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The Management of Antiphospholipid Antibodies Affected Pregnancy

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1. Introduction

Antiphospholipid antibody (aPL) is a heterogeneous group of autoantibodies directed against phospholipids-binding proteins. Antiphospholipid syndrome (APS) is defined by two major components: 1) presence of at least one type of aPLs, 2) the occurrence of at least one clinical feature from a list of potential disease manifestations, the most common of which are categorized as venous or arterial thromboses, and pregnancy complications. The pregnancy complications include recurrent spontaneous abortion (RSA), unexplained fetal death, severe pre-eclampsia, fetal growth restriction (FGR), and premature delivery. International consensus conferences have proposed and revised classification criteria for definite APS. Two types of aPLs were originally included in the laboratory criteria: IgG and IgM anticardiolipin antibody (aCL); and lupus anticoagulant (LA) (1). After that, IgG and IgM anti-β2 glycoprotein-I antibody (aβ2GPI) were included as laboratory criteria (2). However, scant evidence exists in regard to a relationship between the aPL profile and serious adverse pregnancy outcome.

With the widespread use of tests to detect aPLs, obstetricians often encounter pregnant or non-pregnant women who have positive aPL tests. Currently, a variety of aPLs in the human blood can be measured by laboratory systems, each of which requires evaluation in regard to whether an association with pregnancy complications exists. This review focused on risks of pregnancy complications and therapeutic modality in women with aPLs.

2. Antiphospholipid antibody and pregnancy complications

The detrimental effects of aPLs are attributed to pathological mechanisms including thrombotic changes, suppression of hCG release (3), induction of complement activation and placental injury (4), and a direct effect on trophoblast cell growth and differentiation (5). Live-birth rates in women with aPLs (range 62–84%) are found to be lower than those in women without aPLs (range 90–98%) (6-9).

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Many studies indicated that aPLs cause thromboembolism and mid-trimester fetal death; and probably RSA. However, the association between aPLs and risks of pregnancy-induced hypertension (PIH), pre-eclampsia, FGR, or premature delivery (PD) still remains controversial. In retrospective case-control studies, it was found that women with a history of severe pre-eclampsia or hemolysis-elevated liver enzymes-low platelets (HELLP) syndrome frequently tested positive for LA and aCL (10,11). However, prospective studies assessing associations between aPLs and PIH, pre-eclampsia or other pregnancy complications found conflicting results. Studies conducted in the 1990s noted that pre-eclampsia was associated with the presence of LA (6), aCL (6, 9), β_2–glycoprotein I dependent aCL (aCLβ_2GPI) (12) and aβ_2GPI (13). Similarly, fetal loss and FGR were associated with the presence of aCL (9, 12). Later prospective studies, however, denied the association between pre-eclampsia and the presence of LA (14), aCL (14-16) or aβ_2GPI (16). PIH (17) and HELLP syndrome (16) were not associated with the presence of aCL or aβ_2GPI.

Our group have assessed whether aPLs measurements during early pregnancy are useful for predicting pregnancy complications (18). The aPLs including LA, IgG, IgM, IgA aCL, IgG, IgM phosphatidylserine dependent antiprothrombin antibody (aPS/PT), and IgG kininogen dependent antiphosphatidylethanolamine antibody (aPE) were measured during the first trimester in a consecutive series of 1,155 women. We for the first time determined predictive risks of pregnancy complications, being adjusted with the life style-related confounding factors such as maternal age, parity, BMI, smoking and drinking. IgG aCL was asssociated with PIH; IgG aPE with PIH, severe PIH and PD; LA with PD and low birth weight (Table 1). Additionally, we found that multi-positive or double-positive aPLs (LA and aCL), were risk factor for severe PIH, PD and low birth weight. This is the first evidence in regard to the association between the multi/double-positive aPLs and severe PIH. Recent studies have also suggested that the multi-positive test is associated with a more severe course of APS disease, increasing significantly the rate of thrombosis (16, 19-21). Pregnant women with multi / double-positive aPLs should be more carefully managed during pregnancy.

