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# Histocompatibility Assessment in Couples Associated with Gestosis/Preeclampsia: Step by Step Focus on an Immunopathogenetical Pathway Hypothesis



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## Aim of the Study

Gestosis/Preeclampsia is still an enigmatic leading killer in the field of obstetrics, affecting up to 8% of pregnancies with a 20% rate of recurrency. The placenta acts as an immunological barrier between the mother and the fetal "graft", allowing two antigenically different organisms to tolerate one another. The syndrome quickly disappears at pregnancy interruption, as the fetus could be the target of a maternal rejective reaction. Moving from a rejection hypothesis of the fetal graft occurring in gestosis, we undertook these studies to evaluate at placental, plasmatic and DNA molecular level, the potential etiopathogenetical role of the MHC-HLA antigens, which are implicated in self and non self recognition and in rejective reactions.

## Materials and Methods

Previously, placentae from gestosis and normal pregnancies were tested by immunohistochemical study of placental endothelium with HLA-DR monoclonal antibodies. Furtherly, a placental ultrastructural and biochemical V-CAM 1 plasmatic study followed and finally laser confocal and electron microscopy assessment was carried out both through immuno-fluorescence and Immunocytochemistry for HLA-G1 antigen and ubiquitin. Gestosis/preeclamptic women, their partners and physiological control couples were also examined for HLA-DR assessment, chronologically performed by serological Terasaki technique, low and high resolution PCR and DNA sequence-based typing.

## Results

Our first immunoistochemical study of placental endothelium showed a marked and widespread expression of HLA-DR

antigens not occurring in normal pregnancy [1]. Subsequently, in placentae from gestosis/preeclamptic women we demonstrated, by ultrastructural evidence, a placental barrier breakage leading to the mixing of maternal and fetal antigenically different blood. This condition could be responsible for the triggering of that maternal rejective reaction presumed to be at the basis of gestosis syndrome. Thus, we investigated the Human Leukocyte class II DR Antigens (HLA-DR), whose role in self and not self recognition is well known, in women with gestosis, their partners and in control couples using the serological Terasaki technique [2-5].

The results showed a statistically significant increase of HLA-DR homozygosity and a reduced antigenical variety in the gestosis women and their partners with respect to control. The following update, studying the 2<sup>nd</sup> exon of the human gene HLA-DR  $\beta$ 1 on the short arm of the chromosome 6, by DNA sequence-based typing (S-BT) PCR, in gestosis and control couples, confirmed the significant excess of HLA-DR homozygosity in partners associated with gestosis versus controls [5-7].

## Discussion and Conclusion

Immunohistochemical and ultrastructural evidence of immunological activation and placental barrier disruption, strenghtly support the rejective hypothesis supposed occurring in gestosis. From serotyping and genotyping results in gestosis and control couples, it emerges that HLA-DR homozygosity and the reduced antigenical variety seem to be associated to a major risk for this syndrome which furtherly appears to be a "couple's disease". The preliminary data of an ongoing case-control study, to evaluate by immunofluorescence and confocal laser, the potential HLA-G etiopathogenetic role in defective trophoblastic

implantation associated with gestosis, are still under discussion [8].

We suggest HLA-DR *pre-conception diagnosis* in the couples. If HLA-DR homozygosity occurs in the woman and/ or in the man and /or HLA-Antigens sharing between partners with reduced antigenic disparity, we recommend to the future mother one year or more of free intercourses to allow the mother to recognize and tolerate the partner seminal histocompatibility antigens and then to tolerate the foetal allograft [9].

In this period, an alloreactive immune response to the paternal HLA antigens could develop, allowed to the male semen exposure during free sexual intercourses, (according to Dekker and Robillard), with protective effect on future embryo implantation. HLA-DR homozygosity, by reducing the Class II MHC Antigens variety between Partners, may be the cause of the failure of the maternal immunological protective reaction, which seems to be at the basis of Preeclampsia [10,11].

Due to the demonstrated reduction of heparin activity in gestosis placentae, a prophylactic treatment with LMWH since placentation, is recommended in couples associated with HLA-DR homozygosity, to prevent the open syndrome, whose real effective therapy is only pregnancy interruption, often related to adverse neonatal outcome, depending on severity and early onset of gestosis. The clinical experience in using heparin of our obstetric department, shared in the OG and OGASH, lead us to encourage the employment of an historical drug for new prophylactic implications in this syndrome, to improve foetal maternal outcome by significantly reducing mortality and morbidity.

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