Immunological challenges during pregnancy : preeclampsia and egg donation

Hoorn, M.L. van der

Clinical and immunologic aspects of egg donation pregnancies: a systematic review

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Marie-Louise van der Hoorn
Lisa Lashley
Diana Bianchi
Frans Claas
Dorrith Schonkeren
Sicco Scherjon

Human Reproduction Update 2010;16(6):704-12

Abstract

Background: Egg donation (ED) makes it possible for subfertile women to conceive. Pregnancies achieved using ED with unrelated donors are unique, since the entire fetal genome is allogeneic to the mother. The aims of this review were to evaluate the consequences of ED pregnancies and to place them in the special context of their atypical immunologic relationships.

Methods: This review comprised an online search of English language publications listed in Pubmed/Medline, up to January 29th 2010. Seventy-nine papers met inclusion criteria. Using the literature and the authors' own experience, the relevant data on pregnancy outcome and complications, placental pathology and immunology were evaluated.

Results: Multiple studies document that ED pregnancies are associated with a higher incidence of pregnancy-induced hypertension and placental pathology. The incidence of other perinatal complications, such as intrauterine growth restriction, prematurity, and congenital malformations, is comparable to conventional *in vitro* fertilisation. During pregnancy, both local and systemic immunologic changes occur. In ED pregnancies these changes are more pronounced. There is almost no information in the literature on the long-term complications of ED pregnancies for the mother.

Conclusion: ED pregnancies have a higher risk of maternal morbidity. Due to the high degree of antigenic dissimilarity, ED pregnancies represent an interesting model to study complex immunologic interactions, as the fully allogeneic fetus is not rejected but tolerated by the pregnant woman. Knowledge of the immune system in ED pregnancies has broader significance, as it may also give insight into immunologic aspects of tolerance in solid organ transplantation.

Introduction

The first successful pregnancy achieved after egg donation (ED) was reported in 1984 [1]. Since then, thousands of pregnancies after ED have occurred worldwide. The original indication was premature ovarian failure [2,3]. More recent indications include advanced maternal age, diminished ovarian reserve, secondary infertility following treatment of childhood malignancies [4], multiple failed *in vitro* fertilisation (IVF) attempts [5], and maternally inherited genetic abnormalities [6]. Infertile women who do not produce euploid embryos also depend upon ED to achieve a successful pregnancy.

Eggs obtained from a suitable donor, either provided by relatives or via independent, sometimes for profit organizations [7], are fertilised with sperm of the recipient's partner or donor and the resulting embryos are transferred into the recipient's uterus. Some pregnancies achieved using ED are unique, since the entire fetal genome is allogeneic to the mother. Therefore, ED pregnancies represent an interesting model to study complex immunologic interactions between the fetus and the pregnant woman. Despite a continued increase in the number of ED pregnancies, relatively little is known about the underlying biology and long-term complications of this approach. Similar immunologic interactions exist in surrogate gestations, in which biological motherhood is achieved without pregnancy by transferring fertilised eggs to the uterus of a second woman. This treatment is used for women without a functioning uterus, or in women for whom pregnancy would be life-threatening [8].

Delaying childbirth and the resulting demand for infertility treatment have resulted in ~1% of United States (US) infants being conceived through assisted reproductive technologies [9]. Currently about 10% of the IVF cases in the US use ED [10]. This has increased the demand for the availability of oocyte donors; in the US more than 100,000 women have donated their oocytes [11]. In Europe, a recent report showed a total of 11491 egg donations [12].

ED was initially developed as a therapy for young women with premature ovarian failure, rather than as a means of overcoming the age-related decline in fertility. However, age-related infertility is now one of the most common reasons to use ED, especially in women over 40 [13]. The data suggest that fertility depends on oocyte age and quality and less on uterine age [14-16]. Some studies report that ED in women of advanced maternal age is as successful in establishing pregnancy as in younger recipients [17-20]. This would suggest that endometrial receptivity is unaltered by age [13,17]. However, in the late 40s and beyond, the success rate of ED starts to decline, so there are likely to be as-yet undiscovered factors that are affected by maternal age [14,15,21]. Advanced maternal age is almost always inherent to ED; thus it will therefore be a confounding factor in research studies of ED.

