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REVIEW

A new era in reproductive medicine: consequences of third-party oocyte donation for maternal and fetal health

Shigeru Saito[1] · **Yasushi Nakabayashi**[1] · **Akitoshi Nakashima**[1] · **Tomoko Shima**[1] · **Osamu Yoshino**[1]

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Abstract The fetus is a semi-allograft for the maternal host in natural pregnancy, but the fetus is a complete allograft after oocyte donation (OD), and there is greater antigenic dissimilarity with the mother. Thus, OD pregnancy is a good model for understanding how the fetus is protected by the maternal immune system. Recent clinical data have revealed a higher risk of miscarriage, gestational hypertension, preterm birth, and low birth weight with OD pregnancy. There is also a higher incidence of chorionic deciduitis, dense fibrinoid deposits in the chorionic basal plate, inflammatory lesions in the chorionic plate, and C4d deposition on syncytiotrophoblasts in OD pregnancy. Impaired accumulation of T cells, regulatory T (Treg) cells, natural killer (NK) cells, and monocytes in the decidua basalis and poor remodeling of spiral arteries are observed in OD pregnancy irrespective of whether preeclampsia occurs. These findings may partly explain why OD pregnancy is associated with a high risk of gestational hypertension and preeclampsia. We need to clarify the immunological and pathological differences between uncomplicated and complicated OD pregnancy. In uncomplicated OD pregnancy, the level of HLA match between mother and baby is significantly higher than would be expected by chance, suggesting that miscarriage may be frequent with marked HLA mismatch. This review discusses the relationship between various aspects of the immune system and complications of OD pregnancy.

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✉ Shigeru Saito
s30saito@med.u-toyama.ac.jp

[1] Department of Obstetrics and Gynecology, University of Toyama, 2630 Sugitani, Toyama 930-0194, Japan

Introduction

There is a problem of declining fertility due to poor ovarian reserve in older women undergoing in vitro fertilization (IVF). Oocyte donation (OD) was first introduced in 1984 [41], and OD increases the pregnancy rate so that it is similar to the rate among younger women [30, 45, 81]. This assisted reproductive technology (ART) is a boom to older patients and those with premature ovarian failure. OD has become relatively common in patients treated by ART, and it was reported that there were 15,973 OD cycles (approximately 10 % of all ART cycles) in 2011 in the USA [7], although this procedure has been prohibited in some countries such as Germany and Japan by ethical reason.

However, it has become clear that OD pregnancy is associated with an increased risk of gestational hypertension, preeclampsia, preterm birth, low birth weight, bleeding complications, and miscarriage compared with natural pregnancy or IVF pregnancy [1, 7, 16, 24, 28, 29, 35, 38, 49, 59, 64, 68, 69, 78, 80].

OD pregnancy is associated with an elevated risk of gestational hypertension and preeclampsia [6, 42, 46, 76]. Meta-analysis of data on 86,515 OD pregnancies has revealed a higher risk of preeclampsia (odds ratio 2.54 compared with ART, odds ratio 4.34 compared with natural conception) and gestational hypertension (odds ratio 3.00 compared with ART, odds ratio 7.94 compared with natural conception) [42]. Interestingly, the incidence of hypertensive disorders (including gestational hypertension and preeclampsia) is lower when the oocyte donor is related to the recipient [25]. There should be less HLA mismatch in OD pregnancy with an egg supplied

by a relative, and preeclampsia is less frequent than when the egg is from an unrelated donor. These findings suggest that a high level of feto-maternal HLA mismatch in OD pregnancy with an egg from an unrelated donor might lead to inadequate induction of tolerance, resulting in gestational hypertension or preeclampsia. Indeed, there is evidence of immunological dysfunction in women who develop preeclampsia during natural pregnancy, such as an increase of Th1-type cells and Th17 cells as well as a decrease of Treg cells [56, 57, 60, 62]. There is a much higher incidence of obstetric complications in multiple OD pregnancies compared to singleton OD pregnancies with regard to preeclampsia (24.8 versus 8 %), preterm delivery at ≦37 weeks (54.9 versus 10.2 %), and cesarean section (81.4 versus 64 %) [2]. The risks of preeclampsia and gestational hypertension in twin OD pregnancies were 2.56 (1.84–3.58) and 3.08 (1.95–4.87) compared to those in twin pregnancies after methods of ART [42]. Therefore, transfer of only a single embryo should be recommended to patients using OD.

The high risk of complicated pregnancy in OD pregnancy suggests that OD pregnancy may be a good model for understanding the immunological mechanisms related to successful pregnancy and the pathophysiology of complicated pregnancy from an immunologic viewpoint. Accordingly, this review discusses the relationship between tolerance of fetal antigens and complications of OD pregnancy.

MHC class I and class II expressions on trophoblasts

After attachment of the blastocyst to the uterine epithelium, trophoblasts invade the maternal decidual layer and differentiate into villous trophoblasts that play an important role in nutrient transport from the maternal side and into extravillous trophoblasts (EVT) that invade the maternal endometrium and uterine wall and have a very important role in spiral artery remodeling (Fig. 1). Uterine natural killer (NK) cells and macrophages are also important for vascular smooth muscle cell separation during spiral artery remodeling, and the musculoelastic coat of the spiral artery is disrupted by NK cells to reduce vascular resistance and promote massive blood flow in these vessels (Fig. 1) [31, 44, 67, 79]. In early stage of remodeling, NK cells and macrophages accumulate around the vascular smooth muscle cells before endovascular EVT presence. These cells produce matrix metalloprotease (MMP) 2, 7, and 9 and urokinase plasminogen activator (uPA) and play some roles for the separation of vascular smooth muscle. And, NK cells and macrophages also induce apoptosis of vascular endothelial cells. After that, endovascular EVT cell attracts toward the spiral arteries and spiral artery lumens are replaced by endovascular EVTs.

Syncytiotrophoblasts and cytotrophoblasts lack the surface expressions of MHC class I and class II molecules (Fig. 1). On the other hand, EVT express polymorphic HLA-C molecules and non-polymorphic HLA-E and HLA-G molecules (Fig. 1) [22, 33]. HLA-E and HLA-G are important for protecting trophoblasts from NK cell-mediated cytotoxicity and may also regulate T cell activation (Fig. 1) [8, 9, 20, 33, 36]. But, HLA-E and HLA-G are invariant, so these molecules play some roles for non-specific immunoregulation. Therefore, the induction of paternal HLA-C antigen-specific tolerance is necessary for preventing fetal rejection. HLA-C is directly recognized by NK cells and $CD8^+$ T cells and indirectly recognized by $CD4^+$ T cells (Fig. 1). Indeed, HLA-C has been reported to induce a direct cytotoxic response by $CD8^+$ T cells during allogeneic organ transplantation [15, 48]. The correct balance among these immunoregulatory systems is required for successful pregnancy.

Fetal antigen-specific $CD8^+$ cytotoxic T cells are observed in half of all human pregnancies and are often detected from the first trimester. These cells have the ability to proliferate, secrete IFNγ, and cause lysis of target cells following recognition of paternal antigens [39]. Highly differentiated $CD8^+$ resident memory T cells are present in the non-pregnant uterus and decidua, and a fetus-specific $CD8^+$ T cell response has been reported in uncomplicated pregnancy [73, 74]. These $CD8^+$ cells show increased expression of perforin and granzyme B messenger RNAs (mRNAs). Interestingly, decidual $CD8^+$ T cells display reduced expressions of perforin and granzyme B proteins, suggesting that microRNA (miRNA) may regulate the production of these proteins at the post-transcriptional level. Trophoblast-derived miRNA might be involved in regulating perforin and granzyme B mRNAs [73], suggesting that we should clarify placental miRNA expression in OD pregnancies.

