of experience and clinical know-how have changed the picture and diagnosis criteria for APS. Today the "Sydney criteria" published in 2006 are still used as the primary guidelines for diagnosis.

Antiphospholipid antibodies (aPL), which are obligatory for diagnosis, are found in approximately 1-5% of the population and are therefore rather common. The aPL are directed against phospholipids located in cell membranes as well as against the complement and interfere with coagulation. Although APS is nearly as frequent as multiple sclerosis (MS), the awareness and knowledge about the disease in the general population is very poor.

Clinical symptoms of APS include arterial and/or venous thrombosis and/or adverse obstetric outcomes. For a reliable diagnosis, one clinical criterion and one laboratory criterion must be met. Any organ or tissue can be affected, which means that all fields of medicine and a great variety of medical professionals may encounter this disease. It is necessary that colleagues collaborate and follow interdisciplinary practice in order to treat this syndrome effectively.

Many women who desire to become pregnant are affected, which is why special attention has to be directed to obstetric APS. Due to the high incidence of clinical symptoms within pregnant women, most diagnoses fall into the hands of the obstetricians. Obstetric APS can have fatal outcomes, which makes experienced practitioners particularly important in this field.

Since the disease is still young and not sufficiently researched, the improvement of knowledge on etiology and pathomechanisms and the optimization of management are necessary. Treatment has to be repeatedly reviewed and adapted accordingly.

This paper describes the APS and focuses on complications occurring during pregnancy, which demands interdisciplinary diagnosis and management. Newest developments and research have been included, described and evaluated in order to publish the latest standards regarding the treatment and management of APS.

2 Definition

APS is an autoimmune disease characterized by the presence of antiphospholipid antibodies (aPL) in the maternal circulatory system, including anticardiolipin antibodies (aCL), lupus anticoagulans (LA) and anti-β_2-glycoprotein I (aβ_2-GPI). These antibodies are associated with arterial and/or venous thrombosis and/or adverse obstetric outcomes such as recurring fetal loss, preeclampsia (PE), intrauterine growth restriction (IUGR) and intrauterine fetal death (IUFD). APS may occur on its own as primary APS (PAPS) or secondary to other autoimmune diseases, such as SLE or other strains of rheumatic diseases. APL can bind and activate platelets and endothelial cells, inhibit fibrinolysis and interfere with the protein C pathway in patients with thrombotic APS. Complement activation is crucial for both thrombotic and obstetric APS. In pregnancy aPL can impair placentation by i.e. by decreasing trophoblast proliferation and invasion.

2.1 PAPS, SAPS, CAPS, OAPS, Seronegative APS

APS can be classified as primary APS (PAPS) or secondary APS (SAPS). PAPS is present when the syndrome is the primary disorder independent of any other underlying diseases. In a study of 1,000 patients, designed to establish an estimate on the occurrence of PAPS, Cervera at al. found that 53.1% of the patients had no other associated disease (Cervera et al., 2002).

On the other hand, the SAPS is associated with other autoimmune diseases. Within these, primarily prevalent is systemic lupus erythematodes (SLE). Therefore, SAPS is also referred to as lupus-like disease. It is less often encountered in association with conditions like rheumatic illnesses as well as a range of infections (particularly HIV), malignancies, after the administration of specific drugs, and in some vasculitides (Asherson, 2008, Cervera et al., 2002).

APS in pregnancy resulting in adverse pregnancy outcomes is often referred to as obstetric APS (OAPS) (Alijotas-Reig, 2013).

The catastrophic APS (CAPS) or also known as the Asherson's syndrome is the most severe form. It is defined as an exacerbated form of APS that leads to multiple organ failure as a result of predominantly small vessel thrombosis (Erkan et al., 2003) and leads to death within 50% of the cases (Asherson et al., 1998, Asherson et al., 2001).

Patients with typical clinical evidence may be seronegative for all types of aPL. This may have several reasons including wrong diagnosis, laboratory problems and temporary negativity due to consumption of aPL (Hughes and Khamashta, 2003).

2.2 Synonyms

Dr. Graham Hughes, a rheumatologist at the Louise Coote Lupus Unit, St Thomas' Hospital in London and at the London Lupus Centre, London Bridge Hospital played a key role in defining the syndrome and its clinical features. Due to his influence in developing the picture of APS it sometimes referred to as the Hughes syndrome.

2.3 Epidemiology and Statistics

Numbers on epidemiology are vague and not extensively researched. APL are estimated to be found in 1-5% of the population, although the actual prevalence is uncertain (Alijotas-Reig, 2013, Cohen et al., 2010, Petri, 2000). However, only a minority of these individuals actually develop the disease. Newer studies indicate that the incidence of APS is around 5 new cases per 100,000 persons per year and the prevalence around 40-50 cases per 100,000 individuals (Petri, 2000). 1% of women with childbearing preferences are affected by recurrent miscarriages. Approximately 10 to 15% of these women are predicted to acquire OAPS (Ruiz-Irastorza et al., 2010a).

Women are more prone to develop APS than men, hence 70% of all individuals suffering from APS are female (Alijotas-Reig, 2013, Cohen et al., 2010, Lockshin, 1997) and 1-5% of healthy women of childbearing age are affected (Ruiz-Irastorza et al., 2004).

Cervera et al. was one of the first to investigate clinical and immunologic manifestations on a larger number of patients. He concluded a male:female ratio of 1:5 for APS, 1:3.5 for PAPS and 1:7 for SAPS (Cervera et al., 2002). The study also indicates that APS occurs mainly in young fertile woman with a mean age onset at 34±13 years and that 85% of the

patients were diagnosed with APS between ages 15 and 50 years. Patients beyond 50 years of age who develop APS are more often male than female (Miyakis et al., 2006).

As SAPS is often related to SLE, a high percentage of SLE patients actually develop the disease. SLE is present in one to 20 of every 100,000 women and around 30% of these develop the secondary form (Alijotas-Reig, 2013, Cohen et al., 2010).

The catastrophic APS is seen in about 1% of individuals with PAPS or SAPS but in nearly half of them the onset occurs with no previous thrombotic event. There are circa 400 documented cases of CAPS registered by the European Forum on Antiphospholipid Antibodies (https://ontocrf.costaisa.com/es/web/caps/home). However, 5-6% of CAPS cases appear throughout pregnancy or puerperium (Alijotas-Reig, 2013, Gomez-Puerta et al., 2007).

APS is one of the most common causes for unexplained recurrent miscarriages (10-25%), whereas the liability for pregnancy loss varies from 5-50%(Drakeley et al., 1998). The wide range of these results may be due to diversity of study groups, different inclusion criteria and lack of standardization in laboratory settings (Alijotas-Reig, 2013). When Rai et al. examined a large cohort of 500 patients suffering from miscarriages in first and second trimester he discovered that in 15% of all miscarriages APS is the cause (Rai et al., 1995).

2.4 Genetics

Genetics in APS have been studied for several decades. Most autoimmune disorders have a genetic background. The high occurrence of aCL in first-degree relatives of patients suffering from APS or SLE came to attention and suggested a genetic influence (Goldberg et al., 1995, Mackworth-Young et al., 1987). Several studies on families have shown that aPL and APS can accumulate in family members closely related (Goldberg et al., 1995, Ford et al., 1990). However, this is only true in few cases. Ravindran et al. reports on monozygotic twins of whom both developed APS (Ravindran et al., 2013).

A genome-wide study has tried to identify new gene loci that might be responsible for APS and aPL. Although they have found several loci suggestive of inducing aPL presence, follow-up studies in independent and larger clusters must be done in order to replicate their findings. (Kamboh et al., 2013)

3 Pathophysiology

The pathophysiology of APS is still not completely researched, but what we do know is that aPL, which are mandatory for diagnosing APS, bind to negatively charged phospholipids and/or proteins on cell surfaces. The responsible antibodies are LA, aCL and aβ_2-GPI.

Several mechanisms have been suggested to explain the pathogenic effects of aPL.

But two main mechanisms can be distinguished:

1) The inhibition of anticoagulant pathways reliant on protein C, antithrombin or annexin V or the inhibition of fibrinolysis (de Laat et al., 2008, Wahl et al., 2009, Rand et al., 2010)
2) The proinflammatory, procoagulant activation of endothelial cells, monocytes or platelets (Oku et al., 2012)

According to several studies on the etiology of APS, thrombotic and inflammatory mechanisms seem to cause aPL-related injury. Nonthrombotic pulmonary syndromes and obstetric complications in connection with aPL may be good examples of not primarily thrombotic but inflammatory manifestations (Asherson et al., 2005, Asherson et al., 2006, Alijotas-Reig and Vilardell-Tarres, 2010).

Some authors even suggest that aPL cross-react with oxidized low-density lipoprotein and bind to oxidized cardiolipin with subsequent oxidant-mediated damage of the vascular endothelium (Horkko et al., 1996) causing the manifestation of thrombi.

Several patients with clinical symptoms of APS have all three antibodies detected but many only show one of them positive. The three aPL should be viewed as related but distinctly different immunoglobulins and will be considered separately. (Bulletins--Obstetrics, 2002)

3.1 Lupus Anticoagulant Antibody

Lupus anticoagulant is an immunoglobulin that is found mainly in patients with APS but also in patients with SLE. Prolonged coagulation is found in patients with APS as well as SLE. As APS was not known in the time when LA was discovered and LA showed anticoagulant properties in vitro, the responsible antigen was called LA. The name can be misleading, as it is neither specific for SLE nor does it cause anticoagulation within the

situs (Furgal et al., 1993). According to the Euro Phospholipid Project LA is present in 53.6% of the patients with APS (Cervera et al., 2009), which means a majority of these patients are faced with the effects LA has on their coagulation. Reynaud et al. state that LA is significantly associated with arterial and venous thrombosis (Reynaud et al., 2014), although the mechanism still seems unclear.

In vivo LA appears to be responsible for thrombosis and interfering with coagulation by binding to phospholipids on membranes of cells that are involved in the coagulation process such as platelets, monocytes and endothelial cells. Through this binding, the LA segregates phospholipids, limiting the rate of phospholipid-dependent enzymatic reactions of the intrinsic cascade, leading to the prolongation of the partial thromboplastin time (aPTT). (Tripodi, 2009)

LA is not directed against phospholipids alone, but apparently recognizes an epitope, which becomes exposed upon Ca^{+2}-mediated binding of human prothrombin to phospholipids (Bevers et al., 1991) as part of the coagulation pathway.

Using these mechanisms, LA interferes with coagulation and can cause thrombosis leading to the clinical symptoms of APS discussed later in this paper.

3.2 Anticardiolipin Antibody

Anticardiolipin antibody is an antibody that can be found not only in APS but also in many other diseases such as Syphilis, SLE, Behçet's Syndrome (BS) and many more. Cervera at al. found aCL in 87.9% of their patients suffering from APS (Cervera et al., 2002). It is directed against cardiolipin, which is located on the inner membrane of the mitochondrion and interacts with enzymes involved in its energy metabolism (Ren et al., 2014) in addition to its anticoagulant effect.

ACL can be classified as IgM, IgG or IgA. It may be β_2-GPI dependent or independent. In Syphilis aCL is β_2-GPI independent, whereas in autoimmune diseases it is β_2-GPI dependent (McNeil et al., 1990). In the latter case β_2-GPI functions as a cofactor. ACL binds to cardiolipin and subsequently inhibits the anticoagulant activity in the presence of β_2-GPI and is therefore strongly associated with thrombosis (Tsutsumi et al., 1996). But researchers have found that aCL binds not only to cardiolipin but also to β_2-GPI even in the absence of cardiolipin (Matsuura et al., 1994, Roubey et al., 1995, Takeya et al., 1997). Development of these aCL immune complexes results in additional exposure of anionic

phospholipids and platelet activation by unidentified signal transducing mechanisms. This cascade eventually leads to the formation of thrombosis. (Arnout and Vermylen, 2003)

3.3 Anti-β_2-glycoprotein I Antibody

β_2-glycoprotein I (β_2-GPI), also known as apolipoprotein H is an ubiquitous and multifunctional 50-kDa human plasma glycoprotein that binds various anionic substances, including phospholipids, like cardiolipin, lipoproteins, activated platelets, apoptotic bodies, DNA, endothelial cells and heparin (Kandiah and Krilis, 1994). The three dimensional structure is composed of five short-consensus-repeat domains, the so-called sushi domains. The fifth sushi domain (domain V) with its sequence of 82 amino acids appears to be the major phospholipid-binding region (Steinkasserer et al., 1992). Studies exist that verify that domain I might be of additional importance (de Laat et al., 2005). The physiological role of β_2-GPI has not yet been entirely discovered but it can function as a natural inhibitor of thrombus formation, as it inhibits the transformation of prothrombin to thrombin on platelets, the stimulation of the intrinsic pathway of coagulation and it modulates ADP-dependent activation of platelets (Schousboe and Rasmussen, 1995, Nimpf et al., 1986, Schwarzenbacher et al., 1999, Bouma et al., 1999, Di Simone et al., 2007b).

Aβ_2-GPI characterize a large group of antibodies with epitopes against β_2-GPI. The IgG and IgM isotype seem clinically relevant as they are directed against β_2-GPI (Li et al., 2014). Arvieux at al. discovered that aβ_2-GPI inhibited the binding of β_2-GPI to cardiolipin (Arvieux et al., 1998) and are shown to be strongly associated with thrombosis and other clinical manifestations of APS (Triplett, 1993, McNeil et al., 1991). IgG antibodies are more related to clinical symptoms like thrombosis than IgM-class antibodies (de Laat et al., 2005).

3.4 Other Relevant Antibodies

Additional antibodies have been discovered that seem to be relevant in the pathology of APS. Annexin V, antiprothrombin antibodies, antiphosphatidylserine antibodies, antiphosphatidylethanolamine, antibodies against the phosphatidylserine-prothrombin complex, phosphatidylcholin, phosphatidylinositol, phosphatidic acid and glycerophospholipid are some of the antibodies under examination for their pathogenic role, clinical relevance and their use as prognostic factors. Their involvement in

coagulation and thrombogenic properties must be researched more profoundly in order to make them useful markers for APS. (Aoki et al., 1993, Miyakis et al., 2006, Yetman and Kutteh, 1996)

3.5 Thrombosis and Thrombocytopenia

Thrombocytopenia is the leading clinical symptom related to APS. The pathogenesis of thrombocytopenia related to aPL has been investigated for almost 30 years now, but the exact mechanisms remain unclear (Cervera et al., 2011). The aPL seem to bind directly to the activated platelets via β2-GPI (Asherson et al., 1989b, Vazquez-Mellado et al., 1994) and promote further activation and aggregation (Uthman et al., 2008) of platelets and therefore cause thrombosis. The excessive use of platelets causes a deficit of thrombocytes in the circulatory system. Some authors reported that antiplatelet glycoprotein antibodies are associated more strongly with thrombocytopenia than any other aPL or clinical feature (Galli et al., 1994, Godeau et al., 1997, Fabris et al., 1994). The majority of these platelet-specific autoantibodies are IgG type antibodies that may cross the placenta and have an impact on babies born to mothers with PAPS (Chou et al., 2009).

There is some discussion whether thrombocytopenia at a platelet count of $<100 \times 10^9$/L should serve as a clinical criterion for the diagnosis, but specificity would suffer and this criterion is therefore not included in the Sydney criteria (Miyakis et al., 2006).

Thrombocytopenia in a clinical setting is generally mild. The severe form is rare and mostly seen in CAPS and in those patients with thrombotic thrombocytopenic purpura. (Chou et al., 2009) Patients with thrombocytopenia have a higher prevalence of platelet antibodies in their serum (Godeau et al., 1997).

3.6 Pathophysiology in Pregnancy

The source of recurrent pregnancy loss, IUGR, PE, HELLP-Syndrome (hemolysis, elevated liver enzymes, low platelet count), preterm delivery, spontaneous abortion or IUFD in OAPS seems to be placental insufficiency and is thought to be a result of thrombotic events in the placental and decidual circulation (Nilsson et al., 1975, De Wolf et al., 1982, Barrou et al., 2010). Recent investigations on the histology of affected placentas have found little evidence of a specific thrombotic pathology. Due to the heterogeneity of these histological findings, thrombotic events cannot be the sole reason

for the severe clinical outcomes (Salafia and Cowchock, 1997, Lyden et al., 1992, Meroni et al., 2011, Cohen et al., 2011).

A theory on a trigger of the disease in pregnancy has to do with the trophoblast tissue remodeling. Usually anionic phospholipids are found only on the inside of the plasma membrane, but throughout the remodeling process of the trophoblast the negatively charged phospholipids are exposed on the exterior surface and can bind to β_2-GPI, which in return is an antigen for aPL (Di Simone et al., 2007b). β_2-GPI has been proven to be present on the membranes of trophoblast cells and could therefore explain the placental tropism of aPL (La Rosa et al., 1994). These studies show that trophoblast cells can express β_2-GPI on their surface. APL have the ability to then bind trophoblast monolayers in vitro and impair trophoblast cell function. In addition increased complement stimulation and increased production of Tumor Necrosis Factor alpha (TNF-α) and chemokines could be witnessed in in vivo murine models of APS. (Gharavi et al., 2004, Meroni et al., 2008, Di Simone et al., 2007c, Meroni et al., 2011, Salafia and Cowchock, 1997, Lyden et al., 1992)

APL bind to endothelial membranes as well (Williams et al., 2000, Meroni et al., 2004a) and in the presence of β_2-GPI they can induce an endothelial disturbance with subsequent activation of coagulation or stimulation of a proinflammatory response (Di Simone et al., 2007b, Meroni et al., 2004b) with infiltration of the decidua by inflammatory immune cells (Magid et al., 1998, Van Horn et al., 2004, Stone et al., 2006). These findings again indicate a pathogenesis on the basis of coagulation as well as an inflammatory origin and require further investigation.

Di Simone et al. could demonstrate the aPL's ability to bind human endometrial endothelial cells (HEEC) resulting in a significant decrease in both number and total length of capillary formations created by HEEC. This indicates that aPL have multiple pathogenic effects on placental development including declined trophoblast invasion and impaired HEEC differentiation. (Di Simone et al., 2010, D'Ippolito et al., 2012)

Some authors have focused their work on irregularities in the decidual spiral arteries as a disease factor and have found narrowing of the spiral arterioles, intimal thickening, acute atherosis, and fibrinoid necrosis in cases of fetal loss associated with APS. Other study groups have discovered extensive placental necrosis, infarction, and thrombosis. (Branch and Khamashta, 2003)

Among these findings, angiogenesis in the process of development of the placenta is one of the major fields of interest. The vascular endothelial growth factor (VEGF) is responsible

for promoting angiogenesis and placental development. It stimulates the survival, migration and differentiation of endothelial cells and facilitates vascular permeability (Yagel, 2011, Olsson et al., 2006). NF-κB and STAT-3 are molecules that regulate VEGF and angiogenesis. APL can impair the effect these molecules and inhibit angiogenesis, which leads to underdevelopment and/or malformation of the placenta. (D'Ippolito et al., 2012)

Katsuragawa et al. was able to demonstrate that monoclonal aPL inhibit the secretion of human chorionic gonadotropin (hCG) and human placental lactogen (Katsuragawa et al., 1997), which are responsible for maintaining the pregnancy and for the development of the fetus. This could explain the high frequency of abortions occurring in women with APS.

Lately complement activation has been in focus for pathophysiology in APS, especially in regards to pregnancy morbidity (Girardi et al., 2004). By binding to trophoblast cells Koike at al. reported that aPL produce complexes, which stimulate the complement via activation of C3 and C5. The formed C5 attracts and activates leukocytes and monocytes and stimulates the secretion of cytokines, resulting in thrombosis, inflammation and fetal harm (Koike, 2014). Studies have shown the connection between activated C3, C5 and thrombosis and activation of endothelial cells in animal studies (Fischetti et al., 2005). The complement titers in the blood of patients with PAPS were significantly lower compared to healthy individuals (Oku et al., 2009). This is due to the consumption of complement after excessive activation. Activation of the complement system results in mediating inflammatory response and generating thrombin, which may explain the influence of the activated complement on coagulation and formation of thrombosis (Girardi, 2010, Tedesco et al., 1997).

4 Signs and Symptoms

One of the main clinical characteristics of APS is a thrombotic tendency. These thrombi can occur in any vessel. Therefore a vast clinical picture can be depicted with a variety of signs and symptoms, which can be seen in Table 1. Not only thrombosis is a characteristic of APS but also thrombocytopenia and pregnancy complications such as recurrent miscarriages, IUGR, PE, HELLP-Syndrome, preterm delivery, spontaneous abortion or IUFD. Cervera et al. did an extensive study on 1000 affected patients determining the prevalence of the most common signs and symptoms as shown in Table 1 (Cervera et al., 2002).

