III

DIAGNOSIS AND MANAGEMENT OF THE ANTIPHOSPHOLIPID SYNDROME

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Introduction

Antiphospholipid syndrome was first described 27 years ago in patients with systemic lupus erythematosus (SLE) and positive anticardiolipin antibodies, who presented with a clotting syndrome that affected arteries and veins.[1] Female patients had a high risk of recurrent miscarriage and late fetal loss. The international classification criteria for this syndrome used today are based on those initial clinical observations.[2]

The syndrome is under-recognised and underdiagnosed and can have devastating consequences if untreated, mainly because of uncontrolled thrombosis. Difficulties in diagnosis are compounded by a lack of standardisation of diagnostic tests. Early recognition is crucial, because treatment can reduce mortality and morbidity in relatively young people who often present with diseases such as stroke, myocardial infarction, and deep vein thrombosis.

Because of its variable clinical presentation, patients with antiphospholipid syndrome present to a variety of medical practitioners. Here, we introduce this complicated and intriguing syndrome, and provide basic guiding principles for the recognition, diagnosis, and management of affected patients.

What is the antiphospholipid syndrome?

Antiphospholipid syndrome is a systemic autoimmune disorder characterized by both arterial and venous thrombosis, adverse outcome in pregnancy (for mother and fetus), and raised titers of antiphospholipid antibodies. It occurs in isolation (primary antiphospholipid syndrome) in more than 50% of patients, but it can be associated with other autoimmune diseases. SLE is the most common–20-35% of patients with SLE develop secondary antiphospholipid syndrome.[2] An acute variant of the syndrome–catastrophic antiphospholipid syndrome–results in widespread thrombotic microangiopathy and multiple organ failure (Box 2).[3] Classification criteria were last updated in 2006 (Box 1). A combination of clinical and laboratory findings is required to confirm the diagnosis.[4]

– BOX 1 –

CLASSIFICATION CRITERIA FOR THE ANTIPHOSPHOLIPID SYNDROME

Antiphospholipid syndrome is present if at least one of the clinical criteria and one of the laboratory criteria that follow are met:

CLINICAL CRITERIA

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 of histopathology). For histopathologic confirmation, thrombosis should be present without significant evidence of inflammation in the vessel wall.

Pregnancy morbidity
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 one or more premature births of a morphologically normal neonate before 34th week of gestation because of: (I) eclampsia or severe preeclampsia defined according to standard definitions, or (II) recognized features of placental insufficiency.
Or three or more unexplained consecutive spontaneous miscarriages before the 10th week of gestation, with maternal anatomic or hormonal abnormalities excluded and paternal and maternal chromosomal causes excluded.

LABORATORY CRITERIA

Lupus Anticoagulant 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 Haemostasis (Scientific Subcommittee on lupus anticoagulant/phospholipid – dependent antibodies).[10]

Anticardiolipin 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, a least 12 weeks apart, measured by standardized ELISA.
Anti-β_2-glycoprotein I 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, a least 12 weeks apart, measured by standardized ELISA, according to recommended procedures.[59]

Who gets it?

SLE may affect up to 1 in 1000 women (depending on ethnic origin), and around 30% of those develop secondary antiphospholipid syndrome. The population prevalence of primary antiphospholipid syndrome is unknown, although it is estimated that this disease affects up to 0,5% of the general population.

Antiphopholipid syndrome occurs mainly in young women of fertile age, rarely occurs in children and only 12% of patients present over the age of 50. In a large international cohort of patients diagnosed with the syndrome the mean age at diagnosis was 34 + 13 years SD. The male:female ratio was 1:3.5 for primary disease and 1:7 for secondary diagnosis associated with SLE.[2] A recently reported, unique cohort of 121 pediatric cases (primary and secondary) had a mean age of 10.7 at disease onset (range 1.0-17.9), and a male:female ratio of almost 1:1.[5] Patients who present after 50 are more often male and present more often with stroke and coronary heart disease.[2] Less than 1% of patients with primary or secondary antiphospholipid syndrome develop the catastrophic form and in almost half of them, catastrophic antiphospholipid syndrome appears *de novo*, without prior thrombotic events.[2]

What are antiphospholipid antibodies and how are they associated with clinical symptoms?

