

# Obstetric antiphospholipid syndrome

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## ABSTRACT

The present clinical and laboratory classification criteria for antiphospholipid syndrome (APS) were established in Sydney, Australia, in 2006. In this review, we focus on the obstetric subset of APS (OAPS), defined by persistent positivity for antiphospholipid antibodies together with either early recurrent pregnancy loss, early fetal death, stillbirth or premature birth <34 gestational weeks due to pre-eclampsia, eclampsia and placental insufficiency. It is important to diagnose these cases since most women suffering from OAPS can, when given appropriate treatment, have successful pregnancies. Furthermore, patients with OAPS may, depending on the antibody profile, be at enhanced risk of thrombotic events later in life. We present an update on the present knowledge of possible underlying pathogenesis, risk factors and risk estimations for adverse pregnancy outcomes before and during pregnancy, current treatment concepts, and long-term outcomes for women with OAPS and their children.

## INTRODUCTION

Antiphospholipid syndrome (APS) is an autoimmune disorder characterised by vascular thrombosis and/or pregnancy morbidity in combination with persistent presence of circulating antiphospholipid antibodies (aPL)—anticardiolipin antibodies (aCL) and/or anti- $\beta_2$  glycoprotein I antibodies (anti- $\beta_2$ GPI)—in medium to high titres or positivity in the functional lupus anticoagulant (LA) test.<sup>1</sup> APS is recognised as one of the main acquired prothrombotic conditions that predispose to venous thromboembolism (also referred to as ‘acquired thrombophilia’). Nevertheless, APS is a unique prothrombotic condition since thrombotic events can also occur in arterial vessels and in the microvasculature. Symptoms are heterogeneous and range from asymptomatic multiple, small ischaemic episodes to catastrophic ischaemic strokes.<sup>2</sup>

The association between repeated spontaneous abortions and a circulating anticoagulant, later named the LA, was first reported by Nilsson *et al* in 1975,<sup>3</sup> while the presence of aCL was linked to miscarriages for the first time by Graham Hughes in 1984.<sup>4</sup> Since then, recurrent pregnancy loss has been considered a hallmark of APS. The presence of aPL is associated with recurrent miscarriages in

the first trimester,<sup>5</sup> and even more convincingly with fetal death or pregnancy morbidity in the second or third trimesters, including symptoms related to placental dysfunction such as severe pre-eclampsia and/or intra-uterine growth restriction (IUGR), necessitating delivery of a premature infant before 34 weeks<sup>2</sup> of gestation. Thus, obstetric APS (OAPS) has been referred to as the most frequent acquired risk factor for a treatable cause of recurrent pregnancy loss and represents an important health burden for women of childbearing age.<sup>6</sup>

The clinical and laboratory classification criteria for APS were first established in 1999 in Sapporo, Japan,<sup>7</sup> and modified in 2006 in Sydney, Australia<sup>8</sup> (box 1). In 2013, in Rio de Janeiro, Brazil,<sup>9</sup> novel clinical criteria were proposed in order to separate two different entities, that is, thrombotic APS (TAPS) and APS associated with obstetric morbidity (OAPS), including either early recurrent pregnancy loss, early fetal death, stillbirth or premature birth <34 gestational weeks due to pre-eclampsia, eclampsia and placental insufficiency. This initiative was undertaken since, in contrast to patients with thrombotic aPL, there are reports that women with low-titre aPL who did not fulfil the criteria<sup>8</sup> had comparable pregnancy outcomes with patients with higher aPL titres.<sup>10</sup> But the results are conflicting since other studies demonstrate that women with low-titre aPL had good pregnancy prognoses.<sup>11</sup> Due to inconsistent results and limitations of existing clinical studies, none of the proposed criteria were accepted.<sup>12</sup>

