Immunological challenges during pregnancy : preeclampsia and egg donation

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Preeclampsia in non donor IVF and egg donation pregnancy: is there a different pathophysiology?

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Abstract

Background: Egg donation (ED) gives women with premature ovarian or other causes of reproductive failure the ability to conceive. This results in a unique pregnancy since the entire fetal genome can be allogeneic to the mother. Two cases of IVF, one after ED and the other non donor IVF, are discussed to demonstrate why we hypothesize a different possibly immunological mechanism as the cause of preeclampsia in ED pregnancies as compared to non donor IVF.

Case 1 describes a 30 year old woman whose pregnancy after non donor IVF resulting in a dizygotic twin was complicated by preeclampsia and intra-uterine growth retardation of both fetuses. The pregnancy was a result of concurrent IVF and spontaneous conception, which is extremely rare.

Case 2 describes a 41 year old woman pregnant after ED of a dizygotic twin whose pregnancy was also complicated by severe preeclampsia. Both fetuses had a normal fetal birth weight.

We suggest a different pathophysiological mechanism of preeclampsia after ED compared with preeclampsia in non donor IVF conception.

Results: ED pregnancies are associated with a higher incidence of pregnancy-induced hypertension and a specific placental pathology. Other perinatal complications, such as intrauterine growth retardation and prematurity are also reported, but the incidence is comparable to conventional IVF. It is known that during pregnancy, both local and systemic immunological changes occur. Possibly, in ED pregnancies these changes are different or more pronounced.

Conclusion: Because of a higher degree of antigenic dissimilarity compared to non donor IVF, ED pregnancies represent an interesting model to study complex immunological interactions, as the allogeneic fetus is not rejected but tolerated by the pregnant woman. Knowledge of the immune system in ED pregnancies might have broader significance, as it may also give insight into immunologic aspects of tolerance in solid organ transplantation.

Introduction

We postulate that preeclampsia in egg donation (ED) pregnancies might have a different pathophysiological mechanism, compared with spontaneously conceived pregnancies. This chapter describes two examples of clinical complications in twin pregnancies resulting from assisted reproductive pregnancies. By describing both cases the differences and similarities become apparent.

Case 1 depicts a pregnancy after a non donor IVF procedure and case 2 illustrates a pregnancy after ED. In case 1 an infertile couple underwent non donor IVF with the transfer of one embryo, however resulting in a dizygotic pregnancy of concurrent IVF and spontaneous conception. Although this is an interesting and rare phenomenon, for the consideration of this chapter the focus is on the possible related development of preeclampsia and intra-uterine growth retardation of both fetuses. The second case discusses a woman pregnant after ED complicated by severe preeclampsia, however without intra-uterine growth retardation in none of the fetuses. By comparing both cases, we hypothesize a possible different pathophysiological immunological mechanism as the cause of preeclampsia in ED pregnancies.

Case 1 Dizygotic twin pregnancy following transfer of one embryo

Introduction

Two case reports suggest spontaneous conception in IVF cycles in which two embryos were transferred resulting in quadruplet pregnancies with different zygosity [1,2]. Although efforts are exerted to reduce the risk of multiple pregnancies, in general no advice against intercourse during the transfer period of an IVF cycle is given as it might have a positive effect on the success rate of IVF procedures [3]. In this case report we discuss a woman who conceived from intercourse and through an embryo transfer in the same menstrual cycle. Already during pregnancy permission was obtained from the couple to publish this report.

