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REVIEW

Are innate lymphoid cells friend or foe in human pregnancy?

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Abstract

Innate lymphoid cells (ILCs) are involved in the innate immune system because they lack specific antigen receptors and lineage markers. ILCs also display phenotypic and characteristic features of adaptive immune cells. Therefore, ILCs are functional in essential interactions between adaptive and innate immunity. ILCs are found in both lymphoid and nonlymphoid tissues and migrate to the area of inflammation during the inflammatory process. ILCs respond to pathogens by producing a variety of cytokines and are involved in the barrier defense of antigens and in many immunological processes such as allergic events. Recent research has shown that ILCs are functional during human pregnancy and have been suggested to be essential for the healthy progression of pregnancy. In this review, we focus on the role of ILCs in human pregnancy by discussing the relationship between ILCs and the pregnancy microenvironment, specifically summarizing the role of ILCs in physiological and pathological pregnancies.

KEYWORDS
adaptive immunity, cytokines, innate immunity, innate lymphoid cells, pregnancy, transcription factors

1 | INTRODUCTION

ILCs are the newly described innate immune cells. ILCs are derived from common lymphoid progenitors (CLP) such as B and T lymphocytes. Typically, All ILC populations have classic lymphoid cell morphology. Because they lack the expression of cell surface molecules that identify other immune cell types, they are described as cell lineage marker negative (Lin-) cells.[1–7] Furthermore, they lack the expression of specific antigen receptors generated by elements of the recombination activating gene (RAG) and are therefore involved in the innate immune system.[8–10] ILCs respond to pathogens by producing effector cytokines and also provide a bridge between the innate and adaptive immune system. There are different classifications of ILC populations in the literature. First, in 2013, they were classified into Group 1 (including NK cells), Group 2, and Group 3 ILC.[11] Second, depending on their killing ability, ILCs were divided into cytotoxic ILCs (NK cells) and noncytotoxic ILCs (ILC1, ILC2 and ILC3).[12] Finally, in 2018, they were classified into NK cells, ILC1, ILC2, ILC3 and LTi cells[13] (Figure 1). NK cells, ILC1, ILC2 and ILC3 are capable of producing $CD8^+$ cytotoxic T cells, CD4+ T helper (Th) cells Th1, Th2 and Th17 related cytokines respectively. These cells are found in almost all tissues, particularly on mucosal and barrier surfaces. ILCs are tissue-resident innate lymphocytes. However, they have the ability to migrate and perform their functions in the region where they migrate. All ILCs except NK cells express CD127. However, since many $CD16^-CD56^{bright}$ NK cells express CD127, CD127 may not be a specific marker for ILCs. These subsets of ILCs are crucial in defending the epithelial barriers in the mucosa during homeostasis or after an infectious or inflammatory challenge.[11–13]

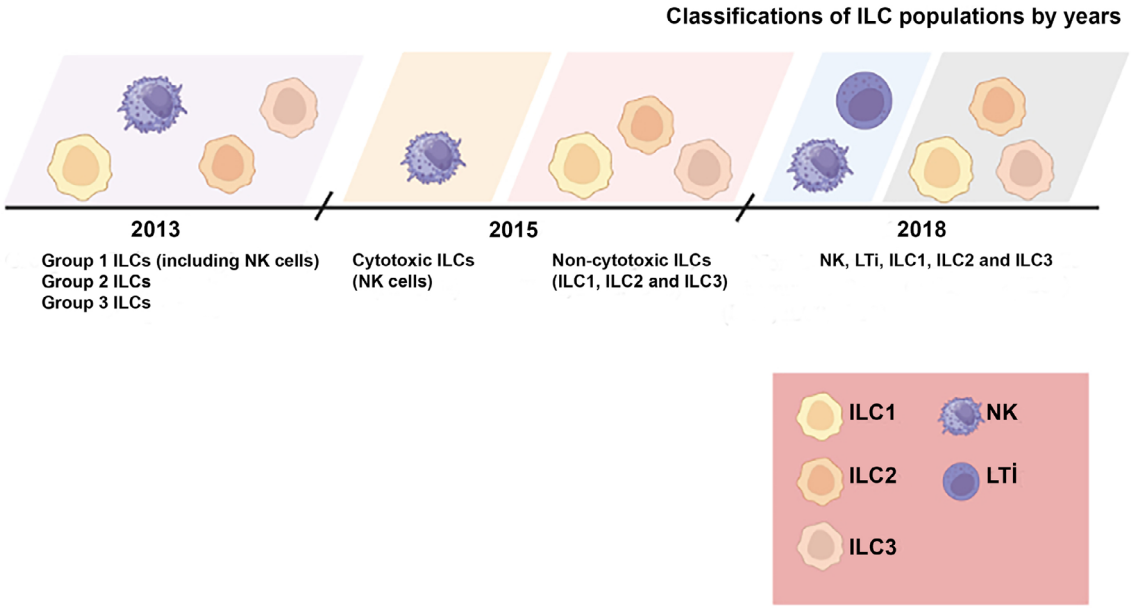

FIGURE 1 Different classifications of ILC populations according to years in the literature. The figure was created by BIORENDER.

