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Short communication

Medium-dose intravenous immunoglobulin therapy for women with six or more recurrent miscarriages

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ABSTRACT

This study aimed to evaluate changes in natural killer (NK) cell activity and the percentage of monocytes in women with recurrent miscarriage who received medium-dose intravenous immunoglobulin (IVIg) therapy. Fourteen women with a history of six or more recurrent miscarriages of unexplained etiology received 60-g IVIg therapy (20 g daily, for three days) during early gestation. NK cell activity in the peripheral blood decreased to 12% one week after therapy compared with before therapy (median, 22%, $P < 0.001$) and the percentage of monocytes increased from 5.2% to 7.5% ($P < 0.005$). Four pregnancies ended in live births of healthy neonates, whereas the other ten pregnancies ended in miscarriages. Excluding one miscarriage with a chromosomal abnormality, the live birth rate was 30.8% (4/13). The rate of reduction of NK cell activity in the success group (−58.8%) tended to be greater than that in the failure group (−14.8%, $P = 0.057$).

1. Introduction

Recurrent miscarriage (RM) is defined as three or more consecutive pregnancy losses during early gestation and affects 1–1.8% of women (Laird et al., 2003). A wide variety of factors are involved in the pathogenesis of RM, including uterine anomalies, cervical incompetence, autoimmune diseases, antiphospholipid antibody, chromosomal abnormalities of couples, thrombophilic disorders, endocrinological abnormalities, and microbial infections. However, the etiology in approximately 50% of RM is unknown, and is thus designated as unexplained RM, which may be associated with aberrant immunity (Laird et al., 2003).

No standard therapeutic modality for unexplained RM has yet been established. However, several lines of evidence have indicated that unfractionated heparin or low-molecular-weight heparin with or without low-dose aspirin (LDA), paternal lymphocyte immunization, intravenous immunoglobulin (IVIg), prednisone, and progestin (Toth et al., 2010) have some therapeutic efficacy. We developed a high-dose IVIg (100-g IVIg) therapy during early gestation for women with four or more RMs of unexplained etiology (Yamada et al., 1998), and its efficacy has been reported (Yamada et al., 2012). We have commenced a medium-dose IVIg therapy for severe RM. This study aimed to evaluate changes in natural killer (NK) cell activity and the percentage of monocytes in women with six or more RMs of unexplained etiology who received 60-g IVIg therapy.

2. Patients and methods

This prospective study was approved by the institutional ethical boards of Kobe University Hospital, and was

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conducted with informed consent from all of the subjects. Between February 2010 and September 2013, women with RM were admitted to the study if they met all of the following requirements:

(1) Unexplained etiology for RM,
(2) A history of six or more consecutive miscarriages,
(3) Failure of LDA plus heparin therapy,
(4) No history of IVIg therapy, and
(5) No allergy to immunoglobulin or IgA deficiency disease.

All of the patients underwent ultrasound examination, hysterosalpingography, endometrial biopsy, and conventional blood analyses for RM screening, and were diagnosed as having RM of unexplained etiology. Blood analyses included the following: analysis of chromosome karyotypes of couples; measurement of progesterone levels in the mid-luteal phase and prolactin levels; measurement of hemostatic coagulation factors, such as d-dimer, factor XII, protein C, protein S; and measurement of autoimmune factors, such as antinuclear antibody, complements, lupus anticoagulant, anticardiolipin, and β2-glycoprotein I-dependent anticardiolipin antibodies. Thyroid, liver, and kidney function were analyzed.

The patients received 60-g IVIg therapy (immunoglobulin 20 g daily over the course of three days; a total dose of 60 g) with written informed consent immediately after a gestational sac was detected in the uterus by ultrasound. Intact-type immunoglobulin (Sanglopor; CSL Behring, Tokyo, Japan) was used for therapy. NK cell activity and the percentage of monocytes in the peripheral blood were measured before and 1 week after commencement of 60-g IVIg therapy. The ^{51}Cr release assay for NK cell activity was performed as previously described (Morikawa et al., 2001). Briefly, 1×10^4 labeled K562 target cells were incubated with 2×10^5 effector cells (peripheral blood mononuclear cells) in triplicate in the ^{51}Cr release assay.

