Antiphospholipid Antibodies and Antiphospholipid Syndrome: Diagnosis and Management

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Abstract. The antiphospholipid syndrome is an acquired autoimmune thrombophilia that produces significant morbidity and mortality. Its diagnosis requires the presence of antiphospholipid antibodies and clinical manifestations that include thrombotic phenomena and/or recurrent miscarriages. The antiphospholipid antibodies may be detected in many instances, including healthy subjects without an underlying disease. The clinical manifestations are varied and may occur in episodes and also appear in other situations. Therefore, it is important to have clear guidelines in order to establish a correct diagnosis, carry out an adequate treatment, and to know which are the prophylactic measures and when they should be undertaken. In this article we explain the most recent diagnostic criteria reviewed in the 11th International Congress on Antiphospholipid Antibodies (Sydney 2004), comment on the varied clinical manifestations with special focus on cutaneous lesions, and revise current guidelines for the treatment and prophylaxis of thrombotic and obstetric pathology.

Key words: antiphospholipid antibodies, antiphospholipid syndrome, thrombophilia.

ANTICUERPOS ANTIFOSFOLÍPIDO Y SÍNDROME ANTIFOSFOLÍPIDO: ACTITUDES DIAGNÓSTICAS Y TERAPÉUTICAS

Resumen. El síndrome antifosfolípido es una forma de trombofilia autoinmune adquirida que produce una morbilidad y mortalidad importantes. Su diagnóstico exige la presencia de anticuerpos antifosfolípido y unas manifestaciones clínicas que incluyen fenómenos trombóticos y/o pérdidas fetales recurrentes. Los anticuerpos antifosfolípido se pueden detectar en muchas situaciones, incluyendo la población sana sin provocar enfermedad, y la clínica, que es muy variada, puede ocurrir de forma episódica y aparecer en otras situaciones, por lo tanto es preciso tener unas pautas claras para establecer correctamente su diagnóstico, realizar un tratamiento adecuado del cuadro ya establecido, y conocer las medidas preventivas que debemos tomar y cuándo ponerlas en marcha. En este trabajo exponemos los últimos criterios diagnósticos revisados en el Decimoprimer Congreso Internacional sobre anticuerpos antifosfolípido de Sydney 2004, comentamos las variadas manifestaciones clínicas del cuadro con especial mención a las lesiones cutáneas, y hacemos un repaso de las pautas que se proponen en este momento para el tratamiento y prevención de la patología trombótica y obstétrica.

Palabras clave: anticuerpos antifosfolípido, síndrome antifosfolípido, trombophilia.
Antiphospholipid Antibodies

Antiphospholipid antibodies are a heterogeneous group of immunoglobulins (Ig)—mainly IgG, IgM, and IgA—which bind to the complex formed by anionic phospholipids, principally cardiolipin, and plasma proteins that bind to these phospholipids. These proteins are basically β-2-glycoprotein I (B2GP1) and prothrombin, although other antibodies target protein C, protein S, annexin, antithrombin III, and others. Antiphospholipid antibodies lead to thrombosis by disrupting protein function in the coagulation process and acting directly on the vascular endothelium and the immune system. Some antibodies can bind directly to phospholipids without the need for plasma proteins, generally in situations such as infection, drug intake, and neoplastic disease, and they are not associated with thrombotic phenomena.

They can be detected in the laboratory in 2 ways: a) by interference with phospholipid-dependent coagulation tests: lupus anticoagulant (LAC), or b) by enzyme-linked immunosorbent assay (ELISA). The second type allows us to detect antibodies targeting the phospholipid–plasma protein complex by using the phospholipid as an antigen (mainly cardiolipin): anticardiolipin antibodies (ACA), or by directly using purified protein extracts as antigen (mainly B2GP1): anti-B2GP1 antibodies (Table 1).

Lupus Anticoagulant

This should be determined following the criteria of the International Society on Thrombosis and Hemostasis. This test detects both anti-B2GP1 antibodies and prothrombin. In patients suffering from autoimmune disease, those associated with anti-B2GP1 seem to correlate much better with thrombosis, and studies are being carried out to discriminate between both types of antibody and confirm this observation. This test is more specific but less sensitive than the one based on ACA, and its correlation with the risk of thrombosis and maternal mortality is very high, especially in patients with systemic lupus erythematosus (SLE). It may be impossible to measure this antibody in subjects who are receiving oral anticoagulant therapy.

