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## **Studies on Neuropsychiatric SLE**

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### **Citation**

Steup-Beekman, G. M. (2011, June 17). *Studies on Neuropsychiatric SLE*. Retrieved from <https://hdl.handle.net/1887/17714>

Version: Corrected Publisher's Version

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**Note:** To cite this publication please use the final published version (if applicable).

# CHAPTER 6

## Diagnosis and management of the antiphospholipid syndrome

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*British Medical Journal* 2010;340:c2541:1125-1132

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### **Summary points**

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 stroke

## 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 both arteries and veins.<sup>1</sup> Female patients had a high risk of recurrent miscarriages and late fetal loss. The international classification criteria for this syndrome used today are based on those initial clinical observations.<sup>2</sup>

### Sources and selection criteria

We searched the following databases for evidence from systematic reviews, clinical trials, and prospective cohort studies: PubMed (1949 to January 2010), Embase (1980 to January 2010), Web of Science (1945 to January 2010), Cochrane Library (1990 to January 2010), CINAHL (1982 to January 2010), and Academic Search Premier (1865 to January 2010). All relevant keyword variations were used. In general, the search consisted of the combination of the following terms: "antiphospholipid syndrome", "Hughes syndrome", "antiphospholipid antibodies", "lupus anticoagulant", "anticardiolipin antibodies", "anti- $\beta$ 2 glycoprotein I antibodies", and "catastrophic antiphospholipid syndrome". Results were limited to articles written in English.

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

Because of its variable clinical presentation, patients with antiphospholipid syndrome may present to a wide 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 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.<sup>2</sup> An acute variant of the syndrome—catastrophic antiphospholipid syndrome—results in widespread thrombotic microangiopathy and multiple organ failure (Box 1).<sup>3</sup> Classification criteria were last updated in 2006 (Box 2). A combination of clinical and laboratory findings is required to confirm the diagnosis.<sup>4</sup>

### **BOX 1.** The catastrophic antiphospholipid syndrome

Catastrophic antiphospholipid syndrome is a rare life threatening condition, characterized by the rapid development of multiple microthrombi in various organ systems, typically the brain (Figure 1A), kidneys (Figure 1B), lung and skin.<sup>60</sup> Thrombocytopenia, hemolysis, schistocytes (Figure 1C) and activation of the coagulation system are frequent laboratory findings, so thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, and disseminated intravascular coagulation are important differential diagnoses. Mortality in this syndrome approaches 50%.<sup>61</sup>

Data on treatment are limited, but current treatment regimens have reduced mortality when compared with historical case series.<sup>61</sup> Successful treatment regimens 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. Precipitating disorders such as infection should be treated promptly.

### **BOX 2.** Classification criteria for the antiphospholipid syndrome<sup>4</sup>

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

##### *Morbidity in pregnancy*

One or more unexplained deaths of a morphologically normal fetus at or beyond the 10<sup>th</sup> week of gestation, with normal fetal morphology documented by ultrasound or by direct examination of the fetus.

One or more premature births of a morphologically normal neonate before 34<sup>th</sup> week of gestation because of eclampsia or severe pre-eclampsia defined according to standard definitions, or recognized features of placental insufficiency.

Three or more unexplained consecutive spontaneous miscarriages before the 10<sup>th</sup> 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.<sup>11</sup>

Medium or high titre (>40 IgG or IgM phospholipid units (1 unit is 1 µg of antibody), or >99th centile) of IgG or IgM anticardiolipin antibody in serum or plasma on two or more occasions, a least 12 weeks apart, measured by standardized enzyme linked immunosorbent assay (ELISA).

Medium or high titre (>40 IgG or IgM phospholipid units, or >99th centile) of IgG or IgM anti-β<sub>2</sub> glycoprotein I antibody in serum or plasma on two or more occasions, a least 12 weeks apart, measured by standardized ELISA, according to recommended procedures.<sup>59</sup>

## Who gets it?

SLE affects one to 20 in every 100 000 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 it affects up to 0.5% of the population.