Regulatory T (Treg) cells play a very important role in controlling activated T cells in the decidua during HLA-C mismatch pregnancy [73]. Tilburgs et al. reported that maternal decidual-activated $CD4^+$ T cells were increased when feto-maternal HLA-C mismatch was present [72]. The number of decidual-activated $CD4^+$ T cells shows a positive correlation with the number of HLA mismatches between mother and fetus, and activation of decidual $CD4^+$ T cells only occurs when feto-maternal HLA-C mismatch exists, although there is no information about differences of activated NK cells and $CD8^+$ T cells between HLA-C-mismatched and HLA-C-matched pregnancies [72]. However, HLA-A, HLA-B, HLA-DR, and HLA-DQ mismatch does not induce the activation of $CD4^+$ T cells. Maternal antigen-presenting cells (APCs) in the decidua pick up trophoblast cell debris and present paternal HLA-C-derived peptides through maternal MHC class II to maternal $CD4^+$ T cells. This system is called as indirect antigen recognition. HLA-C cross-reactive T cells have not identified, but it is likely that cross-reactive T cells exist and directly bind and respond to paternal HLA-C molecules expressed on EVT [74]. HLA-C molecules act as ligands for killer immunoglobulin-like receptors (KIRs). KIR haplotype A has only the inhibitory

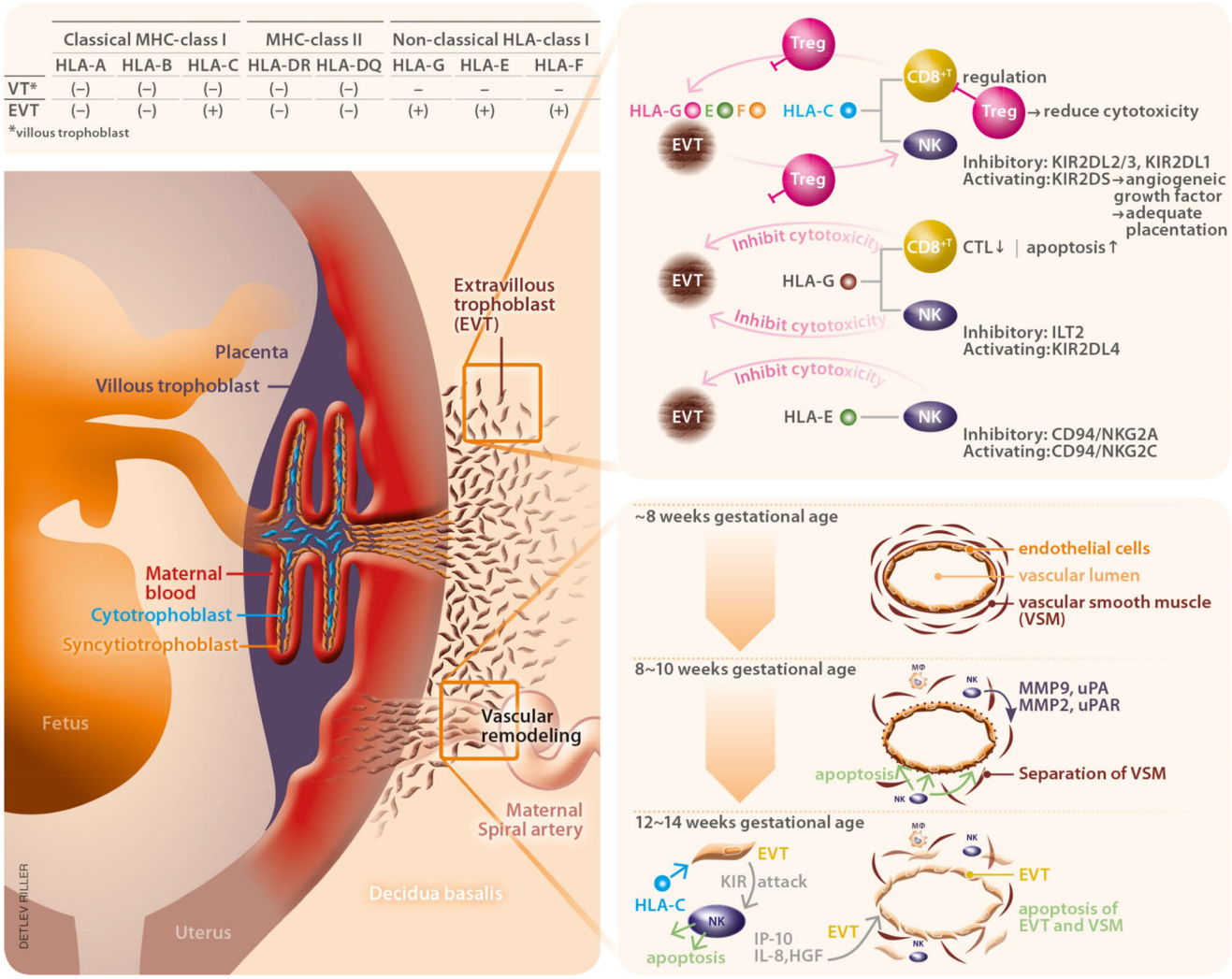

Fig. 1 MHC class I and II expressions on trophoblasts and remodeling of spiral arteries by extravillous trophoblasts. Extravillous trophoblasts (EVT) express polymorphic HLA-C molecules and non-polymorphic HLA-E, HLA-G, and HLA-F, while villous trophoblasts lack expression of MHC class I and class II molecules (*upper left* in the table). HLA-C antigens are directly recognized by $CD8^+$ T cells and NK cells. HLA-C mismatch induces the cytoxic T lymphocyte response, but Treg cells regulate the activation of $CD8^+$ T cells. Cytotoxicity of uterine NK cells is low, but those cells are a rich source of angiogeneic growth factors. These cytokines produced by NK cells via HLA-C recognition may be important for placentation. HLA-G reduces the cytotoxic T cell activity by induction of apoptosis of $CD8^+$ T cells. HLA-E and HLA-G prevent NK cell-mediated cytotoxicity for trophoblasts by inhibitory signals. Maternal macrophages and NK cells play an important role in the remodeling of spiral arteries by EVT. Uterine NK cells and macrophages in 8–10 weeks of gestation produce MMP-2, MMP-9, uPA, and uPAR, and these enzymes can initiate vascular smooth muscle cell separation. During 12 to 14 weeks of gestation, apoptosis of EVT and VSM was observed. After that, EVT accumulate and vascular lumens are replaced by EVTs

receptors, whereas haplotype B has both stimulating and inhibitory receptors. HLA-C genotype is classified into HLA-C1 and HLA-C2. In pregnant women with KIR-AA, NK cells lack the activating receptor for HLA-C2 expressed on EVT. Interestingly, the combination with maternal KIR-AA and fetal HLA-C2C2 genotype is one of the risks for preeclampsia and recurrent pregnancy loss [17, 18]. These findings suggest that mild or moderate immunoactivation might be necessary for pregnancy success. Uterine NK cells are major source of angiogenetic growth factors, so activation of NK cells might be necessary for adequate placentation. The balance between immunostimulation and regulation might be important for maintenance of pregnancy.

