Reprod Med Biol (2010) 9:217–221
DOI 10.1007/s12522-010-0056-3

CASE REPORT

Intravenous immunoglobulin therapy for aspirin-heparinoid-resistant antiphospholipid syndrome

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Received: 10 April 2010 / Accepted: 26 May 2010 / Published online: 15 June 2010

Abstract We encountered a woman who had a history of repeated fetal losses and positive tests for lupus anticoagulant, phosphatidylserine-dependent antiprothrombin (aPS/PT) IgG, IgM and kininogen-dependent antiphosphatidylethanolamine (aPE) IgG, IgM. Her previous pregnancy had ended in intrauterine fetal death at 24 weeks of gestation despite a therapy of low-dose aspirin, prednisolone and danaparoid. During the present pregnancy, she was treated with repeated intravenous infusions of immunoglobulin (IVIg) together with low-dose aspirin, prednisolone and heparin. When thrombocytopenia developed, she delivered a female baby weighing 2,152 g at 34 weeks of gestation by cesarean section. Titers of aPS/PT IgM and aPE IgM were reduced or maintained at low levels by repeated IVIg therapies. The IVIg therapy might be effective for aspirin-heparinoid-resistant antiphospholipid syndrome.

Keywords Antiphospholipid syndrome · Aspirin · Heparin · Heparinoid · Immunoglobulin

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Introduction

Women with antiphospholipid syndrome (APS) have an increased risk of pregnancy loss and obstetrical complications. Detrimental effects of antiphospholipid antibody (aPL) are attributed to pathological mechanisms including thrombotic changes, suppression of hCG release [1], induction of complement activation and placental injury [2], and a direct effect on trophoblast cells [3]. Although the management of pregnancy in women with APS has been a subject of much debate, antiplatelet and anticoagulation therapies are usually recommended [4]. A randomized controlled study demonstrated a high live birth rate (71%) with low-dose aspirin (LDA) plus heparin as compared with 42% with LDA alone in APS women [5]. The women treated with LDA plus heparin had fewer maternal adverse effects, and this treatment was found to be superior to LDA plus steroids [6].

However, we encounter APS women who undergo LDA plus heparin/heparinoid with or without steroids and fail to have a healthy infant. Such patients can be designated as having aspirin-heparin/heparinoid-resistant APS. In the present report, a case of aspirin-heparinoid-resistant APS was treated successfully with repeated intravenous infusions of immunoglobulin (IVIg), LDA, heparin and prednisolone. We assessed changes in levels of serum complements and antiphospholipid antibodies (aPLs) through the course of pregnancy.

Case report

A 38-year-old non-pregnant woman with a history of repeated fetal losses and APS was referred to the infertility clinic of The Hokkaido University Hospital for

consultations. Her first pregnancy had ended in spontaneous abortion at 7 weeks of gestation (GW). Only the gestational sac was detected without fetal heart movement in this missed abortion. She was treated with LDA (81 mg/day), danaparoid sodium (Orgaran™, Schering-Plough Co., Ltd., Tokyo, Japan; 2,500 unit/day) and prednisolone (PSL 10 mg/day) during the second pregnancy. However, growth restriction and mild preeclampsia developed at 22 GW, and this pregnancy resulted in intrauterine death of a female fetus weighing 344 g at 24 GW. Pathological examination of the placenta revealed ischemic changes with relatively small villi, abundant syncytial nodes, fibrin depositions and necrosis.

Laboratory data obtained in our infertility clinic after her first visit were as follows: white blood cells 6,400/μl, red blood cells 336 × 10^4/μl, hemoglobin 11.9 g/dl, hematocrit 34.4%, platelet 29.4 × 10^4/μl, fibrinogen 255 mg/dl, fibrinogen degradation product <2.6 mg/ml, D-dimer 0.58 mg/ml (normal < 1.0), prothrombin time 11.6 s, APTT 44.2 s (normal 26.1–36.5), coagulation factor XII 30.5% (normal > 50.0), C-reactive protein 0.03 mg/dl, C3 55 mg/dl (normal 86–160), C4 8 mg/dl (normal 17-45), CH50 20.3 U/ml (normal 31.5–48.4), antinuclear antibody (ANA) 1:640, anti-DNA antibody 0.0 IU/ml, anti-SSA antibody 122.3 index (normal < 10.0), anticardiolipin (aCL) IgG < 8 U/ml, aCL IgM < 5 U/ml, β2 glycoprotein I-dependent anticardiolipin (aCLβ2GPI) IgG < 1.3 U/ml, phosphatidylserine dependent anti-prothrombin (aPS/PT) IgG 235 U/ml (normal < 2.0), aPS/PT IgM 37.5 U/ml (normal < 9.2), lupus anticoagulant (LA) 2.01 (normal < 1.3; DRVVT method), PAIgG 33.5 ng/10^7 cells (normal 9.0–25.0), and negative tests for anti-platelet antibody or proteinurea. Thus, decreases in levels of serum C3, C4, CH50 concentrations and factor XII activity, and positive tests for ANA, anti-SSA antibody, aPS/PT IgG, aPS/PT IgM, LA and PAIgG were detected prior to her third pregnancy. On that occasion, kininogen-dependent anti-phosphatidylethanolamine (aPE) IgG or IgM was not measured.