Antiphospholipid antibodies form a heterogeneous group of autoantibodies directed at plasma proteins that bind to phospholipids.[6] Some antibodies from the antiphospholipid family have a paradoxical effect on coagulation: in vivo they are associated with recurrent thrombosis, but in vitro they increase phospholipid dependent clotting times, a phenomenon known as 'lupus anticoagulant' activity. This peculiar phenomenon was named 'Lupus anticoagulant' and refers to the *ability* of certain antibodies to prolong phospholipid dependent clotting time. The so-called 'lupus anticoagulant assay'

– BOX 2 –

THE CATASTROPHIC ANTIPHOSPHOLIPID SYNDROME

Management of catastrophic antiphospholipid syndrome is an extremely rare life threatening condition, characterized by the rapid development of multiple microthrombi in various organ systems, typically the brain, kidneys, lung and skin.[60] Thrombocytopenia, hemolysis, schistocytes, and activation of the coagulation system are frequent laboratory findings and thus thrombotic thrombocytopenic purpura, hemolytic uremic syndrome and disseminated intravascular coagulation are important differential diagnostic considerations. The mortality of the catastrophic antiphospholipid syndrome approaches 50%.[61] Figure 3 gives examples of schistocutes and microthrombi in the kidneys and the brain.

Data on how to treat the catastrophic antiphospholipid syndrome is limited but current treatment regimes seem to have led to a marked reduction of the mortality when compared to historical case series.[61] Successful treatment regimes include anticoagulation, high dose corticosteroids and plasma exchange with or without intravenous immunoglobulins. Plasma exchange seems to be particularly useful in the setting of thrombotic microangiopathy. Possible precipitating disorders such as infection should be treated promptly.

is a functional assay based on a combination of several clotting tests. Two other antibodies are useful for diagnosing antiphospholipid syndrome: anticardiolipin antibodies and anti-β2 glycoprotein I antibodies (box 1), both of which can be detected by enzyme linked immunosorbent assays (ELISAS).[4]

Antibodies with lupus anticoagulant activity are of major importance clinically as two systematic reviews found them to be strongly correlated with thrombotic and obstetric complications of anti-phospholipid syndrome.[7;8] Table 1 describes assays for lupus anticoagulant, anticardiolipin antibodies, and anti-β2 glyco-protein I antibodies.

Unfortunately, agreement between laboratories for all of these assays is poor. A recent survey that evaluated lupus anticoagulant positive plasma samples found a false positive rate of 24%.[9] This highlights the importance of good communication between the laboratory and the clinician when making a diagnosis and of ensuring that guidelines are followed.[10]

Antiphospholipid antibodies are found in 1-5% of apparently healthy subjects. Prevalence increases with age and may be influenced by chronic disease, infections, malignancies, and the use of certain drugs. Positivity in these conditions usually arises from IgM antibodies at low titres and is not associated with thrombosis or adverse pregnancy outcome.[11]

Persistent positivity is rare. In a cross sectional study of 552 healthy blood donors, 6.5% had anticardiolipin IgG, but fewer than 2% still had increased titres nine months later.[12] A definitive diagnosis of antiphospholipid syndrome requires the presence of clinical criteria and positive results for at least one of the three assays on at least two separate occasions 12 weeks apart because only persistent antiphospholipid antibodies are clinically relevant.[4;13]

The assays currently used for detecting antiphospholipid antibodies show variable correlations with clinical symptoms. Well designed prospective diagnostic studies are scarce. Difficulties in interpreting clinical-serological studies arise from non-standardised assays, variable inclusion criteria, and broad definitions for case selection. Overall, the evidence supports the following:

* Lupus anticoagulant strongly associates with venous thrombosis, both in SLE and in the general population (OR 11).[7] This effect is stronger in younger age groups (◂ 50).[14]
* Lupus anticoagulant strongly associates with stroke, both in SLE and the general population. (OR 8,1 95% CI 2.4–27.5) This effect is stronger in young age groups (◂50).[15;16]
* Lupus anticoagulant is strongly associated with fetal loss ▸ 10 wks of gestation. (OR 7,8 95% CI 2.30–26.45).[8]
* Lupus anticoagulant predicts venous thrombosis and fetal loss more strongly than anticardiolipin antibodies (OR ranging from 1,6-3,5).[7;8]
* The anticardiolipin ELISA is considered to have high sensitivity but low specificity. It has a stronger association with morbidity in pregnancy than with thrombosis.[8;17;18]
* Studies that have investigated the relationship between anti-$\beta_2$glycoprotein I antibodies and clinical symptoms have shown

contradictory findings.[8;13;19] The clinical relevance of isolated a anti-$\beta_2$glycoprotein I antibodies remains uncertain.

* Patients with triple positivity for lupus anticoagulant, anticardiolipin and anti-$\beta_2$glycoprotein I antibodies seem to have a particularly high risk for future pregnancy morbidity or thromboembolism (OR = 34.4, 95% CI 3.5-335).[20;21]
* Established risk factors for thrombosis such as smoking (arterial disease) and oral contraception (venous thrombosis) contribute to a further increased risk of thrombosis in the presence of antiphospholipid antibodies.[15]
* The risk of apparently healthy people with persistently positive antiphospholipid antibodies to eventually develop a clinical event, such as thrombosis or adverse pregnancy outcome remains unknown.

What is known about the aetiology and pathophysiology of antiphospholipid syndrome?