## ANTI-PHOSPHOLIPID ANTIBODIES

The laboratory criterion for APS depends on the detection of aPL, defined as LA positivity, and/or anticardiolipin (aCL IgG/M) and/or anti- $\beta_2$ GPI IgG/M antibodies. Asymptomatic aPLs are present in 1%–5% of healthy individuals without a history of thrombotic events<sup>13</sup>; higher frequencies occur in rheumatic diseases, especially in SLE, where between 20% and 40% are aPL-positive.<sup>14</sup> These wide estimates reflect in part the use of different



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### Box 1 High-risk and low-risk serological features in patients with antiphospholipid antibodies

#### High risk

- ▶ LA positivity.
- ▶ Triple positivity (LA+aCL+anti- $\beta_2$ GPI).
- ▶ Isolated persistently positive aCL at medium-high titres (studied only in patients with SLE).

#### Lower risk

- ▶ Isolated, intermittently positive aCL or anti- $\beta_2$ GPI at low-medium titres

aCL, anticardiolipin antibodies; anti- $\beta_2$ GPI, anti- $\beta_2$ glycoprotein I antibodies; LA, lupus anticoagulant.

assays and non-standardised approaches to detect aPL.<sup>15 16</sup> LA is a functional coagulation test measuring the ability of aPL to prolong phospholipid-dependent

### Box 2 Classification criteria for antiphospholipid syndrome<sup>3</sup>

#### Clinical criteria\*

##### Vascular thrombosis

- ▶ One or more clinical episodes of arterial, venous or small vessel thrombosis, in any tissue or organ.
- ▶ Thrombosis must be confirmed by appropriate imaging studies or histopathology.
- ▶ Thrombosis should be present without significant evidence of inflammation in the vessel wall.

##### Pregnancy morbidity

- ▶ One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation, with normal fetal morphology documented by ultrasound or by direct examination of the fetus.
- ▶ One or more premature births of a morphologically normal neonate before the 34th week of gestation due to eclampsia and severe pre-eclampsia, or to recognised features of placental insufficiency.
- ▶ Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation, with maternal anatomical or hormonal abnormalities, and paternal and maternal chromosomal causes excluded.

#### Laboratory criteria\*

- ▶ Lupus anticoagulant (LA). Present in plasma, on more than two occasions at least 12 weeks apart, detected according to the guidelines of the International Society on Thrombosis and Haemostasis (Scientific Subcommittee on LAs/phospholipid-dependent antibodies).
- ▶ Anticardiolipin antibody of IgG and/or IgM isotype. Present in serum or plasma at medium or high titre (>40 GPL or MPL, or >99th percentile), on more than two occasions at least 12 weeks apart, measured by a standardised ELISA.
- ▶ Anti- $\beta_2$ GPI antibody of IgG and/or IgM isotype. Present in serum or plasma (titre >99th percentile), on more than two occasions at least 12 weeks apart, measured by a standardised ELISA, according to recommended procedures.

\*Antiphospholipid syndrome is present if at least one clinical criterion together with one laboratory criterion are met.

Anti- $\beta_2$ GPI, anti- $\beta_2$  glycoprotein I; GPL, IgG phospholipid units; GPM, IgM phospholipid units.

coagulation assays. Laboratory assays currently used for assessment of LA do not meet the standards of good laboratory test practice; thus, guidelines for LA testing have been proposed.<sup>17</sup> According to these recommendations, two assays of different principles, the diluted Russell viper venom test and a sensitive activated partial thromboplastin time (aPTT), are simultaneously used for detection of LA. If one of the tests is prolonged, the sample is first mixed with the same amount of normal plasma in order to exclude coagulation factors deficiency. Finally, in a true LA-positive sample, the prolonged aPTT should revert to normal when excess phospholipids are added, since these bind the autoantibodies so that they will not interfere with the coagulation process. aCL and anti- $\beta_2$ GPI antibodies of IgM and IgG isotypes are detected by ELISA assays and expressed as the internationally accepted MPL/GPL units (IgM antiphospholipid units/mL (MPL)/IgG antiphospholipid units/mL (GPL)). More recently IgA isotypes are also measured and expressed as IgA units. The standardisation of these assays is also challenging,<sup>18</sup> as the specificity of aPL increases with the titre and it is also higher for IgG compared with IgM isotypes. However, some patients may only have a positive IgM test, and a few are only IgA-positive.<sup>19</sup>

