



Antiphospholipid Syndrome In Pregnancy

Authors

**Dr Arati Nayak¹, Dr Arata Kumar Swain², Dr Pradipta Kumar Patel³,
Dr Harekrusna Dalai⁴**

¹MD, Senior Specialist in Obstetric & Gynaecology & Specialist in Infertility & Laparoscopic Surgeries
Capital Hospital, Bhubaneswar

²MD, FCCM, FCCS, Department of Anaesthesiology & Critical Care VIMSAR, Burla

^{3,4}Associate Professor, Department of Anaesthesiology & Critical Care VIMSAR, Burla

ABSTRACT

The antiphospholipid syndrome (APS) is a multisystemic disease, characterized by venous or arterial thromboses, or certain obstetric complications, and the presence of antiphospholipid antibodies (APAs)⁽¹⁻⁴⁾.

Lupus anticoagulant (LA), anticardiolipin antibodies (aCL) and anti-beta 2 glycoprotein 1 (anti-β2GP1) antibodies are the main antibodies in this syndrome (1;2;) APS occurs in isolation as a primary APS in more than 50% of the cases, but can be associated with other autoimmune diseases, most often with systemic lupus erythematosus (SLE). Twenty to 35% of women with SLE develop APS⁽⁶⁾. APS occurs for the most part in young women of fertile age⁽⁷⁾. The most characteristic feature of obstetrical APS is miscarriage, It occurs rarely in children, and only 12% of all APS occur after 50 years of age⁽⁸⁾

Introduction

Antiphospholipid syndrome (APS) predominantly affects young women and there has been a growing awareness of this condition amongst obstetricians and gynecologists over the last 15 years. Although clinicians are becoming increasingly familiar with these management options, knowledge of the pathogenesis of poor pregnancy outcome in APS remains incomplete.

The catastrophic variant of the antiphospholipid syndrome (APS) is a life-threatening form of presentation of this syndrome that can be triggered by several factors.

The antiphospholipid syndrome (APS) is a systemic autoimmune disorder characterised by a combination of arterial and/or venous thrombosis, pregnancy morbidity, usually accompanied by a

mild-to-moderate thrombocytopenia, and raised titres of antiphospholipid antibodies (aPL)—namely, the lupus anticoagulant (LA) and/or anticardiolipin antibodies (aCL).⁽⁹⁾

The most characteristic feature of obstetrical APS is miscarriage. Currently, recurrent miscarriage is a potentially treatable condition when it is associated with aPL.⁽¹⁰⁾ Additionally, several other serious obstetric complications have been associated with APS, including pre-eclampsia, fetal growth restriction, uteroplacental insufficiency, fetal distress and medically induced preterm delivery^(11,12). Catastrophic APS (also known as “Asherson’s syndrome”) is an unusual (<1%) but usually a life-threatening variant of APS.

Diagnosis of APS in non-pregnant and pregnant women

According to the last updated consensus the diagnosis of obstetric APS needs to be based on:

- 1) one or more unexplained deaths of normal fetuses at or beyond the 10th week of gestation, or
- 2) one or more premature births before the 34th week of gestation because of eclampsia, severe preeclampsia, or placental insufficiency, or
- 3) three or more unexplained consecutive spontaneous abortions before the 10th gestational week⁽¹³⁾. with such complications should have laboratory testing.

The diagnosis of APS must be based both on clinical criteria and persistent positivity for APA. Laboratory testing for APA is used to confirm or refute the diagnosis. Thrombosis must be confirmed by strict objective criteria (angiography, venography, Doppler ultrasound examination or CT. CT is considered to be first-line investigation of suspected thrombosis in patients with abdominal symptoms. CT features of mesenteric ischemia are thickening of both small and large bowel walls with prominence of the supplying mesenteric vessels. For histopathological confirmation thrombosis should be present without evidence of inflammation in the vessel wall. Cerebral thrombosis can be diagnosed by cerebral angiography, transcranial Doppler technique, or magnetic resonance imaging.⁽¹⁵⁾. In some cases, MRI has revealed small foci of high signal in subcortical white matter scattered throughout the brain⁽¹⁶⁾

4)

Table I. Research criteria for defining the antiphospholipid syndrome. © 2006 International Society on Thrombosis and Haemostasis.

