# Killer-cell immunoglobulin-like receptor/human leukocyte antigen-C combination and 'great obstetrical syndromes' (Review)

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**Abstract.** Recurrent pregnancy loss (RPL), pre-eclampsia (PE), fetal growth restriction (FGR), and preterm delivery are examples of 'great obstetrical syndromes' (GOS). Placental dysfunction is the most common pathogenesis of GOS. In human pregnancies, the effects of uterine natural killer cells involve angiogenesis, promoting the remodeling of uterine spiral artery, and improving the invasion of trophoblast cells. The uNK cells supply killer immunoglobulin-like receptors (KIRs), which come into contact with human leukocyte antigen-C (HLA-C) ligands expressed by extravillous trophoblast cells (EVTs). Numerous studies have investigated the association between GOS and KIR/HLA-C combination. However, the outcomes have not been conclusive. The present review aimed to reveal the association between GOS and KIR/HLA-C combination to screen out high-risk pregnancies, strengthen the treatment of pregnancy complications, and reduce the frequency of adverse maternal and fetal outcomes. It has been reported that a female with a KIR AA genotype and a neonate with a paternal HLA-C2 molecule is more prone to develop GOS and have a small fetus since less cytokines were secreted by uNK cells. Conversely, the combination of KIR BB haplotype (including the activating KIR2DS1) and HLA-C2 can induce the production of cytokines and increase trophoblast invasion, leading to the birth of a large fetus. KIR/HLA-C combinations may be applicable in selecting third-party gametes or surrogates. Detection of maternal KIR genes and HLA-C molecules from the couple could serve as useful markers for predicting and diagnosing GOS.

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*Abbreviations:* RPL, recurrent pregnancy loss; PE, pre-eclampsia; FGR, fetal growth restriction; GOS, great obstetrical syndromes; EVT, extravillous trophoblast cell; KIR, killer immunoglobulin-like receptor; HLA-C, human leukocyte antigen-C; uNK cells, uterine natural killer cells; ADCC, antibody-dependent cell-mediated cytotoxicity; dNK cells, decidual NK cells; GM-CSF, granulocyte-macrophage colony-stimulating factor; Ang 1, angiopoietin 1; VEGF, vascular endothelial growth factor; TGF-β1, transforming growth factor-β1; ASRM, American Society for Reproductive Medicine; DET, double embryo transfer

*Key words:* KIR, HLA-C, recurrent pregnancy loss, pre-eclampsia, fetal growth restriction, great obstetrical syndromes

## Contents



## 1. Introduction

Nearly 10% of all global diseases are due to pregnancy complications (1). Recurrent pregnancy loss (RPL), pre-eclampsia (PE), fetal growth restriction (FGR), and preterm delivery are examples of 'great obstetrical syndromes' (GOS) (2). Placental dysfunction is the most common pathogenesis of GOS (3). The placenta starts to form once implantation begins. The extravillous trophoblast cells (EVTs) form the endometrium and move into the decidua. The process of decidualization requires the morphological and functional changes of uterine stromal cells and involvement of immune cells. Immune cells account for nearly 40% of the decidual cells (4). The immune cells located in the myometrium and decidua come into contact with EVT cells. The removal of immune cells from the area of implantation or impeding their signaling pathway could lead to miscarriages (5,6).

From the window of implantation to the first trimester, most immune cells at the maternal-fetal interface are uterine natural killer (uNK) cells (70%) (1). An increasing number of studies have focused on the importance uNK cells in preserving the pregnancy (7-9). In normal human pregnancies, the effects of uNK cells involve angiogenesis, promoting the remodeling of uterine spiral artery, and improving the invasion of trophoblast cells (10-13). Moreover, uNK cells supply killer immunoglobulin-like receptors (KIRs), which come into contact with human leukocyte antigen-C (HLA-C) ligands expressed by EVTs. The parents influence the HLA-C

genotypes in trophoblasts (14). Since KIR and HLA-C are both polymorphic, the bindings of KIR and HLA-C differ from one pregnancy to another. Numerous studies have investigated the association between GOS and KIR/HLA-C combination [for example, RPL (15-19), PE (20-23), and FGR (14)]. However, the outcomes have not been conclusive.

