Analysis On The Long Term Alteration of MLR-Blocking Effect Appeared In Patients With Habitual Abortion After Immunotherapy With Husband’s Lymphocytes - Its Correlation With The Outcome Of Pregnancy, Especially With The Second Pregnancy In Those Who Had Obtained Good Outcome In Their First Pregnancy -

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Introduction
The effectiveness of immunotherapy for patients with habitual abortion has been reported by several investigators for these few years (1,2,3,4,5). Although the reason why the immunotherapy is advantageous for habitual abortions has not yet fully elucidated, the implication of some individually specific immune factors in the effectiveness of the therapy has been suggested to exist (1,2,3,5). We have previously reported that the blocking effect which significantly inhibited one-way mixed lymphocyte culture reaction (MLR) between wife and husband could be detected in all patients after immunotherapy for the unexplained habitual aborters using husband’s lymphocytes, and that there was a correlation between the appearance of MLR-blocking effect (BE) and the successful outcome of pregnancy. In addition, we recently reported the relationship between the MLR-BE and trophoblast, employing the trophoblast membrane vesicles prepared from term placentas obtained from successful cases of the immunotherapy protocol, which suggested the importance of MLR-BE for immunologically successful continuation of pregnancy (6). In this study, the long term alteration of MLR-BE appeared after the immunotherapy was analyzed, especially its relationship with the following pregnancy. In addition, it was also examined whether the additional immunotherapy was necessary or not at the second pregnancy of the patients who had obtained good outcome in the first pregnancy just after the immunotherapy.

Materials, Methods and Conclusion
The protocol for immunotherapy for habitual abortion in our department is shown in Figure I. The primary habitual aborters who had experienced three or more consecutive first trimester abortions and had no other pregnant history were enrolled into this protocol. And routinely performed tests for habitual abortions such as genetic impairment, mullerian anomalies, hormonal deficiency, infectious diseases, metabolic disorders and autoimmune abnormalities were examined for the patients. In the patients with negative findings, the immunologic examinations such as HLA-tissue typing of spouse, MLR-BE in patient’s sera and
general immunologic competency were performed. After these examinations, the patients with negative MLR-BE underwent vaccination with husband's lymphocytes as an immunotherapy under sufficiently informed consent. After the appearance of significant MLR-BE, the patients were allowed to be pregnant. The sera were serially obtained from patients and stored at -20°C for further investigations.

The details of the methods of MLR-blocking assay (stimulator; husband, responder; wife) and vaccination with husband's lymphocytes were described elsewhere. (1).

To date, out of 42 patients who had become pregnant after the immunotherapy, in 34 cases, their pregnancy has continued their critical period, thus the success rate of the immunotherapy was 80.1%. MLR-BE in successful patients before immunotherapy was -7.9±21.0% (n=34), and 68.9±21.5% (n=34) after vaccination(s) with husband's lymphocytes, which is significantly higher than that before vaccination(s) (p<0.001). In all successful cases, the significant MLR-BE was detected at very early stage of new pregnancy, followed by gradual increase during their perinatal course, and reached its peak at delivery. The MLR-BE at delivery was 87.3±7.9% (n=22). At 12 months after the delivery, the BE was 71.9±15.5% (n=14), thus the significantly high level of MLR-BE was demonstrated to be maintained in patients' sera during long term from the delivery (Figure II).

Out of 28 cases in whom their first pregnancy had already
terminated with good outcome after the immunotherapy, so far seven cases have experienced another pregnancy. All of them have become pregnant without an additional vaccination because significantly high level of MLR-BE was demonstrated in their sera just before the second conception, and all of the pregnancies have already terminated with a favorable outcome.

There have not yet been the reports concerning the necessity of an additional immunotherapy at the second pregnancy for a patient with habitual abortions who had got a good outcome at the first pregnancy after the immunotherapy. From this study, it is strongly suggested that the additional immunotherapy is unnecessary for these patients. And moreover, the crucial role of MLR-BE in the immunologically successful continuation of pregnancy is strongly suggested to exist.

This immunologic procedure is still an indefinite one and its adverse effects should always be taken into consideration. In this context, we are now proceeding on the follow-up practices of the infants born to mothers with immunotherapy, especially from the immunologic points of view, and which, so far, indicate no infant impairment (7).

Figure II  Long Term Alteration of MLR-Blocking Effect in Patients with Successful Outcome After Immunotherapy for Habitual Abortion

References


4) Smith, J.B. and Cowchock, F.S.: Immunological studies in recurrent spontaneous abortion: effect of immunization of women with paternal mononuclear cells on lymphocytotoxic and mixed lymphocyte reaction blocking antibodies and correlation with sharing of HLA and pregnancy outcome, J Reprod Immunol., 1988; 14, 99-113

