Journal of Reproductive Immunology 133 (2019) 15–17

Contents lists available at ScienceDirect

Journal of Reproductive Immunology

journal homepage: www.elsevier.com/locate/jri

Short communication

Reciprocal HLA-DR allogenicity between mother and child affects pregnancy outcome parameters

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ARTICLE INFO

Keywords:
Birth weight
Blood pressure
Gestational age
HLA-DR allogenicity
Pregnancy

ABSTRACT

Successful pregnancy outcome depends on local immunoregulatory mechanisms preventing a detrimental immune response towards the semi-allogeneic fetus. We investigated the influence of HLA-DR (in)compatibility on pregnancy outcome parameters in 480 women. The parameters tested were birth weight, individualized birthweight ratio (IBR), gestational age, and maternal highest diastolic blood pressure. Irrespective of pregnancy complications, maternal-fetal HLA-DR incompatibility resulted in increased IBR. We conclude that reciprocal HLA-DR allogenicity between mother and child positively affect pregnancy outcome parameters.

1. Introduction

Successful pregnancy outcome depends on local immunoregulatory mechanisms preventing a detrimental maternal immune response towards the semi-allogeneic fetus. Paternally-inherited fetal HLA antigens can induce maternal immune activation, and a variety of immune cells are recruited to the placental bed to secure and promote the pregnancy. Regulatory T cells (Tregs) play an important role in successful pregnancy. These Tregs are generally CD4+ and are thus HLA class II restricted. In organ transplantation, matching for HLA-DR leads to a better graft survival and function (Opelz et al., 1999).

In the setting of pre-transplant blood transfusion it has been shown that at least one HLA-DR antigen has to be shared between donor and recipient in order to induce a tolerogenic effect on the course of a subsequent renal transplantation, while incompatibility for the second HLA-DR antigen enhances a stable, rejection-free, allograft function (Lagaaij et al., 1989; Lazda et al., 1990).

In line with this blood transfusion concept, the pregnant mother has to accept the semi-allogeneic fetus. Trophoblast cells do not express HLA-DR, but fetal chimeric cells can cross the placenta and trigger a maternal immune response. Moreover, such transfer is bidirectional (Adams and Nelson, 2004). Both maternal and fetal cells can cross the placenta and fetal immune cells can also respond to maternal alloantigens.

Several studies have aimed at finding a correlation between pregnancy complications such as preeclampsia (PE) and recurrent miscarriage (RM) and the presence of certain HLA alleles, maternal homozygosity or sharing of HLA between mother and father or between mother and fetus. Recently, a systematic review showed that HLA-B sharing and HLA-DR sharing were both associated with the occurrence of RM (Meuleman et al., 2015). This is in line with previous findings, suggesting that HLA sharing between mother and child is associated with pregnancies complicated by PE (Hoff et al., 1992). These studies focused on pregnancy complications, and they do not necessarily represent the interaction of HLA molecules and immune cells during uncomplicated pregnancy. Therefore, we sought to take a different approach to examine the possible effect of HLA on pregnancy outcome with the use of objective parameters.

We conducted a retrospective, observational study to investigate the influence of fetal and maternal HLA-DR sharing on pregnancy outcome using objective outcome parameters as birth weight, gestational age, and maternal highest diastolic blood pressure.

2. Materials & methods

We retrospectively studied a cohort of 480 women who gave birth in

Abbreviations: HLA, human leukocyte antigen; IBR, individualized birthweight ratio; NIMA, non-inherited maternal antigen; PE, preeclampsia; RM, recurrent miscarriage; Tregs, regulatory T cells

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https://doi.org/10.1016/j.jri.2019.04.002
Received 10 January 2019; Received in revised form 7 March 2019; Accepted 16 April 2019

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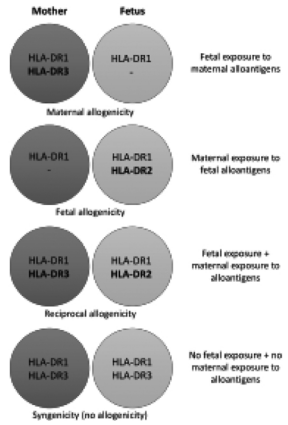

B

Variable	Allogenicity	N	Median	Min	Max	P-value
IBR	Maternal	54	1.00	0.51	1.39	**0.030***
	Fetal	50	0.97	0.62	1.43	
	Reciprocal	309	1.06	0.44	1.49	
	Syngenicity	53	1.03	0.53	1.49	
Birth weight (gram)	Maternal	55	3100	657	4975	**0.029***
	Fetal	51	3170	879	4550	
	Reciprocal	319	3365	625	5285	
	Syngenicity	55	3230	990	4155	
Highest diastole (mmHg)	Maternal	52	80	65	120	0.939
	Fetal	50	80	60	110	
	Reciprocal	317	80	60	160	
	Syngenicity	53	80	60	130	
Gestational age (days)	Maternal	55	269	202	292	0.898
	Fetal	51	270	209	295	
	Reciprocal	319	271	190	297	
	Syngenicity	55	270	210	294	

* P <0.05. The p-values were calculated using the Kruskal-Wallis test.

