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## Immunological challenges during pregnancy : preeclampsia and egg donation

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# Egg donation pregnancy as an immunological model for solid organ transplantation



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## Abstract

In egg donation (ED) pregnancies the fetus is allogeneic to the gestational carrier. During these ED pregnancies the mother has to cope with a higher degree of antigenic dissimilarity compared with spontaneously conceived pregnancies. At the fetal-maternal interface maternal cells and fetal cells come in close contact. Understanding the immune mechanisms at this fetal-maternal interface gives more insight into the question why the (semi-)allogeneic fetus is accepted and not rejected by the mother. The degree of antigenic dissimilarity in ED pregnancies is comparable with that in solid organ transplantations with HLA mismatched unrelated donors. Therefore, the immunologic interactions between mother and child in successful ED pregnancies may be relevant for the induction of immunological tolerance in solid organ transplantation.

## Introduction

The fetus is a semi-allograft expressing both maternal (self) and paternal (non-self) genes. The placenta and fetal membranes are directly exposed to maternal tissue. Therefore during the accomplishment of uncomplicated pregnancy specific, local immune adaptations are necessary at the fetal-maternal interface. As in egg donation (ED) pregnancies the fetus can be fully allogeneic to the mother, ED pregnancies represent an interesting model to study complex immunologic interactions between the fetus and the pregnant women. During these ED pregnancies the mother has to cope with a higher degree of antigenic dissimilarity compared to spontaneously conceived pregnancies. Understanding immune mechanisms involved in successful ED pregnancies can possibly lead to new strategies for the induction of immunological tolerance in human leukocyte antigen (HLA) mismatched solid organ transplantations. To elucidate aspects of ED pregnancies as an immunological model for solid organ transplantation, knowledge of maternal mechanisms during spontaneously conceived pregnancies in the acceptance of the developing fetus and placenta is essential. In this review immunogenetic and immunological similarities between ED pregnancy and transplantation are discussed. In addition an overview of immunological aspects of spontaneous, uncomplicated pregnancy is given, showing why fetal tissues are immunologically tolerated in the maternal host environment.

## Egg donation pregnancies

ED pregnancies are a result of in vitro fertilization (IVF) of an oocyte, donated by a related or, more commonly, by an unrelated donor. Hereby, neither of the fetal haplotypes will match with the gestational carrier. Increased knowledge in the field of assisted reproductive technologies, a more liberal interpretation of medical indications and social acceptance of the procedure has led to an ever increasing number of ED pregnancies. Clinically relevant complications in ED pregnancies, presumably related to the allogeneic nature of the fetus, occur more frequently. The literature reports on a higher risk of pregnancy induced hypertension, a higher incidence of cesarean sections, an increased risk of postpartum hemorrhage and more first trimester vaginal bleeding complications [1-5]. Although these maternal complications are higher in ED pregnancies compared to spontaneously conceived pregnancies, they are not associated with an increase in fetal and/or neonatal complications [3,4,6,7]. This suggests that downregulation of the maternal immune response preventing a detrimental maternal immunological response is possible, even in a completely allogeneic situation. Histological findings of ED placentas show some resemblance with a host versus graft rejection phenomenon as seen with solid organ transplantations [8]. Severe chronic deciduitis admixed with fibrinoid deposition has been observed in ED placentas compared with non donor IVF placentas [8]. Histological findings, as chronic deciduitis, found in the basal plate of the placenta where extravillous cytotrophoblast interfaces with the maternal decidua, are thought to resemble immune mediated placenta pathology.

Although the possible maternal complications in ED pregnancies are clearly described, relatively little is known on the underlying immune regulation in ED pregnancies. Research in this field will not only help us to understand the role of the immune system in ED pregnancies but may give insight into strategies to induce immunologic tolerance in HLA mismatched solid organ transplantations.