One or more clinical episodes of arterial, venous or small vessel thrombosis

2. Pregnancy morbidity

- (a) One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation
- (b) One or more pre-term births of a morphologically normal neonate before the 34th week of gestation because of: (i) eclampsia or severe pre-eclampsia or (ii) recognized features of placental insufficiency
- (c) Three or more unexplained consecutive spontaneous miscarriages before the 10th week of gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded

Laboratory criteria

1. Lupus anticoagulant (LA) present in plasma, on two or more occasions at least 12 weeks apart
2. Anticardiolipin (aCL) antibody of immunoglobulin (Ig)G and/or IgM isotype in serum or plasma, present in medium or high titre i.e. >40GPL units or MPL units, or > the 99th centile), on two or more occasions, at least 12 weeks apart.
3. Anti-b2-glycoprotein I antibody of IgG and/or IgM isotype in serum or plasma (in titre >the 99th centile), present on two or more occasions at least 12 weeks apart

Antiphospholipid antibody syndrome (APS) is present if at least one of the clinical criteria and one of the laboratory criteria are met

GPL units, IgG antiphospholipid units; MPL units, IgM antiphospholipid units

48^a 2012 Blackwell Publishing Ltd

British Journal of Haematology, 2012, 157, 47–58
Guideline

The Effect of Pregnancy on APS

Pregnancy is a hypercoagulable state and women with APS are at increased risk of thrombosis unless thromboprophylaxis or ticoagulation is adequate. Some studies have demonstrated that a significant proportion of pregnant patients still

Clinical criteria:

1. Vascular thrombosis

have thrombotic episodes despite thromboprophylaxis^[17,18]. Pregnancy can also exacerbate pre-existing thrombocytopenia, and this may be further compounded by medication because aspirin and heparin administered during pregnancy may cause thrombocytopenia.

Thromboprophylaxis, full anticoagulation, and the management of thrombocytopenia in pregnant women with APS are discussed in more detail below.

The Effect of APS on Pregnancy

APS and Early Pregnancy Complications:

Many cases of APS are diagnosed following investigation of recurrent miscarriage.

The association between APS and recurrent miscarriage is well known^[19-22]. With second trimester loss being particularly common⁽²³⁾.

The prospective fetal loss rate in primary APS is reported to be 50% to 75% [24, 25]. In patients with systemic lupus erythematosus (SLE) and secondary APS some studies suggest this may be as high as 90%^[24, 25] although this is likely to be an overestimate. It has been suggested that the risk of fetal loss is directly related to the antibody titer^[26, 27]

but this is certainly not true of all cases. Some studies have shown maternal IgG aCL to be a particularly reliable predictor of miscarriage^[28] outcome. A prospective study. Ann Intern Med 1994;120:470-475.. Although this makes theoretical sense as this subfraction of antibodies can cross into the fetoplacental circulation^[29]. Specific antiphospholipid antibodies (aPL) eluted from placentae of pregnant women with aPL-Positive sera..., many women with recurrent miscarriage have IgM aCL antibodies only.

It is impossible to predict which women will develop complications in pregnancy, and some women with persistently elevated aPL titers and a history of thromboses and/or thrombocytopenia will have no obstetric complications at all. Previous poor pregnancy outcome remains the most important predictor of future risk^[30-31]

APS and Late Pregnancy Complications

In pregnancies that do not end in miscarriage or fetal loss, there is a high incidence of early onset pre-eclampsia (PET)^{.(32-35)}

Underlying disorders associated with severe early onset preeclampsia. and intrauterine growth restriction (IUGR), placental abruption^[36].

Neonatal outcome in women treated for the antiphospholipid syndrome during pregnancy. Because patients with APS form a heterogeneous group, the incidence of these complications varies between units. Indeed it is now clear that the substantial differences in APS patient populations in studies of pregnancy inevitably results in large differences in reported adverse pregnancy outcomes, and whilst attempts are being made to define management in certain subgroups, many recommendations are not strictly evidence based . Those units which manage women with systemic manifestations of APS have a higher incidence of complications in pregnancy^[37]

Outcome of treated pregnancies in women with antiphospholipid syndrome: an update of the Utah experience. Obstet Gynecology whilst those which recruit women predominantly from recurrent miscarriage clinics have a lower incidence of these complications^[38,39]

Pregnancy complications in women with recurrent miscarriage associated with antiphospholipid antibodies treated with low dose

aspirin and heparin(Br J Obstet Gynaecol 1999;106:102-107). It is essential to appreciate these differences in order to critically appraise the literature, advise women appropriately, and rationalize therapy .attention of women with APS who are likely to develop complications in pregnancy remains a challenge. Several studies have recommended uterine artery Doppler waveform analysis in these women.

Therapeutic Options in APS Pregnancies

The most commonly used medications are aspirin, heparin, warfarin, and steroids. A summary of the side-effects of these drugs is shown in Table 2. Pre-conceptual review of medication is useful as it

allows clinicians to place each patient in a risk category and treat her accordingly.