The abovementioned study for the first time demonstrated IgG aPE was associated with PIH (18). aPE was frequently detected in patients with unexplained recurrent early fetal loss, mid-to-late fetal loss, unexplained thrombosis, systemic lupus erythematosus, heart valvulopathies and livedo reticularis (22-26). Sugi *et al.* measured the kininogen dependent aPE that probably binds to kininogen as a cofactor (27). The kallikrein-kinin system is involved in the blood pressure control and angiogenesis. Tissue kallikrein cleaves low-molecular-weight kininogen substrate to produce the vasodilator Lys-bradykinin, whereas plasma kallikrein forms bradykinin (BK) from high-molecular-weight kininogen (HMWK). Kininogen-deficient rats are susceptible to the development of salt-induced hypertension (28), and the *in vivo* angiogenesis is suppressed (29). The proangiogenic effect of BK and HMWK has been demonstrated in both *in vitro* and *in vivo* studies (30). Therefore, we assume that aPE pathophysiologically causes impairment of fetoplacental angiogenesis and vessel development, which subsequently may predispose women to PIH. Alternatively, disruption of kininogen cascade in the kallikrein-kinin system may reduce vasodilator production and cause a hypertensive disorder. A recent multicenter study demonstrated that aPE, but not LA or aCL, was closely associated with thrombosis with the highest odds ratio (31). The thrombotic insult may be causally associated with PIH.

Pregnancy complication	Antiphospholipid antibody	Odds ratio	95% CI
PIH	IgG aCL	11.4	2.7-48
	IgG aPE	8.3	2.4-29
Severe PIH	IgG aPE	20.4	4.5-91
	Multi-positive	143	9.8-1000
	Double-positive (LA and aCL)	250	11.1-1000
Premature delivery (<37 weeks)	LA	11.0	2.8-44
	Multi-positive	11.6	1.5-91
	Double-positive (LA and aCL)	22.2	1.9-250
Premature delivery (<34 weeks)	IgG aPE	12.7	3.1-50.0
Low birth weight	LA	8.0	2.1-31
	Double-positive (LA and aCL)	13.7	1.2-167

PIH, pregnancy induced hypertension; aCL, anticardiolipin antibody; aPE, kininogen dependent antiphosphatidylethanolamine antibody; LA, lupus anticoagulant;

Table 1. Antiphospholipid antibodies as risk factors for pregnancy complications determined by multivariate analysis

Subsequently, whether IgG, IgM aβ2GPI was associated with the development of PIH or pre-eclampsia, we evaluated in the case-control study in cohort (32). The case group comprises 36 patients who developed PIH during their pregnancies. Normal ranges of IgG (<2.2 Unit/ml) and IgM (<6.0 Unit/ml) aβ2GPI values with cut-off values of 99th percentile have been established using non-pregnant 132 healthy controls. The cut-off values of IgG (normal <1.0 Unit/ml) and IgM (normal <1.2 Unit/ml) aβ2GPI were established from the most appropriate values dividing pregnant subjects in this study. It was found that titers of IgG aβ2GPI ≥1.0 Unit/ml represent a risk factor for severe PIH (P=0.023, OR 5.7 95%CI 1.4-23). In addition, titers of IgM aβ2GPI ≥1.2 Unit/ml were found to be a risk factor for PIH (P=0.001, OR 8.8 95%CI 1.6-47.5). These results support the utility of aβ2GPI determination as one of the laboratory criteria for APS classification.

There is a large body of evidence for an involvement of aβ2GPI in hypercoagulation status and thrombosis. (33-38). A multivariate analysis in a multicenter study has demonstrated that aβ2GPI and aPE, but not LA or aCL, were significantly associated with thrombosis (31). aβ2GPI induce the activation of endothelial cells, resulting in a proinflammatory state which favours the prothrombotic diathesis (39). Recently, a study has demonstrated β2GPI naturally inhibits von Willebrand factor (VWF)-dependent platelet adhesion and aggregation. aβ2GPI of APS patients neutralized the β2GPI-VWF interactions, contributing to hypercoagulation status in these patients (40). It is likely that the thrombotic insult of aβ2GPI to placental angiogenesis or circulation is causally associated with PIH. Additionally, β2GPI binds to trophoblast cells (41). The antibody binding to β2GPI downregulates trophoblast chorionic gonadotropin synthesis and secretion (42). Such a direct effect to trophoblast cells may contribute to inhibition of trophoblast invasiveness and defective placentation (41), causing PIH.

