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The development of preeclampsia in oocyte donation pregnancies is related to the number of fetal-maternal HLA class II mismatches

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ABSTRACT

In oocyte donation (OD) pregnancy, a fetus can be completely allogeneic to the recipient. Consequently, the maternal immune system has to cope with greater immunogenetic dissimilarity compared to naturally conceived pregnancy. Previously, we showed an association between successful OD pregnancy and lower immunogenetic dissimilarity, reflected by the number of fetal-maternal Human Leukocyte Antigen (HLA) mismatches, than expected by chance. In this study we aimed to determine whether the development of preeclampsia in OD pregnancies is related to the number of fetal-maternal HLA mismatches.

A retrospective, nested case-control study was performed within a cohort of 76 singleton OD pregnancies. Maternal and fetal umbilical cord blood was typed for HLA-A, -B, -C, -DR and -DQ, and the number of fetal-maternal HLA mismatches was calculated. In addition, the incidence of child-specific HLA antibodies was determined.

13 pregnancies were complicated by preeclampsia. To demonstrate an influence of HLA mismatches on the development of preeclampsia, a univariate logistic regression analysis was performed adjusted for maternal age and socio-economic status. A significant association between the number of fetal-maternal HLA class II mismatches and the development of preeclampsia was observed (OR = 3.8, 95 % CI: 1.6–9.0; p = 0.003). This association was not linked to the development of HLA class II antibodies.

According to our findings, an increased number of HLA class II mismatches is a risk factor for the development of preeclampsia in OD pregnancies. The effect of HLA class II mismatches might be explained by the induction of a cellular rather than a humoral immune response.

1. Introduction

The first successful oocyte donation (OD) pregnancy was achieved in 1984 (Lutjen et al., 1984). Since then, thousands of OD procedures have been performed worldwide, and numbers are growing as a result of delay of childbirth (De Geyter et al., 2018). In OD pregnancies, the fetus obtains genes from the father and the oocyte donor, and it can therefore be completely allogeneic to the gestational carrier. Consequently, the mother has to cope with a higher degree of immunogenetic dissimilarity to the fetus compared to naturally conceived (NC) and autologous in vitro fertilization (IVF) pregnancies. A comparable situation of immunogenetic dissimilarity is present in solid organ transplantation, where the recipient is treated with immunosuppressive drugs to prevent rejection of the donor organ (van der Hoorn et al., 2011).

In comparison to NC and IVF pregnancies, OD pregnancies are associated with a higher incidence of pregnancy complications, such as premature birth, low birthweight, caesarean section, bleeding complications, and hypertensive disorders (van der Hoorn et al., 2010; Savasi et al., 2016; Storgaard et al., 2017; Masoudian et al., 2016). Possibly, the allogeneic nature of the fetus in OD pregnancies plays a role in the development of these complications. Kim et al. showed that when the oocyte donor and recipient are not genetically related, the incidence of pregnancy induced hypertension is higher (20 % versus 3.7 % for standard IVF, p = 0.03) (Kim et al., 2005). In addition, a significantly higher number of HLA matches between mother and child was shown in uncomplicated OD pregnancies than expected by chance (Lashley et al., 2015). In the current study, we aimed to answer the question whether

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the number of fetal-maternal HLA mismatches in OD pregnancies is related to the development of preeclampsia.

2. Methods

2.1. Subjects

A retrospective, nested case-control study was performed within a cohort of 76 singleton OD pregnancies. The delivery took place between February 2004 and June 2016 in medical centers in the region of Leiden, the Netherlands. Twin pregnancies were excluded. Preeclampsia was defined as pregnancy-induced hypertension (diastolic blood pressure ≥90 mmHg and/or systolic blood pressure ≥140 mmHg detected after 20 weeks of gestation) with proteinuria (> 0.3 g/24 h) (Tranquilli et al., 2014). Clinical data, e.g. maternal age, BMI, ethnicity, parity, gravidity, gestational age, mode of delivery, and birthweight were obtained from the medical records. Socio-economic status (SES) was determined using a scale from 1 (low SES) to 3 (high SES) based on zip code. Indication for the OD procedure was unknown to our laboratory. The study protocol was approved by the ethics committee of the Leiden University Medical Center (LUMC) and informed consent of every patient was obtained (P16.048/P13.084).

2.2. HLA typing

Paired samples of peripheral maternal blood and umbilical cord blood (UCB) were collected after delivery. The maternal blood and UCB samples were typed for HLA-A, -B, -C, -DR, and -DQ using the Sequence Specific Oligonucleotides PCR technique. The number of fetal-maternal HLA mismatches at a 2-digit DNA level was calculated at the Dutch National Reference Laboratory for Histocompatibility Testing in the LUMC. On basis of the 5 HLA genes typed for, the maximum number of fetal-maternal HLA mismatches in OD pregnancies is 10.