The cause of the production of autoantibodies to phospholipid binding proteins such as anti-β_2-glycoprotein I is largely unknown.[6;22]

EFFECT ON COAGULATION AND INFLAMMATORY PATHWAYS Antiphospholipid antibodies affect the coagulation cascade and inflammation. In a process mediated by β2 glycoprotein I, antiphospholipid antibodies bind to platelets and endothelial cells, activating endothelial cells and inducing a procoagulant state. Antibody binding also activates complement[23], resulting in recruitment of other inflammatory cells, activation of tissue factor, endothelial damage, and finally thrombosis.[24] Although cerebral involvement is thought to be mainly thrombotic in nature, evidence now suggests that antiphospholipid antibodies may have more direct effects, causing neurological impairment unrelated to thrombosis through antibody-cellular interactions, possibly because of complement activation[25] or a disrupted blood-brain barrier.[26;27]

IS THERE AN ADDITIONAL TRIGGER? Most patients develop a discrete thrombotic event at a certain site in the body, suggesting that an additional trigger or risk factor–a 'second hit'–is needed for the development of thrombosis. Infection, local endothelial damage, and pregnancy are possible candidates.

PREGNANCY Thrombosis in the placental vasculature was initially thought to be the main cause of adverse outcomes in pregnancy. However, placental thrombosis and infarction are not specific to antiphospholipid syndrome but occur in other conditions, such as non-antiphospholipid syndrome pre-eclampsia and HELLP syndrome.[28] In vitro and animal studies showing that antiphospholipid antibodies can bind directly to trophoblast cells and cause direct cellular injury, defective invasiveness, and a local inflammatory response as a result of activation of the classical and alternative pathways of complement provided important insights into the pathophysiology of pregnancy loss.[24;29] Moreover, they showed that the protective effect of heparin resulted from its anti-complement activity and not only from its effects on coagulation.[30] Antiphospholipid antibodies seem to cause direct dysfunction of the trophoblast as well as activation of complement at the fetomaternal interface, resulting in an impaired exchange of blood components between mother and fetus, which can lead to early miscarriage, preeclampsia, intrauterine growth restriction or even intrauterine fetal death.

How do patients with antiphospholipid syndrome present?

The clinical features of antiphospholipid syndrome are diverse and can affect all organ systems. Figure 1 gives an overview of the most common clinical findings. Venous thrombosis, along with its complications, is more common than arterial thrombosis. In a large cohort of 1000 patients deep vein thrombosis in the leg

was the first symptom in 32%, and pulmonary embolism in 14%.[2] Other vesseIs such as renal veins, hepatic, subclavian, and retinal veins, cerebral sinuses and vena cava are more often affected than in non antiphospholipid syndrome related thrombosis.[2]

The most common arterial thrombotic events are stroke and transient ischaemic attack, which are the initial clinical manifestation in 13% and in 7% of patients, respectively.[2] Recurrent thrombotic events are common. The vascular pattern of recurrent thrombosis is fairly consistent for venous thrombosis (70% venous recurrence) and arterial thrombosis (90% arterial recurrence).[31]

CEREBRAL INVOLVEMENT Cerebral involvement is common in antiphospholipid syndrome[32] and was highlighted in the original description of the syndrome.[1] Cerebral ischaemia, migraine, cognitive dysfunction, seizures, chorea, transverse myelitis, psychosis, depression, and Guillain-Barré syndrome have all been associated with the presence of antiphospholipid antibodies.[27] Despite a strong observed association between chronic headache, including migraine, and antiphospholipid syndrome [33], studies exploring the relationship between headache and antiphospholipid antibodies have shown contradictory results.[34] An association has been reported between valvular heart disease and central nervous system manifestations of the syndrome, which suggests that cerebral emboli from valvular lesions may be a risk.[35]

OTHER ORGAN INVOLVEMENT The most common cardiac abnormality in patients with antiphospholipid syndrome is non-bacterial thrombotic endocarditis characterized by adherent platelet-fibrin thrombi on the endocardial surface of valves, which has been reported in 11.6% of patients during the evolution of disease.[2;36] Myocardial infarction is the presenting symptom of the syndrome in 2.8% of patients.[2] Prospective studies have shown that presence of antiphospholipid antibodies is associated with an increased risk of myocardial infarction.[15;17]

– BOX 3 –

CONDITIONS THAT POINT TO ANTIPHOSPHOLIPID SYNDROME

Red Flags

Unexplained deep vein thrombosis and/or pulmonary embolism under 50
Stroke under 50
Transient ischemic attack under 50
Recurrent thrombosis
Thrombosis in an unusual site
Unexplained fetal loss after 10 weeks gestation
Severe and/or early preeclampsia
Severe intrauterine growth restriction
Preeclampsia with severe thrombocytopenia
Cardiac valve disease *(in combination with other symptoms in this box)*
If a patient is diagnosed with SLE