Table 1 Clinical features of APS

Adapted from (Cervera et al., 2009)

Manifestations	No.	(%)
Peripheral thrombosis		
Deep vein thrombosis	389	(38.9)
Superficial thrombophebilitis in legs	117	(11.7)
Arterial thrombosis in legs	43	(4.3)
Venous thrombosis in arms	34	(3.4)
Arterial thrombosis in arms	27	(2.7)
Subclavian vein thrombosis	18	(1.8)
Jugular vein thrombosis	9	(.9)
Neurologic manifestations		
Migraine	202	(20.2)
Stroke	198	(19.8)
Transient ischemic attack	111	(11.1)
Epilepsy	70	(7)
Multi-infarct dementia	25	(2.5)
Chorea	13	(1.3)
Acute encephalopathy	11	(1.1)
Transient amnesia	7	(.7)
Cerebral venous thrombosis	7	(.7)
Cerebellar ataxia	7	(.7)
Transverse myelopathy	4	(.4)
Hemiballisms	3	(.3)
Pulmonary manifestations		
Pulmonary embolism	141	(14.1)
Pulmonary hypertension	22	(2.2)
Pulmonary microthrombosis	15	(1.5)
Fibrosant alveolitis	12	(1.2)
Other (adult respiratory distress syndrome, pulmonary hemorrhage, pulmonary artery thrombosis)	7	(.7)
Cardiac manifestations		
Valve thickening/dysfunction	116	(11.6)
Myocardial infarction	55	(5.5)
Angina	27	(2.7)
Myocardiopathy	29	(2.9)
Vegetations	27	(2.7)
Coronary by-pass rethrombosis	11	(1.1)
Intracardiac thrombus	4	(.4)
Intra-abdominal manifestations		
Renal manifestations (glomerular thrombosis, renal infarction, renal artery thrombosis, renal vein thrombosis)	27	(2.7)
Gastrointestinal manifestations (esophageal or mesenteric ischemia)	15	(1.5)
Splenic infarction	11	(1.1)
Pancreatic infarction	5	(.5)
Addison's syndrome	4	(.4)
Hepatic manifestations (Budd-Chiari syndrome, small hepatic vein thrombosis)	7	(.7)
Osteo-articular manifestations		
Arthralgia	387	(38.7)
Arthritis	271	(27.1)
Avascular necrosis of bone	24	(2.4)

Table 1. (continued)

Manifestations	No.	(%)
Cutaneous manifestations		
Livedo reticularis	241	(24.1)
Ulcers	55	(5.5)
Pseudovasculitic lesions	39	(3.9)
Digital gangrene	33	(3.3)
Cutaneous necrosis	21	(2.1)
Splinter hemorrhages	7	(.7)
Ophthalmologic manifestations		
Amaurosis fugax	54	(5.4)
Retinal artery thrombosis	15	(1.5)
Retinal vein thrombosis	9	(.9)
Optic neuropathy	10	(1)
Ear Nose Throat manifestations		
Nasal septum perforation	8	(.8)
Hematological manifestations		
Thrombocytopenia (<100,000/**μ**L)	296	(29.6)
Hemolytic anemia	97	(9.7)
Obstetric manifestations (pregnant female = 590)		
Preeclampsia	56	(9.5)
Eclampsia	26	(4.4)
Abruptio placentae	12	(2)
Post-partum cardio-pulmonary syndrome	3	(.5)
Fetal manifestations (pregnancies = 1580)		
Early fetal losses (<10 weeks)	560	(35.4)
Late fetal losses (≥10 weeks)	267	(16.9)
Live births	753	(47.7)
Prematures	80/753	(10.6)

4.1 Vascular Manifestations

The most common presentation of the APS is thrombosis. Arteries or veins, small or big vessels, peripheral or central vessels and any region or organ can be affected. Deep veins of the lower limbs are the most common manifestation sites of thrombosis with 38.9% and the cerebral arterial circulation with 19.8% (Cervera et al., 2009). According to several studies the positivity of multiple aPL is associated with a more severe course of the disease, increasing significantly the rate of thrombosis (Miyakis et al., 2006, Neville et al., 2003, Obermoser et al., 2004)

4.2 Cerebral Manifestations

The brain is one of the human's most fragile organs and as a prothrombotic disease APS can also cause impairment in our cerebrum. Detriment to the brain can occur in the form of a stroke, transient ischemic attacks (TIAs), headaches, migraines, balance problems, memory loss, seizures and spasms and MS-like symptoms (Sanna et al., 2006).

Migraine appears in 20.2% of the 1,000 patients Cervera et al. registered in the Euro-Phospholipid cohort in 2001 and is therefore the most frequent neurologic concomitant of APS (Cervera et al., 2009). However, the connection of the two has not yet been sophistically proven (Sanna et al., 2003).

Strokes may occur as a symptom of the condition in 19% (Cervera et al., 2009) of the patients and is a result of blood clotting in the arteries supplying brain matter. One in five strokes under the age of 45 is due to APS (Nencini et al., 1992). In CAPS 62% of the 250 patients in the European Catastrophic Antiphospholipid Antibody Syndrome registry had cerebral thrombosis or ischemia. Stroke was the cause of death in 13% of the 114 deaths in this CAPS registry (Bucciarelli et al., 2009).

TIAs may be present in 11% (Cervera et al., 2009) of the patients with APS and can cause severe headache or migraine, temporary eyesight loss, temporary loss of speech and weakness or numbness on one side of the body as a result of cerebral ischemia. TIAs are most often present due to middle cerebral artery ischemia, but may occur in any other cerebral artery as well (Sanna et al., 2000).

Epilepsy is prevalent in 7% (Cervera et al., 2009) of the individuals. Although the pathomechanism is still unclear, it is thought to be related to thrombotic events, as APS patients with epilepsy show a higher tendency for thrombosis and especially strokes (Shoenfeld et al., 2004). The prevalence of epilepsy in PAPS is lower than in SAPS (Shoenfeld et al., 2004, Sanna et al., 2000) and has a particularly high association to SLE patients with high aCL titers and may be connected to impaired blood supply (Herranz et al., 1994, Liou et al., 1996, Sanna et al., 2000).

Patients with APS have also been shown to have cognitive impairment and a certain type of dementia due to multi infarct lesions to the brain (Sanna et al., 2003) which is found in 2.5% of subjects (Cervera et al., 2009). This dementia is often presented with loss of cognitive functions and impairment of skills, poor concentration, memory dysfunction, language impairment, judgmental defects and cannot be differentiated from other forms of dementia (Sanna et al., 2003). Elevated levels of aCL and LA strongly correlate with

cognitive dysfunction in contrast to the patients of the control group without these aPL (Hanly et al., 1993, Denburg et al., 1997).

Chorea is a movement disorder that may be associated with oral contraceptives and pregnancy, but there is an established connection between chorea and aPL. It appears to be more frequent in patients with PAPS than SAPS and seems to be a consequence of vascular pathogenesis. (Sanna et al., 2003)

APS may cause symptoms that feign the picture of multiple sclerosis (MS including vertigo, aphasia, unilateral visual loss, diplopia, hemiparesis, progressive myelopathy, spinocerebellar syndrome or neuromyelitis optica (Karussis et al., 1998, Scott et al., 1994). It is hard to distinguish the two on the basis of the clinical examination or even MRI (Cuadrado et al., 2000). White matter tract lesions and basal ganglia damage are more common in patients with high titers of aCL (Erkan et al., 2010).

Other neurological manifestations in APS patients are acute encephalopathy (1.1%), transient amnesia (0.7%), cerebral venous thrombosis (0.7%), cerebellar ataxia (0.7%), transverse myelopathy (0.4%) and hemiballism (0.3%). (Cervera et al., 2009)

4.3 Ocular Manifestations

Ocular involvement can occur as a manifestation of APS in 8-88% of the cases (Utz and Tang, 2011). Monocular or binocular blurring of vision, amaurosis fugax, transient scotoma and visual field defect (Cervera et al., 2009, Asherson et al., 1989b, Castanon et al., 1995, Demirci et al., 1998) can occur but also dry eye symptoms, redness and pain can be some of the symptoms described in affected patients. However, amaurosis fugax is considered to be associated with central nervous system ischemia (Gelfand et al., 1999).

Ocular findings can be divided into anterior and posterior neuro-ophthalmological signs. Anterior ophthalmological findings can be conjunctivitis sicca, vascular tortuosity, microaneurysms, telangiectasia, anterior uveitis, episcleritis and scleritis, punctuate epithelial keratopathy or filamentary keratopathy, marginal thinning, infiltrates and ulceration. (Utz and Tang, 2011)

Posterior findings include venous tortuosity, dilation and flame hemorrhages of the retina, unilateral and bilateral central retinal vein occlusion, central retinal artery occlusion, branched retinal vein occlusion and branched retinal artery occlusion, choroidal infarction via occlusion of the cilioretinal artery, or localized choroidal infarction associated with scotoma (‘triangle syndrome’). (Utz and Tang, 2011)

Most common signs of ocular involvement are amaurosis fugax (5.4%), retinal artery thrombosis (1.5%), retinal vein thrombosis (0.9%) and optic neuropathy (1%) (Cervera et al., 2009).

4.4 Ophthalmological Manifestations

APS can cause problems of the inner ear, such as balance problems, hearing impairment, tinnitus, sudden hearing loss, etc. Mouadeb et al. investigated such complications of the ear and discovered that a significantly high number of patients showed elevated aPL, presumably causing microthrombosis (Mouadeb and Ruckenstein, 2005).

4.5 Pulmonary Manifestations

According to Stojanovich et al. pulmonary manifestations mainly include pulmonary thromboembolic disease, pulmonary hypertension, acute respiratory distress syndrome, primary thrombosis of large and small lung vessels, diffuse alveolar hemorrhage and fibrosing alveolitis. Their study compared the presence of aPL and pulmonary symptoms in PAPS and SAPS, concluding that LA is strongly associated with pulmonary embolism and infarction in SAPS and pulmonary microthrombosis in both APS groups. Major pulmonary arterial thrombosis, acute respiratory distress syndrome and fibrosing alveolitis seem to be associated with aCL IgG antigens especially in SAPS. (Stojanovich et al., 2012) Pulmonary embolism is a result of blood clots travelling from peripheral veins to the lungs and as deep vein thrombosis is the most common manifestation of APS it can cause pulmonary embolism in 14% of these patients (Cervera et al., 2009). It is a life threatening condition and a high proportion of people with untreated deep vein thrombosis will develop a pulmonary embolism with a mortal outcome of 11-23% (Markel, 2005). Symptoms can range from dyspnea, tachypnea, light-headedness, feelings of anxiety and nervousness, angina, hemoptysis to sudden collapse (Miniati et al., 2012). Pulmonary hypertension occurs in 2% of the patients with APS (Cervera et al., 2009) and can cause symptoms like dyspnea, light-headedness during activity, tachycardia, edema, angina, syncope and fatigue. Pulmonary manifestations of APS may not be the most common ones, but the severity of these symptoms demand a quick diagnosis and therapy.

4.6 Cardiac Manifestations

Cardiac manifestations can be detected quite frequently in patients suffering from APS. These appearances include not only stroke but also valvular heart disease, ventricular thrombi and higher risk for coronary heart disease CAD (Cervera et al., 2009). Data are contradictory because of differences in echocardiography technique and descriptions of findings, inconsistent associations with aPL, and population heterogeneity (Wilson et al., 1999).

Valvular heart disease with leaflet thickening due to deposition of immune complexes that may lead to vegetations and valve dysfunction are the most common of these manifestations in APS patients with a prevalence of approximately 30% (Zuily et al., 2013). In patients with primary APS cardiac manifestations are characterized by thrombotic or fibrotic/calcific lesions (Gorki et al., 2008, Cervera, 2000). The mitral valve is affected in most of the cases, followed by the aortic and tricuspid valves, because the surface of the left-sided valves are more vulnerable to micro injuries due to stress, jet effect and turbulence (Gorki et al., 2008). Several studies have shown a significantly higher prevalence of valve defects ranging from 14% to 86% in patients suffering from SLE with aPL than in those without these antibodies (Cervera et al., 2011). The aCL titers correlate directly with the severity of the valvular heart disease (Weiss et al., 2008, Erdogan et al., 2005), which might result in valvular regurgitation and can lead in 4-6% of the cases to valve replacement (Sakaguchi et al., 1998).

CAD may also be present in correlation with age, hypertension and obesity and especially SLE and have to be demarcated from these factors (Singh et al., 1999). CAD is a result of the thrombotic tendency in APS and is part the diagnosis criteria as a thrombotic event (Miyakis et al., 2006). Greco et al. discovered that approximately 40% of their patients with CAD were positive for aPL (Greco et al., 2009). Symptoms can include mild angina to serious myocardial infarction.

Intracardiac thrombi can occur in any heart chamber and present a fatal symptom of APS but it is most common on the right side (Weiss et al., 2008).

4.7 Abdominal Manifestations

4.7.1 Kidneys

Kidney involvement in APS is mostly due to thrombosis within the renal vascular system. The most frequently affected vessels are: preglomerular arterioles, small interlobular arteries and glomerular capillaries (Nochy et al., 1999). Symptoms of renal involvement in APS can be renal artery lesions, hypertension, oliguria, hematuria, lumbar pain, APS nephropathy, renal vein thrombosis, end stage renal disease/renal transplant (Mandreoli and Zucchelli, 1993, Uthman and Khamashta, 2006) but also glomerulonephritis is described (Nochy et al., 2002, Fakhouri et al., 2003, Sinico et al., 2010). 2.7% of all APS patients show one of these Symptoms (Cervera et al., 2009). In CAPS 78% of the patients show kidney related symptoms (Uthman and Khamashta, 2006).

Hypertension occurs fairly often in APS and seems to be the most common feature in kidney related manifestations and can occur in up to 93% of the patients as Nochy et al. discovered in a study with 16 subjects suffering from PAPS and high blood pressure (Nochy et al., 1999), though it is difficult to distinguish from other diseases like idiopathic hypertension. If vascular lesions are already pre-existent, hypertension can worsen these lesions.

The antiphospholipid syndrome nephropathy is characterized by thrombotic microangiopathy, arteriosclerosis, fibrous intimal hyperplasia of arterioles and interlobular arteries, organized thrombi in arteries and arterioles with or without recanalization, fibrous arterial and arteriolar occlusions or focal cortical atrophy and the presence of APS with typical symptoms like arterial hypertension, acute or chronic renal failure, proteinuria and microscopic hematuria (Nochy et al., 1999).

According to Nochy et al. renal insufficiency occurred in 87% of his patients, ranging from mild to end stage renal failure (Nochy et al., 1999).

Renal vein thrombosis seems to be less common, but more often in SAPS (Nochy et al., 2002).

4.7.2 Bowel

Manifestations of the intestines have been reported a number of times. According to Cervera at al. 1.5 % of the APS patients show intestinal manifestations as a result of the thrombotic tendency in APS (Cervera et al., 2009). The most affected organs are the

esophagus and mesenterium (Cervera et al., 2002). Abdominal thrombosis, ischemic bowel and infarction of the intestine can cause symptoms like sudden and severe abdominal pain, fever, emesis, diarrhea, hematochezia and may cause an acute abdomen with a subsequent necessary excision of the affected bowel (Cervera et al., 2007).

4.7.3 Liver and Gallbladder

Hepatic manifestations are rare but occur in 0.7% of the cases causing small hepatic vein thrombosis, gallbladder infarctions, Budd-Chiari syndrome (Cervera et al., 2009), hepatic artery thrombosis and infarction, nodular regenerative hyperplasia, multiple fibrin thrombi (Asherson et al., 1991), cirrhosis, portal hypertension, autoimmune hepatitis and biliary cirrhosis (Uthman and Khamashta, 2007). Symptoms may include nausea, vomiting, jaundice, dark urine and swelling of the abdomen.

The Budd-Chiari syndrome (BCS) is characterized by obstruction of the outflow of hepatic venous blood. Clinically it presents with abdominal pain, hepatomegaly and ascites, and the clinical presentation may range from almost asymptomatic to fulminant liver failure (Uthman and Khamashta, 2007).

4.8 Dermatological Manifestations and Dermis Appendage

A high number of patients show signs of skin involvement. These findings include symptoms like livedo reticularis, skin ulcerations, pseudo-vasculitic lesions, digital gangrene, superficial phlebitis, malignant atrophic papulosis-like lesions, subungual splinter hemorrhages, and anetoderma (Miyakis et al., 2006). Livedo reticularis is found in 24.1% of the patients and is therefore one of the most common symptoms of APS (Cervera et al., 2009). It is usually widespread and present on the limbs, but may also present on the trunk and buttocks but does not grow infiltratively (Frances et al., 2005). It is the result of microthrombosis and decreased blood flow in the peripheral vessels that cause livid and net-like patterns and is more severe in cold conditions. Figure 1 shows livedo reticularis in a patient with SLE.

Poor circulation can cause skin ulcers and present mostly on the lower legs (Frances et al., 2005). 5.5% of the patients are affected by ulcers (Cervera et al., 2009). If the circulation is cut off completely, skin necrosis is the result of lack of blood supply. It is found in 2.1% of the subsets with APS (Cervera et al., 2009) but more often seen in CAPS.

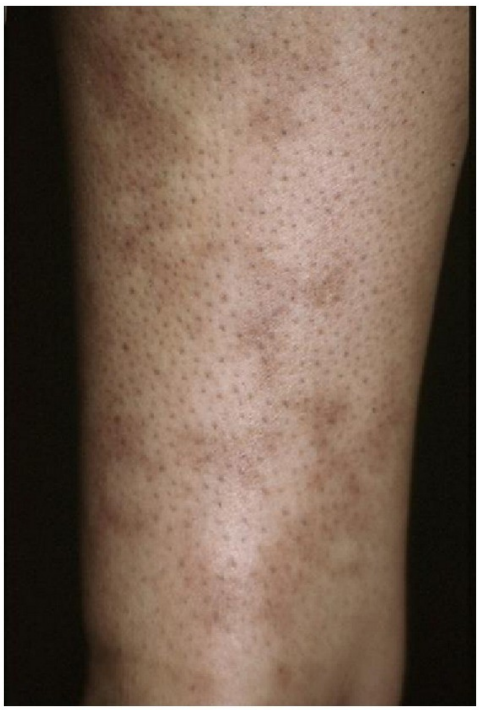

Figure 1 Livedo reticularis in a patient with SLE (Uva et al., 2012)

4.9 Osteo-Articular Manifestations

Bones and joints are not the first manifestation sites to be thought of when diagnosing APS and it is an under-recognized location. Osteonecrosis and avascular necrosis may be caused by impaired blood flow to the bone, which therefore disintegrates. This is seen in 2.4% of the patients with APS (Cervera et al., 2009). The most often affected bone is the femoral head because the collateral blood supply is limited. (Gorshtein and Levy, 2007)

Arthralgia (38.7%) and Arthritis (27.1%) are more frequent symptoms in APS (Cervera et al., 2009) although the latter is more common in SAPS (Tektonidou and Moutsopoulos, 2006). This can cause pain in the affected area and reduced range of motion in the joint.

Sangle et al. has reported spontaneous fractures especially in the metatarsals, which probably is also a result of limited blood supply to the bone (Sangle et al., 2004).

4.10 Hematological Manifestations

Thrombocytopenia in connection with APS is defined as a reduction of platelets <100 x 10^9/L as proposed by Miyakis at al. (Miyakis et al., 2006). According to newer studies, the prevalence of thrombocytopenia can range from 20-53% in patients with APS and is more common than pregnancy morbidity (Cervera et al., 2011). After serious consideration,

thrombocytopenia has not been adopted as a clinical criterion, but can be distinguished as aPL-associated thrombocytopenia (Miyakis et al., 2006). Symptoms of thrombocytopenia include bleeding, petechiae and purpura due to the lack of clotting ability.

Idiopathic thrombocytopenic purpura (ITP) is the result of the autoimmunologic destruction of platelets and is characterized by a purpuric rash and increased tendency to bleed. Cervera et al. reviewed several studies and identified the risk of thrombosis in ITP with a mean of 43% (Cervera et al., 2011).

Patients with APS are in a procoagulant state and due to excessive use of platelets can develop thrombotic thrombocytopenic purpura (TTP), which leads to characteristic schistocytes (Diaz-Cremades et al., 2009).

In rare cases immune mediated destruction of the erythrocytes can cause hemolytic anemia, which is associated with the Evans Syndrome. Hemolytic anemia is seen in 9.7% (Cervera et al., 2009) of the patients and can cause symptoms like lethargy, weakness, dizziness and feeling faint.

4.11 Pregnancy Complications

Pregnancy in APS is associated with a number of complications such as thrombosis, recurrent miscarriages, IUGR, PE, HELLP-Syndrome, preterm delivery, spontaneous abortion, IUFD and placental insufficiency. These complications can be severe and may even endanger the life of the child and the mother.

80% of all fetal losses occur before the 12^{th} week of gestation (Rai and Regan, 2006). The predominant etiology is spontaneous abortion due to abnormal embryonic karyotype (Liu et al., 2015). Nevertheless, APS is the most common thrombotic disorder causing recurrent miscarriages in pregnancies (Bick, 2000, Bick and Hoppensteadt, 2005, Bick, 2008). Women with APS suffer from early fetal loss (before 10 weeks of gestation) in 35.4% and late fetal loss in 16.9% of APS affected pregnancies so that it occurs in the majority of the cases in the first trimester but also strikes in second and third (Bick and Hoppensteadt, 2005, Bick, 2000, Cervera et al., 2009). A sophisticated association has been established between fetal loss and the presence of aPL. According to a study from Oshiro et al. 80% of his patients with aPL had suffered at least one miscarriage (Oshiro et al., 1996). Borelli et al. studied patients with unexplained pregnancy loss and found that 60% of these women had APS (Borrelli et al., 1997). An explanation could be that the vessels in early pregnancy

are still very small and clots can easily block viable and vital vessels nourishing the fetus (Bick, 2008).

Treatment has improved life birth rates immensely. Treating the mothers with aspirin and heparin has achieved live births in almost 80%, while no treatment only achieved this in 20% (Alijotas-Reig et al., 2012). This gives hope to those mothers bearing a desire to have children and shows the importance of meticulous control and follow up.

On the maternal side, complications include preeclampsia, eclampsia (4.4%), abruptio placentae (2%) (Cervera et al., 2009), maternal thrombosis and complications due to treatment such as hemorrhage, osteoporosis with fracture, and heparin-induced thrombocytopenia (Branch and Khamashta, 2003).

The data on prevalence of aPL in these complications show that preeclampsia is associated with aPL in 14%, HELLP syndrome in 28% (Ferrer-Oliveras et al., 2012) and recurring pregnancy loss in 20-40%, compared with 2% of women with a normal obstetric history (Di Simone et al., 2007b).

Preeclampsia seems to be associated with APS in 9.5% (Cervera et al., 2009) of the pregnancies although the relationship is not entirely clear. Circulating aPL in association with severe preeclampsia is of statistical significance, which is why it has been added to the clinical criteria as part of the diagnosis (Miyakis et al., 2006). It is characterized by high blood pressure, proteinuria and edema complicating a pregnancy to the extent of red blood cell break down, liver function impairment, seizures and can lead to a full blown eclampsia, which occurs in 4.4% of pregnancies (Cervera et al., 2009). A delivery is compulsory for the sake of the baby's and the mother's life.

Patients suffering from APS as well as SLE have been under close evaluation and several case studies indicate a higher complication rate concerning preeclampsia (32-50%), placental insufficiency requiring delivery and preterm delivery in 32-65% (Branch and Khamashta, 2003, Branch et al., 1992, Lima et al., 1996, Lockshin et al., 1989, Caruso et al., 1993, Huong et al., 2001).

According to Le Thi Thuong et al. HELLP syndrome can be diagnosed in 10.5% of the patients with APS (Le Thi Thuong et al., 2005), in comparison to the general population, where it is found only in 0.2-0.8%. HELLP in APS coexists with preeclampsia in 70-80% of the cases (Abildgaard and Heimdal, 2013). Anemia, elevated levels of LDH, bilirubin and aminotransferases, low platelet counts and the characteristic presence of schistocytes on a blood smear are features of HELLP syndrome helping to distinguish the condition.

IUGR is seen in 15-30% of APS pregnancies (Branch et al., 1992, Fernandez-Caldas et al., 1996, Caruso et al., 1993) and may be caused by placental injury through activation of the complement cascade (Chou et al., 2009).
Pregnancy can also be complicated by post partum thrombosis during treatment (Branch et al., 1992) therefore screening for thrombosis and anticoagulation is necessary.
Despite the number of possible complications, a pregnancy with APS is not out of the question and very well controllable with modern treatment.

