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Case Report

Intravenous immunoglobulin therapy for aspirin-heparinoid-resistant antiphospholipid syndrome

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Running title: Immunoglobulin therapy for antiphospholipid syndrome

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 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 baby female weighing 2,152g 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.

Key words: antiphospholipid syndrome, aspirin, heparin, heparinoid, immunoglobulin

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 high live birth rate (71%) with low dose aspirin (LDA) plus heparin as compared with 42% with LDA alone in APS women [5]. The LDA plus heparin had fewer maternal adverse effects and was found to be superior to LDA plus steroids [6].

However, we encountered APS women who underwent LDA plus heparin/heparinoid with or without steroids and failed to have a healthy infant. Such cases can be designated as 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 an infertility clinic of The Hokkaido University Hospital for consultations. Her first pregnancy ended in spontaneous abortion at 7 weeks of gestation (GW). Only 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 cell 6400 /μl, red blood cell 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 sec, APTT 44.2 sec (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, ß2 glycoprotein I-dependent anticardiolipin (aCLß2GPI) 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), 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 antiphosphatidylethanolamine (aPE) IgG or IgM was not measured.

A combined therapy of LDA (81 mg/day, orally), PSL (10 mg/day, orally), unfractionated heparin (5000 unit x2 sc/day), and intravenous infusions of intact type immunoglobulin (IVIg) for the third pregnancy was planed with informed consent. LDA was commenced before conception. Immediately after 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; and PSL was increased to 30 mg/day for two weeks at 26 GW, because serum levels of C4 and CH50 tended to be further decrease. Unfractionated heparin (10000 unit/day) was increased to 12000 unit/day at 24 GW (Fig 1).

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 eruption developed. Therefore, additional IVIg (20 g/day, 1 day) was applied at 22 GW. At 24 and 28 GW, 40 g of IVIg were 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 $14.5\times10^4/\mu l$ to $6.9\times10^4/\mu l$. 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 $8.3\times10^4/\mu l$. Therefore, we performed cesarean section at 34 GW, and she delivered a baby female 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, dalteparin sodium (Fragmin™, Eisai Co., Ltd., Tokyo, Japan). PSL was tapered off after the operation. The patient with the 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 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 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) decrease after each IVIg therapy. The levels of aPE IgM (mean + S.D 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 or 3 days after completion of IVIg. Titers of aPS/PT IgM were reduced; and titers of aPS/PT IgG at 13GW was higher than that of nonpregnant status, but were maintained at low levels during repeated IVIg therapies (Fig. 3, Fig. 4). The measurement methods of all abovementioned aPLs and the normal ranges were shown elsewhere [7, 8].

DISCUSSION

The present case of aspirin-heparinoid-resistant APS was treated successfully by repeated IVIg together with LDA, heparin and steroid. Titers of aPS/PT IgG, IgM and aPE IgG, IgM were reduced or maintained at low levels. The level of aPE IgM and 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 increase a 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 9 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 G et al [13]. reported that LDA plus low molecular weight heparin had a higher birth rate (84%) than that of IVIg alone (57%) in RPL women with aCLβ2GPI. But later, they also reported successful IVIg therapy in 8 of 10 APS women previously unresponsive to LDA plus heparin [14].

Therefore, a certain subgroup of APS women, who were resistant to aspirin-heparin therapy as presented in the present report, might be necessary to undergo the possible advantage of IVIg therapy.

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 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 1g/kg IVIg therapies [14]. The present case had a history of intrauterine fetal death at 24 GW, so we planed a high dose IVIg therapy at 12 GW followed by cyclic courses of 40 g IVIg every four weeks from 12 to 32 GW.

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 [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 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 case with aspirin-heparinoid-resistant APS; and IVIg might have anti-idiotypic antibody effects against these aPLs.

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Figure legends

Figure 1

Changes in serum complement levels.

Figure 2

Changes in titers of kininogen-dependent antiphosphatidylethanolamine antibodies.

aPE, kininogen-dependent antiphosphatidylethanolamine.

Figure 3

Changes in titers of phosphatidylserin-dependent antiprothrombin IgG.