2.3. HLA antibody screening

To detect the presence of HLA class I and II IgG antibodies in the serum of the mother, we used the same screening methods previously applied by Lashley et al. (2014), which is an enzyme-linked immunosorbent assay (LAT ™, One Lambda). In case of positive sera (ELISA ≥ 20 %), antibodies for HLA class I and II were determined with single antigen beads for class I and II and Luminex method (Gen Probe, Stamford, CT) following the manufacturer's instructions. A mean fluorescence intensity > 1000 was considered positive (Billen et al., 2008; Zoet et al., 2011). By comparing the HLA typing of the fetus with the specificity of maternal HLA antibodies, the child-specific HLA antibodies were defined. The HLA antibody screening was performed in 55 out of 76 included OD pregnancies (72 %), since postpartum serum and UCB was not available in all cases.

2.4. Statistical analysis

Descriptive statistical analysis was performed using SPSS Statistics 24 (IBM SPSS Software). To analyze differences between the two groups, the Mann-Whitney *U* test was used for continuous data and the Chi-square test or Fisher's exact test for categorical data. To demonstrate a relation between the development of preeclampsia and the number of HLA mismatches, a univariate logistic regression analysis was performed, including the confounding factors maternal age and SES. We adjusted for maternal age, as increasing age is positively correlated with the development of preeclampsia (Mol et al., 2016; Duckitt and Harrington, 2005; Dekker, 1999; Talaulikar and Arulkumaran, 2012; Jacobsson et al., 2004). In more than 50 percent of the OD cases from our cohort the origin of the oocyte donor was known. In this group, older women went abroad more frequently for an OD procedure, which could reflect in more fetal-maternal HLA mismatches as a result of greater genetic dissimilarity with the foreign population. We also adjusted for SES, since a lower SES is associated with a higher prevalence of hypertensive disorders in pregnancy (Sarwar et al., 2015; Kim et al., 2018; Heshmati et al., 2013) and women with a higher SES are more able to go abroad for an OD procedure. For all tests, a value of $p < 0.05$ was defined as significant.

Table 1
Clinical characteristics of the included subjects.

		OD pregnancies without preeclampsia N = 63		OD pregnancies with preeclampsia N = 13		
		percentage	N	percentage	N	p-value
Caucasian	Yes	95,6	43	100.0	9	1.000 $
	No	4.4	2	0.0	0	
	missing		18		4	
SES scale	1, 2	45.1	23	75.0	9	0.062 #
	3	54.9	28	25.0	3	
	missing		12		1	
Mode of delivery	Vaginally	52.4	33	30.8	4	0.341 #
	Caesarean section	38.1	24	53.8	7	
	missing		6		2	
		mean	min-max	mean	min-max	
Maternal age (years)		37.7	26-51	40.5	30-54	0.192 &
	missing		0		0	
Maternal BMI (kg/m^2)		23.4	17-32	23.9	19-27	0.532 &
	missing		31		6	
Gestational age (days)		279	245-297	261	204-284	0.001 &
	missing		1		0	
Birthweight (gram)		3563	2290-4775	2851	1395-4360	0.022 &
	missing		2		2	
		median	min-max	median	min-max	
Gravidity (N)		2	1-8	1	1-6	0.875 &
	missing		1		0	
Parity (N)		0	0-1	0	0-1	0.588 &
	missing		1		0	

SES = socio-economic status; N = number.
All p-values are 2-sided.
# p-values calculated with Chi-square test.
$ p-values calculated with Fisher's exact test.
& p-values calculated with Mann-Whitney *U* test.

3. Results

3.1. Subject characteristics

We included 76 singleton OD pregnancies, of which 13 were complicated by preeclampsia. In Table 1 the clinical characteristics of the included subjects are shown. Maternal age, ethnicity, SES, BMI, gravidity, parity and mode of delivery did not differ significantly between the two groups. Gestational age and birthweight were significantly lower in OD pregnancies complicated by preeclampsia compared to uncomplicated OD pregnancies.

Table 2
Univariate logistic regression analysis adjusted for maternal age and socio-economic status.

	OR	95 % CI	p-value
HLA class II mismatches	3.8	1.6–9.0	0.003
HLA-DR mismatches	9.2	1.8–47.2	0.008
HLA-DQ mismatches	5.5	1.5–19.6	0.009

OR = odds ratio; CI = confidence interval.