Antiphospholipid syndrome occurs mainly in young women of fertile age, rarely occurs in children and only 12% of patients present after age 50. In a large international cohort, mean age at diagnosis was 34 standard deviation 13) years. The male:female ratio was 1:3.5 for primary disease and 1:7 for secondary diagnosis associated with SLE.<sup>2</sup> A recently reported, unique cohort of 122 paediatric 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.<sup>5</sup> Patients who present after age 50 are more often male and present more often with stroke and coronary heart disease.<sup>2</sup> Fewer 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.<sup>2</sup>

## What are antiphospholipid antibodies and how might they cause symptoms?

Antiphospholipid antibodies form a heterogeneous group of autoantibodies directed at plasma proteins that bind to phospholipids.<sup>6</sup> 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.<sup>7</sup> The “lupus anticoagulant assay” 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- $\beta_2$  glycoprotein I antibodies (Box 2),<sup>4</sup> both of which can be detected by enzyme-linked immunosorbent assays (ELISAs).

Antibodies with lupus anticoagulant activity are important clinically—two systematic reviews found them to be strongly correlated with thrombotic and obstetric complications of the syndrome.<sup>8,9</sup> Table 1 describes assays for lupus anticoagulant, anticardiolipin and anti- $\beta_2$  glycoprotein 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%.<sup>10</sup> This highlights the importance of good communication between the laboratory and the clinician when making a diagnosis and of ensuring that guidelines are followed.<sup>11</sup>

Antiphospholipid antibodies are found in 1-5% of apparently healthy control 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 titers and is not associated with thrombosis or adverse pregnancy outcome.<sup>12</sup> Persistent positivity is rare. In a cross-sectional study of 552 healthy blood donors, 6.5% had

**Table 1.** Antiphospholipid antibodies.

Test details	Antibody type		
	Anticardiolipin antibodies	Anti- $\beta_2$ glycoprotein I antibodies	Lupus anticoagulant
Test	Anticardiolipin ELISA	anti- $\beta_2$ glycoprotein I ELISA	The lupus anticoagulant assay *
Test guidelines	Pierangeli et al (2008) <sup>59</sup>	None yet	Pengo et al (2009) <sup>11</sup>
Which antibodies are detected?	Antibodies against cardiolipin and cardiolipin bound $\beta_2$ glycoprotein I	Antibodies against $\beta_2$ 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 to high: >99th centile, or >40 IgG or IgM phospholipid units <sup>‡</sup>	Medium to high: >99th centile, or >40 IgG or IgM phospholipid units <sup>‡</sup>	Not applicable
Is the test influenced by anticoagulation therapy?	No	No	Yes: both heparin and warfarin influence the test results, so testing during treatment is controversial.
Is there overlap with other tests?	Yes, this test overlaps with that for lupus anticoagulant	Yes, this test overlaps with that for lupus anticoagulant	Yes: anti- $\beta_2$ glycoprotein I and anticardiolipin antibodies can have an anticoagulant effect, but other antibodies such as antiprothrombin and antiannexin V antibodies 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).

<sup>‡</sup> 1 unit = 1  $\mu$ g of antibody.

anticardiolipin IgG, but fewer than 2% still had increased levels 9 months later.<sup>13</sup> 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.<sup>4,14</sup>

The correlation between current antiphospholipid antibody and clinical symptoms is variable. 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 is strongly associated with venous thrombosis, in SLE and the general population (odds ratio 11).<sup>8</sup> This effect is stronger in younger age groups (< 50).<sup>15</sup>
- Lupus anticoagulant is strongly associated with stroke, both in SLE and the general population. (odds ratio 8.1 95% confidence interval 2.4–27.5) This effect is stronger in young age groups (<50).<sup>16,17</sup>
- Lupus anticoagulant is strongly associated with fetal loss at greater than 10 weeks' gestation. (7.8, 2.30 to 26.45).<sup>9</sup>