It has been observed that many aPLs are directed to epitopes on the  $\beta_2$ GPI,<sup>20</sup> molecule and many nowadays consider  $\beta_2$ GPI to be the main antigen in APS.<sup>21</sup> The occurrence of anti- $\beta_2$ GPI antibodies was consequently included in the updated classification criteria for APS in Sydney in 2006.<sup>8</sup> However, in patients with clinical features of APS, anti- $\beta_2$ GPIs are rarely the sole antibodies detected.<sup>22</sup> Usually anti- $\beta_2$ GPI and aCL of the same isotype occur together.<sup>23</sup>

#### PATHOGENESIS

Presently we do not understand why some individuals develop aPL. Genetic predisposition seems to contribute,<sup>24 25</sup> and environmental factors, especially smoking, has been reported to be important.<sup>25–27</sup> However, all individuals with aPL do not develop clinical symptoms. Thus, the mere presence of aPL is not sufficient to cause APS manifestations. According to the ‘second hit hypothesis’, postulated by several authors,<sup>21 28</sup> it is assumed that triggers, for example, oxidative stress, surgery, trauma or infections, which involve states of systemic inflammation and tissue damage, are necessary as ‘second hits’ to initiate the assemblage of immune complexes at the surface of endothelial cells. The exact mechanisms underlying thrombosis formation in APS are still unknown, but aPL can activate endothelial cells, platelets, monocytes, the complement system and coagulation factors, leading to impaired protein C activation and fibrinolysis and subsequent clot formation.

Placental infarctions were initially thought to be the main cause of fetal loss. A specific prothrombotic effect in the maternal–fetal circulation is suggested by the demonstration of interference of aPL with trophoblast-associated

annexin V.<sup>29</sup> However, the pathophysiology of TAPS involvement seems to be quite different from that associated with the obstetrical manifestations.<sup>30</sup> Furthermore, it is likely that the pathogenesis of APS-related early recurrent pregnancy loss differs from late pregnancy complications. In early pregnancy losses, the direct effects of aPL on placentation and apoptosis of trophoblast cells may have more relevance.<sup>31</sup> Although inflammation is not the most prominent characteristic of APS, there is mounting evidence that an inflammatory state is involved in the pathophysiology of both thrombotic<sup>32–34</sup> and obstetric events.<sup>35–37</sup> In particular, several reports demonstrate that the complement cascade is activated in APS.<sup>38–42</sup> Complement component C5 and its cleavage product C5a together with neutrophils were found to be key mediators of fetal injury in a mouse model, where pregnant mice were given human IgG containing aPL or monoclonal aPL.<sup>35</sup> Interestingly, genetic complement deficiency or treatment with complement blocking agents protected these mice from aPL-induced pregnancy complications.<sup>42</sup> Additionally, treatment with heparins, which also inhibit complement,<sup>43</sup> was protective.

The findings from these animal studies are supported by recent case reports which present evidence that treatment with an anti-C5a monoclonal antibody successfully prevents further thrombotic events in catastrophic APS.<sup>44</sup> Together, these findings indicate that both thrombosis and inflammation seem to mediate aPL-related pregnancy complications in women with aPL.

### RISK ESTIMATION BEFORE PREGNANCY

The specificities of aPL, isotypes and titres, and the presence of multiple antibodies, have been associated with different risk profiles for both thrombotic and obstetric manifestations. The presence of LA has repeatedly been described as the best predictor for pregnancy loss and thrombosis.<sup>45–48</sup> The simultaneous presence of aCL, a $\beta_2$ GPI antibodies and a positive LA (referred to as ‘triple positivity’) is associated with the highest risk for thrombotic manifestations in APS.<sup>49</sup> High-risk aPL profile (Box 1) correlates with increased risk of maternal vascular thrombotic events during pregnancy (OR 12.1),<sup>50</sup> (pre-) eclampsia (OR 2.3),<sup>51 52</sup> APS-related pregnancy morbidity (OR 9.2),<sup>53</sup> IUGR (OR 4.7)<sup>51</sup> and preterm birth.<sup>10 53</sup> On the other hand, isolated positivity for aCL or a $\beta_2$ GPI seems to be associated with a lower risk of adverse pregnancy outcomes (APOs).<sup>54</sup>

