Discover Immunity

Perspective

Immunological harmony: the dynamic influence of cellular and humoral immunity on pregnancy success

Manoj Kumar Pandey[1,2]

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Abstract
This study is a crucial step in understanding the dynamics of the maternal immune response directed at paternal human leukocyte antigen (HLA) molecules. HLA molecules are proteins on cell surfaces that play a critical role in immune system regulation. Our findings focus on the pivotal role of maternal antibodies targeting fetal HLA molecules in inhibiting antigen-induced activation of uterine immune cells, which is essential for successful pregnancies. Antibodies are proteins produced by the immune system that recognize and neutralize foreign substances. The primary focus is to unravel maternal anti-fetal rejection by drawing parallels to transplant rejection and emphasizing the role of allorecognition—the process by which an individual's immune system recognizes and responds to antigens from another individual of the same species—in both cellular (involving immune cells) and humoral (involving antibodies) refusal. Although exploring anti-HLA antibodies in preventing fetal loss in patients with recurrent spontaneous abortion is captivating, there are still significant knowledge gaps that need to be addressed. Further studies are imperative to reveal the precise mechanism by which these antibodies generate and prevent maternal immune responses, critical determinants of pregnancy outcomes. It is vital to investigate the specificity of these antibodies and whether they exclusively target specific HLA molecules on trophoblasts (cells forming the outer layer of a blastocyst, providing nutrients to the embryo). This review paper not only offers insights into the development of these protective antibodies in pregnancy but also lays the foundation for future research on therapeutic implications, particularly in cases of recurrent spontaneous abortion.

Keywords Pregnancy · Abortion · Therapeutic targets

1 Introduction

Pregnancy introduces a unique challenge to the maternal immune system as it encounters the fetus, typically considered "semi-foreign" due to the presence of paternal antigens alongside maternal antigens [1, 2]. The success of pregnancy hinges on the sophisticated balance between maternal immune tolerance to the semi-allogeneic fetus and the defense mechanisms guarding against fetal loss. Rather than dismissing paternal antigens, a complex interplay of regulatory mechanisms unfolds, shielding the fetal allograft from rejection [3]. This narrative investigates the development and potential failure of these mechanisms, particularly focusing on the formation of antibodies to paternal human leukocyte antigen (HLA). These antibodies play a crucial role in maintaining normal pregnancy by preventing maternal immune cells from attacking the fetus. However, in patients with recurrent spontaneous abortion

✉ Manoj Kumar Pandey, manoj.pandey@cchmc.org | [1]Division of Human Genetics, Cincinnati Children's Hospital Medical Center, 3333 Burnet Avenue, Cincinnati, OH 45229-3026, USA. [2]Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH 45267-0515, USA.

(RSA), the formation of anti-HLA antibodies can become dysregulated, leading to an adverse immune response that triggers fetal loss [4–6].

RSA is defined by the loss of three or more consecutive pregnancies before 20-28 weeks of gestation, affecting approximately 2.5% of women attempting to conceive [6–9]. The risk increases with maternal age and history of RSA elevates the risk for subsequent occurrences [10]. Chromosomal abnormalities contribute to 50-85% of RSA cases, underscoring their significant role [11, 12]. Other contributing factors include autoantibodies such as antiphospholipid antibodies, anti-thyroid antibodies, antinuclear antibodies, anti-transglutaminase antibodies, and anti-endomysial antibodies, as well as smoking, caffeine intake, contraceptive drug use hormonal problems, abnormal glucose metabolism, stress, and depression [13–22].

The elusive etiology of RSA remains unknown in over half of cases, but the deficiency of antibodies to paternal HLA molecules has been observed, suggesting their role in maintaining healthy pregnancies [5, 23–29]. Paternal cell immunization, akin to methods dampening organ allograft rejection, emerges as a hopeful therapeutic avenue. This approach aims to instill tolerance to paternal antigens, orchestrating the suppression of allogeneic immune reactions and fostering immune tolerance to the growing fetus. Clinical trials and preclinical studies demonstrated promising results, not only improving pregnancy outcomes but also reducing abortion rates in RSA patients [5, 25].

In the landscape of pregnancy success and recurrent pregnancy loss, anti-HLA antibodies stand as an ideal, offering a promising therapeutic strategy against allogeneic immune responses contributing to abortion. This paper serves as a current and insightful update on the impactful role of the critical HLA molecules, steering the course toward controlling adverse immune reactions that precipitate fetal loss in resilient women grappling with RSA.

1.1 Embarking on the odyssey of fetal development: a chronicle of marvels in human pregnancy

The immunology governing fetal survival during pregnancy remains a profound paradox, and deciphering this mystery requires understanding the intricate interplay between embryonic developmental events and fundamental immunological mechanisms.

Pregnancy unfolds as a series of events, encompassing fertilization, implantation, embryonic and fetal growth, culminating in birth after approximately 266 days or later (the gestation period), which is divided into the first, second and third trimesters [30]. The initial gestational period, particularly the first trimester is particularly critical, marked by a underlying cascade of events that shape the outcome of the pregnancy [31].

1.2 Conception chronicles: showing the details of fertilization in human reproduction

Fertilization is a complex process wherein the genetic material from spermatozoa and ovum converges into a single nucleus. Despite the introduction of approximately 300 to 500 million sperm cells into the vagina, less than 1% manage to reach the secondary oocyte. Normally occurring in the uterine (Fallopian) tube about 12 to 24 hours after ovulation, fertilization is a precise event. Sperm undergo maturation in the epididymis, becoming capable of fertilizing an oocyte after spending around 10 hours in the female reproductive tract [32, 33].

During fertilization, only one spermatozoon penetrates and enters a secondary oocyte (Fig. 1A) a process termed syngamy [34]. This event induces depolarization, triggering the release of calcium ions inside the cell [33]. These calcium ions stimulate the release of granules by the oocyte, promoting changes that block the entry of other sperm and prevent polyspermy [35].