Anticardiolipin Antibodies

This test detects both antibodies that bind to phospholipid–protein complexes and those that bind directly to phospholipids. It is more sensitive but less specific than ACA. At the Sydney meeting, the value of 40 IgG phospholipid units or IgM phospholipid units was set as the limit between low titers, which would not be significant, and medium–high titers. IgG and IgM are usually determined and these are included as diagnostic criteria. At low titers, there may be false positives in the presence of cryoglobulins and rheumatoid factor. IgM ACA can also be detected transiently and at low titers in patients with infection or neoplastic disease, and in those who are taking certain drugs. There may be no association with thrombotic phenomena. These antibodies usually bind directly to phospholipids in the absence of plasma proteins. Standard laboratory techniques for differentiating them from other antibodies that would be associated with thrombosis are not yet available. IgA ACA seem to be more common in a subgroup of patients with autoimmune disease, thrombocytopenia, skin ulcers, and vasculitis, although they are not considered a diagnostic criterion.

Table 1. Antiphospholipid Antibodies

<table>
<thead>
<tr>
<th>Lupus Anticoagulant</th>
<th>Anti-B2GP1</th>
</tr>
</thead>
<tbody>
<tr>
<td>– The best marker of thrombosis and maternal disease</td>
<td>– Less sensitive but more specific than ACA</td>
</tr>
<tr>
<td>– More common in a subgroup of patients with autoimmune disease, thrombocytopenia, skin ulcers, and vasculitis</td>
<td>– Usually associated with other APA</td>
</tr>
<tr>
<td>– Usually determined and these are included as diagnostic criteria</td>
<td>– Good markers of thrombosis and maternal disease, especially at high titers</td>
</tr>
<tr>
<td>– IgM, at low titers, common in infections, not associated with thrombosis</td>
<td>– Titers above percentile 99 of the healthy population can be evaluated</td>
</tr>
<tr>
<td>– IgG are better markers of thrombosis than IgM</td>
<td>– The best marker of thrombosis and maternal disease</td>
</tr>
<tr>
<td>– Can be evaluated at titers &gt;40. Higher titers, better marker of thrombosis</td>
<td>– Less sensitive but more specific than ACA</td>
</tr>
<tr>
<td>– IgG are better markers of thrombosis than IgM</td>
<td>– More than 1 positive APA in any combination, better marker of thrombosis than when isolated. In isolation, ACA and anti-b2GP1 are better markers than ACA</td>
</tr>
<tr>
<td>– IgM, at low titers, common in infections, not associated with thrombosis</td>
<td>– Do not request testing unless there is clinical suspicion of APS</td>
</tr>
<tr>
<td>– The best marker of thrombosis and maternal disease</td>
<td>May be present without causing thrombotic phenomena in 5% to 10% of the healthy population (percentage increases with age). Infections (syphilis, tuberculosis, leprosy, mycoplasma, HIV, hepatitis, varicella, mononucleosis, parvovirus, and adenovirus), drugs (hydantoin, chlorpromazine, phenothiazine, hydralazine, streptomycin, procainamide), neoplastic disease (adenocarcinoma, leukemia, lymphoma, myeloma, paraproteinemia)</td>
</tr>
</tbody>
</table>

Abbreviations: ACA, anticardiolipin antibodies; Anti-B2GP1, anti-β-2-glycoprotein 1 antibodies; Ig, immunoglobulin; SLE, systemic lupus erythematosus; APS, antiphospholipid syndrome; APA, antiphospholipid antibodies; HIV, human immunodeficiency virus.
Anti-b-2-glycoprotein 1 Antibodies

These are usually detected together with other APA, although they can appear in isolation in 3% to 10% of patients with antiphospholipid syndrome. Their predictive value for the risk of thrombosis and obstetric disease is good—even better than ACA—especially at high titers.\(^5,6\)

Measurement of anti-B2GP1 antibody levels is still in the process of being standardized and, for now, only values above percentile 99 of control samples should be considered positive.\(^3\) IgG and IgM antibodies can be detected in the laboratory. The clinical utility of IgA has not yet been established and testing for this is not currently recommended.\(^3\) There may be false positives, especially for IgM antibodies, in patients positive for rheumatoid factor or who have cryoglobulins.