During the last years there have been several reports that antibodies targeting domain-1 of the  $\beta_2$ GPI molecule, that is, the non-phospholipid binding tail of the molecule, are more pathogenic<sup>55</sup> and associated with ‘triple positivity’.<sup>56</sup> Anti- $\beta_2$ GPI domain-1 antibodies were recently also associated with pregnancy complications, especially with late pregnancy morbidity.<sup>57</sup>

Additionally, ethnicity and clinical features such as a concomitant SLE diagnosis,<sup>51 58</sup> history of vascular thrombosis,<sup>54 59</sup> previous APOs<sup>60–62</sup> and low complement levels

during the first trimester<sup>59</sup> are associated with a higher risk for pregnancy morbidity in women with aPL/APS.

### OAPS IN PATIENTS DIAGNOSED WITH SLE

Women with SLE are at enhanced risk of pregnancy loss, affecting 15%–25% of all pregnancies.<sup>63 64</sup> Moreover, live birth complications are not uncommon, including premature birth, IUGR, hypertension, pre-eclampsia and eclampsia. The presence of a high-risk aPL profile is a well-documented and strong risk factor for APOs in SLE.<sup>63</sup> Conversely, in aPL-positive women, the risk of pregnancy complications is higher in women who are also diagnosed with SLE.<sup>52 65</sup> Overall, approximately 30%–40% of women with SLE are positive for at least one aPL, and the frequency of aPL positivity varies with ethnicity. In our cohort in Stockholm, where the majority are European Caucasians, 12% are triple-positive and 20% are positive for LA; both features imply a high risk for both thrombosis and APO. All patients with SLE should be tested for aPL at diagnosis and again before planned pregnancies so that the best prophylactic treatments can be given.

In patients with SLE high-titre IgG<sup>63</sup> and even more consistently a positive LA<sup>64 66</sup> have been associated with pregnancy complications. Patients with SLE who have a definite APS diagnosis based on thrombosis prior to pregnancy are also at higher risk.<sup>64</sup> The prospective Predictors of Pregnancy Outcome: Biomarkers in APL Syndrome and SLE (PROMISSE) study comprised 385 patients with SLE and 81% of them had uncomplicated pregnancies. APO (defined as fetal and neonatal death, preterm delivery and small for gestational age) affected 19%. To be LA-positive at baseline was strongly predictive of APO with an OR of 8.3 (95% CI 3.6 to 19.3).<sup>66</sup> These results were recently confirmed by Mankee *et al*<sup>47</sup> in 202 pregnancies followed in the Hopkins lupus cohort. Among women with SLE with a single positive LA during the first trimester, the pregnancy loss rate was 38% as compared with 9% in patients with SLE who were negative for LA. Notably a history of LA positivity did not influence these results.

### Clinical manifestations of APS during pregnancy

#### Recurrent early miscarriages

Recurrent pregnancy loss is defined as three consecutive early miscarriages (before the 10th week of gestation) and should lead to an investigation for underlying pathology, including chromosomal karyotyping in both partners, analysis of factors for thrombophilia including aPL, hormone levels and immunological markers, and also a pelvic examination of the mother. In the second trimester, miscarriage and fetal loss are less likely to be caused by chromosomal abnormalities, whereas factors like structural abnormalities, IUGR, placental insufficiency, infections and cervical insufficiency are more commonly involved.

The persistent presence of LA was confirmed in about 10% of women with a history of recurrent miscarriages

in a cohort of 500 women, while aCL IgG and IgM were found in 3.3% and 2.2%, respectively.<sup>66</sup> The prevention of recurrent early miscarriages is the only situation in OAPS where treatment is based on several clinical trials, as discussed later in this review.