These individualized treatment regimes limit the problems associated with polypharmacy in pregnancy and enable resources to be invested appropriately.

Aspirin

Women with APS are advised to take low-dose aspirin (75 mg daily) in pregnancy.

The rationale for this is aspirin-mediated inhibition of thromboxane, increased vasodilation, and subsequent reduced risk of thromboses in the placenta and elsewhere. Management of Antiphospholipid Syndrome in Pregnancy. Pregnancy outcomes in different populations of women with antiphospholipid syndrome.

where. However, the use of aspirin in APS pregnancies has never been subjected to a randomized trial, although several non-randomized studies suggest it is beneficial^[42,43] that is, no previous thromboses or miscarriages, a randomized controlled trial of aspirin versus no aspirin failed to show any benefit of treatment^[44]. Damage to the developing trophoblast occurs early in pregnancy and therefore if aspirin is used it is likely to be of most benefit if administered from the pre-conceptual period as use of aspirin from the mid-trimester onwards has been shown to be of no benefit in reducing the incidence of adverse pregnancy outcome in high risk groups^[45].

7. Randomized controlled trial using low-dose aspirin in the prevention of pre-eclampsia in women with abnormal uterine artery Doppler at 23 weeks' gestation. Ultrasound Obstet Gynecol 2003;22:233–239..

Treatment is usually continued at least until delivery if not into the puerperium. Low-dose aspirin does not affect the use of regional anesthesia during labor. Renal and hepatic impairment do not occur with this dose of aspirin and bronchospasm is exceptionally rare affecting a minority of asthmatics. There are no adverse fetal or neonatal effects from the use of low-dose aspirin.

Heparin

Women with APS and a previous history of thromboembolism are treated with heparin as thromboprophylaxis in pregnancy. For those with recurrent pregnancy loss or previous adverse pregnancy outcome but without a history of thromboembolism, there is as yet no consensus of opinion. Which patients with antiphospholipid antibody should be treated and how? Rheum Dis Clin N Am 1993;19:235–247.. Some studies have suggested that heparin therapy in addition to aspirin may contribute to improved fetal outcome^[46].

Repeated fetal losses associated with antiphospholipid antibodies: a collaborative randomised trial comparing prednisolone with low-dose heparin treatment. Am J Obstet Gynecol 1992;166:1318–1323.. One group has shown improved fetal outcome using heparin^[47] LMWH alone^[48]. Efficacy and safety of nadroparin in the treatment of pregnant women with antiphospholipid syndrome. Lupus 2004. In press.. Most specialist units caring for pregnant women with APS use aspirin and low-molecular-weight heparin (LMWH) together in women with a history of thrombosis or second trimester loss, and there is some evidence of improved pregnancy outcome with the use of heparin in women with recurrent first trimester loss^[49].

Randomised controlled trial of aspirin and aspirin plus heparin in pregnant women with recurrent miscarriage associated with phospholipid antibodies (or antiphospholipid antibodies). Br Med J 1997;314:253–257., although not all studies have shown a benefit in this subgroup^[50]. Those women who wish to take LMWH during pregnancy for fetal indications, for example, recurrent miscarriage, previous intrauterine death, pre-eclampsia, or fetal growth restriction, usually receive once daily thromboprophylactic doses. However, those with previous thromboses are often given high dose

thromboprophylaxis in the form of twice daily administration (e.g., Enoxaparin 40 mg SC b.i.d.) to minimize the risk of recurrent thromboses during pregnancy which might necessitate

treatment with either therapeutic doses of LMWH or oral anticoagulation with warfarin. Whether LMWH is being administered for fetal or maternal indications or both, the potential benefits of treatment should be balanced against the risk of heparin-induced osteoporosis^[51-53]

is compounded by concomitant use of steroid medication, and indeed by pregnancy itself^[54-56]. LMWHs are commonly used in APS patients because of the convenience of once daily administration (in most cases), the improved antithrombotic (aXa) to anticoagulant (aIIa) ratio, the decreased risk of heparin-induced thrombocytopenia, and the probable decreased risk of heparin-induced osteoporosis^[57]. However, there have been small case series reporting osteoporotic fractures with LMWH administered in therapeutic doses, Byrd LM, Johnston TA, Shiach C, Hay CRM. Osteopenic fractures and low molecular weight heparin in pregnancy. *J Obstet Gynaecol* 2004;24:S11.. Systematic review of all studies of LMWH use in pregnancy confirms a very low (0.09%) risk of osteoporosis^[58].