Yellow Flags

Livedo Reticularis
Raynaud phenomenon
Unexplained persistent thrombocytopenia
Recurrent early pregnancy loss

Thrombosis can occur anywhere in the renal vasculature, ranging from occlusion of the renal veins and arterial trunk to microthrombi in glomerular capillaries. The latter can cause rapid decline of renal function.[2] In secondary antiphospholipid syndrome it is debated whether presence of antiphospholipid antibodies leads to a worsened outcome for traditional lupus nephritis. Although prospective studies have not addressed this matter so far, retrospective analyses provide good evidence for this.[37]

Haematological manifestations such as thrombocytopenia and haemolytic anaemia, and dermal symptoms such as livedo reticularis occur in 10-30% of patients although these features are not included in the classification criteria.[2] Box 3 lists red and yellow flag conditions that indicate when antiphospholipid syndrome should be included in a differential diagnosis.

MATERNAL AND FETAL EFFECTS IN PREGNANCY Obstetric criteria used to define antiphospholipid syndrome are fetal loss after 10 weeks' gestation, three or more unexplained consecutive embryonic losses before the 10th week of gestation, and pre-eclampsia or features of placental insufficiency associated with the premature birth of a morphologically normal neonate before the 34th week of gestation.[4]

Other manifestations that are not stated in the criteria, but are sequelae of the syndrome, are pregnancy-related maternal thrombosis and unexplained intrauterine growth restriction.

Late fetal loss is strongly associated with presence of antiphospholipid antibodies, and particularly lupus anticoagulant. Prospective studies have shown that positive lupus anticoagulant and/or high titers of cardiolipin IgG increase the risk of recurrent adverse outcome in a subsequent pregnancy.[38;39]

Evidence for a causal association between antiphospholipid antibodies and early miscarriage is limited.[8] Early miscarriage is relatively common and has many causes, of which fetal chromosomal abnormalities are the most likely. Observational studies of the association between antiphospholipid syndrome and recurrent early miscarriage are likely to be heavily confounded, especially by inclusion of women with sporadic rather than recurrent miscarriage. Therefore international guidelines (Royal College of Obstetricians and Gynaecologist, European Society of Human Reproduction and Embryology) advise screening for antiphospholipid antibodies in women with more than three early miscarriages.[40;41]

Women with antiphospholipid syndrome have an increased incidence of early or severe pre-eclampsia, which often leads to iatrogenic preterm birth due to termination of pregnancy for maternal or fetal reasons. Pre-eclampsia with severe thrombocytopenia may also point towards the presence of the syndrome, and is a red flag condition (box 3). [42]

Who should be tested for antiphospholipid antibodies?

Box 4 lists the indications for testing for antiphospholipid antibodies.[43]

SLE Testing for antiphospholipid antibodies is recommended in the initial evaluation of patients with SLE and should be reevaluated if new risk factors for thromboembolic events emerge.[44]

– BOX 4 –

SITUATIONS WHEN YOU SHOULD TEST FOR ANTIPHOSPHOLIPID ANTIBODIES

Thrombosis
- Arterial thrombosis before the age of 50
- Unprovoked venous thrombosis before the age of 50
- Recurrent thrombosis
- Thrombosis in an unusual site
- Patients with both arterial and venous thrombotic events
- Any patient admitted with thrombotic microangiopathy of unknown etiology

Obstetric manifestations
- One or more unexplained fetal losses after 10 weeks of gestation
- Unexplained severe intrauterine growth restriction
- Early and/or severe preeclampsia
- Three or more spontaneous miscarriages before 10 weeks of gestation

SLE patients
- At baseline
- Repeat testing prior to pregnancy, surgery, transplant and use of oestrogen-containing treatments, or in the presence of a new neurological, vascular or obstetric event

Lupus anticoagulant and the persistent presence of anticardiolipin antibodies increase the risk of thromboembolic events in patients with SLE. [45;46] Data on antiphospholipid antibodies can help when interpreting new symptoms in these patients and may influence therapeutic decisions in situations with increased thromboembolic risk, such as surgery, pregnancy, puerperium, or the use of oestrogen containing drugs.

PREGNANCY A recent prospective study of pregnant women with only one previous spontaneous abortion before the 10th week of gestation reported that the presence of antiphospholipid antibodies significantly increased the risk of embryonic loss, pre-eclampsia, and intrauterine growth restriction in the next pregnancy.[38] However, after single pregnancy loss, most subsequent pregnancies are uneventful without treatment. Therefore, testing after one early miscarriage, or even testing all women who plan to become pregnant, is not advised. [43]

How to treat antiphospholipid syndrome

Antithrombotic agents aim to reduce the risk of recurrent thromboembolism and are the mainstay of treatment. Recently guidelines on how to treat antiphospholipid syndrome subdivided patients into those with venous thrombosis, those with arterial thrombosis, and obstetric antiphospholipid syndrome.[47] A treatment algorithm containing an overview of these guidelines is presented in figure 2.