Case

A 30 year old nulliparous, ovulatory woman and her 39 year old partner (normospermia) were examined for primary infertility. Her medical history revealed appendectomy after perforation, menorrhagia due to an intramural myoma and a treated PID due to Chlamydia trachomatis. Shortly thereafter, a hysterosalpingogram and a laparoscopy showed a myoma (diameter 8 cm) in the anterior uterine wall and possible tubal obstruction as tube permeability for contrast fluid was absent. The couple was referred to a university center for uterine and possibly tubal surgery. During surgery, directly after myomectomy and myometrium closure whereby the cavum uteri was not opened, different approaches for testing tubal patency showed no tubal patency. An intramural obstruction of both tubes was considered. Seven months after surgery an IVF procedure resulted in 7 fertilized oocytes out of 10 collected. One of them was transferred and ended in a biochemical pregnancy and 5 were suitable for cryopreservation. Three months after the first transfer a 10-cell stage cryo embryo was transferred in a spontaneous cycle at the 16th cycle day, leaving 4 cryopreserved embryos. Ultrasound at 7 weeks gestation revealed a dichorial twin pregnancy with a septum of 6mm. The crown rump lengths were 8.74mm and 8.77mm, both conform a pregnancy duration of 6 weeks and 6 days. Routine ultrasound scan at

19 weeks gestational age showed a severely growth retarded boy (p<3), and a girl with a normal growth pattern (p10-50). The growth retardation of the boy persisted throughout gestation and at 35+6 weeks gestational age the abdominal circumference of boy was below p3, whereas the girl showed an abdominal circumference in between p3 and p10, with an estimated fetal weight of 1,720 g and 2,200 g, respectively. Ultrasound scan of the flows in the artery cerebri media of the boy showed a high end diastolic flow, with brainsparing, indicative of placental insufficiency [4]. The patient developed preeclampsia (high blood pressure and proteinuria) from the 29th week onwards. Throughout gestation the cardiotocograms (CTG) were normal, the fetal movements were good, and the patient had no other clinical complaints, besides gastric acid complaints.

At 36+0 weeks gestation, after spontaneously ruptured membranes, the boy showed signs of fetal distress (a raised basal heart frequency of 175/min combined with decelerations), indicating a caesarean section. The girl was born in cephalic position with an Apgar score of 10 after 1 minute, with a body weight of 2,025g. The boy was born after version and extraction, with an Apgar score of 6 after 1 minute and 7 after 5 and 10 minutes, with a body weight of 1,475g. The boy was admitted to the NICU because of a need for mechanical ventilation and hypoglycemia. The girl developed a mild hyperbilirubinemia without a need for phototherapy. After 9 days the twins were transferred in good condition to a non-academic centre with body weights of 1,550g (boy) and 2,055g (girl). The mother was discharged in good clinical condition three days after the cesarean section.

Human leukocyte antigen (HLA) typing showed that both children are of maternal and paternal origin as both inherited one set of antigen from the mother and the other from the father. By coincidence, the father and mother share 5 HLA antigens (Figure 1A, blue). Macroscopically the placentas were separated (Figure 1B). Microscopically, the dividing fetal membrane showed two amniotic and two chorionic membranes with fused trophoblast (Figure 1C). Fluorescence in situ hybridization (FISH) staining clearly shows that the one of the membranes originates from the girl and the other from the boy (Figure 1D).

Discussion

Ultrasound scan around 20 weeks of gestation was compatible with dizygotic twins as the fetuses had different genders. After birth two separate placentas were identified (Figure 1B) and no vascular anastomoses were present. HLA typing demonstrates that the children are derived from two different oocytes of the same mother (Figure 1A). Histological examination of the dividing fetal membranes showed that this was a diamniotic, dichorionic membrane (Figure 1C). Both findings strongly support dizygosity. Possibility of transfer of two embryos, instead of one, or laboratory mishandling have been considered, but rejected in favor of natural fertilization as the most plausible hypothesis. Four fertilized oocytes are still cryopreserved. The embryo transfer took place in the patients' own cycle, the sperm characteristics were normal and the couple confirmed intercourse without contraception in the period around embryo transfer. An increased rate of monozygotic twin pregnancy is observed after the transfer of one blastocyte [5]. The assumption of monozygosity in cases of twin pregnancies of the same gender could be an overestimation of monozygosity as one of the twins might be conceived after natural conception. Therefore, we hypothesize that dizygotic twin pregnancy following transfer of one embryo occurs more often than is expected.

It is known that hysterosalpingography is of limited use for detecting tubal patency because of its low sensitivity; however its high specificity makes it a useful test for ruling in tubal obstruction [6]. The negative tubal patency test, even after several attempts at laparoscopy, was possibly caused by swollen tissue after myoma surgery. This case report shows that at least one oocyte was able to travel through one of the tubes.