Studies have indicated the deficiency of activation as the reason for RPL, which is influenced by the improper binding of KIR/HLA-C (16.24,25). The KIR/HLA-C combination modulates the placental development physiologically. It contradicts the traditional idea that the mother has an immune defense response to the fetus (20). Specific KIR/HLA-C binding occurs between maternal NK cells and EVT cells in the decidua. This binding addresses activated tissue-remodeling issues occurring in implantation and placentation. The present review aimed to reveal the association between GOS and a combination of KIR/HLA-C, which may aid high-risk pregnancy screening, strengthen the treatment of pregnancy complications, and reduce the frequency of adverse maternal and fetal outcomes. Related articles were searched independently in PUBMED by two academics using the medical subject headings: 'KIR', 'HLA-C', 'recurrent pregnancy loss', 'recurrent miscarriages', 'pre-eclampsia', 'fetal growth restriction', or 'pregnancy'. All articles were published from January 2003 to November 2020 in English since there are few related articles published before 2003. If a relationship exists between the HLA-C haplotype and KIR, it may be useful to use the KIR genotype and HLA-C molecule to select gametes from donors with favorable combinations.

## 2. uNK cells and their receptors

During the first trimester of pregnancy, the decrease of trophoblast invasion and poor recasting of uterine spiral artery affect the blood flow in placenta, resulting in pregnancy loss. NK cells are vital for the placental formation and fetal development during implantation and the initial stage of pregnancy. NK cells contain CD16 markers, which mediate antibody-dependent cell-mediated cytotoxicity (ADCC). In general, $CD56^{dim}$ NK cells belong to $CD16^{+}$. $CD16^{+}CD56^{dim}$ NK cells have cytotoxicity, while $CD16^{-}CD56^{bright}$ NK cells exhibit immunomodulatory effects (26). Nearly 90% of uNK cells belong to the latter type. Hence, uNK cells do not harm the fetus (27). Numerous possibilities have been proposed about the origin of decidual NK (dNK) cells; i) peripheral NK cells flow into the uterus; ii) uterine stem cells differentiate into dNK cells; iii) from bone marrow; iv) endometrial NK cells in the lining form dNK cells by development and transformation (28). The dNK cells can produce numerous cytokines, such as granulocyte-macrophage colony-stimulating factor (GM-CSF), chemokine C motif ligand (XCL) 1, angiopoietin (Ang) 1, Ang 2, vascular endothelial growth factor (VEGF), transforming growth factor-β1 (TGF-β1), pleiotrophin and osteoglycin, which play essential roles in sustaining uterine blood flow and fetal development (10,13,29-32).

NK cell receptors include the immunoglobulin-like transcripts (LILRB), C-type lectin heterodimer family (CD94:NKGs) and KIRs (33). The inhibiting NKG2A and activated NKG2C receptors are classified under the family of CD94:NKGs, which could distinguish and combine with HLA-E (34). HLA-G can discern the inhibiting receptor LILRB1 (35). EVT cells supply class I HLA-C, non-classic HLA-G, and HLA-E antigens (36,37). However, only the polymorphic HLA-C ligands combine with KIRs expressed by uNK cells (33). The process of placentation is affected by KIRs and HLA-C allotypes (15).

## 3. NK education and KIR/HLA-C combination

Previously, studies involving mice (38) and humans (39-41) have indicated that NK cells may experience 'education' and 'licensing' with the combined specific KIR and cognate HLA-C allotypes to be effective. One likely scenario includes KIRs from the mother interacting with her own HLA-C allotypes during the growth of uNK cells, following this, 'educating' or 'licensing' the uNK cells of the mother and modifying the method of interaction with HLA-C allotypes of her child in the formation of the placenta (14,42). However, how dNK cells educate, license, or modulate in the uterus is yet to be established. Considering NK cell education experiments, it has been revealed that specific $CD56^{bright}$ NK cells react to interleukin (IL)-12 or IL-15, and the licensing function was not strong in resting NK cells, which implies that certain scenarios may neglect the licensing needs (39). The dNK cells exhibit an abundance of CD56 (43), and release receptors and respond to IL-15 (44). Evidently, invasive trophoblast cells are likely to increase the accumulation of dNK cells to the maternal-fetal interface via the production of different cytokines (13,45,46). Regarding the education mechanism of NK cells in the association between GOS and combined KIR/HLA-C, certain inhibiting KIRs and HLA-C molecules from the father may lead to pregnancy complications.

## 4. KIR family and HLA-C in pregnancy

The expression levels of KIR members partially influence the response of NK cells. The polymorphic KIRs include both activating and inhibitory receptors located on chromosome 19q13.4.11 in humans (47). KIRs are extraordinarily polymorphic, and the types of genes located in the KIR locus change prominently across different people and regions. The phenotype of dNK cells renders them more likely to express higher levels of KIRs specific for HLA-C molecules than what appears in peripheral blood for the same individual (48). For each pregnancy, the maternal KIR genes could be AA or Bx (47). KIR AA haplotype is short of the majority of activating KIRs, except KIR2DS4. However, the KIR Bx haplotype contains multiple activating KIRs (49,50). AB and BB haplotypes are both included in KIR Bx genotype (51). HLA-C molecules are ligands for KIRs, which are sorted into two types. HLA-C molecule with the C1 epitope (with asparagine at location 80) combines with inhibiting KIR2DL2 and KIR2DL3. However, HLA-C molecule with C2 epitope (with lysine at location 80) connects with inhibiting KIR2DL1 and activating KIR2DS1. C2 is a more potent ligand than C1 (52). Despite both HLA-C1 and HLA-C2 combining with KIR genes, the degree of the downstream uNK activity is fundamentally affected through C1 and C2 zygosity in a specific pregnancy (53).

