

The Management of Antiphospholipid Antibodies Affected Pregnancy

Kenji Tanimura, Yashuhiko Ebina,
Yoko Maesawa, Ryoichi Hazama and Hideto Yamada*

*Department of Obstetrics and Gynecology,
Kobe University Graduate School of Medicine, Kobe
Japan*

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- β 2 glycoprotein-I antibody (a β 2GPI) 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).

* Corresponding Author

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 (aCL β_2 GPI) (12) and a β_2 GPI (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 a β_2 GPI (16). PIH (17) and HELLP syndrome (16) were not associated with the presence of aCL or a β_2 GPI.

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 associated 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 $\alpha\beta$ 2GPI 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) $\alpha\beta$ 2GPI 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) $\alpha\beta$ 2GPI were established from the most appropriate values dividing pregnant subjects in this study. It was found that titers of IgG $\alpha\beta$ 2GPI \geq 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 $\alpha\beta$ 2GPI \geq 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 $\alpha\beta$ 2GPI determination as one of the laboratory criteria for APS classification.

There is a large body of evidence for an involvement of $\alpha\beta$ 2GPI in hypercoagulation status and thrombosis. (33-38). A multivariate analysis in a multicenter study has demonstrated that $\alpha\beta$ 2GPI and aPE, but not LA or aCL, were significantly associated with thrombosis (31). $\alpha\beta$ 2GPI induce the activation of endothelial cells, resulting in a proinflammatory state which favours the prothrombotic diathesis (39). Recently, a study has demonstrated β 2GPI naturally inhibits von Willebrand factor (VWF)-dependent platelet adhesion and aggregation. $\alpha\beta$ 2GPI of APS patients neutralized the β 2GPI-VWF interactions, contributing to hypercoagulation status in these patients (40). It is likely that the thrombotic insult of $\alpha\beta$ 2GPI to placental angiogenesis or circulation is causally associated with PIH. Additionally, β 2GPI binds to trophoblast cells (41). The antibody binding to β 2GPI 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, aCL β 2GPI, aCL, aPS/PT and aPE. The most frequent type of aPL was IgG aPE (20.2%), followed by IgG aCL and then IgG aCL β 2GPI. The standard combinations of aPL measurements upon RSA screening may be LA plus IgG, IgM aCL β 2GPI, 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 aCL β 2GPI, 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 aCL β 2GPI	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 aCL β 2GPI	2.6	13.3 ^f	1.0 ^f
LA or aCL	4.4	20.0 ^g	2.0 ^g
LA, aCL β 2GPI, aCL or aPS/PT	7.0	20.0	5.1
All aPLs measurement	26.3	20.0	27.3

aCL, anticardiolipin antibody; aCL β 2GPI, anticardiolipin β 2-glycoprotein 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 aCL β 2GPI, 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, aCL β 2GPI, 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.

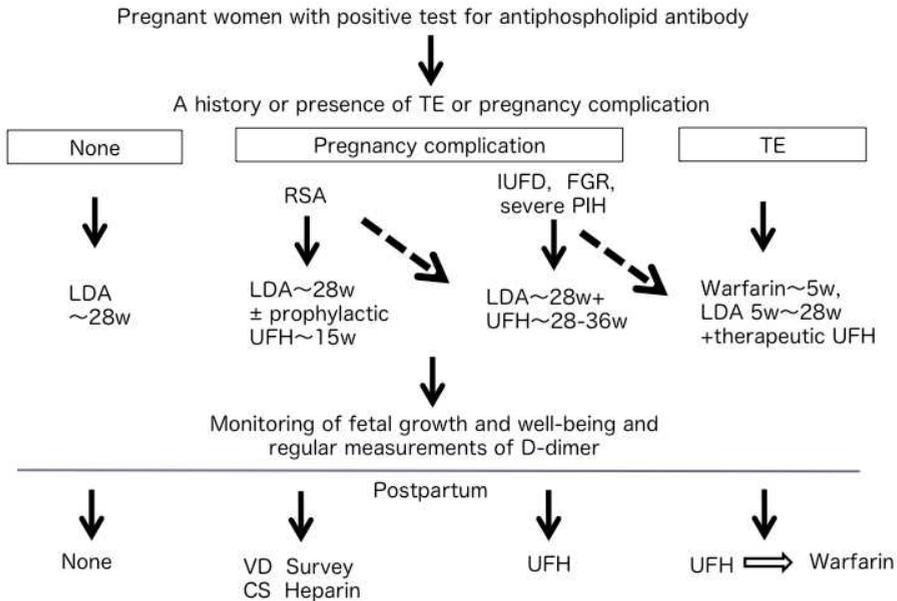
4. Management and therapy for women with antiphospholipid antibody

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, a β 2GPI, or aCL β 2GPI). 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 μ g/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- β_2 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 aCL β_2 GPI. 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).

