Journal of Reproductive Immunology 122 (2017) 21–27

Contents lists available at ScienceDirect

Journal of Reproductive Immunology

journal homepage: www.elsevier.com/locate/jri

Factors associated with adverse pregnancy outcomes in women with antiphospholipid syndrome: A multicenter study

Masashi Deguchi[a], Hideto Yamada[a,*], Mayumi Sugiura-Ogasawara[b], Mamoru Morikawa[c], Daisuke Fujita[d], Akinori Miki[e], Shintaro Makino[f], Atsuko Murashima[g]

[a] Department of Obstetrics and Gynecology, Kobe University Graduate School of Medicine, 7-5-2 Kusunoki-cho, Chuo-ku, Kobe 650-0017, Japan
[b] Department of Obstetrics and Gynecology, Nagoya City University, Graduate School of Medical Sciences, 1 Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya 467-8601, Japan
[c] Department of Obstetrics and Gynecology, Hokkaido University Graduate School of Medicine, Kita 15, Nishi 7, Kita-ku, Sapporo 060-0818, Japan
[d] Department of Obstetrics and Gynecology, Osaka Medical College, 2-7 Daigakumachi, Takatsuki, Osaka 569- 8686, Japan
[e] Department of Obstetrics and Gynecology, Kitasato University Medical Center, 6-100 Arai, Kitamoto City, Saitama 364-8501, Japan
[f] Department of Obstetrics and Gynecology, Juntendo University Faculty of Medicine, 3-1-3 Hongo, Bunkyo-ku, Tokyo 113-8431, Japan
[g] Center for Maternal-Fetal, Neonatal and Reproductive Medicine, National Center for Child Health and Development, 2-10-1 Okura, Setagaya-ku, Tokyo 157-8535, Japan

ARTICLE INFO

Keywords:
Antiphospholipid syndrome
Pregnancy
Pregnancy complications
Risk factor
Therapy modality

ABSTRACT

The aim of this study was to understand the clinical features of antiphospholipid syndrome (APS)-complicated pregnancies and evaluate risk factors for the adverse pregnancy outcomes. This multicenter study evaluated live-birth rates according to therapy modality for APS and risk factors of pregnancy loss in 81 pregnancies. Risk factors for pregnancy complications, including premature delivery before 34 gestational weeks, hypertensive disorders of pregnancy, thrombocytopenia, and light-for-date neonate, were evaluated in 51 women who received low dose aspirin (LDA) plus unfractionated heparin (UFH) and delivered after 24 GW. The live-birth rate in APS pregnancies with LDA + UFH therapy was 92.6%. A multiple logistic regression analysis demonstrated that LDA + UFH therapy decreased the risk of pregnancy loss (OR 0.13, 95%CI 0.03–0.62), and that a history of pregnancy loss despite LDA + UFH therapy increased the risk of pregnancy loss (OR 8.74, 95%CI 1.69–45.2). LDA therapy prior to pregnancy decreased the risk of premature delivery (OR 0.14, 95%CI 0.03–0.69). Positive tests for two or more anti-phospholipid antibodies increased the risks of premature delivery (OR 9.61, 95%CI 1.78–51.8) and thrombocytopenia (OR 4.90, 95%CI 1.11–21.7). Laboratory findings of low complements increased the risk of hypertensive disorders of pregnancy (OR 12.1, 95%CI 1.61–91.0). Standard therapy yielded high live-birth rates. Positive tests for two or more anti-phospholipid antibodies and low complements were associated with adverse pregnancy outcomes. These results have important implications for clinicians.

1. Introduction

Antiphospholipid syndrome (APS) causes pregnancy complications (Hughes, 1993) and vascular thrombosis (Roubey et al., 1997) in patients who test positive for antiphospholipid antibody (aPL). A wide variety of pregnancy complications in APS, including recurrent early miscarriages, late pregnancy loss, hypertensive disorders of pregnancy (HDP), pre-eclampsia, placental insufficiency, fetal growth restriction, and premature delivery are recognized.