The significance of other antibodies that target proteins other than B2GP1 or antiphospholipids other than cardioliopin is not clear, and laboratory techniques for detecting them have not yet been standardized. Particular attention is being paid to antiprothrombin antibodies, the prothrombin–phosphatidylserine complex, and antiphosphatidylethanolamine, although there are no conclusive data to justify their determination.\(^3,6\)

Diagnostic Criteria for Antiphospholipid Syndrome

Antiphospholipid syndrome is a multisystem autoimmune disease with a multifactorial genetic and environmental etiology. It is characterized by the presence of APA,
Clinical Features of Antiphospholipid Syndrome

The clinical features of the antiphospholipid syndrome are varied, given that the veins and arteries of any organ can be infected by thrombosis. The most common manifestation in veins is deep vein thrombosis in the legs, with or without pulmonary thromboembolism. In the arteries, the most common manifestation is acute stroke, although any other venous or arterial system can be involved, including superficial, myocardial, retinal, and abdominal vessels. In obstetric cases, the placenta may be affected.

Table 4 shows the most frequent clinical manifestations in a series of 1000 patients diagnosed with antiphospholipid syndrome according to the Sapporo criteria who were recruited by the Euro-Phospholipid Project Group. 

Skin Involvement in Antiphospholipid Syndrome

Some lesions are very common, others less so, but they can all help to establish a diagnosis. They are sometimes the first or only symptom of a disease (Table 5):

1. Livedo reticularis: a very frequent lesion that can appear in 25% of cases of antiphospholipid syndrome and in 20.4% as the first manifestation. It has been included in the clinical manifestations associated with antiphospholipid syndrome. It is extensive, involves the limbs, trunk, and buttocks, although at onset only the back of the hands and feet may be involved. Its pattern is fine, reticulated, and irregular. It is associated with a greater frequency of arterial thrombosis with brain and eye symptoms, heart valve disease, arterial hypertension, and Raynaud phenomenon.

Clinical Manifestations of Antiphospholipid Syndrome

Common clinical manifestations in antiphospholipid syndrome were defined at the Sydney meeting. They cannot be used to establish a definitive diagnosis of antiphospholipid syndrome, although their presence in patients whose laboratory criteria are not indicative of the syndrome could lead us to suspect a "probable antiphospholipid syndrome" (Table 3).

Table 3. Clinical Manifestations Associated With Antiphospholipid Syndrome

<table>
<thead>
<tr>
<th>Heart valve disease</th>
<th>Insufficiency and/or stenosis (moderate–severe) of the aortic and/or mitral valves confirmed by Doppler ultrasound. Libman–Sacks endocarditis confirmed by histology in patients with systemic lupus erythematosus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin manifestations</td>
<td>Persistent, extensive livedo reticularis affecting the trunk and limbs, with a reticulated, irregular pattern. The histological changes (thrombosis of arterioles and small–medium arteries in the dermis and subcutaneous cell tissue, with no inflammatory component and with negative direct immunofluorescence) confirm the diagnosis, although they are not indispensable</td>
</tr>
<tr>
<td>Renal manifestations</td>
<td>Thrombotic microangiopathy in arterioles and capillary glomerules and/or intimal fibrosis involving reorganized thrombi, fibrosis and/or fibrocellular occlusion of arteries or arterioles, focal cortical atrophy, tubular atrophy with eosinophilic material (exclude other causes of chronic renal ischemia)</td>
</tr>
<tr>
<td>Neurologic manifestations</td>
<td>Migraine, dementia, chorea, symptoms of demyelinating disease, transverse myelitis, epilepsy. Acute strokes and transient ischemic attacks are considered diagnostic criteria</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Below 100 000 on at least 2 occasions 12 weeks apart (exclude thrombotic thrombocytopenic purpura, disseminated intravascular coagulation, heparin-induced thrombocytopenia)</td>
</tr>
</tbody>
</table>


thrombosis (arterial or venous), and/or repeated miscarriages. The criteria for definitive diagnosis were established at the Eighth International Congress on Antiphospholipid Antibodies held in Sapporo, Japan, in 1998 and were later revised at the Eleventh Congress in Sydney, Australia, in 2004 (Table 2).