3.2. HLA mismatches

We observed no significant differences in the total number of HLA mismatches, number of HLA class I or number of HLA class II mismatches between the uncomplicated OD group and the OD group with preeclampsia. In this association, however, maternal age and SES are confounding factors. A univariate analysis adjusted for these factors showed no significant association for both the total number of HLA mismatches and the number of HLA class I mismatches with the development of preeclampsia. We did observe a significant association between the number of HLA class II mismatches and the chance of developing preeclampsia, with an odds ratio of 3.8 (95 % CI 1.6–9.0; p = 0.003) as shown in Table 2. In our cohort, we observed that 26 out of 63 pregnancies in the uncomplicated OD group (41.3 %) had a maximum of two HLA-DR mismatches, compared to 10 out of 13 OD pregnancies with preeclampsia (76.9 %; p = 0.019). Regarding HLA-DQ mismatches, we observed two mismatches in 11 uncomplicated OD pregnancies (17.5 %), compared to 6 OD pregnancies with preeclampsia (46.2 %; p = 0.029). Analyzing the influence of HLA-DR and HLA-DQ mismatches separately, both appeared to have a significant influence on the development of preeclampsia in OD pregnancies, showing an odds ratio of 9.2 (95 % CI 1.8–47.2; p = 0.008) and 5.5 (95 % CI 1.5–19.6; p = 0.009) respectively, though with wide confidence intervals (Table 2). Thus, a higher number of HLA class II mismatches, and specifically HLA-DR mismatches, is associated with a higher chance of developing preeclampsia in OD pregnancies.

3.3. HLA antibody screening

As the development of preeclampsia was shown to be significantly influenced by increasing number of HLA class II mismatches, we investigated child-specific HLA antibodies in OD pregnancies (Table 3). After logistic regression, adjusted for maternal age, neither the production of child-specific HLA class I nor class II antibodies had a significant influence on the development of preeclampsia in OD pregnancies.

Table 3
Presence of child-specific HLA antibodies.

	OD pregnancies without preeclampsia N = 48[a]		OD pregnancies with preeclampsia N = 7[a]		p-value
	percentage	N	percentage	N	
Presence of HLA class I or II antibodies	68.8	33	57.1	4	0.479
Presence of HLA class I antibodies	66.7	32	57.1	4	0.479
Presence of HLA class II antibodies	37.5	18	42.9	3	0.523

N = number.
[a] Since serum was not available in all cases, the HLA antibody screening was performed in 55 out of 76 included OD pregnancies.

4. Discussion

In this study we examined the relationship between fetal-maternal HLA mismatches and the development of preeclampsia in singleton OD pregnancies. We demonstrated a significant influence of HLA class II mismatches on the development of preeclampsia in OD pregnancies, corrected for maternal age and SES. Although a higher number of HLA class II mismatches results in a higher chance of developing preeclampsia in OD pregnancies, this was not reflected in a higher percentage of women producing child-specific HLA antibodies.

Previous studies have acknowledged the immunogenetic dissimilarity in OD pregnancies by comparing related and unrelated OD (Kim et al., 2005; Hasson et al., 2016). A genetically related donor (e.g. sister or cousin) will often result in a lower extent of immunogenetic dissimilarity, since donor and recipient potentially share a haplotype. Kim et al. demonstrated a higher incidence of pregnancy induced hypertension when the oocyte donor and recipient were not genetically related (Kim et al., 2005). In contrast, Hasson et al. found that outcomes of sister-to-sister OD are similar to those of unrelated OD (Hasson et al., 2016). However, these outcomes were restricted to early pregnancy complications; hypertensive complications developing later in pregnancy were not studied. To our knowledge, this study is the first to quantify the immunogenetic dissimilarity and study the association between the extent of HLA mismatching and the development of preeclampsia.

In our study, the clinical characteristics of the included subjects showed a significantly lower gestational age and birthweight in OD pregnancies complicated by preeclampsia. We did not adjust for these factors in our univariate logistic regression analysis, since they are a considered consequence of preeclampsia and not a confounding factor. We did adjust for maternal age and SES as explained in the methods section. In addition to these factors, also the ethnicity of the recipient is a confounding factor. A difference in ethnicity between donor and recipient may be related to more HLA mismatches. In addition, it is known that the prevalence of preeclampsia is higher among certain ethnic groups, such as African American women (Breathett et al., 2014; Pare et al., 2014). Unfortunately, we were not able to adjust for ethnicity as a result of missing data. The majority of included subjects were of European ancestry and the influence of this confounder is therefore probably minimal.