Obesity [22], an endometrial thickness of < 8mm, and the need for the use of GnRH analogue to down-regulate the pituitary before endometrial priming negatively influences pregnancy rates [23]. In contrast, high birth rates have been observed in frozen-thawed embryo replacement cycles in which embryos are derived from cycles that used GnRH analogues [24]. Besides the recipient's mid-cycle endometrial thickness, the quality of the transferred embryos is also important for a successful pregnancy [25-27].

Methods

The aims of this systematic review were to evaluate the consequences of ED pregnancies and to place the findings in the literature in the special context of their atypical immunologic relationships in ED pregnancies.

A search in PubMed, using the Medical Subject Headings (MeSH) terms 'oocyte donation' and 'egg donation', in combination with 'pregnancy outcome' or 'pregnancy complications' or 'immunology' or 'placenta' was performed. English language was used as a limit. Time was not limited but the search was completed on January 29th 2010. The titles and abstracts of the resulting articles were scanned and evaluated by the first, second and last authors (M.L.P.H, E.E.L.O.L. and S.A.S). Inclusion criteria were original and review articles that focused on current knowledge in ED pregnancies regarding pregnancy outcome and complications, placental pathology, and immunologic aspects. In addition, some background articles on reproductive and transplantation immunology were included. Exclusion criteria were: case reports, letters, and articles with an exclusive focus on ethics of ED. The main search identified 505 potentially relevant studies. Figure 1 shows the flow chart, which led to the final 79 references included in the review.

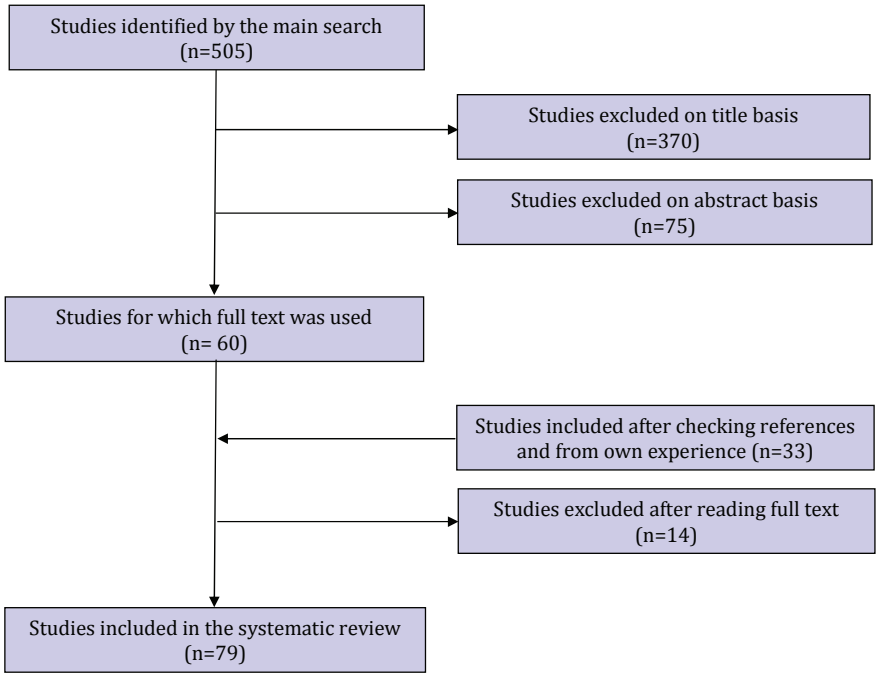

Figure 1 Flow chart depicting selection of articles for systematic review.

Consequences of egg donation pregnancies

Many studies of ED pregnancies have focused on perinatal complications, such as preeclampsia, the mode of delivery, and immediate neonatal problems, such as prematurity. In addition, ethical and medical concerns have been raised regarding the effects of treatment on the donor [11]. With regard to the recipient, most of the emphasis has been on short-term complications of pregnancy, because of the higher incidence of both early and late obstetrical problems. The reason for the higher incidence of complications in ED pregnancies is unclear from the literature reviewed.