The ideal outcome of IVF is a singleton pregnancy after single embryo transfer, since multiple gestations have a higher risk of complications for the mother and fetus [7]. The couple in this case was not advised against having intercourse without contraception. This case is also an example of a twin pregnancy showing a substantial increased risk of maternal and fetal complications since the mother developed preeclampsia and both children showed severe intra-uterine growth retardation. Interestingly, the HLA typing of the mother and boy is similar, which is possible since the mother and father share one set of HLA antigens. It is assumed that a certain level of HLA mismatches is necessary to develop an uncomplicated pregnancy. We hypothesize that because of the high level of HLA sharing, and therefore the low level of mismatches, the boy has a more severe growth retardation compared to the girl.

Based on this case, we suggest that couples should abstain from intercourse without contraception during an IVF procedure to prevent multiple gestations, which are related to higher maternal and fetal complications.

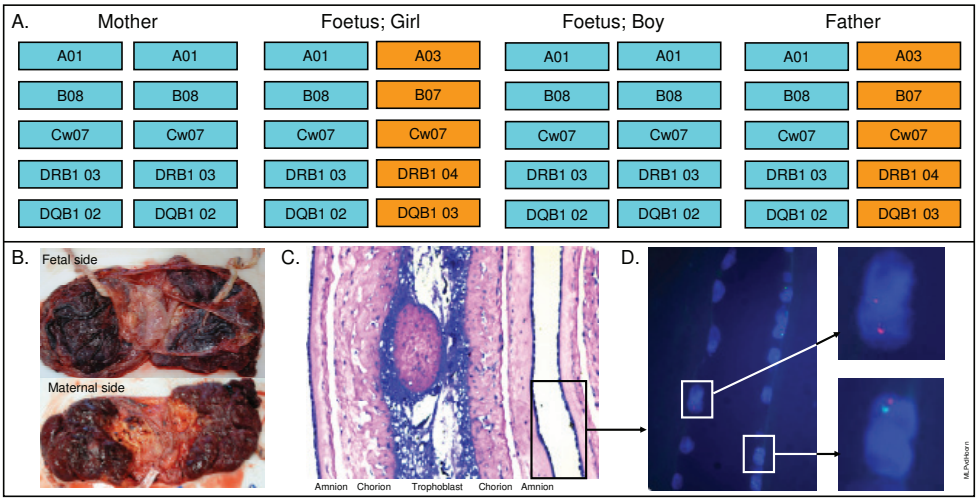

Figure 1 Four evidences strongly suggesting that the twin in this case report was dizygotic. HLA-typing of the mother, both children and father; macroscopic examination of the placenta; histology of the dividing fetal membrane; FISH staining of the X and Y chromosome. **A.** HLA typing of 5 HLA antigens shows that both children inherited one set of antigens from the mother. The other set of HLA antigens is inherited from the father. By coincidence, the father and mother share 5 HLA antigens (blue). **B.** Pictures of the placenta from the fetal side (upper picture) and from the maternal side (lower picture). These pictures show that two separate placentas were present, without vascular anastomoses. **C.** May-Grünwald-Giemsa staining of the dividing fetal membrane showing that the twin was dichorionic and diamniotic. **D.** FISH staining of two adjacent amniotic membranes. Blue stains the cell nucleus, red stains the X-chromosome and green the Y-chromosome. The enlargement clearly shows that one amniotic membrane originates from the girl and the other from the boy.

Case 2 Preeclampsia as complication in egg donation pregnancies: is there a different pathophysiological mechanism?

Introduction

In 1984 the first successful egg donation (ED) pregnancy was described [8]. The initial indication was premature ovarian failure. Nowadays, several indications leading to ED or embryo donations have increased the use of this technique worldwide. Pregnancy after ED is unique since the fetal genome can be entirely allogeneic towards the mother (Figure 2). It is suggested that therefore these pregnancies may result in more, mainly hypertensive, complications in comparison to spontaneously conceived or *in vitro* fertilization (IVF) pregnancies [9,10]. Remarkably, especially the mothers can be afflicted by these severe complications, while in contrast fetal parameters may be completely normal. This article describes a patient, pregnant after ED, suffering from severe preeclampsia, without growth retardation of none of the children.