- Lupus anticoagulant predicts venous thrombosis and fetal loss more strongly than anticardiolipin antibodies (odds ratio 1,6-3,5).<sup>8,9</sup>
- The anticardiolipin ELISA is thought to have high sensitivity but low specificity. A positive result has a stronger association with morbidity in pregnancy than with thrombosis.<sup>9,18,19</sup>
- Studies that have investigated the relationship between anti- $\beta_2$ glycoprotein I antibodies and clinical symptoms have shown contradictory findings.<sup>9,14,20</sup> The clinical relevance of isolated anti- $\beta_2$ glycoprotein I antibodies remains uncertain.
- Patients with triple positivity for all three antibodies have a particularly high risk for pregnancy morbidity or thromboembolism (34.4, 3.5 to 335).<sup>21,22</sup>
- Risk factors for thrombosis such as smoking (arterial disease) and oral contraception (venous thrombosis) further increase the risk of thrombosis in the presence of antiphospholipid antibodies.<sup>16</sup>
- The risk of apparently healthy people with persistently positive antiphospholipid antibodies eventually developing a clinical event, such as thrombosis or adverse pregnancy outcome, is unknown.

### **What is known about its aetiology and pathophysiology?**

Despite investigations into the mechanisms by which antiphospholipid antibodies, once present, cause thrombotic and obstetric manifestations the cause of the production of autoantibodies to phospholipid binding proteins such as anti- $\beta_2$ -glycoprotein I is largely unknown.<sup>6,23</sup>

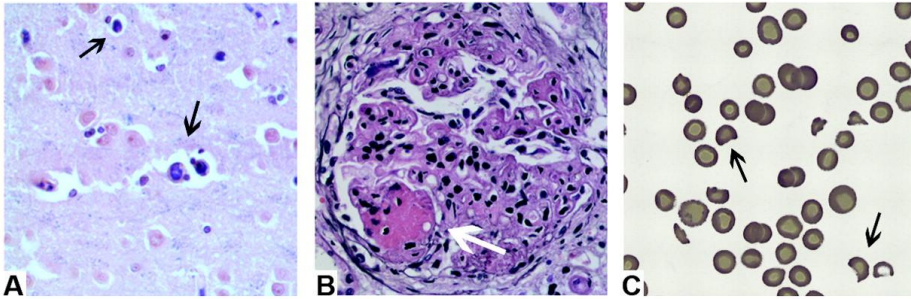
#### *Effect on coagulation and inflammatory pathways*

Antiphospholipid antibodies affect the coagulation cascade and inflammation. In a process mediated by  $\beta_2$  glycoprotein I, antiphospholipid antibodies bind to platelets and endothelial cells, activating endothelial cells and inducing a procoagulant state. Antibody binding also activates complement<sup>24</sup>, in recruitment of other inflammatory cells, activation of tissue factor, endothelial damage, and finally thrombosis.<sup>25</sup> 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<sup>26</sup> or a disrupted blood-brain barrier.<sup>27,28</sup>

#### *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.





**Figure 1.** 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.

### *Pregnancy*

Thrombosis in the placental vasculature was initially thought to be the main pathogenic mechanism that resulted in 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.<sup>29</sup> 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.<sup>25,30</sup> Moreover, they showed that the protective effect of heparin resulted from its anti-complement activity and not only from its effects on coagulation.<sup>31</sup> 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.