FIRST EPISODE For a first episode of unprovoked venous thrombosis or thromboembolism associated with persistent positive antiphospholipid antibodies international guidelines recommend long term anticoagulation with vitamin K antagonists such as warfarin to reduce the risk of recurrence of a thrombotic event.[48] However, if a reversible risk factor for thromboembolism – such as surgery, immobilisation, oestrogen therapy, or pregnancy – is reliably eliminated indefinite anticoagulation may not be justified.[47]

The only prospective study focusing on arterial cerebral events showed similar rates of recurrent thromboembolism and risk of major bleeding in patients treated with warfarin or low dose aspirin.[49] However, inappropriate criteria for defining antiphospholipid antibody positivity limit the generalisability of this study.[50] In patients with antiphospholipid syndrome and stroke, long term anticoagulation with warfarin or low dose aspirin is advised.

Two randomised controlled trials compared high intensity anticoagulation (aimed at an international normalised ratio (INR) of 3.1-4) with moderate intensity anticoagulation (INR 2-3) for the prevention of recurrent venous and arterial thrombotic events in non-pregnant adults with antiphospholipid syndrome. Both trials used oral warfarin and found that high intensity treatment was no better at preventing thrombotic events.[51;52] When results were pooled, the risk of bleeding was slightly increased in patients on high intensity treatment.[53] The limitations of these trials (patients with arterial events were in the minority and many patients randomised to a target INR ▸3 did not achieve this target), and the fact that the results contradict those of observational studies, mean that treatment aims are still a point of ongoing debate.[50] International guidelines and systematic reviews currently recommend aiming for an INR between 2 and 3. [47;48;54;55]

PREVENTING OBSTETRIC COMPLICATIONS Few well designed trials have been carried out and studied populations are heterogeneous, so the level of evidence for all treatment options is low. Table 2 gives suggestions for primary and secondary prevention of thrombosis and adverse pregnancy outcome; these are based on the limited available evidence and our own experience.

PREVENTING MATERNAL THROMBOTIC COMPLICATIONS Warfarin crosses the placenta and is teratogenic in the first trimester of pregnancy so low molecular weight heparins are the agents of choice for antenatal thromboprophylaxis.[41;56] Observational studies have shown that low molecular weight heparin is at least as effective as unfractionated heparin and safer. [41;56] Women who are on long term warfarin because of previous thrombosis should switch to heparin when trying to conceive or on confirmation of conception. The dose of heparin will depend on the woman's clinical history and should be discussed with a haematologist.

PREVENTING ADVERSE PREGNANCY OUTCOME A meta-analysis of intervention trials for recurrent (early) miscarriage have concluded that heparin with low dose aspirin reduces pregnancy loss by 54%.[57]

No randomised controlled trials have investigated prevention in patients with a history of late miscarriage, fetal death, and intrauterine growth restriction. Most clinicians would consider treatment with low dose aspirin and heparin (mostly low molecular weight heparin) in such cases. In patients with antiphospholipid antibodies and a history of severe pre-eclampsia at least low dose aspirin (75-80 mg once daily) is recommended.[47]

Glucocorticoids, cytotoxic agents, and intravenous immunoglobulin have no confirmed benefit and may even be teratogenic.[47]

SLE In patients with SLE and antiphospholipid antibodies, low dose aspirin may be considered for primary prevention of thrombosis and pregnancy loss.[58] In non-pregnant patients with SLE and antiphospholipid syndrome associated thrombosis, long term anticoagulation with vitamin K antagonists is effective for secondary prevention of thrombosis. In pregnant patients with SLE and antiphospholipid syndrome, combined unfractionated heparin or low molecular weight heparin and aspirin reduce pregnancy loss and thrombosis and should be considered.[58]

CATASTROPHIC ANTIPHOSPHOLIPID SYNDROME Box 2 summarises the management and characteristics of this rare manifestation of the syndrome. Figure 3 gives examples of typical histologic findings in patients with catastrophic antiphospholipid syndrome.

Future challenges in for the management of patients with Antiphospholipid syndrome

A reliable diagnostic test is still needed. Antiphospholipid syndrome mimics many other conditions, which leads to misdiagnosis and thwarts efforts to perform studies of sufficient size to give unequivocal support for diagnostic and treatment strategies. However, left untreated the syndrome can have serious sequelae. We advise that any patient with a suspected antiphospholipid syndrome should be seen by a multidisciplinary team of specialists that ideally includes a rheumatologist, haematologist, neurologist, nephrologist, and obstetrician for diagnosis, treatment, and education.

