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Uncomplicated oocyte donation pregnancies are associated with a higher incidence of human leukocyte antigen alloantibodies

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ABSTRACT

Background: Fetuses in pregnancies conceived after oocyte donation (OD) have a higher degree of antigeneic dissimilarity with the mother compared to semi-allogeneic fetuses after natural conception. We questioned whether this leads to higher level of HLA antibody formation in OD pregnancies.
Method: Uncomplicated pregnancies after OD were compared with pregnancies conceived either spontaneously or by IVF. We calculated the number of HLA- and epitope mismatches. Maternal sera were screened for HLA antibodies with ELISA; child HLA specific antibody production was determined using CDC and Luminex with single antigen beads for class I and II.
Results: A significantly ($p < 0.0001$) higher incidence of HLA antibody production was observed in women conceiving after OD (69%) compared to non-donor pregnancies (24–25%). The antibody formation was positively correlated with the number of fetomaternal antigen (Spearman's rho 0.95, $p < 0.0001$) and epitope mismatches (Spearman's rho 0.91, $p < 0.0001$). The number of HLA-DR mismatches between women and child was an independent risk factor for the production of HLA class I specific alloantibodies.
Conclusion: Women conceiving after OD have a higher risk of developing child-specific HLA antibodies; the higher the number of immunogenetic differences, the higher the chance these antibodies are formed. The high incidence of antibody production also strongly depends upon the number of HLA-DR mismatches. Despite the stronger antibody response, OD was associated with uncomplicated pregnancy in cases included in this study.

1. Introduction

During pregnancy antibodies are induced that target the paternal human leukocyte antigens (HLA) of the semi-allogeneic fetus. These HLA antibodies have been first described by van Rood et al. and Payne et al. in 1958 [1,2]. Nowadays, we know that 10–30% of healthy women produce HLA antibodies during pregnancy and the presence of these antibodies increases after 28th week of pregnancy [3]. This is probably due to the peak of influx of fetal material into the circulation in the last trimester. There is a clear association between the degree and persistence of fetal cell trafficking, or microchimerism, and the presence of HLA antibodies in the mother. The incidence of HLA antibodies also increases with the number of pregnancies [4] and furthermore depends on the HLA phenotype of the mother and fetus [5]. The immunogenicity of a HLA mismatch can be explained by specific amino acid sequence differences between the HLA alleles of fetus and mother. Indeed, in transplantation settings antibodies to HLA mismatches are more specific for epitope rather than for antigen mismatches [6]. Dankers et al. [7] studied the correlation between the number of amino acid triplets (epitope) mismatches for HLA-A and HLA-B between pregnant women and their children, and the percentage of women producing antibodies. A positive correlation was found between the number of triplet mismatches of the fetus and antibody production by the pregnant woman.

Oocyte donation (OD) pregnancies represent a unique situation with higher level of antigeneic dissimilarity between mother and fetus compared to normal pregnancies [8]. HLA antigens have

Abbreviations: OD, oocyte donation; HLA, human leukocyte antigen; IVF, *in vitro* fertilization; SP, spontaneously conceived pregnancy; CDC, complement dependent cytotoxicity; SAB, single antigen beads; UCB, umbilical cord blood; MFI, median fluorescence intensity; Th, T helper.

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multiple epitopes that can be recognized by specific antibodies and it is to be expected that in OD pregnancies the number of epitope mismatches is higher than in spontaneously conceived pregnancies. The higher level of immunogenetic differences could affect the extent of maternal humoral immune response in OD pregnancies, which may have clinical consequences.

In this study we examined the effect of the classic HLA antigen- and epitope mismatches on HLA antibody formation in pregnancies conceived after oocyte donation and with the woman's own oocytes.