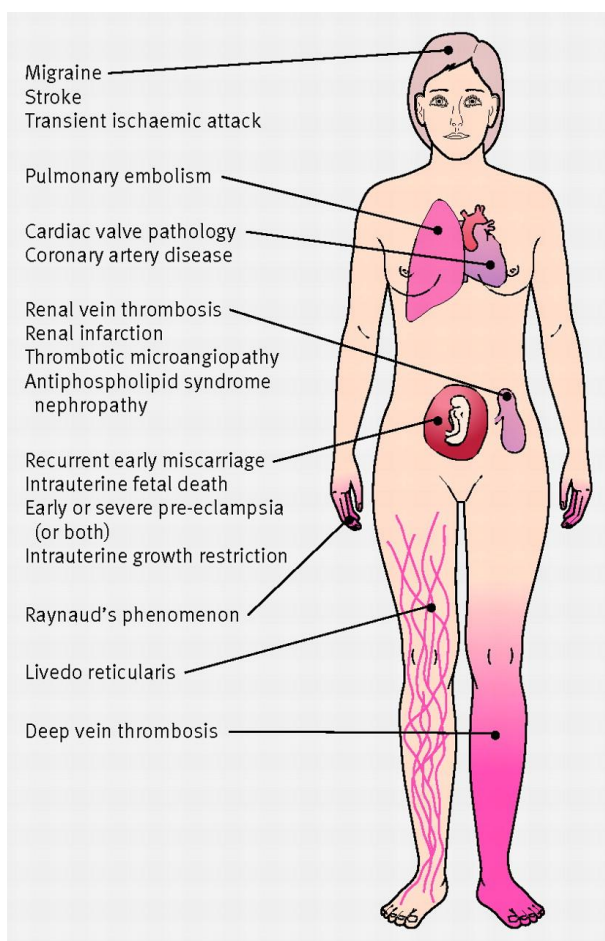
### **How do patients with antiphospholipid syndrome present?**

The clinical features of antiphospholipid syndrome are diverse and can affect all organ systems. Figure 2 gives an overview of the most common clinical findings. Venous thrombosis, along with its complications, is more common than arterial thrombosis. In a cohort of 1000 patients, the first symptom was deep vein thrombosis in the leg in 32% and pulmonary embolism in 14%.<sup>2</sup> Other vessels such as renal, hepatic, subclavian, and retinal veins, cerebral sinuses, and vena cava are more often affected than in thrombosis not related to antiphospholipid syndrome.<sup>2</sup> 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.<sup>2</sup> 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).<sup>32</sup>

### *Cerebral involvement*

Cerebral involvement is common in antiphospholipid syndrome<sup>33</sup> and was highlighted in the original description of the syndrome.<sup>1</sup> 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.<sup>28</sup> Despite a strong observed association between chronic headache, including migraine, and antiphospholipid syndrome<sup>34</sup>, studies have shown contradictory results.<sup>35</sup> An association has been reported between valvular



**Figure 2.** Clinical manifestations of antiphospholipid syndrome.

### **Tips for Non Specialists**

Early recognition of antiphospholipid syndrome helps prevent recurrent thrombosis and recurrent maternal and fetal morbidity

A delayed diagnosis can cause permanent disability, as a result of uncontrolled thrombosis formation, or even death

When testing for this syndrome, perform all three laboratory tests in Box 2

Try to obtain the first test results before starting anticoagulants, which influence the results the lupus anticoagulant test

Refer patients with a positive test result to a specialist

Pregnancy carries a high risk, and women should be managed at specialized centers

Traditional risk factors for cardiovascular disease increase the risk of thrombosis in this syndrome, even at young age. Provide support for patients to stop smoking, lose weight, and avoid oral contraception and hormone replacement therapy

heart disease and central nervous system manifestations of the syndrome, which suggests that cerebral emboli from valvular lesions may be a risk.<sup>36</sup>

### *Involvement of other organs*

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.<sup>2,37</sup> Myocardial infarction is the presenting symptom of the syndrome in 2.8% of patients.<sup>2</sup> Prospective studies have shown that antiphospholipid antibodies are associated with an increased risk of myocardial infarction.<sup>16,18</sup>

Thrombosis can occur anywhere in the renal vasculature. Occlusion of the renal veins and arterial trunk can occur, and microthrombi in glomerular capillaries can cause rapid decline of renal function.<sup>2</sup> In secondary antiphospholipid syndrome, no prospective studies have looked at whether antiphospholipid antibodies worsen the outcome for traditional lupus, but retrospective analyses provide good evidence for this.<sup>38,39</sup>