6. Acknowledgments

This work was supported in part by Grants-in-Aid from the Ministry of Health, Labor and Welfare of Japan (grant number; H23-Jisedai-Ippan-001), the Ministry of Education, Science, Sports and Culture of Japan (grant number; 23592403), and Japan Association of Obstetricians and Gynecologists (grant number; H22-Ogyah-Kenkin).

7. References

- [1] Wilson WA, Gharavi AE, Koike T, Lockshin MD, Branch DW, Piette JC, Brey R, Sherer Y, Levy Y, Derksen R, Harris EN, Hughes GR, Triplett DA, Khamashta MA. 1999. International consensus statement on preliminary classification criteria for definite antiphospholipid syndrome: report of an international workshop. *Arthritis Rheum.* 42, 1309-1311.
- [2] Miyakis S, Lockshin MD, Atsumi T, Branch DW, Cervera R, Derksen RH, DE Groot PG, Koike T, Meroni PL, Reber G, Shoenfeld Y, Tincani A, Vlachoyiannopoulos PG, Krilis SA. 2006. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J Thromb Haemost.* 4, 295-306.
- [3] Di Simone N, De Carolis S, Lanzone A, Ronsisvalle E, Giannice R, Caruso A. 1995. In vitro effect of antiphospholipid antibody-containing sera on basal and gonadotrophin releasing hormonedependent human chorionic gonadotrophin release by cultured trophoblast cells. *Placenta.* 16,75-83.
- [4] Holers VM, Girardi G, Mo L, Guthridge JM, Molina H, Pierangeli SS, Espinola R, Xiaowei LE, Mao D, Vialpando CG, Salmon JE. 2002. Complement C3 activation is required for antiphospholipid antibody-induced fetal loss. *J Exp Med.* 195, 211-20.
- [5] Chamley LW, Duncalf AM, Mitchell MD, Johnson PM. 1998. Action of anticardiolipin and antibodies to beta2-glycoprotein-I on trophoblast proliferation as a mechanism for fetal death. *Lancet.* 35, 1037-8.
- [6] Pattison NS, Chamley LW, McKay EJ, Liggins GC, Butler WS. 1993. Antiphospholipid antibodies in pregnancy: prevalence and clinical associations. *Br J Obstet Gynaecol.* 100, 909-13.
- [7] Lynch A, Marlar R, Murphy J, Davila G, Santos M, Rutledge J. 1994. Antiphospholipid antibodies in predicting adverse pregnancy outcome: a prospective study. *Ann Intern Med.* 120, 470-5.