2 | ALL ASPECTS OF INNATE LYMPHOID CELLS AND THEIR CLASSIFICATION

2.1 | Group 1 innate lymphoid cells (gILC1)

Group 1 ILCs have two subpopulations: ILC1s and NK cells. ILC1s and NK cells produce IFNγ and TNF stimulated with IL-12, IL-15 and IL-18 are involved in the immune response against intracellular pathogens and viruses. They express transcription factor T-bet (encoded by TBX21). T-bet is necessary for ILC1 development. NK cells and a proportion of ILC1s express transcription factor EOMES and have cytotoxic properties.[14–17] ILC1s develop in the absence of EOMES. Therefore, ILCs and NK cells have distinct developmental pathways. NK cells are cytotoxic cells and secrete high levels of cytotoxic molecules such as perforin and granzyme to kill virus-infected cells and tumor cells. ILC1s, another member of gILC1, are generally noncytotoxic or weakly cytotoxic. A study showed that a proportion of ILC1 displayed cytotoxic functions [15]. Although ILC1s are primarily tissue-resident cells, NK cells are mainly found in the bloodstream, make up a smaller population of circulating lymphocytes, and can migrate to inflammation sites rapidly. ILC1s are primarily present in many tissues such as tonsils, gut, lungs, liver, adipose tissue, skin, lymph nodes, and spleen. Two main ILC1 subsets have been detected in the human and mice gut: intraepithelial ILC1s (ieILC1s) and lamina propria (LP ILC1s).[18–20] Intraepithelial ILC1s (ieILC1s) were first identified in tonsils and in the epithelial layer of the gut. They were identified to be CD56+ CD127- NKp44+ CD103+ CD49a cells. Moreover, these cells express transcription factors T-bet and EOMES and produce IFNγ stimulated with IL-12 and IL-15.[21] ieILC1-like cells have been identified within tumor tissues and in the intra-abdominal adipose tissue (omental) of obese patients.[22] These cells exhibit varying levels of NKp44 expression and concomitantly express CD56 and CD103, while lacking CD127. However, the categorization of these cells remains a subject of contention owing to their concurrent expression of transcription factors T-bet and EOMES, as well as the presence of cytolytic effectors, namely perforin and granzyme.[21,22] The other intestinal ILC1 type, LP ILC1, expresses high levels of CD127. These cells are c-Kit^{-} NKp44^{-} NKp46^{+} CD161^{+}[18]. These cells express the T-bet transcription factor but not EOMES and produce IFNγ in response to inflammation.[20] They lack the cytotoxic properties that are seen in conventional NK (cNK) cells.[23]

2.2 | Group 2 innate lymphoid cells (gILC2)

Group 2 innate lymphoid cells gILC2 have only one subtype in humans. They are found in peripheral blood, skin, lungs, gastrointestinal tract, spleen, bone marrow, liver, kidney, nasal tissue and mesenteric lymph nodes.[13,24,25] In humans, gILC2 are described by the expression of CD45, CRTH2 (prostaglandin d2 receptor), IL-33R (ST2), IL-25R, c-kit, CD161, CD127 (IL-7R).[13,26] Their development depends on the transcription factor GATA3. When stimulated by cytokines (IL-25, IL-33 and thymic stromal lymphoetin), lipid mediators (prostoglandin D2, LTC_4, LTD_4) and cell surface ligands (ICOS, OX40 and NKp30), they produce type 2 cytokines such as IL-4, IL-5, IL-9 and IL-13 which are important for promoting Th2-type immune responses. They can also produce IL-6, IL-8, IP-10 and GM-CSF.[24] ILC2s have also been shown to play a role in the regulation of immune responses during infection, especially in response to helminths and respiratory viruses.[9] Recent studies have implicated alterations in ILC2s in the development of a range of human diseases, including allergy and asthma, autoimmune diseases, and inflammatory bowel disease.[27,28] ILC2s have been shown to be increased in the blood and lung, skin and bowel tissues of patients

with these diseases, and their activation state has been associated with disease severity.[29]

2.3 | Grup 3 innate lymphoid cells (gILC3)

Group 3 innate lymphoid cells are innate immune cells that play a role in innate immunity against fungi and extracellular microbes and are involved in the regulation of antibacterial immunity, chronic inflammation, and tissue repair. ILC3s depend on the transcription factor RORγt (encoded by *RORC*) and produce cytokines such as IL-17A, IL-17F, IL-22, GM-CSF, and TNF in response to IL-23 and IL-1β.[30–33] In mice, ILC3s can be divided into two subpopulations based on their expression of the chemokine receptor CCR6 and the natural cytotoxicity receptor (NCR) NKp46 CCR6$^+$ ILC3s include both CD4$^+$ and CD4$^-$ lymphoid tissue inducer (LTi) cells. On the other hand, CCR6$^-$ ILC3s consist of two subpopulations that can be differentiated based on the expression patterns of NCR NKp46. In humans, all ILC3s express CCR6 and CD117 and at least two subsets can be distinguished based on expression patterns of the NCR (active NK cell receptor) NKp44.[30–32] LTi cells are a distinct subset of ILC3s and play a role in the formation of secondary lymph nodes and Peyer's patches during embryonic development via action of lymphotoxin.[34] ILC3s participate in the secondary immune response, present antigens to CD4$^+$ T cells, and modulate adaptive immunity through antigen presentation and MHC-II.[35–37] They are primarily found in mucosal tissues, such as the gut, and respond to extracellular bacteria and intestinal commensal bacteria.[38]