Once a spermatozoon has entered a secondary oocyte, equatorial division (meiosis II) is completed. This division results in a larger ovum (mature egg) and a smaller second polar body that fragments and disintegrates. The tail is shed, and the nucleus in the head develops into a structure known as the male pronucleus. Simultaneously, the nucleus of the ovum develops into a female pronucleus. Upon the formation of pronuclei, they fuse to create a segmentation nucleus containing 23 chromosomes (n) from the male pronucleus and 23 chromosomes (n) from the female pronucleus. This fusion restores the diploid number (2n), and the fertilized ovum, now a zygote (Fig. 1B), comprises a segmented nucleus, cytoplasm, and zona pellucida [33, 36].

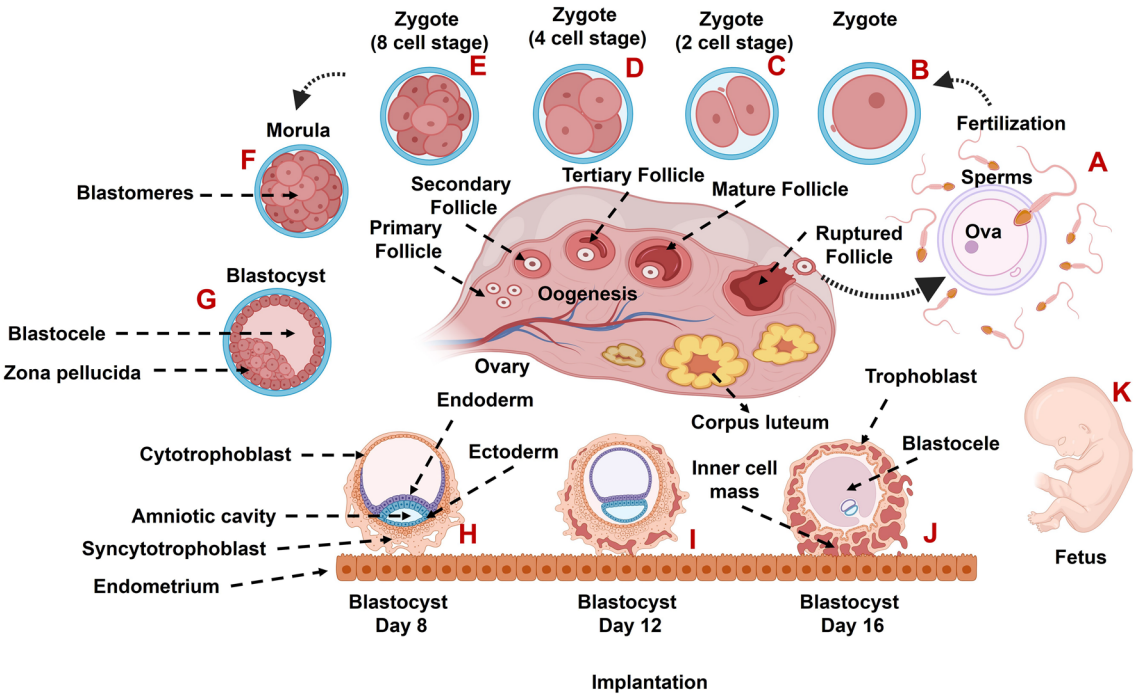

Fig. 1 Sequential events from fertilization to implantation in human pregnancy. A Fertilization: Illustrates the convergence of genetic material from spermatozoa and ovum into a single nucleus, resulting in the formation of a zygote. The process includes syngamy, equatorial division (meiosis II), and the formation of male and female pronuclei. **B**–**G** Development of Blastocyst: Demonstrates the progression from zygote to blastocyst through rapid mitotic cell divisions. The stages include the formation of blastomeres, the development of the morula, and the transformation into a blastocyst with an outer trophoblast, inner cell mass, and blastocoel. **H**–**K** Implantation: Depicts the process of blastocyst attachment to the uterine wall. The disintegration of the zona pellucida, development of syncytiotrophoblast and cytotrophoblast, and enzymatic penetration into the endometrium are highlighted. The blastocyst becomes embedded in the endometrium, with the trophoblast contributing to placental development

1.3 Blossoming potential: the enigmatic journey of blastocyst development in early embryogenesis

On the fifth day after fertilization, the zygote undergoes rapid mitotic cell divisions, leading to an increase in the number of cells. However, the size of the embryo does not enlarge, as it remains confined within the zona pellucida. The first cleavage is accomplished within approximately 36 hours, with subsequent divisions taking slightly less time. By the second day post-fertilization, the second cleavage is completed, resulting in 2, 4, 8, and 16 cells (Fig. 1C–F). These progressively smaller cells, formed through cleavage, are referred to as blastomeres [33].

Successive cleavages give rise to a solid mass of cells, still enveloped by the zona pellucida, known as the Morula (Fig. 1F). A few days after fertilization, the morula reaches a size like that of the original zygote. By the end of the fourth day, the number of cells in the morula increases, and it progresses along the uterine (Fallopian) tubes toward the uterine cavity [37]. Around four and a half to five days post-fertilization, the dense cell clusters transform into a hollow ball of cells, entering the uterine cavity and now referred to as a blastocyst (Fig. 1G). The blastocyst comprises an outer covering of cells called the trophoblast, an inner cell mass (embryoblast), and an internal fluid-filled cavity known as the blastocoel [33, 38]

1.4 Nesting perfection: decoding the enigmatic ballet of implantation in human reproduction

Implantation is a critical step in the initial stages of pregnancy, marking the attachment of the fertilized egg to the lining of the uterus. This process typically occurs around six to ten days after fertilization, just as the blastocyst, a ball of cells resulting from the transformation of the morula into the blastocyst, consisting of two main cell types, i.e., the inner cell mass and the outer layer known as the trophoblast. The blastocyst, now with the differentiated trophoblast, undergoes implantation into the endometrial lining of the uterus [39–41]. As the blastocyst burrows into the endometrial tissue,

trophoblast undergoes differentiation into two layers: the cytotrophoblast and the syncytiotrophoblast [39–41] indicated in the Fig. 1H, I, and J.