2. Material and methods

2.1. Subjects

We selected 45 women who conceived by oocyte donation (OD) and women who conceived with the woman's own oocytes, either spontaneously (SP, $n = 51$) or by *in vitro* fertilization (IVF, $n = 36$). All women were Caucasian and delivered after uncomplicated pregnancy in the Leiden University Medical Center (LUMC) from February 2004 to December 2012. Exclusion criteria were maternal autoimmune diseases (e.g. antiphospholipid syndrome or systemic lupus erythematosus), use of drugs or immunosuppressive medication and blood transfusions or organ transplantation in medical history. Medical records were reviewed and clinical data were summarized. The indication for OD was unknown to our laboratory.

Maternal blood- and umbilical cord blood (UCB) samples were obtained within 24 h after delivery for HLA typing. Maternal serum samples were cryopreserved and stored at −80 °C until use. The study protocol was approved by the ethics committee of the LUMC and informed consent of every woman was obtained.

2.2. HLA typing

The peripheral blood samples and UCB samples were DNA typed for the loci HLA-A, -B, -C, -DQ and -DR using the Sequence Specific Oligonucleotides PCR technique. For class I, a commercially available assay was applied (RELI tm SSO, Invitrogen, DC), HLA-DRB and HLA-DQB typing was performed with a locally developed SSO technique [9]. Both maternal and fetal HLA allele frequencies were tested for Hardy Weinberg equilibrium. The number of fetal-maternal HLA mismatches was calculated at the national reference laboratory for histocompatibility testing (LUMC). On basis of the HLA-A, -B, -C, -DR and -DQ antigens, the maximal number of (mis)-matches between mother and child is 10 for OD pregnancies and 5 for non-donor pregnancies. For twin pregnancies the mother–child combination with the highest number of HLA mismatches was used.

The number of epitope mismatches was calculated using the HLAMatchmaker program developed by Duquesnoy [10]. With HLAMatchmaker histocompatibility between mother and child is determined on basis of polymorphic amino acid configurations that represent defined areas of HLA epitopes on protein sequences of HLA-A, -B, and -C chains accessible to alloantibodies. A specific epitope mismatch occurring more than one fetal HLA allele was calculated as a single mismatch. For twin pregnancies the mother–child combination with the highest number of epitope mismatches was included.

2.3. Antibody screening

The detection of HLA class I and II antibodies was performed by an enzyme-linked immunosorbent assay (LAT TM, One Lambda, CA) with OD readouts at 630 nm. Positive sera (ratio OD patient/OD control >2.0) were further tested for HLA antibody specificity by the standard NIH complement dependent cytotoxicity (CDC) assay [11] against a panel of 54 HLA-typed individuals. To identify only immunoglobulin G antibodies dithiothreitol was added, breaking down disulphide bonds of pentameric IgM. In addition antibody specificity of all ELISA positive samples was established with single antigen beads (SAB) for class I and II and Luminex method (Gen Probe, Stamford, CT) following the manufacturer's instructions. MFI (median fluorescence intensity) >1000 was considered positive as reported elsewhere [12,13]. Child-specific HLA antibodies were assigned by comparing the HLA antigen of the fetus with the specificity of the maternal HLA antibody.

2.4. Statistical analysis

Descriptive statistical analysis was performed using GraphPad Prism version 5.04 for Windows (GraphPad Software, San Diego California USA) and SPSS Statistics 20 (IBM SPSS Software).

To analyse differences between the three different groups the non-parametric ANOVA (Kruskal–Wallis) test was performed for continuous data, when significant, the post-test Dunns was used. For categorical variables the Chi-squared test or Fisher's exact test was used. To indicate a relation between the formation of child-specific HLA antibodies (dichotomous outcome; absence or presence of antibodies) and other parameters, first a univariate logistic regression model was executed. All variables with $p < 0.1$ [14] were then included in a multiple logistic regression analysis to identify factors predictive of child specific antibody formation. To assess the relation between categorical variables the Spearman's rank correlation coefficients were calculated. For all tests the value of $p < 0.05$ was defined as significant.