3 | CONTROVERSY CONTINUES: ANOTHER INNATE LYMPHOID CELL POPULATION

Regulatory ILC (ILCreg) is a recently described subpopulation of innate lymphoid cells with a regulatory phenotype, characterized by Lin−CD45+CD127+IL-10+.[39] These cells are found in mouse and human intestines and kidneys and secrete high amounts of IL-10 and TGF-β. ILCreg has a distinct gene expression profile and plays a role in resolving innate intestinal inflammation by suppressing ILC1 and ILC3.[39] In the gut, TGF-β acts autocrinally to support the expansion of ILCreg during inflammation. The existence of ILCreg as a distinct population remains controversial, with some studies suggesting that the main source of IL-10 in the gut is activated ILC2. Another regulatory population of ILC, named follicular regulatory ILC, has been described in human tonsils and lymph nodes, secreting high amounts of TGF-β.[40]

4 | ORIGIN AND DEVELOPMENT OF INNATE LYMPHOID CELLS

In humans and mice, ILCs develop from CLP, which gives rise to common innate lymphoid progenitors (CILPs) (Figure 2). CILPs serve as a common precursor for both NK cells and ILCs. CILPs differentiate into NK cell precursors (NKPs) or into common helper innate lymphoid progenitors, which give rise to lymphoid tissue inducer progenitors (LTiPs) and innate lymphoid cell precursors (ILCP).[20,41] LTiPs differentiate into lymphoid tissue inducers (LTis) and ILCPs into ILC1, ILC2, or ILC3 subsets. NK cells develop from NK NKPs. The development of each ILC subset is dependent on the expression of specific transcription factors and is regulated by cytokines, including IL-7 and IL-15 for ILC1, and IL-7 for ILC2 and ILC3. It is suggested that ILC1 may originate from precursors other than ILCPs, but this is not yet fully understood.[19] The expression of transcription factors, including NFIL3, Id2, TOX, TCF-1, ETS1, GATA3, PLZF, T-bet, Eomes, RUNX3, RORα, Bcl11b, Gfi1, RORγt, and AhR, is crucial in regulating the differentiation of ILCs from CLPs.[13]

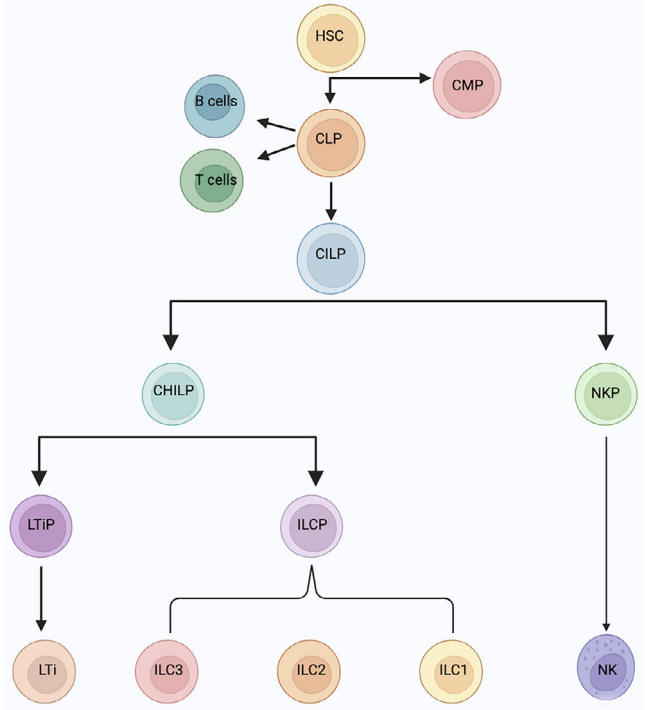

FIGURE 2 Human ILC development. The figure was created by BIORENDER.

5 | THE FRIENDLY ASPECT OF INNATE LYMPHOID CELLS DURING PREGNANCY

In pregnancy, the fetus and placenta are semi-allografts derived from the maternal and paternal host, requiring the presence of immune mechanisms to prevent allograft rejection.[42–44] ILCs play an important role in maintaining the delicate balance of inflammation and tolerance that is critical to successful pregnancy. ILCs contribute to tissue assembly (implantation and invasion) and remodeling, neoangiogenesis, and support pregnancy by secreting various factors.[45–47] They act as a bridge between the innate and adaptive immune systems and have opened up new avenues for research to understand the complex immune state of pregnancy.

