HLA COMPATIBILITY AND HUMAN REPRODUCTION

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Summary: Studies carried out on inbred strains of mice have shown that conceptuses which differ at the MHC antigens from their mothers appear to enjoy a selective advantage when compared with conceptuses which are more compatible. In humans a highly significant degree of MHC compatibility can be found in couples with a history of repetitive spontaneous abortions with unknown aetiology.

We HLA - typed 28 selected couples with a history of three or more consecutive spontaneous abortions of unknown aetiology and 28 normal couples as control. We found that 22/23 (79%) aborter couples shared common HLA antigens, while normally fertile couples only 7/28 (25%) ($p < 0.001$). The finding of a significant HLA compatibility in couples having abortions might be consistent with the hypothesis that blocking antibodies, formed in early pregnancy as response to HLA antigens, are perhaps necessary for a successful gestation. The factor causing abortion in couples sharing HLA antigens might also refer to the homozygosity for fetal genes in linkage with HLA alleles. The sharing of HLA alleles could be a marker for other genes of the same region which are lethal for the embryo in the homozygous state.

Several lines of evidence suggest that heterozygosity is a reproductive advantage in nature.

Self-incompatibility is a well known and widespread phenomenon in the reproductive process of certain plants. Many hermaphrodyte fertile plants (such as almond trees, olive trees, roses, tulips, tea etc.) are incapable of producing seeds either when autopollinated or when pollinated from other individuals with the same alleles at the in histocompatibility loci.

This happens even if the pollen is vital and carries functioning gametes ([2]).

Highly inbred strains of mice have a reduced reproductive capacity ([6]). Studies carried out on inbred strains shown in fact that: MHC homozygous conceptuses, gestated in mothers sharing the same H-2 alleles have a greatly curtailed reproductive performance, while conceptuses which differ at MHC antigens from their mothers appear to enjoy a selective advantage when compared with conceptuses which are more compatible ([1]).

Now of course, the question is: does this phenomenon occur only with plants and/or with higly inbred strains, or can it be applied to normal reproductive mechanisms even in outbred populations, including humans? All we know is that a higly significant degree of MHC-compatibility can be found in couples with a history of repetitive spontaneous abortios with unknown aetiology ([5]). Studies on repetitive abortions in humans do provide evidence of a relationship between HLA compatibility in the couple, and the abortions.

An analysis carried out on the published data with reference to the correlation between HLA antigens and repetitive abortions shows that about 20% of the women who had miscarried shared MHC antigens with their husbands. In normal fertile couples the frequency of antigens in common (at the loci HLA-A, B) was about 8% ([5]). In table 1 the

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Table 1. — *MHC shared antigens at two loci.*

Authors		Aborters	Controls
Komlos *et al.*	(1977)	3/23	3/18
Gerencer *et al.*	(1979)	5/18	ND
Schacter *et al.*	(1979)	5/39	0/17
Taylor and Faulk	(1981)	2/4	ND
Beer *et al.*	(1981)	6/10	1/16
Amar *et al.*	(1983)	2/21	2/21
Total		23/115	6/72
Frequency		0,20	0,08

Modified from Gill's tatble (1983)

most important data from literature are listed.

Women with a history of repetitive abortions may also show a higher frequency of the HLA allele A9 [3] or of the HLA allele BW35 [11].

PATIENTS AND METHOD

We selected 28 couples with a history of three or more consecutive spontaneous abortions of unknown aetiology and 28 normal couples presenting normal fertility as control group. We HLA-typed the single individuals for all the antigens controlled by the HLA-A, B, C loci as defined by the VIII International Istocompatibility Workshop. We have just started to work on HLA D/DR antigens and we hope to produce results in a very near future.

The clinical criteria used for the selection of the aborter couples were the following.

- Number of miscarriages ≥ 3.
- Normal karyotype in both parents.
- Normal routine clinical investigations, both morfological (ultrasound and ISG in all cases) and functional.
- Absence of hypertension, diabetes, AB0 and/or Rh sensitization, absence of infections like toxoplasma, listeria, chlamydia, etc.

The control group consisted of 28 normal couples with at least two children and no record of infertility. Of course all individuals (in each couple and between the couples) were unrelated, and came from the same geographic area in order to avoid any difference in ethnic composition. No predominant blood group was found and no environmental adversing factors were detected. The mean age was 27.3 in wives and 30.5 in husbands.

The following HLA specificities were defined:

HLA-A A1, A2, A3, A9 (W23, W24), A10 (W25, 26), A11, AW32, AW30, AW31, A29, AW33.

HLA-B B5 (W51, W52, BW53), B7, B8, B12, (W44, W45), B13, B14, B15 (W62, W63), BW16 (W38, W39), B17 (W57, W58), B18, BW21 (W49, W50), W22 (W54, W55, W56), 27, W35, 37, 40 (W60, W61).