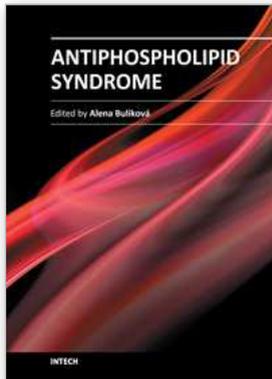
- [8] Lockwood CJ, Romero R, Feinberg RF, Clyne LP, Coster B, Hobbins JC. 1989. The prevalence and biologic significance of lupus anticoagulant and anticardiolipin antibodies in a general obstetric population. *Am J Obstet Gynecol.* 161, 369-73.
- [9] Yasuda M, Takakuwa K, Tokunaga A, Tanaka K. 1995. Prospective studies of the association between anticardiolipin antibody and outcome of pregnancy. *Obstet Gynecol.* 86, 555-9.
- [10] van Pampus MG, Dekker GA, Wolf H, Huijgens PC, Koopman MM, von Blomberg BM, Buller HR. 1999. High prevalence of hemostatic abnormalities in women with a history of severe preeclampsia. *Am J Obstet Gynecol.* 180, 1146-1150.
- [11] von Tempelhoff GF, Heilmann L, Spanuth E, Kunzmann E, Hommel G. 2000. Incidence of the factor V Leiden-mutation, coagulation inhibitor deficiency, and elevated antiphospholipid-antibodies in patients with preeclampsia or HELLP-syndrome. Hemolysis, elevated liver-enzymes, low platelets. *Thromb Res.* 100, 363-365.
- [12] Katano K, Aoki K, Sasa H, Ogasawara M, Matsuura E, Yagami Y. 1996. Beta 2-Glycoprotein I-dependent anticardiolipin antibodies as a predictor of adverse pregnancy outcomes in healthy pregnant women. *Hum Reprod.* 11, 509-512.
- [13] Faden D, Tincani A, Tanzi P, Spatola L, Lojacono A, Tarantini M, Balestrieri G. 1997. Anti-beta 2 glycoprotein I antibodies in a general obstetric population: preliminary results on the prevalence and correlation with pregnancy outcome. Anti-beta2 glycoprotein I antibodies are associated with some obstetrical complications, mainly preeclampsia-eclampsia. *Eur J Obstet Gynecol Reprod Biol.* 73, 37-42.
- [14] Dreyfus M, Hedelin G, Kutnahorsky R, Lehmann M, Viville B, Langer B, Fleury A, M'Barek M, Treisser A, Wiesel ML, Pasquali JL. 2001. Antiphospholipid antibodies and preeclampsia: a case-control study. *Obstet Gynecol.* 97, 29-34.
- [15] Branch DW, Porter TF, Rittenhouse L, Caritis S, Sibai B, Hogg B, Lindheimer MD, Klebanoff M, MacPherson C, VanDorsten JP, Landon M, Paul R, Miodovnik M, Meis P, Thurnau G. 2001. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Antiphospholipid antibodies in women at risk for preeclampsia. *Am J Obstet Gynecol.* 184, 825-834.
- [16] Lee RM, Brown MA, Branch DW, Ward K, Silver RM. 2003. Anticardiolipin and anti-beta2-glycoprotein-I antibodies in preeclampsia. *Obstet Gynecol.* 102, 294-300.
- [17] Lynch A, Byers T, Emlen W, Rynes D, Shetterly SM., Hamman RF. 1999. Association of antibodies to beta2-glycoprotein 1 with pregnancy loss and pregnancy-induced hypertension: a prospective study in low-risk pregnancy. *Obstet Gynecol.* 93, 193-198.
- [18] Yamada H, Atsumi T, Kobayashi G, Ota C, Kato E, Tsuruga N, Ohta K, Yasuda S, Koike T, Minakami H. 2009. Antiphospholipid antibodies increase the risk of pregnancy-induced hypertension and adverse pregnancy outcomes. *J Reproduct Immunol.* 79,188-195.
- [19] Detkova D, Gil-Aguado A, Lavilla P, Cuesta MV, Fontan G, Pascual-Salcedo D. 1999. Do antibodies to beta2-glycoprotein 1 contribute to the better characterization of the antiphospholipid syndrome? *Lupus.* 8, 430-438.
- [20] Obermoser G, Bitterlich W, Kunz F, Sepp NT. 2003. Thromboembolic risk in patients with high titre anticardiolipin and multiple antiphospholipid antibodies. *Thromb Haemost.* 90, 108-115.