When the index pregnancy ended in miscarriage, the patient was recommended to undergo chromosome karyotype analysis of the villi. Information on pregnancy outcome was collected from medical records. The Mann–Whitney *U* test and the Wilcoxon matched-pairs signed-ranks test were used for comparison of two groups. Statistical significance was determined by $P < 0.05$.

3. Results and discussion

The 60-g IVIg therapy was performed in 14 women with RM who had a median age of 37 years old (range, 29–40 years old) and who had a median history of seven (range, 6–14) miscarriages. The pregnancy history, pregnancy outcome, and changes in NK cell activity and percentage of monocytes in the 14 women with RM are shown in Table 1. Only one (Case 14) woman had secondary RM, whereas the other 13 women had primary RM. All of the 14 women had a history of refractory RM with resistance to LDA plus heparin therapy. Four of the 14 pregnancies with IVIg therapy ended in live births of healthy neonates between 36 and 40 weeks' gestation, whereas the other eight pregnancies ended in early miscarriages between 6 and 11 weeks' gestation. The remaining two pregnancies ended in stillbirths at 17 and 21 weeks' gestation subsequent to premature rupture of the membranes. Pathological examinations of these two stillbirths demonstrated that they had chorioamnionitis. Karyotype analyses of the villi/placentas of the women with miscarriages showed a chromosomal abnormality of 47, XY, +22 in one case, a normal chromosomal karyotype in six, and the result was "unknown" in three because of insufficient specimens or no consent. Excluding one pregnancy with chromosomal abnormality of conception, the live birth rate was 30.8% (4/13) in the present study. Four women whose pregnancies ended in live births had a median age of 37 years (range, 29–37 years), and they had a median history of 8.5 (range, 7–12) miscarriages.

Natural killer cell activity in the peripheral blood was significantly decreased (median, 12%; range, 4–53%) one week after IVIg therapy compared with before IVIg therapy (median, 22%; range, 14–58%, $P < 0.001$). The percentage of monocytes was significantly increased one week after IVIg (median, 7.5%; range, 4.6–12.0%) compared with before IVIg therapy (median, 5.2%; range, 3.4–8.0% $P < 0.005$). The rates of change in NK cell activity and the percentage of monocytes in the peripheral blood were compared between the success group (live birth, $n = 4$) and failure group (miscarriage with a normal chromosome karyotype, $n = 6$). The rate of change (%) was calculated as follows: value at 1 week after IVIg therapy – value prior to IVIg therapy/value prior to IVIg therapy × 100. The rate of reduction of NK cell activity in the success group (median, −58.8%; range, −75.5% to −50.0%) was greater than that in the failure group (median, −14.8%; range, −38.9% to +22.2%), but there was no significant difference ($P = 0.057$). The rate of change in the percentage of monocytes in the success group (median, +57.5%; range, −9.8% to +83.3%) was not significantly different from that in the failure group (median, +54.3%; range, −6.7% to +135.3%, $P = 0.562$).

Several mutually non-exclusive mechanisms of action, which include the suppression of inflammation and modification of the Fc receptor, T cells, B cells, or macrophage function, are proposed to account for the immunoregulatory effects of IVIg therapy (Kazatchkine and Kaveri, 2001). Researchers have assessed the efficacy of IVIg therapy for women with unexplained RM by performing randomized, double-blind, placebo-controlled trials, in which 20–40 g of immunoglobulin/person was infused weekly or every 2–4 weeks during early and mid-gestation. Conclusions that were drawn from previous IVIg trials are controversial. Thereafter, meta-analyses and systematic reviews have suggested that IVIg therapy might be effective among women with secondary RM (Practice Committee of the American Society for Reproductive Medicine, 2006; Hutton et al., 2007) or might not be beneficial in the latest report (Ata et al., 2011), excluding two large trials for obscure reasons (Christiansen et al., 2011).

We previously commenced 100-g IVIg therapy for severe cases of RM in which 20 g of intact-type immunoglobulin was infused daily for 5 days during early gestation (Yamada et al., 1998). This 100-g IVIg therapy has been administered to 60 women with four or more RMs of unexplained etiology. When 11 pregnancies with chromosomal abnormalities of conception were excluded, there was a high birth rate (89.8%, 44/49) with 100-g IVIg