Maternal complications

ED enables women of advanced age to achieve successful pregnancies. However, advanced maternal age leads to potential medical and obstetric complications. Pregnant recipients above the age of 40 are at an increased risk for gestational diabetes, preeclampsia and thrombophlebitis [28]; above the age of 45 they are at an increased risk of hypertension, proteinuria, premature rupture of membranes, second- and third trimester haemorrhage, preterm delivery and lower mean infant birth weights [15,29]. One study that corrected for maternal age and multiple gestation concluded that women who conceived with donor oocytes remain at high risk for preterm labor, preeclampsia, and protracted labor, requiring caesarean section delivery [30]. The rate of caesarean section deliveries in ED pregnancies is increased compared to spontaneous conceptions, and is reported to range from 40-76% of cases [4,5,18,31-35].

Pregnancy-induced hypertension

ED pregnancies are associated with a higher than expected incidence of pregnancy-induced hypertension (PIH), ranging from 16-40% of cases [5,31-34,36-39]. This is most likely due to a higher incidence of placental pathology [6]. It has been suggested that the increased rate of hypertension in ED pregnancies is related to advanced maternal age, nulliparity and ovarian failure [6], since these factors are associated with multiple obstetric complications [40]. However, a study by Sheffer-Mimouni *et al.* found that these factors were not independent risk factors for PIH [33]. They concluded that the higher incidence of PIH in ED pregnancies is due to an altered immune response. In another report, an increased risk for PIH was observed in women with ED pregnancies in women < 35 years or > 40 years of age [41].

In the studies above the control groups were spontaneously conceived pregnancies. Since IVF pregnancies are associated with more obstetric complications than naturally conceived pregnancies [42], they represent a more appropriate control group to examine the consequences of ED. Wiggins *et al*. found a 3-fold increased incidence of hypertensive complications in ED compared to standard IVF pregnancies (26% vs. 8%, respectively, p=0.02) [39]. For nulliparous women this difference was even more significant, with 37% of the ED group and 8% of the standard IVF group affected by hypertension (p<0.003). Multiple logistic regression analysis in nulliparous patients showed an odds ratio of 7.1 (p=0.019). In singleton and twin pregnancies the same effect was found (OR: 4.9, p=0.017). Maternal age was not an added risk factor for the development of PIH (OR: 1.0) [39]. Interestingly, the incidence of PIH appears to be significantly higher if the oocyte donor is unrelated to the recipient (20% vs. 3.7% for standard IVF, p=0.03), versus a related, sibling donor (8% vs. 3.7% for standard IVF, p=0.31) [43]. This study retrospectively analyzed 61 ED pregnancies that were classified into two subgroups according to the relationship between the ED and recipient, and 127 non donor IVF pregnancies. The groups were matched for age, parity and number of fetuses. This study is the only one that has specifically examined the immunogenetic origin of the egg and its relationship to complications of pregnancy. These data suggest that PIH is more frequent with an immunologically unrelated donor.

Bleeding

A possible result of the unique, non-physiological immunologic relationship between the fertilised oocyte and the maternal decidua is shallower placental invasion [44,45]. The higher incidence of bleeding complications in the first trimester could be related to this insufficient placentation. On the other hand, excessive invasion might result in more postpartum haemorrhage in ED pregnancies as a result of placenta praevia or abnormal placentation [33].

The incidence of first trimester vaginal bleeding is increased in ED pregnancies, ranging from 12-53% of cases [6,31,34]. Significant blood loss is estimated to occur in 43-53% of first trimester cases [33,34] and 6% of second trimester cases [6,33]. The incidence of first trimester bleeding is