### Late pregnancy loss

Late pregnancy loss, after 20–22 weeks of gestation (definitions vary between countries, according to the WHO up to 28 weeks), is also referred to as stillbirth. Sometimes stillbirth before 22 weeks of gestation is referred to as a late miscarriage. There is only one study assessing aPL in a cohort of women with stillbirth, comprising 582 cases and demonstrating that aPLs (aCL and anti- $\beta_2$ GPI) were positively associated with stillbirths.<sup>67</sup> However, LA was not analysed in this study and positivity of aPL was not confirmed.

### Placental insufficiency and pre-eclampsia

Pre-eclampsia occurs in about 3% of all pregnancies in Sweden. Pre-eclampsia usually develops after week 20, but may occur earlier. Onset is often gradual and initially asymptomatic; the first signs are commonly detected as hypertension and/or proteinuria during routine controls. Other, apparently healthy, women develop a rapidly accelerating pre-eclampsia with severe multiorgan involvement, resulting in symptoms like hyper-reflexia, nausea, epigastralgia, oliguria, coagulation abnormalities and preterm placental detachment. Pre-eclampsia is related to an increased fetal mortality.<sup>68</sup> In recent years, pre-eclampsia has been divided into early-onset and late-onset pre-eclampsia, where early pre-eclampsia occurs before 34 weeks of gestation and is usually very severe.<sup>69</sup>

Pre-eclampsia and/or placental insufficiency can manifest as IUGR. A meta-analysis by do Prado *et al*<sup>70</sup> demonstrated a positive association between moderate to high aCL levels and pre-eclampsia. Several other studies confirmed the association between the persistent presence of high-titre aPL with IUGR and preterm deliveries.<sup>71 72</sup> The ratio of angiogenic biomarkers of placental insufficiency, s-FLTt-1/PIGF ratio (soluble fms-like tyrosine kinase-1/placental growth factor), was demonstrated as a help to predict and diagnose pre-eclampsia in at-risk patients in the general population.<sup>73</sup> Two recent studies have confirmed the predictive role of these biomarkers also in patients with SLE/APS. In the prospective PROMISSE study comprising 492 patients with APS and/or SLE, Kim *et al*<sup>74</sup> demonstrated that high s-FLTt-1 and low PIGF at weeks 12–19 were highly predictive of APO. Women belonging to the highest quartile of s-FLTt-1 and the lowest quartile of PIGF, with a positive LA test and hypertension at weeks 16–19, were at very high risk of severe APO: 94% (95 % CI 70 to 99.8). Conversely lower levels of s-FLTt-1 and higher levels of PIGF were associated with substantially decreased risk of APO. A recent study by Rodríguez-Almaraz *et al*<sup>75</sup>, which included 44 patients with SLE and/or APS, demonstrated a correlation between high sFLTt-1/PIGF ratio as well as an

increased uterine mean arterial pulsatile index in patients with an adverse obstetric outcome, such as pre-eclampsia or growth restriction, while patients with a normal pregnancy or an SLE flare did not have the same changes. More studies are needed, but early measurements of circulating angiogenic factors may become a useful tool for risk stratification in SLE and APS pregnancies.

### THROMBOEMBOLIC COMPLICATIONS

The most common thromboembolic events in patients with APS are deep venous thrombosis (DVT), pulmonary embolism, stroke and transient ischaemic attacks.<sup>1</sup>

Many of the haemodynamic changes during pregnancy increase the risk of thromboembolism. The plasma volume is increased by about 50% at 32 weeks of gestation.<sup>76</sup> The increased plasma volume plus anatomical changes lead to a higher venous pressure and reduced speed of the venous blood flow in the lower limbs. Furthermore, the uterus and the fetus compress the common, internal and external iliac veins and the lower vena cava, especially on the left side. During pregnancy, there is a shift towards increased production of coagulation factors (f VII, f VIII, fibrinogen and von Willebrand factor), diminished synthesis of natural anticoagulants (protein C and protein S) as well as decreased fibrinolytic activity. These changes make pregnancy a hypercoagulable condition.