3. Antiphospholipid antibody and recurrent spontaneous abortion

The mechanism of fetal loss is believed to be due to binding of aPLs to trophoblast cells, resulting in defective placentation.(43) Thromboembolic events in the uteroplacental circulation have also been proposed as a contributing mechanism(44). Jane *et al.* shown that complement activation plays an essential and causative role in pregnancy loss, and that blocking activation of the complement cascade rescues pregnancies using a mouse model of APS induced by passive transfer of human aPL (45).

It remained uncertain whether any combination of aPL screening in women with RSA is clinically valid. Our group determined the prevalence of a variety of aPLs, with and without a combination of measurements, present in 114 women who had a history of two or more spontaneous abortions (Table 2). aPLs measured included LA, aCLß2GPI, aCL, aPS/PT and aPE. The most frequent type of aPL was IgG aPE (20.2%), followed by IgG aCL and then IgG aCLß2GPI. The standard combinations of aPL measurements upon RSA screening may be LA plus IgG, IgM aCLß2GPI, and LA plus IgG, IgM aCL. Using these standard combinations as definition, 2.6% and 4.4% of women with RSA could be diagnosed as having aPL. When IgA aCLß2GPI, IgA aCL and IgG, IgM aPS/PT were combined with the standard aPL measurements for RSA screening, positive frequencies of aPL reached 7.0%. If IgG, IgM aPE were additionally included, positive frequencies of aPL increased remarkably to 26.3% among women with RSA.

Antiphospholipid antibody	Prevalence (%)	Mid-trimester (≥14 weeks) fetal losses	
		Yes (n =15)	No (n = 99)
LA	1.8	13.3[a]	0[a]
IgG/IgM/IgA aCLβ2GPI	2.6/0.9/1.8	13.3[b]/6.7/13.3[c]	1.0[b]/0/0[c]
IgG/IgM/IgA aCL	4.4/0.9/4.4	20.0[d]/6.7/13.3	2.0[d]/0/3.0
IgG/IgM aPS/PT	1.8/0	13.3[e]/0	0[e]/0
IgG/IgM aPE	20.2/2.6	6.7/0	22.2/3.0
Combined measurements			
LA or aCLβ2GPI	2.6	13.3[f]	1.0[f]
LA or aCL	4.4	20.0[g]	2.0[g]
LA, aCLβ2GPI, aCL or aPS/PT	7.0	20.0	5.1
All aPLs measurement	26.3	20.0	27.3

aCL, anticardiolipin antibody; aCLβ2GPI, anticardiolipin β2-glyciprotein I antibody; aPS/PT, antiphosphatidylserine prothombin antibody; aPE, antiphosphatidylethanolamine antibody; LA, lupus anticoagulant. [a,b,c,d,e,f,g] $P<.05$

Table 2. Prevalence of antiphospholipid antibodies in women with recurrent spontaneous abortion

The prevalence of each aPL and the combinations of aPLs was compared between women with RSA who had experienced at least one mid-trimester fetal loss and those who did not. As a result, RSA women with mid-trimester fetal losses yielded a significantly higher prevalence of LA, IgG, IgA aCLß2GPI, IgG aCL, and IgG aPS/PT, but not aPE, as compared with women with early RSA. Thus, it was confirmed that mid-trimester fetal losses were associated with the presence of LA, aCLß2GPI, aCL, and aPS/PT in women with RSA (Table 2). The information provided here constituted a beneficial reference for clinical practice in the area of infertility.