Fig. 1. HLA-DR allogenicity and pregnancy outcome. (A) The different types of maternal-fetal HLA relationships and potential for maternal and/or fetal exposure to alloantigens. Maternal allogenicity: the mother expresses two distinct HLA-DR antigens and the fetus only expresses one allelic form. Fetal allogenicity: the fetus expresses two distinct HLA-DR antigens, whereas the mother only expresses one allelic form. Reciprocal allogenicity: both the mother and fetus express two distinct HLA-DR antigens of which one of the HLA-DR antigens is mismatched between mother and child. Syngenicity: the mother and child express the same HLA-DR antigens. (B) Results of pregnancy outcome parameters for different HLA-DR allogenicity groups.

the Leiden University Medical Center between 1992 and 2011, and their children. The majority of the pregnancies (59%) investigated were uncomplicated term pregnancies representing successful pregnancy. All women signed informed consent and the study was approved by the Ethics Committee of the Leiden University Medical Center. HLA-DRB1 typing of both mother and child was performed by SSO PCR technique using a reverse dot-blot method at the national reference laboratory for histocompatibility testing (Leiden University Medical Center, the Netherlands). We divided the woman-child pairs into four previously described groups (Hoff et al., 1992) based on the degree of HLA-DR compatibility, as depicted in Fig. 1. Maternal allogenicity was defined as the situation in which the mother expresses two distinct HLA-DR antigens and the fetus only expresses one allelic form. In the situation of fetal allogenicity the fetus expresses two distinct HLA-DR antigens, whereas the mother only expresses one allelic form. In the reciprocal allogenicity group both the mother and fetus express two distinct HLA-DR antigens of which one of the HLA-DR antigens is mismatched between mother and child. Syngenicity was defined as the situation in which the mother and child express the same HLA-DR antigens.

The parameters tested were birth weight, individualized birthweight ratio (IBR), gestational age, and maternal highest diastolic blood pressure. The IBR is a ratio of the actual birthweight divided by the predicted birthweight (Wilcox et al., 1993). It is calculated by dividing the actual birth weight by the mean birth weight of children of the same sex born after a pregnancy with equal parity and gestational age, as derived from the Kloosterman tables (Kloosterman, 1969). Supplementary Tables S1 and S2 show the characteristics of the study population.

All other statistical analyses were performed using SPSS Statistics 23 software (IBM SPSS Software, New York, USA). Non-parametric tests were used, since data were not normally distributed according to the Shapiro-Wilk normality test. The Kruskal-Wallis test was used to analyze the distribution of the pregnancy outcome parameters between the different HLA-DR groups. P-values lower than 0.05 were considered statistically significant. To test for independent effects of HLA-DR on pregnancy outcome parameters, we included covariates in a regression model. Inclusion criterion for inclusion in the multivariate analysis was a univariate P-value of < 0.1.

3. Results and discussion

The present study showed that reciprocal allogenicity is significantly related to a higher IBR (Fig. 1). The group in which both the mother and fetus express two distinct HLA-DR antigens, with one HLA-DR mismatch between mother and child, had the highest birth weight ($P = 0.029$) and IBR ($P = 0.030$). After correction for maternal age, gravidity, parity, spontaneous abortion, PE/HELLP, and smoking, we found a trend for reciprocal HLA-DR allogenicity and birth weight ($P = 0.068$). The association between reciprocal HLA-DR allogenicity and IBR was independent of these factors ($P = 0.042$). The IBR is a superior measure for abnormal and normal growth, because this factor effectively controls for physiological birthweight determinants. These results indicate that the optimal situation for pregnancy is reciprocal allogenicity. Our results suggest that incompatibility for one HLA-DR antigen between mother and fetus leads to triggering and activation of the immune response, while the other HLA-DR antigen has to be shared in order to induce immune regulation. Since reciprocal allogenicity was the most optimal situation found in our study, both fetal and maternal immune responses seem to be important. Although trophoblast cells do not express HLA-DR, HLA-DR + fetal chimeric cells can cross the placenta (Adams and Nelson, 2004) and interact with the maternal immune system leading to a similar immune regulation as previously has been described for pretransplant blood transfusions (Lagaaij et al., 1989). During pregnancy, increased numbers of CD4 + Tregs are indeed present in the decidua and contribute to the regulation of fetus-specific responses (Tilburgs et al., 2008).

Similarly, HLA-DR + chimeric maternal cells in the fetus will interact with the developing fetal immune system, leading to the establishment of a large pool of fetal Tregs (Mold et al., 2008). This T cell tolerance towards maternal alloantigens perceived in utero may even be maintained after birth through the establishment of long-lived Tregs, which play a crucial role in the clinical observations showing that mismatches for non-inherited maternal antigens (NIMAs) are better tolerated than non-inherited paternal alloantigens in the setting of adult solid organ transplantation (van Rood et al., 2005).

The percentage of preterm births in this study (26%) is quite high. This is the direct result of collecting retrospective data from women who gave birth in a Dutch academic hospital. In the Netherlands it is still common to give birth at home under supervision of a midwife, which will have led to a relatively high percentage of deliveries with pregnancy complications in hospitals.

We did not collect any information on socioeconomic status, marital status, education, and race-ethnicity. Even though we think it is unlikely that these variables would have influenced the effect of HLA-DR allogenicity on pregnancy outcome parameters, we cannot fully exclude the effect of these factors.

In summary, we conclude that the most optimal situation for a successful pregnancy is that of reciprocal HLA-DR allogenicity. This suggests that active induction of immune tolerance from both maternal and fetal side is important.

Declarations of interest

None.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jri.2019.04.002.

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