Patients with thrombotic manifestations and APS should be treated with warfarin for many years, possibly lifelong, with a target prothrombin time-international normalised ratio (PT-INR) of 2.0–3.0.<sup>77</sup> The optimal PT-INR level in TAPS is presently debated, since some clinicians advocate a PT-INR target of 3.0–4.0, especially in patients with arterial thrombotic manifestations.<sup>78</sup>

As soon as a patient presents with a positive pregnancy test, warfarin treatment should be paused and switched to low molecular weight heparin (LMWH). Warfarin passes the placenta and can cause bleeding complications for the fetus. Warfarin can also cause fetal malformations, known as fetal warfarin embryopathy, if the fetus is exposed to warfarin during organogenesis (6th–12th week of gestation). In contrast to warfarin, LMWH does not significantly cross the placenta because of its high molecular weight and has therefore no direct effect on the fetus.<sup>79</sup>

### MANAGEMENT OF OAPS

Pregnancies in APS are considered as high-risk pregnancies, and the treatment as well as the frequency and modality to monitor these women should be determined according to maternal and/or fetal status. To optimise treatment, it is therefore important that women with APS, and women diagnosed with SLE who are aPL-positive, receive preconceptional counselling. Risk factors need to be individually assessed, including the aPL profile. Close surveillance during pregnancy, if possible at a centre for specialist maternal care, is also needed.

Using current standard of care treatment including low-dose aspirin (LDA: 75–100 mg/day) and LMWH or

**Table 1** Factors of importance for risk assessment in obstetric APS and suggested treatments

Clinical/Serological manifestations	Suggested treatment
All carriers of significant aPL titres.	Monitored in specialist maternity care units, if possible. Screen for other CVD risk factors. LDA if high-risk aPL profile. Consider adding LMWH in risk situations such as presence of other CVD risk factors or immobility.
Patients with SLE diagnosis and positive aPL, but no previous thrombotic events or pregnancy morbidity.	Hydroxychloroquine+LDA. Individual risk assessment depending on aPL profile, in some cases LMWH in prophylactic dose during pregnancy.
Previous early miscarriage and positive aPL.	LMWH, prophylactic dose during pregnancy. LDA.
Late fetal loss/pre-eclampsia/ IUGR and positive aPL.	LMWH, intermediate or full therapeutic dose. LDA.
Thrombotic APS. Late fetal loss/pre-eclampsia/IUGR despite LMWH in prophylactic dose.	LMWH, intermediate or full therapeutic dose. LDA.
Post partum. All carriers of significant aPL titres.	During 6–12 weeks post partum: Continue same treatment as during pregnancy. If not given previously, consider adding LMWH to women with high thrombotic risk profile, for example, obesity-complicated delivery and so on.

aPL, antiphospholipid antibodies; APS, antiphospholipid syndrome; CVD, cardiovascular disease; IUGR, intrauterine growth restriction; LDA, low-dose aspirin; LMWH, low molecular weight heparin.

unfractionated heparin (prophylactic, intermediate or therapeutic dose) has led to live births in 71% of APS pregnancies.<sup>80</sup> These treatment recommendations are based on the results from two randomised clinical trials comparing the LDA treatment alone or in combination with heparin.<sup>81 82</sup> Together 140 pregnant women with a history of recurrent miscarriages and persistent aPL positivity were randomised to treatment on LDA alone or LDA+heparin, and a significantly higher rate of live births was observed in women receiving the combined treatment. Two subsequent studies could however not confirm these results,<sup>83 84</sup> possibly due to unexpectedly high frequency of live births in the LDA group. A follow-up meta-analysis could not verify the favourable outcomes in the group treated with LDA alone.<sup>85</sup>

Since LMWH is easier to administer than heparin, it is in the great majority of cases the drug of choice. The dose of LMWH should be individually determined, depending on the patient's history and aPL profile. Prophylactic dose is used in patients with a more favourable profile, while intermediate or full therapeutic dose LMWH should be given to patients with previous thrombosis or pregnancy morbidity (see [table 1](#) for suggested dosages).