Recently, antiphospholipid score, a quantitative marker representing the aPL profile, has been determined to predict thrombotic events in patients with APS (Oku et al., 2014; Otomo et al., 2012). On the other hand, in terms of pregnancy complications, a positive test for lupus anticoagulant (LA) rather than anti-cardiolipin (aCL) or anti-ß2 glycoprotein I (aß2GPI) antibody has been found to be a risk factor for adverse pregnancy outcomes (Lockshin et al., 2012; Sailer et al., 2006). Other investigators have found that a positive test for aß2GPI, triple positive tests for aCL/aß2GPI/LA, a high value of aPL antibody, secondary APS, and thrombotic history are associated with adverse pregnancy outcomes (Ruffatti et al., 2011; Simchen et al., 2011). Therefore, some controversy remains about risk factors for adverse pregnancy outcomes in women with APS.

This multicenter study aimed to understand the clinical features of APS-complicated pregnancies, and evaluate whether any clinical factors were associated with adverse pregnancy outcome.

* Corresponding author at: Department of Obstetrics and Gynecology, Kobe University Graduate School of Medicine, 7-5-2 Kusunoki-cho Chuo-ku, Kobe 650-0017, Japan.
E-mail address: yhideto@med.kobe-u.ac.jp (H. Yamada).

http://dx.doi.org/10.1016/j.jri.2017.08.001
Received 19 April 2017; Received in revised form 6 July 2017; Accepted 2 August 2017

2. Patients and methods

This study was approved by the institutional review boards of seven hospitals with perinatal centers in Japan, including Kobe University, Nagoya City University, Hokkaido University, Osaka Medical College, Saitama Medical University, Juntendo University, and the National Center for Child Health and Development. Clinical data were retrospectively collected from medical records of pregnant women with APS who received perinatal management and medication between November 2008 and October 2013.

This study enrolled pregnancies from women who were diagnosed as having APS according to the clinical and laboratory criteria of the updated Sydney classification criteria (Miyakis et al., 2006). The clinical criteria used in the present study included vascular thrombosis and obstetrical manifestations of the following: premature delivery of a morphologically normal neonate before 34 gestational weeks (GW) due to eclampsia, severe preeclampsia or placental insufficiency, unexplained miscarriage without fetal abnormality at 10 GW or later, and three or more recurrent early miscarriages. The laboratory criteria used in the present study included repeated positive tests for LA, IgG/IgM aCL, and IgG ß2 glycoprotein I-dependent anti-aCL (aCLß2GPI). A dilute Russell's viper venom time-based test (Gradipore LA Screen and LA Confirm, Gradipore Ltd., Australia) was used for LA measurements. Screen clotting times/Confirm clotting time ratio of 1.3 (99%ile) was defined as the cut off value of LA. IgG/IgM aCL was measured using specific enzyme-linked immunosorbent assay for cardiolipin (MESACUP cardiolipin test IgG/IgM, MBL Co Ltd., Japan), based on the methods described by Harris et al. (Harris et al., 1987); 19.2 unit/ml of IgG (99%ile) and 23.4 unit/ml of IgM (99%ile) were defined as cut off values. IgG aCLß2GPI was measured using specific enzyme immunoassay for ß2GPI (Yamasa kit, Yamasa Co., Japan); 3.5 unit/ml (+6SD) was defined as the cut off value. In the present study, data for IgG aCLß2GPI were used as the measurement of aß2GPI or IgM aCLß2GPI is not commercially available in Japan.

Clinical and laboratory data including maternal age, primary/secondary APS, histories of thrombosis and pregnancy, therapy modality for APS, positive testes of LA, IgG/IgM aCL, IgG aCLß2GPI, antinuclear antigen, activated partial thromboplastin time (aPTT) prolongation, and low complements (C3, C4, or CH50), and therapy modality were collected. Information about chromosome karyotype of the conceptus in cases of pregnancy loss was also obtained. Live-birth rates according to therapy modality for APS and risk factors for pregnancy loss were evaluated for all enrolled pregnancies. Risk factors for pregnancy complications including premature delivery before 34 GW, HDP, thrombocytopenia during pregnancy, and light-for-date (LFD) neonate were evaluated for women who received standard APS therapy of low-dose aspirin (LDA) plus unfractionated heparin (UFH), and delivered after 24 GW. The present study focused on the preterm birth before 34 GW, because the updated Sydney classification criteria adopt the preterm birth before 34 GW as one of the clinical criteria. HDP was defined as an in-hospital systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg, based on the average of at least apart two measurements, using the same arm. LFD was defined as a birthweight less than 10 percentile.