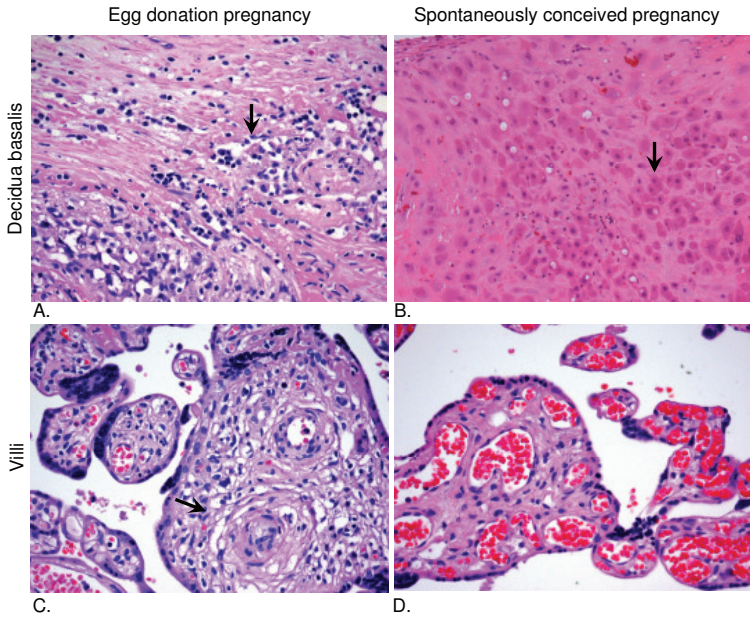

Figure 2 Photomicroscopic images from ED and spontaneously conceived pregnancies placentas. (H&E stained sections, original magnification 400X). A. Decidua basalis of ED pregnancy placenta with deciduitis illustrated by the infiltration of mononuclear cells (arrow). **B.** Normal decidua basalis from a spontaneously conceived pregnancy with normal decidual cells (arrow). **C.** Villi from an ED pregnancy placenta. The stromal cellularity is increased by an infiltrate of mononuclear cells (arrow). **D.** Villi of a spontaneously conceived pregnancy placenta.

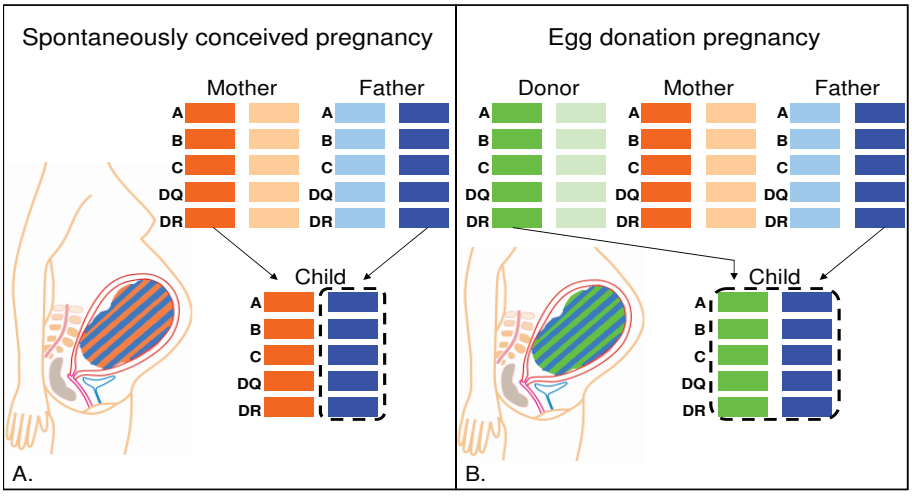

Figure 3 Schematic drawing of the inheritance of the most immunogenic HLA-antigens in a spontaneously conceived and an ED pregnancy. A. In a spontaneously conceived (or non donor IVF) pregnancy the child inherits antigens of the father and antigens of the mother. The 5 most immunogenic HLA antigens (HLA-A, -B, -C, -DR and -DQ) are depicted in orange 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 (dashed line). **B.** In an unrelated ED pregnancy no antigens from the mother are present in the fetus. The antigens of the donor are depicted in green 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 (dashed line).

substantially higher if compared to standard IVF pregnancies [34] and second trimester bleeding is higher if compared to the spontaneously conceived population (< 1%) [46]. It has been assumed that more bleeding complications are associated with multiple implantation sites and early fetal loss [47]. However, in ED cases in which only two oocytes per cycle are transferred, the frequency of bleeding still remains high [34]. Other explanations, such as endometrial preparation therapy, have been suggested, but a possible relationship between various steroid replacement regimens and first trimester bleeding is difficult to assess.