. The cytotrophoblast is a layer of individual, undifferentiated cells closest to the inner cell mass and serve as the stem cells of the placenta and differentiate into the other two types of trophoblasts, namely syncytiotrophoblasts and extravillous trophoblast [39, 40, 42, 43]. The syncytiotrophoblast expands and facilitates nutrient and gas exchange between maternal and fetal circulations, while extravillous trophoblasts act as a barrier between maternal blood vessels and the embryo, enabling exchange of gases, nutrients, and waste products [44–47]. As pregnancy advances, extravillous trophoblasts differentiate into endovascular and interstitial trophoblasts, contributing to placental structure formation and growth of the fetus [42, 44–49]. In essence, implantation is a remarkable example of the complex and finely orchestrated series of events that occur during the initial stages of pregnancy. It lays the groundwork for the subsequent development of the placenta and the maturation of the embryo into a fully formed fetus (Fig. 1K)

1.5 Unlocking genetic identity: human leukocyte antigen system operation in pregnancy

The successful formation of the placenta and embryo during pregnancy presents a unique immunological challenge due to the fetus being a semi-allograft, inheriting half of its genes from the father, which differ from those of the mother [50–52]. This genetic disparity, particularly evident in the human leukocyte antigen (HLA) genes, poses a significant obstacle to maternal immune tolerance, as the maternal immune system typically recognizes and eliminates foreign tissues [53].

Despite defying traditional transplantation principles, the embryo remarkably survives within the potentially hostile maternal immune environment [54, 55]. The HLA gene, which is the human equivalent of the major histocompatibility complex (MHC), was first identified in mice as a genetic locus associated with organ transplant acceptance or rejection. In humans, Jean Dausset and Jan van Rood described this genetic system in 1954, naming it the HLA [56].

Comprising more than 200 genes located on short arm of chromosome 6, the HLA system is recognized as the most polymorphic genetic system in humans [57–59]. It consists of three groups known as Class I, II, and III [60–67]. Risk alleles associated with pregnancy failure predominantly involve HLA I and HLA II [63, 68–76].

1.6 HLA-class I: orchestrating immune vigilance in pregnancy

The HLA I gene is categorized into classical HLA Ia and non-classical HLA Ib. HLA Ia includes HLA A, B, and C, while HLA Ib comprises HLA E, F, and G [77–80]. HLA Ia encodes HLA A, B, and C molecules, consisting of a glycosylated heavy chain with α1, α2, and α3 domains, and a light chain composed of β2 macroglobulinprotein [81]. HLA Ib encodes HLA E, F, and G molecules. The HLAI molecule's α chain has a transmembrane domain facilitating association with the cell membrane, determining antigenic specificities. The molecular weights of the α chain and β2 macroglobulin protein are approximately 45 kDa and 12 kDa, respectively. They are expressed on the membrane surface in a non-covalently bound state [82]. HLA I-encoded proteins are expressed on nearly all nucleated cells and platelets, presenting peptides from endogenous proteins of virus-infected or tumor cells. These peptides bind to the peptide-binding cleft of HLAI proteins, presenting them on CD8+ T cells [83–85]. Classical HLA Ia molecules (A and B) are exclusively found on fetal tissues, while HLA C is present on both trophoblast and placenta (Table1). Certain HLA I alleles, such as HLAC1 C1 and HLA C2C2, have shown an increased proportion in patients with RSA compared to control women [75]. Non-classical HLA-Ib molecules (E, F, and G) are detected on both trophoblast and placenta (Table1). In contrast to HLA-Ia, HLA-Ib molecules demonstrate reduced polymorphisms and diminished cell surface expression [86, 87].

The extravillous trophoblast, integral to the success of pregnancy, is characterized by the lack of expression of HLA-II molecules, while prominently expressing HLA-Ia, (e.g., HLA-C) and HLA-Ib molecules, such as HLA-E, HLA-F, and HLA-G. (Table1). Notably, the upregulation of HLA Class I molecules in the placenta is observed in villitis, an inflammatory condition associated with miscarriage and stillbirth [88, 89]. Studies have also underscored the essential interaction between HLA-Ib molecules and NK cells in promoting pregnancy success [63, 76, 77, 87, 90–96]. This raises the intriguing possibility that the differential expression of HLA-Ib compared to HLA-Ia could play a distinct role in the mechanisms underlying pregnancy loss. Exploring this nuanced interplay between HLA-Ib expression and immune regulation in the placental environment may uncover new insights into the etiology of pregnancy complications and inform innovative therapeutic strategies.

Table 1 Presence of HLA molecules on embryo and fetus

	Cytotrophoblast	Syncytio-trophoblast,	Extravillous trophoblast		Placenta	Fetal tissue	References
			Endovascular trophoblast	Interstitial trophoblast			
HLA-A		–	–	–		S +	[63, 97]
HLA-B		–	–	–		S +	[63, 97]
HLA-C	IC +	IC +	S +	S +	S +	S +	[63, 76, 97–101]
HLA E	SI-ICs +	SI-ICs +	SI-ICs +	SI-ICs +	SI-ICs +	S +	[63, 97, 102, 103]
HLAF	SI-ICs +	SI-ICs +	SI-ICs +				[76, 104–106]
HLAG	SI-ICs +	SI-ICs +	SI-ICs +			S –	[63, 76, 77, 97, 104, 107]
HLADP						S +	[63]
HLADQ						S +	[63]
HLADR			–			S +	[63, 97]

S, Surface expression, IC, Intracellular expression, S-ICs, Surface and intracellular expression, + positive expression, –, no expression

1.7 HLA-class II: simplifying immune complexity in pregnancy

HLA-Class II genes play a vital role in regulating immune responses during pregnancy. These genes, including HLA DRA1, DQA1, DPA1, DQB1, and DPB1, encode a variety of HLA DR, DP, and DQ proteins [84, 108, 109]. Among these, HLA DRA1, DQA1, and DPA1 encode the α chain, while HLA DRB1, DRB3, DRB4, DRB5, DQB1, and DPB1 encode the β chain. HLA DRA1 forms heterodimers with HLA DRB1, DRB3, DRB4, or DRB5, whereas HLA DQA1 and DPA1 are associated respectively with HLA DQB1 and DPB1 [110–112].

HLA DR is classified into five distinct groups: DR1, DR51, DR52, DR53, and DR8, based on antigen groups. While the DR1 and DR8 groups exclusively consist of DRB1, the DR51, DR52, and DR53 groups include DRB1 along with additional expressions of DRB5, DRB3, and DRB4, attributed to DRB1 gene duplication [113–116]. The primary function of HLA-Class II proteins lies in processing and presenting peptides derived from exogenous antigens to $CD4^+$ T cells [108, 117–119]. Initial analyses of HLA-Class II began with the discovery of HLA-D via the mixed lymphocyte culture test, followed by the identification of HLA-DR and HLA-DQ through subsequent test [120–122]. Studies have shown that patients with RSA exhibit an increased proportion of specific HLA alleles, such as HLA DQA105/B102, HLA DQA10505, HLA DQ2, HLA DQ8, HLA-DRB103, and HLA-DRB107, compared to control subjects [68–74].