The fact that there are additional hereditary or acquired risks of thrombosis does not justify ruling out diagnosis of antiphospholipid syndrome. In fact, 2 groups of patients should be recognized: a) those with associated risk factors for thrombosis and b) those with no risk factors for thrombosis. The main risk factors for thrombosis are age (over 55 years in men and 65 years in women), risk factors for cardiovascular disease (arterial hypertension, hyperlipidemia, and obesity), nephrotic syndrome, smoking, oral contraceptives, hereditary thrombophilia, neoplastic disease, immobility, and surgery. These must be taken into account when making a diagnosis in order to decide on preventive measures.
8. Extensive cutaneous necrosis. Onset is usually sudden. The condition is characterized by necrotic plaques with an active purpuric border and blisters.


10. Primary anetoderma.

Histological examination may reveal thrombosis of the veins, arterioles, and small-to-medium-sized arteries in the dermis or subcutaneous cell tissue, with no inflammatory component in the vascular wall. These lesions are very uncommon in livedo reticularis (with the exception of livedo reticularis in catastrophic antiphospholipid syndrome), and when they do appear, they do so both in the center and at the border of the lesion. The histology of anetoderma is similar to that of other entities, although thrombosis is also rarely observed.

### Primary and Secondary Antiphospholipid Syndrome

The disease can occur in isolation—primary antiphospholipid syndrome (PAPS)—or with other, mainly autoimmune conditions—secondary antiphospholipid

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**Table 4. Principal Manifestations of Antiphospholipid Syndrome**

| **Peripherial thrombosis** | Deep venous thrombosis in the legs, 38.9% (arms 3.4%); superficial thrombophlebitis in the legs, 11.7%; arterial thrombosis in the limbs 7%
| **Neurological** | Migraine, 20%; stroke, 19.8%; transient ischemic attack, 11%; epilepsy, 7%; multi-infarct dementia, 2.5%; and chorea, 1.3%
| **Pulmonary** | Pulmonary embolism, 14.1%; pulmonary hypertension, 2.2%
| **Cardiac** | Valve dysfunction, 11.6%; myocardial infarction, 5.5%; angina, 2.7%; cardiomyopathy, 2.9%; and vegetations 2.7%
| **Hematological** | Thrombocytopenia, 29.6%; hemolytic anemia, 9.7%
| **Intra-abdominal** | Renal, 2.7% (glomerular thrombosis, thrombosis of the cortex, renal arteries or veins); gastrointestinal (mesenteric or esophageal ischemia, 1.5%; splenic infarction, 1.1%; and pancreatic infarction, 0.5%); Budd–Chiari syndrome, 0.7%; Addison syndrome, 0.4%
| **Musculoskeletal** | Arthralgia, 38.7%; arthritis, 27.1%; avascular bone necrosis, 2.4%
| **Ophthalmological** | Amaurosis fugax, 5.4%; arterial retinal thrombosis, 1.5% or venous retinal thrombosis, 0.9%; optic neuropathy, 1%
| **Dermatological** | (Table 5)

| **Obstetric complications** | (590 pregnant women, 1580 pregnancies). Pre-eclampsia, 9.5%; eclampsia, 4.4%; placental detachment, 2%; postpartum cardiopulmonary syndrome, 0.5%; early miscarriage, 35.4%; late miscarriage, 16.9%; premature births, 10.6% (of liveborn babies)

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**Table 5. Skin Lesions in Antiphospholipid Syndrome**

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Percentage</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Livedo reticularis</td>
<td>24.1%</td>
<td>25.5% (as first manifestation, 17.5%)</td>
</tr>
<tr>
<td>Superficial thrombophlebitis</td>
<td>11.7%</td>
<td>5%</td>
</tr>
<tr>
<td>Leg ulcers</td>
<td>5.5%</td>
<td>4.5%</td>
</tr>
<tr>
<td>Pseudovasculitis</td>
<td>3.9%</td>
<td>3%</td>
</tr>
<tr>
<td>Digital gangrene</td>
<td>3.3%</td>
<td>7.5%</td>
</tr>
<tr>
<td>Skin necrosis</td>
<td>2.1%</td>
<td>3.5% (limited), 2 (extensive)</td>
</tr>
<tr>
<td>Subungual bleeding</td>
<td>0.7%</td>
<td>5%</td>
</tr>
<tr>
<td>Thrombocytopenic purpura</td>
<td>3.5%</td>
<td></td>
</tr>
<tr>
<td>Primary anetoderma</td>
<td>2%</td>
<td></td>
</tr>
</tbody>
</table>