3. Results

3.1. Subject characteristics

The clinical characteristics of included subjects are shown in Table 1. The maternal age was significantly higher in the OD group compared to the spontaneously conceived group; no difference existed with the IVF group. The number of earlier deliveries (parity) was significantly different between the three groups, however the gravidity, as well as the number of spontaneous and elective abortions (data not shown) did not differ. No ectopic pregnancies or molar pregnancies occurred in either of the groups.

With respect to gestational age we found no statistical difference between the OD and non donor pregnancies. In the OD group more twins were born compared to the spontaneously respectively IVF conceived pregnancy groups (28.9% vs. 3.9% or 8.3%); there were no triplets in the groups. No significant differences in mode of delivery, subdivided into vaginally or caesarean delivery, existed between the groups. Further subdivision into primary- and secondary caesarean or into spontaneously - and vacuum vaginally delivery also revealed no differences (data not shown).

Finally, the gender of the child and the weight of the placenta did not significantly differ between the three groups.

3.2. Immunogenetic differences

To exclude the possibility of selection of a certain genotype within our groups, we analysed the genotype frequencies. The separate HLA loci in the subject groups and their children appeared to be in Hardy–Weinberg equilibrium (data not shown).

For all subjects the number of HLA antigen mismatches between mother and child was calculated. Moreover, HLAMatchmaker was used to determine the number of epitope mismatches. The number of classical HLA antigen differences was significantly higher in the

Table 1
Clinical data of included subjects.

	OD pregnancy ($n = 45$)	SP pregnancy ($n = 51$)	IVF pregnancy ($n = 36$)	p-Value overall comparison	Post test
Mother					
Maternal age (years)*	38 [27–48]	34 [24–42]	36 [27–41]	<0.0001	OD vs. SP*** OD vs. IVF ns SP vs. IVF ns
Gravidity (%)					
1	45.2	31.4	30.6	ns	
>1	54.8	68.6	69.4		
Parity (%)					
0	66.7	37.3	55.6	<0.0001	OD vs. SP***
1	31.0	29.4	38.9		OD vs. IVF ns
>1	2.4	33.3	5.6		SP vs. IVF***
Delivery					
Gestational age (days)*	272.5 [241–293]	274 [259–295]	274 [228–294]	ns	
Singleton pregnancy (%)	71.1	96.1	91.7	0.001	OD vs. SP*** OD vs. IVF*** SP vs. IVF ns
Mode of delivery (%)					
Vaginally	42.9	29.4	47.2	ns	
Caesarean	57.1	70.6	52.8		
Child					
Male sex (%)	45.6	51.0	52.8	ns	
Placenta weight (gram)	680 [360–1270]	605 [310–1210]	590 [410–1000]	ns	

ns = not significant.
* Values are medians with minimum and maximum.

OD group (median of total HLA mismatches 7) and ranged from 3 to 10 mismatches, as shown in Table 2. The number of epitope mismatches in non donor pregnancies ranged from 0 to 23, in pregnancies conceived by donor oocytes it ranged from 4 to 36 (Table 2).

3.3. Antibody formation

Table 3 shows the percentage of women producing child-specific HLA antibodies (class I and/or II) after oocyte donation and non donor pregnancies; this is visualized in Fig. 1. The χ^2 analysis indicates a significantly higher percentage of child specific antibodies in the OD group (69%), compared to the spontaneously conceived (24%) and IVF (25%) groups.

For the non donor pregnancies 75–88% of the child specific antibodies were HLA class I antibodies, whereas this was 100% for the OD group. HLA class II antibodies consisted 55% of the total formed child HLA specific antibodies in the OD group, 50–88% in the non donor groups.

3.4. Predictive variables on antibody formation

The influence of all the different variables on the formation of child-specific antibodies was analysed in a logistic regression model (Table 4). The variables with $p < 0.1$ in a univariate logistic regression analysis (maternal age, number of HLA mismatches, number of epitope mismatches, method of conception and usage of own oocytes) were analysed in a multivariate model. The variable remaining significant was the number of HLA mismatches, showing an odds ratio for child-specific antibody formation of 1.66 (95% CI 1.08-2.55 $p = 0.02$).