The KIR genotype appears comparatively later during the growth of NK cells. These NK cells are induced by IL-15,

which is secreted by stromal cells to respond to progesterone in the uterus (38). The uNK cells may originate from the uterine progenitor cells instead of peripheral blood NK cells. Hence, the KIR gene is changeable through semaphores appearing in specific locations (54). The number of dNK cells during early pregnancy exhibits a higher percentage of NK cells delivering KIRs that can combine with HLA-C compared with the peripheral NK cells and with uNK cells that originated from the endometrium of non-pregnant females (55), implying that HLA-C molecules on EVTs may be crucial for NK cell education in the uterus.

Pregnancy is a unique physiological status, where the particular non-self HLA molecules of KIRs could encounter their cognate ligands. Polymorphic KIR/HLA-C binding has evolved partially due to birth pressures occurring with human evolution and the enlargement of brain tissues (42). Some bindings of KIR/HLA-C could be unfavorable for a normal pregnancy than others. Activating KIRs have protective effects during pregnancy complications, however, people with activating KIRs are susceptible to other autoimmune diseases (56). Insufficient activation of NK cells may cause adverse maternal and neonatal outcomes (57). If uNK cells gain an activating signal in a female having a KIR B haplotype (including KIR2DS1) and HLA-C2, the secretion of GM-CSF increases, which can enhance the ability of migration and invasion of trophoblast cells in cell lines (13).

## 5. KIR/HLA-C combination and GOS

*KIR/HLA-C combination and RPL*. RPL refers to the loss of embryos before twenty weeks of gestation in three or more pregnancies; however, the American Society for Reproductive Medicine (ASRM) defines it as two times or more (58). RPL is caused by numerous factors, such as chromosomal abnormalities, genetic factors (26), anatomical factors, endocrine abnormalities, and immune factors. Amidst these, the etiology of certain patients is unknown and may be related to autoimmune abnormalities. The correlation between KIR/HLA-C combination and RPL is listed in Table I, a few are inconsistent (14-17,19,25,26,59-65). Reportedly, RPL females had an elevated rate of maternal KIR AA haplotype and fetal HLA-C2 binding (14,15,60,66). However, other empirical results were different (16-19). A recent study reported a higher frequency of abortion after double embryo transfers (DETs) in KIR AA females compared with KIR AB or KIR BB (24). The genotype KIR AA has an inhibitory effect, indicating the essentialness of activation of uNK cells in early pregnancy. However, in a research from northern India, it was revealed that RPL females had an increased possibility of B haplotype rather than A haplotype (53). Likewise, it was reported that the KIR AA genotype has a protective effect on pregnant women (16). However, there were some shortcomings in this report; the sample size of the study was small (n=40), and the abortion group was defined as a single spontaneous abortion (16). Furthermore, Nowak *et al* (17) indicated that KIR AA and HLA-C1C2 females with HLA-C2C2 husbands had a higher probability of a normal pregnancy. Pregnancies with C1/C1 fetuses lead to a 2.5 times lower abortion rate relative to C2/C2 pregnancies (53). The higher rate of successful pregnancies of C1/C1 babies did not emerge when the transfer happened on an individual with a KIR B haplotype (53).

A few empirical studies have indicated that RPL females may lack proper KIR genes (e.g., KIR2DL1 and KIR2DL2) that can combine with HLA-C in trophoblast cells and transfer inhibitory signals for NK cell activity (59,60,67-71). Compared with the normal controls, the levels of KIR2DL1/S1 on $CD56^{+}CD16^{-}$ NK cells in the deciduae of RPL females were reduced (63). HLA-C1 is the ligand for KIR2DL2. Compared with healthy females, RPL patients exhibited higher KIR2DL2 and HLA-C2/C2 or HLA-C2/x combinations (65). Initially, the authors established that KIRs in partners could not directly result in a miscarriage; however, since the fetal KIR genotype is unclear, distributed fetal cells with potentially unfavorable KIRs can accelerate the ending course (65). It was recently reported that KIR2DL2-positive RPL females exhibited decreased molecules of HLA-C1 compared with KIR2DL2-negative RPL females ($P<0.05$) (26). Reduced ligands for inhibiting KIRs may cause inadequate inhibition of maternal uNK cells to the trophoblast, thus giving rise to RPL.

