Effect of Sairei-To Combined with Aspirin and Prednisolone on Four Recurrent Reproductive Failure Women who are Positive for Anti-Phospholipid Antibodies


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Abstract: We treated four pregnancy cases positive for antiphospholipid antibodies (APLs) who had experienced recurrent second trimester fetal or neonatal losses using a Japanese modified Chinese herbal medicine, Sairei-to, low dose aspirin and adrenocorticosteroid hormone. The clinical courses of their new pregnancies in conjunction with the dynamic changes in their APL titers are described in this paper, and the possible efficacy of this treatment is discussed.

The concept that autoimmune abnormalities, especially positive APLs, are generative factors for a range of reproductive failures, such as recurrent abortions, intrauterine growth retardation, intrauterine fetal death and preeclampsia, is now attracting a great deal of attention in the fields of reproductive immunology and perinatal medicine (Yasuda et al., 1995). The main mechanisms in the generation of reproductive failures are considered to be direct damage to chorionic villi by APLs during the period of placentation (Rote et al., 1998), as well as the formation of thrombi intervillous spaces (Arakawa et al., 1999). Considering these mechanisms of the reproductive failure generation by APLs, the application of immune suppressive therapy in combination with anti-coagulation therapy should be reconsidered as a treatment option.

In this context, we treated four pregnancy cases positive for APLs who had experienced recurrent second trimester fetal or neonatal losses using a Japanese modified Chinese herbal medicine, Sairei-to, low dose aspirin and an adrenocorticosteroid hormone.

Keywords: Reproductive Failure; Antiphospholipid Antibodies; Sairei-to; Low Dose Aspirin; Corticosteroid Hormone.
Case Reports

The pregnancy history, the laboratory examinations and pregnancy outcome of all four cases are summarized in Table 1 and the clinical courses of these patients are summarized in Fig. 1. We previously reported the clinical course of Case 1 as a short communication in a critical peer-reviewed journal (Yasuda et al., 1993).

Figure 1. (a) Summary of the clinical course and laboratory findings of Case 1. Activated partial thromboplastin time (APTT) is in seconds (closed circles) and the anticardiolipin antibody (aCL-Ab) is the standard deviation above the mean (open circles). PSL: Corticosteroid hormone (prednisolone), and C/S: cesarean section. (b) Summary of the clinical course and laboratory findings of Case 2. Anti-cardiolipin-β2-glycoprotein I (aCL-β2GPI) is in U/ml (closed circles) and APTT is in seconds (open circles). PSL: Corticosteroid hormone (prednisolone), IUFD: intrauterine fetal death, and NVD: normal vaginal delivery. (c) Summary of the clinical course and laboratory findings of Case 3. Anti-cardiolipin-β2-glycoprotein I (aCL-β2GPI) is in U/ml (closed circles) and the anticardiolipin antibody is the standard deviation above the mean (open circles). PSL: Corticosteroid hormone (prednisolone), IUFD: intrauterine fetal death, and C/S: cesarean section. (d) Summary of the clinical course and laboratory findings of Case 4. APTT (open circles) and lupus anticoagulant (LAC) evaluated by a diluted APTT method (closed circles) are in seconds. The abbreviations are the same as in Fig. 1c. The broken line indicates the cut-off value of LAC (55.5 seconds).
Table 1. Summary of Four Cases

<table>
<thead>
<tr>
<th>Age</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>29</td>
<td>30</td>
<td>34</td>
<td>31</td>
</tr>
<tr>
<td>Pregnancy history</td>
<td>1–8 spontaneous abortions including one abortion at 15 wks</td>
<td>1 24 wks, IUFD, 600 g, severe preeclampsia</td>
<td>1 17 wks, IUFD, 50 g</td>
<td>1 26 wks, IUFD, 630 g</td>
</tr>
<tr>
<td>APLs</td>
<td>Anti-CL-β2GPI</td>
<td>Positive: 10.2 u/ml</td>
<td>Positive: &gt; 125 u/ml</td>
<td>Positive: &gt; 125 u/ml</td>
</tr>
<tr>
<td></td>
<td>LAC</td>
<td>Not done (APTT: 42.0 sec)</td>
<td>Not done (APTT: 99.7 sec)</td>
<td>Negative</td>
</tr>
<tr>
<td></td>
<td>Anti-CL-Ab</td>
<td>Positive: 6.5 SD</td>
<td>Positive: 11.9 SD</td>
<td>Positive: 3.9 SD</td>
</tr>
<tr>
<td>Treatment</td>
<td>Sairei-to</td>
<td>9.0 g/day</td>
<td>9.0 g/day</td>
<td>9.0 g/day</td>
</tr>
<tr>
<td></td>
<td>Low dose aspirin</td>
<td>81 mg/day</td>
<td>81 mg/day</td>
<td>81 mg/day</td>
</tr>
<tr>
<td></td>
<td>Prednisolone</td>
<td>40 mg/day → 5 mg/day</td>
<td>30 mg/day → 5 mg/day</td>
<td>40 mg/day → 10 mg/day</td>
</tr>
<tr>
<td>Pregnancy outcome</td>
<td>Gestational weeks</td>
<td>37 wks</td>
<td>37 wks</td>
<td>37 wks</td>
</tr>
<tr>
<td></td>
<td>Mode of delivery</td>
<td>Cesarean section</td>
<td>Vaginal delivery</td>
<td>Cesarean section</td>
</tr>
<tr>
<td></td>
<td>Infant</td>
<td>3752 g, mature infant</td>
<td>2762 g, mature infant</td>
<td>2476 g, mature infant</td>
</tr>
</tbody>
</table>

