Linköping University Medical Dissertation
No. 772

Recurrent spontaneous abortion.

A clinical, immunological and genetic study

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Akademisk avhandling
som för avläggande av doktorsexamen kommer att offentligt försvaras i Berzeliussalen, Hälsouniversitet, Linköping den 31 januari 2003 kl 13.00

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Abstract

Recurrent spontaneous abortion (RSA) is defined as the loss of three or more consecutive pregnancies before 20 completed gestational weeks. The condition affects 0.5-1% of all women. In the majority of women with RSA, the cause remains unexplained after genetic, endocrine, immunological and anatomical investigations of the couple. However, there is increasing evidence that immunological mechanisms might contribute in the pathogenesis of RSA. Therefore high doses of intravenous immunoglobulin (IVIG), known to modulate immune responses, has been suggested as a treatment of RSA. The aim of this study was to evaluate IVIG in the treatment of RSA, and to elucidate immunological and genetic mechanisms behind this condition. In a prospective, double blind, placebo-controlled IVIG study we investigated 41 women with a history of unexplained RSA. They received 20g IVIG or placebo-saline every 3 weeks on five occasions from 6-7 gestational weeks. The overall success rate was 77% in the IVIG group compared with 79% in the placebo group, indicating that IVIG was not better than placebo and that both groups had better results than the predicted outcome.

We also investigated the presence of blocking effect of maternal serum in a mixed leukocyte culture (MLC). Blood samples were obtained before and after pregnancy in the IVIG/placebo groups. As RSA controls we used 31 RSA women who did not achieve pregnancy during this study and were not enrolled in the IVIG study. As normal controls we used 10 non-pregnant women without a history of spontaneous abortions. Blocking antibodies were present in 20% of women with unexplained RSA and in 30% of the control group. The blocking effect before pregnancy was the same for IVIG-, placebo-, and untreated RSA controls as well as in the normal controls. We found no significant differences in blocking effect before compared with after IVIG or placebo treatment.

We measured lymphocyte subset distributions in blood samples obtained in the first trimester and after pregnancy in 39 RSA women in the IVIG study and compared them with previous results from pregnant and non-pregnant controls. In the first trimester of pregnancy, the RSA women had significantly increased proportions of B-cells (CD19), T cells subsets including activated HLA-DR expressing T cells (CD3+HLA-DR+), and T killer/effector cells (CD+S6F1+). The proportion of T suppressor/inducer cells (CD4+CD45RA+) was significantly decreased. Thus, in early pregnancy the immune system seems to be activated in RSA patients in contrast to the suppression noted in normal pregnancy. These changes in subpopulations do, however, not correlate to the outcome of pregnancy.

We studied the compatibility of HLA-DRB1 alleles in the couples with unexplained RSA and the frequency of HLA-DRB1 and HLA-G alleles in these couples compared with fertile controls. We did not find significantly increased sharing of HLA-DRB1 alleles between partners. We found no significant differences for HLA-DRB1 and HLA-G allele frequencies in RSA couples compared with fertile controls.

In conclusion, RSA patients have no genetic differences, their immune reaction during pregnancy is altered, their levels of blocking antibodies is of no use to predict pregnancy outcome and intravenously given high dose IVIG does not effect their pregnancy outcome.

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Linköping 2003
ISBN 91-7373-529-9 ISSN 0345-0082