HLA-C CW1, CW2, CW3, CW4, CW5, CW6.

The statistical significance of the compatibility was evaluated by Fisher's exact test.

RESULTS

The couples with fertility problems shared a higher percentage of common HLA antigens. 22/28 couples with a history of repetitive abortion (79%) shared common HLA antigens, while only 7/28 normally fertile couples (25%) shared HLA antigens in common. The difference is higly significant ($p<0.001$) (tab. 2). In the following tables 3, 4, 5

Table 2.

	Aborters	Controls
HLA-A, B, C antigens in common	22/28 (79%)	7/28 (25%)
	$p<0.001$	

Table 3. — *Locus HLA-A.*

No. Ag in common	Aborters		Controls	
0	16/28	58%	26/28	93%
1 or more	12/28	42%	2/28	7%
	$p<0.01$			

Table 4. — *Locus HLA-B.*

No. Ag in common	Aborters		Controls	
0	19/28	68%	23/28	82%
1 or more	9/28	32%	5/28	18%
	N.S.			

Table 5. — *Locus HLA-C.*

No. Ag in common	Aborters		Controls	
0	22/28	79%	27/28	96,5%
1 or more	6/28	21%	1/28	3,5%
	N.S.			

the frequency of HLA-A, B, C antigens in common is reported in detail.

Of the 22 couples with a history of repetitive abortion and with HLA antigens in common we found that: 16 couples shared 1 antigen, 5 couples shared 2 antigens (1 couple shared 2 HLA-A, 4 couples shared 1 HLA-A and 1 HLA-C), 1 couple shared 3 antigens (the antigens HLA-A11, BW35, CW4) (tab. 6).

Table 6.

No. of antigens shared	No. of couples	Specificities
1	16	
2	5	1 couple: 2 HLA-A 4 couples: HLA-A and HLA-C
3	1	HLA-A11; BW35; CW4

The 7/28 normally fertile couples with antigens in common, shared only one antigen.

It has been reported that the occurrence of HLA-A9 ([3]) and HLA-BW35 ([11]) is greater in women who have miscarried.

The frequency of each single HLA antigen has been investigated in our study group. A frequency of 43% of HLA-BW35 was found in aborters.

This frequent is higher than the one found in control women (25%) and in the Italian population (27%), but it is not significant.

As to other HLA specificities, no frequency difference was detected between couples having abortions and normally fertile couples.

DISCUSSION

The finding of a significant HLA compatibility in couples having abortions indicate that HLA region may be involved and may influence the reproductive efficiency.

Blocking antibodies formed in early pregnancy in response to HLA antigens seem to be important, and perhaps necessary for a successful gestation.

Women who share HLA antigens with their husbands might not develop enhancing antibodies and therefore be at risk for fertility.

A normal woman's pregnancy seems to be associated with the production of non-fixing complement antibodies to an HLA linked alloantigenic system.

Power *et al.* ([10]) found non-cytotoxic antibodies to paternal B lymphocytes in 11/11 multiparous and in 11/16 normal primigravidal during the first weeks of pregnancy. However these antibodies were not detected in sera from 9/10 women at comparable stages for pregnancy, at the time of spontaneous abortion. These antibodies do not seem to be directed to the known HLA specificities (HLA-A, B, C or DR) but against determinants controlled by genes in linkage to the HLA complex. These data were suggested by family studies. Non cytotoxic antibodies have sometimes been found also in renal allograft recipients and their presence seems to be related to an improved graft survival ([8]).

Infertility in couples sharing HLA antigens could, however, be explained differently and might not involve immunological mechanisms. The factor causing abortion might be referred to the homozigosity for lethal genes in linkage with HLA alleles. Genes linked to the MHC in the mouse and in the rat can cause foetal or neonatal death or ab-

normalities in viable animals. Why not consider a similar mechanism in humans? These is a close parallel between the HLA in humans and the H-2 system in the mouse. The sharing of HLA alleles could be a marker of the sharing of genes which are lethal for the embryo in the homozygous state ([5]).

The most simple explanation for an association between HLA marker and a particular disease is that there are loci within the MHC, which control the susceptibility to disease or, as in our field of interest, antigen involved in organogenesis of the foetus and in the relationship with the mother. The observed data would imply that there is a significant linkage disequilibrium between the alleles controlling the serologically detected antigen (shared in infertile couples) and alleles (lethal at the homozygotes condition) of loci involved in differentiation antigens.

The strongest association in our analysis concerned locus HLA-A. For all mechanisms known to create the linkage disequilibrium, we can imagine to localize the human genes involved in the normal differentiation of conceptuses in the HLA region on the side of locus HLA-A.

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