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Successful preventive treatment of congenital heart block during pregnancy in a woman with systemic lupus erythematosus and anti-Sjögren's syndrome A/Ro antibody

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Congenital heart block (CHB) that is a manifestation of neonatal lupus syndrome (NLS) carries a poor prognosis. The treatment response of established heart block in NLS is usually unsatisfactory. Preventive treatment during pregnancy, however, before the critical period of cardiac development, can prevent the development of CHB. A Taiwanese woman with systemic lupus erythematosus (SLE) was positive for anti-Sjögren's syndrome A (SSA)/Ro antibody. Her first pregnancy resulted in intra-uterine fetal death. Her second pregnancy resulted in CHB, despite dexamethasone treatment, and neonatal death at age 1 day despite pacemaker implantation. During her third pregnancy, dexamethasone was given starting at week 10, azathioprine at week 18, and plasmapheresis was performed every other day for 5 times starting at week 20 of gestation. Cesarean section was performed due to oligohydramnion at week 31 of gestation and a healthy girl was delivered. This case suggests that judicious use of fluorinated glucocorticoids, immunosuppressants, and plasmapheresis may prevent development of CHB in pregnant women with SLE who are anti-SSA/Ro antibody positive and have previous children with CHB.

Key words: Congenital heart defects, heart block, plasmapheresis, SS-A antibodies, systemic lupus erythematosus

Neonatal lupus syndrome (NLS) is a classic model of passively acquired autoimmunity. Congenital heart block (CHB) is a manifestation of NLS. Pregnant women whose sera contain anti-Sjögren's syndrome A (SSA)/Ro antibodies (in the presence or absence of anti-SSB/La antibodies) have a 1-7.5% risk of having a child with third-degree CHB [1-3]. The CHB is presented as fetal bradycardia and cardiac failure, i.e., pericardial effusion and hydrops, after 16 and 24 weeks of gestation. The recurrence rate of CHB ranged from 16-20% in different series [3-6], and the prognosis is poor. About 31% of involved children die and 71% of deaths occur in the first month of life because of heart failure. Sixty seven percent of cases require pacemakers [4,5].

The most important treatment is preventive, involving fluorinated glucocorticoids, immunosuppressants, intravenous immunoglobulin (IVIG) [7], and plasmapheresis [8-10] during pregnancy before the critical period of cardiac development [9,11]. Treatment response of established cases is poor and the reversal of established heart block is rare [9,12,13]. Other treatments are mostly symptomatic, including digitalis, beta-adrenergic agonists, and inotropic agents [5,14,15]. They are bridges to pacemaker treatment after birth and essential for the baby's survival.

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Case Report

This 32-year-old woman was diagnosed as having systemic lupus erythematosus (SLE) in May 1997, according to the American College of Rheumatology 1997 revised criteria. She presented with polyarthritis, pancytopenia, nephrotic syndrome, positive antinuclear antibody (ANA) and anti-double-stranded DNA (anti-ds DNA) antibody. Anti-SSA/Ro antibodies were positive by fluorescence immunoassay (EliA™; Pharmacia Diagnostics, Freiburg, Germany). Anti-SSB/La antibodies (EliA™; Pharmacia Diagnostics), anticardiolipin immunoglobulin M (IgM) and immunoglobulin G (IgG) were all negative.

Her first pregnancy was a twin pregnancy in February 1999. Her lupus status during the pregnancy was stable though serum complement level was

depressed, C3 57.9 mg/dL (normal range, 73-134) and C4 6.05 mg/dL (18.2-45.5) at 5 weeks of gestation. There was no proteinuria. Anti-SSA/Ro antibody was >240 U/mL (<7); anti-SSB/La antibody and anti-cardiolipin IgG and IgM were negative. Prednisolone 10 mg/day was given before the fifth week of gestation and tapered to 5 mg/day from then on until termination. Fetal ultrasonography revealed a normal fetal heart and no evidence of cardiac failure at 21 weeks of gestation. Fetal bradycardia about 70 beats/min and preterm rupture of membrane occurred at 25 weeks of gestation and both of the fetuses died in utero. Post-partum examination of the placenta revealed some calcified spots without evidence of placental insufficiency. No abnormalities were detected on post-mortem examination of the babies. However, the hearts were not examined microscopically.