Unlike HLA Class I molecules, HLA Class II molecules have not been observed on the trophoblast and placenta. However, their presence has been documented in fetal tissues (Table 1) indicating a potential connection between HLA-Class I and HLA-Class II risk alleles and pregnancy failure. Nevertheless, the mechanisms driving HLA sensitization during pregnancy are primarily associated with fetal cell trafficking, feto-maternal hemorrhage, organ transplantation, and blood transfusion [123–129]. Further research is imperative to unravel the complexities of HLA sensitization and its impact on maternal–fetal immune tolerance.

1.8 HLA function in defeating the cellular ballet in graft rejection

HLA-induced cellular immune responses play a pivotal role in graft rejection, particularly in transplant scenarios where both donor-derived and recipient-derived immune cells are implicated. This includes CD4+ T cells, CD8+ T cells, myeloid-derived suppressor cells, neutrophils, and natural killer cells, collectively contributing to allograft rejection [130–137].

There are mainly three pathways characterizing the interaction between donor and recipient cells. In the direct pathway, donor-derived antigen-presenting cells (APCs) directly present donor antigens via HLA to recipient-derived $CD4^+$ T/ $CD8^+$T cells [138]. The indirect pathway involves recipient APCs processing donor antigen and presenting specific molecules through their HLA to recipient derived $CD4^+$ T/ $CD8^+$T cells [139]. The semi-direct pathway, intriguingly, utilizes non-processed donor antigens through recipient APCs HLAII and recipient-derived CD4+ T cells [140]. These pathways lead to the activation of alloantigen-specific $CD4^+$T/ $CD8^+$ T cells, recognizing alloantigen through HLA II and CD4 TCR or HLA I and CD8 TCR [137–146].

HLA I-mediated antigen presentation involves the processing of peptides derived from endogenous proteins, which happens through peptide-binding cleft of HLA I proteins and their presentation on CD8+ T cells. These peptides are typically 8 to 11 amino acids in length. In contrast, HLA II-mediated antigen presentation involves the processing of non-self-peptides derived from exogenous proteins, which happens through peptide-binding cleft of HLA II proteins and their presentation on $CD4^+$ T cells. The peptides binding to the peptide-binding cleft of HLA II-encoded proteins are longer, approximately 15 to 30 amino acids [83–85, 147–151].

Notably, primary villous trophoblast cells do not express HLA I or HLA II molecules, suggesting that $CD4^+$ and $CD8^+$ T cells may not engage with the placental barrier, providing a highly effective mechanism for protecting the placenta from harm [97, 152]. Extra villous trophoblasts express HLA C, E, F, and G, but not HLA A, B, and DR molecules (Table-1). Furthermore, interaction between decidual HLA E and maternal CD8+ T cells has been observed [153]. Antigen presentation by HLA I-$CD8^+$ T cells pathway causes the activation of $CD8^+$ T cells and resulting massive release of cytotoxic granules containing perforin or granzymes, which lead to the lysis of virus-infected cells, cancer cells, and non-self-cells while preventing the growth of non-autologous cells [83–85, 147–151]. It is proposed that extra villous trophoblasts expressing HLAI molecules (e.g., C, G, E, and F) may utilize endogenous antigens, activating maternal CD8+ T cell effector functions, potentially leading to adverse pregnancy outcomes.

Conversely, the polymorphic nature of HLA C categorizes it into two allotypes, HLA C1 and HLA C2. Corresponding receptors expressed on decidual natural killer cells (dNKCs), termed killer cell immunoglobulin receptors (KIRs), comprise inhibitory receptors (KIR2DL2 or KIR2DL3 specific for HLA C1 and KIR2DL1 specific for HLA C2) and activating receptors (KIR2DS1 specific for HLA C2) [100, 154]. The interplay of KIR inhibitory receptors with HLA-C is crucial for dNK cells to recognize and tolerate fetal antigens, while the absence of appropriate activation mediated by KIR activating receptors may result in increased interferon-gamma (IFN γ) production. This dysregulation in dNK cell function is pivotal in inducing adverse pregnancy outcomes such as RSA and preeclampsia [76, 155–157]. Additionally, besides HLA C, trophoblasts also express HLA E, F and G (Table 1) These findings suggest that the interaction of KIR inhibitory receptors with certain HLAI molecules (e.g., C, E, F, and G) could skew immune responses towards a tolerogenic rather than an immunogenic response.

The activation process of CD4+ T cells rely on three pivotal signals. First, the antigen-specific signal is conveyed through the T cell antigen receptor (TCR), which interacts with peptide-HLA class II complexes present on the surface of antigen-presenting cells. Second, the co-stimulatory signal, which is antigen nonspecific, emerges from the interaction between co-stimulatory molecules (e.g., CD80 and CD86) expressed on APCs. Third, the establishment of the third signal occurs through the interaction of stimulatory molecules (e.g., CD28/CD40L) on $CD4^+$ T cells with TCR/CD40 present on antigen-presenting cells [158, 159]. This cellular activation leads to the differentiation of CD4+ T cells into distinct types of effectors $CD4^+$ T cells T helper 1 (Th1), Th2, Th17, T regulatory (Treg), and T follicular helper (Tfh) cells, each associated with signature cytokines [160–163]. These T helper cell subsets, along with their respective cytokines such as interferon-gamma (IFNγ; Th1), interleukin 4 (IL4; Th2), IL17 (Th17), transforming growth factor-beta (TGFβ; Treg), and IL6 (Tfh), contribute to tissue inflammation in various visceral and brain diseases [164–170].