Treg cells are central to induction of fetal (paternal) antigen-specific tolerance and successful pregnancy

Treg cells have an important regulatory role in both the induction and maintenance of fetal antigen-specific tolerance, resulting in successful pregnancy in mice and humans [3, 61]. In mice, Treg cells (especially paternal antigen-specific Treg cells) increase in the uterine-draining lymph nodes before implantation and rapidly accumulate in uterus

after implantation (Fig. 2) [3, 13, 51, 66, 82]. Depletion of Treg cells at the implantation period induces fetal resorption in allogeneic mouse pregnancy, but not in syngeneic mouse pregnancy, suggesting that Treg cells are essential for successful implantation in allogeneic pregnancies [10, 65, 82]. In primary pregnancy, $Ki67^{+}$ proliferating paternal antigen-specific Treg cells increase in the peripheral blood during mid to late gestation (Fig. 2) [54, 66]. These cells are induced when tolerogenic dendritic cell (DC) presents paternal antigens to naïve CD4 T cells (Fig. 2). Priming by seminal plasma may play a role in this process by inducing paternal antigen-specific Treg cells in uterine-draining lymph nodes and the pregnant uterus, resulting in successful implantation (Fig. 2) [51, 52, 66]. Self-specific activated/memory Treg cells are present before pregnancy, and these Treg cells also protect embryos at implantation in mice [5]. Therefore, paternal antigen-specific Treg cells and preexisting self-specific activated/memory Treg cells collaborate in establishment of implantation. The same findings are observed in human. Endometrial expression of Treg cell transcription factor Foxp3 mRNA is decreased in women with primary unexplained infertility, suggesting that reduction of Treg cells in the endometrium might lead to implantation failure and infertility [23]. It has also been reported that a decrease of peripheral blood Treg cells in the late follicular phase is associated with failure of artificial insemination by donor (AID) sperm [40], which supports the above hypothesis. It has been reported that seminal priming increases the success rate of IVF-embryo transfer (ET) [75]. Further large-scale randomized study is necessary to prove this hypothesis whether the priming of seminal fluid improve pregnancy rate in human.

Depletion of Treg cells during early pregnancy induces fetal resorption in mice with allogeneic pregnancy but not syngeneic pregnancy [3, 65]. In addition, adoptive transfer of Treg cells from normal pregnant mice prevents fetal loss

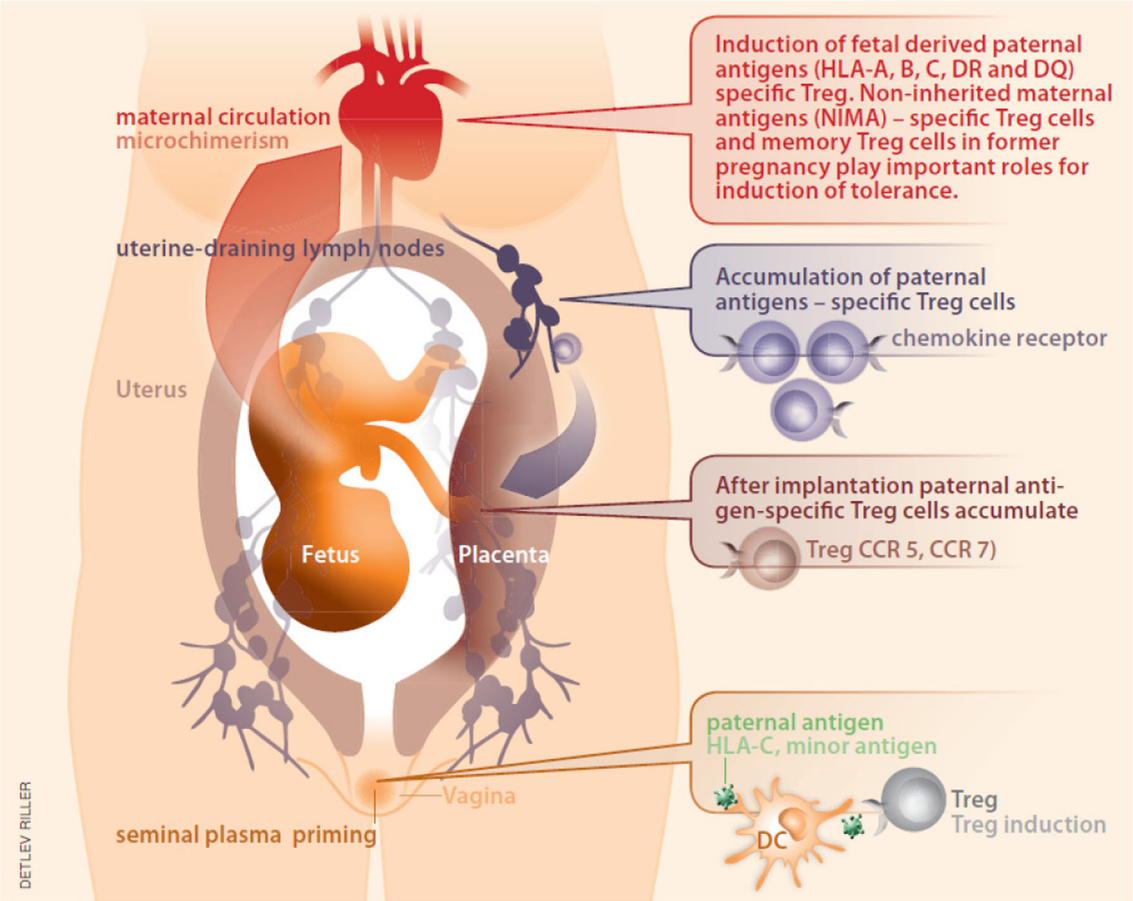

Fig. 2 Expansion of Treg cells during pregnancy. Seminal plasma contains paternal antigens that are presented by dendritic cells (DCs), resulting in induction of Treg cells. After sexual intercourse, paternal antigen-specific Treg cells accumulate in uterine-draining lymph nodes before the implantation. After implantation, paternal antigen-specific Treg cells rapidly accumulate in the pregnant uterus and establish paternal antigen-specific tolerance. Some chemokines may play important roles for accumulation of Treg cells at feto-maternal interface. Non-inherited maternal antigen (NIMA)-specific Treg cells and memory Treg cells from prior pregnancies also play an important role in the induction of tolerance. Paternal antigen-specific Treg cells, NIMA-specific Treg cells, and memory Treg cells might collaborate in the establishment of tight materno-fetal tolerance

in abortion-prone mice [82]. Moreover, Foxp3^{high}CD45RA^{-} functional Treg cells are decreased in the decidua, but not in the peripheral blood, of women with miscarriage despite normal fetal chromosomes, suggesting that inadequate immune tolerance at the feto-maternal interface might induce miscarriage in humans [21].

A small number of maternal cells migrate into the fetus, and these cells are not rejected by the fetal immune system because feto-maternal tolerance is established during pregnancy. Fetal-derived cells are detected in mother, and maternal cells are also detected in fetuses. Microchimeric maternal cells can be detected in adult humans, and maternal antigen-specific tolerance persists for a long time (Fig. 2). And, fetal antigen-specific tolerance also persists for a long time. If a partner has the same HLA profile as a pregnant woman's mother, non-inherited maternal antigen (NIMA)-specific Treg cells will expand rapidly, resulting in successful pregnancy [27]. Therefore, Treg cells responding to maternal microchimerism enforce tolerance to overlapping fetal antigens during pregnancies in female offspring [27]. If a partner does not share NIMA antigens, the risk of fetal loss and preeclampsia might be increased, but this hypothesis has not been proven in humans.

Therefore, paternal antigen-specific Treg cells promoted by seminal plasma priming, NIMA-specific Treg cells, and preexisting autologous antigen-specific Treg cells might collaborate in the establishment of tight materno-fetal tolerance.

Relationship between clinical manifestations, such as implantation failure, early pregnancy loss, and preeclampsia, and immunological changes in OD pregnancy

Implantation in OD pregnancy

The European Society of Human Reproduction and Embryology (ESHRE) published the pregnancy and delivery rates for OD and conventional IVF-ET pregnancies in 2010 (Table 1), revealing a higher OD pregnancy rate than that achieved by conventional IVF-ET (47.4 versus 33.2 %). These data demonstrated that the implantation process is not disturbed in OD pregnancy, although tolerance is necessary for successful allogeneic implantation in mice. Even when the fetus is completely allogeneic, implantation seems to proceed normally in human.