A combined therapy of LDA (81 mg/day, orally), PSL (10 mg/day, orally), unfractionated heparin (5,000 unit × 2 sc/day) and intravenous infusions of intact type immunoglobulin (IVIg) for the third pregnancy was planned with informed consent. LDA was commenced before conception. Immediately after a positive pregnancy test was obtained, she was hospitalized, and received PSL and unfractionated heparin. LDA was maintained until 31 GW. PSL (10 mg/day) was increased to 15 mg/day at 13 GW, because serum levels of complements (C3, C4, CH50) decreased; PSL was increased to 30 mg/day for 2 weeks at 26 GW, because serum levels of C4 and CH50 tended to decrease further. Unfractionated heparin (10,000 unit/day) was increased to 12,000 units/day at 24 GW (Fig. 1).

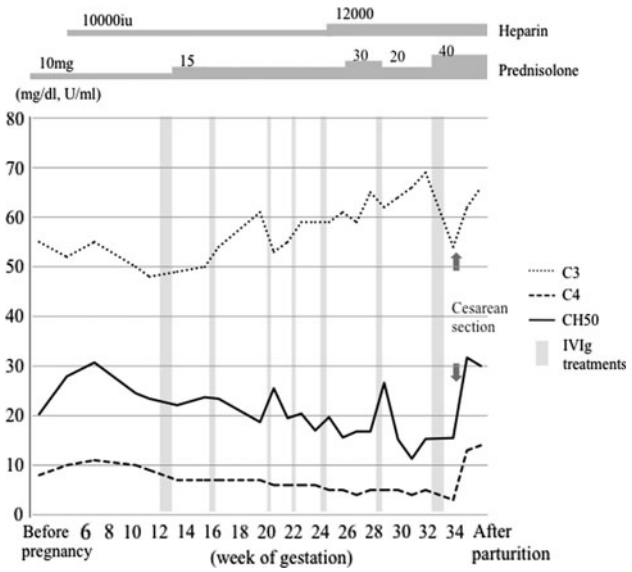

Fig. 1 Changes in serum complement levels

At 12 GW, the first course of IVIg therapy (20 g/day, 5 consecutive days, total 100 g) was employed using Kenketsu Glovenin-I™ (Nihon Pharmaceutical Co., Ltd., Tokyo) or Kenketsu Venilon-I™ (Teijin Co., Ltd., Tokyo, Japan) followed by 40 g (20 g/day, 2 consecutive days) of IVIg at 16 GW. After IVIg (20 g/day, 1 day) at 20 GW skin eruptions developed. Therefore, additional IVIg (20 g/day, 1 day) was applied at 22 GW. At 24 and 28 GW, administration of 40 g of IVIg was completed without adverse effects (Fig. 1).

The fetal growth was appropriate for the gestational age, and no sign of pregnancy-induced hypertension or abnormal maternal blood tests was detected until 32 GW. Then, platelet counts decreased from 14.5 × 10^4/μl to 6.9 × 10^4/μl. PSL was increased to 40 mg/day, and IVIg therapy (20 g/day, 5 consecutive days, total 100 g) was performed with informed consent. However, platelet counts minimally increased to 8.3 × 10^4/μl. Therefore, we performed cesarean section at 34 GW, and she delivered a female baby weighing 2,152 g without thrombocytopenia or neonatal lupus erythematosus. Before cesarean section, unfractionated heparin was changed to 5,000 unit/day of low molecular weight heparin and dalteparin sodium (Fragmin™, Eisai Co., Ltd., Tokyo, Japan). PSL was tapered off after the operation. The patient, with a platelet count of 15.6 × 10^4/ml, was discharged 11 days after delivery. Placental pathological findings indicated small infarctions and calcification.

