

HLA-DR in couples associated with preeclampsia: background and updating by DNA sequencing

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The placenta acts as an immunological barrier between the mother and the fetal “graft”, allowing two antigenically different organisms to tolerate one another. In placentae from preeclamptic women, we have demonstrated, by an ultrastructural assessment and an immunohistochemical study, a placental barrier breakage leading to the mixing of maternal and fetal antigenically different blood. This condition could be responsible for the triggering of a maternal rejection reaction that we presume to be at the basis of the preeclamptic syndrome. Thus, we have investigated the Human Leukocyte class II DR antigens (HLA-DR), whose role in self and non-self recognition is well known, in women with preeclampsia, their partners and in control couples using the serological Terasaki technique. The results showed a statistically significant increase of HLA-DR homozygosity and a reduced antigenic variety in the preeclamptic women and their partners with respect to controls. In this update, we have examined the 2nd exon of the human gene, HLA-DRB1, on the short arm of the chromosome 6 using DNA sequence-based typing (S-BT) PCR in 56 preeclamptic couples and 64 control couples. The results have confirmed the significant excess of HLA-DR homozygosity in couples associated with preeclampsia versus controls. From our results, it emerges that HLA-DR homozygosity and the reduced antigenic variety seem to be associated to a major risk for preeclampsia, which further appears to be a “couple’s disease”.

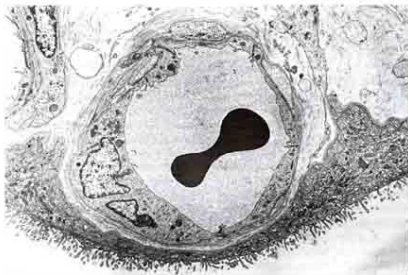


Fig. 1. An ultrastructural study of physiological term placenta: we observed the integrity of the syncytiotrophoblast and endothelial villous vessel cells, with perfect adhesion of the endothelial intercellular junctions.

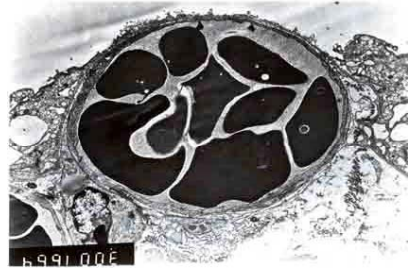


Fig. 2. An ultrastructural study of placenta from preeclamptic women: we observed the severe syncytiotrophoblast damage, which appears extremely thin with a wide necrotic area. The endothelial cells are flattened, suffering as not alive.

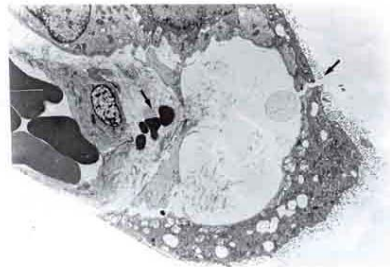


Fig. 3. An ultrastructural study of placenta from preeclamptic women: we observed the breakage of syncytiotrophoblast and endothelial cell junctions. Therefore the fetal blood cells were outside, in the maternal stroma.

In conclusion, our results appear to confirm the hypothesis that a fetal rejection response may occur in **EPH-Gestosis** :

- 1) Ultramicroscopical evidence of placental endothelial breakage in pre-eclampsia, in agreement with other authors (Fournie et al., 1981; Rodgers et al., 1988; Roberts et al., 1989; Rappaport et al., 1990; Sibai, 1991; Burrows et al., 1994). These authors have asserted the currently accepted concept regarding the cause of **EPH-Gestosis** due to endothelial cell dysfunction (Schuling et al., 1997).
- 2) The immunohistochemical evidence of intense and widespread HLA-DR antigen expression in placentae from preeclamptic women versus controls.
- 3) Significant HLA-DR antigen homozygosity excess in couples of pre-eclamptic women versus controls, confirmed by DNA sequencing.
- 4) A significant increase of VCAM-1 plasma levels, as demonstrated also in other graft graft rejection reactions (Taylor et al., 1992).
- 5) Last, but not least, the clinical evidence that **EPH** syndrome quickly disappears after pregnancy interruption, and hence the fetus could be the cause of the maternal rejection reaction.

We believe that modern reproductive immunology could be the lighthouse which highlights the route to elucidate the aetiology of **EPH-Gestosis**.

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