Although Factor Xa levels may be used to monitor LMWH⁽⁵⁹⁾ Thromboprophylaxis with low molecular weight heparin (Fragmin) in high risk pregnancies. *Thromb Haemost* 1997;77:39–43., experience has shown that doses are virtually never altered as a result, and therefore it is not necessary to measure Factor Xa levels routinely. Thromboprophylaxis with unmonitored intermediate-dose low molecular weight heparin in pregnancies with a previous arterial or venous thrombotic event. *Blood Coagul Fibrinolysis* 2003;14:735–739.. LMWH administration is omitted at least 12 hours prior to elective delivery, but in caseurgent delivery is necessary, reversal with protamine sulphate is possible. The molecular weight of unfractionated heparin ranges from 12–15 kDa and that of LMWH from 4–5 kDa therefore neither preparation is able to cross the placenta. Heparin is not excreted into breast milk^[60]

Warfarin

When there has been a thrombotic event in the index pregnancy despite heparin thromboprophylaxis, or in women with a history of previous cerebrovascular thromboses, the risk of recurrence is sufficiently high to consider antenatal administration of warfarin^[59] Thromboprophylaxis in antiphospholipid syndrome pregnancies with previous cerebral arterial thrombotic events: is warfarin preferable? *Thromb Haemost* 1998;79:1060–1061.. In practice the use of warfarin is avoided in the first trimester unless a woman develops transient ischemic attacks or other thrombotic events at that time. This is because, unlike heparin, warfarin does cross the placenta and is potentially teratogenic producing a typical embryopathy characterized by nasal hypoplasia, stippled epiphyses, rhizomelia (short proximal limbs), digital dysplasia, eye abnormalities, and developmental delay^[61]

The exact incidence of these anomalies is unknown largely due to case-reporting bias. Review of the literature suggests that it is between 2% to 4%^[62]

but there appears to be a dose dependent incidence of complications with a higher number of complications in pregnant women receiving more than 5 mg per day^[63,64]

Patients require close supervision and regular INR estimates maintaining values between 2.0–2.5. It must be remembered that the maternal INR does not accurately reflect the fetal coagulation status and animal studies show that the risk of fetal intravascular hemorrhage is still present despite optimum maternal control^[28]. Howe AM, Webster WS. Exposure of the pregnant rat to warfarin and vitamin K1: an animal model of intraventricular hemorrhage in the fetus. *Teratology* 1990;42:413–420.. The fetus is therefore at risk throughout pregnancy during the period of warfarin administration. A fortnight before planned delivery, warfarin is discontinued and either an intravenous infusion of unfractionated heparin or therapeutic doses of

subcutaneous LMWH is commenced. This allows sufficient time for clearance of warfarin by both mother and fetus to occur. Every attempt should be made to avoid rapid reversal of warfarin. Management of Antiphospholipid Syndrome in Pregnancy Warfarin anticoagulation with vitamin K at the time of delivery as this makes subsequent anticoagulation in the post-natal period difficult. There is no evidence to suggest that fetal outcome is improved with the use of warfarin. There is no significant excretion of warfarin into breast milk. Steroids

In the past, high dose steroids (greater than or equal to 60 mg daily) were used to suppress lupus anticoagulant (LA) and anticardiolipin antibodies (aCL) and some studies reported improved fetal survival^[65]

However, these therapeutic regimes resulted in considerable maternal morbidity including gestational diabetes, hypertension, and sepsis, and subsequent studies failed to show an improvement in pregnancy outcome. Lockshin MD, Druzin ML, Qamar T. Prednisolone does not prevent recurrent fetal death in women with antiphospholipid antibody. Am J Obstet Gynaecol 1989;160:439–443.. Cowchock et al demonstrated that aspirin and heparin gave equivalent fetal outcomes when compared with aspirin and steroids with significantly less maternal morbidity, and more recently there have been suggestions that steroid use may be detrimental to fetal outcome by promoting preterm delivery^[66]. Therefore the use of steroids in APS pregnancies has been abandoned except for the treatment of maternal thrombocytopenia or co-existent SLE for which prednisolone is still first line therapy. Regular blood glucose monitoring is required with long-term administration of steroids. Patients requiring more than 7.5 mg prednisolone daily for more than 2 weeks prior to delivery should be given intra-partum intravenous hydrocortisone 100 mg t.i.d.. Breastfeeding is rarely contraindicated, although women taking greater than 60 mg prednisolone with healthy term babies may consider bottle-feeding because of the

theoretical risk of neonatal hypothalamic–pituitary adrenal suppression at these high doses.