Th1 cells produce IFNγ, IL2, and tumor necrosis factor-alpha (TNFα) to combat intracellular pathogens and evoke cell-mediated immunity. On the other hand, Th2 cells produce IL4, IL5, and IL13 to eliminate extracellular organisms and trigger robust allergic responses. Notably, Th17 cell differentiation, unlike Th1 and Th2, does not require IL17 but is critically dependent on TGFβ and IL6 [148, 160, 171–176]. Treg cells, on the other hand, produce IL10 and TGFβ, promoting immune tolerance and inhibiting IFNγ synthesis. They also play a role in blocking the differentiation of naïve T cells into effector T cells, contributing to immune homeostasis. Additionally, T helper cell subsets have the capacity to produce IL-10, a cytokine with broad immunoregulatory properties [177, 178]. These findings suggest that systemic differentiation and cytokine production by $CD4^+$ T cells contribute to the complex orchestration of immune responses and immune regulation in various physiological and pathological contexts.

Multiparous women, including blood donors, showed heightened mismatching with paternal/fetal HLA I and II alleles (e.g., HLA A, B, C, E, F, G, DQ, and DR), leading to increased pregnancy success [25, 179–187]. Studies indicate that patients with RSA exhibit a higher proportion of specific HLA alleles (e.g., HLA DQA105/B102, HLA-DQA10505, HLA DQ2, HLA DQ8, HLA-DRB103, and HLA-DRB1*07) compared to control women [68–74]. In addition altered infiltration of decidual APCs, (e.g., dendritic cells, and macrophages), NK cells, B cells, and T cells as well as their effector Th1, Th2, Th17, and Treg cytokines have been linked to both pregnancy success and adverse pregnancy outcomes, encompassing RSA, preterm birth and pre-eclampsia [22, 188–211].

Th1 cells are associated with pro-inflammatory responses, producing cytokines like IFN γ [212–215]. In the context of pregnancy, an overactive Th1 response can pose a threat by promoting inflammation and potentially leading to fetal rejection [216–221]. On the other hand, Th2 cells are recognized for their anti-inflammatory nature, producing cytokines

such as IL4, IL5, and IL13 [222, 223]. A balanced TH2 response is crucial for fostering an environment conducive to implantation and maintaining pregnancy [216, 218–220, 224]. Th17 cells, known for generating pro-inflammatory cytokines like IL-17, contribute to tissue inflammation and the defense against pathogens [214, 215, 225, 226]. However, an exaggerated Th17 response may contribute to adverse pregnancy outcomes by promoting inflammation and tissue damage [192, 195, 227]. T reg cells suppres immune responses and help prevent the immune system from attacking fetal tissues [228–231]. Insufficient T reg cell activity can result in immune-mediated complications during pregnancy [195, 227].

Overall, the delicate interplay of these T-helper cell subsets is vital for a successful pregnancy. Imbalances, such as an excessive Th1 or Th17 response or inadequate T reg cell function, can contribute to conditions like RSA or preeclampsia. Understanding the critical network of these T-cell subsets and their effector functions provides insights into the immunological complexities of pregnancy.

Many of the immune regulatory and inflammatory molecules found in the circulation of women with normal pregnancy and RSA play critical roles in protecting against fetal loss triggered by various infectious agents. This protection is particularly important as trophoblast cells, expressing exclusively HLAI molecules, can face direct lysis through interaction with maternal $CD8^+$ T cells. Future research in this area should explore the specific interactions between different HLAI molecules (such as HLAC, E, F, and G) and $CD8^+$ T cells. Understanding these interactions will illuminate how they contribute to immune responses at the maternal-fetal interface, emphasizing the precise balance necessary for ensuring a healthy and successful pregnancy.

1.9 HLA operates humoral immune responses

The role of HLA-induced humoral immune responses is critical in the context of organ transplantation. When there are mismatches in HLA alleles between the donor and recipient, it can initiate the production of donor-specific anti-HLA antibodies, ultimately leading to organ rejection [232, 233]. In the indirect pathway, B cells play a crucial role by presenting processed alloantigens to $CD4^+$ T cells in a manner restricted by self-HLA. This interaction serves as the catalyst for initiating humoral allo-immunity. Consequently, this activation process triggers responses in both $CD4^+$ T cells and B cells, ultimately leading to the formation of long-lived plasma cells [234–237]. The presence of donor-specific anti-HLA antibodies, particularly in large quantities, poses significant concerns due to their profound impact on transplantation outcomes. These antibodies can manifest categorically as acute or chronic reactions, which exhibit clear pathological distinctions in kidney and liver transplantation settings [238–240].

However, in heart, lung, pancreas, and small bowel transplantation, universally articulated differential definitions are lacking, despite the presence of diagnostic criteria for antibody-mediated reactions. [241, 242]. Generally, class I donor-specific antibodies are pivotal in crossmatch positive transplantation, while de novo class II donor-specific antibodies significantly influence long-term graft loss post-transplantation [243, 244].

In theory, HLA II antigens are generally limited in abundance across most graft tissues, except for endothelial cells, smooth muscle cells, and certain APCs, whereas class I antigens exhibit widespread expression. As a result, HLA I donor-specific antibodies offer numerous targets, while those for HLA II donor-specific antibodies are comparatively fewer, with antibody-mediated reactions primarily influenced by the presence of HLA I donor-specific antibodies.

Nevertheless, the expression of HLA II antigens in pre-transplant tissues varies based on circulating cells, and the initial presence of HLA II antigens may impact transplantation outcomes [245]. Conversely, in cases of persistent tissue injury from rejection, infection, or drug toxicity, there may be an up-regulation of HLA II antigens, rendering them susceptible targets for HLAII donor-specific antibodies [246–249]. Antibody-mediated reactions mediated by class II donor-specific antigens seem to present a persistent and substantial burden on graft function in kidney, liver, heart, and lung transplants, compared to rejection due to class I donor-specific antibodies [243, 250–252].

Multiparous women, encompassing both blood donors and individuals in the first, second, and third trimesters, as well as the postpartum period, exhibited elevated mismatching when compared to paternal/fetal HLA class I alleles (e.g., HLA A, B, C, E, F, and G) and HLA class II alleles (e.g., HLA DQ and DR). This enhanced mismatching was associated with an increased development of corresponding IgG antibodies targeting HLA class I and II molecules and the pregnancy success [25, 179–187].