*Series of 1000 patients with antiphospholipid syndrome. Adapted from Cervera et al.*

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"Table 4. Principal Manifestations of Antiphospholipid Syndrome*"
syndrome (SAPS). In one series of 1000 patients diagnosed with antiphospholipid syndrome, 53% had PAPS and the remainder SAPS associated with other conditions. The most common associated condition was SLE or lupus-type symptoms, which accounted for 41% of the cases. The others were primary Sjögren syndrome (2.2%), rheumatoid arthritis (1.8%), systemic scleroderma (0.7%), systemic vasculitis (0.7%), and dermatomyositis (0.5%). No major differences have been found between the clinical or serological manifestations of PAPS and SAPS and this terminology is not recommended.

Given the frequent associations, any diagnosis of antiphospholipid syndrome should exclude an autoimmune process, such as SLE. The associated picture can occur throughout the process. In one series of 128 patients diagnosed with PAPS, followed for 14 years and with a mean duration of the condition of 8.2 years, SLE only appeared in 8%, and lupus-type symptoms in 5%.

Likewise, the approach to a patient with SLE must always take into account the possibility of antiphospholipid syndrome during the outcome. APA are very common in patients with SLE: 15% to 30% were positive for LAC and 86% for ACA. A follow-up of patients with SLE and APA revealed that, after 7 years, 30% had developed antiphospholipid syndrome, and after 20 years this figure increased to 50% to 70%. Patients with SLE who end up developing antiphospholipid syndrome more frequently suffer from arthritis, livedo reticularis, thrombocytopenia, leukopenia, reduced C4, autoimmune hemolytic anemia, and heart valve disease.

Catastrophic Antiphospholipid Syndrome

This is a peculiar clinical form of antiphospholipid syndrome defined by the presence of simultaneous thrombosis in 3 or more organs. It progresses quickly, with an associated mortality as high as 50%. Although large vessels can be involved, multiorgan thrombotic microangiopathy of small vessels is typical and must be confirmed histologically. Renal involvement is the most common (78%), followed by the lungs (66%), brain (60%), heart (50%), skin (50%: livedo reticularis, extensive skin necrosis, and digital gangrene), liver (40%), and suprarenal glands (30%), with a lower frequency of gastrointestinal, splenic, gall bladder, bone marrow, and reproductive system involvement. Also common are conditions such as thrombocytopenia (60%), hemolytic anemia (39%), and disseminated intravascular coagulation (19%).

Catastrophic antiphospholipid syndrome is uncommon (0.8% of antiphospholipid syndrome in a series of 1000 patients). In up to 65% of cases, a trigger factor is detected, such as infection, surgery, trauma, neoplastic disease, initiation of anticoagulant therapy, outbreaks of SLE, drug intake (contraceptives, thiazides, captopril, danazol, etc.), induced ovulation, and vaccination. It can appear in PAPS (49%) and in SAPS, and is mainly associated with SLE or lupus-like features (45%). Differential diagnosis can be difficult and should be made with sepsis, thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, and disseminated intravascular coagulation.

Management of Patients With Antiphospholipid Antibodies and Antiphospholipid Syndrome

For patients with an established picture of thrombosis, the cornerstone of therapy is oral anticoagulant drugs. There is some discrepancy concerning how aggressive therapy should be and if it should be defined according to the affected area or to whether the episode is the first or a recurrent episode. The most controversial aspects are preventive therapy in patients with APA who have not yet developed symptoms and regimens during pregnancy (Table 6).