- [21] Obermoser G, Bitterlich W, Kunz F, Sepp NT. 2004. Clinical significance of anticardiolipin and anti-beta2-glycoprotein I antibodies. *Int. Arch. Allergy Immunol.* 135, 148-153.
- [22] Gris JC, Quere I, Sanmarco M, Boutiere B, Mercier E, Amiral J, Hubert AM, Ripart-Neveu S, Hoffet M, Tailland ML, Rousseau O., Monpeyroux F, Dauzat M., Sampol J, Daures JP, Berlan J, Marès P. 2000. Antiphospholipid and antiprotein syndromes in non-thrombotic, non-autoimmune women with unexplained recurrent primary early foetal loss. The Nimes Obstetricians and Haematologists Study-NOHA. *Thromb Haemost.* 84, 228-236.
- [23] Sanmarco M, Alessi MC, Harle JR, Sapin C, Aillaud MF., Gentile S, Juhan-Vague I, Weiller PJ. 2001. Antibodies to phosphatidylethanolamine as the only antiphospholipid antibodies found in patients with unexplained thromboses. *Thromb Haemost.* 85, 800-805.
- [24] Balada E, Ordi-Ros J, Paredes F, Villarreal J, Mauri M, Vilardell-Tarres M. 2001. Antiphosphatidylethanolamine antibodies contribute to the diagnosis of antiphospholipid syndrome in patients with systemic lupus erythematosus. *Scand J Rheumatol.* 30, 235-241.
- [25] Yamada H, Atsumi T, Kato E, Shimada S, Morikawa M, Minakami H. 2003. Prevalence of diverse antiphospholipid antibodies in women with recurrent spontaneous abortion. *Fertil Steril.* 80, 1276-1278.
- [26] Sugi T, Matsubayashi H, Inomo A, Dan L, Makino T. 2004. Antiphosphatidylethanolamine antibodies in recurrent early pregnancy loss and mid-to-late pregnancy loss. *J Obstet Gynaecol Res.* 30, 326-332.
- [27] Sugi T, Katsunuma J, Izumi S, McIntyre JA, Makino T. 1999. Prevalence and heterogeneity of antiphosphatidylethanolamine antibodies in patients with recurrent early pregnancy losses. *Fertil Steril.* 71, 1060-1065.
- [28] Majima M, Mizogami S, Kuribayashi Y, Katori M, Oh-ishi S. 1994. Hypertension induced by a nonpressor dose of angiotensin II in kininogen-deficient rats. *Hypertension.* 24, 111-119.
- [29] Hayashi I, Amano H, Yoshida S, Kamata K, Kamata M, Inukai M, Fujita T, Kumagai Y, Furudate S, Majima M. 2002. Suppressed angiogenesis in kininogen-deficiencies. *Lab Invest.* 82, 871-880.
- [30] Guo YL, Colman RW. 2005. Two faces of high-molecular-weight kininogen (HK) in angiogenesis: bradykinin turns it on and cleaved HK (HKa) turns it off. *J Thromb Haemost.* 3, 670-676.
- [31] Sanmarco M, Gayet S, Alessi MC, Audrain M, de Maistre E, Gris JC, de Groot PG, Hachulla E, Harlé JR, Sié P, Boffa MC. 2007. Antiphosphatidylethanolamine antibodies are associated with an increased odds ratio for thrombosis. *Thromb Haemost.* 97, 949-954.
- [32] Yamada H, Atsumi T, Olga A, Koike T, Furuta I, Ohta K, Kobayashi G. 2010. Anti- β 2 glycoprotein-I antibody increases the risk of pregnancy-induced hypertension: a case-controlled study. *J Reproduct Immunol.* 84, 95-99.
- [33] Martinuzzo, M.E, Forastiero, R.R. Carreras, L.O, 1995. Anti beta 2 glycoprotein I antibodies: detection and association with thrombosis. *Br J Haematol.* 89, 397-402.

- [34] Amengual O, Atsumi T, Khamashta M, Koike T, Hughes GRV. 1996. Specificity of ELISA for antibody to beta2-glycoprotein I in patients with antiphospholipid syndrome. *Br J Rheumatol.* 35, 1239-1243.
- [35] Zanon E, Prandoni P, Vianello F, Saggiorato G, Carraro G, Bagatella P, Girolami A. 1999. Anti-beta2-glycoprotein I antibodies in patients with acute venous thromboembolism: prevalence and association with recurrent thromboembolism. *Thromb Res.* 96, 269-274.
- [36] Zoghalmi-Rintelen C, Vormittag R, Sailer T, Lehr S, Quehenberger P, Rumpold H, Male C, Pabinger I. 2005. The presence of IgG antibodies against beta2-glycoprotein I predicts the risk of thrombosis in patients with the lupus anticoagulant. *J Thromb Haemost.* 3, 1160-1165.
- [37] Pengo V, Biasiolo A, Pegoraro C, Cucchini U, Noventa F, Iliceto S. 2005. Antibody profiles for the diagnosis of antiphospholipid syndrome. *Thromb Haemost.* 93, 1147-1152.
- [38] de Laat B, Derksen RH, Urbanus RT, de Groot PG. 2004. IgG antibodies that recognize epitope Gly40-Arg43 in domain I of beta 2-glycoprotein I cause LAC, and their presence correlates strongly with thrombosis. *Blood.* 105, 1540-1545.
- [39] D'Ippolito S, Di Simone N, Di Nicuolo F, Castellani R, Caruso A. 2007. Antiphospholipid antibodies: effects on trophoblast and endothelial cells. *Am J Reprod Immunol.* 58, 150-158.
- [40] Hulstein JJ, Lenting PJ, de Laat B, Derksen RH, Fijnheer R, de Groot PG. 2007. beta2-Glycoprotein I inhibits von Willebrand factor dependent platelet adhesion and aggregation. *Blood.* 110, 1483-1491.
- [41] Di Simone N, Meroni PL, D'Asta M, Di Nicuolo F, D'Alessio MC, Caruso A. 2007. Pathogenic role of anti-beta2-glycoprotein I antibodies on human placenta: functional effects related to implantation and roles of heparin. *Hum Reprod Update.* 13, 189-196.
- [42] Di Simone N, Raschi E, Testoni C, Castellani R, D'Asta M, Shi T, Krilis SA, Caruso A, Meroni PL. 2005. Pathogenic role of anti-beta 2-glycoprotein I antibodies in antiphospholipid associated fetal loss: characterisation of beta 2-glycoprotein I binding to trophoblast cells and functional effects of anti-beta 2-glycoprotein I antibodies in vitro. *Ann Rheum Dis.* 64, 462-467.
- [43] Di Simone N, Luigi MP, Marco D, Fiorella DN, Silvia D, Clara DM, Alessandro C. 2007.. Pregnancies complicated with antiphospholipid syndrome: the pathogenic mechanism of antiphospholipid antibodies: a review of the literature. *Ann N Y Acad Sci.* 1108:505-514.
- [44] Greer IA. 2003. Thrombophilia: implications for pregnancy outcome. *Thromb Res.* 109, 73-81.
- [45] Jane E. Salmon, G. 2008. Antiphospholipid antibodies and pregnancy loss: a disorder of inflammation. *J Reprod Immunol;* 77(1), 51-56
- [46] Rai R, Cohen H, Dave M, Regan L. 1997. Randomised controlled trial of aspirin and aspirin plus heparin in pregnant women with recurrent miscarriage associated with phospholipid antibodies (or antiphospholipid antibodies). *BMJ.* 314, 253-7.
- [47] Cowchock FS, Reece EA, Balaban D, Branch DW, Plouffe L. 1992. Repeated fetal losses associated with antiphospholipid antibodies: a collaborative randomized trial