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.<sup>2</sup> 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.<sup>4</sup>

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 or high titers of cardiolipin IgG increase the risk of recurrent adverse outcome in a subsequent pregnancy.<sup>40,41</sup>

Evidence for a causal association between antiphospholipid antibodies and early miscarriage is limited.<sup>9</sup> Early miscarriage is relatively common and has multiple possible 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. International guidelines therefore advise screening for antiphospholipid antibodies only in women with more than three early miscarriages.<sup>42,43</sup>

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).<sup>44</sup>

### **BOX 3. Conditions that point to antiphospholipid syndrome**

#### *Red Flags*

- Unexplained deep vein thrombosis or pulmonary embolism in patients under 50
- Stroke in patients 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's phenomenon
- Unexplained persistent thrombocytopenia
- Recurrent early pregnancy loss

## **Who should be tested for antiphospholipid antibodies?**

Box 4 lists the indications for testing for antiphospholipid antibodies.<sup>45</sup>

### *Systemic lupus erythematosus*

Testing for antiphospholipid antibodies is recommended in the initial evaluation of patients with SLE and should be re-evaluated if new risk factors for thromboembolic events emerge.<sup>46</sup>

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**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

*Patients with systemic lupus erythematosus*

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

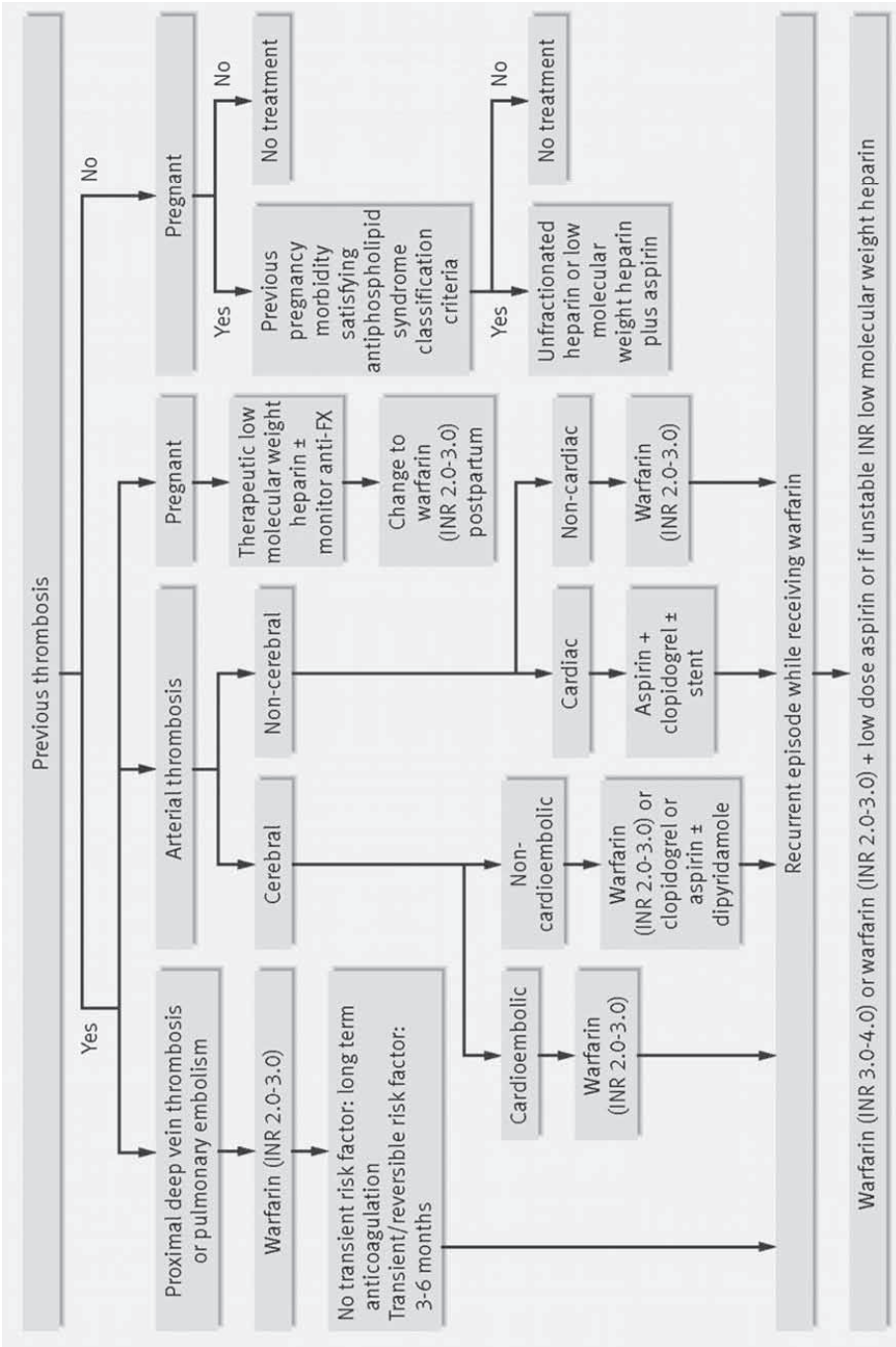
Lupus anticoagulant and the persistent presence of anticardiolipin antibodies are associated with an increased risk of thromboembolic events in patients with SLE.<sup>47,48</sup> Data on antiphospholipid antibodies can help when interpreting new symptoms in these patients and may influence therapeutic 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.<sup>40</sup> 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.<sup>45</sup>