We furthermore described the percentage of women producing child-specific alloantibodies and the number of HLA- and epitope mismatches, this is depicted in Fig. 2. Statistical analysis using Spearman's correlation analysis shows a significant positive correlation for HLA mismatches (Spearman's rho 0.95, $p < 0.0001$). Also for epitope mismatches a significant positive correlation was found (Spearman's rho 0.91, $p < 0.0001$).

3.5. HLA-DR compatibility

Finally, we analysed the percentage of women producing HLA class I antibodies in relation to the number of HLA-DR mismatches. The χ^2 analysis showed a significant higher percentage of child-specific class I antibodies in women with two HLA-DR mismatches (76%), compared to single (33%) HLA-DR mismatch or zero HLA-DR mismatches (5%, data not shown).

To investigate an independent influence of the number of HLA-DR mismatches on alloantibody formation, we calculated the percentage of women producing child-specific HLA class I antibodies with DR (in)compatibility for a group of low- and high number of HLA class I mismatching and for a group of low- and high number of epitope mismatches (Fig. 3). The percentage of women producing child-specific HLA class I antibodies is significantly higher when there is HLA-DR incompatibility, independent of the

Table 2
Immunogenetic differences between oocyte donation and non donor pregnancies.

	OD pregnancy ($n = 45$)	SP pregnancy ($n = 51$)	IVF pregnancy ($n = 36$)	p-Value ANOVA	Post test
Total HLA mismatches	7 [3–10]	3 [0–5]	4 [0–5]	<0.0001	OD vs. SP:*** OD vs. IVF:*** SP vs. IVF: ns
Epitope mismatches	17 [4–36]	10 [0–22]	11 [0–23]	<0.0001	OD vs. SP: *** OD vs. IVF: *** SP vs. IVF: ns

Values are medians with minimum and maximum. ns = not significant.

Table 3
Immunization of oocyte donation and non donor pregnancies.

	OD pregnancy(n = 45)	SP pregnancy(n = 51)	IVF pregnancy (n = 36)
Presence of child specific antibodies class I or II (%)	31 (68.9%)	12 (23.5%)	9 (25.0%)
Presence of child specific antibodies class I (%)	31 (68.9%)	9 (17.6%)	8 (22.2%)
Presence of child specific antibodies class II (%)	17 (37.8%)	6 (11.8%)	8 (22.2%)

χ^2 test (overall comparison): $p < 0.0001$.

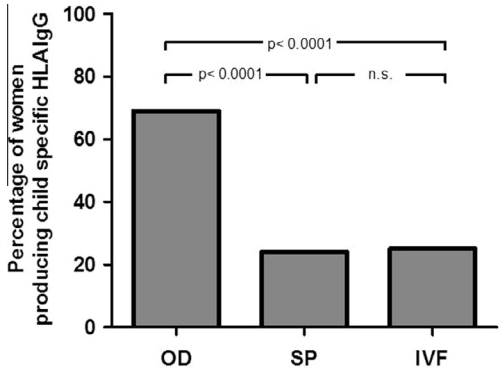

Fig. 1. Percentage of women producing antibodies after oocyte donation (OD) pregnancy, spontaneously conceived (SP) and *in vitro* fertilization (IVF).

number of HLA class I or epitope mismatches ($p < 0.001$). Furthermore, we show a significantly ($p < 0.001$) higher percentage of women producing HLA class I antibodies in the two HLA-DR mismatches group, compared to the single HLA-DR mismatch group. This difference between HLA-DR 1 or HLA-DR 2 mismatches is however not significant for the group with low number (0–3) of HLA mismatches.

In addition we performed a multivariate logistic regression analysis with the number of epitope mismatches, number of HLA class I mismatches and number of HLA-DR mismatches. The number of HLA-DR mismatches indeed showed an independent effect on HLA class I antibody production (OR 3.93, 95% CI 1.53-10.08 $p = 0.004$, further data not shown).