Case

A 41-year-old primigravida, was pregnant of a dichorial, diamniotic twin pregnancy after ED. The oocytes were donated by the patient her sister. The indication for ED was idiopathic premature ovarian failure. The patient had no specific medical history. At a gestational age of 28 weeks, patient was referred to our academic center, due to a severe, early preeclampsia. Besides a progressive edema in the face and ankles, patient had headache complaints and was nauseous. Patient used methyldopa 500mg 3 times a day.

Patients blood pressure was 130/80 mmHg and there were signs of edema of the legs. From the start of pregnancy patient had gained 40 kilo's of weight. Her fluid balance was positive (400-800 ml per day), while her urine production was decreased: 25-30 ml/h. Reflexes of the limbs were normal.

Blood tests showed the following results (with references values in brackets): hemoglobin 6.9 mmol/l (7.5-10), hematocrit 0.34 l/l (0.37-0.47), thrombocytes $187x10^9$/l (150-450), creatinine 81 µmol/l (44-80), urea 10.7 mmol/l (2.5-7.5), uric acid 0.58 mmol/l (0.14-0.34), ASAT17 U/l (5-30), ALAT 7 U/l (5-34), LDH 355 U/l (100-248). Total protein loss was 2.6 g/24 h. Ultrasound showed of both children normal fetal movements and a normal biometry. Estimated fetal weight of the first child was 1371 grams (p50) and the second child 1275 grams (p30). Doppler ultrasound examination of the umbilical artery was comparable with a normal placenta perfusion.

As maternal blood pressure was acceptable and stable a conservative management was installed. To induce fetal lung maturation betamethason (12 mg 2 times within 48 hours) was given. During hospitalization edema became more prominent and the positive fluid balance increased up till 1 liter/day. Urine production was stable on average 30 ml/day. The blood test result for creatinine, ureum and uric acid became gradually more abnormal with maximum values of 92µmol/l, 14.7 and 0.72 mmol/l respectively. The total loss of protein increased up to 17 grams/24 hours, which made the decision to terminate pregnancy.

Delivery started spontaneously at gestational age 29+1. The first fetus (boy) was born in head position with a birth weight of 1363 grams (p50-75). By primary breech extraction a daughter was born with a birth weight of 1369 grams (p50-75). Both children had normal Apgar scores. Post partum patient recovery was quick. Urine production normalized and the peripheral edema disappeared. In one week 20 kilograms of body weight were lost and the kidney function became

normal again (creatinine 63 µmol/l, ureum 4.9 mmol/l and uric acid 0.4 mmol/l). Two weeks after delivery patient could leave hospital in good condition. Six weeks after delivery patient reported no complaints. Blood pressure was 125/75 mmHg without medication and no proteinuria. Both children were transferred to a non-academic hospital.

Discussion

In the literature several perinatal complications of ED pregnancies as compared to spontaneous and IVF pregnancies have been described. There is an increased incidence of early pregnancy complications (in particular blood loss), but late complications as well [11,12]. Reasons for these higher incidences of complications, although some of them might be explained by the higher incidence of multiplets, are still unidentified. Interestingly, the incidence of pregnancy induced hypertension is significantly higher if the donor of the egg is not related to the recipient, compared to a related donor [11].

HLA incompatibility

Complete HLA-incompatibility refers to a situation whereby the fetal genome is completely different as compared to the genome of the mother. This situation normally does not occur in natural conceived pregnancies. It is suggested that partner choice by women aims at an optimal possible number of HLA-matches and mismatches [12]. Sharing of too many HLA-molecules with the partner might be unfavorable, as this is hypothesized to be related to occurrence of preeclampsia [13,14]. This suggests that preeclampsia in ED pregnancies where the number of mismatches is increased might be based on a different pathophysiological mechanism, compared to preeclampsia in non-ED pregnancies. As shown in our patient, although an increased incidence of hypertensive complications in ED pregnancies has been reported, surprisingly no effect on placental perfusion or birth weight has been demonstrated [15]. The incidence of other perinatal complications as prematurity are similar to non donor IVF pregnancies [15].

