

## Diagnosis and management of the antiphospholipid syndrome

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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.<sup>1</sup> 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.<sup>2</sup>

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 antiphospholipid syndrome?

Antiphospholipid syndrome is a systemic autoimmune disorder characterised by arterial and venous thrombosis, adverse outcomes in pregnancy (for mother and fetus), and raised titres 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

### 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.

most common—20–35% of patients with SLE develop secondary antiphospholipid syndrome.<sup>3</sup> An acute variant of the syndrome—catastrophic antiphospholipid syndrome—results in widespread thrombotic microangiopathy and multiple organ failure (box 1).<sup>4</sup> Classification criteria were last updated in 2006 (box 2). A combination of clinical and laboratory findings is needed to confirm the diagnosis.<sup>2</sup>

### Box 1 | Catastrophic antiphospholipid syndrome

Catastrophic antiphospholipid syndrome is a rare life threatening condition, characterised by the rapid development of multiple microthrombi in various organ systems, typically the brain (fig 1A), kidneys (fig 1B), lungs, and skin.<sup>w1</sup> Thrombocytopenia, haemolysis, schistocytes (fig 1C) and activation of the coagulation system are common laboratory findings, so thrombotic thrombocytopenic purpura, haemolytic uraemic syndrome, and disseminated intravascular coagulation are important differential diagnoses. Mortality in this syndrome approaches 50%.<sup>w2</sup>

Data on treatment are limited, but current treatment regimens have reduced mortality when compared with historical case series.<sup>w2</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 thrombotic microangiopathy. Precipitating disorders such as infection should be treated promptly.

### SUMMARY POINTS

If untreated, antiphospholipid syndrome can lead to permanent disability, severe maternal or perinatal morbidity, or even death

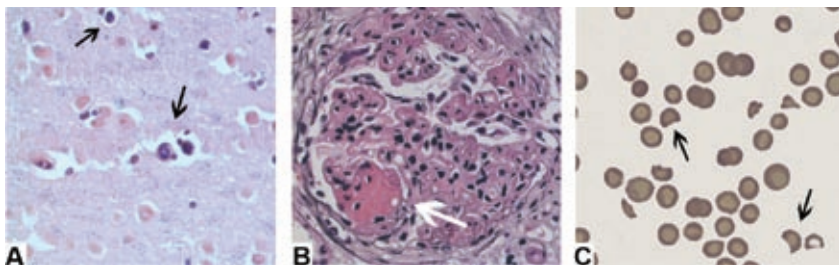
Symptoms can occur in virtually all organ systems

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



**Fig 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

### 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 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>3</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>7</sup> Patients who present after 50 are more often male and present more often with stroke and coronary heart disease.<sup>2</sup> Fewer than 1% of patients with

### Box 2 | Classification criteria for the antiphospholipid syndrome<sup>2</sup>

Antiphospholipid syndrome is present if at least one of the clinical criteria and one of the laboratory criteria below 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 histopathological confirmation, thrombosis should be present without evidence of inflammation in the vessel wall.

##### Morbidity in pregnancy

One or more unexplained death 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.

One or more premature birth of a morphologically normal neonate before the 34th week of gestation because of eclampsia or severe pre-eclampsia defined according to standard definitions, or recognised features of placental insufficiency.

Three or more unexplained consecutive spontaneous miscarriages before the 10th week of gestation, with maternal anatomical 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>5</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 standardised enzyme linked immunosorbent assay (ELISA).<sup>6</sup>

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 standardised ELISA, according to recommended procedures.

primary or secondary antiphospholipid syndrome develop the catastrophic form, and in almost half of them it appears de novo, without previous thrombotic events.<sup>3</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>8</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>w3</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-β<sub>2</sub> glycoprotein I antibodies (box 1),<sup>2</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>9,10</sup> Table 1 describes assays for lupus anticoagulant, anticardiolipin antibodies, and anti-β<sub>2</sub> 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>w4</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>5</sup>

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.<sup>11</sup> 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.<sup>w5</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>2 w6</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 in the general population (odds ratio 11).<sup>9</sup> This effect is stronger in younger age groups (<50).<sup>w7</sup>
- Lupus anticoagulant is strongly associated with stroke, in SLE and the general population (odds ratio 8.1, 95% confidence interval 2.4 to 27.5). This effect is stronger in young age groups (<50).<sup>9 w8 w9</sup>

**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>6</sup>	None yet	Pengo et al (2009) <sup>5</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 titres 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†	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, 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  $\mu$ g of antibody.