Long-term consequences

The study of the trafficking of intact fetal cells into the maternal circulation (fetal cell microchimerism) is relevant to ED pregnancies, because it is not yet known if these circulating fetal cells play a role in establishing or maintaining tolerance to the conceptus. This merits further investigation. Furthermore, the consequences of the persistence of foreign circulating fetal cells for the mother's long-term health are currently unknown. In one study, however, allogeneic male fetal cells were shown to persist for up to 9 years in the circulation of healthy post-partum women who conceived using egg donors and delivered male infants [48]. The implications of becoming microchimeric with an unmatched population of fetal progenitor cells are an area for future research.

ED conception is often hidden from the mother's and the baby's medical records, so correlations between ED and specific adverse outcomes are difficult to make. In approximately 40-50% of the cases the fact that it was an ED pregnancy is never disclosed to the child or other family members [49]. The literature search revealed no studies evaluating long-term effects of ED for the mother. Long-term outcome studies are therefore warranted [50].

Fetal and neonatal complications

In most studies that assessed the obstetrical outcome after ED relatively little has been reported on fetal and/or neonatal complications. Elevated risks (relative to the general population) are primarily related to the higher incidence of multiple gestation [6,51]. The incidence of intrauterine growth restriction is also not increased compared to the general population [34]. The incidence of preterm deliveries in ED singleton pregnancies (10.6%) is not increased if compared to the general population [34,35]. Significantly, there appears to be no effect of ED pregnancy (with or without PIH) on neonatal birth weight [18,34]. The general health status of children under 5 years old who were conceived using ED is at least as good as that of children conceived using standard IVF procedures [52]. There is also no increase in the incidence of congenital malformations in infants resulting from ED pregnancies [33,35].

Placental pathology

At the fetal-maternal interface significant histological and immunohistochemical differences are present when comparing ED and non donor IVF pregnancies. Characteristic pathologic findings in ED cases include a higher incidence of villitis of unknown etiology, chronic deciduitis, massive chronic intervillositis, maternal floor infarction, and ischemic changes, as seen with preeclampsia [53-55] (Figure 2). The chronic deciduitis observed in ED placentas is characterized by its severity and the presence of a dense, fibrinoid deposition in the basal plate. Furthermore, an increased infiltration of CD4+ T helper cells and CD56+ NK cells is present in the basal plate of ED placentas [55]. It is in the basal plate where extravillous trophoblast (of fetal origin) interfaces with and invades the maternal tissue. The extravillous trophoblast cells do not express classical Human Leukocyte Antigen (HLA) -A and HLA-B molecules, thereby preventing interaction with cytotoxic

T cells. However, they do express a unique combination of HLA antigens (HLA-C and the non-classical HLA-E and HLA-G) that interact with KIR receptors on uterine natural killer cells [56-58], although HLA-C can also serve as a target molecule for CD8+ T cells [59]. The striking findings of a dense fibroid deposition and mononuclear cell infiltration in the basal plate suggest that the placental abnormalities are related to an immune-mediated response that is more pronounced in ED pregnancies. The placental damage may be the consequence of a type of graft-versus-host disease and/or organ rejection type of reaction [55].

Immunologic aspects of egg donation pregnancies

Normal fetal-maternal immunology

A successful pregnancy is an interesting immunologic paradox. The fetus carries paternal and maternal genes but is not rejected by the maternal immune system, over a period of nine months (Figure 3). In spontaneously conceived gestations, several specific protective mechanisms have been postulated to explain the maternal tolerance of the fetus. Since the fetal tissue is directly exposed to the maternal blood, it is at risk of being attacked by components of both the innate and acquired immune system, with the potential risk of death. Therefore, to develop tolerance to the fetus, humans need an immune privileged site at the fetal-maternal interface in order to reproduce [60]. In spontaneously conceived pregnancies, immune recognition of the semi-allogeneic fetus takes place, but the soluble and cellular components of the maternal immune system are kept under control (or are locally down-regulated), leading to a maternal immune system that favours implantation of the embryo [61]. The currently accepted view is that a successful pregnancy depends on an appropriate balance of the different components of the maternal immune system, with predominance of T helper 2 immunity [62-65]. At the human fetal-maternal interface, maternal recognition of fetal antigens presented by trophoblast cells or by fetal cells trafficking into the maternal circulation, is essential for the induction of immunoregulatory mechanisms [66]. It is apparent that activated T cells at the maternal interface include regulatory T cells [66,67]. These regulatory T cells have an important role in the local down-regulation of human fetal-specific allogeneic T cell responses [68]. In studies of peripheral blood only minor differences in systemic immunoregulation were found between pregnant women and non-pregnant female controls (unpublished data). All of these protective mechanisms maintain the immunosuppressive environment in the pregnant uterus, and in this way the semi-allogeneic fetus is capable of surviving in the uterus.

