Review

A Brief Analysis of Tissue-Resident NK Cells in Pregnancy and Endometrial Diseases: The Importance of Pharmacologic Modulation

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Abstract: NK cells are lymphocytes involved in the innate and adaptive immune response. These cells are located in peripheral blood and tissues with ample functions, from immune vigilant to tolerogenic reactions. In the endometrium, NK cell populations vary depending on age, hormones, and inflammation. When pregnancy occurs, tissue-resident NK cells and conventional NK cells are recruited to protect the fetus, a tolerogenic response. On the contrary, in the inflamed endometrium, various inflammatory cells down-regulate NK tolerance and impair embryo implantation. Therefore, NK cells’ pharmacological modulation is difficult to achieve. Several strategies have been used, from progesterone, lipid emulsions to steroids; the success has not been as expected. However, new therapeutic approaches have been proposed to decrease the endometrial inflammatory burden and increase pregnancy success based on understanding NK cell physiology.

Keywords: NK cells; tolerance; pregnancy; tissue-resident NK cells; conventional NK cells; decidual NK cells; uterine NK cells

1. NK Cell Subpopulations

Natural killer cells (NK) have been considered an essential subtype of lymphocytes involved in innate and adaptive immune responses [1]. In peripheral blood, two main subpopulations have been described; one cytotoxic CD3-CD56dim CD16high, and one cooperative or tolerogenic CD3-CD56bright CD16dim [1]. NK cells can be transformed from one type to another depending on tissue milieu, cytokine or receptor stimulation, or pharmacologic therapy [1,2]. However, NK activity modulation does not come solely by expressing CD16 and CD56 receptor. A complex array of molecules are responsible for NK cell activity. There are activating or cytotoxic receptors, integrin, selectins, killing inhibitory receptors (KIR), PD-1 receptors, CD161, and cytokine receptors responsible for NK cell activity [1,2]. The expression of different receptors may be dependent on the stimulus or tissue milieu.

Reports of NK cells in innate immune response and memory events have led to a better understanding of NK cells’ tissue-specific role in the immune response [2–7]. In a similar fashion as tissue macrophages, tissue-resident NK cells (trNK cells) differ in antigen expression and function. Differences have been described for NK cells from skin, liver, adipose tissue, suggesting that trNK cells may be unique depending on the location [6,7]. Most probably, the variance between normal physiological responses, inflammation and remodeling involves trNK cells, macrophages, and the migration of other cell types [6–13]. Chemokines secreted by the tissue may recruit tissue independent NK cells from the bloodstream, and once they arrive at their destination, their cell functions may be modulated by tissue milieu [10–12]. There is still a debate concerning the responses of tissue-resident and conventional NK cells in humans’ upon inflammatory stimulus.

In humans, tissue-specific uterine NK cells (uNK) is the most abundant lymphocyte, around 70 %, in decidua and mesometrial tissue (Table 1) [10–13]. These cells highly express
CD56, CD103, CD9, NKp46, KIR inhibitory receptors, CD94 NKG2A, and a low amount of CD16 receptor and killing receptors. As expected, uNK cells are non-cytotoxic and heterogeneous [10–13]. Three different subpopulations have been described in the uterus based on CD56 expression. Two of them express CD117, CD49a, CD103, integrin β7, CD9, and CD69, and transcription factor Eomes, but one produces IFNγ and the other TGFβ/VEGF. The expression of CD103 and CD69 defines the difference in subpopulations (Table 1). A third cell subpopulation expresses CD49a, has an increased amount of Eomes transcription factor, and responds to IL4 [13]. Interestingly, ILC1 cells, associated with Th1 IFNγ transcription and function, are present in the endometrium before puberty. Thus, local ILC1 cells may be involved in the uterine milieu and crucial for the recruitment of uNK and cNK migration to the tissue in the menarche.