Fetal loss in OD pregnancy

The estimated fetal loss rate in OD pregnancy was 38.0 %, and this was higher than in conventional IVF-ET pregnancy (Table 1). It seems that paternal antigen-specific Treg cells are important for establishment of paternal antigen-specific tolerance, resulting in uncomplicated pregnancy, and seminal plasma may play an important role in the induction of paternal antigen-specific Treg cells [51, 52, 58, 66]. This effect of seminal plasma is absent in OD pregnancy. Lashley et al. [32] reported a significantly higher level of HLA-A, HLA-B, HLA-C, HLA-DR, and HLA-DQ matching between mother and child in uncomplicated OD pregnancy, suggesting that HLA-mismatched OD pregnancy might be associated with an increased risk of fetal loss. It has not been reported whether functional Treg cells are decreased or activated CD8^{+} T cells are increased when miscarriage of OD pregnancy occurs, and there are also no reports about feto-maternal HLA mismatch in relation to miscarriage. Investigation of Treg cells and effector CD8^{+} T cells in the decidua after miscarriage of HLA-matched and HLA-mismatched OD pregnancies might help to explain the immunological requirements for successful pregnancy in the near future. There are no reports about progesterone concentration in OD pregnancies. Endocrinical study in OD pregnancy is also required.

Hypertensive disorders in OD pregnancy

Preeclampsia occurs in 3–8 % of pregnancies and is a major cause of maternal and neonatal mortalities. Meta-analysis has revealed that the risk of preeclampsia and gestational hypertension is higher in OD pregnancy compared with IVF-ET pregnancy or natural conception [2, 42, 46]. Epidemiological studies have shown that the lack of or insufficient seminal plasma priming in condom users and a short cohabitation period are risk factors for preeclampsia [47]. When pregnancy is established by OD, donated embryo transfer, or AID sperm, there is no priming effect of the partner's seminal plasma. Interestingly, these pregnancies are associated with a high risk of preeclampsia [59]. A decrease of Treg

Table 1 Pregnancy rate, actual delivery rate, and estimated fetal loss rate in oocyte donation cases and IVF-ET cases (ESHRE Report 2010)

	Pregnancy rate/transfer	Actual delivery rate/transfer	Fetal loss (pregnancy rate minus delivery rate)	Estimated fetal loss/pregnancy
Oocyte donation (n = 22,804)	47.4 %	29.4 %	18.0 %	38.0 %
Conventional IVF-ET (n = 103,972)	33.2 %	25.5 %	7.7 %	23.2 %

Source: [30]

cells and dysfunction of these cells have been reported in preeclampsia [60, 62]. Hsu et al. [19] reported that the altered phenotype of decidual DC in preeclampsia (reduced expressions of HLA-G and ILT4). The number of DC-SIGN$^+$ APCs was significantly higher in preeclampsia compared with healthy pregnancies. But, the contact between DC-SIGN$^+$ APCs and Treg cells was rare in preeclampsia. And, DCs in preeclampsia had a decreased ability to induce Treg cells in vitro, suggesting that DC function to induce Treg cells decrease in preeclampsia [19].

It has been reported that high TGF-β concentration is important for induction of Treg cells from progenitor cells [47]. On the other hand, Th17 cell differentiation occurs by low concentration of TGF-β and IL-6 in mice or IL-1β and IL-6 or IL-1β and IL-23 in humans. Inflammatory cytokines such as IL-1β and IL-6 were elevated in preeclampsia [50]. Interestingly, the serum level of soluble endoglin (sEnd), an inhibitor of TGF-β, increases before the onset of preeclampsia [37], and endoglin mRNA expression in chorionic villous samples obtained at 11 weeks of gestation is significantly higher in women who subsequently develop preeclampsia than in those with uncomplicated pregnancy [12]. These findings suggest that TGF-β level is reduced and inflammatory cytokine levels are increased at feto-maternal interface. When the TGF-β level is reduced and IL-1β and IL-6 levels are increased, progenitor cells differentiate into Th17 cells that induce inflammation or rejection. Indeed, a decrease of Treg cells and an increase of Th17 cells have been reported in preeclampsia [60]. Unfortunately, there have been no reports about the levels and function of peripheral or decidual Treg cells and Th17 cells in OD pregnancy with preeclampsia, so further studies are necessary. But in uncomplicated OD pregnancy, Treg cells and activated CD4$^+$ T cells are increased [77]. We should clarify the balance between immunostimulation and immunoregulation in OD pregnancy with preeclampsia.

During the process of placentation, EVT invade the maternal myometrium and invade the walls of maternal spiral arteries, and EVT finally replace the endothelial cells of the spiral arteries (Figs. 1 and 3). This process is very important for dilating the spiral artery and decreasing vascular resistance to ensure adequate maternal blood volume in the intervillous space. Uterine NK cells produce MMP-2, MMP-9, and uPA, enzymes that induce the separation of vascular smooth muscle. Uterine NK cells also induce apoptosis of endothelial cells and vascular smooth muscle cells, partly through Fas-Fas ligand signaling (Fig. 1). Treg cells may also play a role in preventing maternal CD8$^+$ T cells and NK cells from attacking EVT, thus allowing normal placentation to proceed. Shallow trophoblast invasion and impaired remodeling of spiral arteries have been reported in early-onset preeclampsia (Fig. 3). Interestingly, there is a decrease of macrophages, NK cells, CD4$^+$ T cells, CD8$^+$ T cells, and Treg cells in the decidua basalis in OD pregnancy, irrespective of the presence or absence of preeclampsia (Fig. 3) [43]. Remodeling of the spiral arteries is also disturbed in OD pregnancy regardless of whether preeclampsia occurs [43]. These findings help to explain why OD pregnancy is associated with an elevated risk of preeclampsia and gestational hypertension, but the crucial difference between OD with and without preeclampsia has not been found. Redman et al. proposed that poor placentation is not the direct cause of preeclampsia but rather a powerful predisposing factor [50]. Indeed, poor placentation is also observed in cases with small for gestational age fetus. These cases do not show hypertension or proteinuria. They proposed that poor placentation is not the direct cause of preeclampsia, and an excessive maternal inflammatory response to pregnancy might induce preeclampsia. Leucocyte activation and maternal excessive inflammatory response in OD pregnancy might develop preeclampsia. And, combinations of maternal KIR-AA and fetal HLA-C2C2 in OD pregnancy might be a great risk for preeclampsia. Until now, there are no reports about these, so we should clarify these points in the near future.

Placental pathology in OD pregnancy

The placenta is the feto-maternal interface, and various immune-mediated pathological changes are observed in villitis of unknown etiology (VUE), chronic deciduitis with or without plasma cells, massive chorionic intervillositis, and maternal floor infarction [4, 11, 26, 32, 34, 53, 55]. These findings may suggest that maternal immune cells are attacking the fetus in such conditions. Therefore, it is interesting to examine placental pathology in OD pregnancy for better understanding of immunological reactions at the feto-maternal interface.