Parallels with blood transfusions

The mechanism(s) involved in the effective down-regulation of the maternal immune response to the semi-allogeneic fetus can be compared to the ones involved in the tolerizing effect of pre-transplant blood transfusions. Blood transfusions have an immunomodulating effect, as demonstrated by the positive association of kidney graft survival and the number of allogeneic transfusions [69]. In addition, a beneficial effect of HLA-DR matched transfusions has been shown in kidney [70] and heart [71] transplantation. Furthermore, more HLA alloantibodies are formed after HLA mismatched transfusions compared with HLA-DR shared transfusions [72]. Down-regulation of the immune response may occur by the induction of regulatory CD4+ T cells, which are induced when the donor and recipient share at least one HLA-class II molecule [73]. This immunomodulating effect only occurs in case of semi-allogeneic or one HLA-DR shared blood transfusions. Blood transfusions that are fully HLA mismatched with the recipient lead to immunization, rather than tolerization of the patient.

Immune studies in egg donation

Although other mechanisms can be involved, it is likely that down-regulation of the maternal alloimmune response to the fetus in an ED pregnancy is far more difficult than in spontaneously conceived pregnancies with semi-allogeneic fetuses. Compared with spontaneously conceived pregnancies, there is a higher degree of antigenic dissimilarity in ED cases. If the 5 most immunogenic HLA antigens (HLA-A, -B, -C, -DR, and -DQ) are taken into consideration, the maximal number of mismatches in spontaneous conceived pregnancies would be 5. In ED pregnancies this could reach a maximum of 10 mismatches (Figure 3). Since ED pregnancies are characterized by more HLA mismatches, it is to be expected that a possible relationship between aspects of immune regulation and the number of HLA mismatches will become more apparent in ED pregnancies. In pregnant women who conceived by ED, an increased percentage of intracellular IFN-γ (Th1) and IL-4 (Th2) positive CD4+ T lymphocytes was found in peripheral blood compared with pregnant women after spontaneous conception [74]. This hyperactivation of Th1 and Th2 cells, induced by the allogeneic fetus, is specific for ED pregnancies. IFN-γ is also involved in spiral artery formation. Furthermore, the Th2 effect was more pronounced in ED pregnancies than in spontaneously conceived pregnancies [74]. This suggests that the additional mechanism of Th2 immunity in ED pregnancies leads to a successful pregnancy, even with a completely allogeneic fetus. Although this study investigated immune cells in the peripheral blood, the widely accepted view is that the active immune mechanisms take place at the fetal-maternal interface; therefore, it is possible that an effect will be even more prominent at this location. Recently, a statistically significant correlation between the extent of HLA mismatches and the percentage of CD4+CD25dim activated T cells in the decidua parietalis of uncomplicated pregnancies was described [75].

In spontaneously conceived pregnancies, the correlation between the number of amino acid triplet sequence (HLA epitope) mismatches between pregnant women and their children, and antibody production in the pregnant woman against the paternal antigens inherited by the child has been studied [76]. A positive correlation was found between the number of triplet mismatches (0-22) and the percentage of women producing HLA antibodies ($p<0.0001$). If 0 triplet mismatches were present, no antibodies were formed, even in the case of 1 or 2 classical HLA antigen mismatches. It remains to be established whether the actual number of HLA mismatches or epitope mismatches is more important in establishing tolerance to the fetus. However, it is likely that in ED pregnancies, the number of both HLA antigen and epitope mismatches will be even higher than in spontaneously conceived pregnancies. Therefore, the percentage of women producing antibodies will be higher, and this may have clinical implications. Although the clinical relevance of specific anti-fetal HLA antibodies is controversial, a recent study clearly showed that the presence of these antibodies in early pregnancy is associated with a reduced chance of a live birth (Nielsen *et al.*, 2010 unpublished).