4.11.1 Neonatal Outcome

Not only does APS have an effect on the mother and her pregnancy but also on the neonatal outcome. Newborns of APS affected mothers are at risk for prematurity and its associated complications, to be small for gestational age and for thrombocytopenia (Chou et al., 2009).
According to Chou at al. prematurity occurs in 10-24% of live births with a high incidence of the newborns being small for gestational age (SGA) (Brewster et al., 1999) due to placental impairment through complement activation (Chou et al., 2009). Prematurity is very dangerous for neonates and can lead to a fatal condition. Complications may include extremely low birth weight infant, infections, pulmonary malformation, acute respiratory distress syndrome, cerebral hemorrhage/intraventricular hemorrhage and congenital deformities.
Thrombosis may not only affect the mother but also the child. Some authors have reported on thrombosis located in the brain and other regions although the etiology remains unclear (Silver et al., 1992, Tabbutt et al., 1994).
In APS patients thrombocytopenia can be detected in 20-40% (Galli et al., 1996), but also their offspring might be affected by a decreased number of platelets. In a small study of 11 patients thrombocytopenia was present in four of these women. Three babies of affected mothers had thrombocytopenia as well and one of these babies had subsequent intracranial hemorrhage. (Chou et al., 2009)

4.11.2 Pregnancy and SLE

In pregnant patients with underlying SLE, complications may include lupus exacerbation (Branch and Khamashta, 2003) especially in the third trimester (Doria et al., 2008), lupus nephritis (Rahman et al., 2005), gestational diabetes, preeclampsia, arterial hypertension, pulmonary hypertension, renal failure, thrombophilia and mortality (Clowse et al., 2008). Patients with SLE are at greater chance for serious medical conditions and even mortality than pregnant women without SLE (Clowse et al., 2008).

Women with APS and SLE should insure stable remission, to reduce chances of flares during gestation, as disease activity 4 months prior to pregnancy is associated with higher rates of pregnancy loss (Clowse et al., 2005, Ko et al., 2011, Peart and Clowse, 2014). In case of diagnosed lupus nephritis during pregnancy, these patients are at greater risk for complications during pregnancy than without renal involvement (Rahman et al., 2005).

According to Andreoli pregnancy is not advised in case of the following conditions:

severe pulmonary hypertension (estimated systolic PAP>50mmHg or symptomatic), heart failure, severe restrictive lung disease, moderate/severe chronic renal failure (clearance of serum creatinine below 50ml/min), high-dose steroid therapy (above 25-30mg of prednisone per day), disease flare in the last 4 months, previous severe preeclampsia or HELLP syndrome despite therapy with aspirin and heparin (Ruiz-Irastorza and Khamashta, 2011, Ko et al., 2011, Peart and Clowse, 2014). In these cases appropriate birth control must be counseled and performed.

Regarding pregnancy outcome, babies are at higher risk for preterm delivery, IUFD (20%) (Yan Yuen et al., 2008), neonatal death, SGA, IUGR and neonatal lupus (Andreoli et al., 2012).

Neonatal lupus may occur by anti-Ro/SSA and anti-La/SSB antibodies crossing the placenta and affecting the fetus. The severity of the disease can range from benign to severe. (Andreoli et al., 2012)

If their mothers suffer from SLE and are Ro/SSA positive, the newborns are at risk of a congenital atrioventricular block as well as other less severe echocardiographic abnormalities, such as PQ prolongation and sinus bradycardia (Brucato et al., 2002). Pregnancy has to be monitored closely and SLE complications have to be considered.

5 Diagnosis

Diagnosing APS has been a continuing process for more than 20 years. Finding a consensus on diagnostic criteria has proven to be difficult and is based on experience and clinical know-how. For a long time APS was considered a derivative of SLE, thus called Lupus-like disease and first suspicion of a disease interacting with coagulation started with testing for syphilis.

5.1 Syphilis, Cardiolipin and Lupus Anticoagulant

The first steps of diagnosing APS can be traced back to the 1950s in connection with screenings for syphilis. Practitioners had individually described abnormalities in serological testing. At this point in time, screenings for syphilis had been introduced by the Venereal Disease Research Laboratory that tested for cardiolipin as an active regent. Precipitation of the probe meant a positive test for syphilis. (Aggeler et al., 1946, Ley et al., 1951) Patients with syphilis have aCL in their bloodstream, but so do patients with APS. The only difference being that aCL in patients with syphilis is β_2-GPI independent, whereas aCL in APS is β_2-GPI dependent. Both conditions test positive for syphilis.

Positive test results came to attention of patients with a circulating inhibitor, which prolonged the activated partial thromboplastin time (aPTT) and showed a biologic “false-positive” syphilis test. Frick and Weimar reported on three patients with concluding confirmation of coagulation inhibitors, which involved one patient with definite SLE. All three cases showed positive serological tests for syphilis and suggested an underlying disease that interferes with blood clotting (Frick, 1955). The authors concluded that this disease must be responsible for the positive test results and the clinical picture of blood clots and prolonged aPTT. In time, screening showed that only in 20% of the false positive test results patients were actually suffering from SLE. A different disorder had to be the underlying disease, now named APS (Moore and Mohr, 1952). The inhibitor responsible for the prolonged aPTT is now known as LA and could be discovered thanks to its link to aCL and the false positive syphilis testing. Although LA prolongs the aPTT in the in vitro experiment, it is associated to blood clots and thrombosis in vivo. This paradox occurrence is known as the lupus anticoagulant phenomenon. (Rand et al., 1998, Rand and Wolgast, 2012, Jayakody Arachchillage and Greaves, 2014, Frick, 1955)

Dr. Graham Hughes, a rheumatologist from London, described the syndrome as such in 1983 (Hughes, 1983). This was the first time the disease was described as a separate syndrome from Lupus, although closely related. The impact of Hughes' research on APS has given it the eponym Hughes Syndrome.

Finally in 1989 Asherson at al. stated APS to be categorized also as a primary disease and not only secondary in association with SLE, as it was previously defined by the American College of Rheumatology in 1982 (Asherson et al., 1989a).

In 1990 three independent research groups reported that in order to bind to cardiolipin, aPL need a cofactor, now known as β_2-GPI. (Galli et al., 1990, Matsuura et al., 1990, McNeil et al., 1990)

5.2 Diagnosing APS

In order to complete the picture of the APS syndrome, testing for the antibodies LA, aCL and aβ_2-GPI is not enough to determine the disease, but the clinical signs and symptoms play an important role in the diagnosis. The patients testing positive for aPL also showed a tendency for thrombosis and blood clotting. (Bowie et al., 1963) Subsequent case reports indicated that the LA-associated prothrombotic state could also occur in the absence of SLE or in other connective tissue disorders (Manoharan et al., 1977). These findings conjugate a picture where laboratory findings and clinical signs result in a diagnosis.

In order to diagnose this fairly new illness, a group of specialists came together in 1996 in Sapporo, Japan, to designate preliminary criteria for diagnosing APS, which was a milestone in the history of diagnosing APS. These criteria are referred to as the Sapporo criteria and consisted of laboratory as well as clinical features that needed to be fulfilled in order to definitely determine APS. (Wilson et al., 1999)

These clinical and laboratory guidelines were later revised in 2006 in Sydney when practitioners gathered and reported on new evidence and experience with the old guidelines (Miyakis et al., 2006). Since then, these guidelines have been accepted as the foundation of diagnosis worldwide (see Table 2).

Table 2 Revised classification criteria for the antiphospholipid syndrome
(Adapted from Miyakis et al. (Miyakis et al., 2006))

APS is present if at least one of the clinical criteria and one of the laboratory criteria that follow are met*

Clinical criteria

1. *Vascular thrombosis*❖

   One or more clinical episodes‡ of arterial, venous, or small vessel thrombosis§, in any tissue or organ. Thrombosis must be confirmed by objective validated criteria (i.e. unequivocal findings of appropriate imaging studies or histopathology). For histopathologic confirmation, thrombosis should be present without significant evidence of inflammation in the vessel wall.

2. *Pregnancy morbidity*

   (a) One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation, with normal fetal morphology documented by ultrasound or by direct examination of the fetus, or

   (b) One or more premature births of a morphologically normal neonate before the 34th week of gestation because of: (i) eclampsia or severe preeclampsia defined according to standard definitions, or (ii) recognized features of placental insufficiency¶, or

   (c) Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded.

   In studies of populations of patients who have more than one type of pregnancy morbidity, investigators are strongly encouraged to stratify groups of subjects according to a, b, or c above.

Laboratory criteria**

1. LA present in plasma, on two or more occasions at least 12 weeks apart, detected according to the guidelines of the International Society on Thrombosis and Hemostasis (Scientific Subcommittee on LAs/phospholipid-dependent antibodies)

2. ACL antibody of IgG and/or IgM isotype in serum or plasma, present in medium or high titer (i.e. >40 GPL or MPL, or >the 99th percentile), on two or more occasions, at least 12 weeks apart, measured by a standardized ELISA

3. Aβ_2-GPI of IgG and/or IgM isotype in serum or plasma (in titer >the 99th percentile), present on two or more occasions, at least 12 weeks apart, measured by a standardized ELISA, according to recommended procedures

*Classification of APS should be avoided if less than 12 weeks or more than 5 years separate the positive aPL test and the clinical manifestation.

❖Coexisting inherited or acquired factors for thrombosis are not reasons for excluding patients from APS trials. However, two subgroups of APS patients should be recognized, according to: (a) the presence, and (b) the absence of additional risk factors for thrombosis. Indicative (but not exhaustive) such cases include: age (>55 in men, and >65 in women), and the presence of any of the established risk factors for cardiovascular disease (hypertension, diabetes mellitus, elevated LDL or low HDL cholesterol, cigarette smoking, family history of premature cardiovascular disease, body mass index ≥30 kg m^{-2}, microalbuminuria, estimated GFR <60 mL min^{-1}), inherited thrombophilias, oral contraceptives, nephrotic syndrome, malignancy, immobilization, and surgery. Thus, patients who fulfil criteria should be stratified according to contributing causes of thrombosis.

‡A thrombotic episode in the past could be considered as a clinical criterion, provided that thrombosis is proved by appropriate diagnostic means and that no alternative diagnosis or cause of thrombosis is found.

§Superficial venous thrombosis is not included in the clinical criteria.

¶Generally accepted features of placental insufficiency include: (i) abnormal or non-reassuring fetal surveillance test(s), e.g. a non-reactive non-stress test, suggestive of fetal hypoxemia, (ii) abnormal Doppler flow velocimetry waveform analysis suggestive of fetal hypoxemia, e.g. absent end-diastolic flow in the umbilical artery, (iii) oligohydramnios, e.g. an amniotic fluid index of 5 cm or less, or (iv) a postnatal birth weight less than the 10th percentile for the gestational age.

**Investigators are strongly advised to classify APS patients in studies into one of the following categories: I, more than one laboratory criteria present (any combination); IIa, LA present alone; IIb, aCL antibody present alone; IIc, anti-b2 glycoprotein-I antibody present alone.

5.3 Laboratory Diagnosis

In order to come to a final diagnosis the clinical criterion is insufficient. Laboratory testing for a positive aPL is required. According to the current guidelines of diagnosis three different aPL must be tested for and testing must be positive twice at least 12 weeks apart (see Table 3). Testing has proven to be difficult regarding specificity, sensitivity and standardization. All three aPL should be tested for in different assays as they have different properties concerning clinical relevance, risk for further thrombosis, specificity and sensitivity. Many patients test positive for APS but show no clinical consequences (Levine et al., 2002). Physicians should keep in mind that aPL are found in up to 5% of the general population and in up to 35% of patients with SLE (Branch and Khamashta, 2003). The prevalence of aPL increases with age, particularly in elderly patients with concomitant chronic diseases (Cervera et al., 2002). Furthermore, aPL may only be transient in certain circumstances. During a thrombotic event, especially aCL and LA may fall due to their consumption during thrombotic events. Therefore testing is not advised during or immediately after a thrombotic event. (Drenkard et al., 1989) An overview of the aPL is given in Table 3.

Table 3 Antiphospholipid antibodies

(Adapted from (Cohen et al., 2010))

Antibody type	**aCL**	**aβ_2-GPI**	**LA**
Test	aCL ELISA	aβ_2-GPI ELISA	LA assay*
Test guidelines	Pierangeli et al. (2008) (Pierangeli and Harris, 2008)	None yet	Pengo et al. (2009) (Pengo et al., 2009)
Which antibodies are detected	Antibodies against cardiolipin and cardiolipin bound β2 glycoprotein I	Antibodies against β2 glycoprotein I	Detects immunoglobulins that cause prolonged clotting times in vitro but are associated with thrombosis in vivo
Relevant isotypes	IgG, IgM	IgG, IgM	NA
What titers are considered positive	Medium to high: >99th centile, or >40 IgG or IgM phospholipid units†	Medium to high: >99th centile, or IgG or IgM phospholipid units†	NA
Is the test influenced by oral anticoagulation	No	No	Yes. Both heparin and warfarin influence the test results, so testing during treatment is controversial
Is there an overlap with other tests	Yes, this test overlaps with that for lupus anticoagulant	Yes, this test overlaps with that for lupus anticoagulant	Yes, anti-β2 glycoprotein I and anticardiolipin antibodies can have an anticoagulant effect, but other antibodies, such as antiprothrombin and antiannexin V, can contribute to this effect

*A set of coagulation assays in three steps: screening (identification of a prolonged clotting time), mixing (confirmation of an inhibitor and exclusion of factor deficiencies), and confirmation (confirmation of phospholipid dependence of the inhibitor).

†1 unit=1 μg of antibody.

5.3.1 Lupus Anticoagulans

LA was the first aPL to be discovered and it appears to be the most clinically relevant aPL as it represents the greatest risk factor for pregnancy morbidity and thrombosis (Galli et al., 2003b, Urbanus et al., 2009, Lockshin et al., 2012, Tuthill and Khamashta, 2009, Miyakis et al., 2006). The LA is a misnomer as it is neither specific for Lupus nor does it inhibit coagulation. On the contrary, it induces coagulation in vivo (Furgal et al., 1993). There are several assays that can test for LA which include using activated partial aPTT-based assays and dilute Russell's viper venom time (dRVVT) (Miyakis et al., 2006). For a positive result at least one of the two must be positive. Other tests are not recommended due to lack of experience rather than poor performance (Pengo et al., 2009).

Testing is not advised while the patient receives oral anticoagulants because medication influences the final results. Cut-off levels remain a topic of discussion. Each laboratory should use their own cut-off levels, as fixed levels do not correlate with the different laboratories and their instruments. It would be advisory to rather use a normalized ratio (test sample:control sample) individualized in each institution. A suitable method to institute cut-off levels is to measure LA in 40 healthy controls and determine the geometric mean ±2SD. The results are considered positive when they are above the local cut-off value. (Miyakis et al., 2006)

Furthermore, aβ_2-GPI-depandant LA assays show a greater association to thrombosis than antibodies directed at prothrombin (Swadzba et al., 2011).

Table 4 shows the classical laboratory procedures in LA detection.

Table 4 Classical findings for LA

(Modified from Keeling et al. (Keeling et al., 2012))

1. Prolongation of a phospholipid-dependent clotting assay (preferably aPTT or dRVVT)
2. Mixing study with 1:1 proportion (patient's plasma/normal pooled plasma) without preincubation and reassessment of the clotting assay (Step 1); if still prolonged either LAC or a specific factor inhibitor are present; if corrected, LAC is excluded and the cause is rather a specific factor deficiency
3. Confirmation that the inhibitory activity is phospholipid-dependent by relative rectification of the atypical clotting time when the concentration of phospholipid is increased in the screening test(s) that showed atypical results
4. Exclusion of other coagulopathies, which may show similar results or accompany the LAC presence; specific factor assay might be necessary

5.3.2 Anticardiolipin Antibody

The test for aCL is probably the most sensitive aPL test, although standardization is still poor (de Groot et al., 2008). The enzyme-linked immunosorbent assay (ELISA) is used to detect aCL indirectly. The detected protein binds to Cardiolipin, which is coated on a microtiterplate surface (Delgado Alves et al., 2005).

Three immunoglobulin types are tested for: IgG, IgM and IgA with the patient's own β_2-GPI as a cofactor. Depending on the type of immunoglobulin the risk of thrombosis or pregnancy complications may vary. IgG have the highest incidence of thrombosis (de Laat et al., 2005), whereas high IgA titers are not a criterion for laboratory diagnosis (Miyakis et al., 2006).

Cut-off levels are defined as >40 GPL or MPL, or >the 99th percentile of healthy controls. These tests are more sensitive but less specific than aβ_2-GPI ELISAs and have to test positive at least twice 12 weeks apart in order to suffice as a diagnostic criterion. (Miyakis et al., 2006)

5.3.3 Anti-β_2-Glycoprotein I

In 1990 β_2-GPI was found to enhance the detection of aCL and LA (Koike, 2014) and plays a major role in APS. This antibody is also detected via ELISA. IgG and IgM isotypes are an independent risk factor for thrombosis and pregnancy complications (Galli et al., 2003a, Reber and de Moerloose, 2004, Faden et al., 1997, Lee et al., 2001).

The cut-off limit is >the 99th percentile of IgG and IgM isotype, tested at least twice 12 weeks apart (Miyakis et al., 2006). Interlaboratory standardization with detecting β_2-GPI is better than with aCL but still variable, wherefore standardized plates as well as purity, concentration and source of β_2-GPI, calibrators and units of measurement are encouraged (Miyakis et al., 2006).

5.4 Differential Diagnosis

5.4.1 Thrombocytopenia and Other Prothrombotic Disorders

One of the many symptoms of APS is thrombocytopenia which may show as a first sign of the disease. Essential differential diagnoses are TTP, heparin-induced thrombocytopenia (HIT) and disseminated intravascular coagulation (Lim, 2009). It remains a challenge to differentiate these conditions. In order to diagnose APS, close monitoring of persistent aPL and clinical manifestations like thrombosis or pregnancy morbidity is necessary (Miyakis et al., 2006). Nevertheless, in TTP, HIT and other thrombotic microangiopathies including hemolytic uremic syndrome and HELLP syndrome aPL seem to be present (Uthman and Khamashta, 2007). In TTP one of the main symptoms is microangiopathic hemolytic anemia. Usually the blood smear shows typical schistocytes and evidence of hemolysis, which is not common in APS.

If the patient is taking heparin, a HIT must be considered and can be diagnosed by an immunoassay antigen test (Lee and Arepally, 2013) and usually occurs within 5-14 days of heparin treatment (Warkentin, 1998).

Patients with DIC typically test negative for aPL and often show signs of thrombocytopenia, coagulopathy and thrombotic or hemorrhagic complications (Lim, 2009). Severe DIC presents not only with a low platelet count but also decreased fibrinogen and antithrombin (consumption coagulopathy).

Homocysteinemia, myeloproliferative disorders, and hyperviscosity should be tested for in a routine blood examination (Levine et al., 2002).

5.4.2 Systemic Lupus Erythematodes

To distinguish SLE and APS may be one of the hardest differential diagnoses as the two are closely related to each other and one may present a platform for the other one to develop on (Miyakis et al., 2006). APS was initially thought only to be present in SLE patients, according to the 1982 criteria of the American College of Rheumatology for the classification of SLE. These guidelines were subsequently revised in 1997, when APS was established as a disease on its own (Asherson, 2008).

Both conditions may present with aPL positivity and vascular involvement or obstetrical manifestations APS can also show some SLE features like autoimmune hemolytic anemia and mild reduction in complement and anti-nuclear antibodies (ANA), which makes differential diagnosis nearly impossible.

Renal involvement in APS is common and can be distinguished from SLE renal involvement by the significant titer of ANA. Also with the presence of other autoantibody specificities such as anti-native DNA, anti-Sm or anti-C1q, complement consumption, and specific histological findings from a renal biopsy (Emmi et al., 2014).

Neurological symptoms in APS and SLE can be so similar that not even an MRI can distinguish the lesions undisputably (Sanna et al., 2006). The discrimination is vital because the treatment regiments are completely different. APS would require anticoagulants whereas in neuro-SLE the use of pulse high dose steroids associated with immunosuppressive drugs is indicated (Fanouriakis et al., 2013). Findings of significant titer of specific circulating autoantibodies like anti-ribosomal P, low complement levels, or other organs involvement would be more indicative of SLE (Emmi et al., 2014).

5.4.3 Genetic and Acquired Thrombophilia

A hereditary or acquired disorder that induces thrombotic events may imitate APS as one of the clinical criteria is thrombosis (Miyakis et al., 2006). In every case of thrombosis, other causes have to be ruled out.

5.4.4 Behçet Syndrome

BS is a systemic autoimmune vasculitis with mucocutaneous, ocular, and neurological involvement. A variety of the patients with BS show recurrent vascular thrombosis. This could represent the main clinical manifestation of the disease, thus obscuring the

differential diagnosis with APS. Therapy in this case would be corticosteroid or immunosuppressive therapy rather than anticoagulation, because of its primary inflammatory vascular origin (Silvestri et al., 2014).

Strikingly the incorrect administration of anticoagulants in BS could be dangerous if used in patients with clinically silent pulmonary artery aneurisms. Given that the risk of rupture is very high in this case (Hatemi et al., 2008).

In conclusion, aPL can be found in BS with doubtful clinical significance (Zivkovic et al., 2011). Yet, frequent bipolar aphthosis and ocular involvement, are highly suspicious for BS (Emmi et al., 2014).

5.4.5 Multiple Sclerosis

Senna et al. have concluded in a paper on the involvement of the central nervous system in APS that distinguishing APS from MS can be very difficult. A detailed medical history, a previous history of thrombosis and/or fetal loss and the response to anticoagulant therapy might be helpful in the differential diagnosis. The sudden onset and decree of symptoms, especially in regard to visual symptoms and atypical neurological characteristics in MS, such as headaches or epilepsy specifically suggest APS rather than MS. If not at all, they think that at least a subgroup of patients with 'non-classic' MS should be tested for aPL. (Sanna et al., 2003)

5.4.6 Physiological Pregnancy, HELLP, Preeclampsia, Lupus Flare

In case of OAPS, several other conditions have to be taken into account when the patient suffers from APS. It can be a difficult task to distinguish an SLE flare from physiological changes in pregnancy. Critical conditions like preeclampsia and HELLP syndrome can occur early in pregnancy and must be detected as early as possible in order to prevent life threatening conditions. (Andreoli et al., 2012) Table 5 presents a guideline for clinicians to distinguish a physiological pregnancy from HELLP, preeclampsia and a lupus flare.