Some studies have revealed an apparent increase in the frequency of activating KIRs in RPL females (60-62,72). Patients with elevated activation of KIRs were nearly three times more susceptible to RPL (62). KIR2DS2 and KIR2DS3 are both activating KIRs, which are hazardous elements for RPL (73). The KIR genotypes in 205 RPL women and 224 normal subjects were analyzed (25). Accordingly, RPL patients had more activating KIRs than normal controls (25). Similar results were obtained in the Chinese Han population (61), the authors suggested that relative to fertile females, there was a lower rate of $C2^{+}$ HLA-C molecules in RPL women (61). Reportedly, an elevated rate of KIR2DS2 in HLA-C1 homozygous parents was associated with RPL (16). Consequently, the physiological reason underlying the high frequency of activating KIR genotypes could be attributed to an extensive scope of diverse activating KIR receptors making NK cells to discriminate more activation ligands, which originated from fetal cells. This causes an induced percentage of cytotoxic and apoptotic signals; these fight the inhibiting function of receptors against semiallogeneic fetuses at the maternal-fetal interface and end in abortion.

It has been suggested that KIR2DS1 assumes a critical role in pregnancy, mainly because activation of dNK cells through KIR2DS1 induces the production of soluble mediators, such as GM-CSF. Reportedly, GM-CSF has been confirmed to be useful for placentation and promoting fetal growth (74). Additionally, $C2^{+}$ HLA-C molecules were revealed to be more common among partners of $KIR2DS1^{+}$ women in the Caucasian population (64). One possible reason is that NK cell education may lead to the hypo-responsiveness of $KIR2DS1^{+}$ deciduae, and inhibit the positive effect of KIR2DS1 in a normal pregnancy. Since $C2^{+}$ HLA-C molecules are supposed to combine with KIR2DS1, it is hard to conclusively elucidate the potential function of activating KIR2DS1 in the absence of its ligand.

On the other hand, in the Brazilian population, there was no difference between KIR genes and susceptibility to RPL (19). Therefore, future studies on the functionality of KIRs and their ligands should include a higher sample size of RPL couples in a specific area compared with fertile controls

Table I. Experiments on the association between KIR/HLA-C combination and recurrent pregnancy loss.

| Nationality | Authors (Refs.) | Year of publication | Experimental group | Control group | Samples | Findings |
|---|---|---|---|---|---|---|
| Greek | Varla-Leftherioti *et al* (59) | 2003 | RPL couples (n=26) | Fertile couples (n=26) | Peripheral blood | RPL women had decreased inhibiting KIR genes |
| Brazilian Caucasian | Witt *et al* (19) | 2004 | RPL women (n=51) | Fertile women (n=55) | NA | KIR genes did not change between RPL patients and controls |
| Northern Irish | Flores *et al* (60) | 2007 | RPL couples (n=88) | Fertile couples (n=30) and healthy controls (n=139) | NA | RPL patients had decreased KIR2DL2; the KIR AA genotype was more common in RPL women |
| Chinese | Wang *et al* (61) | 2007 | RPL couples (n=73) | Healthy couples (n=68) | Peripheral blood | RPL patients had increased numbers of activating KIR genes including KIR2DS1 |
| European | Hiby *et al* (15) | 2008 | RPL women (n=95) and their partners (n=67) | Fertile women (n=269) | Peripheral blood | RPL women had a higher frequency of KIR AA haplotype and decreased KIR2DS1 |
| Indian | Faridi *et al* (25) | 2009 | RPL women (n=205) | Healthy women (n=224) | Peripheral blood | RPL patients had more activating KIR genes and they tended to be BB genotypes |
| South Brazilian Caucasian | Vargas *et al* (62) | 2009 | RPL couples (n=68) | Fertile couples (n=68) | Peripheral blood | Females having more activating KIR genes were three times more likely to develop RPL |
| European | Hiby *et al* (14) | 2010 | RPL women (n=115) and their partners (n=81) | Fertile couples (n=592) | Placental tissues and maternal blood | RPL patients were less frequent in women with a KIR B haplotype |
| Polish | Nowak *et al* (17) | 2011 | RPL couples (n=125) | Fertile couples (n=117) | Peripheral blood | Among KIR AA females who had HLA-C2C2 partners, HLA-C1C2 females tended to have a normal pregnancy |
| Turkish | Ozturk *et al* (16) | 2012 | RPL women (n=40) | Fertile women (n=90) | Peripheral blood | RPL patients tended to be KIR Bx genotypes |
| Chinese | Wang *et al* (63) | 2014 | RPL women (n=30) | Fertile women (n=30) | Decidual tissues | There was decreased frequency of $CD56^{+}$ $CD16^{-}$ natural killer cell staining for KIR2DL1/S1 and KIR2DL2/S2/L3 in RPL women |
| American | Dambaeva *et al* (64) | 2016 | RPL women (n=139) and their partners (n=42) | HLA-C controls: 1,070 North American Caucasian Population (n=1,070) KIR controls: American Caucasian population (n=255) | Peripheral blood | KIR2DS1-positive RPL females had increased HLA-C2 |
| Turkey | Elbaşı *et al* (65) | 2020 | RPL couples (n=25) | Healthy couples (n=39) | Peripheral blood | HLA-C2C2 were more common in RPL partners; KIR2DL5 gene was more common in RPL couples |
| Caucasian | Yang *et al* (26) | 2020 | RPL patients (n=160) and their partners (n=99) | HLA-C controls: 1,070 North American Caucasian Population (n=1,070) KIR controls: American Caucasian population (n=255) | Women: peripheral blood; Partners: buccal cells | KIR2DL2-positive RPL females had lower HLA-C1C1, and their partners had increased HLA-C2C2 compared with KIR2DL2 negative RPL patients |