We repeatedly measured aPLs during the pregnancy. Serum levels of aCL IgG, aCL IgM or aCLβ2GPI IgG were all negative through the course of pregnancy. LA tests were constantly positive at similar levels (1.7–1.9) during pregnancy. We measured aPE IgG and IgM from 13 GW

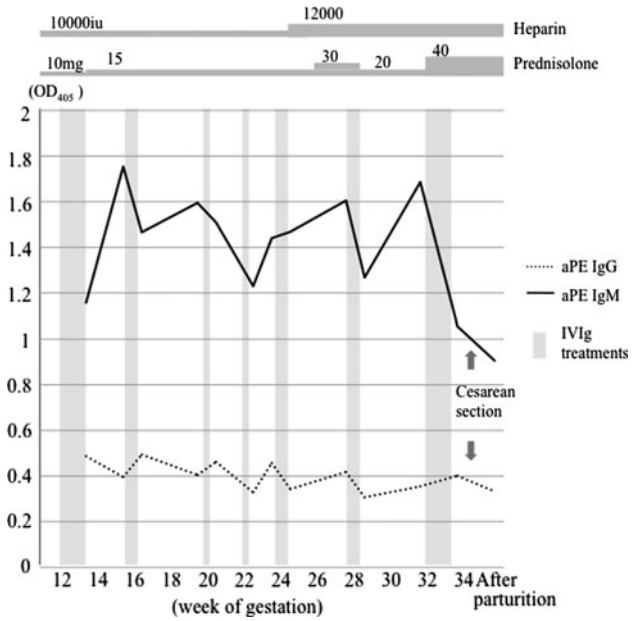

Fig. 2 Changes in titers of kininogen-dependent antiphosphatidylethanolamine antibodies. aPE, kininogen-dependent antiphosphatidylethanolamine

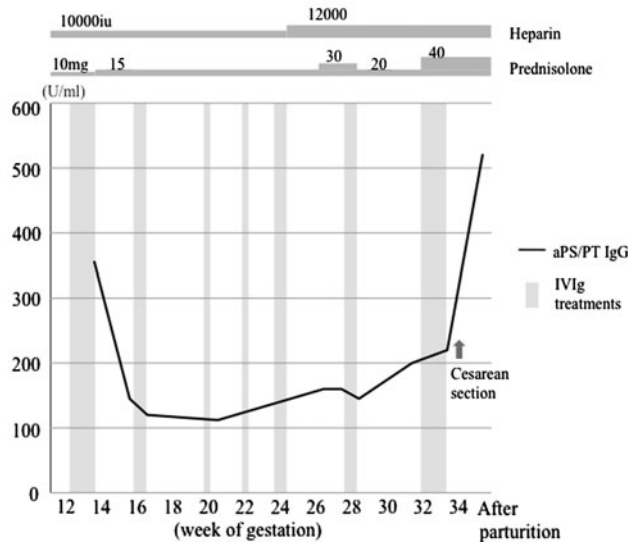

Fig. 3 Changes in titers of phosphatidylserin-dependent antiprothrombin IgG. aPS/PT, phosphatidylserin-dependent antiprothrombin

of the index pregnancy. Figure 2 shows the changes of serum levels of aPE IgG (normal range < 0.300) and IgM (normal range < 0.450). The level of aPE IgG tended to decrease during pregnancy. The level of aPE IgM increased from 1.16 at 13 GW to 1.75 at 15 GW, and significantly ($P = 0.028$ by paired t test) decreased after each course of IVIg therapy. The levels of aPE IgM (mean + SD 1.60 + 0.10, range 1.48–1.75) 4 days before commencement of IVIg decreased to 1.33 + 0.18 (range 1.06–1.51) 2