## Blood transfusion

In ED pregnancy, the mother is exposed to foreign cells and antigens, a situation that has some resemblance to blood transfusions and organ transplantation (Figure 1). It is to be conceived that the downregulation of the maternal alloimmune response to the fetus during ED pregnancies needs more adaptation compared to a spontaneously conceived pregnancy. The degree of antigenic dissimilarity (reflected by the number of HLA mismatches) is in general higher in ED pregnancies compared to spontaneously conceived pregnancies. In the transplantation setting the degree of HLA compatibility between the donor and recipient is relevant for graft survival. More mismatches will lead to poorer graft survival [9]. Enhanced graft survival has been observed in kidney transplant recipients who prior to transplantation received a blood transfusion [10]. However, as discussed later, pretransplant blood transfusion can have different immunomodulatory effects as they either activate or suppress the immune system of the recipient.

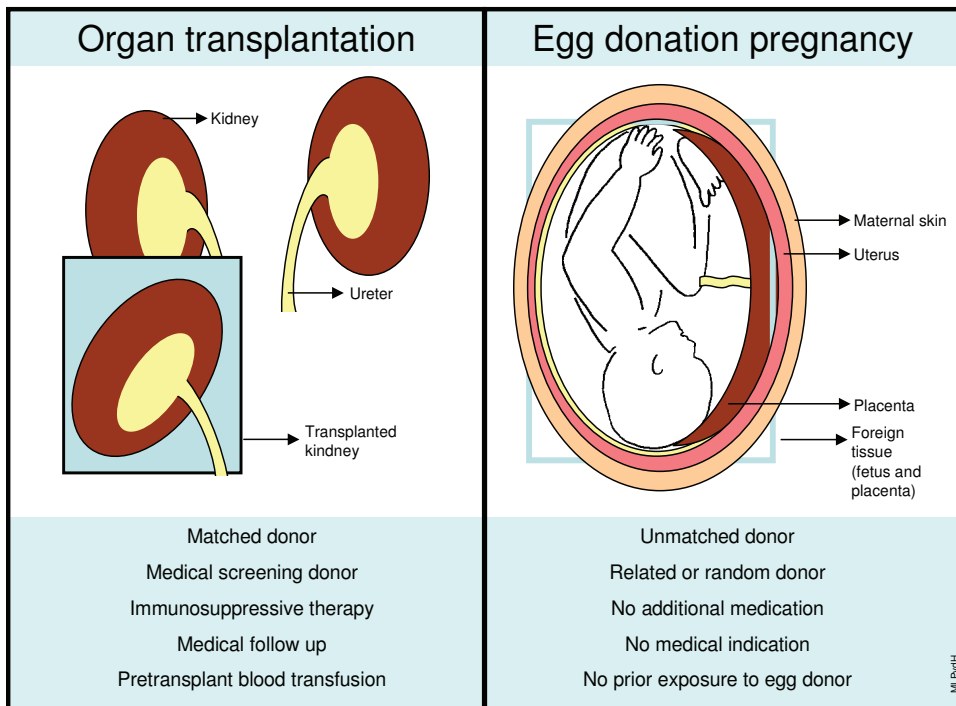
### Downregulation of the immune system by HLA-DR matched blood transfusions

Pretransplant allogeneic blood transfusion has a positive effect on kidney graft survival [10]: patients transfused with one HLA-DR matched transfusion (semi-allogeneic, a situation similar to a normal pregnancy) showed an enhanced kidney [11] and heart [12] transplant survival. No beneficial effect was seen for pretransplant blood transfusion with fully HLA-DR mismatched blood transfusions (a situation similar to ED pregnancies). In addition, HLA alloantibody formation was significantly higher after fully HLA mismatched transfusions compared to one HLA-DR matched transfusions [13]. The immune mechanism suggested to be involved in modulation of alloreactivity by blood transfusion might as well occur during conception and prior exposure to semen [14]. The shared HLA-DR allele is supposed to play a pivotal role in the downregulation of the immune response [15,16] as CD4+ regulatory T cells may recognize an allopeptide in the context of this self HLA-DR on the transfused blood cells. When this allopeptide is shared between the blood donor and organ donor, CD4+ T cells are capable of downregulating all activated T cells involved in graft rejection, leading to an enhanced graft survival. A similar mechanism may play a role during a normal pregnancy or during an ED pregnancy where the fetus shares the HLA class II allele with the mother. However, the situation is different in fully allogeneic ED pregnancies, where the fetus is completely HLA mismatched. It is to be expected that a stronger or different immune regulation is necessary to prevent rejection of the fully allogeneic fetus. Studies in mice demonstrate that the maternal T cell repertoire is aware of paternal antigens during pregnancy, but in healthy pregnancy reactive T cells do not mediate a detrimental anti-fetal immunity [17]. In humans, it has been shown that a distinct subset of HLA-DR+ regulatory T cells is involved in the induction of preterm labor and in the induction of organ rejection after transplantation [18]. All these studies suggest that a HLA-DR match play an important role in the induction of immunological tolerance. Since more HLA mismatches are inherent to ED pregnancies, one can imagine that the higher number of HLA-DR mismatches in ED pregnancies led to more complications. As the allogeneic fetus is able to survive nine months in the uterus, without any additional immunosuppressive medication as is needed in solid organ transplantation, it is likely that a very efficient local and peripheral immune regulation is responsible for such a successful ED pregnancy.