Severe chronic deciduitis with dense fibrinoid deposition is a characteristic finding in OD pregnancy (Fig. 3) [14], affecting the border zone between mother and fetus. Accumulation of maternal lymphocytes suggests conflict between the immune cells of the mother and fetus. The main populations of lymphocytes that accumulate in this zone are CD4$^+$ T cells and CD56$^+$ NK cells [14]. CD4$^+$ T cells recognize MHC class II antigens, and feto-maternal HLA-DR and HLA-DQ mismatch is correlated with an increase in the percentage of activated CD4$^+$ T cells in the peripheral blood of the mother during uncomplicated OD pregnancy [77]. These activated CD4$^+$ T cells may attack fetal tissue at the border zone between mother and fetus, and dense fibrin deposits may be an indicator of such conflict. It has been reported that selective migration of fetus-specific Treg cells from the peripheral blood to the decidua regulates the fetus-specific immune response of the mother [71]. Interestingly, accumulation of Treg cells in the decidua basalis is decreased in OD pregnancy

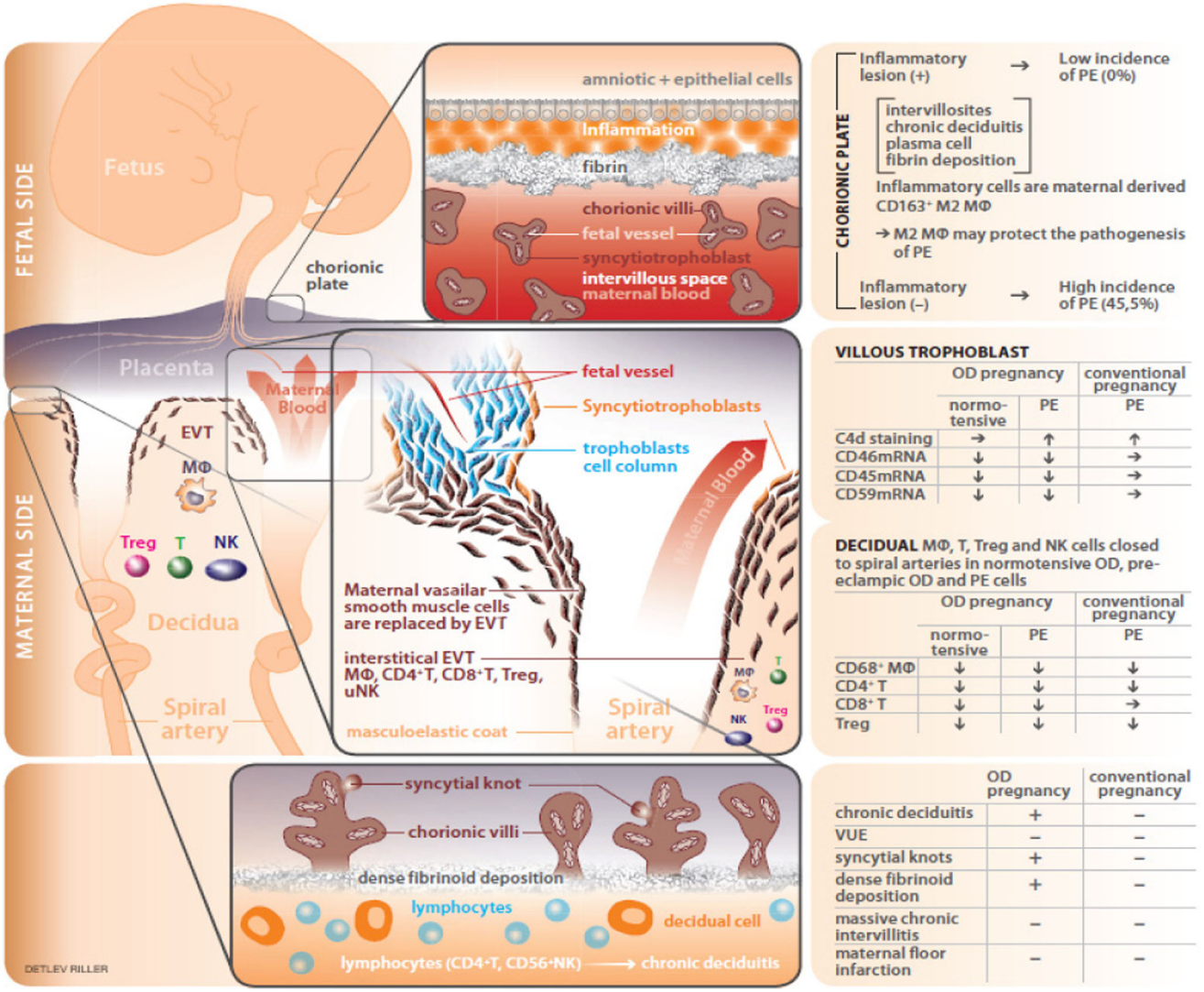

Fig. 3 Pathological and immunological changes in uncomplicated OD pregnancy and OD pregnancy complicated by preeclampsia. Several findings are observed in the villous trophoblast, chorionic plate, and decidua in women with uncomplicated OD pregnancy and OD pregnancy complicated by preeclampsia. In the villous trophoblast (*lower part* in the figure), syncytial knots, chronic deciduitis, and dense fibrinoid deposition are observed in OD pregnancy, but villitis unknown etiology (VUE), massive chorionic intervillitis, and maternal floor infarction are not recognized. CD4d staining in villous trophoblast is increased in preeclamptic OD pregnancy, preeclamptic cases in natural pregnancy, but not change in normotensive OD pregnancy, suggesting that placental CD4d deposition might be a sign of antibody-mediated fetal rejection. Placental biopsy samples show decreased numbers of $CD68^+$ Mφ, $CD4^+$ T cells, and Treg cells in preeclamptic cases in natural pregnancy. The same findings are observed in OD pregnancies, regardless of the presence or absence of preeclampsia. The numbers of $CD8^+$ T cell in preeclamptic cases in natural pregnancy are not changed, but these levels are decreased in OD pregnancies, regardless the presence or absence of preeclampsia. In chorionic plate (*upper part* in the figure), intervillositis, chronic deciduitis, plasma cell infiltration, and fibrin deposition are observed. M2Mφ are main population in chorionic plate. When inflammatory lesions are found in this area, the incidence of preeclampsia is very low, suggesting that inflammation in chorionic plate may represent a protective response to fetal rejection

regardless of the occurrence of preeclampsia [43]. Such immunological changes suggest possible conflict between the immune systems of the mother and fetus in OD pregnancy. Fibrin deposition with chronic deciduitis is associated with an increase of syncytial knots, which is a sign of hypoxia or stress in the intervillous space (Fig. 3) [14]. These findings also support the existence of an immune interaction between mother and fetus in OD pregnancy, although an increase of syncytial knots was not found in another study [47].

VUE is an inflammatory condition that has been reported in 5–15 % of all third-trimester placentas. VUE is associated with fetal growth restriction and stillbirth [11]. Because maternal $CD8^+$ T cells and fetal macrophages accumulate around fetal-derived placental (villous) stromal cells, it seems that VUE is based upon a maternal immunological response to

the semi-allograft fetus (Fig. 3) [11, 26]. Styer et al. [70] reported that there is a twofold increase of VUE in OD pregnancies, suggesting that immune-related inflammation may be present in these pregnancies. However, Gundogan et al. [14] reported that the incidence of VUE in OD pregnancy was similar to that in conventional IVF-ET pregnancy, so further studies are necessary to confirm the relation with VUE.

Deposition C4d, a degradation product of complement factor C4, is considered to be evidence of antigen-mediated allograft rejection. C4d deposition in the placenta is observed in VUE, spontaneous preterm birth, maternal floor infarction, and preeclampsia [4, 32, 34, 53, 55]. Placental C4d deposition is significantly increased in women with preeclampsia irrespective of whether they have spontaneous or OD pregnancy (Fig. 3) [32]. Importantly, diffuse CD4 deposition is not observed in the chorionic villi in uncomplicated OD pregnancy, suggesting that placental C4d deposition might be a sign of antibody-mediated fetal rejection in preeclampsia (Fig. 3). Placental expression of mRNAs for complement regulatory proteins, such as CD46, CD55, and CD59, is significantly reduced in both uncomplicated and preeclamptic OD pregnancies [32], while upregulation of placental CD55 and CD59 mRNA expressions is observed in autologous preeclamptic pregnancies [4]. Therefore, downregulation of complement regulatory proteins in the placenta is unique to OD pregnancy, and this may trigger C4d deposition in the syncytiotrophoblasts.

The placental chorionic plates of women with uncomplicated OD pregnancy show inflammatory changes such as intervillositis, chronic deciduitis, plasma cell infiltration, and fibrin deposition (Fig. 3) [63]. Interestingly, when inflammatory lesions are found in the chorionic plate in OD pregnancy, the incidence of preeclampsia is very low (0 %), while preeclampsia shows a very high incidence (45.5 %) when inflammation of the chorionic plate is not detected [63]. These findings suggest that chorionic plate inflammation may represent a protective response to attack by the maternal immune system. However, maternal type 2 macrophages (M2Mφ) that control the inflammation accumulate in this region, suggesting that immune regulatory mechanisms might contribute to the prevention of preeclampsia. These findings suggest that the balance between inflammation and regulation of inflammation might be important for successful pregnancy.