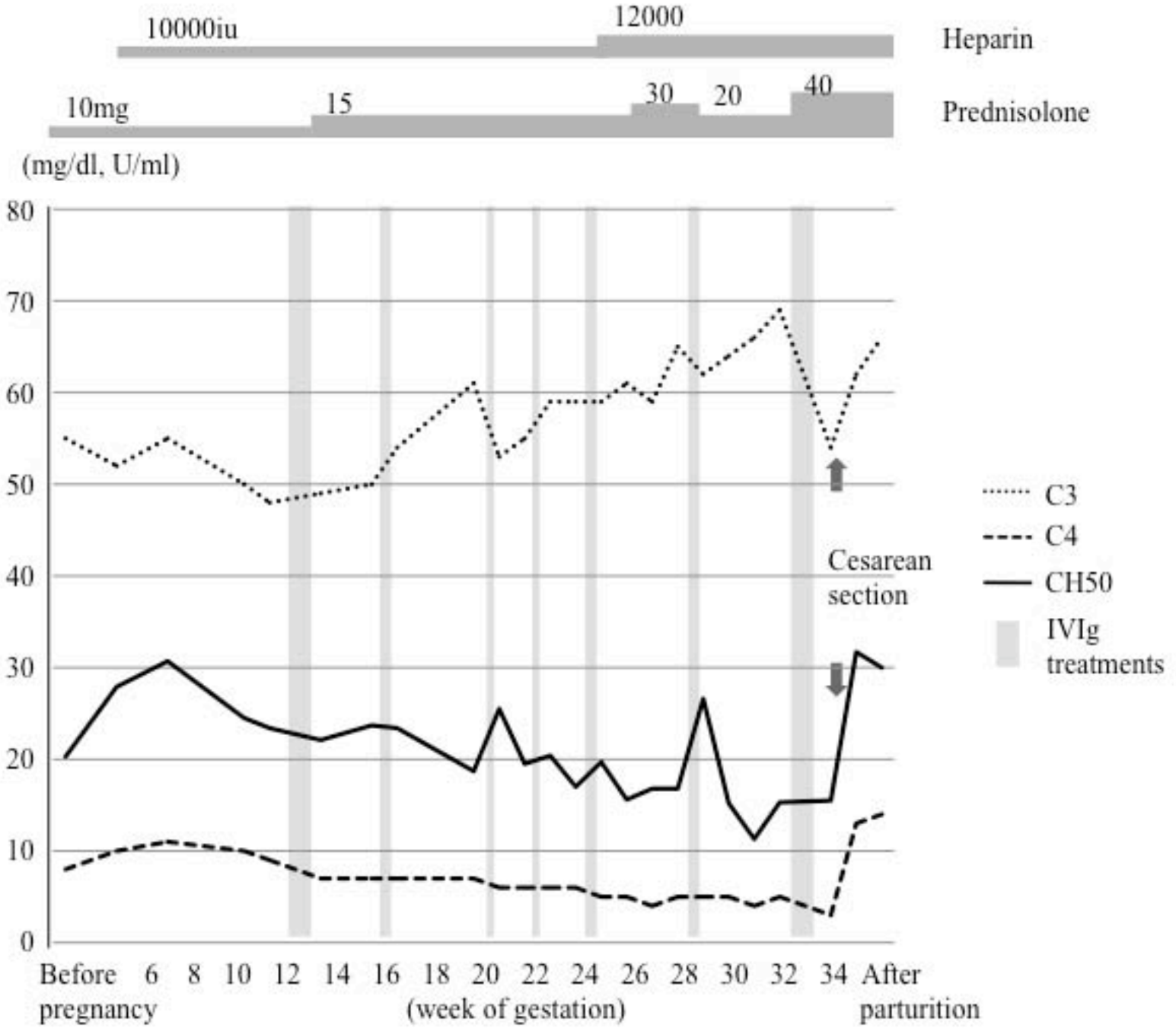
aPS/PT, phosphatidylserin-dependent antiprothrombin