According to our findings, a higher number of HLA class II mismatches is a risk for the development of preeclampsia in OD pregnancies. The influence of HLA class II mismatches on the development of preeclampsia in OD pregnancies could possibly be explained by the activation of the maternal $CD4^+$ T cell immune response. Van der Hoorn et al. found a positive correlation between the number of HLA-DR and -DQ mismatches and the number of $CD4^+CD25^{dim}$ cells in the peripheral blood of women pregnant through OD (van der Hoorn et al., 2014). Possibly, fetal cells that migrate into the maternal circulation, expressing both paternal and donor antigens, are able to affect the maternal immune response to be more pro-inflammatory and less regulatory. Indeed, in OD pregnancies the presence of fully allogeneic fetal cells in the maternal circulation has been demonstrated, and these cells persist in the maternal blood for decades after delivery (Bianchi et al., 1996; Williams et al., 2009).

Among the mechanisms explaining the acceptance of the (semi) allogeneic fetus is the unusual expression of HLA molecules (van der Hoorn et al., 2011). Until recently, HLA-C was the only classical HLA antigen detected on the trophoblast (Apps et al., 2009; Hackmon et al., 2017). However, Tersigni et al. showed that under preeclamptic conditions also HLA-DR can be detected in the syncytiotrophoblasts, which constitutes the fetal-maternal interface between the placenta and maternal blood. However, whether the HLA-DR is of fetal or maternal origin remains unknown (Tersigni et al., 2018). In the light of those previously described results, our study indicates that HLA class II, including HLA-DR, is of significant influence in the development of

preeclampsia in OD pregnancies. As mentioned before, a higher number of activated $CD4^+CD25^{dim}$ T cells is found in maternal peripheral blood of uncomplicated OD pregnancies with two HLA-DR mismatches compared to those with one HLA-DR mismatch. The $CD4^+CD25^{dim}$: $CD4^+CD25^{bright}$ ratio was not changed, suggesting also higher numbers of regulatory T cells when there is a higher degree of mismatching (van der Hoorn et al., 2014). Regulatory T cells seem to play a key role in immune regulation at the fetal-maternal interface and have been found to be key players of fetal survival and acceptation by the mother (Bartmann et al., 2014; Svensson-Arvelund et al., 2015). In pre-eclamptic pregnancies, there is evidence for an alteration towards pro-inflammatory $CD4^+$ T cells and less regulatory and anti-inflammatory $CD4^+$ T cells (Saito et al., 1999, 2010; de Groot et al., 2010; Rolfo et al., 2013). Hence, in case of preeclampsia in OD pregnancies, the maternal immune regulation is failing, which is possibly induced by HLA class II mismatches.

Since we found a significant association between the extent of HLA class II mismatching and the development of preeclampsia in singleton OD pregnancies, we investigated the production of child-specific IgG HLA antibodies in uncomplicated OD pregnancies and OD pregnancies with preeclampsia. Lashley et al. demonstrated a significantly higher number of HLA mismatches in OD pregnancies and, consequently, a significantly higher incidence of child-specific HLA antibodies compared to NC and IVF pregnancies. The number of HLA-DR mismatches appeared to have an independent effect on HLA class I antibody production, probably by inducing $CD4^+$ T helper cells (Lashley et al., 2014). Likewise, in organ transplantation, the number of HLA-DR mismatches is shown to affect graft survival (Doxiadis et al., 2010, 2007). In blood transfusion, sharing of an HLA-DR antigen between donor and recipient reduces the risk of sensitization, and is needed to induce specific T-cell tolerance (Lagaaij et al., 1989; van Twuyver et al., 1991). In our cohort, the occurrence of two HLA-DR mismatches was significantly higher in the OD pregnancies complicated by pre-eclampsia.

In our study, we did not take the source of the sperm into account. Pregnancies achieved by donor sperm insemination have a significant increased risk of developing preeclampsia compared to pregnancies achieved with the sperm of the partner (Gonzalez-Comadran et al., 2014). Consequently, the high risk of preeclampsia associated with OD pregnancy and the risk of preeclampsia associated with sperm donation may be cumulative in double donation pregnancies. However, a recent cohort study showed that double gamete donation is not associated with a higher risk of hypertensive complications than OD alone (Preaubert et al., 2018). Another limitation is that we do not have preconception blood samples from included multigravida, so we do not know if HLA antibodies were already present before the OD pregnancy. In this study we are limited by the small sample size of our cohort and the retrospective study design, which may have caused selection bias. To tackle these issues, we are conducting a multicenter prospective cohort study in the Netherlands, relating the number of HLA mismatches to pregnancy complications in OD pregnancies.

The influence of HLA class II mismatches on the development of preeclampsia in OD pregnancies could be relevant for future perspectives in the clinic. For example, HLA class II matching and preventive treatment (e.g. immunosuppressive medication) could be an option for women who are willing to conceive through OD. However, more research is needed to establish whether the development of hypertensive disorders in future oocyte donation pregnancies may be prevented by HLA matching and immunosuppressive medication.

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Declaration of Competing Interest

None of the authors has any conflict of interest related to this manuscript.

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