She had a second pregnancy 1 year later in January 2000. At 9 weeks of gestation, serum complement level was 47.4 mg/dL (C3) and <5.73 mg/dL (C4). Anti-SSA/Ro antibody was >240 U/mL, anti-SSB/La antibody and anti-cardiolipin IgG/IgM were negative. Prednisolone 5 mg/day was given before 13 weeks of gestation and was increased to 10 mg/day thereafter. Fetal bradycardia (60 beats/min) was detected at 21 weeks of gestation and dexamethasone 4.5 mg/day was given starting from the 25th week of gestation. At 34 weeks of gestation, she delivered a female baby with CHB by cesarean section. The C3 and C4 level of the baby after birth was 94.5 mg/dL and 8.10 mg/dL, respectively; anti-ds DNA titer was 11 IU/mL (<40). A pacemaker was implanted but the baby died of cardiac failure 1 day later.

She had her third pregnancy in June 2002. Anti-SSA/Ro titer in May was 1520 U/mL. Dexamethasone 4.5 mg/day was started at 10 weeks of gestation, and anti-SSA/Ro was 750 U/mL 4 weeks later. Azathioprine 100 mg/day was added from 18 weeks of gestation but there was no further decrease in anti-SSA/Ro titer (990 U/mL). After informed consent was obtained from the mother on November 5, 2002, plasmapheresis was performed every other day for 5 times. Plasmapheresis was carried out using an OP-05 (Asahi Kasei Medical Co., Ltd., Tokyo, Japan) and AC-1770 (Asahi Kasei Medical Co.) plasma filter through peripheral venous access. Total exchange volume was 3000 mL each time and replacement fluids were 2 vials of 20% albumin (200 mL/vial). The titer of anti-SSA/Ro was decreased to 233 IU/mL after completion of the plasmapheresis sessions. Dexamethasone was tapered to 3 mg/day on week 23 of gestation and continued until delivery. At the end of week 31 of gestation, cesarean section was performed due to oligohydramnion, and a healthy female baby was born. The mother's titer of anti-SSA/Ro was 459 U/mL 1 week before delivery and was 630 U/mL 2 months after delivery. The changes of anti-SSA/Ro titers during pregnancy and plasmapheresis are shown in Fig. 1 and Fig. 2.

The birth weight of the baby was 1440 g. Her heart rate was 150 beats/min and the electrocardiography was normal. The placenta was oval with some calcification and weighed 300 g. Blood cell count

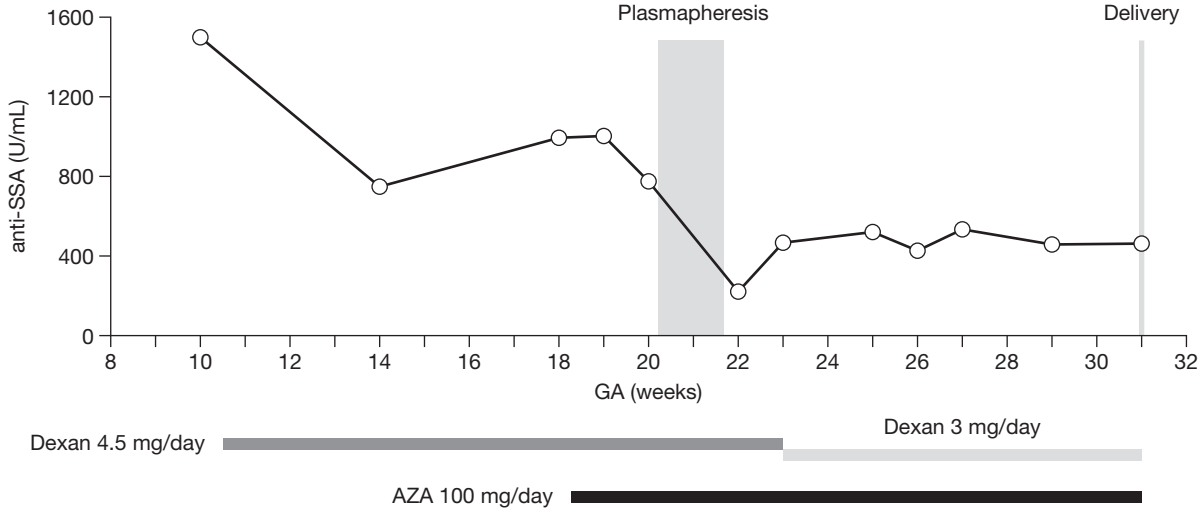

Fig. 1. The titer of anti-Sjögren's syndrome A (SSA)/Ro antibody in the pregnancy course and its relation with therapy and plasmapheresis. Plasmapheresis was performed every other day for 5 times from November 5, 2002 (week 20 of gestation). GA = gestational age; Dexan = dexamethasone; AZA = azathioprine.