Others Immunosuppression with azathioprine, intravenous immunoglobulin^[67-69] plasma exchange . Fulcher D, Stewart G, Exne T, Trudinger B, Jeremy R. Plasma exchange and the anticardiolipin syndrome

in pregnancy. Lancet 1989;ii:171., and interleukin-3 therapy^[70] have all been tried in APS pregnancies. Due to the cost of immunoglobulin therapy, this treatment has previously been limited to salvage therapy in women who develop complications despite treatment with aspirin and heparin^[36]. Gordon C, Kilby MD. Use of intravenous immunoglobulin therapy in pregnancy in systemic lupus erythematosus and antiphospholipid antibody syndrome. Lupus 1998;7:429–433.. Initial reports using a 2 g/kg course of intravenous immunoglobulin administered in divided doses over 2–5 days in the second or early third trimester in pregnancies complicated by IUGR suggested a temporary improvement in uteroplacental Doppler waveforms^[71]

More recently,a randomized controlled trial of intravenous immunoglobulin versus aspirin and heparin in 40 women with APS associated recurrent miscarriage showed a live birth rate of only 57% in the immunoglobulin group compared with 84% in the aspirin and heparin group^[72] heparin plus aspirin versus intravenous immunoglobulin in the treatment of recurrent pregnancyloss Thus, although initially promising, immunoglobulin therapy does not appear to be beneficial in APS pregnancies.

Summary

Pregnant women with APS are at risk of complications at all stages of pregnancy.

They require specialist care and a team approach involving obstetricians, obstetric physicians, rheumatologists, hematologists, neonatologists, and specialist midwives.

Close monitoring of the various aspects of the condition may reduce maternal morbidity and

improve fetal outcome. Therapeutic options include aspirin, LMWH, and, less commonly, warfarin and steroids.

The pathogenesis of the adverse pregnancy outcome in APS has not yet been fully elucidated although there is active research in this field. Until this is ascertained, we must accept that many aspects of management are purely empirical and it is our duty to counsel women thoroughly such that they understand the risks and benefits of the treatment options they are offered.

Abbreviations

aCL - anticardiolipin antibodies

aPL - antiphospholipid antibodies

APS - antiphospholipid syndrome

CAPS Registry - Catastrophic Antiphospholipid Syndrome Registry

CNS - central nervous system

DIC - disseminated intravascular coagulation

HELLP - haemolysis, elevated liver enzymes, low platelets

LA - lupus anticoagulant

TMA - thrombotic microangiopathy

TPP - thrombotic thrombocytopenic purpura

References

1. de LB, Mertens K, de Groot PG. Mechanisms of disease: antiphospholipid antibodies from clinical association to pathologic mechanism. *Nat Clin Pract Rheumatol* 2008 Apr;4(4):192-9.
2. Branch DW, Khamashta MA. Antiphospholipid syndrome: obstetric diagnosis, management, and controversies. *Obstet Gynecol* 2003 Jun;101(6):1333-44.
3. Ahmed K, Darakhshan A, Au E, Khamashta MA, Katsoulis IE. Postpartum spontaneous colonic perforation due to antiphospholipid syndrome. *World J Gastroenterol* 2009 Jan 28;15(4):502-5.
4. Carp HJ. Antiphospholipid syndrome in pregnancy. *Curr Opin Obstet Gynecol* 2004 Apr;16(2):129-35.
5. do Prado AD, Piovesan DM, Staub HL, Horta BL. Association of anticardiolipin antibodies with preeclampsia: a systematic review and meta-analysis. *Obstet & Gynecol* 2010 Dec;116(6):1433-43.
6. Tincani A, Andreoli L, Chighizola C, Meroni PL. The interplay between the antiphospholipid syndrome and systemic lupus erythematosus. *Autoimmunity* 2009 May;42(4):257-9
7. Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, Cervera R, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J Thromb Haemost* 2006 Feb;4(2):295-306.)
8. Cohen D, Berger SP, Steup-Beekman GM, Bloemenkamp KW, Bajema IM. Diagnosis and management of the antiphospholipid syndrome. *BMJ* 2010;340:c2541.
9. Cervera R, Piette J C, Font J, Khamashta M A, Shoenfeld Y, Camps M T. et al Antiphospholipid syndrome: clinical and immunologic manifestations and patterns of disease expression in a cohort of 1000 patients. *Arthritis Rheum* 2002 461019-1027.1027 [PubMed]
10. Cervera R, Balasch J. The management of pregnant patients with antiphospholipid syndrome. *Lupus* 2004;13:683-687.687 [PubMed]
11. Branch D W, Khamashta M A. Antiphospholipid syndrome: obstetric diagnosis, management, and controversies. *Obstet Gynecol* 2003;101:1333-1344.1344 [PubMed]
12. Carmona F, Balasch J. Fetal and obstetric manifestations and infertility in the antiphospholipid syndrome. In: Asherson RA, Cervera R, Piette, Shoenfeld Y, eds. *The antiphospholipide syndrome II: autoimmune thrombosis* Amsterdam: Elsevier, 2000:205-211.211

