ELSEVIER

Journal of Reproductive Immunology 79 (2009) 188–195

JOURNAL OF REPRODUCTIVE IMMUNOLOGY

www.elsevier.com/locate/jreprimm

Antiphospholipid antibodies increase the risk of pregnancy-induced hypertension and adverse pregnancy outcomes

Hideto Yamada [a,*], Tatsuya Atsumi [b], Gen Kobashi [c], Chikako Ota [d], Emi H. Kato [a], Noriko Tsuruga [a], Kaori Ohta [c], Shinsuke Yasuda [b], Takao Koike [b], Hisanori Minakami [a]

[a] *Department of Obstetrics and Gynecology, Hokkaido University Graduate School of Medicine, Kita-ku N15 W7, Sapporo 060-8638, Japan*
[b] *Department of Medicine II, Hokkaido University Graduate School of Medicine, Sapporo, Japan*
[c] *Molecular Biostatistics Research Team, Research Center for Charged Particle Therapy, National Institute of Radiological Science, Chiba, Japan*
[d] *Department of Obstetrics and Gynecology, Hirosaki University School of Medicine, Hirosaki, Japan*

Received 4 June 2008; received in revised form 5 November 2008; accepted 11 November 2008

Abstract

Antiphospholipid antibody (aPL) is associated with thromboembolism. There is scant evidence of a relationship between the aPL profile and serious adverse pregnancy outcome. The aim of this study was to assess whether aPL measurements during early pregnancy were useful in predicting a serious adverse pregnancy outcome. In this prospective study, we measured aPLs, including lupus anticoagulant (LA), IgG, IgM, IgA anticardiolipin antibody (aCL), IgG, IgM phosphatidylserine-dependent antiprothrombin antibody, and IgG kininogen-dependent antiphosphatidylethanolamine antibody (aPE) during the first trimester in a consecutive series of 1155 women. The 99th percentile cut-off values in each aPL were determined using samples from 105 women who did not exhibit any pregnancy morbidity. We assessed the predictive risk of a serious adverse pregnancy outcome adjusted for confounding factors. We found that IgG aCL was asssociated with developing pregnancy-induced hypertension (PIH) (odds ratio 11.4, 95% CI 2.7–48); IgG aPE with PIH (8.3, 2.4–29), severe PIH (20.4, 4.5–91), and premature delivery (PD) (12.7, 3.1–50); and LA with PD (11.0, 2.8–44) and low birth weight (8.0, 2.1–31). The combinations of IgG aPE plus IgG aCL (17.5, 4.7–66.7) or IgG aPE plus LA (22.2, 5.4–909) measurements predicted severe PIH with 30.8% sensitivity and 99.2% specificity. We conclude that aPL measurements during early pregnancy may be useful in predicting adverse pregnancy outcome.

Keywords: Antiphospholipid antibody; Pregnancy-induced hypertension; Premature delivery; Fetal loss; Fetal growth restriction

1. Introduction

Pregnancy-induced hypertension (PIH) is a major cause of mortality and morbidity during pregnancy and childbirth and is a multifactorial disease with genetic and environmental factors involved in its etiology. Severe PIH and pre-eclampsia can lead to multiple organ failure including the cardiovascular system, central nervous system, coagulation, liver, and kidneys. The association between antiphospholipid antibodies (aPLs) and the risk of PIH, pre-eclampsia, fetal growth restriction (FGR), or premature delivery (PD) still remains

* Corresponding author. Tel.: +81 11 706 7720; fax: +81 11 706 7711.
E-mail address: yhideto@med.hokudai.ac.jp (H. Yamada).

0165-0378/$ – see front matter © 2009 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.jri.2008.11.001

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 lupus anticoagulant (LA) and anticardiolipin antibody (aCL) (Van Pampus et al., 1999; Von Tempelhoff et al., 2000).