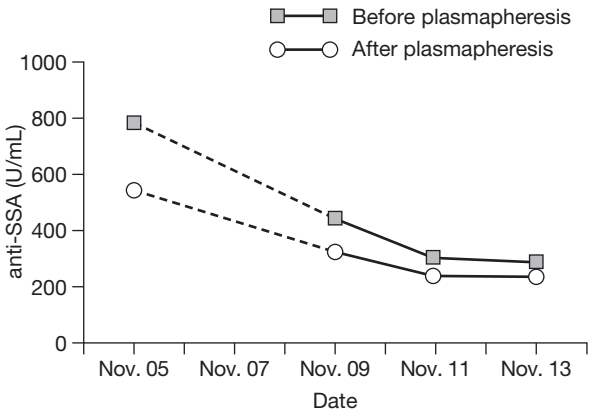

Fig. 2. Titer of anti-Sjögren's syndrome A (SSA)/Ro antibody during plasmapheresis. Plasmapheresis was started on November 5 and given every other day, for 5 times. The titer of SSA on November 7 was not available.

showed hemoglobin 15.5 g/dL, platelet $307 \times 10^3/\mu L$, and white blood cells $7.1 \times 10^3/\mu L$. Aspartate and alanine aminotransferase were within normal limits. Chest roentgenography was normal and showed no evidence of interstitial infiltration. Three weeks after birth, ANA was negative, anti-SSA/Ro was 14.7 U/mL and anti-SSB/La antibody was negative. The baby did not show any dermatologic change characteristic of NLS in the first year of life.

Discussion

CHB is the most severe manifestation of NLS, and is associated with high morbidity and mortality. The frequency of CHB in a primigravida with positive antibodies is 1-7.5%; however, the recurrence rate is about 2-3 times higher, i.e., around 20% [3-6]. Risk factors for recurrence other than a previous child affected with CHB are positive anti-52-kd SSA/Ro and/or anti-SSB/La antibodies [3-5], and the presence of human leukocyte antigen-DR3 in the mother [9,12,16]. Fifty three percent of CHB is diagnosed between 16 and 24 weeks of gestation, and 24% between 25 and 30 weeks. The fetus at risk should be closely followed with echocardiograms starting at 16 to 24 weeks of gestation and continuing thereafter, because this is the most prevalent period for detection of fetal bradyrhythmia [17]. Incomplete heart block can be detected earlier by measuring the electrocardiogram equivalent of the PR interval by echocardiography [18]. Myocarditis may be followed by CHB. Therefore, the detection of a pericardial effusion, decreased systolic ejection fraction, and biphasic Doppler flow in the inferior vena cava suggesting probable myocarditis may be deemed early signs of CHB [19,20].

The pathogenic mechanisms of CHB remain unclear [21]. Maternal IgG is present in fetal circulation after 6-11 weeks of gestation, but the fetal concentration of total IgG remains low until week 17. It increases steadily to 4-fold by 24 weeks of gestation and around 8-fold by 32 weeks as the placental transfer becomes more efficient. The fetal heart reaches its functional maturity by 16 weeks of gestation. Most CHB is diagnosed after 16 to 24 weeks of gestation, and the earliest documented case of CHB in the absence of structural defects was made at 16 weeks of gestation [1]. Therefore, the timing of fetal injury does not appear to be random, but rather occurs during a defined gestational period, after the fetus passively acquires maternal anti-SSA/Ro and/or anti-SSB/La antibodies. There are probably 2 mechanisms by which these autoantibodies react with the fetal heart. First, direct interaction with cardiac ion channels due to cross-reactivity is suggested by an inhibitory effect of anti-52-kd SSA/Ro antibodies on calcium fluxes across cell membranes [22]. Second, the fetal intracellular antigens are translocated to the cell surface by physiologic apoptosis [21]. In this manner, cognate maternal antibodies bind to these antigens (Ro/La) and inadvertently program an inflammatory response by macrophages. Repeated inflammation results in fibrosis [21]. Therefore, the rationales for management are: (1) to decrease maternal autoantibodies and then to decrease the placental transfer of these antibodies, and (2) to decrease the inflammation once it occurs and as early as possible before it leads to permanent fibrosis and irreversible CHB.