### The role of antibody formation

Preceding organ transplantation a screening for HLA antibody is performed as in organ transplantation preformed donor specific HLA antibodies are associated with (hyper) acute graft failure. It is well known that blood transfusions are associated with the induction of HLA alloantibodies. The degree of HLA mismatches determines the immunization; HLA alloantibodies

are formed more frequently after transfusion of donors with two HLA class II mismatches compared to one HLA class II mismatch [11]. Since more than 30% of the women produce HLA antibodies directed against the paternal HLA antigens of the fetus already before delivery [19], it is commonly assumed that during pregnancy the formation of these antibodies is a harmless phenomenon. However, recently it has been shown that HLA alloantibodies are associated with a reduced chance of live birth in patients with recurrent miscarriages [20]. Only 41% of HLA-antibody positive pregnant recurrent miscarriage patients had a live birth compared to 76% of HLA-antibody negative recurrent miscarriage patients. Furthermore, placental abruption is increased in patients with a higher prevalence of HLA class I antibodies whereby the presence of these antibodies possibly serve as a marker for the activation of maternal immune response against the fetus [21]. It remains to be elucidated which role HLA alloantibody formation plays in pregnancy complications. They may either play a role in the etiology or may be a parameter associated with a detrimental immune response by maternal immune cells. Similarly, the induction of donor specific HLA antibodies after kidney transplantation is associated with a higher incidence of chronic rejection [22], although patients with donor specific HLA antibodies may have an excellent graft function for many years [23]. Also here, it is unclear whether the antibodies are the direct cause of the clinical problems.



**Figure 1 Organ transplantation versus egg donation pregnancy.** Schematic overview of the differences in the medical consequences between solid organ transplantation and egg donation pregnancies, while in both situation antigenic dissimilarity is present.

## Preeclampsia

Preeclampsia is a syndrome characterized by the newly onset hypertension and proteinuria after 20 weeks of gestation, which disappears after delivery. Immunologic abnormalities, similar to those observed in allograft rejection, have been observed in preeclamptic women [24]. For example, the most dangerous form of preeclampsia is HELLP (hemolysis, elevated liver enzymes and low platelets) which is in addition to hypertension characterized by elevated liver enzymes and low platelet counts and this disease may lead to multi organ failure. Cytopenias and multi organ failure are as well reported in organ transplant rejection [25]. Women with preeclampsia have an increased level of circulating fetal DNA in comparison to controls [26]. Also after organ transplantation a substantial degree of donor lymphocyte chimerism may be present in the recipient [27]. Furthermore, as a host versus graft immune response is stopped by removal of the transplanted organ, also in preeclampsia a rapid maternal recovery occurs after removal of the placental products [28].

Preeclampsia might be the consequence of an unsuccessful attack of the maternal innate immune system towards the implanting blastocyst, eventually results in defective implantation which may lead to stimulation of the maternal inflammatory response [29]. In ED pregnancies there is only a short duration of exposure to non-maternal antigens, which could lead to an altered or inadequate immunoprotection of placentation, eventually resulting in preeclampsia. The incidence of preeclampsia in pregnancies conceived with assisted reproductive technologies and thus related with potentially less exposure of sperm, is indeed higher [30].