Table 5 Differential diagnosis between physiological pregnancy, lupus flare, pre-eclampsia and HELLP syndrome

(Adapted from (Andreoli et al., 2012))

Signs and symptoms	**Physiological pregnancy**	**Active Lupus**	**Pre-eclampsia**	**HELLP syndrome**
Constitutional symptoms	Fatigue, Palmar erythema, Melasma, Hair loss, Increased respiratory rate and dyspnea, Back pain, Non-inflammatory joint effusion, Headache	Fatigue, Lupus-associated rash, Lymphadenopathy, Serositis, Inflammatory arthritis, Headache	Headache, Confusion, Visual changes, Stroke	Uncommon
Anemia	50% of healthy pregnancies. Hemolytic anemia is not usual	Possible hemolytic anemia: LDH, direct Coomb's, peripheral blood smear alterations.	Usually absent	Microangiophatic hemolytic anemia. LDH ≥ 600 UI/ml; schistocytes at peripheral blood smear
Thrombocytopenia	Possible (8% of healthy pregnancies) usually values ≥ 100.000	Normal or low	Normal or low in severe pre-eclampsia	Low, ≤100,000
Serum creatinine	Decreased	Normal or rising	Normal or rising	Normal
Proteinuria	≤300 mg/24 h	Normal or rising	≥300 mg/24 h up to ≥5000 mg/24 h in severe pre-eclampsia	Normal or rising
Blood pressure	Decreased	Normal or rising	Rising up to ≥160/110 in severe pre-eclampsia	Normal or rising
Liver function tests	Normal	Normal or high	Normal or high	AST and ALT generally ≥1000 UI/ml
Complement levels	Rising	Normal or decreased	Normal	High levels of split components (C3a, C5a)
Anti-dsDNA antibodies	Negative	High		

6 Management

Patients with APS are at great risk of thrombosis and therefore the combination of low dose aspirin (LDA) and heparin is used to inhibit coagulation, despite the danger of bleeding.

In general patients must be evaluated on clinical status, history of thrombosis and miscarriages, and laboratory findings (Branch and Khamashta, 2003). Asymptomatic patients with laboratory findings do not require treatment if no further co-morbidities exist (Tuthill and Khamashta, 2009). Prophylactic therapy in these patients may include reducing risk factors like oral contraceptives, smoking, hypertension, or hyperlipidemia (Keeling et al., 2012). In case of surgery or hospitalization medicinal prophylaxis is needed, as well as management of any related autoimmune disease. Usually low-dose aspirin is administered in this case (Tuthill and Khamashta, 2009). Nonetheless, the efficacy of low-dose aspirin as a first line prevention of adverse effects in APS remains controversial (Barbhaiya and Erkan, 2013).

Second-line treatment may include steroids, hydroxychloroquine (HCQ), statins, intravenous immunoglobulin injections, and plasmapheresis (Alijotas-Reig, 2013, Comarmond and Cacoub, 2013).

The APS Treatment Trends Task Force recommends hydroxychloroquine only for patients suffering from APS and SLE as it can reduce the risk of thrombosis in experimental models and SLE patients. It reduces lupus flares, has multiple targeted effects and a good safety profile. It may be considered as an adjunctive treatment in refractory cases. (Broder and Putterman, 2013, Erkan et al., 2014, Izmirly et al., 2010)

In patients with hyperlipidemia or refractory APS the use of statins should be considered (Erkan et al., 2014). Lefkou et al. was able to show an effective use of pravastatin in a woman with preeclampsia, allowing her to carry to term (Lefkou et al., 2014). Trials for randomized studies are currently recruiting.

In case of thrombosis a full anticoagulation with subcutaneous or intravenous heparin succeeded by warfarin therapy is required (Erkan et al., 2014). Recent studies evaluated the target for the international normalized ratio (INR) to level off at 2.0-3.0 for venous thrombosis and 3.0 for arterial thrombosis (Ruiz-Irastorza et al., 2011, Keeling et al., 2012). An INR of 3.0-4.0 should be aimed for Patients with recurrent thrombotic incidents, if their target INR was achieved at the time of occurrence. For grave or refractory cases, a combination of warfarin and additional anticoagulant may be used. (Lim et al., 2006)

After a clinical symptom like thrombosis, stroke, MI or obstetric complications treatment in patients with APS is generally for life. (Erkan et al., 2014)

Sufficient data do not exist regarding new oral anticoagulants (i.e., direct thrombin inhibitors and factor Xa inhibitors) in APS patients. They may be considered in patients with an allergy towards warfarin or difficult to treat patients. (Barbhaiya and Erkan, 2013, Erkan et al., 2014) The RAPS (Rivaroxaban in antiphospholipid syndrome) trial is currently ongoing and the usefulness of new oral direct thrombin or anti-factor Xa inhibitors shall be proven (Erkan et al., 2014).

Rituximab, a B-cell inhibitor may be considered for patients with hematologic and microthrombotic/microangiopathic manifestations and those with refractory to treatment, as a nonrandomized prospective study showed that rituximab could be effective for seronegative aPL manifestations (i.e. thrombocytopenia and skin ulcers) (Nalli et al., 2014, Erkan et al., 2014).

The terminal complement inhibitor eculizumab has proven to be successful in CAPS especially in refractory cases (Shapira et al., 2012, Lonze et al., 2010, Canaud et al., 2013, Lonze et al., 2014, Strakhan et al., 2014)

6.1 Obstetric Management

APS is one of the few causes of pregnancy failure that can be treated successfully with pregnancy rates of 70-80%(Branch and Khamashta, 2003, Cervera et al., 2009).

6.1.1 Primary Care

For optimal care of patients suffering from APS it is necessary for the women to consult a specialist in case they desire to have children. Patients need to know about the signs of thrombosis and thromboembolism and must be informed accordingly (Andreoli et al., 2010). Not only is it important for the patient to look out for clinical signs of APS, but the practitioner has to examine the patients frequently and meticulously for signs and symptoms of thrombosis and thromboembolism, eclampsia or decreased fetal agility. Perinatal visits should be completed every 2-4 weeks of gestation and then every 1-2 weeks to monitor fetal growth, preeclampsia and vitality of the fetus. Ultrasonography is advised every 3-4 weeks commencing at 17-20 weeks' gestation to assess evidence of

preeclampsia, evidence of fetal growth restriction and amniotic fluid volume. (Branch and Khamashta, 2003) This process is described in Figure 2.

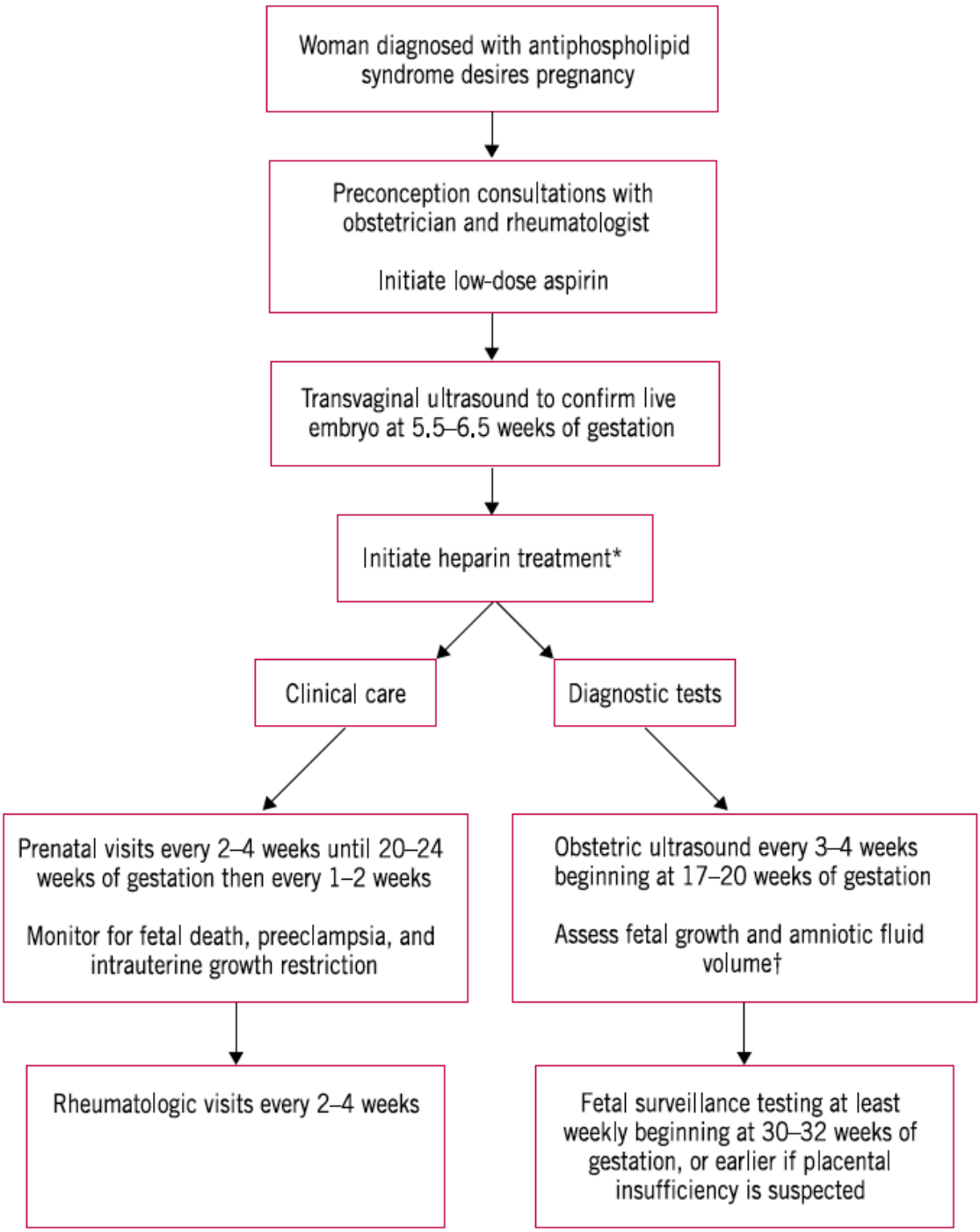

Figure 2 Suggested algorithm for the management of APS in pregnancy

*See Table 7 for dosing. †In the United Kingdom, Doppler assessment of the uterine arteries is commonly used at 20–24 weeks' gestation for the prediction of preeclampsia and placental insufficiency risks. This is not commonly done in the United States. (Branch and Khamashta, 2003)

In uncomplicated APS, ultrasonography is recommended at 30-32 weeks' gestation to assess fetal growth. Stalling fetal growth may indicate uteroplacental insufficiency in patients with APS. (Branch and Khamashta, 2003)

A good marker for general practitioners can be the hCG. Katsuragawa at al. demonstrated that aPL have the ability to decrease secretion of hCG (Katsuragawa et al., 1997). Abnormalities in hCG levels may indicate adverse pregnancy progression.

Cytotoxic and teratogen drugs are not recommended during pregnancy. If a pregnancy is desired, these drugs should be stopped several months in advance of a pregnancy or replaced by a less harmful drug. This is true especially for drugs like methotrexate, leflunimod, cyclophosphamide and Marcumar. Patients requiring immunosuppressant therapy after an organ transplant or to treat certain autoimmune diseases may change to tacrolimus, because of its feasible use during pregnancy (Nevers et al., 2014).

In patients with thrombocytopenia and refractory to glucocorticoids, splenectomy during pregnancy may be considered (Hardwick et al., 1999, Galindo et al., 1999).

6.1.2 Therapeutic Treatment

The main aim of medicinal treatment is to reduce the risk of maternal thrombosis, preeclampsia, placental injury, IUGR, preterm birth and fetal death. Usually low dose aspirin and low molecular weight heparins (LMWH) are used in pregnant women (Empson et al., 2005).

6.1.2.1 Effects of Low Molecular Weight Heparin

LMWH has not only an antithrombotic effect but also works as ananti-inflammatory in the presence of aPL (Han et al., 2011). At the fetal-maternal border, heparin has an anti-inflammatory effect and increases survival (Hills et al., 2006, Mulla et al., 2009). These effects are different from its anticoagulant stereotype, which may be a crucial step to preventing aPL-mediated pregnancy loss.

LMWH can inhibit the binding of aPL to trophoblast cell membranes and reduce the subsequent complement activation at various interfaces in the classical, alternative and terminal pathways of coagulation (Cohen et al., 2011, Meroni et al., 2011, Di Simone et al., 1999, Girardi et al., 2004, Di Simone et al., 1997). It can identify and bind to the positively charged molecule on domain V of the β_2-GPI and functions on the aPL binding

location as a competitive inhibitor (Guerin et al., 2002) and hinders the subsequent loss of placental invasion and differentiation of trophoblast cells (Di Simone et al., 1999, Di Simone et al., 1997, Di Simone et al., 2007a). This may protect the trophoblast cells from aPL-mediated injury and damage, especially in the early stages of pregnancy and improve the course and outcome of pregnancy (Di Simone et al., 2007a, Di Simone et al., 2007c).
Heparin can also have a positive impact on complement activation due to its anti-inflammatory effect by preventing leucocytes from binding to the endothelium, avoiding cytokine secretion (Girardi, 2005, Berman et al., 2005).
D'Ippolito at al. describes an additional effect of LMWH in an extensive study on angiogenesis in in vitro and in vivo experiments. They found that LMWH also has an effect on aPL-mediated HEEC angiogenesis in terms of up-regulation of signaling pathways and transcriptional factors, which are down-regulated in the presence of aPL (D'Ippolito et al., 2012). Vascular endothelial growth factor (VEGF) promotes the survival, migration and differentiation of endothelial cells and mediates vascular permeability and is therefore a key element in angiogenesis as a cornerstone of placental development (Yagel, 2011, Olsson et al., 2006). NF-κB and STAT-3 regulate VEGF and angiogenesis, which is negatively affected by aPL. LMWH may prevent the aPL-mediated inhibition of HEEC angiogenesis by stimulation of NF-κB and STAT-3 and re-establishing the angiogenic competence of HEEC. Therefore, LMWH not only has an effect on the fetal side (trophoblast cells) but also on the maternal side (HEEC). These findings complement the therapy for APS with LMWH in addition to its anti-coagulant potentials. (D'Ippolito et al., 2012)

6.1.2.2 Effects of Intravenous Immunoglobulin Therapy

The efficacy of intravenous immunoglobulin therapy (IVIG) has been proven in connection with SLE. IgG pooled from plasma of healthy donors may bring relief to the clinical symptoms shown by the individual with autoimmune disorders like Guillain Barré syndrome, chronic inflammatory demyelinating polyneuropathy, myasthenia gravis, corticosteroid resistant dermatomyositis, Kawasaki's syndrome and SLE. (Triolo et al., 2004) These immunoglobulins work in various manners as shown in Table 6.

Table 6 Immunoregulatory effects of immune globulin
Adapted from Triolo at al. (Triolo et al., 2004)

1. Modulation of the expression and function of fc-receptors
2. Interference with activation of complement and the cytokine network
3. Provision of anti-idiotypic antibodies and effects on the activation
4. Differentiation and effector functions of T cells and B cells

IVIG is recommended for patients with refractory APS and SAPS, but not as a first-line treatment, but rather as a second line in addition to LMWH (Triolo et al., 2004). Unfortunately more extensive randomized trials are needed to obtain knowledge about the right dosage of IVIG and to understand the proper mechanisms and efficacy of this treatment (Sciascia et al., 2012). Several case reports show that IVIG can be successful in treating APS (Kronbichler et al., 2014, Tenti et al., 2013, Mar et al., 2014, Ensom and Stephenson, 2011).

6.1.2.3 Effects of Plasmapheresis and Therapeutic Plasma Exchange

Plasmapheresis in APS is the process of separating blood components extracorporeally and filtering out undesired components like aPL, cytokines, and returning the filtered plasma product to the body.

Therapeutic plasma exchange is the procedure of discharging the filtered plasma and replacing it with fresh frozen plasma (FFP). This process eliminates pathologic IgG aCL and aβ_2-GPI as well as cytokines, TNFα and complement. In addition, FFP contains natural anticoagulants, like antithrombin III and protein C. The removal of 2-3 liters of plasma for a minimum of 3-5 days is the usual procedure. Plasma exchange is mostly used for TTP and CAPS. The aPL and their pathomechanism can be reduced through plasmapheresis and plasma exchange and can protect a patient during a difficult period, such as throughout a surgery or even pregnancy. (Erkan et al., 2003)

6.1.2.4 Effect of Hydroxychloroquine

The antimalarial hydroxychloroquine has been tested on mice and is found to reduce the degree and time of thrombus perseverance (Edwards et al., 1997). It has reverse thrombogenic capabilities and can reverse aPL-mediated platelet stimulation (Keeling et

al., 2012). It can also reduce the binding of aPL-β_2-GPI complexes to phospholipid bilayers and cells (Asherson, 2008), reverse the connection between aPL and human placental syncytiotrophoblasts, restore annexin A5 expression and inhibit Toll-like receptors (Keeling et al., 2012, Rand et al., 2010, Wu et al., 2011). In patients with SLE hydroxychloroquine has been shown to reduce flares, damage, cardiovascular events and mortality (Ruiz-Irastorza et al., 2010b). Keeling et al. recommend hydroxychloroquine in all patients with SLE due to its primary thrombosis prevention competences (Keeling et al., 2012).

6.1.2.5 Treatment and Dosage

According to Branch at al. women with APS and a wish for children should start on low dose aspirin as soon as they are considering conception. Maternally administered heparin is then given in the early first trimester after ultrasonographic evidence of a live embryo (see Figure 1). (Branch and Khamashta, 2003) Women that are taking oral anticoagulants should switch to heparin as soon as a pregnancy is confirmed due to the teratogen effect of oral anticoagulants (Marchetti et al., 2013).

In Europe LMWH are generally used, however in the United States unfractured heparin (UFH) is administered mainly due to cost considerations (Branch and Khamashta, 2003). Although LMWH has a better safety profile and has to be administered only once a day, data on direct comparison are scarce (Keeling et al., 2012). There are two small pilot studies that show an equivalent outcome with either LWMH with LDA or UFH with LDA in preventing pregnancy loss (Stephenson et al., 2004, Noble et al., 2005). Despite the little evidence, LMWH has widely replaced UFH in obstetric treatment of APS, because of safety and simple use (Keeling et al., 2012).

The dosages vary according to risk factors and medical history although sufficient studies have not been undertaken. Recommendations for UFH and LMWH are shown in Table 7.

Table 7 Subcutaneous Heparin Regimens Used in the Treatment of Antiphospholipid Syndrome During Pregnancy

Adapted from Branch at al. (Branch and Khamashta, 2003)

Prophylactic regimens
Recommended in women with no history of thrombotic events-diagnosis because of recurrent preembryonic and embryonic loss or prior fetal death or early delivery because of severe preeclampsia or severe placental insufficiency
Standard heparin
1) 7500–10,000 U every 12 hours in the first trimester, 10,000 U every 12 hours in the second and third trimesters
Low molecular weight heparin
1) Enoxaparin 40 mg once daily or dalteparin 5000 U once daily or enoxaparin 30 mg every 12 hours or dalteparin 5000 U every 12 hours
Anticoagulation regimens
Recommended in women with a history of thrombotic events
Standard heparin
1) Every 8–12 hours adjusted to maintain the midinterval heparin levels* in the therapeutic range
Low molecular weight heparin
1) Weight adjusted (e.g. enoxaparin 1 mg/kg every 12 hours or dalteparin 200 U/kg every 12 hours)
2) Intermediate dose (e.g. enoxaparin 40 mg once daily or dalteparin 5000 U once daily until 16 weeks of gestation and every 12 hours from 16 weeks of gestation onwards)

* Heparin levels = anti-factor Xa levels. Women without a lupus anticoagulant in whom the activated partial thromboplastin time is normal can be observed using the activated partial thromboplastin time.

Women with no history of thrombotic events nor diagnosis because of either recurrent preembryonic and embryonic loss or prior fetal death or early delivery because of severe preeclampsia or severe placental insufficiency are recommended the prophylactic use of either standard heparin with 7500–10,000 U twice a day in the first trimester, 10,000 U every 12 hours in the second and third trimesters or Low molecular weight heparin, that is to say enoxaparin 40 mg once daily or dalteparin 5000 U once daily or enoxaparin 30 mg every 12 hours or dalteparin 5000 U every 12 hours (Branch and Khamashta, 2003).

Women with a history of thrombotic events have a greater risk of thrombosis and have to adapt their regiment accordingly. Treated with standard heparin, these women should receive a dosage every 8-12 hours sufficient to maintain the midinterval anti-factor Xa levels in the therapeutic range. Using low molecular weight heparin there are two options: On the one hand it can be administered weight adjusted (e.g. enoxaparin 1 mg/kg every 12 hours or dalteparin 200 U/kg every 12 hours) or an intermediate dose can be applied (e.g.

enoxaparin 40 mg once daily or dalteparin 5000 U once daily until 16 weeks of gestation and every 12 hours from 16 weeks of gestation onwards) (Branch and Khamashta, 2003). Branch at al. suggest that women with an extensive history of recurrent thrombotic events or a cerebral thrombotic event should make reasonable use of warfarin rather than heparin (Branch and Khamashta, 2003). Women that are otherwise healthy with repeated pregnancy loss and low titers of aPL may use LDA or may not require treatment at all (Pattison et al., 2000). Patients with aPL and a history of preeclampsia or IUGR are advised to take LDA during their pregnancy (Keeling et al., 2012). Treatment regimens according to the state of research are shown in Table 8.