NA, non-analyzed; KIR, killer-cell immunoglobulin-like receptor; HLA, human leukocyte antigen; RPL, recurrent pregnancy loss.

Table II. Experiments on the relationship between KIR/HLA-C combination and PE.

| Nationality | Authors (Refs.) | Year of publication | Experimental group | Control group | Samples | Findings |
|---|---|---|---|---|---|---|
| British | Hiby *et al* (20) | 2004 | PE patients and their fetuses (n=200) | Normal pregnant women and their fetuses (n=201) | Maternal blood, cord samples or neonatal mouth swabs | The female with an AA genotype and a fetus with the HLA-C2 molecule tended to have PE |
| British | Hiby *et al* (14) | 2010 | PE couples (n=742) and their fetuses (n=733) | Normal pregnant couples (n=592) and their fetuses (n=423) | Maternal blood, cord samples or neonatal mouth swabs | There was a higher PE incidence for females whose fetuses inherited another C2 from males |
| Mexican | Sanchez-Rodriguez *et al* (22) | 2011 | PE patients (n=9) | Normal pregnant women (n=10) | Decidual samples | There were more inhibitory KIRs in deciduae of PE patients than those in normal pregnancies |
| Ugandan | Nakimuli *et al* (21) | 2015 | PE patients (n=254) | Normal pregnant women (n=484) | Maternal blood, cord samples | KIR2DS5 on Cen-B of Africans protected pregnancies from PE |
| Chinese Han population | Long *et al* (79) | 2015 | PE patients (n=271) | Normal pregnant women (n=295) | Maternal blood | Reduced KIR activation was observed in PE women |
| British | Huhn *et al* (77) | 2018 | PE patients (n=693) | Normal pregnant women (n=679) | Maternal blood | KIR2DL1A was associated with increased PE risk |
| Danish | Larsen *et al* (84) | 2019 | Severe PE patients (n=259) | Normal pregnant women (n=259) | Maternal and neonatal blood | A relationship was not found between maternal KIR genotypes and HLA-C in the fetuses |
| Ethiopian | Kelemu *et al* (76) | 2020 | PE patients (n=131) | Normal pregnant women (n=157) | Maternal blood, cord samples | There was a significant association between KIR AA genotype and PE |

KIR, killer-cell immunoglobulin-like receptor; HLA, human leukocyte antigen; PE, pre-eclampsia.

in the same region. Preferably, genotyping of embryos should also be included.