In severe cases with recurrent late pregnancy morbidities, despite treatment with LDA and LMWH, low-dose steroids (10 mg prednisolone) and hydroxychloroquine may be added.<sup>86</sup> In severe treatment-resistant cases, intravenous gamma globulin or repeated plasma exchange/apheresis could, based on small case series with favourable outcomes, be considered.<sup>87</sup>

After delivery, it is important to continue treatment with LMWH for 6–12 weeks to protect the mother from thrombotic events during this high-risk period.

Statins have emerged as a possible treatment for pre-eclampsia in the general population, recently reviewed by Maieran *et al.*<sup>88</sup> It is a problem that a small percentage of all individuals are intolerant to statins, but as of now there is no convincing evidence that statins are teratogenic in humans. In a small study of 21 women with APS who developed pre-eclampsia and/or IUGR while on treatment with LMWH and LDA, the addition of pravastatin reduced complication rates.<sup>89</sup> Another study reported reduction of prothrombotic and proinflammatory markers in patients with APS during statin treatment.<sup>90</sup> Although promising, these studies are small and confirmations are clearly needed before more general recommendations regarding the use of statins in OAPS can be made. Also, vitamin D supplementation could have a positive protective effect for thromboembolic events by inhibition of anti-beta-2GP1-mediated tissue factor expression, according to results from *in vitro* studies.<sup>91</sup> However, more studies are needed to confirm this observation.

### ASYMPTOMATIC CARRIERS OF ANTIPHOSPHOLIPID ANTIBODIES

Screening of healthy women without APOs for the presence of aPL is generally not recommended. Early studies assessing aPL in single blood samples in healthy pregnant women reported lower live birth rates in

those who tested positive for aPL (range 62%–84%) as compared with women lacking these antibodies (range 90%–98%).<sup>80–82</sup> Ever since Lubbe *et al*<sup>83</sup> in 1983 reported good pregnancy outcomes in LA-positive pregnant women with previous pregnancy complications when treated with LDA and prednisone, almost all women with aPL and poor pregnancy outcomes have received pharmacological treatment. However, a recent review of studies comparing prophylactic treatment with aspirin to placebo or usual care in otherwise healthy women with aPL did not find evidence of superiority of aspirin treatment for prevention of unfavourable obstetric outcomes.<sup>4</sup>

A prospective study of triple-positive aPL carriers reported a 5.3% annual incidence of thromboembolism that was not significantly diminished in the subgroup treated with aspirin in a non-controlled manner.<sup>49</sup> But in the meta-analysis by Arnaud *et al*<sup>92</sup>, LDA protected from arterial but not venous events among asymptomatic aPL carriers. Furthermore, treatment with LDA is recommended by the 13th Congress of Antiphospholipid Antibodies task force in carriers with a high-risk aPL profile in the presence of other cardiovascular risk factors.<sup>93</sup> In high-risk situations, such as surgery and hospitalisation, prophylaxis with LMWH or aspirin may be considered.<sup>62</sup> The use of oestrogen-containing oral contraceptives is a major risk factor for arterial thrombotic events in young women with aPL and should not be used,<sup>26</sup> and smoking should be strongly discouraged since it seems to potentiate the thrombotic risk in aPL-positive patients.<sup>26 27</sup>

In patients with underlying autoimmune disease, in particular SLE, close collaboration with a rheumatologist is important. In these patients, the presence of proteinuria, thrombocytopenia and hypertension is, next to the presence of APS, a risk factor for pregnancy loss especially when such symptoms and laboratory aberrations present during the first trimester of pregnancy.<sup>84</sup>