4. Discussion

In this study we examined the immunogenetic differences between pregnancies conceived after oocyte donation and with the woman's own oocytes and their association with the induction of HLA antibodies. We demonstrated a significantly ($p < 0.0001$) higher number of HLA antigen and epitope mismatching in OD pregnancies. As a consequence, women conceiving after OD showed a significantly ($p < 0.0001$) higher incidence of child-specific HLA antibody formation.

The enhanced immunization in women conceived by donor oocytes could possibly be explained by the enhanced maternal age in this group, enabling a longer period for immunizing events such as unrecognized pregnancies to occur. This would generate antibodies against only the paternal HLA though. Additionally, aging is associated with an impairment of the defense to new pathogens [15], possibly contributing to an in fact lower humoral immune response. Women in the OD group gave more frequently birth to twin pregnancies, associated with higher volumes of feto-maternal haemorrhage and enlarged exposure to fetal antigens [16]. The number of preceding deliveries, which is positively correlated with the presence of HLA antibodies [4], was however higher in the spontaneously conceived pregnancies.

Multivariate logistic regression analysis indicated only the number of HLA mismatches as independent risk factor for HLA antibody formation (OR 1.66 per HLA mismatch). The positive association between the number of epitope mismatches and antibody formation did not reach significance in the multivariate logistic regression analysis. The number of antigen- and epitope mismatches is however highly correlated but the range of epitope mismatches largely exceeds the range of HLA mismatches (maximum of 10), possibly diluting an effect on antibody formation and explaining this unexpected result.

We studied the correlation of both epitope and antigen mismatches and the percentage of women producing child HLA specific antibodies. This correlation was positive and significant (Spearman's rho 0.95, $p < 0.0001$) for HLA antigen mismatches and also for epitope mismatches and child specific antibody formation a positive and significant correlation was observed (Spearman's rho 0.91, $p < 0.0001$). This result is in agreement with the results of Dankers et al. [7]. They demonstrated that when 0 triplet mismatches were present, no antibodies were formed and when 11 or 12 mismatches were present, 27% of pregnant women produced anti paternal antibodies. Similarly, in our analysis no antibodies were formed when no epitope mismatches were present and combinations with 11 or 12 epitope mismatches resulted in 30% of women producing HLA antibodies. The immunogenicity of a fetus towards the mother

Table 4
Univariate and multivariate logistic regression analysis for HLA antibody formation.

	Univariate OR [95% CI]	p-value	Multivariate OR [95% CI]	p-value
Maternal age	1.062 [0.991–1.138]	0.087	0.980 [0.897–1.071]	0.656
Gravidity	1.367 [0.648–2.886]	0.412	#	
Parity	1.035 [0.641–1.671]	0.887	#	
Gestational age	0.994 [0.964–1.024]	0.684	#	
Singleton	1.273 [0.467–3.471]	0.638	#	
Mode of delivery	0.969 [0.470–1.998]	0.932	#	
Sex child	0.807 [0.444–1.467]	0.482	#	
Placenta weight	1.000 [0.998-	0.998	#	
Method of conception	1.002]0.315 [0.145–0.688]	0.004	0.934 [0.326–2.678]	0.900
Use of own oocyte	0.144 [0.065–0.320]	<0.0001	0.555 [0.137–2.258]	0.411
HLA mismatches	1.777 [1.412–2.237]	<0.0001	1.656 [1.077–2.548]	0.022
Epitope mm	1.437 [1.204–1.714]	<0.0001	1.031 [0.793–1.340]	0.820

OR = Odds ratio, CI = Confidence interval, # = not included in multivariate analysis.