- Asherson R A. The catastrophic antiphospholipid syndrome. *J Rheumatol* 1992;19:508–512.512 [PubMed]
13. Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, Cervera R, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J Thromb Haemost* 2006 Feb;4(2):295-306
14. Si-Hoe CK, Thng CH, Chee SG, Teo EK, Chng HH. Abdominal computed tomography in systemic lupus erythematosus. *Clin Radiol* 1997 Apr;52(4):284-9.
15. Brey RL. Antiphospholipid antibodies in young adults with stroke. *J Thromb Thrombolysis* 2005 Oct;20(2):105-1218] Raval M, Paul A. Cerebral Venous Thrombosis and Venous Infarction: Case Report of a Rare Initial Presentation of Smoker's Polycythemia. *Case Rep Neurol* 2010;2(3):150-6
16. Csepany T, Bereczki D, Kollar J, Sikula J, Kiss E, Csiba L. MRI findings in central nervous system systemic lupus erythematosus are associated with immunoserological parameters and hypertension. *J Neurol* 2003 Nov; 250(11):1348-54..
17. Ringrose DK. Anaesthesia and antiphospholipid syndrome – a review of 20 patients. *Int J Obstet Anaesth* 1997;6: 107–111.
18. Levine JS, Branch DW, Rauch J. The antiphospholipid syndrome. *N Engl J Med* 2002;346:752–763.
19. Julkunen H. Pregnancy in systemic lupus erythematosus. Contraception, fetal outcome and congenital heart block. *Acta Obst Gynecol Scand* 1994;73:517–520.
20. MacLean M, Cumming G, McCall F, Walker I, Walker J. The prevalence of lupus anticoagulant and anticardiolipin antibodies in women with a history of first trimester miscarriages. *Br J Obstet Gynaecol* 1994;101:103–106.
21. Silver RM, Branch DW. Recurrent miscarriage: autoimmune considerations. *Clin Obstet Gynaecol* 1994;37:745–760.
22. Rai RS, Clifford K, Cohen H, Regan L. High prospective fetal loss rate in untreated pregnancies of women with recurrent miscarriage and antiphospholipid antibodies. *Hum Reprod* 1995;10:3301–3304.,
23. Lockwood CJ, Romero R, Feinberg RF, Clyne LP, Coster B, Hobbins JC. The prevalence and biologic significance of lupus anticoagulant and anticardiolipin in a general obstetric population. *Am J Obstet Gynecol* 1989;161:369–373.
24. Perez MC, Wilson WA, Brown HL, Scopelitis E. Anti-cardiolipin antibodies in unselected pregnant women in relationship to fetal outcome. *J Perinatol* 1991;11:33–36
25. Branch DW, Scott JR, Kochenour NK. Obstetric complications associated with lupus anticoagulant. *N Engl J Med* 1985;313:1322–1326.
26. Lubbe WF, Butler WS, Palmer SJ, Liggins GC. Fetal survival after prednisolone suppression of maternal lupus anticoagulant. *Lancet* 1983;i:1361–1363.,
27. Harris EN, Chan JK, Asherson RA, Aber VR, Gharavi AE, Hughes GRV. Thrombosis, recurrent fetal loss and thrombocytopenia. Predictive value of the anticardiolipin antibody test. *Arch Intern Med* 1986;146:2153–2156.
28. Reece EA, Garofalo J, Zheng XZ, Assimakopoulos E. Pregnancy outcome – influence of antiphospholipid antibody titer, prior pregnancy loss and treatment. *J Reprod Med* 1997;42:49–55.,
29. Lynch A, Marlar R, Murphy J, et al. Antiphospholipid antibodies in predicting adverse pregnancy outcome. A prospective study. *Ann Intern Med* 1994;120:470–475..

