THE ROLE OF IMMUNOGENETIC FACTORS IN THE AETIOLOGY OF PRE-ECLAMPTIC TOXAEMIA OF HUMAN PREGNANCY

Volume I

by

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The present study examined the role of some immunogenetic factors in the aetiology of pre-eclamptic toxaemia.

A normal pregnant population was used as a reference population for a compatative study of a group of women who developed severe pre-eclampsia/eclampsia.

Rigid diagnostic criteria were employed in an attempt to make the clinical diagnosis as unequivocal as possible. This made the number of cases available for study quite small, but was necessary to avoid the inclusion of such mild cases of pre-eclampsia that the diagnosis must be seriously in doubt.

The genetic marker studies revealed no linkage association between susceptibility to the disease and any particular leucocyte antigen. However, there appeared to be a higher degree of HLA antigen matching between the pre-eclamptic women and their husbands than between the normal pregnant women and their husbands. This has some similarity to the Oxford data (Redman 1975, personal communication) which shows a high degree of parental HLA homozygosity in severe pre-eclampsia.

This matching would provide for less histoincompatibility between mother and fetus and thereby the fetus would fail to induce a sufficiently strong maternal immunological recognition of itself, necessary for the maintenance of normal pregnancy.

Such an hypothesis is supported by the failure of women with severe pre-eclampsia in this study to develop anti-HLA cytotoxic antibodies.

The immunological studies examined both the cellular and humoral immune response of the mothers.

The PHA-induced responsiveness of the maternal lymphocytes was reduced in women with severe pre-eclamptic toxaemia. While other studies have shown a reduced response to PHA of lymphocytes from normal pregnant women, this seems to be a purely serum mediated inhibition - the intrinsic function of the lymphocytes being normal in the absence of maternal serum. The results of the present study were consistent with this also. However, the women with severe pre-eclampsia had a greater reduced responsiveness to PHA and the suppressing effect of maternal serum was not as great as in normal pregnancy.

This raises two possibilities. Firstly, that the lymphocytes of women with severe pre-eclampsia are depressed by a non-serum factor. Secondly, that there is a reduced ability of the women with severe pre-eclampsia to produce serum blocking or inhibitory factors.

The specific immunological response of the pre-eclamptic mothers against paternal antigens was similar to that of normal pregnant

women and little or no serum effect was noted. Where cord leucocyte antigens were stimulatory in the mixed leucocyte culture, however, there was less maternal response noted in pre-eclamptic pregnancies. Again, there was a suggestion that the inhibitory effect of maternal serum on this response was less in pre-eclamptic pregnancies than in normal pregnancies.

The role of the fetus in the development of pre-eclamptic toxaemia has generally been ignored. The fetus is immunologically competent at an early stage of its development (Jones 1976) so that it may well take an active role in its survival as an allograft. Cord lymphocyte responses to PHA were studied and noted to be higher than that of their mothers, but similar to that of non-pregnant adults. Cord serum had no effect on the autologous leucocyte response to PHA.

Cord leucocyte response to maternal antigens was also similar in the two groups studied and the effect of cord serum on this response was interesting. Where the pregnancy was normal, there was no effect but in severe pre-eclamptic pregnancies the serum was immunosuppressive.

The difference is difficult to explain. It may be due to the fact that maternal serum seromucoid is elevated in severe pre-eclampsia and was also elevated in cord serum and that this non-specific immunosuppressive substance may be responsible. Such

effect, however, was not noted in the cord responses to PHA as would be expected.

There is no evidence, from this study, therefore, that the fetus has an active role to play in the immunological aetiological mechanisms of severe pre-eclamptic toxaemia.

The serum immunoglobulins were also examined. IgA levels were similar in the control and study groups, but IgM and IgG levels were reduced in the women with severe pre-eclampsia. While IgG is lost in large quantities in the urine, this is not so of IgM. Furthermore, in severe pre-eclampsia where there is a loss of fluid from the intravascular space so that the blood is haemo-concentrated (Williams 1966) these low levels of immunoglobulins are even more significant.

While loss of IgG in the urine must be accepted as the most likely explanation, an immunological explanation is possible also (Benster and Wood 1970). Accordingly, the following possibility exists. IgM is the immunoglobulin produced in the initial immunological response with IgG produced later in the immunological response (Rowe 1975). The initial challenge of a first pregnancy may, therefore, induce first IgM and then IgG later. If this immunological response is inadequate, then the production of both these immunoglobulins would be reduced.

It is possible, then, that the lower levels of IgM and IgG observed in the women with severe pre-eclampsia may be compatible with the overall hypothesis that women who develop severe pre-eclampsia are immunologically hypo-responsive to the fetal antigenic challenge. This is further supported by the findings of this study in relation to the specific anti-HLA antibody formation. Women with severe pre-eclampsia failed to produce detectable anti-HLA antibodies, unlike the women whose pregnancies were normal.

The non-specific serum factor studied was serum seromucoid. This was significantly elevated in the women with severe pre-eclampsia and confirms other studies. It has been suggested that the production of seromucoid is a compensation by the maternal organism for her inability to mount an adequate specific immunological response (Good 1975).

That the maternal host with severe pre-eclampsia is unable to mount an adequate immunological response is further supported by the lower response to phytohaemagglutinin and the reduced blocking activity of maternal serum.

The results of this study, therefore, suggest that women who develop severe pre-eclampsia make an inadequate immunological adaptation to the antigenic challenge of their pregnancy. The possible mechanism proposed is that the recognition phase of blocking antibody production is impaired. This results in inadequate enhancing

antibodies for the maintenance of normal pregnancy so that pre-eclamptic toxamia develops.

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