The concept of selecting oocyte for OD to reduce the risk for pregnancy complications

The risk for preeclampsia and gestational hypertension is low when oocyte donor is related to the recipient, suggesting that less HLA mismatch between mother and fetus seems to be favorable for maintenance of OD pregnancy. NIMA-specific Treg cells are present, and when partner has shared NIMA antigens, NIMA-specific Treg cells rapidly increase after pregnancy and enforce feto-maternal tolerance [27]. Therefore, we might select the oocytes which express the same HLAs especially HLA C antigens for OD recipient. In OD recipient with KIR-AA, oocyte donor with HLA-C2C2 genotype might be avoided. Furthermore, single-embryo transfer is recommended to reduce multiple pregnancy because multiple pregnancy in OD pregnancy is a great risk for preeclampsia. Those attempts have not been performed, so prospective study to reduce the risk in OD pregnancy should be tried in the near future.

Conclusion

OD pregnancy is associated with a high rate of complications. Recent immunopathological studies have revealed some of the immunological characteristics of uncomplicated OD pregnancy, but we have not yet identified the crucial factors that lead to preeclampsia, preterm labor, and miscarriage in OD pregnancy (Table 1). Some of the immunological abnormalities were proven in OD pregnancy, but some of the immune statuses have not been clarified. Further investigation of immunological changes in OD pregnancy may help to clarify the mechanisms involved in maintenance of normal pregnancy and the pathophysiology of preeclampsia.

References

1. Abdalla HI, Billett A, Kan AK, Baig S, Wren M, Korea L, Studd JW (1998) Obstetric outcome in 232 ovum donation pregnancies. Br J Obstet Gynaecol 105(3):332–337
2. Adams DH, Clark RA, Davies MJ, de Lacey S (2015) A meta-analysis of neonatal health outcomes from oocyte donation. J Develop Orig Health Dis. doi:10.1017/S2040174415007898
3. Aluvihare VR, Kallikourdis M, Betz AG (2004) Regulatory T cells mediate maternal tolerance to the fetus. Nat Immunol 5(3):266–271
4. Buurma A, Cohen D, Veraar K, Schonkeren D, Class FH, Bruijn JA, Bloemenkamp KW, Baelde HJ (2012) Preeclampsia is characterized by placental complement dysregulation. Hypertension 60(5):1332–1337
5. Chen T, Darrasse-Jèze G, Bergot AS, Courau T, Churlaud G, Valdivia K, Strominger JL, Ruocco MG, Chaouat G, Klatzmann D (2013) Self-specific memory regulatory T cells protect embryos at implantation in mice. J Immunol 191(5):2273–2281
6. Clua E, Meler E, Rodríguez D, Coroleu B, Rodríguez I, Martínez F, Tur R. Obstetric and perinatal complications in an oocyte donation programme. Is it time to limit the number of embryos to transfer? Gynecol Endocrinol, 2015 (DOI:10.3109/09513590.2015.1111330).
7. Cobo A, Serra V, Garrido N, Olmo I, Pellicer A, Remohí J (2014) Obstetric and perinatal outcome of babies born from vitrified oocytes. Fertil Steril 102(4):1006–1015.e4
8. Colonna M, Samaridis J, Cella M, Angman L, Allen RL, O'Callaghan CA, Dunbar R, Ogg GS, Cerundolo V, Rolink A (1998) Human myelomonocytic cells express an inhibitory receptor for classical and nonclassical MHC class I molecules. J Immunol 160(7):3096–3100