Uterine NK cells are supposed to play a pivotal role during implantation and preeclampsia. NK cells express killer immuno-globulin like receptors (KIR) to which HLA is able to bind. KIR receptors can be divided in inhibiting (AA) and activating (BB) KIRs. The combination of maternal KIR AA genotype especially with an HLA-C2 is associated with an increased risk of preeclampsia [31]. HLA-C2 has a much stronger binding with inhibiting KIRs than with activating KIRs. The interaction of maternal uNK cells with an AA genotype with a fetal C2 allele expressed on placental trophoblast tissue will possibly result in an inhibition of uterine NK cells. It is thought that the inhibition of uterine NK cells results in inadequate trophoblast invasion into the spiral arteries, which will eventually lead to preeclampsia. Such a KIR AA – HLA-C2 combination is supposed to have an evolutionary disadvantage. In populations with a high frequency of KIR AA, a low frequency of HLA-C2 and vice versa was found [31]. If the fetus has a HLA-C2 gene, the risk of getting preeclampsia is two times higher (OR 2.09, 95% CI: 1.24-3.58,  $p=0.007$ ) [32]. Of course, preeclampsia not based on this KIR AA – HLA-C2 combination should not be excluded and other mechanisms as well play a role in the pathogenesis of preeclampsia.

## Immunology in complicated ED pregnancies

### Success of egg donation procedures

The European Society of Human Reproduction and Embryology (ESRHE) publishes annual data on assisted reproductive technology. After ED, 5516 clinical pregnancies were reported resulting from 12685 embryo transfers, giving a clinical pregnancy rate of 43.5%. The mean birth rate of these embryo transfers was 27.2% ( $n=3448$ ) [33]. This means that a total of 71.8% of all embryo transfers after ED do not result in a continuing pregnancy. For IVF the pregnancy rate was 32.4% (31665 pregnancies from 96572 embryo transfers). At a first glance this higher pregnancy rate in ED pregnancies compared to IVF pregnancies is surprising. However, the reason to perform ED is ovarian failure and, as there are no uterine abnormalities, ED might be more successful

compared to IVF pregnancies, in which there may be an underlying and unknown mechanism responsible for implantation failure. Unsuccessful embryo transfers in ED procedures, resulting in miscarriage may be related to a non optimal HLA-match between the egg donor, sperm and gestational carrier. Surprisingly, nearly 30% of all embryo transfers in ED pregnancies result in a continuing pregnancy, resulting in a mother who carries a completely allogeneic fetal allograft. A number of complications have been described, of which some might be due to the allogeneic nature of the fetus.

Taking the more vigorous immune response in ED into account, it could be of importance to perform HLA-typing of the egg donor and recipient in order to select haplo-identical combinations which would be more similar to spontaneously conceived pregnancies. However, this suggestion has to be evaluated in well designed studies. HLA-typing could then be performed before fertilization of the donated egg, whereby the combination of maternal KIR AA – fetal HLA-C2 and sperm donors with the C2/C2 genotype should be avoided in order to decrease the incidence of preeclampsia. In the Netherlands commercial and anonymous egg donations are forbidden by law. ED based on a non-commercial basis is allowed, but infertile women should find their egg donor by themselves. In several cases this might be a family member who is donating an oocyte, but many women, who want to make use of the opportunity of ED to get pregnant, go abroad for the treatment. It might be useful to perform an international study on the relevance of HLA/KIR matching and the success rate of ED pregnancies. The sperm of donors with a C1/C1 genotype is predicted to be safer than C2/C2 males, since this certain results in a fetus expressing C2 [32].

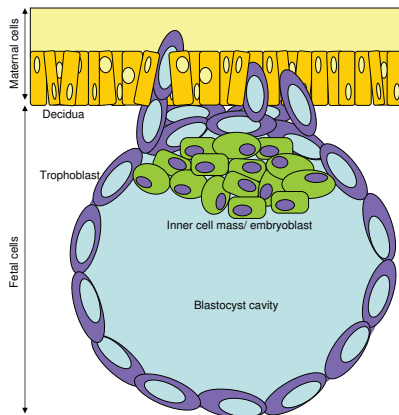
The underlying immunogenetic differences between donor and recipient in solid organ transplantation and ED pregnancies are similar and form the basis of their most important complications (graft rejection and preeclampsia). However, the medical regimes for women pregnant via ED or for transplantation patients are totally different. For solid organ transplantation the donor requires an extensive screening and the patient receives immunosuppressive therapy besides a comprehensive medical follow up. In contrast, an ED pregnancy occurs mostly via an unknown donor, the pregnant women does not receive extra medical care, and does not use any additional medication (Figure 1). ED pregnancies results in an immunologically unique situation and until now the immunological mechanism behind the success of these pregnancies remains unclear. It remains to be established whether immunological principles additional to those present in spontaneously conceived pregnancies are operating in the ED fully allogeneic pregnancies.