5.1 | gILC1s in human pregnancy

Group 1 innate lymphoid cells contain NK cells and non-NK ILC1s. Within this group, dNK cells account for 50%—70 % of total leukocytes in decidua during the first trimester of pregnancy.[48] However, the number of dNK cells decreases from midgestation and is almost unavailable at term. In mice, dNK cells are abundant in the mesometrial decidua during pregnancy.[49,50] Sojka et al. investigated dNK cells in the mouse uterus during pregnancy. The authors propose that the early accumulation of these cells is due to the proliferation of tissue-resident NK cells. At later stage, pNK cells appear to migrate into the uterine compartment, as they are not proliferative, but increase in number to assist with placentation.[51] Consistent with this, NF-IL3-deficient mice lack pNK cells and have abnormal remodelling of the spiral arteries, which are critical for proper placentation.[52,53] trNK cells in the uterus are not dependent on NF-IL3.[51] Therefore, it is suggested that pregnancy regulates the movement and retention of subsets of NK cells at different times, and that each subset has a different set of functions during pregnancy. In addition to dNK cells, non-NK ILC1s, NCR+ and NCR- ILC3s are present in the decidua.[54–56] In contrast to cNK cells, dNK cells exhibit a low cytotoxic potential and possess a distinct profile of cytokines and receptors.[48,57–62] dNK cells are found in the vicinity of invasive fetal trophoblasts and spiral arteries[63] expressing the KIR, the natural killer group 2 receptor (NKG2) and the immunoglobulin-like transcript 2 receptor (ILT2).[64–66] Through these receptors, dNK cells can identify invasive trophoblast cells and play important roles in maternal-fetal immune tolerance, trophoblast invasion, and spiral artery remodelling.[43] In addition, CXCL8 and CXCL10 produced by dNK cells bind to their receptors on invasive trophoblast, thereby regulating trophoblast invasion. As the mouse is not a suitable model for deep trophoblast invasion, the rat model is used to study deep trophoblast invasion and the interaction of uNK cells and trophoblast invasion.[67,68] Staining of uNK cells and trophoblasts in consecutive sections of the mesometrial triangle, equivalent to the human placental bed, on days 15, 17 and 20 of rat pregnancy showed that extravillous trophoblast invasion followed the demise of uNK cells towards the myometrium, suggesting that uNK cells regulate extravillous trophoblast invasion.[69] Depletion of NK cells in early pregnancy resulted in increased endovascular trophoblast invasion at day 13, suggesting that uNK cells may also regulate endovascular trophoblast invasion.[70] The remodeling of the spiral artery is essential to the supply the developing foetus with the necessary nutrients and oxygen for successful delivery. This process involves apoptosis of endothelial cells, and vascular smooth muscle and endovascular trophoblast cells replace endothelial cells. dNk cells play an important role in this process. During the first trimester of pregnancy, dNK cells produce MMP-2, MMP-9 and uPα enzymes that specifically target vascular smooth muscle and induce apoptosis of endothelial cells. Extravillous trophoblast cells (EVT) accumulate and attach themselves to spiral arteries via chemoattractive factors such as IL-10, IL-8 and HGF produced by dNK, replacing endothelial cells. The angiogenic role of dNK cells is mediated by their secretion of soluble factors such as TGF-β, VEGF (C) and PIGF, angiopoietin 1 and 2.[45,71] A subset of dNK cells inhibits the expansion of Th17 cells, which produce proinflammatory cytokines. In addition, dNK cells induce the expression of IDO in macrophages and some dendritic cells through the production of IFN-γ, providing immune tolerance by inhibiting T-cell activation and tryptophan metabolism.,[72–74]

The function of memory is one of the important roles of dNK cells. Multifactorial diseases characterized by abnormal placental development such as preeclampsia and miscarriages have a higher risk in the first pregnancy.[75] A prospective cohort study shows that the risk of preeclampsia was 4.1% overall in the first pregnancy and 1.7% in later pregnancies.[76] Repeat pregnancies are associated with improved placentation.

Mandelboim et al. identified a new population of human NK cells exclusively present in repeated pregnancies, referred to as pregnancy-trained decidual NK cells (PTdNKs).[77] PTdNK cells express higher levels of NKG2C and LILRB1 receptors and, upon stimulation, secrete VEGF A and IFN-γ. VEGF A supports placental vascularization, which is essential for preventing the development of multifactorial diseases characterized by poor placentation. These properties of PTdNK cells may help to explain improved placentation, higher birth weight and reduced pregnancy complications in second pregnancies. A recent report provides data on how ILC1 memory develops during gestation in mice. Eomes-CD49a^{+} ILC1s upregulate CXCR6, a receptor involved in innate memory. They expand 4-5-fold in second pregnancies.[78] These cells have not been the subject of in-depth characterisation until now.