- comparing prednisone with low-dose heparin treatment. *Am J Obstet Gynecol.* 166, 1318–23.
- [48] Bates SM, Greer IA, Pabinger I, Sofaer S, Hirsh J. 2008. Venous thromboembolism, thrombophilia, antithrombotic therapy, and pregnancy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest.* 133, 844S-886S.
- [49] Shimada S, Yamada H, Atsumi T, Yamada T, Sakuragi N, Minakami H, 2010. Intravenous immunoglobulin therapy for aspirin-heparinoid-resistant antiphospholipid syndrome. *Reprod Med Biol.* 9, 217-221.
- [50] Carreras LD, Perez GN, Vega HR, Casavilla F. 1988. Lupus anticoagulant and recurrent fetal loss: successful treatment with gammaglobulin. *Lancet.* 2, 393-394.
- [51] Branch DW, Peaceman AM, Druzin M, Silver RK, El-Sayed Y, Silver RM, Esplin MS, Spinnato J, Harger J. 2000. A multicenter, placebo-controlled pilot study of intravenous immune globulin treatment of antiphospholipid syndrome during pregnancy. The Pregnancy Loss Study Group. *Am J Obstet Gynecol.* 182, 122-127.
- [52] Triolo G, Ferrante A, Ciccica F, Accardo-Palumbo A, Perino A, Castelli A, Giarratano A, Licata G. 2003. Randomized study of subcutaneous low molecular weight heparin plus aspirin versus intravenous immunoglobulin in the treatment of recurrent fetal loss associated with antiphospholipid antibodies. *Arthritis Rheum.* 48, 728-731.
- [53] Triolo G, Ferrante A, Accardo-Palumbo A, Ciccica F, Cadelo M, Castelli A, Perino A, Licata G. 2004. IVIG in APS pregnancy. *Lupus.* 13, 731-735.
- [54] Parke A, Maier D, Wilson D, Andreoli J, Ballow M. 1989. Intravenous gammaglobulin, antiphospholipid antibodies and pregnancy. *Ann Intern Med.* 110, 495-6.
- [55] Scott JR, Branch DW, Kochenour NK, Ward K. 1989. Intravenous immunoglobulin treatment of pregnant patients with recurrent pregnancy loss caused by antiphospholipid antibodies and Rh immunization. *Am J Obstet Gynecol.* 159, 1055-6.
- [56] Wapner RJ, Cowchock FS, Shapiro SS, 1989. Successful treatment in two women with antiphospholipid antibodies and refractory pregnancy losses with intravenous gammaglobulin infusions. *Am J Obstet Gynecol.* 616, 1271-2.
- [57] Ron-el R, Vinder A, Golan A, Herman A, Raziell A, Caspi E, Sidi Y. 1993. The use of intravenous gammaglobulin, heparin and aspirin in the maintenance of pregnancy of freeze thawed embryo in a patient with lupus-type anticoagulant. *Eur J Obstet Gynecol Reprod Biol.* 52, 131-3.
- [58] Caccavo D, Vaccaro F, Ferri GM, Amoroso A, Bonomo L. 1994. Anti-idiotypes against antiphospholipid antibodies are present in normal polyspecific immunoglobulins for therapeutic use. *J Autoimmun.* 7, 537-48.
- [59] Galli M, Cortelazzo S, Barbui T. 1991. *In vivo* efficacy of intravenous gammaglobulins in patients with lupus anticoagulant is not mediated by anti-idiotypic mechanism. *Am J Hematol.* 30, 184-8.
- [60] Said PB, Martinuzzo ME, Carreras LO. 1992. Neutralization of lupus anticoagulant activity by human immunoglobulin 'in vitro'. *Nouv Rev Fr Hematol.* 34, 37-42.
- [61] Matsuda J, Gohchi K, Kawasaki K., Tsukamoto M, Saitoh N, Kinoshita T. 1993. *In vitro* lupus anticoagulant neutralizing activity of intravenous immunoglobulin. *Thromb Res.* 70, 109-10 (letter).