*KIR/HLA-C combination and PE*. PE is a severe pregnancy complication; it is characterized by hypertension (≧140/90 mmHg) and proteinuria following twenty weeks of pregnancy. Additionally, the prevalence of PE is 5-8% (75). Since the invasion ability of the trophoblast is affected, inappropriate combinations of KIR/HLA-C are reasons that cause PE. Reportedly, if a woman carries the KIR AA genotype and her baby has HLA-C2 from the father, then the possibility of PE in the pregnancy was increased (20,76) (Table II). This is because KIR AA/HLA-C2 binding may lead to inadequate activation of uNK cells, affecting uterine artery recasting and leading to PE. Furthermore, Hiby *et al* (14) revealed a higher PE incidence for females whose fetuses inherited another C2 from males. For women with the KIR AA genotype, the pregnancy with fetal HLA-C1C1 is more prone to PE than that of HLA-C1C2 or HLA-C2C2. According to the NK education theory, maternal HLA-C2 molecules educate KIR2DL1$^+$ uNK cells to obtain functional properties during period of rest rather than during an immune response, and counteract the inhibitory input of fetal HLA-C2 molecules in pregnancy (14). A method for estimating KIR2DL1 allotypes coded by the diverse KIR genes has promoted the development of various anti-KIR antibodies and genotyping to indicate that KIR2DL1 on the KIR A instead of the KIR B haplotype is related to the higher probability of PE (77). Mexican researchers collected ten normal pregnant decidua tissues and nine PE decidua samples during cesarean section (22). It was revealed that there were more inhibitory KIRs in deciduae of PE patients than those in normal pregnancies (22). Due to the lack of activating KIRs, the activation signals cannot be provided concurrently. Thus, NK cells in these females exhibited a decreased physiological effect, without adequate support for placental development.

Reduced KIR activation was observed in PE women (78,79). In Europe and Ethiopia, the protective function of the maternal B haplotype is regulated by an activating C2 receptor, called KIR2DS1 (20,76,80). It stimulates uNK cells that increase the

angiogenesis and immune reaction, which induces a successful pregnancy (81). KIR2DS4 and KIR2DS5 exhibited protective effects from PE development in Caucasians and Africans, respectively (21,30,82). Clinically, in some patients, the resistance index of the uterine artery increased, which indicated poor uterine artery recasting, and the levels of KIR2DL/S1, 3, and 5 were simultaneously reduced on the portion of dNK cells (78). The change of blood flow in the uterine artery reflects the clinical application of combined KIR/HLA-C in PE (83). In a Chinese study with a large sample size, it was revealed that PE women exhibited decreased activating receptors, including KIR2DS2, KIR2DS3, and KIR2DS5 (83). Notably, the total number of activating KIRs in PE patients was less than that in controls (P=0.03) (83).

However, it has been established that Caucasian partners are more likely to have HLA-C2 molecules than Japanese men. Therefore, Japanese women having children with Caucasian partners are more likely to develop PE than those with Japanese men. Nevertheless, a previous study has reported a 1.54% chance of developing PE with a Caucasian partner, compared with 2.67% with a Japanese partner for a Japanese woman (78). A recent study in Denmark involved 259 patients with PE or eclampsia and 259 normal controls (84). Peripheral blood samples were obtained from both mothers and newborns (84). A relationship was not revealed between maternal KIR genotypes and HLA-C in the fetuses (84). Since the babies had additional HLA-C2 molecules compared with the mothers, there was no report of any difference in maternal KIR AA genotype between the experimental and control groups (84).

*KIR/HLA-C combination and FGR*. Hiby *et al* conducted a trial involving 118 FGR patients (fetal weight less than or equal to the 5th percentage) (14). Allegedly, the binding of maternal KIR AA genotype and fetal HLA-C2 was related to an induced possibility of developing FGR (14). This trend was consistent with PE previously discussed (14).

## 6. KIR/HLA-C combination and birth weight

Human birth weight is influenced by stable selection (42). Macrosomia may cause obstructive dystocia, shoulder dystocia, and postpartum hemorrhage, affecting maternal and neonatal health (42). Often, a fetus that is too small will find it difficult to survive (42). An abundance of research has indicated that this process is regulated by the KIR genotype and their relevant HLA-C ligands on invasive trophoblast cells (42). Females having a KIR AA genotype and a baby with a paternal HLA-C2 molecule have restrained production of cytokines by uNK cells, which results in delivering a small fetus (85). Since the combination of KIR2DS1 and HLA-C2 can induce cytokine production and promote trophoblast invasion, the female having a KIR2DS1 gene and an HLA-C2 baby tends to have a large fetus (74,86). If the fetus is HLA-C1C1, the function of maternal KIR is invalid, and this correlation does not exist (14,74), which is attributable to the strict peculiarity and obvious restraining granted by KIR2DL1/HLA-C2 bindings relative to the weaker KIR2DL2/3 bindings with HLA-C alleles (87). In summary, in the placentation region, all effects of HLA-C in pregnancy are regulated by paternal HLA-C2, and the maternal KIR genotype decides the size of the baby (Fig. 1).