IUFD: Intrauterine fetal death, weight refers to the body weight of an infant.
All four cases had experienced recurrent second trimester fetal or neonatal losses. They were positive for anti-cardiolipin-β₂ glycoprotein I antibodies (cut-off value: 3.5 u/ml), and/or lupus anticoagulant evaluated by diluted activated partial thromboplastin time (APTT) method (cut-off value: 55.5 seconds). Anticardiolipin antibodies (cut-off value: +3.0 SD) were also positive in all patients. None of them had history suggestive of systemic lupus erythematosus (SLE).

Autoimmune abnormalities were considered to be the cause of the recurrent reproductive failure, and treatment was started to improve their abnormal autoimmune condition. At first, a Japanese modified Chinese herbal medicine, Sairei-to (9.0 g/day), was administered before pregnancy. An adrenocorticosteroid hormone (prednisolone, PSL), at an initial dose of 30 or 40 mg/day, and low dose aspirin (81 mg/day) (LDA) were also administered during the first trimester of pregnancy. The dose of PSL was reduced to 5–10 mg per day during the prenatal course. The titer of APLs (anti-cardiolipin-β₂ glycoprotein I antibodies, lupus anticoagulant, or anticardiolipin antibodies) decreased after the treatment, and all of the pregnancies treated with this therapy resulted in normal term delivery.

**Discussion**

It is widely recognized that reproductive failures, such as recurrent spontaneous abortion, intrauterine fetal growth retardation (IUGR), intrauterine fetal death (IUFD), and preeclampsia, are accompanied during pregnancy by clinical autoimmune diseases such as SLE. Recently, autoimmune abnormalities, such as positive APLs, have been demonstrated in patient populations with the above-mentioned reproductive failures (Takakuwa et al., 1996). Prospective studies, in which the incidence of reproductive failures was significantly higher in pregnant women positive for APLs compared with those negative for them, strongly support the association between APLs and adverse pregnancies (Yasuda et al., 1995).

The treatment recommended for patients with reproductive failures who are positive for APLs is administration of heparin and aspirin, while PSL is avoided, according to recent reports (Silver et al., 1993).

The main mechanisms of manifestation of reproductive failures by APLs are considered to be direct damage to chorionic villi by APLs during the period of placentation (Rote et al., 1998), and hyperthrombogenic state intervillous space by APLs (Arakawa et al., 1999). Considering these mechanisms, the application of immune-suppressive therapy in combination with anti-coagulant therapy may be rational as a treatment option for the patients with reproductive failure due to APLs. In addition, treatment using internal medicines is superior to treatment using injected agents, when considering the quality of life of the pregnant patients.

In this context, we treated typical cases with reproductive failures by APLs using a Chinese herbal medicine, Sairei-to, LDA and PSL. All four pregnancies resulted in normal term deliveries with an uneventful prenatal course, accompanied by a decrease in the level of APLs. One of the criticisms for using PSL is the adverse effect of the agents (Silver et al., 1993).
In this treatment, we first used a Japanese modified Chinese herbal medicine, Sairei-to. Sairei-to has been used to minimize the dose of PSL in patients with nephrotic syndrome (Kimura et al., 1990; Liu, 1995). In this series, we used both Sairei-to and PSL, which enabled us to taper the dosage of PSL during pregnancy. This may have contributed to the uneventful prenatal course in each case.

Our experience in these cases indicates the possible efficacy of treating patients with reproductive failures due to APLs. However, further studies and treatment of more patients will be necessary to elucidate its efficacy.

References