Immune response

For an adequate immune reaction associated with normal implantation, maternal (allogeneic) immune recognition needs a certain level of HLA-incompatibility [16]. In ED pregnancies it is possible that this immunological response against fetal and placental tissue is inadequate, which may play a role in the development of specific hypertensive complications. This might be the pathophysiological background for of preeclampsia in ED pregnancies [11]. Indeed, at the fetal-maternal interface of the placentas of ED pregnancies an increased immunological activation and fibrin deposition are found, which resembles graft-versus-host disease after solid organ transplantation [17].

Activation of the immune system may lead to an increased production of certain cytokines and antiangiogenic factors. In a pilot study of pregnancy complicated by preeclampsia it was found that in ED pregnancies a higher amount of soluble fms-like tyrosine kinase (sFlt, an antagonist of the pro angiogenic vascular endothelial growth factor (VEGF)), and soluble endogline (sEng, a co receptor of transforming growth factor (TGF)-β) were found. Serum levels of these substances were determined in our patient (Table 1). Remarkably high levels of sFlt, sEng and TGF-β were found, compared to levels in uncomplicated spontaneously conceived pregnancies. These values are also found severe forms of preeclampsia and are suggested to possibly explain kidney disorders in preeclampsia. The source of sFlt could be, other than the placenta, maternal monocytes. Recent studies showed that monocytes in chronic kidney disease patients also produce sFlt [18]. Post partum the production of sFlt by monocytes will decrease and thereby the kidney function will return back to normal, as in our patient.

Cytokine	Function	Patient	Control
TGF-β (pg/ml)	Immune regulation	45506	158
sEng (ng/ml)	TGF-β co receptor	71	13
sFlt (pg/ml)	Anti-angiogenic VEGF antagonist Antagonist of pro- angiogenic molecules	14298	8396

Table 1 Cytokine levels. Level of specific cytokines in serum (tested by Luminex) of the patient discussed in this case compared with median levels of 51 uncomplicated pregnancies. TGF-β: transforming growth factor-β. sEng: soluble endoglin. sFlt: soluble fms-like tyrosine kinase. VEGF: vascular endothelial growth factor.

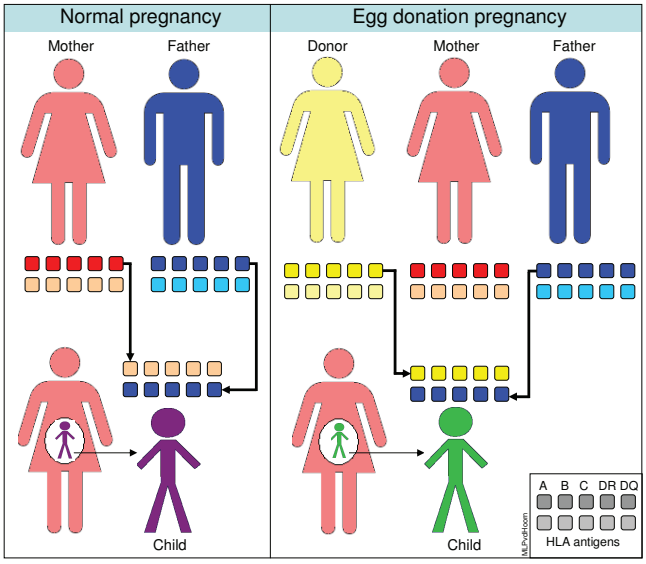

Figure 2 Schematic drawing of the inheritance of the most immunogenic HLA-antigens in a normal and ED pregnancy. A. In a spontaneously conceived (or non donor IVF) pregnancy the child inherits antigens of the father and antigens of the mother. The 5 most immunogenic HLA antigens (HLA-A, -B, -C, -DR and -DQ) are depicted in red for the mother and in blue for the father. The child inherits one set from the mother and one set from the father. Comparing the antigens of the child with the mother a maximum of 5 mismatches is possible. **B.** In an unrelated ED pregnancy no antigens from the mother are present in the fetus. The antigens of the donor are depicted in yellow and the antigens from the father in blue. The set of genes inherited by the child contains no antigens of the mother; therefore, a maximum of 10 mismatches is possible between the mother and the child in an ED pregnancy.