Figure 4

Changes in titers of phosphatidylserin-dependent antiprothrombin IgM.

aPS/PT, phosphatidylserin-dependent antiprothrombin

Figure 1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Cesarean section
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Before pregnancy
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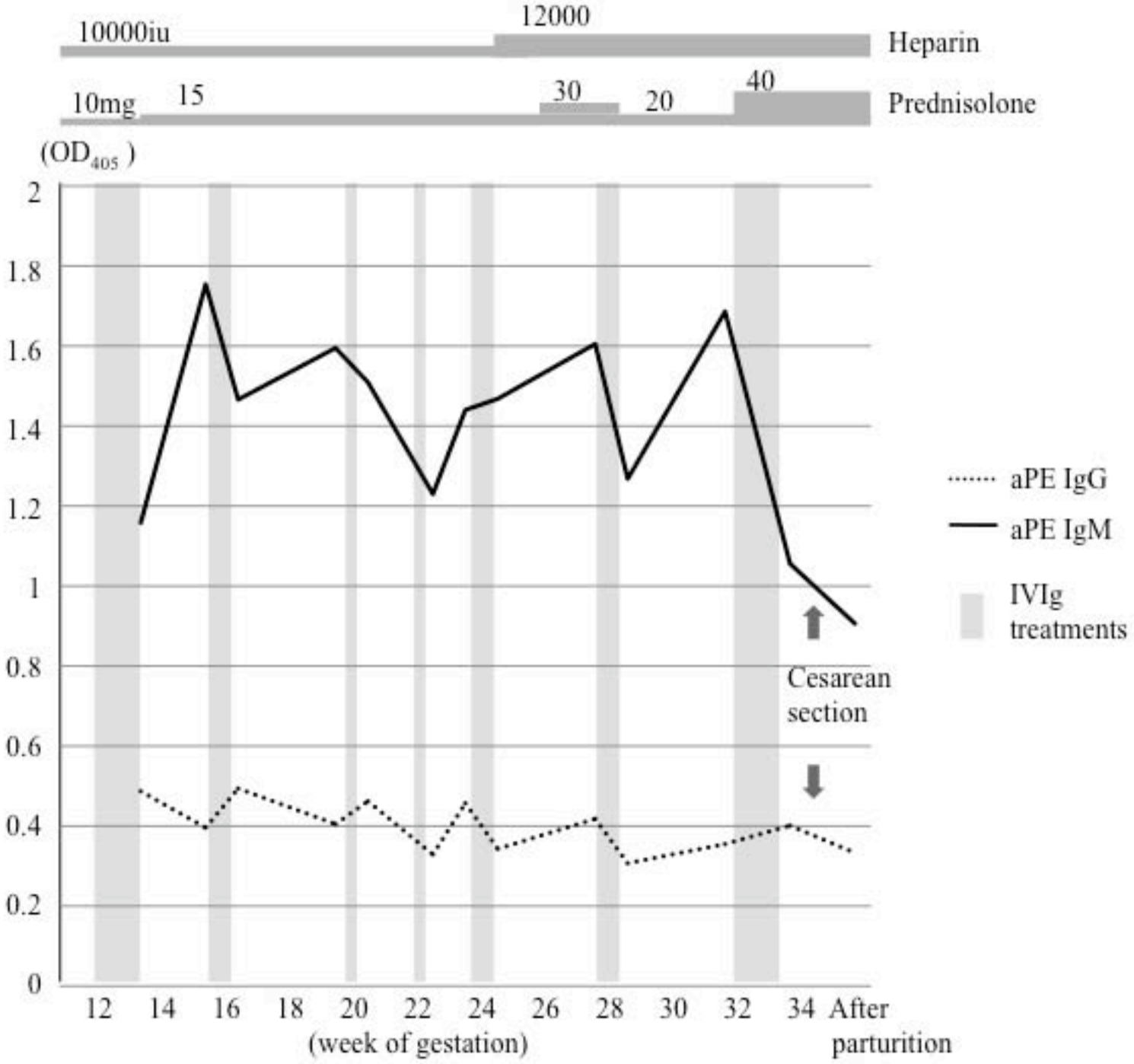
After parturition
(week of gestation)