The immune system clearly plays an important role in ED pregnancies. Unfortunately, there is a lack of information from the mother's perspective about the long-term effects of exposure to foreign cells and antigens in the recipient, since the usual clinical endpoint is the chance of having a take-home baby. From the literature it is unknown at present whether, later in life, the consequences of having conceived using ED may be harmful or not. In addition, when investigating immunologic aspects of ED pregnancies it is important to analyze the underlying reason why ED was necessary. For example, it is accepted that premature ovarian failure is a heterogeneous disorder in which some of the idiopathic forms are based on abnormal self-recognition by the immune system [77]. It is possible that the preexisting immunologic mechanisms involved in premature ovarian failure may contribute to the immunologic differences between ED and spontaneously conceived pregnancies.

Discussion

Although ED gives infertile women the opportunity to conceive, it may lead to harmful consequences during pregnancy if compared with spontaneously conceived pregnancies. This review gave an overview of the consequences of ED pregnancies with respect to their atypical fetal-maternal immunologic relationships. Review of the literature showed that women who conceived by ED have an increased risk of PIH [5,31-34,36-39,41], an increased rate of caesarean section deliveries [4,5,18,31-35], an increased risk of postpartum haemorrhage [33], and an increased risk of first trimester vaginal bleeding [6,31,34]. All of these complications can be the consequence of ED pregnancies; however other factors that correlate with infertility and age could also be an underlying cause. For example, women conceiving through ED are more often primigravidas, and more frequently have ovarian failure compared with women who conceive spontaneously. These factors are all associated with obstetrical complications [40]. More studies that correct for these confounding variables (e.g. maternal age, nulliparity, and ovarian failure) are needed to determine the specific role that ED plays in these important obstetrical complications. The higher risk of maternal morbidity in women who conceived through ED is a limitation of this form of treatment for infertility. For the benefits to outweigh the risks it might be important to select low risk donor-recipient combinations. The egg donors should be less than 35 years old [78] and unaffected by infectious diseases or hereditary syndromes [5,79]. Considering the immunologic mechanisms in ED, it might be worthwhile to perform HLA-typing of donor and recipient in order to select haplo-identical combinations that would be more comparable to spontaneously conceived pregnancies than fully HLA mismatched combinations.

Although the literature conclusively demonstrates an increased risk of ED-related pregnancy complications for the mother, it does not show an increased complication rate for the fetus or newborn [33,35,52]. Since there is a general lack of studies on the long-term outcome of ED pregnancies, it is currently unknown whether the child or mother experiences any consequences later in life. It is therefore important to document ED conception in the medical record to evaluate the subsequent consequences of carrying an allogeneic fetus. In ED pregnancy, the mother is exposed to foreign cells and antigens, a situation that is comparable to blood transfusions and organ transplantation. ED pregnancy leads to a hyperactivation of Th1 and Th2 cells compared to spontaneously conceived pregnancies [74]. This suggests that the allogeneic fetus induces an additional mechanism that leads to a successful pregnancy. It is possible that these mechanisms may have its consequences later in life. Therefore, long-term follow-up studies are strongly recommended.

Conclusions

ED provides a valuable addition to the list of treatment options for women who require assisted reproductive therapy. The benefits of having a take-home baby are counter-balanced by the higher risk of maternal morbidity. The increased rate of complications may be related to the allogeneic nature of the fetus. To understand the underlying mechanism(s) of acceptance of the allogeneic fetus, more research regarding the unique immunologic aspects of ED pregnancies is warranted. Understanding the role of the immune system in successful ED pregnancies also has broader biomedical significance in that it may also give insight into immune mechanisms leading to immunologic tolerance for HLA mismatched solid organ transplants.

Acknowledgements

The authors thank Stefan Willems for critically evaluating the microscope images shown in Figure 2, as well Fusun Gundogan, Drucilla Roberts, Ananth Karumanchi, Angela van Lochem and Tamara Tilburgs for their helpful discussion and critical insights on this topic. Funding is acknowledged from: MACROPA foundation, Leiden, the Netherlands and the Natalie V. Zucker Professorship fund at Tufts University School of Medicine.

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