Maternal/paternal sharing of DQ-Alpha type II histocompatibility antigens not associated with pregnancy outcome following in vitro fertilization (IVF)-embryo transfer (ET)

J. H. Check, *M.D., Ph.D.*; **J. K. Choe,** *M.D.*; **L. Ubelacker,** *B.S.*; **A. DiAntonio,** *B.S.*

The University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School at Camden, Cooper Hospital/University Medical Center, Department of Obstetrics and Gynecology, Division of Reproductive Endocrinology & Infertility, Camden, New Jersey (USA)

Summary

Purpose: To determine if maternal/paternal sharing of DQ alpha major histocompatibility (MHC) type II antigens is associated with reduced pregnancy and implantation rates following in vitro fertilization-embryo transfer (IVF-ET).

Methods: Prospective study with type II MHC DQ alpha alleles detected by polymerase chain reaction (PCR) technology using Perkin Elmer Amyli-type HLA DQ alpha PCR amplification and typing kit. The tests were only performed on patients having their first IVF cycle.

Results: No difference was found in clinical pregnancy rates per transfer between those couples sharing DQ alpha 1 alleles and those who did not (43.7% vs 40%). There were no spontaneous abortions in the group sharing DQ alpha 1 alleles.

Conclusion: Maternal/paternal sharing of DQ alpha 1 antigens does not reduce fecundity following IVF-ET.

Key words: IVF-ET; Major histocompatibility antigens; Fecundity; Sharing.

Introduction

The molecular technique of DNA extraction, polymerase chain reaction (PCR) and allele specific hybridization is considered to be a far more accurate method than previous obsolete serological techniques for HLA typing [1]. Using this molecular DNA technique, Ober *et al.*, suggested that parental sharing of alleles at the human leukocyte antigen (HLA) DQ alpha locus may be associated with recurrent miscarriage [2]. They found that 18% of couples with recurrent miscarriage but only 3% of fertile couples shared two HLA DQ alpha alleles [2].

However, subsequent studies using the same HLA typing DNA methodology failed to show any greater frequency in sharing of DQ alpha antigens in those with recurrent miscarriages vs fertile controls [3, 4].

However, in the study by Ober *et al.* they also found that the proportion of aborted fetuses that were typed for HLA showed a significant reduction compared to expected of the proportion of fetuses compatible for HLA-DQA1 alleles [2]. Thus, these data suggest that compatibility for HLA-DQA1 could result in very early losses which would manifest more in decreased fecundity [2].

Thus the study presented herein evaluated parental sharing of DQ alpha 1 alleles to see if this could be a factor in lowering pregnancy rates following in vitro fertilization-embryo transfer (IVF-ET).

Revised manuscript accepted for publication June 15, 2001

Materials and Methods

Blood samples were obtained on male and female partners of 31 patients undergoing their first IVF-ET cycle. Three EDTA tubes were collected on each patient and sent by Federal Express to the immunology laboratory at Finch University of Health Sciences, The Chicago Medical School Clinical Immunology Laboratory in North Chicago, Illinois.

DQ alpha alleles were detected by PCR methodology using Perkin Elmer Amyli-type HLA DQ-alpha PCR amplification and typing kit. More details of this technique have been previously described [2].

Results

There were 16 couples who shared a DQ-alpha antigen and 15 who did not. The clinical pregnancy rate (ultrasound evidence of pregnancy) was 43.7% (7/16) in those couples sharing DQ-alpha 1 alleles and 40% (6/15) in those not sharing (p=NS). Spontaneous abortions were subsquently found in none (0/7) of the women who shared alleles with male partners and 16.6% (1/6) who did not share alleles.

There were seven patients who shared the 4.1 antigen and three conceived (42.5%), while eight shared a 1.1, 1.2, or 1.3 antigen and four conceived (50%).

There was one patient sharing two alleles with no conception.

The mean age for the female partners in the group that conceived was 33.5±4.3 years and was 35.0±7.3 years in those not conceiving.

Discussion

Though the study by Ober *et al.* using more accurate DNA methodology for determining HLA typing suggested that DQ-alpha 1 compatibility could be a cause of primary and/or recurrent abortions [2], subsequent studies failed to corroborate these data [3, 4]. In fact one Finnish study found that feto-maternal incompatibility was increased in those couples with primary abortions [5].

Nevertheless, the impetus for this study was the hope that from the other suggestion, that compatibility for DQ-alpha 1 alleles, could result in such early losses that it would manifest more in decreased pregnancy rates rather than increased abortion rates. Had such a trend been found we would have persued the study beyond the 31 couples. Furthermore, we would have considered this group for subsequent randomization to lymphocyte immunotherapy or not to see if this immune treatment could increase pregnancy rates following IVF-ET in those patients sharing DQ-alpha 1 alleles. However, since it was very clear that there was not even the slightest trend for a lower pregnancy rate in those sharing the alleles, the study was stopped. Though the patients were aware, and in fact, gave written permission for their blood to be sent to the Clinical Immunology Laboratory at Finch University, the Cooper Center for IVF paid for the testing.

These data do not allow the conclusion that histocompatibility is not a cause of infertility or spontenous abortion, just that if it does play some role in these two areas, it does not seem to be related to DQ-alpha 1. Clinicians and researchers should still keep an open mind that histocompatibility of some other allele could be a factor. The role played by HLA-C, E, and G needs to be explored in more detail in future studies [1]. Also future study of HLA alleles may find not so much that fetal compatibility is not such an important factor but that the presence of certain alleles may through genetic means render the fetus more susceptible to immune attack [6].

References

[1] Christiansen O. B.: "The possible role of classical human leukocyte antigens in recurrent miscarriage". *Am. J. Reprod. Immunol.*, 1999, *42*, 110.

[2] Ober C., Steck T., van der Ven K., Billstrand C., Messer L., Kwak J. *et al.*: "MHC class II compatibility in aborted fetuses and term infants of couples with recurrent spontaneous abortion". *J. Reprod. Immunol.*, 1993, *25*, 195.

[3] Dizon-Townson D., Nelson L., Scott J. R., Ware Branch D., Ward K.: "Human leukocyte antigen DQ alpha sharing is not increased in couples with recurrent miscarriage". *Am. J. Reprod. Immunol.*, 1995, *34*, 209.

[4] Wagenknecht D. R., Green K. M., McIntyre J. A.: "Analyses of HLA-DQ alleles in recurrent spontaneous abortion (RSA) couples". *Am. J. Reprod. Immunol.*, 1997, *37*, 1.

[5] Laitinen T., Koskimies S., Westman P.: "Foeto-maternal compatibility in HLA-DR,-DQ, and -DP loci in Finnish couples suffering from recurrent spontaneous abortions". *Euro J. Immunogenet.*, 1993, *20*, 249.

[6] Christiansen O. B., Rasmussen K. L., Jersild C., Grunnet N.: "HLA class II alleles confer susceptibility to recurrent fetal losses in Danish women". *Tissue Antigens*, 1994, *44*, 225.

Address reprint requests to:
JEROME H. CHECK, M.D., Ph.D.
7447 Old York Road
Melrose Park, PA 19027 (USA)