- Lupus anticoagulant is strongly associated with fetal loss at greater than 10 weeks' gestation (7.8, 2.30 to 26.45).<sup>10</sup>
- Lupus anticoagulant predicts venous thrombosis and fetal loss more strongly than do anticardiolipin antibodies (odds ratio 1.6-3.5).<sup>9,10</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>10 w10 w11</sup>
- Studies that have investigated the relation between anti- $\beta_2$  glycoprotein I antibodies and clinical symptoms have shown contradictory findings.<sup>10 w6 w12</sup> The clinical relevance of isolated anti- $\beta_2$  glycoprotein I antibodies is uncertain.
- Patients with positivity for all three antibodies have a particularly high risk for pregnancy morbidity or thromboembolism (34.4, 3.5 to 335).<sup>w13 w14</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>w8</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?

The cause of the production of autoantibodies to phospholipid binding proteins such as anti- $\beta_2$  glycoprotein I is largely unknown.<sup>8,12</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>w15</sup> resulting in recruitment of other inflammatory cells, activation of tissue factor, endothelial damage, and finally thrombosis.<sup>w16</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>w17</sup> or a disrupted blood-brain barrier.<sup>w18 w19</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.

### Pregnancy

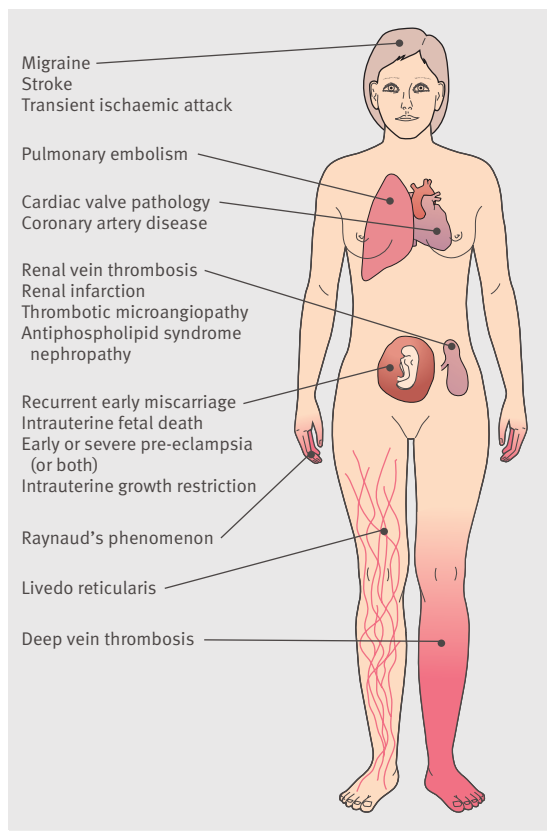
Thrombosis in the placental vasculature was initially thought to be the main cause of adverse outcomes in pregnancy. However, placental thrombosis and infarction are not specific to antiphospholipid syndrome but occur in other conditions, such as non-antiphospholipid syndrome pre-eclampsia.<sup>w20</sup> 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>w16 w21</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>w22</sup> Antiphospholipid antibodies seem to cause direct dysfunction of the trophoblast as well as activation

### 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**



**Fig 2 | Clinical manifestations of antiphospholipid syndrome**

of complement at the fetomaternal interface, resulting in an impaired exchange of blood components between mother and fetus, which can lead to early miscarriage, pre-eclampsia, 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