Table 8 Proposed Management for Women with aPL Antibodies

Feature	**Risk of thrombosis**	**Management**		
		Pre-conception	**Pregnant**	**Postpartal and nonpregnant**
APS with prior fetal death or recurrent pregnancy loss	high	Low dose aspirin as soon as pregnancy is desired	Heparin in prophylactic doses (e.g. Enoxaparin 40 mg once daily or dalteparin 5000 U once daily or enoxaparin 30 mg every 12 hours or dalteparin 5000 U every 12 hours) administered subcutaneously with low-dose aspirin daily as soon as pregnancy is detected Calcium and vitamin D supplementation	Post partum: Heparin 3-5 days post partum Nonpregnancy: Optimal management uncertain; options include no treatment or daily treatment with low-dose aspirin
APS with prior thrombosis or stroke	22 to 69%	Low dose aspirin as soon as pregnancy is desired, change warfarin to Heparin	Full anticoagulation with heparin (does not cross the placenta) every 8–12 hours adjusted to maintain the midinterval heparin levels in the therapeutic range (e.g. enoxaparin 1 mg/kg every 12 hours or dalteparin 200 U/kg every 12 hours)	Warfarin as soon as clinically stable, administered daily in doses to maintain international normalized ratio of =3
APS with SLE	52%			Low dose aspirin or hydroxychloroquine
APS without prior pregnancy loss or thrombosis	low	No treatment or daily treatment with low-dose aspirin or daily treatment with prophylactic doses of heparin plus low-dose aspirin; optimal management uncertain		No treatment or daily treatment with low-dose aspirin; optimal management uncertain
aPL Antibodies Without APS				
LAC or medium to high level of aCL IgG			No treatment	No treatment
Low levels of aCL IgG, only aCL IgM, or only aCL IgA without LA, aPL, or aCL			No treatment	No treatment

In the post-partum period in women with preceding thrombosis Branch at al. are in consensus to switch the patient to warfarin thromboprophylaxis as soon as the patient is clinically stable instead of heparin at an INR of 3.0. Women with no preceding thrombosis in whom APS is diagnosed because of prior pregnancy loss or neonatal death after delivery at or before 34 weeks gestation due to severe preeclampsia or placental insufficiency are at great risk of thrombosis and require anticoagulation with heparin for 3-5 days. In the United States the regimen is applied for 6 weeks after delivery. Heparin and warfarin are safe to use in women breastfeeding, although breastfeeding should not be done if the mother is using cytotoxic or immunosuppressive agents. (Branch and Khamashta, 2003)

6.2 CAPS Management

6.2.1 General Treatment

CAPS is a life threatening condition and requires aggressive treatment. General measures include intensive care therapy, hemodialysis for renal failure, mechanical ventilation for pulmonary failure, inotropic drugs for cardiogenic shock, elimination of possible precipitating factors (e.g. infections, tissue necrosis, drugs [mostly oral contraceptives], or surgical procedures). Antibiotics should be administered as soon as possible when infection is suspected. (Erkan et al., 2003)

In case of necrotic organs or tissues, debridement or amputation should be performed as soon as possible, which may improve the outcome of the patient significantly (Amital et al., 2001). Thrombosis in renal arteries or veins or microangiopathy may cause severe hypertension in CAPS and requires aggressive therapy and perhaps surgical intervention. (Erkan et al., 2003)

6.2.2 Therapeutic Treatment

Anticoagulation, corticosteroids, plasmapheresis and possibly IVIG are the treatments of choice in suspected CAPS. Full anticoagulation with heparin seems to have an effect on mortality in CAPS. It is given 7-10 days followed by life-long treatment with warfarin at an INR >3 (Erkan et al., 2003). An acute therapy in life-threatening situations can be the administration of high doses of steroids, immunosuppressants (e.g. cyclophosphamide) or

plasma exchange to reduce or eliminate aPL but this is not as a long-term treatment unless the underlying disease (e.g. SLE) requires this therapy. (Gomez-Puerta and Cervera, 2014) Intravenous immunoglobulin may be of some benefit as it blocks antibody binding, possibly reduces antibody synthesis and increases the catabolism of circulating IgG (Spinnato et al., 1995). fibrinolytics, prostacyclin, ancrod, defibrotide and rituximab or cyclophosphamide may be considered based on the individual case evaluation (Erkan et al., 2003).

7 Risk Factors and Prognosis

For optimal treatment practitioners must identify a patient's risk for thrombosis and prognosis in comparison to the adverse effects of an anticoagulation therapy and then balance the therapy in the patient's best interest. The risk of each patient demonstrated by the patient's immunologic profile, history of thrombosis and type of previous thromboses (Tuthill and Khamashta, 2009).

According to several studies the positivity of multiple aPL is linked with a graver progression of the syndrome, significantly increasing the frequency of thrombosis and obstetric complications (Miyakis et al., 2006, Neville et al., 2003, Obermoser et al., 2004). Single aPL increase can have different influences on risk and prognosis, depending on the type of aPL. Testing positivity for LA is the greatest risk factor for thrombosis and unfavorable pregnancy outcome after 12 weeks of pregnancy in comparison to single positivity of any of the other aPL (Galli et al., 2003b, Urbanus et al., 2009, Lockshin et al., 2012, Tuthill and Khamashta, 2009). In combination with high levels of aCL or aβ_2-GPI the risk is even greater (Tuthill and Khamashta, 2009, Forastiero et al., 2005). Patients with triple positivity, meaning positivity of LA, aCL and aβ_2-GPI, are at risk for a first thrombosis in 5.3% per year (Pengo et al., 2015). Occasionally high aCL, on the other hand, does not increase the risk for thrombosis (Martinez-Berriotxoa et al., 2007). Unselected patients with aPL positivity have been anticipated to have an overall risk of thrombosis between 0 and 2.8% (Finazzi, 2008). The smallest risk for thrombotic events is found in individuals with no previous thrombosis (asymptomatic aPL) and in those with no concomitant autoimmune disorder (Vila et al., 1994, Giron-Gonzalez et al., 2004). Several studies have shown that high titers of IgG aCL (>40 GPL) are an independent risk factor for new and progressive cardiac aberrations (Cervera et al., 2011, Djokovic et al., 2014).

A history of thromboembolism in APS significantly increases the risk for a further event, with estimations ranging from 22-69% (Khamashta et al., 1995, Krnic-Barrie et al., 1997, Schulman et al., 1998, Kearon et al., 1999). A closer look at these patients reveals that the risk of recurrence is smallest in those with a previous venous thrombosis, and is highest in those who suffered from arterial or recurrent thrombosis (Ruiz-Irastorza et al., 2007).

APL are strongly associated with SLE and 40% of these individuals with SLE have aPL circulating in their blood stream (Ruiz-Irastorza et al., 2010a). It is estimated that about 52% of these will eventually develop a thrombotic event within the next 10 years (Shah et al., 1998, Tuthill and Khamashta, 2009). Patients with APS in connection with SLE are more prone to episodes of arthritis, livedo reticularis and more often show thrombocytopenia and leukopenia (Cervera et al., 2002). In relation to sex, women are more disposed to arthritis, livedo reticularis, and migraine, whereas men more prone to myocardial infarction, epilepsy, and arterial thrombosis in the lower legs and feet (Cervera et al., 2002).

APS in patients desiring pregnancy can be very dangerous as without treatment live birth can only be achieved in 20% of the cases, whereas treatment can jolt this rate up to almost 80% (Alijotas-Reig et al., 2012). Regarding obstetric APS specific thrombotic complications can be distinguished. The yearly incidence of deep vein thrombosis (DVT) is 1.46% and the one of stroke is 0.32% in purely obstetric APS (Gris et al., 2012).

Several studies tried to identify a predictive outcome via Doppler velocity measurements of the uterine artery. These studies demonstrated the usefulness of a uterine artery Doppler velocity measurement as a valuable instrument to identify patients with APS at risk of poor pregnancy outcome. (De Carolis et al., 2010)

In pregnancy, hCG levels may also be helpful to identify possible adverse pregnancy outcomes. A decrease in hCG may suggest an obstruction with implantation and can be used as a marker for adverse pregnancy outcomes and thrombosis endangering the child (Schwartz et al., 2007).

8 Material and Methods

The literary research was mainly done with the electronic database PubMed. Search keywords used included “Antiphospholipid Syndrome,” “pathogenesis,” “treatment,” “guidelines,” “pregnancy,” “complications,” “management,” etc.
In general newer research was selected but also older studies and papers were admitted as a comparison and to establish the historical development of the syndrome and its treatment.

The first part of the paper describes the antiphospholipid syndrome and is composed of the fundamentals definition, epidemiology, etiology, statistics and signs and symptoms. The second part focuses more on the obstetric manifestation and treatment options according to the newest literature.

9 Discussion

APS is a complex and diverse disease. Although it is still young in comparison to other well-researched diseases, recent findings regarding pathophysiology, progression and treatment options revealed, a better understanding of APS. Hence, prognosis increases immensely and a positive pregnancy outcome has become probable. Still, there remain certain aspects of the disease that require further testing, studying and experimentation in order to make APS comprehensively understood.

The pathogenesis of APS and the aPL still remains inconcise. The basic mechanisms are identified, but the detailed mechanisms and reactions remain uncertain despite extensive research. Many theories have been proposed on how aPL increase the chance of thrombosis, but none have gathered enough evidence to claim validation. This is especially true for obstetric pathomechanisms.

More research needs be done in order to determine, not only pathogenesis, but also etiology mainly in obstetric APS; which conditions may evoke the presence of aPL and the involvement of medication, malignancies, infections and genetic predispositions therein. For example it is believed that genetics play a major role in APS (Kamboh et al., 2013), but no proper evidence has been found.

Another issue of debate is the seronegative cases of APS. Per definition, this subgroup does not exist (Miyakis et al., 2006). But clinicians insist on such cases being evident (Hughes and Khamashta, 2003). These seronegative cases indicate that other aPL may play a role in APS, but research on this topic is not conclusive. Further investigations are required to insure a connection to the disease and possible adjustment of the diagnosis criteria.

Research is a vital element for the understanding and development of APS as a disease. Unfortunately, we face major limitations and difficulties when it comes to studies and experiments on APS. The Antiphospholipid Syndrome Clinical Research Task Force Report attempted to summarize the current problems concerning APS research (Erkan et al., 2011):

1. APL detection is still a matter of concern, as laboratories are not using standardized assays and are not synchronized when it comes to cut-off levels. Standardization is essential, when it comes to diagnosis. Research relies on exact exclusion criteria in order to make a truthful reflection of the disease, the affected population, interaction of diseases and effectiveness of medication.

2. Clinical diagnosis criteria for APS vary in different study groups and therefore produce a heterogeneous patient collection, which obscures study results. Without precise research the results will not yield clinical applications.
3. Rarely any studies take other risk factors than aPL in thrombosis and pregnancy complication into account. Smoking, the use of medication, genetic risk factors and even ethnic origin can increase chances for thrombosis and pregnancy complications, especially if aPL are present. The risk of diagnosing APS in patients that suffer from a thrombotic event due to other trigger factors, are greater when this specific group of patients are not stratified and excluded.
4. Single positive results and even low titer aPL results have been included in some studies, forming an incorrect patient collection and tampering the results. Additionally, most studies are retrospective and do not resemble the general population. There are only a few studies that are prospective and population controlled. These controls are needed in order to get a truthful depiction of patients actually suffering from APS
5. Lastly, the lack of knowledge concerning aPL functionality and pathogenesis makes an ideal study design difficult.

These issues have to be addressed in order to make research on APS valid and extensive. International cooperation is needed to gather all possible input on patients, disease progression and treatment success.

Treatment has been under development, but clinicians believe that there is more to be done in order to establish the ideal treatment for the individual patient. Studies on pregnant woman are difficult to design and morally questionable. Ideal treatment, especially dosages applied during pregnancies have to be contrived and evaluated.

Screening methods are still a topic of debate. No clinician wants to overlook a diagnosis of APS. Theoretically every woman with pregnancy loss may be at danger of suffering from APS. But testing all women with only one abort before the 10^{th} week of gestation means a huge effort regarding workload, not only in time and effort, but is also financially bearing. Furthermore, the psychological stress for these women is not to be underestimated. For some women it may be reassuring to investigate their child's death, but many cannot withstand the psychological strain of the subsequent procedures. In spite of the high frequency of natural abortions, the positive benefit of such additional measures is not in

relation to the large effort and possible emotional stress. The moral obligation remains disputable.

In all cases professional counselling during any stage of the pregnancy must be considered. Preconceptional, gestational and especially after-delivery, counselling can provide support and psychological assistance for affected mothers and their families. It can also improve the understanding and compliance of the patients.

APS remains a disease with many possibilities for development and investigation. However, the first success of past research was the differentiation between APS and SLE, which has made it possible to selectively develop diagnosis criteria and treatment options. Research has developed a therapy that improves pregnancy outcomes from marginal survival rates to nearly 80% live births (Alijotas-Reig et al., 2012).

References

ABILDGAARD, U. & HEIMDAL, K. 2013. Pathogenesis of the syndrome of hemolysis, elevated liver enzymes, and low platelet count (HELLP): a review. *Eur J Obstet Gynecol Reprod Biol,* 166**,** 117-23.

AGGELER, P. M., LINDSAY, S. & LUCIA, S. P. 1946. Studies on the Coagulation Defect in a Case of Thrombocytopenic Purpura Complicated by Thrombosis. *Am J Pathol,* 22**,** 1181-203.

ALIJOTAS-REIG, J. 2013. Treatment of refractory obstetric antiphospholipid syndrome: the state of the art and new trends in the therapeutic management. *Lupus,* 22**,** 6-17.

ALIJOTAS-REIG, J., FERRER-OLIVERAS, R. & GROUP, E. S. 2012. The European Registry on Obstetric Antiphospholipid Syndrome (EUROAPS): a preliminary first year report. *Lupus,* 21**,** 766-8.

ALIJOTAS-REIG, J. & VILARDELL-TARRES, M. 2010. Is obstetric antiphospholipid syndrome a primary nonthrombotic, proinflammatory, complement-mediated disorder related to antiphospholipid antibodies? *Obstet Gynecol Surv,* 65**,** 39-45.

AMITAL, H., LEVY, Y., DAVIDSON, C., LUNDBERG, I., HARJU, A., KOSACH, Y., ASHERSON, R. A. & SHOENFELD, Y. 2001. Catastrophic antiphospholipid syndrome: remission following leg amputation in 2 cases. *Semin Arthritis Rheum,* 31**,** 127-32.

ANDREOLI, L., BAZZANI, C., TARABORELLI, M., REGGIA, R., LOJACONO, A., BRUCATO, A., MERONI, P. L. & TINCANI, A. 2010. Pregnancy in autoimmune rheumatic diseases: the importance of counselling for old and new challenges. *Autoimmun Rev,* 10**,** 51-4.

ANDREOLI, L., FREDI, M., NALLI, C., REGGIA, R., LOJACONO, A., MOTTA, M. & TINCANI, A. 2012. Pregnancy implications for systemic lupus erythematosus and the antiphospholipid syndrome. *J Autoimmun,* 38**,** J197-208.

AOKI, K., HAYASHI, Y., HIRAO, Y. & YAGAMI, Y. 1993. Specific antiphospholipid antibodies as a predictive variable in patients with recurrent pregnancy loss. *Am J Reprod Immunol,* 29**,** 82-7.

ARNOUT, J. & VERMYLEN, J. 2003. Current status and implications of autoimmune antiphospholipid antibodies in relation to thrombotic disease. *J Thromb Haemost,* 1**,** 931-42.

ARVIEUX, J., REGNAULT, V., HACHULLA, E., DARNIGE, L., ROUSSEL, B. & BENSA, J. C. 1998. Heterogeneity and immunochemical properties of anti-beta2-glycoprotein I autoantibodies. *Thromb Haemost,* 80**,** 393-8.

ASHERSON, R. A. 2008. The primary, secondary, catastrophic, and seronegative variants of the antiphospholipid syndrome: a personal history long in the making. *Semin Thromb Hemost,* 34**,** 227-35.

ASHERSON, R. A., CERVERA, R., PIETTE, J. C., FONT, J., LIE, J. T., BURCOGLU, A., LIM, K., MUNOZ-RODRIGUEZ, F. J., LEVY, R. A., BOUE, F., ROSSERT, J. & INGELMO, M. 1998. Catastrophic antiphospholipid syndrome. Clinical and laboratory features of 50 patients. *Medicine (Baltimore),* 77**,** 195-207.

ASHERSON, R. A., CERVERA, R., PIETTE, J. C., SHOENFELD, Y., ESPINOSA, G., PETRI, M. A., LIM, E., LAU, T. C., GURJAL, A., JEDRYKA-GORAL, A., CHWALINSKA-SADOWSKA, H., DIBNER, R. J., ROJAS-RODRIGUEZ, J., GARCIA-CARRASCO, M., GRANDONE, J. T., PARKE, A. L., BARBOSA, P., VASCONCELOS, C., RAMOS-CASALS, M., FONT, J. & INGELMO, M. 2001. Catastrophic antiphospholipid syndrome: clues to the pathogenesis from a series of 80 patients. *Medicine (Baltimore),* 80**,** 355-77.

ASHERSON, R. A., CERVERA, R., SHEPSHELOVICH, D. & SHOENFELD, Y. 2006. Nonthrombotic manifestations of the antiphospholipid syndrome: away from thrombosis? *J Rheumatol,* 33**,** 1038-44.

ASHERSON, R. A., CERVERA, R. & WELLS, A. U. 2005. Diffuse alveolar hemorrhage: a nonthrombotic antiphospholipid lung syndrome? *Semin Arthritis Rheum,* 35**,** 138-42.

ASHERSON, R. A., KHAMASHTA, M. A. & HUGHES, G. R. 1991. The hepatic complications of the antiphospholipid antibodies. *Clin Exp Rheumatol,* 9**,** 341-4.

ASHERSON, R. A., KHAMASHTA, M. A., ORDI-ROS, J., DERKSEN, R. H., MACHIN, S. J., BARQUINERO, J., OUTT, H. H., HARRIS, E. N., VILARDELL-TORRES, M. & HUGHES, G. R. 1989a. The "primary" antiphospholipid syndrome: major clinical and serological features. *Medicine (Baltimore),* 68**,** 366-74.

ASHERSON, R. A., MERRY, P., ACHESON, J. F., HARRIS, E. N. & HUGHES, G. R. 1989b. Antiphospholipid antibodies: a risk factor for occlusive ocular vascular disease in systemic lupus erythematosus and the 'primary' antiphospholipid syndrome. *Ann Rheum Dis,* 48**,** 358-61.

BARBHAIYA, M. & ERKAN, D. 2013. Top 10 clinical research developments in antiphospholipid syndrome. *Curr Rheumatol Rep,* 15**,** 367.

BARROU, Z., VERNY, C., COHEN-BITTAN, J. & VERNY, M. 2010. Bilateral adrenal necrosis after knee arthroplasty. *J Am Geriatr Soc,* 58**,** 2248-9.

BERMAN, J., GIRARDI, G. & SALMON, J. E. 2005. TNF-alpha is a critical effector and a target for therapy in antiphospholipid antibody-induced pregnancy loss. *J Immunol,* 174**,** 485-90.

BEVERS, E. M., GALLI, M., BARBUI, T., COMFURIUS, P. & ZWAAL, R. F. 1991. Lupus anticoagulant IgG's (LA) are not directed to phospholipids only, but to a complex of lipid-bound human prothrombin. *Thromb Haemost,* 66**,** 629-32.

BICK, R. L. 2000. Recurrent miscarriage syndrome and infertility caused by blood coagulation protein or platelet defects. *Hematol Oncol Clin North Am,* 14**,** 1117-31.

BICK, R. L. 2008. Antiphospholipid syndrome in pregnancy. *Hematol Oncol Clin North Am,* 22**,** 107-20, vii.

BICK, R. L. & HOPPENSTEADT, D. 2005. Recurrent miscarriage syndrome and infertility due to blood coagulation protein/platelet defects: a review and update. *Clin Appl Thromb Hemost,* 11**,** 1-13.