Vento–Tormo et al. classified dNK cells into three groups, namely, dNK1, dNK2 and dNK3 cells, according to single-cell sequencing at the early maternal-fetal interface in humans (Figure 3).[79] These cells co-express CD9 and CD49a which are tissue-resident markers. While dNK1 cells express high levels of Eomes, dNK2 and dNK3 cells express moderate levels of Eomes.[80] DNK1 contains more granules and proteins within these granules (such as PRF1, GNLY, GZMA and GZMB) are expressed at higher levels. DNK1 cells have higher levels of KIRs that can bind HLA-C molecules in EVT. LILRB1, a high-affinity receptor for HLA-G multimers, is only expressed by the dNK1 subset. First pregnancies are associated with lower percentages of dNK cells expressing LILRB1, lower birthweight and increased disorders such as pre-eclampsia.[77,81] In addition, dNK1 and dNK2 cells express both activating and inhibitory receptors for HLA-E. CCR1, the receptor for CCL5, is expressed by EVT. This suggests a role for dNK3 in regulating EVT invasion.[82] It has been shown that dNK1 upregulates the expression of the CSF1 receptor and modulates the expression of the CSF1 receptor on EVT and macrophages. Similarly, it has been hypothesised that dNK2 and dNK3 interact with EVT and express high levels of certain cytokines such as CCL5 and XCL1. These dNK subsets are thought to reduce inflammatory responses by inhibiting harmful maternal T or natural killer cell responses against trophoblast cells. Specifically, dNK1 was found to express higher levels of the anti-inflammatory molecules CD39 and SPINK2.

Vazquez J et al. showed that there are two new subsets within the decidua CD56^{Bright}CD16^{-} ILCs and named C10 and C2. Transcriptome analysis showed that C10 and C2 are distinct from cNKs and from each other. Importantly, C2 may represent an ILC1 group in the human

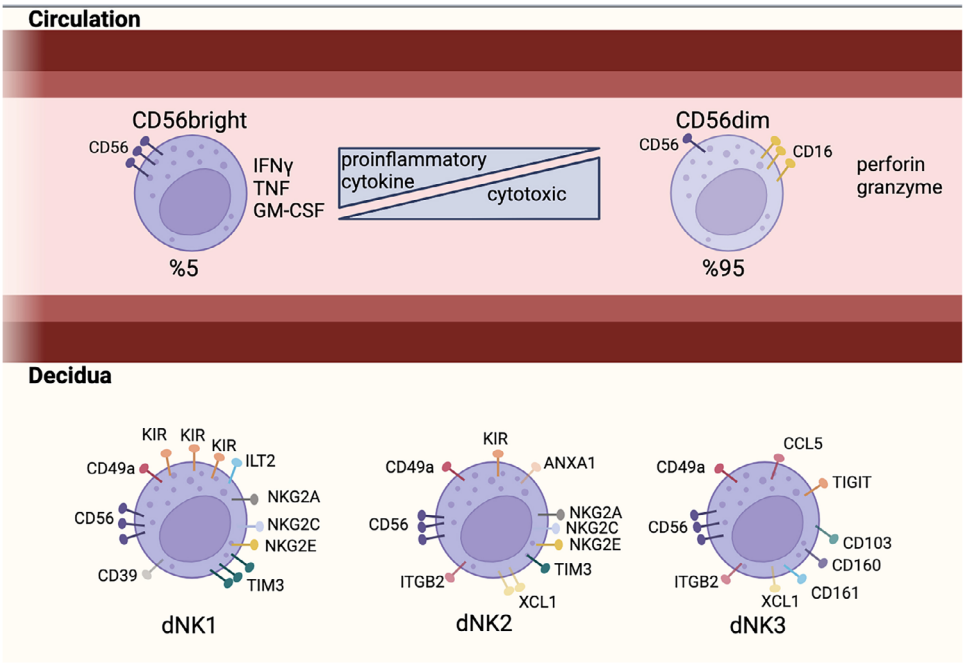

FIGURE 3 Human peripheral blood NK cells can be divided into two main subsets based on CD56 expression, namely CD56dim and CD56bright, which are characterised by different functional and phenotypic properties. DNK cells are simlar to CD56bright NK cells. Subpopulations of human dNK cells in the early stages of pregnancy and their differences in the expression profiles of surface receptors. Single-cell sequencing revealed three subpopulations of early pregnancy dNK cells, including dNK1, dNK2 and dNK3. The cytoplasmic granule proteins (perforin, granzyme and granulysin) were highly expressed in the dNK1 cells. The figure was created by BIORENDER.

uterus with low T-bet expression, but this is inconclusive as Runx3 expression was not detected in these cells. C10 appeared to have an ILC3-like phenotype but did not respond to IL-23 or IL-1β, suggesting that they may represent a distinct group of ILCs. Both C10 and C2 cells were shown to produce lower levels of IFNΥ compared to cNKs. This suggests that decidual C10 and C2 are programmed by the pregnant environment to produce optimal levels of IFNγ. Another important finding of the study is that C10 and C2 limit TNFα production during pregnancy. High levels of TNFα have been associated with pregnancy complications. This suggests that C10 and C2 may play a role in suppressing the production of effector molecules that are involved in the process of parturition in order to maintain the pregnancy.[83]