**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 ischaemic attack in patients under 50
- Recurrent thrombosis
- Thrombosis at an unusual site
- Unexplained fetal loss after 10 weeks' gestation
- Severe or early pre-eclampsia
- Severe intrauterine growth restriction
- Pre-eclampsia with severe thrombocytopenia
- Cardiac valve disease (in combination with other symptoms in this box)
- A new diagnosis of systemic lupus erythematosus

**Yellow flags**

- Livedo reticularis
- Raynaud's phenomenon
- Unexplained persistent thrombocytopenia
- Recurrent early pregnancy loss

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>3</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>3</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>3</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>w23</sup>

**Cerebral involvement**

Cerebral involvement is common in antiphospholipid syndrome and was highlighted in the original description of the syndrome.<sup>1 w24</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>w19</sup> Despite a strong observed association between chronic headache, including migraine, and antiphospholipid syndrome,<sup>w25</sup> studies have shown contradictory results.<sup>w26</sup> 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.<sup>w27</sup>

**Involvement of other organs**

The most common cardiac abnormality in patients with antiphospholipid syndrome is non-bacterial thrombotic endocarditis characterised 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>3 w28</sup> Myocardial infarction is the presenting symptom of the syndrome in 2.8% of patients.<sup>3</sup>

**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 at an unusual site
- Patients with both arterial and venous thrombotic events
- Any patient admitted with thrombotic microangiopathy of unknown aetiology

**Obstetric manifestations**

- One or more unexplained fetal loss after 10 weeks' gestation
- Unexplained severe intrauterine growth restriction
- Early or severe pre-eclampsia
- Three or more spontaneous miscarriages before 10 weeks' gestation

**Patients with systemic lupus erythematosus**

- At baseline
- Repeat testing before pregnancy, surgery, transplantation, and use of oestrogen containing treatments, or in the presence of a new neurological, vascular, or obstetric event

Prospective studies have shown that antiphospholipid antibodies are associated with an increased risk of myocardial infarction.<sup>w8 w10</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>3</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>w29</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>3</sup> Box 3 lists red flag 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>3</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 the presence of antiphospholipid antibodies, particularly lupus anticoagulant. Prospective studies have shown that positive lupus anticoagulant or high titres of cardiolipin IgG increase the risk of recurrent adverse outcome in a subsequent pregnancy.<sup>w30 w31</sup>

Evidence for a causal association between antiphospholipid antibodies and early miscarriage is limited.<sup>10</sup> 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. International guidelines therefore advise screening for antiphospholipid antibodies only in women with more than three early miscarriages.<sup>13 14</sup>

#### 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>8</sup>
- To identify the role of newer, preferably oral, anticoagulants in treatment
- To identify the role of anti-inflammatory drugs (rituximab, anticomplement agents, statins)
- To perform well designed randomised controlled trials in pregnancy related settings

#### 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 1
- 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 specialised centres
- 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

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>15</sup>

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

Box 4 lists the indications for testing for antiphospholipid antibodies.<sup>16</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>17</sup> Lupus anticoagulant and persistent anticardiolipin antibodies increase the risk of thromboembolic events in patients with SLE.<sup>w32 w33</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>w30</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>16</sup>

#### How can antiphospholipid syndrome be treated?

Antithrombotic agents aim to reduce the risk of recurrent thromboembolism and are the mainstay of treatment.