BORRELLI, A. L., BRILLANTE, M., BORZACCHIELLO, C. & BERLINGIERI, P. 1997. Hemocoagulative pathology and immunological recurrent abortion. *Clin Exp Obstet Gynecol,* 24**,** 39-40.
BOUMA, B., DE GROOT, P. G., VAN DEN ELSEN, J. M., RAVELLI, R. B., SCHOUTEN, A., SIMMELINK, M. J., DERKSEN, R. H., KROON, J. & GROS, P. 1999. Adhesion mechanism of human beta(2)-glycoprotein I to phospholipids based on its crystal structure. *EMBO J,* 18**,** 5166-74.
BOWIE, E. J., THOMPSON, J. H., JR., PASCUZZI, C. A. & OWEN, C. A., JR. 1963. Thrombosis in Systemic Lupus Erythematosus Despite Circulating Anticoagulants. *J Lab Clin Med,* 62**,** 416-30.
BRANCH, D. W. & KHAMASHTA, M. A. 2003. Antiphospholipid syndrome: obstetric diagnosis, management, and controversies. *Obstet Gynecol,* 101**,** 1333-44.
BRANCH, D. W., SILVER, R. M., BLACKWELL, J. L., READING, J. C. & SCOTT, J. R. 1992. Outcome of treated pregnancies in women with antiphospholipid syndrome: an update of the Utah experience. *Obstet Gynecol,* 80**,** 614-20.
BREWSTER, J. A., SHAW, N. J. & FARQUHARSON, R. G. 1999. Neonatal and pediatric outcome of infants born to mothers with antiphospholipid syndrome. *J Perinat Med,* 27**,** 183-7.
BRODER, A. & PUTTERMAN, C. 2013. Hydroxychloroquine use is associated with lower odds of persistently positive antiphospholipid antibodies and/or lupus anticoagulant in systemic lupus erythematosus. *J Rheumatol,* 40**,** 30-3.
BRUCATO, A., DORIA, A., FRASSI, M., CASTELLINO, G., FRANCESCHINI, F., FADEN, D., PISONI, M. P., SOLERTE, L., MUSCARA, M., LOJACONO, A., MOTTA, M., CAVAZZANA, I., GHIRARDELLO, A., VESCOVI, F., TOMBINI, V., CIMAZ, R., GAMBARI, P. F., MERONI, P. L., CANESI, B. & TINCANI, A. 2002. Pregnancy outcome in 100 women with autoimmune diseases and anti-Ro/SSA antibodies: a prospective controlled study. *Lupus,* 11**,** 716-21.
BUCCIARELLI, S., ESPINOSA, G. & CERVERA, R. 2009. The CAPS Registry: morbidity and mortality of the catastrophic antiphospholipid syndrome. *Lupus,* 18**,** 905-12.
BULLETINS--OBSTETRICS, A. C. O. P. 2002. ACOG practice bulletin. Diagnosis and management of preeclampsia and eclampsia. Number 33, January 2002. *Obstet Gynecol,* 99**,** 159-67.
CANAUD, G., KAMAR, N., ANGLICHEAU, D., ESPOSITO, L., RABANT, M., NOEL, L. H., GUILBEAU-FRUGIER, C., SBERRO-SOUSSAN, R., DEL BELLO, A., MARTINEZ, F., ZUBER, J., ROSTAING, L. & LEGENDRE, C. 2013. Eculizumab improves posttransplant thrombotic microangiopathy due to antiphospholipid syndrome recurrence but fails to prevent chronic vascular changes. *Am J Transplant,* 13**,** 2179-85.
CARUSO, A., DE CAROLIS, S., FERRAZZANI, S., VALESINI, G., CAFORIO, L. & MANCUSO, S. 1993. Pregnancy outcome in relation to uterine artery flow velocity waveforms and clinical characteristics in women with antiphospholipid syndrome. *Obstet Gynecol,* 82**,** 970-7.
CASTANON, C., AMIGO, M. C., BANALES, J. L., NAVA, A. & REYES, P. A. 1995. Ocular vaso-occlusive disease in primary antiphospholipid syndrome. *Ophthalmology,* 102**,** 256-62.
CERVERA, R. 2000. Recent advances in antiphospholipid antibody-related valvulopathies. *J Autoimmun,* 15**,** 123-5.
CERVERA, R., BOFFA, M. C., KHAMASHTA, M. A. & HUGHES, G. R. 2009. The Euro-Phospholipid project: epidemiology of the antiphospholipid syndrome in Europe. *Lupus,* 18**,** 889-93.
CERVERA, R., ESPINOSA, G., CORDERO, A., OLTRA, M. R., UNZURRUNZAGA, A., ROSSINOL, T., PLAZA, J., BUCCIARELLI, S., RAMOS-CASALS, M., INGELMO, M., ASHERSON, R. A., FONT, J. & CATASTROPHIC ANTIPHOSPHOLIPID SYNDROME REGISTRY PROJECT, G. 2007. Intestinal involvement secondary to the antiphospholipid syndrome (APS): clinical and immunologic characteristics of 97 patients: comparison of classic and catastrophic APS. *Semin Arthritis Rheum,* 36**,** 287-96.
CERVERA, R., PIETTE, J. C., FONT, J., KHAMASHTA, M. A., SHOENFELD, Y., CAMPS, M. T., JACOBSEN, S., LAKOS, G., TINCANI, A., KONTOPOULOU-GRIVA, I., GALEAZZI, M., MERONI, P. L., DERKSEN, R. H., DE GROOT, P. G., GROMNICA-IHLE, E., BALEVA, M., MOSCA, M., BOMBARDIERI, S., HOUSSIAU, F., GRIS, J. C., QUERE, I., HACHULLA, E., VASCONCELOS, C., ROCH, B., FERNANDEZ-NEBRO, A., BOFFA, M. C., HUGHES, G. R., INGELMO, M. & EURO-PHOSPHOLIPID PROJECT, G. 2002. Antiphospholipid syndrome: clinical and immunologic manifestations and patterns of disease expression in a cohort of 1,000 patients. *Arthritis Rheum,* 46**,** 1019-27.
CERVERA, R., TEKTONIDOU, M. G., ESPINOSA, G., CABRAL, A. R., GONZALEZ, E. B., ERKAN, D., VADYA, S., ADROGUE, H. E., SOLOMON, M., ZANDMAN-GODDARD, G. & SHOENFELD, Y. 2011. Task Force on Catastrophic Antiphospholipid Syndrome (APS) and Non-criteria APS Manifestations (I): catastrophic APS, APS nephropathy and heart valve lesions. *Lupus,* 20**,** 165-73.
CHOU, A. K., HSIEH, S. C., SU, Y. N., JENG, S. F., CHEN, C. Y., CHOU, H. C., TSAO, P. N. & HSIEH, W. S. 2009. Neonatal and pregnancy outcome in primary antiphospholipid syndrome: a 10-year experience in one medical center. *Pediatr Neonatol,* 50**,** 143-6.
CLOWSE, M. E., JAMISON, M., MYERS, E. & JAMES, A. H. 2008. A national study of the complications of lupus in pregnancy. *Am J Obstet Gynecol,* 199**,** 127 e1-6.
CLOWSE, M. E., MAGDER, L. S., WITTER, F. & PETRI, M. 2005. The impact of increased lupus activity on obstetric outcomes. *Arthritis Rheum,* 52**,** 514-21.
COHEN, D., BERGER, S. P., STEUP-BEEKMAN, G. M., BLOEMENKAMP, K. W. & BAJEMA, I. M. 2010. Diagnosis and management of the antiphospholipid syndrome. *BMJ,* 340**,** c2541.
COHEN, D., BUURMA, A., GOEMAERE, N. N., GIRARDI, G., LE CESSIE, S., SCHERJON, S., BLOEMENKAMP, K. W., DE HEER, E., BRUIJN, J. A. & BAJEMA, I. M. 2011. Classical complement activation as a footprint for murine and human antiphospholipid antibody-induced fetal loss. *J Pathol,* 225**,** 502-11.

COMARMOND, C. & CACOUB, P. 2013. Antiphospholipid syndrome: from pathogenesis to novel immunomodulatory therapies. *Autoimmun Rev,* 12**,** 752-7.
CUADRADO, M. J., KHAMASHTA, M. A., BALLESTEROS, A., GODFREY, T., SIMON, M. J. & HUGHES, G. R. 2000. Can neurologic manifestations of Hughes (antiphospholipid) syndrome be distinguished from multiple sclerosis? Analysis of 27 patients and review of the literature. *Medicine (Baltimore),* 79**,** 57-68.
D'IPPOLITO, S., MARANA, R., DI NICUOLO, F., CASTELLANI, R., VEGLIA, M., STINSON, J., SCAMBIA, G. & DI SIMONE, N. 2012. Effect of Low Molecular Weight Heparins (LMWHs) on antiphospholipid Antibodies (aPL)-mediated inhibition of endometrial angiogenesis. *PLoS One,* 7**,** e29660.
DE CAROLIS, S., BOTTA, A., SANTUCCI, S., GAROFALO, S., MARTINO, C., PERRELLI, A., SALVI, S., FERRAZZANI, S., CAFORIO, L. & SCAMBIA, G. 2010. Predictors of pregnancy outcome in antiphospholipid syndrome: a review. *Clin Rev Allergy Immunol,* 38**,** 116-24.
DE GROOT, P. G., DERKSEN, R. H. & DE LAAT, B. 2008. Twenty-two years of failure to set up undisputed assays to detect patients with the antiphospholipid syndrome. *Semin Thromb Hemost,* 34**,** 347-55.
DE LAAT, B., DERKSEN, R. H., URBANUS, R. T. & DE GROOT, P. G. 2005. IgG antibodies that recognize epitope Gly40-Arg43 in domain I of beta 2-glycoprotein I cause LAC, and their presence correlates strongly with thrombosis. *Blood,* 105**,** 1540-5.
DE LAAT, B., ECKMANN, C. M., VAN SCHAGEN, M., MEIJER, A. B., MERTENS, K. & VAN MOURIK, J. A. 2008. Correlation between the potency of a beta2-glycoprotein I-dependent lupus anticoagulant and the level of resistance to activated protein C. *Blood Coagul Fibrinolysis,* 19**,** 757-64.
DE WOLF, F., CARRERAS, L. O., MOERMAN, P., VERMYLEN, J., VAN ASSCHE, A. & RENAER, M. 1982. Decidual vasculopathy and extensive placental infarction in a patient with repeated thromboembolic accidents, recurrent fetal loss, and a lupus anticoagulant. *Am J Obstet Gynecol,* 142**,** 829-34.
DELGADO ALVES, J., MASON, L. J., AMES, P. R., CHEN, P. P., RAUCH, J., LEVINE, J. S., SUBANG, R. & ISENBERG, D. A. 2005. Antiphospholipid antibodies are associated with enhanced oxidative stress, decreased plasma nitric oxide and paraoxonase activity in an experimental mouse model. *Rheumatology (Oxford),* 44**,** 1238-44.
DEMIRCI, F. Y., KUCUKKAYA, R., AKARCAY, K., KIR, N., ATAMER, T., DEMIRCI, H. & ONGOR, E. 1998. Ocular involvement in primary antiphospholipid syndrome. Ocular involvement in primary APS. *Int Ophthalmol,* 22**,** 323-9.
DENBURG, S. D., CARBOTTE, R. M., GINSBERG, J. S. & DENBURG, J. A. 1997. The relationship of antiphospholipid antibodies to cognitive function in patients with systemic lupus erythematosus. *J Int Neuropsychol Soc,* 3**,** 377-86.
DI SIMONE, N., CALIANDRO, D., CASTELLANI, R., FERRAZZANI, S., DE CAROLIS, S. & CARUSO, A. 1999. Low-molecular weight heparin restores in-vitro trophoblast invasiveness and differentiation in presence of immunoglobulin G fractions obtained from patients with antiphospholipid syndrome. *Hum Reprod,* 14**,** 489-95.
DI SIMONE, N., DI NICUOLO, F., D'IPPOLITO, S., CASTELLANI, R., TERSIGNI, C., CARUSO, A., MERONI, P. & MARANA, R. 2010. Antiphospholipid antibodies affect human endometrial angiogenesis. *Biol Reprod,* 83**,** 212-9.
DI SIMONE, N., DI NICUOLO, F., SANGUINETTI, M., FERRAZZANI, S., D'ALESSIO, M. C., CASTELLANI, R., BOMPIANI, A. & CARUSO, A. 2007a. Low-molecular weight heparin induces in vitro trophoblast invasiveness: role of matrix metalloproteinases and tissue inhibitors. *Placenta,* 28**,** 298-304.
DI SIMONE, N., FERRAZZANI, S., CASTELLANI, R., DE CAROLIS, S., MANCUSO, S. & CARUSO, A. 1997. Heparin and low-dose aspirin restore placental human chorionic gonadotrophin secretion abolished by antiphospholipid antibody-containing sera. *Hum Reprod,* 12**,** 2061-5.
DI SIMONE, N., LUIGI, M. P., MARCO, D., FIORELLA, D. N., SILVIA, D., CLARA, D. M. & ALESSANDRO, C. 2007b. Pregnancies complicated with antiphospholipid syndrome: the pathogenic mechanism of antiphospholipid antibodies: a review of the literature. *Ann N Y Acad Sci,* 1108**,** 505-14.
DI SIMONE, N., MERONI, P. L., D'ASTA, M., DI NICUOLO, F., D'ALESSIO, M. C. & CARUSO, A. 2007c. Pathogenic role of anti-beta2-glycoprotein I antibodies on human placenta: functional effects related to implantation and roles of heparin. *Hum Reprod Update,* 13**,** 189-96.
DIAZ-CREMADES, J., FERNANDEZ-FUERTES, F., RUANO, J. A., TAPIA, M., SOLER, S., BOSCH, J. M., CABALLERO, M. & GONZALEZ-SAN MIGUEL, J. D. 2009. Concurrent thrombotic thrombocytopenic purpura and antiphospholipid syndrome: a rare and severe clinical combination. *Br J Haematol,* 147**,** 584-5.
DJOKOVIC, A., STOJANOVICH, L., KONTIC, M., STANISAVLJEVIC, N., RADOVANOVIC, S. & MARISAVLJEVIC, D. 2014. Association between cardiac manifestations and antiphospholipid antibody type and level in a cohort of Serbian patients with primary and secondary antiphospholipid syndrome. *Isr Med Assoc J,* 16**,** 162-7.
DORIA, A., TINCANI, A. & LOCKSHIN, M. 2008. Challenges of lupus pregnancies. *Rheumatology (Oxford),* 47 Suppl 3**,** iii9-12.
DRAKELEY, A. J., QUENBY, S. & FARQUHARSON, R. G. 1998. Mid-trimester loss--appraisal of a screening protocol. *Hum Reprod,* 13**,** 1975-80.
DRENKARD, C., SANCHEZ-GUERRERO, J. & ALARCON-SEGOVIA, D. 1989. Fall in antiphospholipid antibody at time of thromboocclusive episodes in systemic lupus erythematosus. *J Rheumatol,* 16**,** 614-7.
EDWARDS, M. H., PIERANGELI, S., LIU, X., BARKER, J. H., ANDERSON, G. & HARRIS, E. N. 1997. Hydroxychloroquine reverses thrombogenic properties of antiphospholipid antibodies in mice. *Circulation,* 96**,** 4380-4.

EMMI, G., SILVESTRI, E., SQUATRITO, D., CIUCCIARELLI, L., CAMELI, A. M., DENAS, G., D'ELIOS, M. M., PENGO, V., EMMI, L. & PRISCO, D. 2014. An approach to differential diagnosis of antiphospholipid antibody syndrome and related conditions. *ScientificWorldJournal,* 2014**,** 341342.

EMPSON, M., LASSERE, M., CRAIG, J. & SCOTT, J. 2005. Prevention of recurrent miscarriage for women with antiphospholipid antibody or lupus anticoagulant. *Cochrane Database Syst Rev***,** CD002859.

ENSOM, M. H. & STEPHENSON, M. D. 2011. A two-center study on the pharmacokinetics of intravenous immunoglobulin before and during pregnancy in healthy women with poor obstetrical histories. *Hum Reprod,* 26**,** 2283-8.

ERDOGAN, D., GOREN, M. T., DIZ-KUCUKKAYA, R. & INANC, M. 2005. Assessment of cardiac structure and left atrial appendage functions in primary antiphospholipid syndrome: a transesophageal echocardiographic study. *Stroke,* 36**,** 592-6.

ERKAN, D., AGUIAR, C. L., ANDRADE, D., COHEN, H., CUADRADO, M. J., DANOWSKI, A., LEVY, R. A., ORTEL, T. L., RAHMAN, A., SALMON, J. E., TEKTONIDOU, M. G., WILLIS, R. & LOCKSHIN, M. D. 2014. 14th International Congress on Antiphospholipid Antibodies Task Force Report on Antiphospholipid Syndrome Treatment Trends. *Autoimmun Rev*.

ERKAN, D., BARBHAIYA, M., GEORGE, D., SAMMARITANO, L. & LOCKSHIN, M. 2010. Moderate versus high-titer persistently anticardiolipin antibody positive patients: are they clinically different and does high-titer anti-beta 2-glycoprotein-I antibody positivity offer additional predictive information? *Lupus,* 19**,** 613-9.

ERKAN, D., CERVERA, R. & ASHERSON, R. A. 2003. Catastrophic antiphospholipid syndrome: where do we stand? *Arthritis Rheum,* 48**,** 3320-7.

ERKAN, D., DERKSEN, R., LEVY, R., MACHIN, S., ORTEL, T., PIERANGELI, S., ROUBEY, R. & LOCKSHIN, M. 2011. Antiphospholipid Syndrome Clinical Research Task Force report. *Lupus,* 20**,** 219-24.

FABRIS, F., STEFFAN, A., CORDIANO, I., BORZINI, P., LUZZATTO, G., RANDI, M. L. & GIROLAMI, A. 1994. Specific antiplatelet autoantibodies in patients with antiphospholipid antibodies and thrombocytopenia. *Eur J Haematol,* 53**,** 232-6.

FADEN, D., TINCANI, A., TANZI, P., SPATOLA, L., LOJACONO, A., TARANTINI, M. & BALESTRIERI, G. 1997. Anti-beta 2 glycoprotein I antibodies in a general obstetric population: preliminary results on the prevalence and correlation with pregnancy outcome. Anti-beta2 glycoprotein I antibodies are associated with some obstetrical complications, mainly preeclampsia-eclampsia. *Eur J Obstet Gynecol Reprod Biol,* 73**,** 37-42.

FAKHOURI, F., NOEL, L. H., ZUBER, J., BEAUFILS, H., MARTINEZ, F., LEBON, P., PAPO, T., CHAUVEAU, D., BLETRY, O., GRUNFELD, J. P., PIETTE, J. C. & LESAVRE, P. 2003. The expanding spectrum of renal diseases associated with antiphospholipid syndrome. *Am J Kidney Dis,* 41**,** 1205-11.

FANOURIAKIS, A., BOUMPAS, D. T. & BERTSIAS, G. K. 2013. Pathogenesis and treatment of CNS lupus. *Curr Opin Rheumatol,* 25**,** 577-83.

FERNANDEZ-CALDAS, E., PUERTA, L., CARABALLO, L., MERCADO, D. & LOCKEY, R. F. 1996. Sequential determinations of Dermatophagoides spp. allergens in a tropical city. *J Investig Allergol Clin Immunol,* 6**,** 98-102.

FERRER-OLIVERAS, R., LLURBA, E., CABERO-ROURA, L. & ALIJOTAS-REIG, J. 2012. Prevalence and clinical usefulness of antiphospholipid and anticofactor antibodies in different Spanish preeclampsia subsets. *Lupus,* 21**,** 257-63.

FINAZZI, G. 2008. Aspirin in asymptomatic patients with confirmed positivity of antiphospholipid antibodies? No. *Intern Emerg Med,* 3**,** 197-200.

FISCHETTI, F., DURIGUTTO, P., PELLIS, V., DEBEUS, A., MACOR, P., BULLA, R., BOSSI, F., ZILLER, F., SBLATTERO, D., MERONI, P. & TEDESCO, F. 2005. Thrombus formation induced by antibodies to beta2-glycoprotein I is complement dependent and requires a priming factor. *Blood,* 106**,** 2340-6.

FORASTIERO, R., MARTINUZZO, M., POMBO, G., PUENTE, D., ROSSI, A., CELEBRIN, L., BONACCORSO, S. & AVERSA, L. 2005. A prospective study of antibodies to beta2-glycoprotein I and prothrombin, and risk of thrombosis. *J Thromb Haemost,* 3**,** 1231-8.

FORD, P. M., BRUNET, D., LILLICRAP, D. P. & FORD, S. E. 1990. Premature stroke in a family with lupus anticoagulant and antiphospholipid antibodies. *Stroke,* 21**,** 66-71.

FRANCES, C., NIANG, S., LAFFITTE, E., PELLETIER, F., COSTEDOAT, N. & PIETTE, J. C. 2005. Dermatologic manifestations of the antiphospholipid syndrome: two hundred consecutive cases. *Arthritis Rheum,* 52**,** 1785-93.

FRICK, P. G. 1955. Acquired circulating anticoagulants in systemic collagen disease; auto-immune thromboplastin deficiency. *Blood,* 10**,** 691-706.

FURGAL, M., JAMROZIK, J., JANKOWSKI, M., PARTYKA, L., SKOWINIAK, A. & SWADZBA, J. 1993. [Lupus anticoagulant--mysterious procoagulant]. *Pol Arch Med Wewn,* 90**,** 348-55.

GALINDO, M., KHAMASHTA, M. A. & HUGHES, G. R. 1999. Splenectomy for refractory thrombocytopenia in the antiphospholipid syndrome. *Rheumatology (Oxford),* 38**,** 848-53.

GALLI, M., COMFURIUS, P., MAASSEN, C., HEMKER, H. C., DE BAETS, M. H., VAN BREDA-VRIESMAN, P. J., BARBUI, T., ZWAAL, R. F. & BEVERS, E. M. 1990. Anticardiolipin antibodies (ACA) directed not to cardiolipin but to a plasma protein cofactor. *Lancet,* 335**,** 1544-7.

GALLI, M., DALDOSSI, M. & BARBUI, T. 1994. Anti-glycoprotein Ib/IX and IIb/IIIa antibodies in patients with antiphospholipid antibodies. *Thromb Haemost,* 71**,** 571-5.

GALLI, M., FINAZZI, G. & BARBUI, T. 1996. Thrombocytopenia in the antiphospholipid syndrome: pathophysiology, clinical relevance and treatment. *Ann Med Interne (Paris),* 147 Suppl 1**,** 24-7.