A PATIENT'S PERSPECTIVE

From the age of 16, I had frequent headaches, sometimes with double vision, and I occasionally had pins and needles in one hand. My general practitioner never found an obvious cause. At 21 I was diagnosed with a deep vein thrombosis in my left leg, after a minor car accident. I was treated with heparin and aspirin for a few months.
A year later I had a miscarriage at 9 weeks' gestation. My platelets were low and did not improve. My gynaecologist sent me to a haematologist, who thought of the antiphospholipid syndrome. The blood test was positive. It was a double feeling: on the one hand I felt relieved to have a diagnosis that explained all my medical problems, but I suddenly had a disease that I had never heard of. My friends and family have difficulty understanding when I try to explain what antiphospholipid syndrome is. The most frustrating thing is that even some of the doctors I talk to have never heard of it. Two years ago they found out that two of my heart valves are leaking. I have had surgery for one valve recently, and one more operation is needed for the other. It is scary to think that if my anticoagulation therapy is stopped I will be at risk of developing things like a stroke. It is surreal to have to think about these things in your early 30s. Because of the heart valves I had to postpone further pregnancies. I hope for the best, and hope that with heparin treatment I'll have a fair chance of becoming a mother one day.

A Meijer-Bezema, Stadskanaal, Netherlands

METHODS

In cooperation with a trained librarian, a search strategy was composed. The following databases were searched for evidence from systematic reviews, clinical trials and prospective cohort studies: PubMed (1949 to January 2010), EMBASE (OVID-version, 1980 to January 2010), Web of Science (1945 to January 2010), Cochrane Library (1990 to January 2010), CINAHL (EbscoHost-version, 1982 to January 2010), and Academic Search Premier (EbscoHost-version (1865 to January 2010). All relevant keyword variations were used, not only keyword variations in the controlled vocabularies of the various databases, but the free text word variations of these concepts as well. In general, the search consisted of the combination of the following terms: 'antiphospholipid syndrome', 'Hughes syndrome', 'antiphospholipid antibodies', 'lupus anticoagulant', 'anticardiolipin antibodies', 'anti β_2-glycoprotein I antibodies' and 'catastrophic antiphospholipid syndrome'. The results were limited to articles written in English.

The search was performed on the 27th of January, 2010.

SUMMARY POINTS

Antiphospholipid syndrome is a relatively common autoimmune disorder that mainly affects young adults
If untreated, antiphospholipid syndrome can lead to permanent disability, severe maternal or perinatal morbidity, or even death
Symptoms can occur in virtually all organ systems
Venous thrombosis and stroke are the most common thrombotic manifestations
In pregnancy the syndrome is associated with adverse maternal and fetal outcomes
The lupus anticoagulant test is the most useful because positivity correlates most strongly with clinical manifestations
Cardiac valvular disease is an important clinical manifestation and may contribute to the risk of strokes

CONTINUING MEDICAL EDUCATION RESOURCES

For professionals

How I treat the antiphospholipid syndrome.[47] Excellent review about recent developments in treatment of antiphospholipid syndrome patients.

How we diagnose the antiphospholipid syndrome.[43] Excellent review about recent developments in diagnosing the antiphospholipid syndrome.

Reducing the risk of thrombosis and embolism during pregnancy and the puerperium.[41] Greentop guidelines of the Royal College of Obstetricians and Gynecologists (RCOG). http://www.rcog.org.uk/

Antithrombotic and thrombolytic therapy, and Antithrombotic therapy for venous thromboembolic disease, 8th edition.[48;54] Guidelines of the American College of Chest Physicians (ACCP) http://www.chestnet.org/accp/

Investigation and medical treatment of recurrent miscarriage.[40] Guidelines from the European Society of Human Reproduction and Embryology (ESHRE). http://www.eshre.eu/

Practical management of coagulopathy associated with warfarin.[62] Useful management strategies for patients who are being treated with a vitamin K antagonist and present with an INR outside the therapeutic range.

For patients

Kay Thackray. *Sticky Blood.* ISBN 1-898030-77-4. A personal account of dealing with the condition.

Triona Holden. 'Positive Options for Antiphospholipid Antibody Syndrome' ISBN 0-89793-409-1

UpToDate: Patient information about antiphospholipid syndrome (http://www.uptodate.com/patients/content/topic.do?topicKey=~CQUbGyAA8E5yqH&selectedTitle=1%7E150&source=search_result)

Youtube: Video in which Dr Graham Hughes of the London Lupus Center explains about antiphospholipid syndrome, and in which 2 patients tell about their experiences with recurrent miscarriage and stroke. (http://www.youtube.com/watch?v=V3J8BLkZyhU)

Youtube: Video showing an excellent animation of deep vein thrombosis. (http://www.youtube.com/watch?v=CETfozLocQg)

ONGOING RESEARCH AND FUTURE CHALLENGES

Pathologic mechanism

To clarify the relation between inflammation and thrombosis in antiphospholipid syndrome.