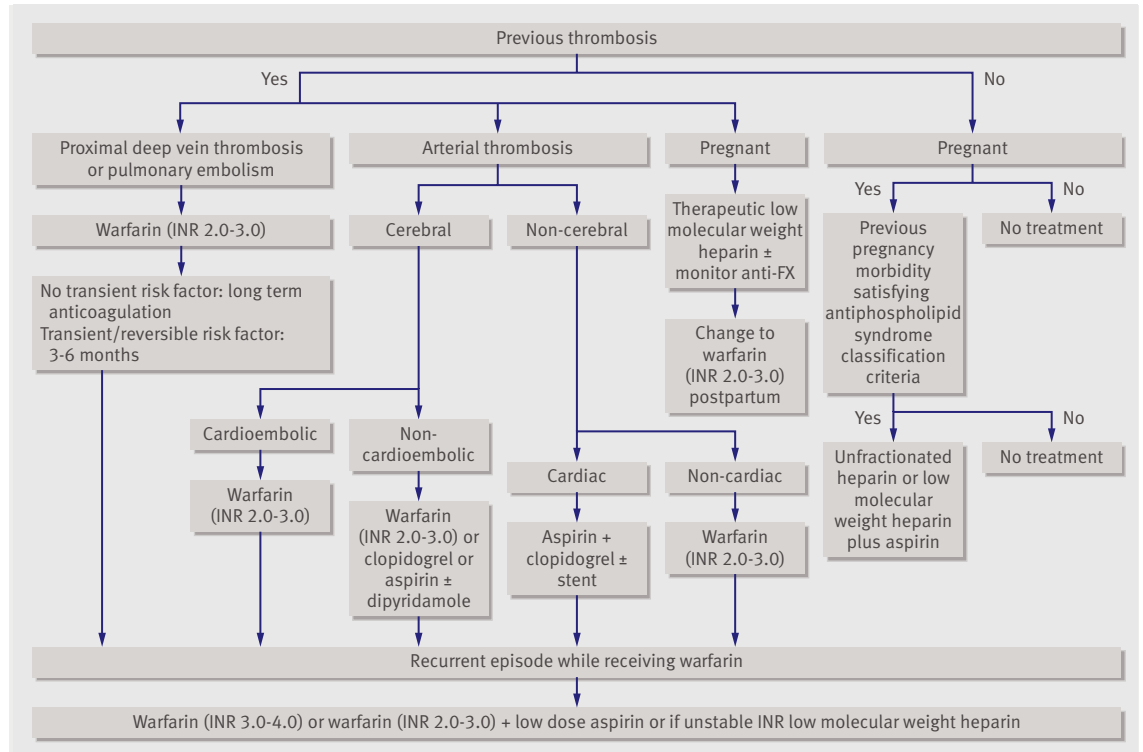


Fig 3 | Treatment algorithm for antiphospholipid syndrome. Adapted, with permission, from Giannakopoulos et al<sup>18</sup>

Recent guidelines on treating the syndrome subdivide patients into those with venous thrombosis, those with arterial thrombosis, and those with obstetric antiphospholipid syndrome.<sup>18</sup> Figure 3 shows a treatment algorithm containing an overview of these guidelines.

**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>19</sup> 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.<sup>18</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>20</sup> However, inappropriate criteria for defining antiphospholipid antibody positivity limit the generalisability of this study.<sup>21</sup> 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.<sup>22 23</sup> When results were pooled, the risk of bleeding was slightly increased in patients on high intensity treatment.<sup>24</sup> 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.<sup>21</sup> International guidelines and systematic reviews currently recommend aiming for an INR between 2 and 3.<sup>18 19 24 25</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.

**ADDITIONAL EDUCATIONAL RESOURCES**

**Resources for healthcare professionals**

References 16 and 18 in the main reference list provide excellent reviews on recent developments in the diagnosis and treatment of antiphospholipid syndrome  
References 13, 14, 19, and 24 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/videoast.aspx?id=555](http://www.healthcare411.ahrq.gov/videoast.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 Hughes of the London Lupus Centre explains the antiphospholipid syndrome and two patients relate their experiences with recurrent miscarriages and stroke

**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‡	C
Women with late fetal loss (>10 weeks)	Low dose aspirin or LMWH§	At least 7 days LMWH or warfarin	C
Women with recurrent miscarriage (<10 weeks)	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§	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 plus LMWH§	At least 7 days LMWH or warfarin	C

\*Abbreviations: LMWH=low molecular weight heparin; SLE=systemic lupus erythematosus.

†A=consistent randomised 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 randomised controlled trial.