GALLI, M., LUCIANI, D., BERTOLINI, G. & BARBUI, T. 2003a. Anti-beta 2-glycoprotein I, antiprothrombin antibodies, and the risk of thrombosis in the antiphospholipid syndrome. *Blood,* 102**,** 2717-23.
GALLI, M., LUCIANI, D., BERTOLINI, G. & BARBUI, T. 2003b. Lupus anticoagulants are stronger risk factors for thrombosis than anticardiolipin antibodies in the antiphospholipid syndrome: a systematic review of the literature. *Blood,* 101**,** 1827-32.
GELFAND, Y. A., DORI, D., MILLER, B. & BRENNER, B. 1999. Visual disturbances and pathologic ocular findings in primary antiphospholipid syndrome. *Ophthalmology,* 106**,** 1537-40.
GHARAVI, A. E., VEGA-OSTERTAG, M., ESPINOLA, R. G., LIU, X., COLE, L., COX, N. T., ROMAGNOLI, P., LABAT, K. & PIERANGELI, S. S. 2004. Intrauterine fetal death in mice caused by cytomegalovirus-derived peptide induced aPL antibodies. *Lupus,* 13**,** 17-23.
GIRARDI, G. 2005. Heparin treatment in pregnancy loss: Potential therapeutic benefits beyond anticoagulation. *J Reprod Immunol,* 66**,** 45-51.
GIRARDI, G. 2010. Role of tissue factor in the maternal immunological attack of the embryo in the antiphospholipid syndrome. *Clin Rev Allergy Immunol,* 39**,** 160-5.
GIRARDI, G., REDECHA, P. & SALMON, J. E. 2004. Heparin prevents antiphospholipid antibody-induced fetal loss by inhibiting complement activation. *Nat Med,* 10**,** 1222-6.
GIRON-GONZALEZ, J. A., GARCIA DEL RIO, E., RODRIGUEZ, C., RODRIGUEZ-MARTORELL, J. & SERRANO, A. 2004. Antiphospholipid syndrome and asymptomatic carriers of antiphospholipid antibody: prospective analysis of 404 individuals. *J Rheumatol,* 31**,** 1560-7.
GODEAU, B., PIETTE, J. C., FROMONT, P., INTRATOR, L., SCHAEFFER, A. & BIERLING, P. 1997. Specific antiplatelet glycoprotein autoantibodies are associated with the thrombocytopenia of primary antiphospholipid syndrome. *Br J Haematol,* 98**,** 873-9.
GOLDBERG, S. N., CONTI-KELLY, A. M. & GRECO, T. P. 1995. A family study of anticardiolipin antibodies and associated clinical conditions. *Am J Med,* 99**,** 473-9.
GOMEZ-PUERTA, J. A. & CERVERA, R. 2014. Diagnosis and classification of the antiphospholipid syndrome. *J Autoimmun,* 48-49**,** 20-5.
GOMEZ-PUERTA, J. A., CERVERA, R., ESPINOSA, G., ASHERSON, R. A., GARCIA-CARRASCO, M., DA COSTA, I. P., ANDRADE, D. C., BORBA, E. F., MAKATSARIA, A., BUCCIARELLI, S., RAMOS-CASALS, M. & FONT, J. 2007. Catastrophic antiphospholipid syndrome during pregnancy and puerperium: maternal and fetal characteristics of 15 cases. *Ann Rheum Dis,* 66**,** 740-6.
GORKI, H., MALINOVSKI, V. & STANBRIDGE, R. D. 2008. The antiphospholipid syndrome and heart valve surgery. *Eur J Cardiothorac Surg,* 33**,** 168-81.
GORSHTEIN, A. & LEVY, Y. 2007. Orthopedic involvement in antiphospholipid syndrome. *Clin Rev Allergy Immunol,* 32**,** 167-71.
GRECO, T. P., CONTI-KELLY, A. M., GRECO, T., JR., DOYLE, R., MATSUURA, E., ANTHONY, J. R. & LOPEZ, L. R. 2009. Newer antiphospholipid antibodies predict adverse outcomes in patients with acute coronary syndrome. *Am J Clin Pathol,* 132**,** 613-20.
GRIS, J. C., BOUVIER, S., MOLINARI, N., GALANAUD, J. P., COCHERY-NOUVELLON, E., MERCIER, E., FABBRO-PERAY, P., BALDUCCHI, J. P., MARES, P., QUERE, I. & DAUZAT, M. 2012. Comparative incidence of a first thrombotic event in purely obstetric antiphospholipid syndrome with pregnancy loss: the NOH-APS observational study. *Blood,* 119**,** 2624-32.
GUERIN, J., SHENG, Y., REDDEL, S., IVERSON, G. M., CHAPMAN, M. G. & KRILIS, S. A. 2002. Heparin inhibits the binding of beta 2-glycoprotein I to phospholipids and promotes the plasmin-mediated inactivation of this blood protein. Elucidation of the consequences of the two biological events in patients with the anti-phospholipid syndrome. *J Biol Chem,* 277**,** 2644-9.
HAN, C. S., MULLA, M. J., BROSENS, J. J., CHAMLEY, L. W., PAIDAS, M. J., LOCKWOOD, C. J. & ABRAHAMS, V. M. 2011. Aspirin and heparin effect on basal and antiphospholipid antibody modulation of trophoblast function. *Obstet Gynecol,* 118**,** 1021-8.
HANLY, J. G., WALSH, N. M., FISK, J. D., EASTWOOD, B., HONG, C., SHERWOOD, G., JONES, J. V., JONES, E. & ELKON, K. 1993. Cognitive impairment and autoantibodies in systemic lupus erythematosus. *Br J Rheumatol,* 32**,** 291-6.
HARDWICK, R. H., SLADE, R. R., SMITH, P. A. & THOMPSON, M. H. 1999. Laparoscopic splenectomy in pregnancy. *J Laparoendosc Adv Surg Tech A,* 9**,** 439-40.
HATEMI, G., SILMAN, A., BANG, D., BODAGHI, B., CHAMBERLAIN, A. M., GUL, A., HOUMAN, M. H., KOTTER, I., OLIVIERI, I., SALVARANI, C., SFIKAKIS, P. P., SIVA, A., STANFORD, M. R., STUBIGER, N., YURDAKUL, S., YAZICI, H. & COMMITTEE, E. E. 2008. EULAR recommendations for the management of Behcet disease. *Ann Rheum Dis,* 67**,** 1656-62.
HERRANZ, M. T., RIVIER, G., KHAMASHTA, M. A., BLASER, K. U. & HUGHES, G. R. 1994. Association between antiphospholipid antibodies and epilepsy in patients with systemic lupus erythematosus. *Arthritis Rheum,* 37**,** 568-71.
HILLS, F. A., ABRAHAMS, V. M., GONZALEZ-TIMON, B., FRANCIS, J., CLOKE, B., HINKSON, L., RAI, R., MOR, G., REGAN, L., SULLIVAN, M., LAM, E. W. & BROSENS, J. J. 2006. Heparin prevents programmed cell death in human trophoblast. *Mol Hum Reprod,* 12**,** 237-43.
HORKKO, S., MILLER, E., DUDL, E., REAVEN, P., CURTISS, L. K., ZVAIFLER, N. J., TERKELTAUB, R., PIERANGELI, S. S., BRANCH, D. W., PALINSKI, W. & WITZTUM, J. L. 1996. Antiphospholipid antibodies are directed against epitopes of oxidized phospholipids. Recognition of cardiolipin by monoclonal antibodies to epitopes of oxidized low density lipoprotein. *J Clin Invest,* 98**,** 815-25.

HUGHES, G. R. 1983. Thrombosis, abortion, cerebral disease, and the lupus anticoagulant. *Br Med J (Clin Res Ed),* 287**,** 1088-9.
HUGHES, G. R. & KHAMASHTA, M. A. 2003. Seronegative antiphospholipid syndrome. *Ann Rheum Dis,* 62**,** 1127.
HUONG, D. L., WECHSLER, B., BLETRY, O., VAUTHIER-BROUZES, D., LEFEBVRE, G. & PIETTE, J. C. 2001. A study of 75 pregnancies in patients with antiphospholipid syndrome. *J Rheumatol,* 28**,** 2025-30.
IZMIRLY, P. M., KIM, M. Y., LLANOS, C., LE, P. U., GUERRA, M. M., ASKANASE, A. D., SALMON, J. E. & BUYON, J. P. 2010. Evaluation of the risk of anti-SSA/Ro-SSB/La antibody-associated cardiac manifestations of neonatal lupus in fetuses of mothers with systemic lupus erythematosus exposed to hydroxychloroquine. *Ann Rheum Dis,* 69**,** 1827-30.
JAYAKODY ARACHCHILLAGE, D. & GREAVES, M. 2014. The chequered history of the antiphospholipid syndrome. *Br J Haematol,* 165**,** 609-17.
KAMBOH, M. I., WANG, X., KAO, A. H., BARMADA, M. M., CLARKE, A., RAMSEY-GOLDMAN, R., MANZI, S. & DEMIRCI, F. Y. 2013. Genome-wide association study of antiphospholipid antibodies. *Autoimmune Dis,* 2013**,** 761046.
KANDIAH, D. A. & KRILIS, S. A. 1994. Beta 2-glycoprotein I. *Lupus,* 3**,** 207-12.
KARUSSIS, D., LEKER, R. R., ASHKENAZI, A. & ABRAMSKY, O. 1998. A subgroup of multiple sclerosis patients with anticardiolipin antibodies and unusual clinical manifestations: do they represent a new nosological entity? *Ann Neurol,* 44**,** 629-34.
KATSURAGAWA, H., KANZAKI, H., INOUE, T., HIRANO, T., MORI, T. & ROTE, N. S. 1997. Monoclonal antibody against phosphatidylserine inhibits in vitro human trophoblastic hormone production and invasion. *Biol Reprod,* 56**,** 50-8.
KEARON, C., GENT, M., HIRSH, J., WEITZ, J., KOVACS, M. J., ANDERSON, D. R., TURPIE, A. G., GREEN, D., GINSBERG, J. S., WELLS, P., MACKINNON, B. & JULIAN, J. A. 1999. A comparison of three months of anticoagulation with extended anticoagulation for a first episode of idiopathic venous thromboembolism. *N Engl J Med,* 340**,** 901-7.
KEELING, D., MACKIE, I., MOORE, G. W., GREER, I. A., GREAVES, M. & BRITISH COMMITTEE FOR STANDARDS IN, H. 2012. Guidelines on the investigation and management of antiphospholipid syndrome. *Br J Haematol,* 157**,** 47-58.
KHAMASHTA, M. A., CUADRADO, M. J., MUJIC, F., TAUB, N. A., HUNT, B. J. & HUGHES, G. R. 1995. The management of thrombosis in the antiphospholipid-antibody syndrome. *N Engl J Med,* 332**,** 993-7.
KO, H. S., AHN, H. Y., JANG, D. G., CHOI, S. K., PARK, Y. G., PARK, I. Y., LEE, G., PARK, S. H. & SHIN, J. C. 2011. Pregnancy outcomes and appropriate timing of pregnancy in 183 pregnancies in Korean patients with SLE. *Int J Med Sci,* 8**,** 577-83.
KOIKE, T. 2014. Antiphospholipid syndrome: 30 years and our contribution. *Int J Rheum Dis*.
KRNIC-BARRIE, S., O'CONNOR, C. R., LOONEY, S. W., PIERANGELI, S. S. & HARRIS, E. N. 1997. A retrospective review of 61 patients with antiphospholipid syndrome. Analysis of factors influencing recurrent thrombosis. *Arch Intern Med,* 157**,** 2101-8.
KRONBICHLER, A., FRANK, R., KIRSCHFINK, M., SZILAGYI, A., CSUKA, D., PROHASZKA, Z., SCHRATZBERGER, P., LHOTTA, K. & MAYER, G. 2014. Efficacy of eculizumab in a patient with immunoadsorption-dependent catastrophic antiphospholipid syndrome: a case report. *Medicine (Baltimore),* 93**,** e143.
LA ROSA, L., MERONI, P. L., TINCANI, A., BALESTRIERI, G., FADEN, D., LOJACONO, A., MORASSI, L., BROCCHI, E., DEL PAPA, N., GHARAVI, A. & ET AL. 1994. Beta 2 glycoprotein I and placental anticoagulant protein I in placentae from patients with antiphospholipid syndrome. *J Rheumatol,* 21**,** 1684-93.
LE THI THUONG, D., TIEULIE, N., COSTEDOAT, N., ANDREU, M. R., WECHSLER, B., VAUTHIER-BROUZES, D., AUMAITRE, O. & PIETTE, J. C. 2005. The HELLP syndrome in the antiphospholipid syndrome: retrospective study of 16 cases in 15 women. *Ann Rheum Dis,* 64**,** 273-8.
LEE, G. M. & AREPALLY, G. M. 2013. Heparin-induced thrombocytopenia. *Hematology Am Soc Hematol Educ Program,* 2013**,** 668-74.
LEE, R. M., BRANCH, D. W. & SILVER, R. M. 2001. Immunoglobulin A anti-beta2-glycoprotein antibodies in women who experience unexplained recurrent spontaneous abortion and unexplained fetal death. *Am J Obstet Gynecol,* 185**,** 748-53.
LEFKOU, E., MAMOPOULOS, A., FRAGAKIS, N., DAGKLIS, T., VOSNAKIS, C., NOUNOPOULOS, E., ROUSSO, D. & GIRARDI, G. 2014. Clinical improvement and successful pregnancy in a preeclamptic patient with antiphospholipid syndrome treated with pravastatin. *Hypertension,* 63**,** e118-9.
LEVINE, J. S., BRANCH, D. W. & RAUCH, J. 2002. The antiphospholipid syndrome. *N Engl J Med,* 346**,** 752-63.
LEY, A. B., READER, G. G., SORENSON, C. W. & OVERMAN, R. S. 1951. Idiopathic hypoprothrombinemia associated with hemorrhagic diathesis, and the effect of vitamin K. *Blood,* 6**,** 740-55.
LI, R., DAGUZAN, M., VANDERMIJNSBRUGGE, F., GYLING, M. & CANTINIEAUX, B. 2014. Both IgG and IgM anti-beta2 glycoprotein I antibodies assays are clinically useful to the antiphospholipid syndrome diagnosis. *Acta Clin Belg,* 69**,** 433-8.
LIM, W. 2009. Antiphospholipid antibody syndrome. *Hematology Am Soc Hematol Educ Program***,** 233-9.
LIM, W., CROWTHER, M. A. & EIKELBOOM, J. W. 2006. Management of antiphospholipid antibody syndrome: a systematic review. *JAMA,* 295**,** 1050-7.
LIMA, F., KHAMASHTA, M. A., BUCHANAN, N. M., KERSLAKE, S., HUNT, B. J. & HUGHES, G. R. 1996. A study of sixty pregnancies in patients with the antiphospholipid syndrome. *Clin Exp Rheumatol,* 14**,** 131-6.

LIOU, H. H., WANG, C. R., CHEN, C. J., CHEN, R. C., CHUANG, C. Y., CHIANG, I. P. & TSAI, M. C. 1996. Elevated levels of anticardiolipin antibodies and epilepsy in lupus patients. *Lupus,* 5**,** 307-12.
LIU, Y., LIU, Y., ZHANG, S., CHEN, H., LIU, M. & ZHANG, J. 2015. Etiology of spontaneous abortion before and after the demonstration of embryonic cardiac activity in women with recurrent spontaneous abortion. *Int J Gynaecol Obstet,* 129**,** 128-32.
LOCKSHIN, M. D. 1997. Antiphospholipid antibody. Babies, blood clots, biology. *JAMA,* 277**,** 1549-51.
LOCKSHIN, M. D., DRUZIN, M. L. & QAMAR, T. 1989. Prednisone does not prevent recurrent fetal death in women with antiphospholipid antibody. *Am J Obstet Gynecol,* 160**,** 439-43.
LOCKSHIN, M. D., KIM, M., LASKIN, C. A., GUERRA, M., BRANCH, D. W., MERRILL, J., PETRI, M., PORTER, T. F., SAMMARITANO, L., STEPHENSON, M. D., BUYON, J. & SALMON, J. E. 2012. Prediction of adverse pregnancy outcome by the presence of lupus anticoagulant, but not anticardiolipin antibody, in patients with antiphospholipid antibodies. *Arthritis Rheum,* 64**,** 2311-8.
LONZE, B. E., SINGER, A. L. & MONTGOMERY, R. A. 2010. Eculizumab and renal transplantation in a patient with CAPS. *N Engl J Med,* 362**,** 1744-5.
LONZE, B. E., ZACHARY, A. A., MAGRO, C. M., DESAI, N. M., ORANDI, B. J., DAGHER, N. N., SINGER, A. L., CARTER-MONROE, N., NAZARIAN, S. M., SEGEV, D. L., STREIFF, M. B. & MONTGOMERY, R. A. 2014. Eculizumab prevents recurrent antiphospholipid antibody syndrome and enables successful renal transplantation. *Am J Transplant,* 14**,** 459-65.
LYDEN, T. W., VOGT, E., NG, A. K., JOHNSON, P. M. & ROTE, N. S. 1992. Monoclonal antiphospholipid antibody reactivity against human placental trophoblast. *J Reprod Immunol,* 22**,** 1-14.
MACKWORTH-YOUNG, C., CHAN, J., HARRIS, N., WALPORT, M., BERNSTEIN, R., BATCHELOR, R., HUGHES, G. & GHARAVI, A. 1987. High incidence of anticardiolipin antibodies in relatives of patients with systemic lupus erythematosus. *J Rheumatol,* 14**,** 723-6.
MAGID, M. S., KAPLAN, C., SAMMARITANO, L. R., PETERSON, M., DRUZIN, M. L. & LOCKSHIN, M. D. 1998. Placental pathology in systemic lupus erythematosus: a prospective study. *Am J Obstet Gynecol,* 179**,** 226-34.
MANDREOLI, M. & ZUCCHELLI, P. 1993. Renal vascular disease in patients with primary antiphospholipid antibodies. *Nephrol Dial Transplant,* 8**,** 1277-80.
MANOHARAN, A., GIBSON, L., RUSH, B. & FEERY, B. J. 1977. Recurrent venous thrombosis with a "lupus" coagulation inhibitor in the absence of systemic lupus. *Aust N Z J Med,* 7**,** 422-6.
MAR, N., KOSOWICZ, R. & HOOK, K. 2014. Recurrent thrombosis prevention with intravenous immunoglobulin and hydroxychloroquine during pregnancy in a patient with history of catastrophic antiphospholipid syndrome and pregnancy loss. *J Thromb Thrombolysis,* 38**,** 196-200.
MARCHETTI, T., COHEN, M. & DE MOERLOOSE, P. 2013. Obstetrical antiphospholipid syndrome: from the pathogenesis to the clinical and therapeutic implications. *Clin Dev Immunol,* 2013**,** 159124.
MARKEL, A. 2005. Origin and natural history of deep vein thrombosis of the legs. *Semin Vasc Med,* 5**,** 65-74.
MARTINEZ-BERRIOTXOA, A., RUIZ-IRASTORZA, G., EGURBIDE, M. V., GARMENDIA, M., GABRIEL ERDOZAIN, J., VILLAR, I. & AGUIRRE, C. 2007. Transiently positive anticardiolipin antibodies and risk of thrombosis in patients with systemic lupus erythematosus. *Lupus,* 16**,** 810-6.
MATSUURA, E., IGARASHI, Y., FUJIMOTO, M., ICHIKAWA, K. & KOIKE, T. 1990. Anticardiolipin cofactor(s) and differential diagnosis of autoimmune disease. *Lancet,* 336**,** 177-8.
MATSUURA, E., IGARASHI, Y., YASUDA, T., TRIPLETT, D. A. & KOIKE, T. 1994. Anticardiolipin antibodies recognize beta 2-glycoprotein I structure altered by interacting with an oxygen modified solid phase surface. *J Exp Med,* 179**,** 457-62.
MCNEIL, H. P., CHESTERMAN, C. N. & KRILIS, S. A. 1991. Immunology and clinical importance of antiphospholipid antibodies. *Adv Immunol,* 49**,** 193-280.
MCNEIL, H. P., SIMPSON, R. J., CHESTERMAN, C. N. & KRILIS, S. A. 1990. Anti-phospholipid antibodies are directed against a complex antigen that includes a lipid-binding inhibitor of coagulation: beta 2-glycoprotein I (apolipoprotein H). *Proc Natl Acad Sci U S A,* 87**,** 4120-4.
MERONI, P. L., BORGHI, M. O., RASCHI, E. & TEDESCO, F. 2011. Pathogenesis of antiphospholipid syndrome: understanding the antibodies. *Nat Rev Rheumatol,* 7**,** 330-9.
MERONI, P. L., BORGHI, M. O., RASCHI, E., VENTURA, D., SARZI PUTTINI, P. C., ATZENI, F., LONATI, L., PARATI, G., TINCANI, A., MARI, D. & TEDESCO, F. 2004a. Inflammatory response and the endothelium. *Thromb Res,* 114**,** 329-34.
MERONI, P. L., GEROSA, M., RASCHI, E., SCURATI, S., GROSSI, C. & BORGHI, M. O. 2008. Updating on the pathogenic mechanisms 5 of the antiphospholipid antibodies-associated pregnancy loss. *Clin Rev Allergy Immunol,* 34**,** 332-7.
MERONI, P. L., RASCHI, E., TESTONI, C. & BORGHI, M. O. 2004b. Endothelial cell activation by antiphospholipid antibodies. *Clin Immunol,* 112**,** 169-74.
MINIATI, M., CENCI, C., MONTI, S. & POLI, D. 2012. Clinical presentation of acute pulmonary embolism: survey of 800 cases. *PLoS One,* 7**,** e30891.
MIYAKIS, S., LOCKSHIN, M. D., ATSUMI, T., BRANCH, D. W., BREY, R. L., CERVERA, R., DERKSEN, R. H., PG, D. E. G., KOIKE, T., MERONI, P. L., REBER, G., SHOENFELD, Y., TINCANI, A., VLACHOYIANNOPOULOS, P. G. & KRILIS, S. A. 2006. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J Thromb Haemost,* 4**,** 295-306.
MOORE, J. E. & MOHR, C. F. 1952. Biologically false positive serologic tests for syphilis; type, incidence, and cause. *J Am Med Assoc,* 150**,** 467-73.
MOUADEB, D. A. & RUCKENSTEIN, M. J. 2005. Antiphospholipid inner ear syndrome. *Laryngoscope,* 115**,** 879-83.

MULLA, M. J., BROSENS, J. J., CHAMLEY, L. W., GILES, I., PERICLEOUS, C., RAHMAN, A., JOYCE, S. K., PANDA, B., PAIDAS, M. J. & ABRAHAMS, V. M. 2009. Antiphospholipid antibodies induce a pro-inflammatory response in first trimester trophoblast via the TLR4/MyD88 pathway. *Am J Reprod Immunol,* 62**,** 96-111.

NALLI, C., ANDREOLI, L., CASU, C. & TINCANI, A. 2014. Management of recurrent thrombosis in antiphospholipid syndrome. *Curr Rheumatol Rep,* 16**,** 405.

NENCINI, P., BARUFFI, M. C., ABBATE, R., MASSAI, G., AMADUCCI, L. & INZITARI, D. 1992. Lupus anticoagulant and anticardiolipin antibodies in young adults with cerebral ischemia. *Stroke,* 23**,** 189-93.

NEVERS, W., PUPCO, A., KOREN, G. & BOZZO, P. 2014. Safety of tacrolimus in pregnancy. *Can Fam Physician,* 60**,** 905-6.

NEVILLE, C., RAUCH, J., KASSIS, J., CHANG, E. R., JOSEPH, L., LE COMTE, M. & FORTIN, P. R. 2003. Thromboembolic risk in patients with high titre anticardiolipin and multiple antiphospholipid antibodies. *Thromb Haemost,* 90**,** 108-15.

NILSSON, I. M., ASTEDT, B., HEDNER, U. & BEREZIN, D. 1975. Intrauterine death and circulating anticoagulant ("antithromboplastin"). *Acta Med Scand,* 197**,** 153-9.

NIMPF, J., BEVERS, E. M., BOMANS, P. H., TILL, U., WURM, H., KOSTNER, G. M. & ZWAAL, R. F. 1986. Prothrombinase activity of human platelets is inhibited by beta 2-glycoprotein-I. *Biochim Biophys Acta,* 884**,** 142-9.

NOBLE, L. S., KUTTEH, W. H., LASHEY, N., FRANKLIN, R. D. & HERRADA, J. 2005. Antiphospholipid antibodies associated with recurrent pregnancy loss: prospective, multicenter, controlled pilot study comparing treatment with low-molecular-weight heparin versus unfractionated heparin. *Fertil Steril,* 83**,** 684-90.

NOCHY, D., DAUGAS, E., DROZ, D., BEAUFILS, H., GRUNFELD, J. P., PIETTE, J. C., BARIETY, J. & HILL, G. 1999. The intrarenal vascular lesions associated with primary antiphospholipid syndrome. *J Am Soc Nephrol,* 10**,** 507-18.

NOCHY, D., DAUGAS, E., HILL, G. & GRUNFELD, J. P. 2002. Antiphospholipid syndrome nephropathy. *J Nephrol,* 15**,** 446-61.

OBERMOSER, G., BITTERLICH, W., KUNZ, F. & SEPP, N. T. 2004. Clinical significance of anticardiolipin and anti-beta2-glycoprotein I antibodies. *Int Arch Allergy Immunol,* 135**,** 148-53.

OKU, K., AMENGUAL, O. & ATSUMI, T. 2012. Pathophysiology of thrombosis and pregnancy morbidity in the antiphospholipid syndrome. *Eur J Clin Invest,* 42**,** 1126-35.

OKU, K., ATSUMI, T., BOHGAKI, M., AMENGUAL, O., KATAOKA, H., HORITA, T., YASUDA, S. & KOIKE, T. 2009. Complement activation in patients with primary antiphospholipid syndrome. *Ann Rheum Dis,* 68**,** 1030-5.

OLSSON, A. K., DIMBERG, A., KREUGER, J. & CLAESSON-WELSH, L. 2006. VEGF receptor signalling - in control of vascular function. *Nat Rev Mol Cell Biol,* 7**,** 359-71.