30. Katano K, Aoki K, Ogasawara M, et al. Specific ntiphospholipid antibodies (aPL) eluted from placentae of pregnant women with aPL-positive sera. *Lupus* 1995;4:304–308..
31. Buchanan NMM, Khamashta MA, Morton KE, Kerslake S, Baguley E, Hughes GRV. A study of 100 high risk lupus pregnancies. *Am J Rep Immunol* 1992;28:192–194.
32. Ramsey-Goldman R, Mientus JM, Kutzer JE, Mulvihill JJ, Medsger JTA. Pregnancy outcome in women with systemic lupus erythematosus treated with immune-suppressive drugs. *J Rheumatol* 1993;20:1152–1157..
33. Branch DW, Andres R, Digre KB, Rote NS, Scott JR. The association of antiphospholipid antibodies with severe pre-eclampsia. *Obstet Gynecol* 1988;73:541–545.
34. Moodley J, Bhoola V, Duursma J, Pudifin D, Byrne S, Kenoyer DG. The association of antiphospholipid antibodies with severe early-onset pre-eclampsia. *South African Med J* 1995;85:105–107.
35. Yasuda M, Takakuwa K, Tanaka K. Studies on the association between the anticardiolipin antibody and pre-eclampsia. *Acta Med Biol* 1994;42:145–149.
36. Dekker GA, de Vries JIP, Doelitzsch PM, et al. Underlying disorders associated with severe earlyonset preeclampsia. *Am J Obstet Gynecol* 1995;173:1042–1048
37. Birdsall MA, Pattison NS, Chamley L. Antiphospholipid antibodies in pregnancy. *Aust N Z J Obstet Gynecol* 1992;32:328–330., and premature delivery [29, 30] 47. Kelly T, Whittle MJ, Smith DJ, Ryan G. Lupus anticoagulant and pregnancy. *J Obstet Gynecol* 1996;16:26–31.
38. Botet F, Romera G, Montagut P, Carmona F, Balasch J. Neonatal outcome in women treated for the antiphospholipid syndrome during pregnancy. *J Perinat Med* 1997;25:192–196..
39. Branch DW, Silver RM, Blackwell JL, Reading JC, Scott JR. Outcome of treated pregnancies in women with antiphospholipid syndrome: an update of the Utah experience. *Obstet Gynecol* 1992;80:614–620..
40. Granger KA, Farquharson RG. Obstetric outcome in antiphospholipid syndrome. *Lupus* 1997;6:509–513.
41. Backos M, Rai R, Baxter N, Chilcott I T, Cohen H, Regan L. Pregnancy complications in women with recurrent miscarriage associated with antiphospholipid antibodies treated with low dose aspirin and heparin. *Br J Obstet Gynaecol* 1999;106:102–107..
42. Cowchock FS. Autoantibodies and pregnancy loss. *N Engl J Med* 1997;337:197–198..
43. Empsom M, Lassere M, Craig JC, Scott JR. Recurrent pregnancy loss with antiphospholipid antibody:a systematic review of therapeutic trials. *Obstet Gynecol* 2002;99:135–144..
44. Silver R, MacGregor SN, Sholl JS, Hobart JM, Neerhof MG, Ragin A. Comparative trial of prednisolone plus aspirin versus aspirin alone in the treatment of anticardiolipin antibody positiveobstetric patients. *Am J Obstet Gynecol* 1993;169:1411–1417.
45. Balasch J, Carmona F, Lopez-Soto A, et al owchock S, Reece EA. Do low-risk pregnant women with antiphospholipid antibodies need to be treated? *Am J Obstet Gynecol* 1997;176:1099–1100..
46. Yu CK, Papageorghiou AT, Parra M, Palma Dias R, Nicolaides KH. Randomized controlled trialusing low-dose aspirin in the prevention of pre-eclampsia in women with abnormal uterine artery Doppler at 23 weeks' gestation.