There are significant differences in the trophoblasts of mice and human beings. Compared with human trophoblasts, the invasion of trophoblasts into deciduae is shallower in mice, and the mice do not express non-classical MHC (88). Murine NK receptors are part of the Ly49 family of receptors. In the mice experiment, when the additional MHC molecule H-2D$^d$ was added, the vessel remodeling ability was decreased, compared with the same type of mice deficient only for H-2D$^d$ (89). H-2D$^d$ combines with the inhibitory receptor Ly49A and can suppress additional uNK cells. Noticeably, regardless of whether there was an H-2D$^d$ molecule from the father or not, the fetal growth was affected. According to these results, some bindings of maternal NK receptors and paternal (or maternal) MHC molecules could affect trophoblast invasion and vascular recasting in mice. Therefore, it can be concluded that in both human and mice, the over inhibition of the function of uNK cells could result in fetal weight loss.

## 7. Future study directions

There are potentially critical clinical applications in these empirical studies. Considering the RPL woman with a KIR AA haplotype, the HLA-C molecules of the female and her partner are usable as a basis for selecting the donor egg or sperm. According to the epidemiology, donors homogeneous for HLA-C1 are considered to be safe; meanwhile, C2/C2 partners or oocyte donors may be harmful (14,90,91). HLA-C and the KIR genotype are applicable in selecting third-party gametes or surrogates (53). Subsequently, these immunological indicators can be detected through laboratory tests, which can be adopted to predict pregnancy outcomes. By detecting the KIR genotype and HLA-C molecule, the possible ligands can be inferred. The optimal binding will cause activation of uNK cells and angiogenesis in placentation, leading to a normal pregnancy. Females having an improper binding may experience difficulties during their pregnancies. The functionalities of these novel immune reactions have caused renewed comprehension of how to protect the fetus and may be useful to estimate and treat GOS. Detection of KIR genes in GOS patients could potentially assume a vital role in diagnosing the alloimmune etiology in these diseases. Studies conducted on a large-scale, employing modified statistical model sets, including the quantitative maternal-fetal genotype experiment, called a linear mixed-effect model (86), would enhance pregnancy outcomes. It entails statistically entering the KIR copy number from the SNP genotype (92) or utilizing a full-length transcript Smart-seq2 data (93).

Nevertheless, certain scholars claim that more conclusiveness is needed before clinical application despite the indications pointing towards credible evidence (94). For example, the binding of the KIR AA genotype and fetal HLA-C2 exists in roughly 10% of Caucasian pregnant females, making them twice as likely to have PE as normal women. Despite elevating the risk, there is a weak clinical application in this association. The only way to use this data predictively is to combine it with other clinical risk factors and serological indicators. KIR gene expression is highly polymorphic, and