Figure 2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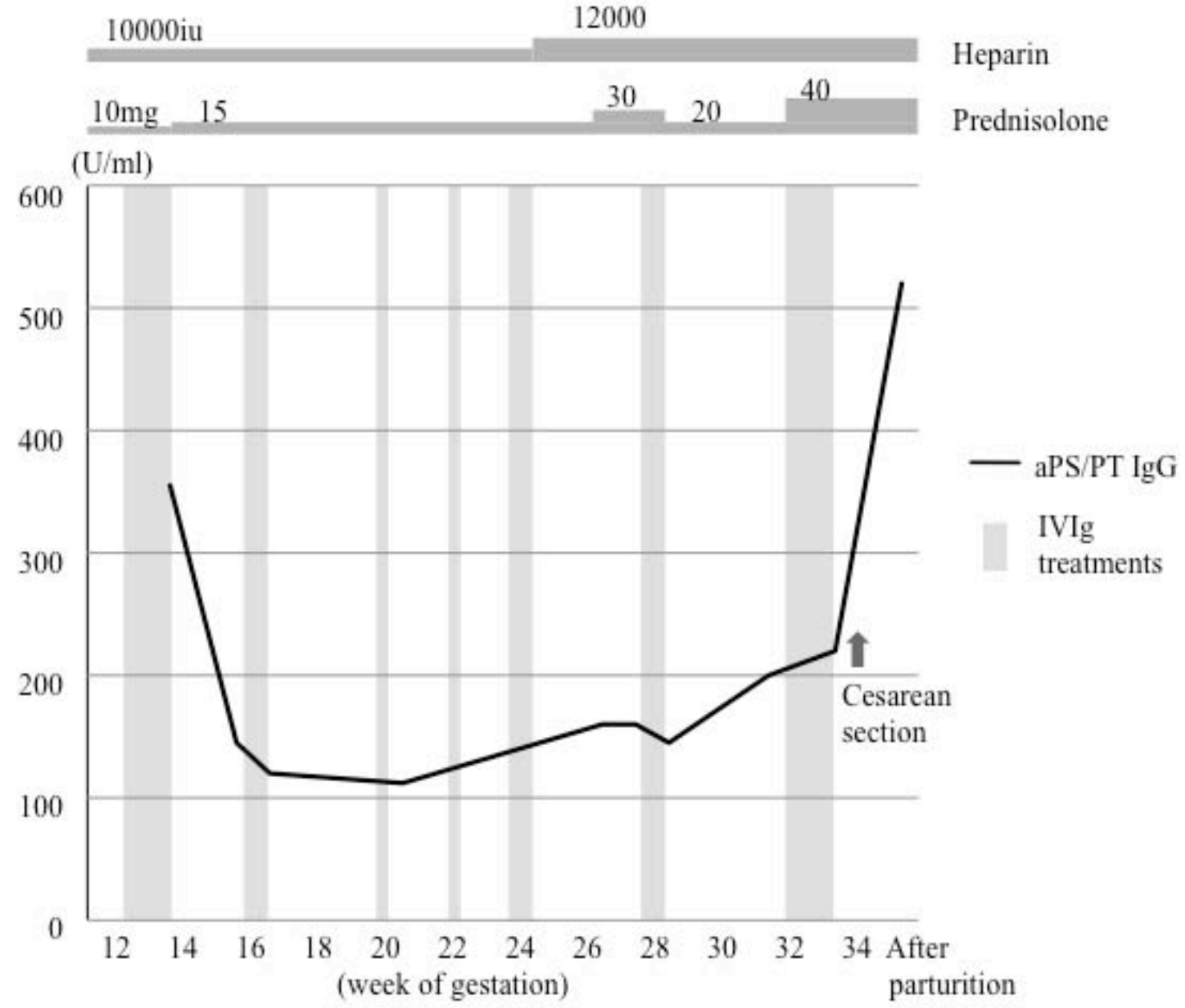
After parturition
(week of gestation)

