Treatment of Antiphospholipid Syndrome in Pregnancy with Low Doses of Intravenous Immunoglobulin

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Key words: antiphospholipid syndrome, neonatal lupus, pregnancy, intravenous immunoglobulin

IMAJ 2007;9:555–556

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Some women with antiphospholipid syndrome may manifest several pregnancy complications simultaneously, such as severe thrombocytopenia, early onset of preeclampsia, and severe intrauterine fetal growth delay. Neonatal lupus is rare, but a serious pregnancy complication is usually seen in patients with secondary APS. It is uncertain whether neonatal lupus could be manifested in patients with primary APS [1].

There are still many dilemmas concerning APS treatment in pregnancy. Clinical studies performed in a limited number of patients reported good results when high doses of human intravenous immunoglobulin were added to standard treatment with aspirin and low molecular weight heparin [2]. Wider administration of IVIG is limited because the drug is extremely expensive. To the best of our knowledge the successful use of low doses of IVIG in the treatment of APS has not been previously reported.

Patient Description

A 34 year old gravida 1 was admitted to the high risk pregnancy unit at 26 weeks gestation with severe fetal growth delay due to uteroplacental insufficiency. Elevated blood pressure together with thrombocytopenia was noted. Results of repeated laboratory tests revealed severe preeclampsia and progressive thrombocytopenia without evidence of the HELLP syndrome (**h**emolysis, **e**levated **l**iver enzymes, **l**ow **p**latelet), but there were increased D-dimer levels, extreme elevation of activated partial thromboplastin time, and significant presence of lupus anticoagulant; positive anticardiolipin antibodies were detected. Hypertension was treated using 750 mg methyldopa daily. Antenatal corticosteroid therapy for induction of pulmonary maturity was administered. Seven days after admission (27 gestational weeks), cesarean section was performed because of the progressive thrombocytopenia and fetal distress. The male child, weighing 800 g and with an Apgar score of 5/7, was transferred to the neonatal intensive care unit. Eight days later the infant died as the result of sepsis. Examination of the placenta revealed the presence of infarcts involving more than 30% of the placental parenchyma.

After pregnancy the patient was tested for both inherited and acquired thrombophilias. Tests for inherited thrombophilias were negative while tests for acquired thrombophilias confirmed the presence of positive antiphospholipid antibodies: lupus anticoagulant, anti-cardiolipin antibodies and beta-2 glycoprotein 1. Antinuclear antibodies, anti-DNA antibodies (anti-DNA) and anti-Ro antibodies were also present [Table]. However, the patient could not be classified as secondary APS due to the lack of the clinical criteria for systemic lupus erythematosus.

Autoantibodies before and during pregnancy in a patient with APS on combined therapy with low molecular weight heparin, aspirin, dexamethasone and low dose IVIG

Autoantibodies	Before pregnancy	6 gest wks*	14 gest wks*	23 gest wks*	30 gest wks*
LA	+	+	+	+	+
aCL-IgG	163.3	53.2	53.2	20.4	20.4
aCL-IgM	1.2	1.2	0	23.2	23.2
β2G-IgG	25.3	23.5	0	4.2	4.2
β2G-IgM	13.9	30.3	12.1	12.1	12.1
Anti-Ro/SSA	41.3	48.3	89.6	29.2	48.3
Anti-La/SSB	0	48.3	89.6	29.2	48.3
ANA	1/20	1/40	1/40	1/40	1/80
aDNA	86.4	90.9	84.4	25.8	32.1

LA = lupus anticoagulant, Ig = immunoglobulin, aCL = anti-cardiolipin antibodies (GPL U/ml): negative < 10, β2-GP = β2 glycoperotein-1 (U/ml): IgG negative < 20, IgM negative < 10, Anti-Ro/SSA antibodies (U/ml): negative < 10, Anti-La/SSB antibodies (U/ml): negative < 10, ANA = antinuclear antibodies, with homogenous pattern, aDNA = anti-DNA antibodies: negative < 30

APS = antiphospholipid syndrome
IVIG = intravenous immunoglobulin

One year after the first delivery the patient was pregnant again. Her second pregnancy was monitored from the first trimester by both an obstetrician and a rheumatologist. From the beginning of the pregnancy she was treated with low molecular weight heparin (Fraxiparin® 0.6 mg/day) and aspirin 100 mg/day. Dexamethasone (1.5–2.5 mg/day) had been given from the 13th to the 36th gestational week. Each month, nine times during the pregnancy, she also received an IVIG infusion at a dose of 5 g/month – a total dose of 45 g.

During the pregnancy the patient was stable, with no signs of arthritis, skin lesions, serositis or kidney disorders. Complete blood count was within normal range. The oral glucose tolerance test was performed at 26 gestational weeks and indicated the presence of gestational diabetes mellitus, which was stabilized after a special diet was introduced. Autoantibody concentrations were monitored at 2 month intervals [Table]. Ultrasound examinations confirmed normal fetal growth during pregnancy and normal uteroplacental and fetoplacental blood flow at 22 weeks.

At 37 gestational weeks, cesarean section was performed and a healthy girl weighing 3060 g and with an Apgar score of 9/10 was born. After the birth the neonate manifested cutaneous lesions and an erythematous scarring rash, which suggested the presence of neonatal lupus. Those changes disappeared during the second month of life.

Comment

Standard treatment with low molecular weight heparin and aspirin was administered considering the diagnosis of primary APS. The decision to institute IVIG therapy was based on severe thrombocytopenia and the poor outcome of a previous pregnancy [3]. Due to the elevated concentrations of anti-Ro antibody titer and the presence of certain markers of the connective tissue disease (antinuclear antibody and anti-DNA antibodies), we opted for dexamethasone in order to prevent congenital heart block. Dexamethasone passes through the placenta without conversion [4]. The fact that the neonate manifested cutaneous lesions as part of neonatal lupus justified the use of dexamethasone since there was a strong possibility that without the therapy congenital heart block would have developed. In the available literature we did not find any data on the presence of anti-Ro and anti-La antibodies in primary APS patients.

IVIG therapy implies the use of high doses (1 g/kg/month). Since this drug is extremely expensive, its use is justified only when standard therapy fails [5]. However, the use of high doses of IVIG to treat APS is not approved by our health insurance companies. In view of the favorable effect of IVIG, its use could be justified in patients with APS and thrombocytopenia. For all these reasons we decided to use IVIG doses ten times lower than standard. Since the pregnancy ended well, our therapy could be considered beneficial.

In order to objectively evaluate the effects of low dose IVIG on pregnancy outcome in patients with APS, large well-controlled clinical studies should be undertaken.

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