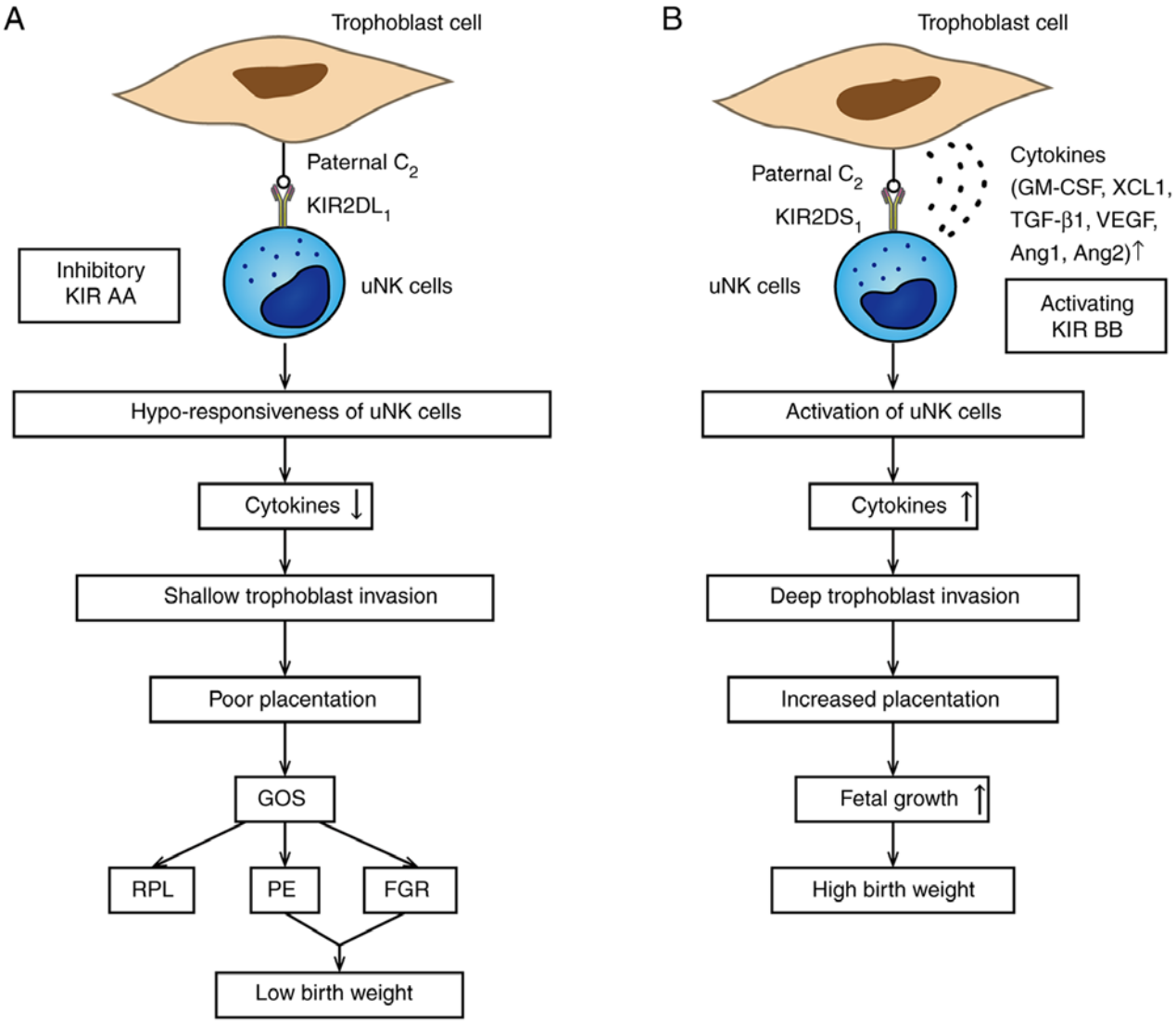


Figure 1. Association between KIR/HLA-C combination and birth weight. (A) In this situation, the neonate inherits an HLA-C2 molecule from the father. The mother is KIR AA genotype; KIR2DL1 strongly combines to trophoblast HLA-C2 alleles leading to hypo-responsiveness of uNK cells, which is related to the poor placentation and leads to low birth weight in GOS. (B) Binding of KIR2DS1/HLA-C2 is associated with high birth weight. The KIR BB haplotype includes the activating KIR2DS1. Once this happens, uNK cells are activated to secrete plenty of cytokines, such as GM-CSF, which could enhance the placentation and lead to higher birth weight. KIR, killer-cell immunoglobulin-like receptor; HLA, human leukocyte antigen; uNK, uterine natural killer; GOS, great obstetrical syndromes; RPL, recurrent pregnancy loss; PE, preeclampsia; FGR, fetal growth restriction; GM-CSF, granulocyte-macrophage colony-stimulating factor; XCL1, chemokine C motif ligand 1; TGF-β1, transforming growth factor-β1; VEGF, vascular endothelial growth factor; Ang 1, angiopoietin 1.

other factors that can regulate NK cells. Moreover, there are numerous ligands for activating receptors, and the mechanism of modulating NK cells is not clearly outlined. Furthermore, the exact manner of KIR/HLA-C combination in regulating NK cell education has not been established. Therefore, novel technologies are useful to distinguish the complex diversity of KIR and HLA-C. Sophisticated laboratory experiments can help determine the specific role of NK cells. Currently, studies detecting the function of uNK cells *in vitro* have not been conducted. The function of uNK cells can only be determined indirectly by detecting some cytokines, which are generally used to detect the functionality of peripheral blood NK cells. Mouse models can help understand the function of uNK cells. Some transgenic mice containing specific KIR and HLA-C molecules can help study the effect of distinct binding modes *in vivo*.

## 8. Conclusion

Medawar's theory states that immune cells in peripheral blood and the uterus need to be suppressed to form a successful pregnancy (95). However, KIR genotypes and HLA-C molecules reexamine the conditions for a successful pregnancy. Sufficient activation of uNK cells is crucial to maintain a normal pregnancy. Emphasis should be given on solving the following problems: Adopting accurate methods to determine KIR genotypes (e.g., by high-throughput genotyping), conforming with uniform clinical inclusion criteria, understanding the interaction between EVT and uNK cells. Moreover, the interaction between KIR/HLA-C and GOS should be studied by targeting women in a specific region since it is difficult to compare studies in different areas. Thus, a large sample-sized research in the same region, having a comparable control population, accurate detection of maternal

KIRs, and both parents and fetal HLA-C molecules may determine the function of KIR and HLA-C in GOS.

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**Authors' contributions**

XY and TM conceived the study, performed the literature search and analyzed the data. XY wrote the manuscript. TM revised the work for important intellectual content. XY and TM confirm the authenticity of all the raw data. Both authors read and approved the final manuscript.

**Ethics approval and consent to participate**

Not applicable.

**Patient consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

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