- Ultrasound Obstet Gynecol 2003;22:233–239.
47. Cowchock FS, Reece EA, Balaban D, Branch DW, Plouffe L. Repeated fetal losses associated with antiphospholipid antibodies: a collaborative randomised trial comparing prednisolone with low dose heparin treatment. *Am J Obstet Gynecol* 1992;166:1318–1323..
48. Ruffati A, Orsini A, Di Lenardo L, et al
49. Kutteh WH. Antiphospholipid antibody-associated recurrent pregnancy loss—treatment with heparin and low-dose aspirin is superior to low-dose aspirin alone. *Am J Obstet Gynecol* 1996;174:1584–1589.
50. Rai R, Cohen H, Dave M, Regan L. Randomised controlled trial of aspirin and aspirin plus heparin in pregnant women with recurrent miscarriage associated with phospholipid antibodies (or antiphospholipid antibodies). *Br Med J* 1997; 314:253–257., although not all studies have shown a benefit in this subgroup
51. Farquharson RG, Quenby S, Greaves M. Antiphospholipid syndrome in pregnancy: a randomized, controlled trial of treatment. *Obstet Gynecol* 2002;100:408–413.
52. de Swiet M, Ward PD, Fidler J, et al. Prolonged heparin therapy in pregnancy causes bone demineralization. *Br J Obstet Gynaecol* 1983;90:1129–1134.
53. Dahlman TC. Osteoporotic fractures and the recurrence of thromboembolism during pregnancy and the puerperium in 184 women undergoing thromboprophylaxis with heparin. *Am J Obstet Gynecol* 1993;168:1265–1270.
54. Nelson-Piercy C, Letsky E, de Swiet M. Low molecular weight heparin for obstetric thromboprophylaxis: experience of 69 pregnancies in 61 high risk women. *Am J Obstet Gynecol* 1997;176:1062–1068..
55. Smith R, Stevenson JC, Winearls CG, Woods CG, Wordsworth BP. Osteoporosis of pregnancy. *Lancet* 1985;1:1178–1180.
56. Khastgir G, Studd J. Pregnancy-associated osteoporosis. *Br J Obstet Gynaecol* 1994;101:836–838.
57. Smith R, Athanasou NA, Ostlere SJ, Vipond SE. Pregnancy-associated osteoporosis. *QJM* 1995;88:865–878..
58. Nelson-Piercy C. Heparin-induced osteoporosis in pregnancy. *Lupus* 1997;6:500–504.
59. Greer IA, Nelson-Piercy C. Systematic review of safety and efficacy of LMWH in pregnancy. *Br J Obstet Gynaecol* 2004. In press.. Although Factor Xa levels may be used to monitor LMWH [67] 67. Hunt BJ, Doughty H, Majumdar G, et al.
60. Hunt BJ, Khamashta MA, Lakasing L, Williams F, Nelson-Piercy C, Hughes GRV. Thromboprophylaxis in antiphospholipid syndrome pregnancies with previous cerebral arterial thrombotic events: is warfarin preferable? *Thromb Haemost* 1998;79:1060–1061..
61. Nelson-Piercy C. Low molecular weight heparin for obstetric thromboprophylaxis. *Br J Obstet Gynaecol* 1994;101:6–8..
62. Shaul WL, Hall JG. Multiple congenital anomalies associated with oral anticoagulants. *Am J Obstet Gynecol* 1977;127:191–198..
63. Ginsberg JS, Hirsh J, Turner DC, Levine MN, Burrows R. Risks to the fetus of anticoagulant therapy during pregnancy. *Thromb Haemost* 1989;61:197–203..
64. Vitale N, Feo M, De Santo LS, Pollice A, Tedesco N, Cotrufo M. Dose-dependent fetal complications of warfarin in pregnant women with mechanical heart valves. *J Am Coll Cardiol* 1999;33:1637–1641.
65. Cotrufo M, De Feo M, De Santo LS, et al. Risk of warfarin during pregnancy with mechanical valve prostheses. *Obstet Gynecol* 2002;99:35–40..

66. Kwak JYH, Barini R, Gilman-Sachs A, Beaman KD, Beer AE. Down-regulation of maternal antiphospholipid antibodies during early pregnancy and pregnancy outcome. *Am J Obstet Gynecol* 1994; 171:239–246.
67. Laskin CA, Bombardier C, Hannah ME, et al. Prednisolone and aspirin in women with autoantibodies and unexplained recurrent fetal loss. *N Engl J Med* 1997;337:148–153..
68. Spinnato JA, Clark AL, Pierangeli SS, Harris EN. Intravenous immunoglobulin therapy for the antiphospholipid syndrome in pregnancy. *Am J Obstet Gynecol* 1995;172:690–694.
69. Kaaja R, Julkunen H, Ammala P, Palouso T, Kurki P. Intravenous immunoglobulin treatment of pregnant patients with recurrent pregnancy losses associated with antiphospholipid antibodies. *Acta Obstet Gynaecol Scand* 1993;72:63–66.
70. Arnout J, Spitz B, Wittevrongel C, Vanrusselt M, Van Assche A, Vermeylen J. High-dose intravenous immunoglobulin in a pregnant patient with antiphospholipid syndrome: immunological changes associated with a successful outcome. *Thromb Haemost* 1994;71:741–747
71. Fishman P, Falach Vaknine E, Zigelman R, et al. Prevention of fetal loss in experimental antiphospholipid syndrome by in vivo administration of recombinant interleukin-3. *J Clin Invest* 1993;21:1834–1837.
72. Gordon C, Kilby MD. Use of intravenous immunoglobulin therapy in pregnancy in systemic lupus erythematosus and antiphospholipid antibody syndrome. *Lupus* 1998;7:429–433.
73. Triolo G, Ferrante A, Ciccia F, et al.