Patients With Antiphospholipid Antibodies and No Clinical Manifestations of Antiphospholipid Syndrome

Take the case of a completely asymptomatic patient in whom the presence of APA has been detected as part of a routine analysis, for example before surgery, and the positive titer persists in subsequent analyses which should be repeated after at least 12 weeks. If LAC is negative and ACA are only positive at titers less than 40, no measures are recommended; however, if LAC is positive or ACA titers are greater than 40, an attempt must be made to control other possible associated risk factors for thrombosis (smoking, obesity, hyperlipidemia, arterial hypertension, and contraceptives). If the situation is particularly risky, such as surgery or prolonged immobility, then heparin should be considered.

Prophylaxis with acetylsalicylic acid at low doses (75-100 mg/day) is recommended by most authors, although studies are being carried out to confirm this approach and even to consider adding oral anticoagulant therapy based on an international normalized ratio (INR) of less than 1.5.

The presence of APA in patients with SLE and no clinical manifestations of antiphospholipid syndrome requires the same criteria as above to be followed (no action if negative LAC and positive IgG ACA <40). If LAC is positive or IgG ACA are positive at a titer greater than 40, hydroxychloroquine should be added to acetylsalicylic acid.
First Thrombotic Episode in Patients With Antiphospholipid Antibodies

1. Venous. Anticoagulation: start with heparin for 5 days, overlapping with the start of oral anticoagulant therapy at an INR of 2 to 3. Most experts recommend that administration should continue indefinitely, although this is not so clear when the first episode appears with other important modifiable risk factors for thrombosis (for example, oral contraceptives, pregnancy, and surgery).

2. Cerebral arterial. Indefinite oral anticoagulant therapy with an INR of 2 to 3, although some authors disagree and propose that acetylsalicylic acid at 325 mg/day would be as efficacious as oral anticoagulant therapy and have fewer side effects, especially in patients with low or moderate ACA titers and no other thrombotic risks.

3. Noncerebral arterial. There are few studies with this type of patient, but most experts recommend indefinite oral anticoagulant therapy with an INR of 2 to 3, although this does depend on the location and severity of the symptoms.

Patients With Recurrent Thrombosis Despite Treatment

There are no well established regimens, although most authors recommend oral anticoagulant therapy with an INR of 3 to 4 or heparin. Some recommend combination with antiplatelet agents or acetylsalicylic acid for recurrent cerebral thrombosis. Corticosteroids or immunosuppressants would only be justified in the case of repeated episodes of thrombosis.

Catastrophic Antiphospholipid Syndrome

Treatment has not yet been well defined and remains unsatisfactory. In addition to oral anticoagulant therapy,
high doses of intravenous corticosteroids, plasmapheresis, intravenous immunoglobulin, and antibiotics if infection is suspected are recommended. Some cases of severe thrombocytopenia have been successfully treated with rituximab.15,16

Skin Lesions in Antiphospholipid Syndrome

Livedo reticularis does not improve despite anticoagulant therapy, and no satisfactory treatment has been reported. Extensive skin necrosis and digital gangrene require oral anticoagulant therapy with an INR of 2 to 3, as is the case for patients with thrombosis in other locations. Pseudovasculitis or livedo vasculitis lesions may respond to low doses of acetylsalicylic acid (100 mg/day) or antiplatelet agents. If they are severe or recurrent, oral anticoagulant therapy could be considered.16

Approach to Therapy During Pregnancy

No published data support the need for treatment in women with APA without clinical manifestations of antiphospholipid syndrome. In fact, given that early miscarriage (before week 10) in healthy women is very common, determination of APA is not recommended until there have been at least 3 unexplained miscarriages and/or a late miscarriage.12 Some authors recommend acetylsalicylic acid at low doses (75–100 mg/day) if the LAC values are positive or IgG ACA or B2GP1 have high titters.17 When the patient has APA and a history of gestational disease (2 or more early miscarriages, and/or 1 or more late miscarriages) and/or has a history of thrombotic disease, treatment with acetylsalicylic acid at low doses is recommended from the moment the decision to conceive is taken. Low molecular weight heparin should be included when pregnancy is confirmed and treatment should be maintained until at least 6 weeks after delivery.12,16,20 Oral anticoagulant therapy can lead to embroyopathy, especially at weeks 6 to 12 of pregnancy. Patients who have already received anticoagulant therapy for thrombosis should be given low molecular weight heparin as soon as pregnancy is confirmed and until the end thereof.13

Conflicts of Interest
The author declares no conflicts of interest.

References