Conclusion

More research is needed for the understanding of underlying mechanism of preeclampsia in ED pregnancies. This might also give insight in the mechanism of occurrence of preeclampsia in non donor pregnancies. This knowledge can also be of significance for other areas of patient care, for example transplantation medicine.

Consideration

Case 1 describes a dizygotic pregnancy of concurrent IVF and spontaneous conception. Although this is an interesting and rare phenomenon, for this discussion the focus was on the development of preeclampsia. Since case 1 describes a dichorial diamniotic pregnancy, conceived by non donor IVF, this pregnancy can be considered as a control pregnancy for the second patient of this chapter. Case 2 is also a dichorial diamniotic pregnancy, however being conceived after ED. Both cases received hormonal treatment for hormonal treatment for endometrium preparation, however only patient 1 received hormonal treatment for oocyte retrieval. Interestingly, patient 1 developed preeclampsia combined with severe growth retardation, while patient 2 developed severe preeclampsia without fetal growth retardation. These findings are illustrating our hypothesis that preeclampsia in ED pregnancies might have a different pathophysiological mechanism, as explained in case 2.

The characteristics of case 1 and case 2 are summarized in Table 2. Figure 3 shows the birth weight of the four children born in the cases, plotted between references values.

	Case 1: IVF	Case 2: ED
Age	35 year	41 year
Gravidity	Primigravida	Primigravida
Choronicity	Dichorial diamniotic	Dichorial diamniotic
Infertility based on	Tubal obstruction	Premature ovarian failure
Onset preeclampsia	29 weeks	28 weeks
Medication	No medication	Methyldopa
Protein loss	0.36 g/24h	2.6 – 17 g/24h
Delivery	36+0	29+1
Mode of delivery	Cesarean section	Spontaneously
Birth weight and gender (percentiles)	1550 g (P<2.3) boy 2025 g (P5-P10) girl	1363 g (P50-P75) boy 1369 g (P50-P75) girl
Number of HLA mismatches	0 (boy) 5 (girl)	5 (boy) 5 (girl)
Placenta weight	980 g	640 g

Table 2 Characteristics of case 1 and case 2.

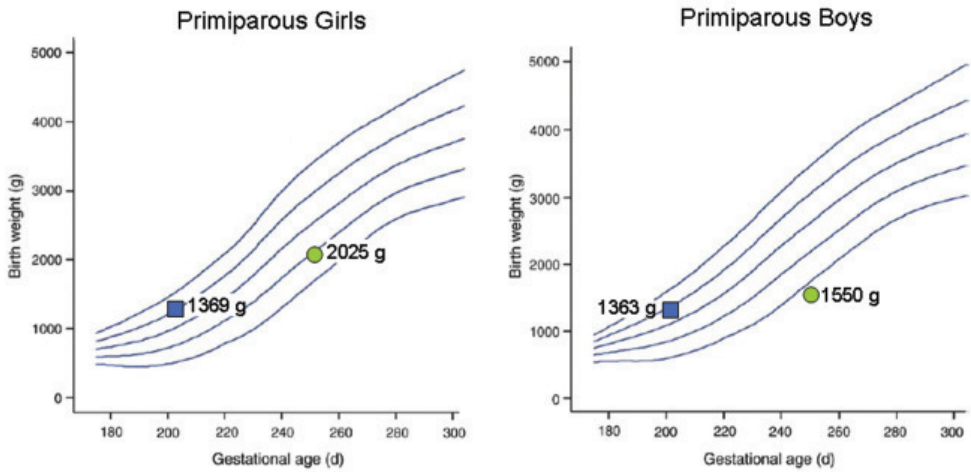

Figure 3 Reference curves (mean and 1 to 2 standard deviations) for boys and girls from primiparous women. The circle indicates case 1; preeclampsia in a non donor IVF pregnancy with severe growth retardation of both fetuses and the square indicated case 2; preeclampsia in an ED pregnancy with normal fetal birth weights. (Curves adapted from [19].)