The maternal autoantibodies are effectively decreased by IVIG [7] and plasmapheresis [8-10,12]. However, there is no consensus about whether steroid and/or azathioprine can effectively decrease the titer of anti-SSA/Ro or anti-SSB/La antibodies, even though they will decrease the titer of anti-ds DNA antibodies [9,19,23]. Fluorinated corticosteroids (dexamethasone or betamethasone), which are not inactivated by placental hydroxylase, are useful in fetal myocarditis and CHB, because they may decrease fetal inflammation [19]. Dexamethasone was reported to reverse carditis and incomplete CHB, and to improve hemodynamics and signs of fetal cardiac failure [19-21,23,24]. Therefore, dexamethasone treatment is recommended if the block is recent or incomplete, or there is evidence of cardiac failure [19,25]. Although maternal tolerability

of dexamethasone in our patient was excellent, dexamethasone may be associated with maternal glucose intolerance, infection in the fetus, adrenal insufficiency of the fetus, intrauterine growth restriction (IUGR), and oligohydramnion [12,25]. As in our case, IUGR was observed and cesarean section was performed at 31 weeks of gestation due to oligohydramnion. While plasmapheresis has been reported to effectively manage CHB in utero, complete CHB persisted after birth despite treatment [12,26].

For most cases of CHB, prednisolone is not likely to prevent recurrence, despite its routine use. Fluorinated corticosteroids, which can transfer into fetal circulation, may prevent the initiation of inflammation in fetal heart; however, data are lacking to demonstrate their effectiveness. IVIG [7] and plasmapheresis [8-10] have been used to decrease the transfer of maternal antibodies to the fetus. If the level of these pathogenic autoantibodies can be decreased before or during the critical period of heart development, it may prevent the development of CHB. The recurrence rate of CHB is 1 in 8 mothers treated with IVIG between 14 and 18 weeks of gestation. However, the 95% confidence interval of the recurrence rate of CHB ranges from 0.3% to 53%, which includes the possible recurrence rate of 15-20% [7]. CHB was prevented by plasmapheresis in 3 previously reported cases. The mothers in these cases all had a previous child with CHB who had died, and all mothers were positive for anti-SSA/Ro antibodies. In the first of these cases, plasma exchange was started from week 25 of gestation and continued for 4 weeks [8]. In the second case, plasmapheresis was performed 3 times a week from 19 weeks of gestation until delivery. In the third case, plasmapheresis was performed twice weekly between 7 and 16 weeks of gestation [10].

In the present case, plasmapheresis was performed every other day for 5 times at 20 weeks of gestation, and the titer of anti-SSA/Ro fell from 780 to 233 U/mL, a 70% reduction, at the end of this treatment. We used peripheral lines as vascular access, which is more convenient, and causes less discomfort to the patient and may be performed easily in outpatient clinics. Although the effectiveness of prevention cannot be demonstrated by a single case, short-term plasmapheresis during the critical period of cardiac development may still provide the best chance to prevent the development of CHB. Further studies are needed to evaluate the efficacy of plasmapheresis in preventing development of CHB.

In summary, this Taiwanese patient with lupus had 2 previous pregnancies with CHB. Her subsequent pregnancy was treated with dexamethasone, azathioprine and plasmapheresis, and she delivered a healthy female infant without CHB. Although the risk of CHB in mothers with anti-SSA/Ro and anti-SSB/La antibodies is low, the recurrence rate is about 3 times higher. Whether CHB can be successfully prevented by plasmapheresis remains to be determined. Nevertheless, this method of performing plasmapheresis is easy, convenient and well tolerated by the patient, and it may therefore be appropriate for high-risk patients. Frequent surveillance between 16 and 20 weeks of gestation and thereafter is required for at-risk pregnancies, as it may offer a chance for early diagnosis and early treatment of incomplete CHB, and may improve the outcome of the fetus.

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