## Uncomplicated pregnancy and immunology

### Placental development in an allogeneic environment

The development of the placenta is essential for fetal development and growth during uncomplicated pregnancy as it prevents rejection of the fetal allograft, and exerts metabolic and endocrine functions. The placenta develops from fetal derived cells and is able to anchor in the maternal myometrium. Several immune escape mechanisms are necessary to enable growth of the immunogenetically foreign fetal cells into the maternal uterine lining. The blastocyst consists of the inner cell mass, which will form the embryo, and the trophoblast, which will form the placenta and fetal membranes. During implantation the blastocyst invades the maternal uterine epithelium (Figure 2). Placental progenitor stem cells develop into invasive extravillous trophoblast or into non-invasive trophoblast cells covering placental villi. Villous trophoblast can be classified in two types; the mononuclear cytotrophoblast and, after fusing, the multinuclear syncytiotrophoblast layer overlying the villi is formed. The syncytiotrophoblast, surrounded by maternal blood, is in direct contact with maternal immune cells. Extravillous trophoblast invades



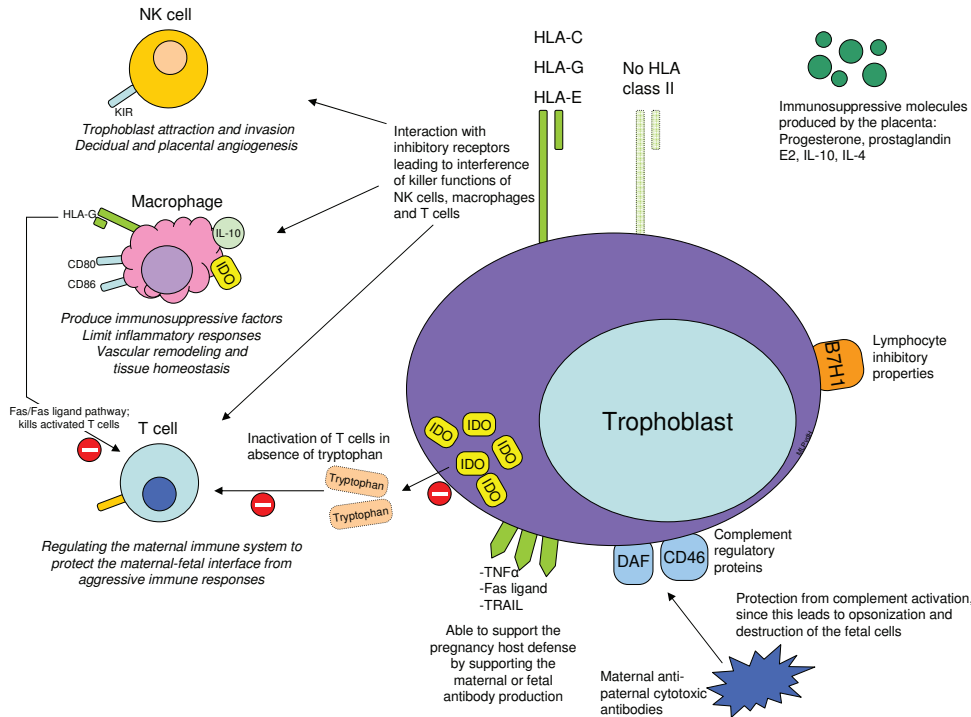


**Figure 2 Implantation of the blastocyst in to the maternal endometrium.** The genetically different blastocyst invades in to the maternal endometrium. Several immunological escape mechanisms are necessary for the fetal cells to be tolerated by the maternal immune cells, as depicted in detail in figure 3.

the maternal decidua and myometrium and is thereby responsible for anchoring the placenta. Maternal endothelial cells in the spiral arteries are replaced by endovascular trophoblast cells originating from extravillous trophoblast. It is also crucial for the supply of oxygen and nutrients to the fetus by changing the maternal vascular system. A balance of this invasion is very important; the cells need to invade enough for the anchoring and for receiving nutrients; on the other hand over-invasion of trophoblast cells has to be limited to protect the mother.