**How can antiphospholipid syndrome be treated?**

Antithrombotic therapies aim to reduce the risk of recurrent thromboembolism and are the mainstay of treatment. Recent guidelines on treating the syndrome subdivide patients into those with venous thrombosis, those with arterial thrombosis, and those with obstetric antiphospholipid syndrome.<sup>49</sup> Figure 3 shows a treatment algorithm containing an overview of these guidelines.



**Figure 3.** Treatment algorithm for antiphospholipid syndrome. Adapted, with permission from Giannakopoulos et al.<sup>49</sup>

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### **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.

### *First episode*

For a first episode of unprovoked venous thrombosis or thromboembolism associated with persistent positive antiphospholipid antibodies, long term anticoagulation with vitamin K antagonists, such as warfarin, is recommended to reduce the risk of recurrence of a thrombotic event.<sup>50</sup> However, if a reversible risk factor for thromboembolism—such as surgery, immobilization, estrogen therapy or pregnancy—is reliably eliminated indefinite anticoagulation may not be justified.<sup>49</sup>

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.<sup>51</sup> However, inappropriate criteria for defining antiphospholipid antibody positivity limit the generalizability of this study.<sup>52</sup> In patients with antiphospholipid syndrome and stroke, long term anticoagulation with warfarin or low dose aspirin is advised.

Two randomized controlled trials compared high intensity anticoagulation (aimed at an international normalized 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.<sup>53,54</sup> When results were pooled, the risk of bleeding was slightly increased in patients on high intensity treatment. The limitations of these trials (patients with arterial events were in the minority and many patients randomized 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.<sup>52</sup> International guidelines and systematic reviews currently recommend aiming for an INR between 2 and 3.<sup>49,50,55</sup>

### *Preventing obstetric complications*

Several strategies have been proposed to prevent maternal thrombotic complications and improve the outcome of pregnancy in women with antiphospholipid syndrome. Few well

**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 previous thrombosis	Graduated elastic compression stockings; weight adjusted, full dose LMWH from <6 weeks' gestation	Graduated elastic compression stockings; 6 weeks LMWH or warfarin <sup>‡</sup>	C
Women with late fetal loss (>10 wks)	Low dose aspirin or LMWH <sup>§</sup>	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 or severe pre-eclampsia or intrauterine growth restriction	Low-dose Aspirin. Consider additional LMWH <sup>§</sup>	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 <sup>§</sup>	At least 7 days LMWH or warfarin	C
Women with SLE with previous obstetric complications	Low dose aspirin plus LMWH <sup>§</sup>	At least 7 days LMWH or warfarin	C

\* LMWH, low molecular weight heparin; SLE, systemic lupus erythematosus.