Fisher's exact and Mann-Whitney tests were used for comparison. Univariate and multivariate logistic regression analyses were performed to identify independent factors yielding odds ratios (OR) and 95% confidence intervals (CI). Covariates with a significant univariate test ($p < 0.05$) were selected as candidates for multivariate analysis. The number of variables in the final model of multivariable analyses was restricted to two covariates based on the case number, to avoid overfitting in multivariable logistic regression analyses. When the sample number of one of four comparative arms was zero in the univariate analysis, Fisher's exact test was applied to calculate *p*-values and OR; these covariates were not selected further for multivariable analyses. Statistical analyses were performed using GraphPad Prism version 6 and R statistics version 3; *p*-values < 0.05 were considered significant.

3. Results

In total, 81 pregnancies from 69 women with APS were enrolled in the present study: 24 pregnancies from Kobe University Hospital; 15 from Nagoya City University Hospital, 14 from Hokkaido University Hospital, 13 from Osaka Medical College Hospital, 10 from National Center for Child Health and Development, three from Saitama Medical University Hospital, and two from Juntendo University Hospital.

Maternal age (mean ± SD) at pregnancy was 34.1 ± 4.0 years. They had a history of median three (range 0–7) gravida, 0 (0–2) para, and two (0–7) pregnancy losses. Twenty-four women had a history of thrombosis. The 81 pregnancies consisted of 45 pregnancies from women with primary APS and 36 from women with secondary APS. Secondary APS included 35 women with systemic lupus erythematosus (SLE) and one with autoimmune hepatitis. None had hypertensive disorder or antihypertensive medications at the time of pregnancy diagnosis.

3.1. Pregnancy outcomes and therapy modality

Table 1 shows live-birth rates according to therapy modality in 81 APS complicated pregnancies. According to therapy modality for APS, the 81 pregnancies were divided into six groups as the following: none (n = 3), LDA alone (n = 7), UFH alone (n = 4), LDA plus danaparoid (LDA + danaparoid, n = 1), LDA plus UFH (LDA + UFH, n = 54), and LDA plus UFH plus high dose intravenous immunoglobulin (HIVIg) before 17 GW (LDA + UFH + HIVIg, n = 12). Doses of 81 or 100 mg/day of LDA, median 10000 (range 5000–24000) IU/day of UFH, and 2500 IU/day of danaparoid were administered. HIVIg (20 g/day, 5 consecutive days, total 100 g) was performed at median 6 (5–16) GW.

Table 1
Live-birth rates according to therapy modality.

Therapy modality	Number of pregnancies (*)	Number of pregnancies with PSL therapy (*)	Pregnancy outcome		Live-birth rate (%)	*P*-value
			Pregnancy loss (number of conceptus with normal chromosome, abnormal chromosome, unknown)	Live birth		
None	3 (1)	N.A.	3 (2, 0, 1)	0	0	
LDA alone	7 (2)	5 (2)	2 (2, 0, 0)	5	71.4[a]	a v.s. c
UFH alone	4 (1)	2 (1)	1 (1, 0, 0)	3	75.0[b]	p = 0.14
LDA + danaparoid	1 (1)	1 (1)	1 (0, 1, 0)	0	0	b v.s. c
LDA + UFH	54 (4)	24 (4)	4** (4, 0, 0)	50	92.6[c]	p = 0.31
LDA + UFH + HIVIg	12 (8)	11 (7)	3 (2, 1, 0)	9	75.0[d]	c v.s. d
Total	81 (17)	43 (15)	14 (11, 2, 1)	67	82.7	p = 0.11

LDA, low dose aspirin; UFH, unfractionated heparin; HIVIg, a high dose intravenous immunoglobulin; PSL, prednisolone; N.A., not applicable.
(*) Parenteses indicate numbers of pregnancies from women who have experienced pregnancy loss despite LDA + UFH therapy.
** One case with stillbirth at 26 gestational weeks is included.