OSHIRO, B. T., SILVER, R. M., SCOTT, J. R., YU, H. & BRANCH, D. W. 1996. Antiphospholipid antibodies and fetal death. *Obstet Gynecol,* 87**,** 489-93.

PATTISON, N. S., CHAMLEY, L. W., BIRDSALL, M., ZANDERIGO, A. M., LIDDELL, H. S. & MCDOUGALL, J. 2000. Does aspirin have a role in improving pregnancy outcome for women with the antiphospholipid syndrome? A randomized controlled trial. *Am J Obstet Gynecol,* 183**,** 1008-12.

PEART, E. & CLOWSE, M. E. 2014. Systemic lupus erythematosus and pregnancy outcomes: an update and review of the literature. *Curr Opin Rheumatol,* 26**,** 118-23.

PENGO, V., TESTA, S., MARTINELLI, I., GHIRARDUZZI, A., LEGNANI, C., GRESELE, P., PASSAMONTI, S. M., BISON, E., DENAS, G., JOSE, S. P., BANZATO, A. & RUFFATTI, A. 2015. Incidence of a first thromboembolic event in carriers of isolated lupus anticoagulant. *Thromb Res,* 135**,** 46-9.

PENGO, V., TRIPODI, A., REBER, G., RAND, J. H., ORTEL, T. L., GALLI, M., DE GROOT, P. G., SUBCOMMITTEE ON LUPUS ANTICOAGULANT/ANTIPHOSPHOLIPID ANTIBODY OF THE, S., STANDARDISATION COMMITTEE OF THE INTERNATIONAL SOCIETY ON, T. & HAEMOSTASIS 2009. Update of the guidelines for lupus anticoagulant detection. Subcommittee on Lupus Anticoagulant/Antiphospholipid Antibody of the Scientific and Standardisation Committee of the International Society on Thrombosis and Haemostasis. *J Thromb Haemost,* 7**,** 1737-40.

PETRI, M. 2000. Epidemiology of the antiphospholipid antibody syndrome. *J Autoimmun,* 15**,** 145-51.

PIERANGELI, S. S. & HARRIS, E. N. 2008. A protocol for determination of anticardiolipin antibodies by ELISA. *Nat Protoc,* 3**,** 840-8.

RAHMAN, F. Z., RAHMAN, J., AL-SULEIMAN, S. A. & RAHMAN, M. S. 2005. Pregnancy outcome in lupus nephropathy. *Arch Gynecol Obstet,* 271**,** 222-6.

RAI, R. & REGAN, L. 2006. Recurrent miscarriage. *Lancet,* 368**,** 601-11.

RAI, R. S., REGAN, L., CLIFFORD, K., PICKERING, W., DAVE, M., MACKIE, I., MCNALLY, T. & COHEN, H. 1995. Antiphospholipid antibodies and beta 2-glycoprotein-I in 500 women with recurrent miscarriage: results of a comprehensive screening approach. *Hum Reprod,* 10**,** 2001-5.

RAND, J. H. & WOLGAST, L. R. 2012. Dos and don'ts in diagnosing antiphospholipid syndrome. *Hematology Am Soc Hematol Educ Program,* 2012**,** 455-9.

RAND, J. H., WU, X. X., ANDREE, H. A., ROSS, J. B., RUSINOVA, E., GASCON-LEMA, M. G., CALANDRI, C. & HARPEL, P. C. 1998. Antiphospholipid antibodies accelerate plasma coagulation by inhibiting annexin-V binding to phospholipids: a "lupus procoagulant" phenomenon. *Blood,* 92**,** 1652-60.

RAND, J. H., WU, X. X., QUINN, A. S., ASHTON, A. W., CHEN, P. P., HATHCOCK, J. J., ANDREE, H. A. & TAATJES, D. J. 2010. Hydroxychloroquine protects the annexin A5 anticoagulant shield from disruption by antiphospholipid antibodies: evidence for a novel effect for an old antimalarial drug. *Blood,* 115**,** 2292-9.

RAVINDRAN, V., RAJENDRAN, S. & ELIAS, G. 2013. Primary antiphospholipid syndrome in monozygotic twins. *Lupus,* 22**,** 92-4.
REBER, G. & DE MOERLOOSE, P. 2004. Anti-beta2-glycoprotein I antibodies--when and how should they be measured? *Thromb Res,* 114**,** 527-31.
REN, M., PHOON, C. K. & SCHLAME, M. 2014. Metabolism and function of mitochondrial cardiolipin. *Prog Lipid Res,* 55**,** 1-16.
REYNAUD, Q., LEGA, J. C., MISMETTI, P., CHAPELLE, C., WAHL, D., CATHEBRAS, P. & LAPORTE, S. 2014. Risk of venous and arterial thrombosis according to type of antiphospholipid antibodies in adults without systemic lupus erythematosus: a systematic review and meta-analysis. *Autoimmun Rev,* 13**,** 595-608.
ROUBEY, R. A., EISENBERG, R. A., HARPER, M. F. & WINFIELD, J. B. 1995. "Anticardiolipin" autoantibodies recognize beta 2-glycoprotein I in the absence of phospholipid. Importance of Ag density and bivalent binding. *J Immunol,* 154**,** 954-60.
RUIZ-IRASTORZA, G., CROWTHER, M., BRANCH, W. & KHAMASHTA, M. A. 2010a. Antiphospholipid syndrome. *Lancet,* 376**,** 1498-509.
RUIZ-IRASTORZA, G., CUADRADO, M. J., RUIZ-ARRUZA, I., BREY, R., CROWTHER, M., DERKSEN, R., ERKAN, D., KRILIS, S., MACHIN, S., PENGO, V., PIERANGELI, S., TEKTONIDOU, M. & KHAMASHTA, M. 2011. 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,* 20**,** 206-18.
RUIZ-IRASTORZA, G., EGURBIDE, M. V., UGALDE, J. & AGUIRRE, C. 2004. High impact of antiphospholipid syndrome on irreversible organ damage and survival of patients with systemic lupus erythematosus. *Arch Intern Med,* 164**,** 77-82.
RUIZ-IRASTORZA, G., HUNT, B. J. & KHAMASHTA, M. A. 2007. A systematic review of secondary thromboprophylaxis in patients with antiphospholipid antibodies. *Arthritis Rheum,* 57**,** 1487-95.
RUIZ-IRASTORZA, G. & KHAMASHTA, M. A. 2011. Lupus and pregnancy: integrating clues from the bench and bedside. *Eur J Clin Invest,* 41**,** 672-8.
RUIZ-IRASTORZA, G., RAMOS-CASALS, M., BRITO-ZERON, P. & KHAMASHTA, M. A. 2010b. Clinical efficacy and side effects of antimalarials in systemic lupus erythematosus: a systematic review. *Ann Rheum Dis,* 69**,** 20-8.
SAKAGUCHI, G., MINAMI, K., NAKAYAMA, S. & TSUNEYOSHI, H. 1998. Aortic valve replacement after previous coronary artery bypass grafting in a patient with antiphospholipid syndrome. *Jpn J Thorac Cardiovasc Surg,* 46**,** 257-9.
SALAFIA, C. M. & COWCHOCK, F. S. 1997. Placental pathology and antiphospholipid antibodies: a descriptive study. *Am J Perinatol,* 14**,** 435-41.
SANGLE, S., D'CRUZ, D. P., KHAMASHTA, M. A. & HUGHES, G. R. 2004. Antiphospholipid antibodies, systemic lupus erythematosus, and non-traumatic metatarsal fractures. *Ann Rheum Dis,* 63**,** 1241-3.
SANNA, G., BERTOLACCINI, M. L., CUADRADO, M. J., KHAMASHTA, M. A. & HUGHES, G. R. 2003. Central nervous system involvement in the antiphospholipid (Hughes) syndrome. *Rheumatology (Oxford),* 42**,** 200-13.
SANNA, G., D'CRUZ, D. & CUADRADO, M. J. 2006. Cerebral manifestations in the antiphospholipid (Hughes) syndrome. *Rheum Dis Clin North Am,* 32**,** 465-90.
SANNA, G., PIGA, M., TERRYBERRY, J. W., PELTZ, M. T., GIAGHEDDU, S., SATTA, L., AHMED, A., CAULI, A., MONTALDO, C., PASSIU, G., PETER, J. B., SHOENFELD, Y. & MATHIEU, A. 2000. Central nervous system involvement in systemic lupus erythematosus: cerebral imaging and serological profile in patients with and without overt neuropsychiatric manifestations. *Lupus,* 9**,** 573-83.
SCHOUSBOE, I. & RASMUSSEN, M. S. 1995. Synchronized inhibition of the phospholipid mediated autoactivation of factor XII in plasma by beta 2-glycoprotein I and anti-beta 2-glycoprotein I. *Thromb Haemost,* 73**,** 798-804.
SCHULMAN, S., SVENUNGSSON, E. & GRANQVIST, S. 1998. Anticardiolipin antibodies predict early recurrence of thromboembolism and death among patients with venous thromboembolism following anticoagulant therapy. Duration of Anticoagulation Study Group. *Am J Med,* 104**,** 332-8.
SCHWARTZ, N., SHOENFELD, Y., BARZILAI, O., CERVERA, R., FONT, J., BLANK, M., YACOBI, S., PATLAS, N., COHEN, A., MEVORACH, D. & ORNOY, A. 2007. Reduced placental growth and hCG secretion in vitro induced by antiphospholipid antibodies but not by anti-Ro or anti-La: studies on sera from women with SLE/PAPS. *Lupus,* 16**,** 110-20.
SCHWARZENBACHER, R., ZETH, K., DIEDERICHS, K., GRIES, A., KOSTNER, G. M., LAGGNER, P. & PRASSL, R. 1999. Crystal structure of human beta2-glycoprotein I: implications for phospholipid binding and the antiphospholipid syndrome. *EMBO J,* 18**,** 6228-39.
SCIASCIA, S., GIACHINO, O. & ROCCATELLO, D. 2012. Prevention of thrombosis relapse in antiphospholipid syndrome patients refractory to conventional therapy using intravenous immunoglobulin. *Clin Exp Rheumatol,* 30**,** 409-13.
SCOTT, T. F., HESS, D. & BRILLMAN, J. 1994. Antiphospholipid antibody syndrome mimicking multiple sclerosis clinically and by magnetic resonance imaging. *Arch Intern Med,* 154**,** 917-20.
SHAH, N. M., KHAMASHTA, M. A., ATSUMI, T. & HUGHES, G. R. 1998. Outcome of patients with anticardiolipin antibodies: a 10 year follow-up of 52 patients. *Lupus,* 7**,** 3-6.
SHAPIRA, I., ANDRADE, D., ALLEN, S. L. & SALMON, J. E. 2012. Brief report: induction of sustained remission in recurrent catastrophic antiphospholipid syndrome via inhibition of terminal complement with eculizumab. *Arthritis Rheum,* 64**,** 2719-23.

SHOENFELD, Y., LEV, S., BLATT, I., BLANK, M., FONT, J., VON LANDENBERG, P., LEV, N., ZAECH, J., CERVERA, R., PIETTE, J. C., KHAMASHTA, M. A., BERTOLACCINI, M. L., HUGHES, G. R., YOUINOU, P., MERONI, P. L., PENGO, V., ALVES, J. D., TINCANI, A., SZEGEDI, G., LAKOS, G., STURFELT, G., JONSEN, A., KOIKE, T., SANMARCO, M., RUFFATTI, A., ULCOVA-GALLOVA, Z., PRAPROTNIK, S., ROZMAN, B., LORBER, M., CHAPMAN, J., VAN-BREDA-VRIEZMAN, P. J. & DAMOISEAUX, J. 2004. Features associated with epilepsy in the antiphospholipid syndrome. *J Rheumatol,* 31**,** 1344-8.

SILVER, R. K., MACGREGOR, S. N., PASTERNAK, J. F. & NEELY, S. E. 1992. Fetal stroke associated with elevated maternal anticardiolipin antibodies. *Obstet Gynecol,* 80**,** 497-9.

SILVESTRI, E., EMMI, G. & PRISCO, D. 2014. Anti-TNF-alpha agents in vascular Behcet's disease. *Expert Rev Cardiovasc Ther,* 12**,** 415-6.

SINGH, J. P., EVANS, J. C., LEVY, D., LARSON, M. G., FREED, L. A., FULLER, D. L., LEHMAN, B. & BENJAMIN, E. J. 1999. Prevalence and clinical determinants of mitral, tricuspid, and aortic regurgitation (the Framingham Heart Study). *Am J Cardiol,* 83**,** 897-902.

SINICO, R. A., CAVAZZANA, I., NUZZO, M., VIANELLI, M., NAPODANO, P., SCAINI, P. & TINCANI, A. 2010. Renal involvement in primary antiphospholipid syndrome: retrospective analysis of 160 patients. *Clin J Am Soc Nephrol,* 5**,** 1211-7.

SPINNATO, J. A., CLARK, A. L., PIERANGELI, S. S. & HARRIS, E. N. 1995. Intravenous immunoglobulin therapy for the antiphospholipid syndrome in pregnancy. *Am J Obstet Gynecol,* 172**,** 690-4.

STEINKASSERER, A., BARLOW, P. N., WILLIS, A. C., KERTESZ, Z., CAMPBELL, I. D., SIM, R. B. & NORMAN, D. G. 1992. Activity, disulphide mapping and structural modelling of the fifth domain of human beta 2-glycoprotein I. *FEBS Lett,* 313**,** 193-7.

STEPHENSON, M. D., BALLEM, P. J., TSANG, P., PURKISS, S., ENSWORTH, S., HOULIHAN, E. & ENSOM, M. H. 2004. Treatment of antiphospholipid antibody syndrome (APS) in pregnancy: a randomized pilot trial comparing low molecular weight heparin to unfractionated heparin. *J Obstet Gynaecol Can,* 26**,** 729-34.

STOJANOVICH, L., KONTIC, M., DJOKOVIC, A., ILIJEVSKI, N., STANISAVLJEVIC, N. & MARISAVLJEVIC, D. 2012. Pulmonary events in antiphospholipid syndrome: influence of antiphospholipid antibody type and levels. *Scand J Rheumatol,* 41**,** 223-6.

STONE, S., PIJNENBORG, R., VERCRUYSSE, L., POSTON, R., KHAMASHTA, M. A., HUNT, B. J. & POSTON, L. 2006. The placental bed in pregnancies complicated by primary antiphospholipid syndrome. *Placenta,* 27**,** 457-67.

STRAKHAN, M., HURTADO-SBORDONI, M., GALEAS, N., BAKIRHAN, K., ALEXIS, K. & ELRAFEI, T. 2014. 36-year-old female with catastrophic antiphospholipid syndrome treated with eculizumab: a case report and review of literature. *Case Rep Hematol,* 2014**,** 704371.

SWADZBA, J., IWANIEC, T., PULKA, M., DE LAAT, B., DE GROOT, P. G. & MUSIAL, J. 2011. Lupus anticoagulant: performance of the tests as recommended by the latest ISTH guidelines. *J Thromb Haemost,* 9**,** 1776-83.

TABBUTT, S., GRISWOLD, W. R., OGINO, M. T., MENDOZA, A. E., ALLEN, J. B. & REZNIK, V. M. 1994. Multiple thromboses in a premature infant associated with maternal phospholipid antibody syndrome. *J Perinatol,* 14**,** 66-70.

TAKEYA, H., MORI, T., GABAZZA, E. C., KURODA, K., DEGUCHI, H., MATSUURA, E., ICHIKAWA, K., KOIKE, T. & SUZUKI, K. 1997. Anti-beta2-glycoprotein I (beta2GPI) monoclonal antibodies with lupus anticoagulant-like activity enhance the beta2GPI binding to phospholipids. *J Clin Invest,* 99**,** 2260-8.

TEDESCO, F., PAUSA, M., NARDON, E., INTRONA, M., MANTOVANI, A. & DOBRINA, A. 1997. The cytolytically inactive terminal complement complex activates endothelial cells to express adhesion molecules and tissue factor procoagulant activity. *J Exp Med,* 185**,** 1619-27.

TEKTONIDOU, M. G. & MOUTSOPOULOS, H. M. 2006. Osteoarticular manifestations of antiphospholipid syndrome. *Rheum Dis Clin North Am,* 32**,** 523-35.

TENTI, S., GUIDELLI, G. M., BELLISAI, F., GALEAZZI, M. & FIORAVANTI, A. 2013. Long-term treatment of antiphospholipid syndrome with intravenous immunoglobulin in addition to conventional therapy. *Clin Exp Rheumatol,* 31**,** 877-82.

TRIOLO, G., FERRANTE, A., ACCARDO-PALUMBO, A., CICCIA, F., CADELO, M., CASTELLI, A., PERINO, A. & LICATA, G. 2004. IVIG in APS pregnancy. *Lupus,* 13**,** 731-5.

TRIPLETT, D. A. 1993. Antiphospholipid antibodies and thrombosis. A consequence, coincidence, or cause? *Arch Pathol Lab Med,* 117**,** 78-88.

TRIPODI, A. 2009. Testing for lupus anticoagulants: all that a clinician should know. *Lupus,* 18**,** 291-8.

TSUTSUMI, A., MATSUURA, E., ICHIKAWA, K., FUJISAKU, A., MUKAI, M., KOBAYASHI, S. & KOIKE, T. 1996. Antibodies to beta 2-glycoprotein I and clinical manifestations in patients with systemic lupus erythematosus. *Arthritis Rheum,* 39**,** 1466-74.

TUTHILL, J. I. & KHAMASHTA, M. A. 2009. Management of antiphospholipid syndrome. *J Autoimmun,* 33**,** 92-8.

URBANUS, R. T., SIEGERINK, B., ROEST, M., ROSENDAAL, F. R., DE GROOT, P. G. & ALGRA, A. 2009. Antiphospholipid antibodies and risk of myocardial infarction and ischaemic stroke in young women in the RATIO study: a case-control study. *Lancet Neurol,* 8**,** 998-1005.

UTHMAN, I., GODEAU, B., TAHER, A. & KHAMASHTA, M. 2008. The hematologic manifestations of the antiphospholipid syndrome. *Blood Rev,* 22**,** 187-94.

UTHMAN, I. & KHAMASHTA, M. 2006. Antiphospholipid syndrome and the kidneys. *Semin Arthritis Rheum,* 35**,** 360-7.

UTHMAN, I. & KHAMASHTA, M. 2007. The abdominal manifestations of the antiphospholipid syndrome. *Rheumatology (Oxford),* 46**,** 1641-7.
UTZ, V. M. & TANG, J. 2011. Ocular manifestations of the antiphospholipid syndrome. *Br J Ophthalmol,* 95**,** 454-9.
UVA, L., MIGUEL, D., PINHEIRO, C., FREITAS, J. P., MARQUES GOMES, M. & FILIPE, P. 2012. Cutaneous manifestations of systemic lupus erythematosus. *Autoimmune Dis,* 2012**,** 834291.
VAN HORN, J. T., CRAVEN, C., WARD, K., BRANCH, D. W. & SILVER, R. M. 2004. Histologic features of placentas and abortion specimens from women with antiphospholipid and antiphospholipid-like syndromes. *Placenta,* 25**,** 642-8.
VAZQUEZ-MELLADO, J., LLORENTE, L., RICHAUD-PATIN, Y. & ALARCON-SEGOVIA, D. 1994. Exposure of anionic phospholipids upon platelet activation permits binding of beta 2 glycoprotein I and through it that of IgG antiphospholipid antibodies. Studies in platelets from patients with antiphospholipid syndrome and normal subjects. *J Autoimmun,* 7**,** 335-48.
VILA, P., HERNANDEZ, M. C., LOPEZ-FERNANDEZ, M. F. & BATLLE, J. 1994. Prevalence, follow-up and clinical significance of the anticardiolipin antibodies in normal subjects. *Thromb Haemost,* 72**,** 209-13.
WAHL, D., MEMBRE, A., PERRET-GUILLAUME, C., REGNAULT, V. & LECOMPTE, T. 2009. Mechanisms of antiphospholipid-induced thrombosis: effects on the protein C system. *Curr Rheumatol Rep,* 11**,** 77-81.
WARKENTIN, T. E. 1998. Clinical presentation of heparin-induced thrombocytopenia. *Semin Hematol,* 35**,** 9-16; discussion 35-6.
WEISS, S., NYZIO, J. B., CINES, D., DETRE, J., MILAS, B. L., NARULA, N. & FLOYD, T. F. 2008. Antiphospholipid syndrome: intraoperative and postoperative anticoagulation in cardiac surgery. *J Cardiothorac Vasc Anesth,* 22**,** 735-9.
WILLIAMS, F. M., PARMAR, K., HUGHES, G. R. & HUNT, B. J. 2000. Systemic endothelial cell markers in primary antiphospholipid syndrome. *Thromb Haemost,* 84**,** 742-6.
WILSON, W. A., GHARAVI, A. E., KOIKE, T., LOCKSHIN, M. D., BRANCH, D. W., PIETTE, J. C., BREY, R., DERKSEN, R., HARRIS, E. N., HUGHES, G. R., TRIPLETT, D. A. & KHAMASHTA, M. A. 1999. International consensus statement on preliminary classification criteria for definite antiphospholipid syndrome: report of an international workshop. *Arthritis Rheum,* 42**,** 1309-11.
WU, X. X., GULLER, S. & RAND, J. H. 2011. Hydroxychloroquine reduces binding of antiphospholipid antibodies to syncytiotrophoblasts and restores annexin A5 expression. *Am J Obstet Gynecol,* 205**,** 576 e7-14.
YAGEL, S. 2011. Angiogenesis in gestational vascular complications. *Thromb Res,* 127 Suppl 3**,** S64-6.
YAN YUEN, S., KRIZOVA, A., OUIMET, J. M. & POPE, J. E. 2008. Pregnancy outcome in systemic lupus erythematosus (SLE) is improving: Results from a case control study and literature review. *Open Rheumatol J,* 2**,** 89-98.
YETMAN, D. L. & KUTTEH, W. H. 1996. Antiphospholipid antibody panels and recurrent pregnancy loss: prevalence of anticardiolipin antibodies compared with other antiphospholipid antibodies. *Fertil Steril,* 66**,** 540-6.
ZIVKOVIC, M., ZLATANOVIC, M., ZLATANOVIC, G., DJORDJEVIC-JOCIC, J. & CEKIC, S. 2011. Anticardiolipin antibodies in patients with Behcet's disease. *Bosn J Basic Med Sci,* 11**,** 58-61.
ZUILY, S., HUTTIN, O., MOHAMED, S., MARIE, P. Y., SELTON-SUTY, C. & WAHL, D. 2013. Valvular heart disease in antiphospholipid syndrome. *Curr Rheumatol Rep,* 15**,** 320.