To further unravel the actions of different antiphospholipid antibodies on hemostasis, endothelial activation and placental invasiveness.

Serology

To find more specific tests for antiphospholipid antibodies that correlate better with clinical symptoms. Lupus anticoagulant inducing anti-$\beta_2$glycoprotein I antibodies and anti-$\beta_2$glycoprotein I domain I antibodies are promising new binding targets.[6]

Treatment

To identify the role of newer, preferably oral anticoagulants in antiphospholipid syndrome.

To identify the role of anti-inflammatory drugs in antiphospholipid syndrome (Rituximab, anti-complement agents, statins)

To perform well designed randomized controlled trials in pregnancy related settings.

TIPS FOR NON SPECIALISTS

Early recognition of antiphospholipid syndrome offers a chance for prevention of recurrent thrombosis, and prevention of recurrent maternal and fetal pregnancy morbidity.

A delayed diagnosis can cause permanent disability due to uncontrolled thrombosis formation, or death.

If you consider testing for antiphospholipid syndrome, perform all three laboratory tests mentioned in the classification criteria (BOX 1) or refer the patient to a specialist for testing.

Try to obtain the first test results before starting with anticoagulation therapy, since anticoagulation therapy influences the outcome of the lupus anticoagulant test.

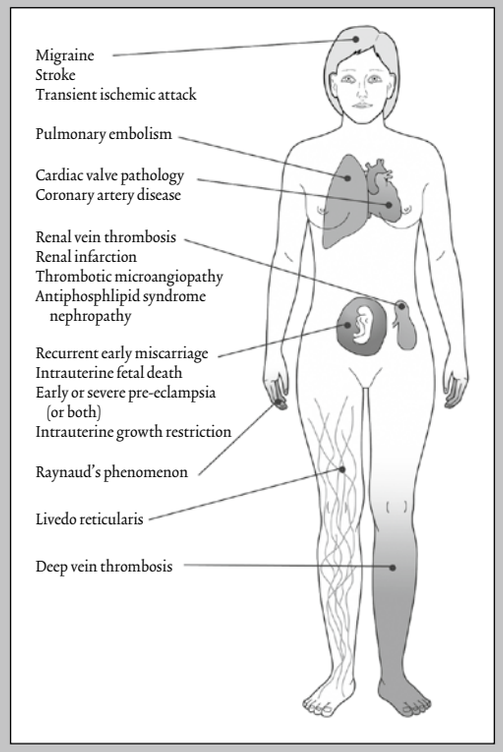
A positive test is an indication to refer the patient to a specialist.

Antiphospholipid syndrome pregnancies are high risk pregnancies, and management at specialized centers is advisable.

Traditional risk factors for cardiovascular disease contribute further to the risk of thrombosis in antiphospholipid syndrome, even at young age.

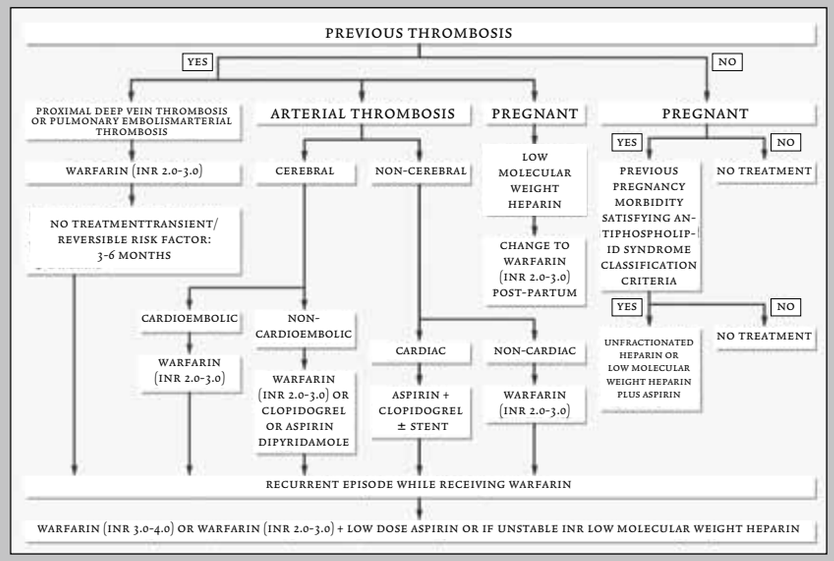
Try to support patients to stop smoking, normalize body weight and try to avoid oral contraception and hormone replacement therapy.