Notably, patients with RSA, experiencing consecutive spontaneous abortions of unknown origin, demonstrated a significantly increased frequency of shared HLA alleles (A, B, C and DQ/DRi) with their spouses compared to control women [69, 70, 253–262] The development of IgG antibodies to HLA I molecules (e.g., A and B) has been noted in the first, second, and third trimesters, whereas IgG antibodies to HLA II molecules (e.g., DQ and DR) show an increase only in

the third trimester [182–187, 262, 263]. Conversely, patients with RSA, compared to normal pregnant women, exhibit a marked reduction in IgG antibodies against several specified HLA I and II molecules [25, 253, 254, 261–267].

Studies have demonstrated the positive impact of immunotherapy using paternal lymphocytes on pregnancy success in patients with RSA [24, 268–275].These therapies have been shown to stimulate the production of antibodies against paternal HLA I and HLA II molecules, thereby contributing significantly to successful pregnancies in RSA patients [4–6, 27, 253, 261, 276–280]. Overall, the efficacy of immunotherapy with paternal lymphocytes is well-supported by extensive research, which emphasizes the beneficial immune responses that these treatments elicit. Specifically, the increased production of anti-paternal HLA antibodies is a key factor in promoting immune tolerance and enhancing pregnancy outcomes in women with RSA. However, it is important to note that while most studies report positive effects, a few have failed to detect significant benefits [281–283]. These studies, however, did not assess the development of anti-HLA antibodies, which is a critical component of the therapeutic mechanism.

This disparity underscores the need for comprehensive evaluation criteria in future research. By incorporating the measurement of all classes of anti-HLA antibody development, we can gain a more accurate understanding of the effectiveness of immunotherapy with paternal lymphocytes. Continued investigation in this area holds the promise of refining therapeutic approaches and improving pregnancy success rates for patients with RSA.

The human fetus produces IgM and IgA antibodies [284–286]. IgM, the initial antibody class generated by B lymphocytes, displays reduced specificity and antigen affinity [287]. Upon encountering antigens, B lymphocytes switch from IgM to IgG, an immunoglobulin with diverse effector functions in human health and disease [285, 288, 289]. Interestingly, the fetus does not produce its own IgG antibodies [285, 288, 289]. Studies have demonstrated the development of CD8 T follicular cells, which acquire CD4 T follicular helper (Tfh)-like functionality termed as CD8 T follicular like cells (CD8TFLCs). These cells produce Tfh effector cytokines and co-receptors, promoting B cell antibody class switching [290–293]. In vitro addition of purified IgG (from normal pregnant women or paternal lymphocyte-immunized patients with RSA) in a lymphocyte proliferation assay resulted in reduced cell proliferation [294]. This suggests the involvement of maternal CD8TFLCs and the fetal HLAIa/b axis in inducing maternal B cell activation and trans differentiation to plasma B cells, resulting in the development of IgG antibodies to fetal HLA I molecules. These antibodies serve to protect against cytotoxic CD8 T cell-mediated fetal damage during pregnancy.

However, the precise mechanism underlying the development of IgG antibodies to specific paternal HLAI molecules in women with normal pregnancy and lymphocyte-immunized patients with RSA remains poorly defined. Further investigation is crucial to elucidate the nature of the fetal antigen and its specificity for distinct HLAI molecules expressed on trophoblast cells. It is imperative to determine whether IgG antibodies developed against these specific HLAI molecules belong to IgG1, IgG2, IgG3, or IgG4 subclasses. Additionally, identifying which isotype optimally inhibits the interaction between fetal-specific HLAI molecules and maternal $CD8^+$ T cells, as well as the resulting effector functions that determine pregnancy success or failure, is essential.

Further studies aimed at elucidating the specific mechanisms underlying antibody production against distinct paternal HLAI molecules, as well as identifying and developing specific HLAI molecule targets, could significantly enhance the clinical relevance of this research. This focused approach is essential for bridging current knowledge gaps and maximizing the impact of these findings.

This deeper understanding not only enriches our comprehension of the immunological factors that influence pregnancy outcomes but also lays the groundwork for potential therapeutic interventions designed to modulate immune responses at the maternal-fetal interface. These advancements are crucial for maintaining the delicate balance required for a healthy and successful pregnancy.

2 Discussion

Pregnancy immunology suggests the fetus as a semi-allograft, an entity tolerated during pregnancy [1, 3, 295–304]. In transplantation, significant differences in donor and recipient HLA antigens may trigger T cell recognition of the donor's HLA molecules as foreign, initiating an immune response leading to the production of anti-HLA IgG antibodies. HLA II molecules, presenting peptides to CD4+ T cells, can similarly induce T cell activation and antibody production, leading to organ rejection [123, 235, 238, 305–307].

In the context of pregnancy, increased matching between maternal and paternal HLA can prevent the development of IgG antibodies to paternal HLA molecules. This situation enhances the interaction between maternal T cells and paternal HLA molecules, resulting in increased processing and presentation of endogenous/exogeneous antigens and the

generation of pro-inflammatory cytokines, leading to fetal loss in patients with RSA [25, 253, 254, 262–267]. Conversely, when maternal and paternal HLA significantly differ, maternal T cells recognize the paternal HLA molecules as foreign, prompting massive production of IgG antibodies to these HLA molecules. These antibodies block the paternal HLA molecules, inhibiting maternal CD8+T cell-induced cellular activation and secretion of cytolytic mediators, perforin, and granule serine proteases (granzymes), and protecting against fetal rejection in normal pregnancy [308, 309]. Additionally, immunization with paternal lymphocytes in RSA patients has shown increased IgG antibody development to paternal HLA molecules, restoring T cell effector function, and protecting against fetal loss [27–29, 261, 270, 276–281, 310–317]. While such immunization has demonstrated promising results in enhancing pregnancy success rates among women with RSA [4–6, 24, 27, 253, 261, 268–280], a conscientious review of the studies is warranted.

Based on the exclusive presence of HLA I molecules (e.g., HLA C, E, F, and G) on trophoblasts (Table 1) and the discovery of CD8 T follicular cytotoxic cells (CD8TFLCs), which can promote T cell-dependent differentiation of plasma cells and antibody class-switching [290–293], we propose an additional layer to our understanding. This evidence suggests that a decrease in maternal-paternal HLA molecule matching specifically triggers the activation of the HLAI-CD8TFLCs axis. This activation leads to B cell plasmacytosis and the massive production of IgG antibodies against paternal HLAI molecules in early pregnancy. These antibodies play a crucial role in inhibiting the expression of HLAI molecules on trophoblast cells, thereby preventing maternal $CD8^+$ cytotoxic T cells from targeting and inducing cell death in trophoblast cells through the secretion of cytolytic mediators such as perforin and granule serine proteases (granzymes). This proposed mechanism points out a potential pathway contributing to the success of pregnancy (Fig. 2A–G).