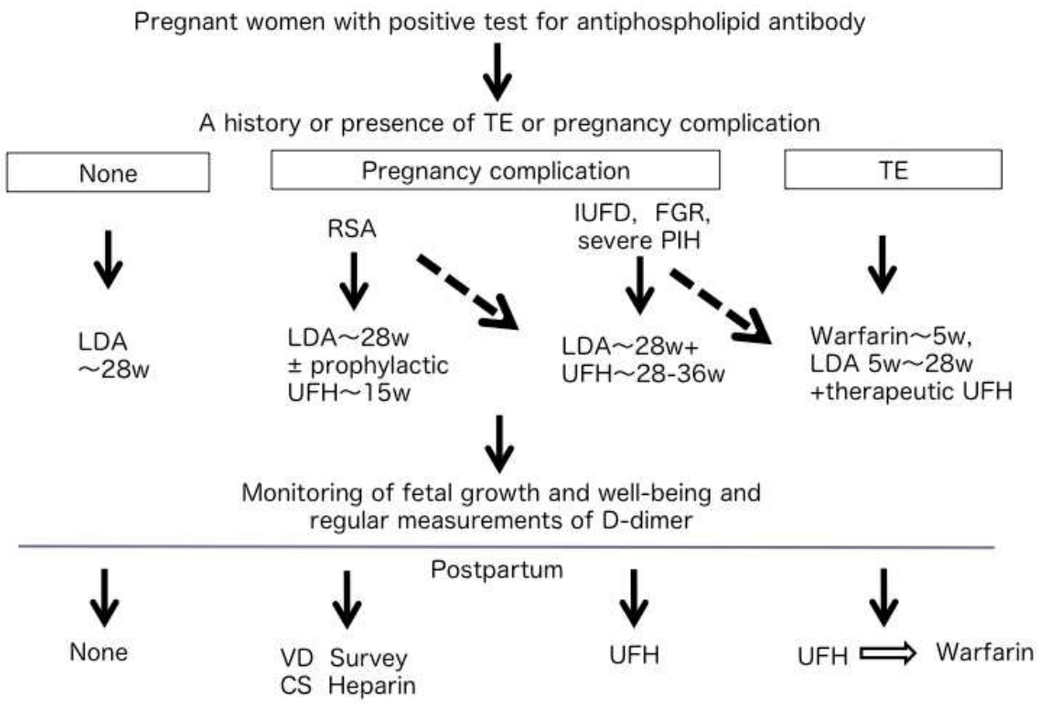
4. Management and therapy for women with antiphospholipid antibody

The management of pregnancy in women with APS has been a subject of much debate, antiplatelet and anticoagulation therapies are usually recommended. A randomized controlled study demonstrated high live birth rate (71%) with low dose aspirin (LDA) plus unfractionated heparin (UFH) as compared with 42% with LDA alone in APS women (46). The LDA plus UFH had fewer maternal adverse effects, and was found to be superior to LDA plus steroids (47). American College of Chest Physicians guidelines recommend LDA in combination with prophylactic or intermediate-dose of UFH, or prophylactic dose of low molecular weight heparin (LMWH) for RSA women with aPL during their pregnancy (48).

Figure 1 shows an algorithm used in the Kobe University Hospital for the management and treatment of pregnant women with positive test of aPLs (LA, aCL, aβ2GPI, or aCLβ2GPI). Treatment modalities are classified by a history or presence of thromboembolism (TE) and pregnancy complications. In women with aPL and no history, LDA is used until 28 weeks of gestation (GW). If women have a history of RSA in the first trimester, LDA is used until 28 GW, plus use of prophylactic dose of UFH (5,000~10,000 U per day) until 15 GW is considered. In women with a history of IUFD, FGR and severe PIH, we recommend use of LDA until 28 GW plus UFH (10,000~12,000U per day) until 28-36GW. The timing of UFH completion can be determined due to a history of previous obstetric complications. In women with a history of TE event, warfarin should be substituted at 5 GW for LDA until 28 GW plus therapeutic dose of UFH, and UFH (continuous infusion or subcutaneous injection to maintain the aPTT within the therapeutic aPTT ranges) is continued throughout their pregnancies. During pregnancy fetal growth and well-being are monitored by ultrasonography including pulse doppler and cardiotocogram; and maternal D-dimer is measured regularly. If women have elevated D-dimer (especially $>$10.0 μg/ml), increases of UFH dose and ultrasound examination for deep venous thrombosis may be considered. If women yield multi-positive tests or a high titer of aPL, more intensive treatment should be considered (Figure 1).