Roger Pique–Regi et al. have shown that the expression of NK cell signatures changes with gestational age and that there is a potential link between the activity of NK cells and the progression of pregnancy. The study highlighted the upregulation of NK cell signatures in women who gave birth spontaneously at term compared to gestational age-matched controls who did not give birth. NK cells have been found to become more activated during the natural process of preterm labour. It was also demonstrated that the mean expression of various immune cell signatures, including NK cells, is increased in the circulation of women in preterm labour and in labour versus age-matched controls. A possible link between the increased activity of immune cells, including NK cells, and the occurrence of preterm birth has been suggested.[84]

Vacca et al. explained that ILC1s, distinct from NK cells are found in the human decidua. These cells are IFNΥ^{+}, Tbet^{+}, EOMES^{-} RORΥt^{-}.When stimulated, ILC1s produce proinflammatory cytokines such as IFNΥ and TNFα. Therefore, ILC1s could be trapped in the inflammatory phase early in pregnancy.[56]

5.2 | gILC2s in human pregnancy

ILC2s, which similar to TH-2 cells are found in decidua, are most common during pregnancy.[85] During pregnancy, the number of ILC2s increases notably at the maternal-fetal interface, especially after dNK cells. They are present in both decidua basalis and parietalis, with higher counts in the third trimester compared to the first.[85] In particular, this can indicate a homeostatic role of ILC2s in the last trimester of pregnancy. In murine uteri, CD127+ ILC2s are mainly located in the myometrium and increase during pregnancy.[86] These cells express ST2, the receptor for IL-33, and estrogen receptors. After estrogen treatment, there is a noticeable increase in the number of ILC2s in the uterus of ovariectomized mice, highlighting the impact of hormonal regulation.[87] ILC2s express cytokines, such as IL-4, IL-5, IL-9 and IL-13. Mouse ILC2s produce Amphiregulin (AREG). IL-4 produced by ILC2 is essential for the differentiation of alternatively activated macrophages, which play a crucial role in trophoblast invasion and spiral artery remodeling. IL-5 production by ILC2s can control eosinophil responses and may promote remodeling of the uterine mucosa. AREG and IL-13 support the homeostasis of the maternal-fetal interface.[88] AREG has a tissue repair function by controlling the proliferation and differentiation of epithelial cells and the integrity of the epithelial barrier.[89]

5.3 | gILC3s in human pregnancy

NKp44+ and NKp44- decidual ILC3s (dILC3s), two subsets of ILC3s, have been described in human decidua.[90] In addition, LTi-like cells expressing low levels of NKp44 are also found in human decidua.[56] ILC3s were found in the uterus of both virgin and pregnant mice.[91] However, a major difference between mouse and human is the uterine localisation of ILC2 and ILC3. In mouse pregnancy, ILC2s and ILC3s are found in the myometrium and ILC3s in the uterine wall embedded mesometrial lymphoid aggregate (MLAp).[55] In contrast, ILC2s and ILC3s are present in the human endometrium as well as in the decidua.[56] These cells are not present in the mouse decidua. Therefore, their effects on trophoblast cells should be limited compared to other ILCs in this species. It has been reported that a large proportion of cells expressing RORγt are found in the decidua. However, this expression did not change dramatically during pregnancy. Studies with the RORγt fate report mouse model have shown that RORγt deficiency has no effect on fertility or embryo resorption, but the effect of RORγt on placental architecture is still unclear.[92] Following stimulation, NKp44$^+$dILC3s express GM-CSF, IL-8 and IL-22. GM-CSF and IL-8 expressed by NKp44$^+$dILC3s are essential for recruitment, activation and survival of neutrophils, which play a role in inducing the inflammatory phase in the early stages of pregnancy. Furthermore, HB-EGF and IL1Ra, which are expressed by these cells, promote immune tolerance in the human decidua.[93] Both NKp44$^+$dILCs and LTi$^-$like cells induce upregulation of ICAM-1 and VCAM-1 adhesion molecules on decidual stromal cells.[88] Thus, upregulation of ICAM-1 and VCAM-1 adhesion molecules is a triggering event for secondary and tertiary lymphoid organ development. NKp44$^+$dILC3 and LTi$^-$like cells have a similar function.[90] In the last trimester, dILC3s can express specific cytokines such as IFN-γ and IL-13 which are produced by ILC1s and ILC2s, respectively. Therefore, both dILC1s and dILC2s can differentiate from dILC3 under the appropriate microenvironmental conditions.