Figure 3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treatments
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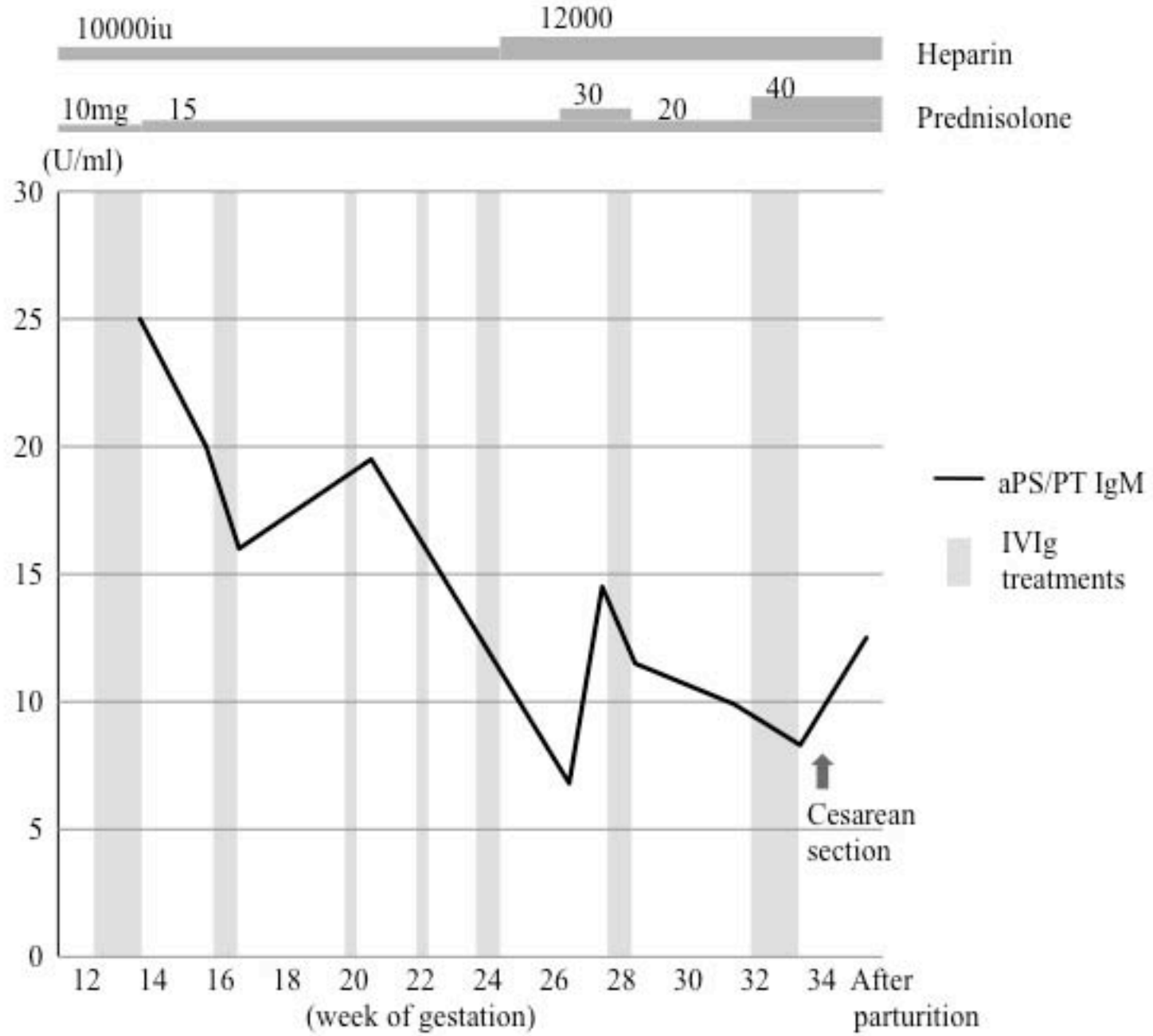
After
parturition
(week of gestation)

Figure 4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After
parturition
(week of gestation)