The case against Pregnancy histocompatibility

Pregnancy represents a semi-allograft in that the fetus inherits half its transplactation antigens from it's father. Paradoxically, it would seem, this semi-allograft is not rejected according to the laws of immunology. Why this should be so has been the basis of continued research for almost thirty years. Organ grafts between identical twins are not rejected and generally it is accepted that the greater the degree of histoincompatibility between donor and recipient of the graft the poorer the graft surivial will be. As the maternal host provides evidence of immune recognition of the fetal graft by producing antibodies specific to the paternal strain it is not surprising that people have not only considered the possibility that pregnancy failure was due, in some way, to the semi-allograft situation but that such failure would be most evident when mother and fetal graft were most histoincompatible. Surprisingly, thirty years later the evidence, although questionable, if anything suggests that histocompatibility is more often associated with pregnancy pathology than histoincompatibility. The rhesus isoimmunisation model had blinded people to the possibility of immune pathology not due to hypersensitivity type response. In other words, a failure of adequate maternal immune response to paternal antigens may be disadvantageous to the pregnancy.

Clarke and Kirby[1] suggested that a balanced polymorphism of the transplantation antigens may be maintained in a mammalian population by a selective system in which the antigenic disparity between mother and fetus is beneficial to the development of the fetus. McLaren[2] reviewed the evidence relating to the effect of antigen disparity on placental size, implantation and genetics and one of a number of conclusions was that the possibility of immunological effects on placental weight in man remained open. Jenkins and Good[3] had reported an association of larger placentas with histoincompatibility. The emphasis of most studies was to confirm or otherwise an advantage to a pregnancy of feto-maternal disparity. Few if any studies looked at or even considered the opposite, i.e. histocompatibility, being associated with a disadvantage to pregnancy outcome. Studies by Scott, Need and Jenkins[4] pointed to a possible association between histocompatibility and pre-eclampsia. A number of other workers found similar associations but more recently Kirkpatrick DC et al[5] have not been able to confirm this. Cooper's[6] team in Australia have within the last year produced evidence from genetic studies which argue against an association between histocompatibility genes and pre-eclampsia.

Recurrent abortions has been reported by a number of workers to be associated with feto-matemal histocompatibility but later studies have again not been supportive and the absence of a blocking antibody does not necessarily result in pregnancy failure in this context.

Increased sharing of HLA, A,B,C, and DR antigens in Hutterite families in association with increased fetal loss has not been confirmed by recent studies and there is no evidence of increased histocompatibility in maternal-abortus antigens in human pregnancy failure. Family studies do not show a selection in favour of fetuses with HLA haplotypes either similar or different from those present in their respective mothers.

Mailman et al reported that HLA sharing of four or five antigens was doubled in 25 maternal-fetal pairs in non-immune Hydrops Fetuses compared to age and parity matched controls whilst Schaefer et al 1979 reported increased HLA and B sharing in 13 couples with recurrent fetal loss and in 11 couples with offspring from lethal neural tube defects.

Gilescher has recently argued that women with reduced tolerance of self antigens may be at risk when faced with the extra challenge of such antigens in pregnancy. He has coined the expression Autoimmune Reproductive Failure Syndrome. Histocompatibility being associated with pregnancy failure would not be inconsistent with his hypothesis and would encompass associations between hyperplacentosis and pre-eclampsia. The matter is not simply of intellectual interest. If associations between pregnancy problems and HLA genes can be defined, then at risk pregnancies can be forecast and management made more cost effective.

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