However, prospective studies assessing associations between aPLs and PIH, pre-eclampsia or other pregnancy adverse outcomes found conflicting results. Studies conducted in the 1990s noted that pre-eclampsia was associated with the presence of LA (Pattison et al., 1993), aCL (Pattison et al., 1993; Yasuda et al., 1995), β_2-glycoprotein-dependent anticardiolipin antibody (aCLβ_2GPI) (Katano et al., 1996), and anti-β_2 glycoprotein-I antibody (aβ_2GPI; Faden et al., 1997). Similarly, fetal loss and FGR were associated with the presence of aCL (Yasuda et al., 1995; Katano et al., 1996). Recent prospective studies, however, failed to show an association between pre-eclampsia and the presence of LA (Dreyfus et al., 2001), aCL (Branch et al., 2001; Dreyfus et al., 2001; Lee et al., 2003b) or aβ_2GPI (Lee et al., 2003b). PIH (Lynch et al., 1999) and HELLP syndrome (Lee et al., 2003b) were not associated with the presence of aCL or aβ_2GPI.

Currently, a wide variety of aPLs in the human blood can be measured by laboratory diagnostic assays, each of which requires evaluation with regard to whether there is an association with obstetric events. The aim of this prospective study was to assess whether aPL measurements during early pregnancy were useful in predicting serious adverse pregnancy outcome in the Japanese population, which has a relatively homogeneous genetic background.

2. Materials and methods

2.1. Subjects

This prospective study, designated Sapporo Multiple Antiphospholipid Testing for the Prediction of Obstetric Outcome study (SAPPORO study) was performed in the city of Sapporo, Japan, and conducted with informed consent from all of the subjects, and was approved by the institutional ethics board of Hokkaido University Graduate School of Medicine. The peripheral blood was obtained at 8–14 weeks' gestation (GW) from 1220 consecutive Japanese women with living fetuses who visited the Hokkaido University Hospital or an affiliate hospital.

Measurements were made of aPLs including lupus anticoagulant (LA), IgG, IgM, IgA anticardiolipin antibody (aCL), IgG, IgM phosphatidylserine-dependent antiprothrombin antibody (aPS/PT), and IgG kininogen-dependent antiphosphatidylethanolamine antibody (aPE). The appropriate cut-off values of each aPL during the first trimester were determined using data obtained from the first 105 women who subsequently delivered a healthy neonate without pregnancy-related morbidity. In this study protocol, when women had a history of recurrent pregnancy loss (RPL) or thromboembolism with a positive test for LA or aCL, they underwent low-dose aspirin therapy (81 mg/day) until delivery. The ethics board directed this intervention in patients who were compatible with the original antiphospholipid syndrome (APS) criteria (Wilson et al., 1999); otherwise the study would not have been approved.

Women who were subsequently found to have a fetal anomaly or multiple pregnancy, and those whose pregnancies were terminated by an induced abortion were excluded from the analysis. We assessed risks of PIH, severe PIH, pre-eclampsia, fetal growth restriction (FGR, <10th percentile and <-1.5 S.D. based on gestational age, parity and fetal sex), premature delivery (PD, <34 and <37 GW), low birth weight (LBW, <2500 g), and fetal loss (fetal death after the blood sampling) with lifestyle-related confounding factors including maternal age, parity, preconception body mass index (BMI), cigarette smoking (preconception/during pregnancy), and drinking alcohol (preconception/during pregnancy). The mean age at blood sampling was 30.6 (S.D. 4.7) ranging from 16 to 44 years of age, and the mean preconception BMI was 20.9 (3.3) ranging from 14.9 to 44.5 kg/m^2.

Pregnancy-induced hypertension was diagnosed during pregnancy when hypertension (systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg) was detected after 20 GW. Severe PIH was diagnosed when at least one of the following criteria was met:

(1) Blood pressure $\geq$160/110 mmHg after 20 GW, regardless of the complication of proteinuria defined as urinary excretion of 300 mg protein/day,
(2) Blood pressure $\geq$140/90 mmHg after 20 GW complicated by proteinuria $\geq$2.0 g/day.

Pre-eclampsia was diagnosed when hypertension ($\geq$140/90 mmHg) and proteinuria ($\geq$300 mg/day) were detected after 20 GW.

Four women who had a history of RPL or thromboembolism with a positive test for LA or aCL underwent low-dose aspirin therapy. Of the four women, two received additional heparin therapy with informed consent.