### Fetal defense mechanisms

Fetal trophoblast cells are the crucial cell population in the placenta which protects the fetus from destruction by the maternal immune system. Villous cytotrophoblast is the inner layer of the villous surface epithelium. Villous syncytiotrophoblast is the superficial layer facing the intervillous space. Villous trophoblasts lack HLA expression and do not provoke an allogeneic immune response by circulating maternal T cells. Until now it is unexplained how these cells circumvent a maternal immune attack by e.g. peripheral NK cells, which normally would destroy cells without any HLA expression. The remaining trophoblast cells, the extravillous trophoblast, migrate into the maternal decidua and are the dominant cell type needed for the development of all nonvillous parts of the placenta. Extravillous trophoblast does not express HLA-A or -B, but does express HLA-E, -F, -G and -C [34], which serve as ligands for leukocyte inhibitory receptors. The consequences of these interactions include activation of pathways in natural killer (NK) cells and macrophages that interfere with the killer functions of these cells [34-36]. HLA-G has potent immunomodulatory functions [37], whereas HLA-C and -E have shown to elicit an allogeneic immunomodulatory response by maternal NK and T cells [38]. Several other immunomodulatory mechanisms have been postulated to contribute to successful pregnancy. Antigen presenting cells express a membrane bound or soluble form of HLA-G, which can activate the Fas/Fas ligand pathway resulting in destruction of activated T cells [39]. HLA class II molecules are not presented by trophoblast cells as the HLA class II transactivator (CIITA) is not expressed [40]. Furthermore, the B7H1 protein, a co-stimulatory molecule of the B7 family, is expressed on syncytiotrophoblast, which leads to inhibition of lymphocytes circulating in maternal blood [41]. In addition trophoblast cells contain indoleamine 2,3-dioxygenase (IDO), an inhibitor of tryptophan metabolism; this may inactivate T cells since they reduce tryptophan, required for T cell activation [42]. TNF $\alpha$ , Fas ligand and TRAIL are ligands identified in or on human trophoblast cells which are able to support the pregnancy host defense by supporting maternal and/or fetal antibody production [43-45]. Th2 cytokines, produced at the maternal-fetal interface, can inhibit Th1 responses, improving fetal survival but impairing responses against some pathogens [46].



**Figure 3 Defense mechanisms of trophoblast and maternal cells.** Schematic overview of defense mechanisms of a trophoblast cell and maternal leukocytes during pregnancy at the fetal-maternal interface. Abbreviations: natural killer (NK), killer immuno-globulin like receptor (KIR), indoleamine 2,3-dioxygenase (IDO), human leukocyte antigen (HLA), decay accelerating factor (DAF), tumor necrosis factor (TNF) and TNF-related apoptosis-inducing ligand (TRAIL).

The human placenta produces immunosuppressive molecules as progesterone, prostaglandin E2, and anti-inflammatory cytokines as IL-10 and IL-4 [35,47]. Finally, trophoblast cells express complement regulatory proteins, which are important to protect the fetal cells from complement dependent destruction [48]. Complement inhibition is required in normal pregnancy and uncontrolled activation at the maternal-fetal interface that leads to bad pregnancy outcomes [49]. All these mechanisms, summarized in Figure 3, maintain the immunosuppressive environment in the pregnant uterus and in this way, and possibly by other still undefined mechanisms, the (semi-)allogeneic fetus is capable to survive during its nine months housing in the uterus.