In case 2 HLA typing of the mother and the boy are identical, which is possible since the mother and father share one set of HLA antigens. It is assumed that a certain level of HLA mismatches is necessary to develop an uncomplicated pregnancy. Partner choice by women seems to aim at an optimal number of HLA matches and mismatches [12]. We hypothesize that because of the high level of HLA sharing, and therefore the low level of mismatches, the boy is more severely growth retarded compared to the girl. Sharing of too many HLA molecules with the partner has also shown to be unfavorable, since this might also be related with the occurrence of preeclampsia [13,14]. In contrast, too many of the same HLA antigens between mother and child may as well be a disadvantage.

It is thought that preeclampsia is the consequence of an unsuccessful attack of the maternal non specific host defense on the implanting blastocyst, resulting in defective implantation resulting in a continuously stimulation of the maternal inflammation response [11]. Control of placentation has an immunological basis, with interaction between maternal and fetal genes. In some of the ED pregnancies there might also be a shorter pre-pregnancy exposure, via sperm, to non-maternal antigens, possibly leading to inadequate immunoprotection of placentation, eventually resulting in preeclampsia.

Further immunological involvement in the pathogenesis of preeclampsia is demonstrated by uterine NK cells and their relation with implantation. NK cells express KIR receptors; HLA is the most important ligand for these receptors. The combination of maternal (inhibitory) KIR AA genotype and fetal HLA-C2 is associated with an increased risk of preeclampsia [20]. The consequence of this interaction is that fetal HLA-C2 will only interact with an inhibitory KIR receptor, resulting in too much inhibition of uterine NK cells. It is thought that this interaction results in inadequate trophoblast invasion and insufficient remodeling of the spiral arteries, which is associated with the causation of preeclampsia. Since this combination has a disadvantage effect in evolution, the frequencies of these genotypes in populations have been investigated. Indeed, populations with a high frequency of the KIR AA genotype, have a low frequency of HLA-C2 and vice versa [20]. As commercial ED is not possible in the Netherlands, many women who are in need of ED go abroad. Hereby, such a population-protective effect might not be present, raising this as a possibility for the increased incidence of preeclampsia in ED pregnancies. The sperm of donors with a C1/C1 genotype is predicted to be safer than sperm of C2/C2 males, since the latter will always results in a fetus expressing C2 [21]. In the future it might become feasible to perform HLA-typing before IVF or ED, the combination of maternal KIR AA, fetal C2 and sperm donors with the C2/C2 genotype should be avoided in order to decrease the risk of preeclampsia. If the fetus has more C2 genes than the mother the risk of getting preeclampsia is two times higher (OR 2.09, 95% CI: 1.24-3.58, p=0.007) [21]. This shows that preeclampsia is not only explained by the combination of KIR genotype and HLA-C genotype; the genotype of mother and both children in case 1 was C1/C1. Even in the presence of the protective fetal phenotype, the patient did develop preeclampsia. In case 2 the mother was C1/C2 and both children were C2/C2. The maternal KIR typing is unknown. It is possible that preeclampsia in case 2 is partly caused by the 'dangerous' C2/C2 phenotype of the fetus.

In this chapter only 2 cases were described. Further investigation of preeclamptic ED placentas is essential to confirm our hypothesis that preeclampsia in ED pregnancies is based on a different pathophysiological mechanism. Because of a higher degree of antigenic dissimilarity, ED pregnancies represent an interesting model to study complex immunological interactions, as even in these pregnancies the allogeneic fetus is not rejected but tolerated by the pregnant woman. Understanding the fetus specific tolerance induction during pregnancy may lead to new insights for the induction of donor specific tolerance also in the transplantation setting.

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