9. Contini P, Ghio M, Poggi A, Filaci G, Indiveri F, Ferrone S, Puppo F (2003) Soluble HLA-A,-B,-C and -G molecules induce apoptosis in T and NK CD8+ cells and inhibit cytotoxic T cell activity through CD8 ligation. Eur J Immunol 33(1):125–134
10. Darrasse-Jèze G, Klatzmann D, Charlotte F, Salomon BL, Cohen JL (2006) $CD4^+CD25^+$ regulatory/suppressor T cells prevent allogeneic fetus rejection in mice. Immunol Lett 102(1):106–109
11. Derricott H, Jones RL, Heazell AE (2013) Investigating the association of villitis of unknown etiology with stillbirth and fetal growth restriction—a systematic review. Placenta 34:856–862
12. Farina A, Sekizawa A, De Sanctis P, Purwosunu Y, Okai T, Cha DH, Kang JH, Vicenzi C, Tempesta A, Wibowo N, Valvassori L, Rizzo N (2008) Gene expression in chorionic villous samples at 11 weeks' gestation from women destined to develop preeclampsia. Prenat Diagn 28(10):956–61
13. Guerin LR, Moldenhauer LM, Prins JR, Bromfield JJ, Hayball JD, Robertson SA (2011) Seminal fluid regulates accumulation of $FOXP3^+$ regulatory T cells in the preimplantation mouse uterus through expanding the $FOXP3^+$ cell pool and CCL19-mediated recruitment. Biol Reprod 85(2):397–408
14. Gundogan F, Bianchi DW, Scherjon SA, Roberts DJ (2010) Placental pathology in egg donor pregnancies. Fertil Steril 93(2): 397–404
15. Heemskerk MB, Roelen DL, Dankers MK, van Rood JJ, Claas FH, Doxiadis II, Oudshoorn M (2005) Allogeneic MHC class I molecules with numerous sequence differences do not elicit a CTL response. Hum Immunol 66(9):969–976
16. Henne MB, Zhang M, Paroski S, Kelshikar B, Westphal LM (2007) Comparison of obstetric outcomes in recipients of donor oocytes vs. women of advanced maternal age with autologous oocytes. J Reprod Med 52(7):585–590
17. Hiby SE, Walker JJ, O'shaughnessy KM, Redman CW, Carrington M, Trowsdale J, Moffett A (2004) Combinations of maternal KIR and fetal HLA-C genes influence the risk of preeclampsia and reproductive success. J Exp Med 200(8):957–965
18. Hiby SE, Regan L, Lo W, Farrell L, Carrington M, Moffett A (2008) Association of maternal killer-cell immunoglobulin-like receptors and parental HLA-C genotypes with recurrent miscarriage. Hum Reprod 23(4):972–976
19. Hsu P1, Santner-Nanan B, Dahlstrom JE, Fadia M, Chandra A, Peek M, Nanan R (2012) Altered decidual DCSIGN+ antigen-presenting cells and impaired regulatory T-cell induction in preeclampsia. Am J Pathol 181(6):2149–60
20. Hunt JS, Petroff MG, McIntire RH, Ober C (2005) HLA-G and immune tolerance in pregnancy. FASEB J 19(7):681–693
21. Inada K, Shima T, Ito M, Ushijima A, Saito S (2015) Helios-positive functional regulatory T cells are decreased in decidua of miscarriage cases with normal fetal chromosomal content. J Reprod Immunol 107:10–19
22. Ishitani A, Sageshima N, Hatake K (2006) The involvement of HLA-E and -F in pregnancy. J Reprod Immunol 69(2):101–113
23. Jasper MJ, Tremellen KP, Robertson SA (2006) Primary unexplained infertility is associated with reduced expression of the T-regulatory cell transcription factor Foxp3 in endometrial tissue. Mol Hum Reprod 12(5):301–8
24. Keegan DA, Krey LC, Chang HC, Noyes N (2007) Increased risk of pregnancy-induced hypertension in young recipients of donated oocytes. Fertil Steril 87(4):776–781
25. Kim HS, Yang KM, Cha SH, Song IO, Kang IS. Obstetric outcomes after oocyte donation in patients with premature ovarian failure. In: Abstracts of the 21st Annual Meeting of the ESHRE, Copenhagen, Denmark. 20. Suppl 1, p.i34, 2005.
26. Kim MJ, Romero R, Kim CJ, Tarca AL, Chhauy S, LaJeunesse C, Lee DC, Draghici S, Gotsch F, Kusanovic JP, Hassan SS, Kim JS (2009) Villitis of unknown etiology is associated with a distinct pattern of chemokine up-regulation in the feto-maternal and placental compartments: implications for conjoint maternal allograft rejection and maternal anti-fetal graft-versus-host disease. J Immunol 182(6):3919–3927
27. Kinder JM, Jiang TT, Ertelt JM, Xin L, Strong BS, Shaaban AF, Way SS (2015) Cross-generational reproductive fitness enforced by microchimeric maternal cells. Cell 162(3):505–515
28. Klatsky PC, Delaney SS, Caughey AB, Tran ND, Schattman GL, Rosenwaks Z (2010) The role of embryonic origin in preeclampsia: a comparison of autologous in vitro fertilization and ovum donor pregnancies. Obstet Gynecol 116(6):1387–1392
29. Krieg SA, Henne MB, Westphal LM (2008) Obstetric outcomes in donor oocyte pregnancies compared with advanced maternal age in in vitro fertilization pregnancies. Fertil Steril 90(1):65–70
30. Kupka MS, Ferraretti AP, de Mouzon J, Erb K, D'Hooghe T, Castilla JA, Calhaz-Jorge C, De Geyter C, Goossens V (2014) Assisted reproductive technology in Europe, 2010: results generated from European registers by ESHRE†. Hum Reprod 29(10): 2099–2113
31. Lash GE, Otun HA, Innes BA, Percival K, Searle RF, Robson SC, Bulmer JN (2010) Regulation of extravillous trophoblast invasion by uterine natural killer cells is dependent on gestational age. Hum Reprod 25(5):1137–1145
32. Lashley LE, Buurma A, Swings GM, Eikmans M, Anholts JD, Bakker JA, Claas FH (2015) Preeclampsia in autologous and oocyte donation pregnancy: is there a different pathophysiology? J Reprod Immunol 109:17–23
33. Le Bouteiller P, Solier C, Pröll J, Aguerre-Girr M, Fournel S, Lenfant F (1999) Placental HLA-G protein expression in vivo: where and what for? Hum Reprod Update 5(3):223–233
34. Lee J, Romero R, Xu Y, Kim JS, Topping V, Yoo W, Kusanovic JP, Chaiworapongsa T, Hassan SS, Yoon BH, Kim CJ (2011) A signature of maternal anti-fetal rejection in spontaneous preterm birth: chronic chorioamnionitis, anti-human leukocyte antigen antibodies, and C4d. PLoS One 6(2), e16806
35. Le Ray C, Scherier S, Anselem O, Marszalek A, Tsatsaris V, Cabrol D, Goffinet F (2012) Association between oocyte donation and maternal and perinatal outcomes in women aged 43 years or older. Hum Reprod 27(3):896–901
36. LeMaoult J, Krawice-Radanne I, Dausset J, Carosella ED (2004) HLA-G1-expressing antigen-presenting cells induce immunosuppressive $CD4^+$ T cells. Proc Natl Acad Sci USA 101(18):7064–7069
37. Levine RJ, Lam C, Qian C, Yu KF, Maynard SE, Sachs BP, Sibai BM, Epstein FH, Romero R, Thadhani R, Karumanchi SA, CPEP Study Group (2006) Soluble endoglin and other circulating antiangiogenic factors in preeclampsia. N Engl J Med 355(10): 992–1005
38. Levron Y, Dviri M, Segol I, Yerushalmi GM, Hourvitz A, Orvieto R, Mazaki-Tovi S, Yinon Y (2014) The "immunologic theory" of preeclampsia revisited: a lesson from donor oocyte gestations. Am J Obstet Gynecol 211(4):383.e1–5
39. Lissauer D, Piper K, Goodyear O, Kilby MD, Moss PA (2012) Fetal-specific CD8+ cytotoxic T cell responses develop during normal human pregnancy and exhibit broad functional capacity. J Immunol 189(2):1072–80
40. Lu Y, Zhang F, Zhang Y, Zeng B, Hu L, Liao A (2012) Quantitative reduction of peripheral $CD4^+CD25^+FOXP3^+$ regulatory T cells in reproductive failure after artificial insemination by donor sperm. Am J Reprod Immunol 69(2):188–193
41. Lutjen P, Trounson A, Leeton J, Findlay J, Wood C, Renou P (1984) The establishment and maintenance of pregnancy using in vitro fertilization and embryo donation in a patient with primary ovarian failure. Nature 307(5947):174–175
42. Masoudian P, Nasr A, de Nanassy J, Fung-Kee-Fung K, Bainbridge SA, El Demellawy D (2016) Oocyte donation pregnancies and the