6 | OPENING PANDORA'S BOX: THE FOE ASPECT OF INNATE LYMPHOID CELLS IN PREGNANCY

6.1 | Preeclampsia

Preeclampsia is a serious blood pressure disorder that can occur during pregnancy. It is estimated that preeclampsia complicates 2%—8% of pregnancies worldwide.[94] The pathophysiology of preeclampsia includes abnormal placentation, abnormal spiral artery remodelling, placental insufficiency and endothelial dysfunction. ILCs, especially NK cells, contribute to these processes by interacting with trophoblast cells and producing cytokines. Disturbances in the function of these cells can lead to an imbalance in the production of proangiogenic and antiangiogenic factors, proinflammatory cytokines and anti-inflammatory cytokines. The resulting abnormal milieu triggers a systemic inflammatory response with widespread activation of the endothelium, resulting in defects in trophoblastic invasion and placental damage.[69] The crosstalk between dNK cells and EVT cells at the maternal-fetal interface plays a crucial role in the pathogenesis of preeclampsia. Specifically, the mismatch between dNK cells and EVT cells can lead to aberrant invasion and remodeling of the maternal spiral arteries, which is a hallmark of the disease. Additionally, maternal KIRs and HLA class I molecules can interact to modulate the activity of dNK cells, influencing the development of preeclampsia and reproductive outcomes.[95] Natural cytotoxicity receptors including NKp44, NKp46 and NKp30, are specific markers expressed on NK cells that play a critical role in cytokine production and cytotoxicity. A notable finding is the decreased percentage of NKp46+ NK cells detected in the peripheral blood of women who develop preeclampsia compared to those who do not, which is evident as early as 3—4 months before the onset of preeclampsia.[96] Studies have shown an increased number or ratio of pNK cells in patients with preeclampsia or at risk of developing preeclampsia.[97–99] Moreover, various studies have demonstrated a correlation between altered numbers of uNK cells and the occurrence of PE. Although some research has suggested that the quantity of dNK cells is significantly elevated in cases of PE compared to normal pregnancies, other studies have reached different conclusions.[61,100–105] ILC3s, another ILC cell group, have been identified as the source of elevated IL-17 in patients with preeclampsia and gestational diabetes.[106]

6.2 | Preterm birth

Preterm birth (PTB), defined as delivery before 37 completed weeks of gestation, affects approximately 15 million infants globally and disproportionately impacts underdeveloped countries.[107] This phenomenon directly contributes to an estimated one million neonatal deaths annually and is a significant factor in childhood morbidity. PTBs are classified into two categories: indicated preterm birth and spontaneous preterm birth. Indicated preterm birth refers to deliveries that are initiated by the clinician for the benefit of either the foetus or the mother. On the other hand, spontaneous preterm birth occurs either as a result of spontaneous preterm birth or spontaneous rupture of the membranes.

The pathophysiology of PTB is associated with inflammation. Preterm birth and preeclampsia share a similar pathophysiology in that both disorders are caused by faulty deep placentation.[108,109] Pathological inflammation may result from activation of immune system and adaptive system by various factors so recent studies on ILCs have been done.[110–112] Studies have shown that both ILC2s and ILC3 were increased in the decidua of women with spontaneous preterm birth. Moreover, studies have shown that ILC3s expressed high levels of IL-22, IL-17, IL-13, and IFNγ at the human maternal-fetal interface during preterm birth, indicating their potential involvement in the pathological process of spontaneous preterm birth.[85,113]

6.3 | Recurrent pregnancy loss

Recurrent pregnancy loss (RPL) is defined as the occurrence of three or more consecutive miscarriages prior to 20 weeks gestation.[114] RPL