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.<sup>14 26</sup> Observational studies have shown that low molecular weight heparin is at least as effective as unfractionated heparin and safer.<sup>14 26</sup> 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%.<sup>27</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>18</sup>

Glucocorticoids, cytotoxic agents, and intravenous immunoglobulin have no confirmed benefit and may even be teratogenic.<sup>18</sup>

#### Systemic lupus erythematosus

In patients with SLE and antiphospholipid antibodies, low dose aspirin may be considered for primary prevention of thrombosis and pregnancy loss.<sup>28</sup> 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>28</sup>

#### Catastrophic antiphospholipid syndrome

Box 2 summarises 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. Thanks to 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 fig 2.

**Contributors:** DC and IMB had the idea for the article. DC did the literature search. DC, GMS-B, KWMB, and SPB wrote and revised sections with which they were most familiar. IMB was involved throughout with the process and provided histological images. DC is guarantor.

**Competing interests:** All authors have completed the Unified Competing Interest form at [www.icmje.org/coi\\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf) (available on request from the corresponding author) and declare: (1) No financial support for the submitted work from anyone other than their employer; (2) No financial relationships with commercial entities that might have an interest in the submitted work; (3) No spouses, partners, or children with relationships with commercial entities that might have an interest in the submitted work; (4) No non-financial interests that may be relevant to the submitted work.

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**Patient consent obtained.**

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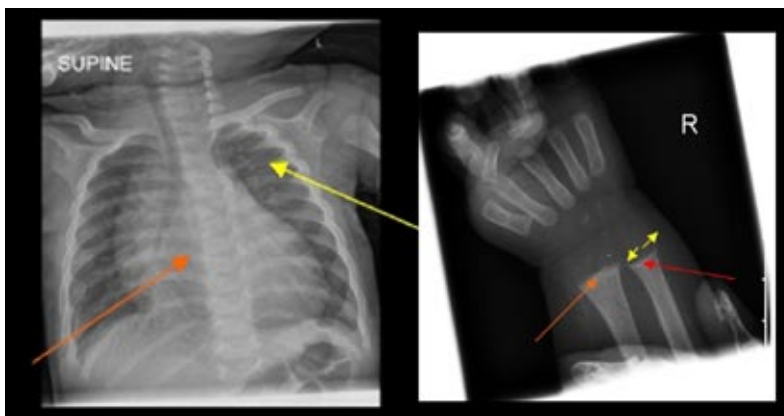
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**ANSWERS TO ENDGAMES, p 1145.** For long answers go to the Education channel on [bmj.com](http://bmj.com)

**STATISTICAL QUESTION**

**Nested case-control studies**

Answers a and b are true; c and d are false.



Chest radiograph showing cardiomegaly (orange arrow) and pulmonary plethora (yellow arrow). Wrist radiograph showing widening (yellow arrows), cupping (red arrow), and fraying (orange arrow) of the epiphysis of the right radius and ulna

**PICTURE QUIZ An infant with respiratory distress**

- 1 The chest radiograph shows cardiomegaly and pulmonary plethora. The wrist radiograph shows widening, cupping, and fraying of the epiphysis of the right radius and ulna suggestive of rickets.
- 2 Electrocardiography, echocardiography, and measurement of vitamin D and parathyroid hormone concentrations.
- 3 Cardiomyopathy secondary to vitamin D deficiency.
- 4 Vitamin D and calcium supplementation for the rickets and anti-heart failure drugs.

**CASE REPORT**

**An elderly woman with recurrent episodes of confusion**

- 1 The most likely diagnosis is a hypoglycaemic disorder, although further investigations are warranted to look for an insulinoma.
- 2 The diagnosis could be confirmed by instigating a supervised 72 hour fast, with measurement of plasma insulin, C-peptide, proinsulin, and  $\beta$ -hydroxybutyrate concentrations if the patient develops hypoglycaemia (plasma glucose  $<3$  mmol/l) during the fast.
- 3 The initial investigation to localise the underlying pathology of the hypoglycaemia symptoms is computed tomography or magnetic resonance imaging of the pancreas.
- 4 The best treatment for insulinomas is surgical resection of the tumour.