risk of preeclampsia or gestational hypertension: a systematic review and metaanalysis. Am J Obstet Gynecol 214(3):328–339
43. Nakabayashi Y, Nakashima A, Yoshino O, Shima T, Shiozaki A, Adachi T, Nakabayashi M, Okai T, Kushima M, Saito S (2016) Impairment of the accumulation of decidual T cells, NK cells, and monocytes, and the poor vascular remodeling of spiral arteries, were observed in oocyte donation cases, regardless of the presence or absence of preeclampsia. J Reprod Immunol 114:65–74
44. Naruse K, Lash GE, Innes BA, Otun HA, Searle RF, Robson SC, Bulmer JN (2009) Localization of matrix metalloproteinase (MMP)-2, MMP-9 and tissue inhibitors for MMPs (TIMPs) in uterine natural killer cells in early human pregnancy. Hum Reprod 24(3):553–561
45. Navot D, Drews MR, Bergh PA, Guzman I, Karstaedt A, Scott RT Jr, Garrisi GJ, Hofmann GE (1994) Age-related decline in female fertility is not due to diminished capacity of the uterus to sustain embryo implantation. Fertil Steril 61(1):97–101
46. Pecks U, Maass N, Neulen J (2011) Oocyte donation: a risk factor for pregnancy-induced hypertension: a meta-analysis and case series. Dtsch Arztebl Int 108(3):23–31
47. Perni SC, Predanic M, Cho JE, Baergen RN (2005) Placental pathology and pregnancy outcomes in donor and non-donor oocyte in vitro fertilization pregnancies. J Perinat Med 33(1):27–32
48. Petersdorf EW, Longton GM, Anasetti C, Mickelson EM, McKinney SK, Smith AG, Martin PJ, Hansen JA (1997) Association of HLA-C disparity with graft failure after marrow transplantation from unrelated donors. Blood 89(5):1818–1823
49. Porreco RP, Harden L, Gambotto M, Shapiro H (2005) Expectation of pregnancy outcome among mature women. Am J Obstet Gynecol 192(1):38–41
50. Redman CW, Sacks GP, Sargent IL (1999) Preeclampsia: an excessive maternal inflammatory response to pregnancy. Am J Obstet Gynecol 180:499–506
51. Robertson SA, Guerin LR, Bromfield JJ, Branson KM, Ahlström AC, Care AS (2009) Seminal fluid drives expansion of the $CD4^+CD25^+$ T regulatory cell pool and induces tolerance to paternal alloantigens in mice. Biol Reprod 80(5):1036–1045
52. Robertson SA, Prins JR, Sharkey DJ, Moldenhauer LM (2013) Seminal fluid and the generation of regulatory T cells for embryo implantation. Am J Reprod Immunol 69(4):315–330
53. Romero R, Whitten A, Korzeniewski SJ, Than NG, Chaemsaithong P, Miranda J, Dong Z, Hassan SS, Chaiworapongsa T (2013) Maternal floor infarction/massive perivillous fibrin deposition: a manifestation of maternal antifetal rejection? Am J Reprod Immunol 70(4):285–298
54. Rowe JH, Ertelt JM, Xin L, Way SS (2012) Pregnancy imprints regulatory memory that sustains anergy to fetal antigen. Nature 490(7418):102–106
55. Rudzinski E, Gilroy M, Newbill C, Morgan T (2013) Positive C4d immunostaining of placental villous syncytiotrophoblasts supports host-versus-graft rejection in villitis of unknown etiology. Pediatr Dev Pathol 16(1):7–13
56. Saito S, Sakai M (2003) Th1/Th2 balance in preeclampsia. J Reprod Immunol 59(2):161–173
57. Saito S, Nakashima A, Shima T, Ito M (2010) Th1/Th2/Th17 and regulatory T-cell paradigm in pregnancy. Am J Reprod Immunol 63(6):601–610
58. Saito S, Shima T, Nakashima A, Inada K, Yoshino O (2016) Role of paternal antigen-specific Treg cells in successful implantation. 75(3):310–6
59. Salha O, Sharma V, Dada T, Nugent D, Rutherford AJ, Tomlinson AJ, Philips S, Allgar V, Walker JJ (1999) The influence of donated gametes on the incidence of hypertensive disorders of pregnancy. Hum Reprod 14(9):2268–2273
60. Santner-Nanan B, Peek MJ, Khanam R, Richarts L, Zhu E, Fazekas de St Groth B, Nanan R (2009) Systemic increase in the ratio between $Foxp3^+$ and IL-17-producing $CD4^+$ T cells in healthy pregnancy but not in preeclampsia. J Immunol 183(11):7023–7030
61. Sasaki Y, Sakai M, Miyazaki S, Higuma S, Shiozaki A, Saito S (2004) Decidual and peripheral blood $CD4^+CD25^+$ regulatory T cells in early pregnancy subjects and spontaneous abortion cases. Mol Hum Reprod 10(5):347–353
62. Sasaki Y, Darmochwal-Kolarz D, Suzuki D, Sakai M, Ito M, Shima T, Shiozaki A, Rolinski J, Saito S (2007) Proportion of peripheral blood and decidual CD4(+) CD25(bright) regulatory T cells in preeclampsia. Clin Exp Immunol 149(1):139–145
63. Schonkeren D, Swings G, Roberts D, Claas F, de Heer E, Scherjon S (2012) Pregnancy close to the edge: an immunosuppressive infiltrate in the chorionic plate of placentas from uncomplicated egg cell donation. PLoS One 7(3), e32347
64. Serhal PF, Craft IL (1989) Oocyte donation in 61 patients. Lancet 1(8648):1185–1187
65. Shima T, Sasaki Y, Itoh M, Nakashima A, Ishii N, Sugamura K, Saito S (2010) Regulatory T cells are necessary for implantation and maintenance of early pregnancy but not late pregnancy in allogeneic mice. J Reprod Immunol 85(2):121–129
66. Shima T, Inada K, Nakashima A, Ushijima A, Ito M, Yoshino O, Saito S (2015) Paternal antigen-specific proliferating regulatory T cells are increased in uterine-draining lymph nodes just before implantation and in pregnant uterus just after implantation by seminal plasma-priming in allogeneic mouse pregnancy. J Reprod Immunol 108:72–82
67. Smith SD, Dunk CE, Aplin JD, Harris LK, Jones RL (2009) Evidence for immune cell involvement in decidual spiral arteriole remodeling in early human pregnancy. Am J Pathol 174(5):1959–1971
68. Söderström-Anttila V, Tiitinen A, Foudila T, Hovatta O (1998) Obstetric and perinatal outcome after oocyte donation: comparison with in-vitro fertilization pregnancies. Hum Reprod 13(2):483–490
69. Stoop D, Baumgarten M, Haentjens P, Polyzos NP, De Vos M, Verheyen G, Camus M, Devroey P (2012) Obstetric outcome in donor oocyte pregnancies: a matched-pair analysis. Reprod Biol Endocrinol 10:42–50
70. Styer AK, Parker HJ, Roberts DJ, Palmer-Toy D, Toth TL, Ecker JL (2003) Placental villitis of unclear etiology during ovum donor in vitro fertilization pregnancy. Am J Obstet Gynecol 189(4):1184–1186
71. Tilburgs T, Roelen DL, van der Mast BJ, de Groot-Swings GM, Kleijburg C, Scherjon SA, Claas FH (2008) Evidence for a selective migration of fetus-specific $CD4^+CD25$ bright regulatory T cells from the peripheral blood to the decidua in human pregnancy. J Immunol 180(8):5737–5745
72. Tilburgs T, Scherjon SA, van der Mast BJ, Haasnoot GW, Versteeg-V D, Voort-Maarschalk M, Roelen DL, van Rood JJ, Claas FH (2009) Fetal-maternal HLA-C mismatch is associated with decidual T cell activation and induction of functional T regulatory cells. J Reprod Immunol 82(2):148–157
73. Tilburgs T, Schonkeren D, Eikmans M, Nagtzaam NM, Datema G, Swings GM, Prins F, van Lith JM, van der Mast BJ, Roelen DL, Scherjon SA, Claas FH (2010) Human decidual tissue contains differentiated $CD8^+$ effector-memory T cells with unique properties. J Immunol 185(7):4470–4477
74. Tilburgs T, Strominger JL (2013) $CD8^+$ effector T cells at the fetal-maternal interface, balancing fetal tolerance and antiviral immunity. Am J Reprod Immunol 69(4):395–407
75. Tremellen KP, Valbuena D, Landeras J, Ballesteros A, Martinez J, Mendoza S, Norman RJ, Robertson SA, Simón C (2000) The effect of intercourse on pregnancy rates during assisted human reproduction. Hum Reprod 15(12):2653–2658
76. van der Hoorn ML, Lashley EE, Bianchi DW, Claas FH, Schonkeren CM, Scherjon SA (2010) Clinical and immunologic

aspects of egg donation pregnancies: a systematic review. Hum Reprod Update 16(6):704–712
77. van der Hoorn ML, van Egmond A, Swings GM, van Beelen E, van der Keur C, Tirado-González I, Blois SM, Karumanchi SA, Bianchi DW, Claas FH, Scherjon SA (2014) Differential immunoregulation in successful oocyte donation pregnancies compared with naturally conceived pregnancies. J Reprod Immunol 101–102:96–103
78. van Dorp W, Rietveld AM, Laven JS, van den Heuvel-Eibrink MM, Hukkelhoven CW, Schipper I (2014) Pregnancy outcome of non-anonymous oocyte donation: a case-control study. Eur J Obstet Gynecol Reprod Biol 182:107–112
79. Wallace AE, Host AJ, Whitley GS, Cartwright JE (2013) Decidual natural killer cell interactions with trophoblasts are impaired in pregnancies at increased risk of preeclampsia. Am J Pathol 183(6):1853–1861
80. Wiggins DA, Main E (2005) Outcomes of pregnancies achieved by donor egg in vitro fertilization—a comparison with standard in vitro fertilization pregnancies. Am J Obstet Gynecol 192(6):2002–2006
81. Yaron Y, Ochshorn Y, Amit A, Kogosowski A, Yovel I, Lessing JB (1998) Oocyte donation in Israel: a study of 1001 initiated treatment cycles. Hum Reprod 13(7):1819–1824
82. Zenclussen AC, Gerlof K, Zenclussen ML, Sollwedel A, Bertoja AZ, Ritter T, Kotsch K, Leber J, Volk HD (2005) Abnormal T-cell reactivity against paternal antigens in spontaneous abortion: adoptive transfer of pregnancy-induced $CD4^{+}CD25^{+}$ T regulatory cells prevents fetal rejection in a murine abortion model. Am J Pathol 166(3):811–822