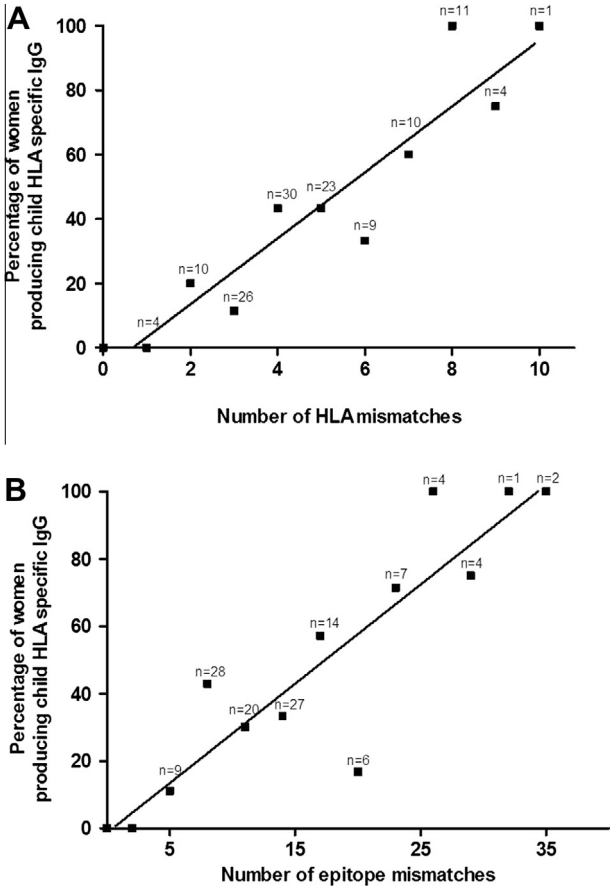

Fig. 2. Correlation between the percentage of women producing HLA antibodies and the number of immunogenetic mismatches between mother and child.

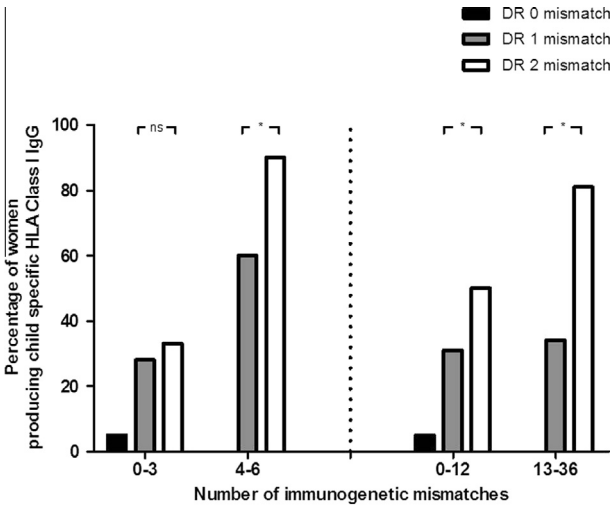

Fig. 3. Percentage of women producing HLA class I antibodies with HLA-DR (in)compatibility for low and high number of HLA class I and epitope mismatching. ns = not significant $^{*}p < 0.001$.

is therefore similar regardless of the origin of the oocyte. In literature the same correlation between triplet mismatches and antibody formation was observed using single HLA-antigen beads and high resolution HLA typing to detect child HLA specific antibodies [17] or when detecting HLA class I antibodies in pregnancies complicated by haemolytic disease of the fetus [18]. On the other hand, Maruya et al. [19] did not show an association between the antibody production rate and the number of epitope mismatches. They suggested a difference in efficiency of class II alleles in antigen-presenting capacity, which may affect antibody production. Indeed, the HLA-DR phenotype of the responder plays a determinative role in the immunogenicity of mismatched HLA antigens [20,21], as T helper cells are triggered based on indirect recognition of allopeptides presented by self-HLA class II molecules. The production of alloantibodies is also related to the degree of HLA-DR compatibility as reflected by the higher incidence of donor specific antibodies in patients transplanted with an HLA-DR incompatible graft [22] compared to HLA-DR compatible transplants. This HLA-DR incompatibility was furthermore associated with reduced graft survival [23]. We demonstrated a significant higher percentage of women producing HLA class I antibodies in case of HLA-DR incompatibility, independent of the number of HLA class I mismatches. Furthermore, women-child combinations with two HLA-DR mismatches showed a higher incidence of HLA class I antibody production compared to one HLA-DR mismatch (Fig. 3). Still, all of our included patients experienced uncomplicated pregnancies. To develop a successful and uncomplicated fully HLA-DR mismatched pregnancy, possibly a stronger peripheral immune regulation is necessary [24]. Van der Hoorn et al. [8] showed a lower proliferation of maternal peripheral blood mononuclear cells after OD pregnancies in a mixed lymphocyte reaction against a 3rd party UCB with two HLA-DR mismatches compared to naturally conceived pregnancies. Moreover, they found a higher number of CD4+CD25dim activated T cells with more HLA-DR mismatches in OD pregnancies while the ratio CD4+CD25dim: CD4+CD25bright was not affected, indicating also higher numbers of regulatory T cells with higher number of mismatching [8]. Chernyshov et al. [25] demonstrated hyperactivation of T helper (Th) 2 and T helper 1 cells in maternal blood of OD pregnancies and suggested an additional Th2 mechanism in successful allogeneic pregnancies. As Th2 cells synthesize cytokines that induce humoral immunity [26], we also suggest that to sustain an uncomplicated pregnancy, allogeneic fetal cells should induce an additional activation of Th2, rather than a Th1 type of immune response.