Conversely, increased maternal-paternal HLAI matching suppresses the development of maternal IgG antibodies against paternal HLAI a and b molecules, i.e., HLA- C, E, F. and G in early pregnancy. This scenario increases antigen processing through indicated HLAI molecules on trophoblast cells and their presentation to maternal $CD8^+$ T cells. Such antigen processing activates $CD8^+$ T cells, differentiating them into effector $CD8^+$ T cells (Cytotoxic T cells). These cells directly target trophoblast cells, inducing cell death through the secretion of cytolytic mediators, perforin, and granule serine proteases (granzymes). This cascade contributes to fetal loss in recurrent spontaneous patients (Fig. 3A–E).

This study proposes an added layer to our understanding of paternal lymphocyte immunization-induced processing and presentation of fetal antigens by HLAI molecules on trophoblast cells to maternal $CD8^+$ T cells. This leads to

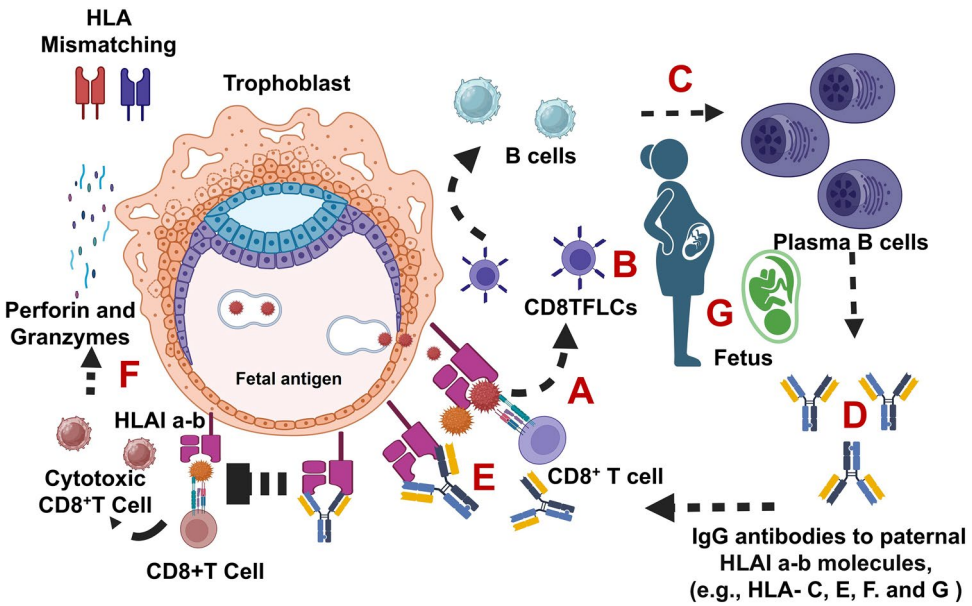

Fig. 2 The crucial role of decreased matching between maternal and paternal HLAI on trophoblast cells in initiating a successful pregnancy. A Reduced matching prompts the process and presentation of fetal antigens to maternal $CD8^+$ T cells. **B** This antigen processing leads to the differentiation of $CD8^+$ T cells into CD8T follicular-like cells (CD8TFLCs). **C** These cells interact with maternal B cells, resulting in the formation of plasma B cells. **D** Plasma B cells generate IgG antibodies to paternal HLAI a and b molecules, i.e., HLA- C, E, F and G (**E**). These antibodies effectively block paternal HLAI a and b molecules, preventing the interaction between maternal $CD8^+$ T cells and trophoblast cells. (**F**, **G**) This blockade inhibits the HLAI–$CD8^+$T cell interaction mediated formation of cytotoxic $CD8^+$ T cells and the production of fetal-damaging cytolytic mediators, (e.g., perforin and granzymes), ultimately protecting trophoblast cells from apoptosis and contributing to the success of pregnancy, ensuring the delivery of a healthy fetus

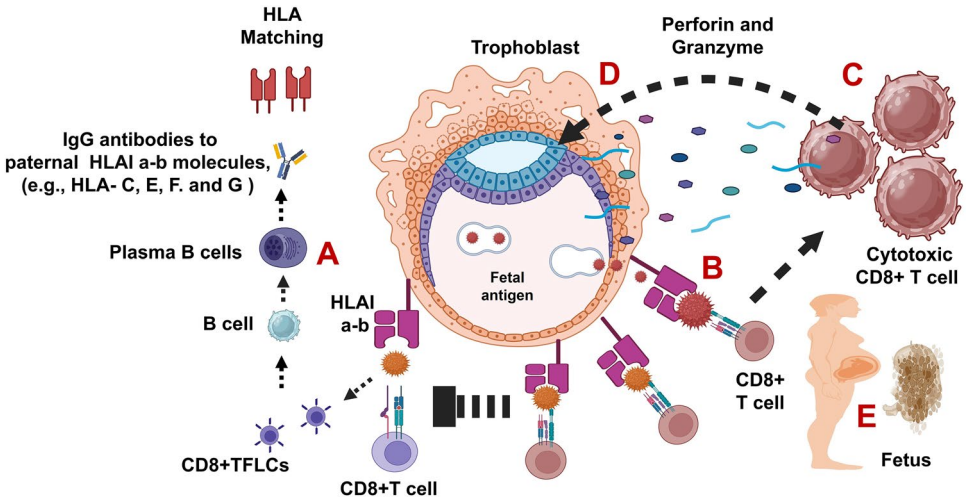

Fig. 3 The impact of increased matching between maternal and paternal HLAI on trophoblast cells, leading to fetal loss in women with recurrent spontaneous abortion. A Increased matching hinders maternal $CD8^+$ T cell-mediated processing of fetal HLAI molecules, preventing $CD8^+$ T cell differentiation into CD8T follicular-like cells (CD8TFLCs). This, in turn, impacts maternal B cell activation, inhibiting the formation of plasma B cells and the production of IgG antibodies specific to paternal HLAI molecules. **B** The deficiency or absence of these specific maternal IgG antibodies to binding to HLAI molecules on trophoblast cells intensifies antigen processing and presentation to maternal $CD8^+$ T cells. **C** Antigen processing activates $CD8^+$ T cells, differentiating them into cytotoxic $CD8^+$ T cells. **D** These cells directly target trophoblast cells, inducing cell death through the secretion of cytolytic mediators, perforin, and granule serine proteases (granzymes). **E** This cascade contributes to fetal loss in recurrent spontaneous patients