† A = consistent randomized controlled trials or cohort studies (or both); B = consistent retrospective cohort, exploratory cohort or case control studies or extrapolations from level A studies; C = Case-series or extrapolations from level B studies; D = expert opinion without explicit critical appraisal.

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

§ If possible try to enrol patients in a randomized controlled trial.

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.<sup>43,56</sup> Observational studies have shown that low molecular weight heparin is at least as effective as unfractionated heparin and safer.<sup>43,56</sup> In women who are on long term Warfarin because of prior thrombosis, it is advised to either switch to heparin when trying to conceive or upon confirmation of conception. 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.



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### *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%.<sup>57</sup> 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.<sup>49</sup>

Glucocorticoids, cytotoxic agents, and intravenous immunoglobulin have no confirmed benefit and may even be teratogenic.<sup>49</sup>

#### **Additional education resources**

##### *Resources for healthcare professionals*

References 45 and 49 in the reference list provide excellent reviews on recent developments in the diagnosis and treatment of antiphospholipid syndrome

References 42, 43, 50, and 55 all provide international guidelines on various aspects of the antiphospholipid syndrome

Garcia D, Crowther MA, Ageno W. Practical management of coagulopathy associated with warfarin. *BMJ* 2010;340:c1813. Useful strategies for patients being treated with a vitamin K antagonist who present with an international normalised ratio outside the therapeutic range

##### *Resources for patients*

Thackray K. Sticky blood explained. Braiswick, 2003. A personal account of dealing with the condition.

Holden T. Positive options for antiphospholipid antibody syndrome. Hunter House, 2003.

UpToDate ([www.uptodate.com/patients/content/topic.do?topicKey=~CQubGyAA8E5yqH&selectedTitle=1%7E150&source=search\\_result](http://www.uptodate.com/patients/content/topic.do?topicKey=~CQubGyAA8E5yqH&selectedTitle=1%7E150&source=search_result))—Patient information about antiphospholipid syndrome  
Agency for Healthcare Research and Quality ([www.healthcare411.ahrq.gov/videocast.aspx?id=555](http://www.healthcare411.ahrq.gov/videocast.aspx?id=555))—A video with general information for patients on anticoagulants

YouTube ([www.youtube.com/watch?v=V3J8BLkZyhU](http://www.youtube.com/watch?v=V3J8BLkZyhU))—Video in which Dr Graham Hughes of the London Lupus Centre explains the antiphospholipid syndrome and two patients relate their experiences with recurrent miscarriage and stroke

YouTube ([www.youtube.com/watch?v=CETfozL0cQg](http://www.youtube.com/watch?v=CETfozL0cQg))—Video showing an excellent animation of deep vein thrombosis

### *Systemic lupus erythematosus*

In patients with SLE and antiphospholipid antibodies, low-dose aspirin may be considered for primary prevention of thrombosis and pregnancy loss. 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.<sup>58</sup>

### *Catastrophic Antiphospholipid syndrome*

Box 1 summarizes the management and characteristics of this rare manifestation of the syndrome.

### **Future challenges for management**

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.

#### **Ongoing research and future challenges**

- To clarify the relation between inflammation and thrombosis in antiphospholipid syndrome.
- To unravel the effects of different antiphospholipid antibodies on haemostasis, endothelial activation and placental invasiveness.
- 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.<sup>6</sup>
- 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.

### **Acknowledgements**

The authors thank L.A. van Es, J.P. Vandenbroucke, A.P. van Rossum and F.J.M. van der Meer for advice and critical manuscript review; J.W. Schoones for help with the literature search; and F. van Meurs for producing Figure 2.

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