- [62] Yamada H, Kishida T, Kobayashi N, Kato EH, Hoshi N, Fujimoto S. 1998. Massive immunoglobulin treatment in women with four or more recurrent spontaneous primary abortions of unexplained aetiology. *Hum Reprod.* 13, 2620-2623.
- [63] Morikawa M, Yamada H, Kato EH, Shimada S, Kishi T, Yamada T, Kobashi G, Fujimoto S. 2001. Massive intravenous immunoglobulin treatment in women with four or more recurrent spontaneous abortions of unexplained etiology: down-regulation of NK cell activity and subsets. *Am J Reprod Immunol.* 46, 399-404.
- [64] Yamada H, Morikawa M, Furuta I, Kato E, Shimada S, Iwabuchi K, Minakami H. 2003. Intravenous immunoglobulin treatment in women with recurrent abortions: increased cytokine levels and reduced Th1/Th2 lymphocyte ratio in peripheral blood. *Am J Reprod Immunol.* 49, 84-89.
- [65] Kazatchkine MD, Kaveri SV. 2001. Immunomodulation of autoimmune and inflammatory diseases with intravenous immune globulin. *N Engl J Med.* 345, 747-755.
- [66] Bayary J, Dasgupta S, Misra N, Ephrem A, Van Huyen JP, Delignat S, Hassan G, Caligiuri G, Nicoletti A, Lacroix-Desmazes S, Kazatchkine MD, Kaveri S. 2006. Intravenous immunoglobulin in autoimmune disorders: an insight into the immunoregulatory mechanisms. *Int Immunopharmacol.* 6, 528-534.
- [67] Caccavo D, Vaccaro F, Ferri GM, Amoroso A, Bonomo L. 1994. Anti-idiotypes against antiphospholipid antibodies are present in normal polyspecific immunoglobulins for therapeutic use. *J Autoimmun.* 7, 537-548.
- [68] Sherer Y, Levy Y, Shoenfeld Y. 2000. Intravenous immunoglobulin therapy of antiphospholipid syndrome. *Rheumatology.* 39, 421-426.



Antiphospholipid Syndrome

Edited by Dr. Alena Bulikova

ISBN 978-953-51-0526-8

Hard cover, 232 pages

Publisher InTech

Published online 20, April, 2012

Published in print edition April, 2012

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. From 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.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Kenji Tanimura, Yashuhiko Ebina, Yoko Maesawa, Ryoichi Hazama and Hideto Yamada (2012). The Management of Antiphospholipid Antibodies Affected Pregnancy, Antiphospholipid Syndrome, Dr. Alena Bulikova (Ed.), ISBN: 978-953-51-0526-8, InTech, Available from:

<http://www.intechopen.com/books/antiphospholipid-syndrome/antiphospholipid-syndrome-during-pregnancy>

INTECH

open science | open minds

InTech Europe

University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China

Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

© 2012 The Author(s). Licensee IntechOpen. This is an open access article distributed under the terms of the [Creative Commons Attribution 3.0 License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.