A limitation of this study is that we lack antibody screening results before pregnancy. The prevalence of both class I and II HLA antibodies among never allo-exposed donors is 1.0–7.0%, indifferent of the sex of the donor [4,27,28]. These antibodies could be produced after unrecognized pregnancies, directed against epitopes found in microorganisms [29] or vaccines [30] or against minor histocompatibility complexes [31,32]. Therefore we cannot exclude the presence of preformed antibodies, even though we detected antibodies specific against the fetal antigen of the index pregnancy and excluded patients with earlier blood transfusions or transplantations. On the other hand Hönger et al. showed in samples taken immediately after delivery, that child-specific HLA antibodies induced by the index pregnancy are dominant while the level of third party antibodies is low and not different amongst first, second, third or more live births [17].

As mentioned earlier, to indicate an association between the immunogenetic mismatches and the production of HLA class I and II antibodies, we assumed equal humoral immunogenicity of the mismatched antigens and epitopes in this study. However, we know that not every HLA mismatch evokes the same immunologic reaction after transplantation [33]; whether this holds for epitope mismatches remains to be investigated.

Finally, in this study not all factors possibly contributing to the presence of child HLA specific antibodies were taken into account. The presence of fully HLA mismatched fetal cells has been demonstrated in the maternal circulation [34] and the level of microchimerism may be different after semi-allogeneic or allogeneic pregnancies. Furthermore, cytokine polymorphism in the mother [35] could play a role in the absence of these HLA antibodies.

Child-specific HLA antibodies can be detected with complement dependent cytotoxicity assay in 10–30% of healthy women during pregnancy [36], which is in coincidence with the 24% found in our spontaneously conceived and the 25% in our IVF group. The question remains nevertheless what the clinical relevance of these child-specific antibodies is. In a recent systematic review we found no significant effect of HLA antibodies class I or II on pregnancy outcome, though high clinical and statistical heterogeneity between the studies existed [37]. Still, in transplantation and transfusion setting these antibodies mediate a number of important clinical detrimental effects, including platelet transfusion refractoriness [15], transfusion-related acute lung injury (TRALI) syndrome [38] and acute and chronic graft failure [39]. We demonstrated that women conceiving after OD form significantly higher level of child HLA specific antibodies. These women are therefore possibly more at risk upon transfusion or transplantation. Furthermore, it is tempting to speculate a detrimental effect of the HLA antibodies on the pregnancy outcome, since OD pregnancies are associated with a higher incidence of certain maternal complications as preeclampsia and postpartum haemorrhage [40]. In a recent study increased activation of the classical complement cascade was shown in the placentas of preeclamptic women and possibly antigen–antibody complexes at the fetal-maternal interface cause this activation [41]. Still, further research is necessary to establish whether the clinical consequences imply future HLA typing and matching of donors and recipients of oocytes.

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