## Maternal defense mechanisms

Multiple strategies are used by trophoblast cells, including altered HLA expression, synthesis of immunosuppressive molecules, and expression of high levels of complement regulatory proteins that may protect the embryonic tissues from destruction by maternal anti-paternal alloantibodies and T cells. Nevertheless, maternal leukocytes are potentially capable to elicit an alloimmune response since syncytiotrophoblasts and circulating syncytiotrophoblasts micro particles may come directly in contact with maternal immune cells [50].

During early pregnancy, the uterus seems to be immune compromised as T and B cells are hardly present. Macrophages and NK cells interact with the trophoblast cells. Decidual NK cells are different compared to peripheral NK cells. Decidual NK cells express perforin, granzyme A and

B but, unlike peripheral NK cells, they have a reduced cytolytic activity to HLA class I negative targets [51], secrete proteins with immunomodulatory potentials [52] and produce angiogenic factors like vascular endothelial growth factor and placental growth factor [53]. Decidual NK cells may recognize fetus HLA-C1 and HLA-C2 by the expression of KIR. Macrophages are antigen presenting cells which are the second most numerous type of leukocytes in the human decidua [54]. Macrophages are involved in both the innate and the adaptive immune system and consist of different functional subpopulations. Some macrophages promote inflammation by production of inflammatory molecules during an innate immune response and, as part of the adaptive immune system are able to present antigens to T cells. Others may have a role in immunosuppression by the expression low levels of costimulatory molecules CD80 and CD86 and the expression of indoleamine 2,3-dioxygenase, both preventing T lymphocyte activation [55]. The number of decidual T cells increases during pregnancy, starting with 5-20% of all CD45+ decidual lymphocytes in early pregnancy, till 40-80% at term [56]. Decidual T cells encompass a very heterogenic subset of T cells that include activated CD4+ and effector memory type CD8+ T cells. These activated T cells are found together with T cells subsets that are capable to suppress the decidual lymphocyte response [57]. T cells are in close contact with fetal trophoblast cells in the decidua; however they do not attack the non villous trophoblast cells, since trophoblast lack HLA class Ia expression. Fetus specific regulatory CD4+CD25bright T cells are present in human decidua in higher numbers compared to peripheral maternal blood [57], suggesting an important role for these cells at the fetal-maternal interface. It has been shown that fetus specific CD4+CD25bright T cells are recruited to the maternal decidua where they are able to suppress the local immune response [58]. T cells are able to produce a variety of type 1 and type 2 cytokines and thereby may contribute to the local regulation of the fetus-specific responses within the decidua. Also specific CD8+ T cell subsets, which do not express perforin and have a reduced expression of granzyme B, are more present in decidual tissue [59]. These cells also express KIR receptors which are then able to communicate with HLA-C expressed on trophoblast. The properties of these CD8+ T cells suggest that they may play a role in immune regulation at the fetal-maternal interface. Fetus specific immunological tolerance during pregnancy depends on a very complex network of cytokines, complement, hormones, immune and non-immune cells. Acceptance is not simply based on the consequence of a balance between the type 1 (associated with abortion) and type 2 (associated with successful pregnancy) cytokines, since many cytokines are pluripotent. However, in an uncomplicated pregnancy the child is able to survive in the semi-allogeneic environment and the mother accepts the semi-allograft. ED pregnancies reflect an extreme immunologic challenge, in which the fetal genome is immunogenetically fully allogeneic to the mother.

## Conclusion

In ED pregnancies the fetus is allogeneic to the gestational carrier. This creates an interesting immunological paradox. The fetus is accepted by the mother although being immunogenetically completely unrelated to the mother (unless the egg is donated by a relative). In solid organ transplantation the same immunogenetic dissimilarity is present; however immunosuppressive drugs are unavoidable to maintain the graft. Resemblances between graft rejection and pregnancy complicated by preeclampsia are clearly present. Multiple immunomodulatory strategies are used by trophoblast cells in the placenta to avoid rejection, including altered HLA expression, synthesis of immunosuppressive molecules, and expression of high levels of complement regulatory proteins. We hypothesize that in ED pregnancies these immunomodulatory strategies lead to an active downregulation of the alloimmune response and as a consequence to acceptance of the fetal allograft. Knowledge of the immune mechanism, leading to successful ED pregnancy might be useful for future strategies to induce immune tolerance in solid organ transplantation.

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