### WHAT HAPPENS TO THE MOTHER AFTER OAPS

Mothers with purely OAPS are generally not given long-term anticoagulation treatment after the postpartum period. Many but not all receive LDA. While the subgroup with SLE is usually monitored by a rheumatologist, there is reason to believe that women with primary OAPS may not be subject to further surveillance. In a retrospective setting Lefèvre *et al*<sup>94</sup> reported high thrombosis rates in women with pure OAPS, and a prospective investigation by Gris *et al*<sup>95</sup> studied a large cohort of women with purely obstetric ‘early’ APS, defined as three or more spontaneous early abortions before the 10th week of gestation, (<w 10) together with repeated aPL positivity. These women with ‘early’ OAPS received LDA prophylaxis, but during the 10-year follow-up they were still at higher risk for both venous thromboembolism and ischaemic cerebrovascular disease, as compared with women with hereditary thrombophilia and women with a negative thrombophilia screening.

During subsequent pregnancies women with OAPS are normally cared for in specialised maternity care clinics. Bouvier *et al*<sup>60</sup> prospectively studied subsequent pregnancy outcomes in 513 women with purely OAPS and in 791 aPL-negative women comparators. They included women with early or late fetal loss, but excluding the third OAPS criterion, that is, premature birth due to placental insufficiency. The OAPS group was treated with a combination of LDA and LMWH, according to recommendations. But despite treatment, pregnancy complications, including fetal loss, pre-eclampsia, placenta-mediated complications and neonatal deaths, were more common in the OAPS group.

Taken together these studies demonstrate that patients with OAPS have increased risk of new pregnancy complications and TAPS manifestations. Although more studies are needed, women with OAPS should be subject to analysis of their aPL profile postpregnancy, and in the case of persistent triple positivity or positive LA some form of tailored anticoagulation treatment should be considered.

### WHAT HAPPENS TO CHILDREN BORN TO MOTHERS WITH OAPS

Antibodies of the IgG isotype are actively transported over the placenta. This process starts at the end of the first semester and is intensified during late pregnancy. IgG antibodies can be detected in the infant at least for 6 months after birth. Consequently, IgG aPLs were detected in approximately 30% of 22 infants born to mothers with APS.<sup>96</sup> While aCL declined and disappeared in all infants by 12 months, a $\beta_2$ GPI antibodies were still present, and at higher titres at 12 months than at birth. But positivity for a $\beta_2$ GPI was similar in two control groups, consisting of children born to mothers with autoimmune diseases but negative for aPL and in children born to healthy mothers, indicating a general de novo synthesis of a $\beta_2$ GPI in infants during the first year of life.

In long-term follow-up of children born to mothers with APS and or SLE, neurological and physical examinations and intelligence levels were normal. Although no control group was studied, learning disabilities in school children (19%), sleep disorder (30%) and epilepsy (10%) were strikingly common. Marder *et al*<sup>97</sup> studied 60 offspring to mothers with SLE with or without aPL. They found that maternal APS and positive LA were associated with an increased need for special educational services for the offspring. Nacinovich *et al*<sup>98</sup> also reported a high rate of learning disabilities (26%) among 17 children born to mothers with primary APS (pAPS)<sup>5</sup>. Although present studies are small and more studies are needed, available results indicate that children born to mothers with aPL/APS are physically normal and have normal intelligence, but may need special attention regarding neurological development and extra learning support.

### CONCLUSION

OAPS is one of the most common conditions causing miscarriage and late pregnancy complications.

Importantly OAPS is in most cases a treatable condition, although this serious condition needs to be recognised, and it is a major task to further spread knowledge about the diagnosis and treatment of OAPS. Prospective studies are needed to determine which treatments are best suited for women with different risk profiles. Given the known overlap between APS and SLE, aPL should be measured in all patients with SLE, as well as in women with repeated miscarriages or late pregnancy morbidity.

**Contributors** AA: study design, data review and selection, and manuscript writing/approval. MS: data review and selection, and manuscript writing/approval. KB: data review and selection, and manuscript writing/approval ES: study design, data review and selection, and manuscript writing/approval.

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