FIG 1 CLINICAL MANIFESTATIONS OF ANTIPHOSPHOLIPID SYNDROME



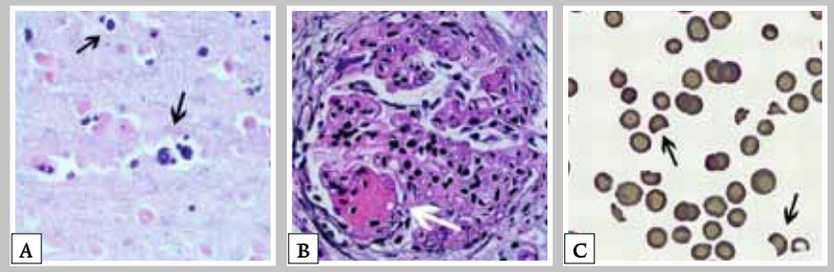
(Illustration by Folkert van Meurs)

FIG 2 TREATMENT ALGORITHM FOR ANTIPHOSPHOLIPID SYNDROME



Adapted, with permission obtained from 'Blood copyright clearance centre', Giannakopoulos *et al*, (2009); How I treat the antiphospholipid syndrome

FIG 3 CLASSIC HISTOLOGICAL FINDINGS IN A PATIENT WITH CATASTROPHIC ANTIPHOSPHOLIPID SYNDROME



(A) Cerebral microthrombi (arrows); the fibrin thrombi are stained blue by phosphotungstic acid haematoxylin. (B) Renal microthrombi, prominently present in a glomerulus (arrow). (C) Blood smear showing schistocytes (fragmented red blood cells), which are formed by fibrin strands that sever red blood cells as they try to move past a (micro)thrombus (arrows), and are indicative of microangiopathic haemolytic anaemia

TABLE 1 ANTIPHOSPHOLIPID ANTIBODIES

	ANTICARDIOLIPIN ANTIBODIES	ANTI-β_2GLYCOPROTEIN I ANTIBODIES	LUPUS ANTICOAGULANT
Test	Anticardiolipin ELISA	anti-$\beta_2$glycoprotein I ELISA	The lupus anticoagulant assay **
Test guidelines	Pierangeli *et al*, 2008 [59]	no guidelines yet	Pengo *et al*, 2009 [10]
Which antibodies are detected?	Antibodies against cardiolipin, and cardiolipin-bound β2-glycoprotein I	Antibodies against beta2-glycoprotein I	Detects immunoglobulins that cause prolonged clotting times in vitro, but are associated with thrombosis in vivo.
Relevant isotypes	IgG +++, IgM +	IgG+++, IgM +	not applicable
What titers are considered positive?	Medium/High: ▸ 99th percentile, or ▸40 GPL or MPL	Medium/High: ▸ 99th percentile, or ▸40 GPL or MPL	not applicable
Is the test influenced by anticoagulation therapy?	no	no	yes: both heparin and warfarin influence the test-results, and testing under coagulation therapy is controversial.
Is there overlap with other tests?	yes, overlap with lupus anticoagulant	yes, overlap with lupus anticoagulant	yes: anti-$\beta_2$glycoprotein I and anticardiolipin antibodies can have an anticoagulant effect, but other antibodies like anti-prothrombin and anti-annexin V antibodies can contribute to this effect too.

** 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)

TABLE 2 TREATMENT OF PATIENTS WITH PERSISTENT POSITIVE ANTIPHOSPHOLIPID ANTIBODIES IN PREGNANCY

CLINICAL PRESENTATION	TREATMENT REGIMEN IN PREGNANCY	TREATMENT REGIMEN POSTPARTUM	EVIDENCE LEVEL **
Women (including patients with SLE) with prior thrombosis	· Graduated elastic compression stockings · Weight adjusted, full-dose LMWH from ◂ 6 wks gestation	· Graduated elastic compression stockings · 6 weeks LMWH or warfarin*	C
Women with late fetal loss (▸ 10 wks)	Low-dose aspirin and/or LMWH ***	at least 7 days LMWH or warfarin	C
Women with recurrent miscarriage (◂10 wks)	Low-dose Aspirin plus LMWH	at least 7 days LMWH or warfarin	A
Women with history of early and/or severe preeclampsia or intrauterine growth restriction	Low-dose Aspirin Consider additional LMWH ***	at least 7 days LMWH or warfarin	C
Women with persistently positive antiphospholipid antibodies without clinical symptoms	Close surveillance	at least 7 days LMWH or warfarin	C
Women with SLE without previous obstetric or thrombotic complications	Low dose Aspirin ***	at least 7 days LMWH or warfarin	C
Women with SLE with previous obstetric complications	Low-dose Aspirin + LMWH ***	at least 7 days LMWH or warfarin	

* Warfarin crosses the placenta, is teratogenic and must be avoided in pregnancy

** Level A: Consistent randomized controlled trials and/or cohort studies / Level B: Consistent retrospective cohort, exploratory cohort or case control studies or extrapolations from level A studies / Level C: Case-series or extrapolations from level B studies / Level D: Expert opinion without explicit critical appraisal

*** If possible try to include patients in a Rct

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