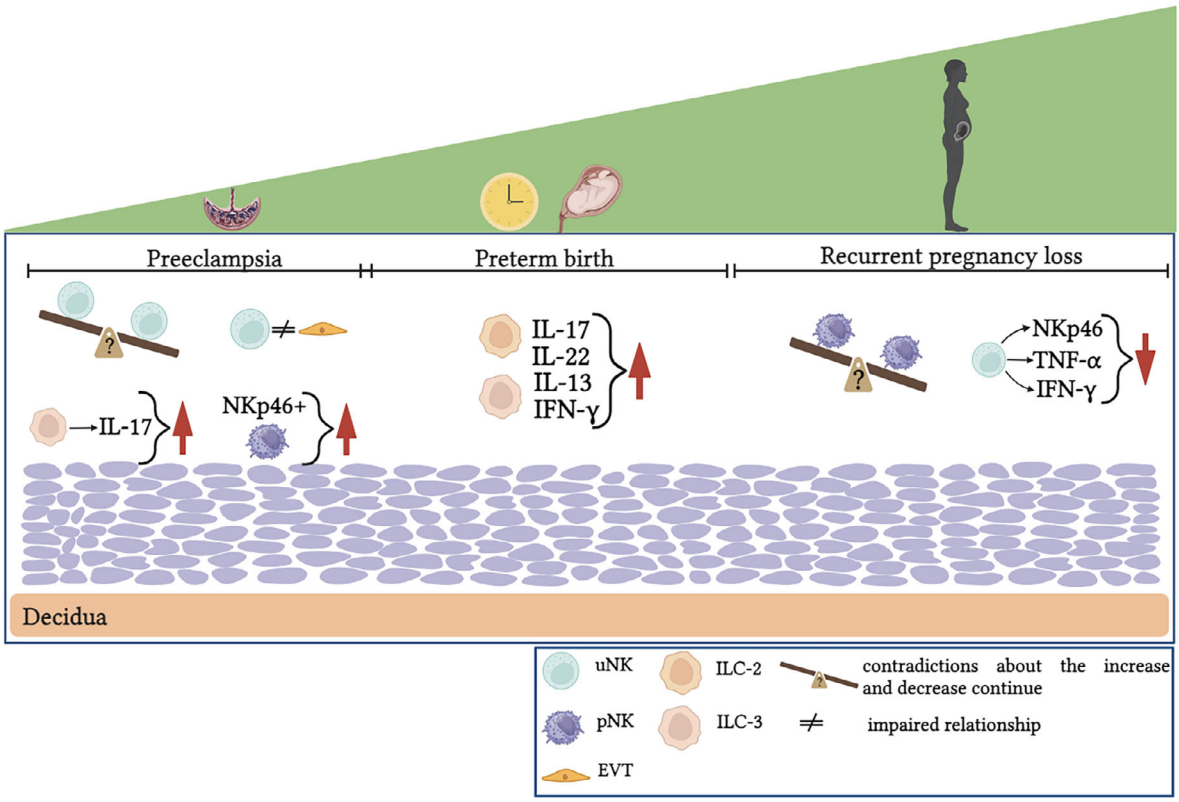

FIGURE 4 Role of innate lymphoid cells in pathological pregnancies. The figure was created by BIORENDER.

affects between 2% and 5% of couples and is an important reproductive health issue.[115,116] The definition of RPL is controversial and varies between international societies. The European Society for Human Reproduction and Embryology (ESHRE), and the Royal College of Obstetricians and Gynaecologists (RCOG) define RPL as three consecutive pregnancy losses, including nonvisualised losses.[116–118] On the other hand, the American Society for Reproductive Medicine (ASRM) defines RPL as two or more clinical pregnancy losses that can be documented by either ultrasound or histopathological examination, but need not be consecutive.[115] The differences in the definition of RPL between these societies may lead to differences in clinical management and research findings.

RPL has been associated with several pathogenic mechanisms. These include chromosomal abnormalities, hormonal imbalances, uterine abnormalities, infections and autoimmune disorders. However, these mechanisms can explain less than half of RPL cases.[119] As a result, an exaggerated maternal immune response to the foetus has been proposed as one of the underlying causes of a proportion of cases of idiopathic RPL.[120] RPL has been associated with dysregulation of ILC numbers and/or cell function (cytotoxicity, receptor expression, cytokine secretion or gene expression).[121] Studies investigating NK cell levels in women with RPL have conflicting results. Some studies have reported an increase in pNK cells in these women.[122,123] Others have found no significant differences in pNK cell levels between women with RPL and healthy controls.[124,125] Fukui and colleagues conducted a study on women with RPL and implantation failure, in which they found that NKp46 expression was reduced in peripheral blood and uterine endometrial NK cells. Additionally, they observed that uterine NK cells from women with RPL produced lower levels of IFN-γ and TNF-α compared to controls.[126] Moreover, recent studies suggest that altered immunity in RPL is dominated by Th1/Th2/Th17 and Treg hypothesis.[127] The cytokines produced by ILC cells resemble those of Th1, Th2, and Th17 cells, indicating that ILC cells may contribute to the pathogenesis of RPL. However, more extensive research on ILC cells, beyond NK cells, is necessary to fully understand their role in RPL.

7 | CONCLUSION

A successful pregnancy is related to interactions between semiallogeneic embryo and mother. Within immune cells present at the maternal-fetal interface, ILCs are involved in spiral artery remodelling, proinflammation, immune tolerance, trophoblastic invasion and homeostasis processes. The faults in these processes can lead to pregnancy-related diseases such as PE, PTB, and RPL (Figure 4). Recent studies have shown that there may be a link between pregnancy-related diseases and ILCs. However, there are many limitations with ILC studies. The classifications of ILCs are unclear. There are many classifications in the literature. The development of ILCs in humans is less well studied. Extensive human in vitro and in vivo studies are needed to elucidate functions and origins of ILCs in pregnancy. This research will help us to understand the occurrence and development

of pregnancy-related diseases and open up possibilities for effective therapy against these diseases in the future.

AUTHOR CONTRIBUTIONS

Ertan Katirci: Writing-Original Draft; Investigation; **Emin Turkay Korgun**; Conceptualization; Writing—Review & Editing; **Remziye Kendirci-Katirci**: Visualizaion. All authors approved the final draft of the manuscript.

CONFLICT OF INTEREST STATEMENT

None of the authors have a conflict of interest in this work.

DATA AVAILABILITY STATEMENT

All data are incorporated into the article and its online supplementary material.

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