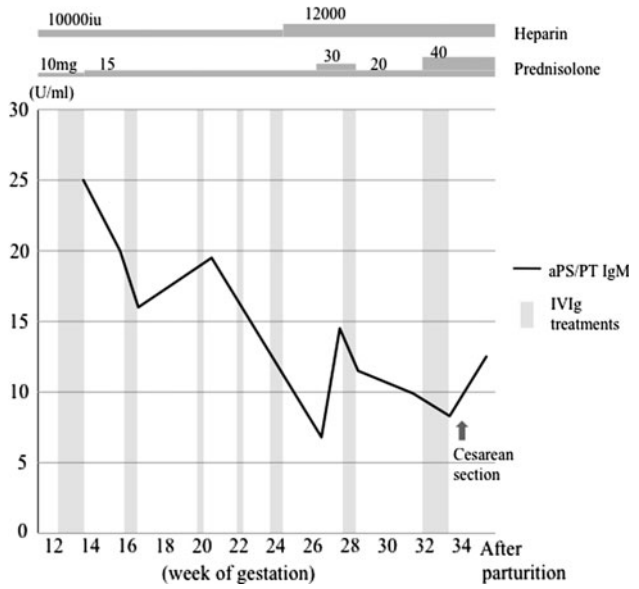

Fig. 4 Changes in titers of phosphatidylserin-dependent antiprothrombin IgM. aPS/PT, phosphatidylserin-dependent antiprothrombin

or 3 days after completion of IVIg. Titers of aPS/PT IgM were reduced; titers of aPS/PT IgG at 13 GW were higher than those of nonpregnant status, but were maintained at low levels during repeated IVIg therapies (Figs. 3, 4). The measurement methods of all of the abovementioned aPLs and the normal ranges were shown elsewhere [7, 8].

Discussion

This case of aspirin-heparinoid-resistant APS was treated successfully by repeated IVIg together with LDA, heparin and steroids. Titers of aPS/PT IgG, IgM and aPE IgG, IgM were reduced or maintained at low levels. The level of aPE IgM significantly decreased after each IVIg treatment. It was known that heparin had a function of suppressing the complement activity and protected mice from pregnancy complications induced by aPL [9]. Other investigators reported the function of heparin to inactivate complements in various diseases [10]. Therefore, we increased a dose of heparin at 24 GW when serum levels of C4, CH50 decreased. However, these complement levels were not restored, so we increased the dose of prednisolone at 26 GW.

Carreras et al. [11] first reported successful IVIg therapy in a pregnant woman with LA and a history of nine recurrent pregnancy losses (RPL). A randomized controlled trial comparing LDA plus heparin plus IVIg with LDA plus heparin therapies in 16 APS patients failed to show differences in the efficacy [12]. Triolo et al. [13] reported that administration of LDA plus low molecular weight heparin resulted in a higher birth rate (84%) than

IVIg alone (57%) in RPL women with aCLβ2GPI. But later, they also reported successful IVIg therapy in eight of ten APS women previously unresponsive to LDA plus heparin [14]. Therefore, a certain subgroup of APS women who are resistant to aspirin-heparin therapy as presented in the present report might benefit from the possible advantages of IVIg therapy.

The optimal dosage of IVIg in APS women during pregnancy was not determined and still needs to be debated. Yamada et al. first performed high-dose IVIg therapy (20 g/day, 5 consecutive days, total 100 g) in early pregnancies of women with unexplained severe RPL, demonstrating a high live birth rate [15–17]. Carreras et al. [11] 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 1 g/kg IVIg therapies [14]. The present patient had a history of intrauterine fetal death at 24 GW, so we planned high-dose IVIg therapy at 12 GW followed by cyclic courses of 40 g IVIg every 4 weeks from 12 to 32 GW.

The mechanisms of IVIg efficacy for pregnant women with APS have not been fully assessed. The following possible mechanisms explain its broad activity: (1) provision of anti-idiotypic antibodies and the function as an 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 [18, 19]. As for the anti-idiotypic antibody function, inhibitory effects of IVIg on aCL and LA were reported [20–22]. Caccavo et al. [20] demonstrated that aCL binding to cardiolipin was suppressed by $F(ab')_2$ fragments derived from IVIg in a dose-dependent manner. Galli et al. [21] also demonstrated dose-dependent suppression of LA activity in patients, using either IVIg or $F(ab)_2$ fragments. IVIg may induce a long-term decrease in autoantibody production by acquiring the inactivation of idiotype-bearing B cell clones [23]. We for the first time found that repeated IVIg reduced serum levels of aPS/PT and aPE in the present patient with aspirin-heparinoid-resistant APS, and IVIg might have anti-idiotypic antibody effects against these aPLs.

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