5. Intravenous immunoglobulin infusion for aspirin-heparin resistant antiphospholipid syndrome

We often encountered APS women who underwent LDA plus heparin and failed to have a healthy infant. Such cases can be designated as aspirin-heparin resistant APS (AHRAPS) (49). In AHRAPS, intravenous immunoglobulin (IVIg) therapy may be effective. Carreras et al. (50) first reported successful IVIg therapy in a pregnant woman with LA and a history of 9 RSA. A randomized controlled trial comparing LDA plus heparin plus IVIg with LDA



Antiphospholipid antibodies include lupus anticoagulant, anticardiolipin antibody, anti-β2 glycoprotein-I antibody, and β_2–glycoprotein I dependent anticardiolipin antibody. If women yield multi-positive tests or a high titer of antiphospholipid antibody, more intensive treatment should be considered as presented by dotted arrows.
TE, thromboembolism; RSA, recurrent spontaneous abortion; IUFD, intrauterine fetal death; FGR, fetal growth restriction; PIH, pregnancy-induced hypertension; LDA, low dose aspirin; UFH, unfractionated heparin; VD, vaginal delivery; CS, cesarean section

Fig. 1. Management strategy for pregnant women with positive test for antiphospholipid antibody

plus heparin therapies in 16 APS patients failed to show differences in the efficacy (51). Triolo et al. (52) reported that LDA plus low molecular weight heparin had a higher birth rate (84%) than that of IVIg alone (57%) in RSA women with aCLβ2GPI. But later, they also reported successful IVIg therapy in 8 of 10 APS women previously unresponsive to LDA plus heparin (53). There were several case reports of successful pregnancy outcome in APS patients with RSA (54-57). Therefore, a certain subgroup of APS women such as AHRAPS must have the possible advantage of IVIg therapy. The inhibitory effect of IVIg on aPLs, especially aCL, and LAC has been reported by several authors (58-61).

The optimal dosage of IVIg in APS women during pregnancy was not determined and still to be debated. Yamada et al., first performed a high dose IVIg therapy (20 g/day, 5 consecutive days, total 100 g) in early pregnancies of women with unexplained severe RSA, demonstrating a high live birth rate (62-64). Carreras et al. (50) performed IVIg therapy (400 mg/kg・day, 5 consecutive days at 17 GW; and 2 days at 22, 27 GW) in APS women. Others reported monthly 1g/kg IVIg therapies (53).

The mechanisms of IVIg efficacy for pregnant women with APS have not been fully assessed. Possible mechanisms to explain its broad activity comprised the following;

1) provision of anti-idiotypic antibodies and the function as immunomodulator; 2) interference with the complement activation and the cytokine network; 3) modulation of the expression and function of Fc receptors; and 4) differentiation and effector functions of T and B cells (65,66). As for the anti-idiotypic antibody function, inhibitory effects of IVIg on aCL and LA were reported (59,60,67). Caccavo et al. (67) demonstrated that aCL binding to cardiolipin was suppressed by $F(ab')_2$ fragments derived from IVIg in a dose-dependent manner. Galli et al. (59) also demonstrated dose-dependent suppression of LA activity in patients, using either IVIg or $F(ab)_2$ fragments. IVIg may induce long-term decrease in autoantibody production by acquiring the inactivation of idiotype-bearing B cell clones (68).

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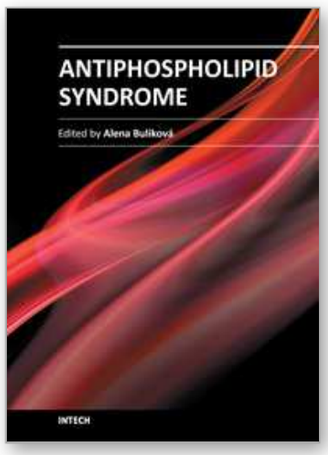

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The antiphospholipid syndrome has been described for the first time by Graham Hughes in 1983 as a condition connected with thromboses or foetal losses and antiphospholipid antibodies presence. Form that time there has been a great progress in knowledge, including antiphospholipid antibodies characterisation, their probable and also possible action, clinical manifestations, laboratory detection and treatment possibilities . This book provides a wide spectrum of clinical manifestations through Chapters written by well known researchers and clinicians with a great practical experience in management of diagnostics or treatment of antiphospholipid antibodies' presence.

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