the development of CD8TFLCs, fostering B cell activation, differentiation of plasma cells, and IgG antibody production targeting paternal HLAI molecules. These antibodies prevent the interaction between maternal naïve $CD8^+$ T cells and paternal HLAI molecules on trophoblast cells, inhibiting $CD8^+$ T cell activation, cytolytic mediator production, and promoting trophoblast cell survival, contributing to the success of pregnancy (Fig. 4A–G).

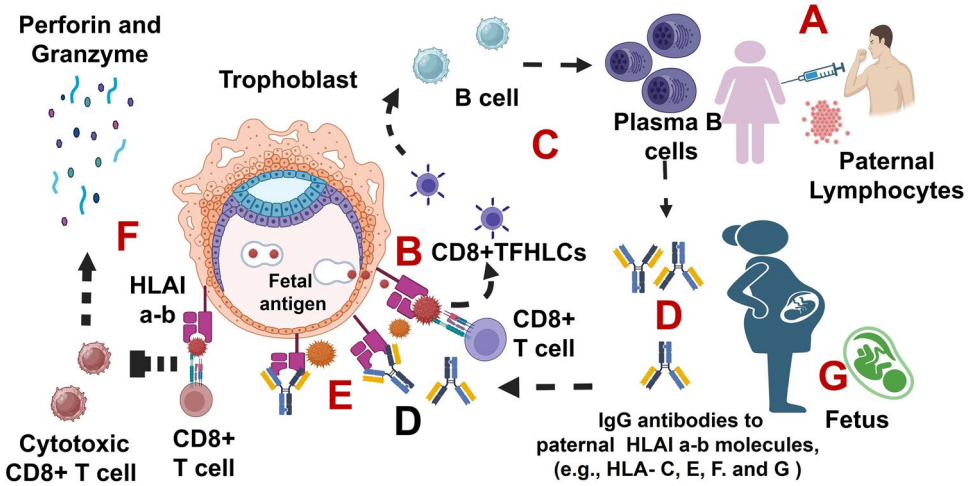

Fig. 4 The potential therapeutic approach of enhancing anti-paternal HLAI IgG antibodies through paternal lymphocyte immunization for promoting successful pregnancy. A Paternal lymphocytes, isolated from the peripheral blood mononuclear cells of the male partner, are administered to the female partner. **B** The injected cells facilitate the process and presentation of fetal antigens by HLAI molecules on trophoblast cells to maternal $CD8^+$ T cells. **C** Antigen processing leads to the differentiation of T cells into $CD8^+$ T follicular-like cells (CD8TFLCs), fostering interaction with maternal B cells and the formation of plasma B cells. **D** Plasma B cells generate IgG antibodies to paternal HLAI a and b molecules, i.e., HLA-C, E, F. and G. **E** These antibodies target indicated paternal HLAI molecules on the trophoblast cell surface. **F** This blockade prevents the interaction between maternal naïve $CD8^+$ T cells and paternal HLAI a and b molecules on trophoblast cells, inhibiting $CD8^+$ T cell activation and the production of cytolytic mediators, such as perforin and granzymes. **G** Consequently, this protective mechanism promotes the survival of trophoblast cells, contributing to the success of pregnancy and the delivery of a healthy fetus

The maternal immune response during pregnancy is influenced by several additional factors, including immune metabolic adaptations, hormonal changes, and the impact of the maternal microbiome [318–323]. A groundbreaking study has investigated into the complexities of immune tolerance during pregnancy, revealing critical elements such as Treg cells, trophoblast HLA interactions affecting T, NK, and NKT cell activity, tryptophan metabolism, T cell apoptosis, galectins, glycodelin co-stimulatory molecules, and mixed lymphocyte blocking factors (MLR-Bf) [4–6, 22, 25, 26, 63, 76, 77, 87, 91–96, 98, 104, 294, 300, 324–335]. These findings underscore the complex web of interactions shaping immune dynamics in pregnancy, highlighting avenues for further exploration and potential therapeutic interventions.

3 Conclusion

While our current review paper primarily investigates the dynamics of HLA matching between maternal and fetal molecules and its role in the development of IgG antibodies to fetal HLAI molecules, the implications extend significantly to various pregnancy-related complications. These include conditions such as preeclampsia, gestational diabetes, villitis, and preterm labor, all of which are linked to inflammation and pregnancy failure [88, 336–338]. However, investigating the role of specific IgG antibodies to HLAI molecules in sustaining successful pregnancies and protecting against fetal loss in RSA patients is a complex and intriguing research area.

However, exploring the role of specific IgG antibodies to HLAI molecules in sustaining successful pregnancies and protecting against fetal loss in RSA patients remains a complex and intriguing research area.

Further studies focusing on the specific mechanisms, antibody targets, and broader therapeutic implications are essential to uncover how the axis involving HLAI-CD8TFLCs mediates the development of IgG antibodies to specific paternal HLAI molecules. This research could potentially shield the fetus from maternal immune responses in women with normal pregnancy and in response to lymphocyte immunization in RSA patients. Addressing these aspects through future studies will contribute to a more comprehensive understanding of the immune processes involved in maternal-fetal interactions. This deeper understanding holds the potential to advance diagnostic and therapeutic strategies aimed at maintaining successful pregnancies and addressing RSA, thereby advancing knowledge in this crucial field.

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Author contributions MKP has authored the manuscript, from conceptualization to meticulous preparation, thorough literature review, and creation of figures, ensuring clarity and coherence. MKP has been responsible for editing, refining, and guaranteeing the manuscript adheres to high academic standards before finalization.

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Declarations

Competing interests The authors declare no competing interest related to the present work.

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