### Table 1. General Characteristics of NK cells.

| Type of NK Cell | Markers | Cytokine Response |
|----------------|---------|-------------------|
| Circulating tolerogenic | CD16<sup>low</sup> CD56<sup>bright</sup> CD94<sup>bright</sup>+, NKG2A(C or E)/CD94, CD161. | IL10, TGFβ |
| Circulating cytotoxic | CD16<sup>low</sup> CD56<sup>bright</sup>+, CD57<sup>+</sup>, CD94<sup>dim</sup>, NKG2D/CD94, Nkp30<sup>+</sup>, Nkp46<sup>+</sup>, CD62L<sup>med</sup> | IFNγ |
| cNK | CD16<sup>high</sup> CD56<sup>dim</sup>, CD49a<sup>−</sup>, DX5<sup>+</sup>, NKG2D/CD94, Nkp30<sup>+</sup>, Nkp46<sup>+</sup>, CD62L<sup>med</sup> | IFNγ |
| uNK | CD56<sup>bright</sup>, CD16<sup>low</sup>, NKG2A/CD94, CD49a<sup>+</sup>, Nkp46<sup>+</sup>, integrin β7<sup>+</sup>, CD117<sup>+</sup>, DX5<sup>−</sup> | |
| uNK1 | CD49a<sup>high</sup>, CD103<sup>high</sup>, CD69<sup>+</sup> | IFNγ |
| uNK2 | CD49a<sup>high</sup>, CD103<sup>med</sup>, CD69<sup>+</sup>, KIR<sup>high</sup> inhibitory | TGFβ/VEGF |
| uNK3 | CD56<sup>high</sup> CD49a<sup>−</sup>, KIR<sup>high</sup> inhibitory, CD69<sup>med</sup> | IL-4 |
| dNK | CD56<sup>high</sup> CD16<sup>low</sup>, CD94<sup>high</sup>, Nkp46<sup>+</sup> | |
| dNK 1 | CD103<sup>low</sup>, CD9<sup>+</sup>, CD39<sup>+</sup>, CD69<sup>low</sup>, CYP26A1, B4GALNT1<sup>+</sup>, Jag1<sup>+</sup>, TIM3<sup>high</sup>, KIR2DL1<sup>+</sup>, KIR2DL2<sup>+</sup>, KIR2DL3<sup>+</sup>, KIR2DS<sup>+</sup>, LIRB1<sup>1</sup>, NKG2A<sup>+</sup>, NKG2C<sup>+</sup>, NKG2E<sup>+</sup> | IFNγ, TGFβ |
| dNK 2 | CD103<sup>high</sup>, CD9<sup>low</sup>, CD69<sup>high</sup>, Jag1<sup>+</sup>, CD83<sup>+</sup>, KIR<sup>high</sup> inhibitory, ANXA1<sup>+</sup>, ITGB2<sup>+</sup>, TGF<sup>−</sup>, TIM3<sup>low</sup>, NKG2A<sup>+</sup>, NKG2C<sup>+</sup>, NKG2E<sup>+</sup> | TGFβ/VEGF |
| dNK 3 | CD103<sup>low</sup>, KIR<sup>high</sup> inhibitory, ITGB7<sup>+</sup>, CD74<sup>+</sup>, CD160<sup>+</sup>, KLRB1<sup>+</sup>, ITGB2<sup>+</sup>, TGF<sup>+</sup> | TGFβ/IL-4 |

The table represents the described markers for different cell populations and the responses to cytokines. The term cNK are conventional NK cells, uNK are uterine resident NK cells, dNK are decidual NK cells. The acronym LIRB1 corresponds to Leukocyte immunoglobulin-like receptor-1, B4GALNT1 refers to β1,4 N acetylgalactosamine transferase 1, CYP26A1 corresponds to Cytochrome P450 26A1, ANXA corresponds to annexin A1, ITGB2 corresponds to integrin subunit beta 2, TGF corresponds to T cell immunoglobulin and ITIM domain.

In a mouse, a new classification was postulated of innate lymphocytes (ILC) as ILC1, ILC2, ILC3, NK tissue-resident (trNK), and conventional NK cells (cNK) [5–7]. Recent reports have shown that trNK cells express CD49a, but lack the expression of DX5, and the reverse is true for cNK [8]. Also, cNK cells are more cytotoxic than trNK and ILC counterparts [5,8–12]. Based on this definition of innate lymphocytes, Sojka and coworkers [12,13] named the NK cells in the uterine tissue as trNK, not uNK cells. Their remark is based on the fact that, in pregnancy, cNK migrate to the tissue and cooperate with trNK cells. The two NK cell subpopulations, tissue-resident and conventional, are distinguishable [10,12,13]. Nfil3 and Eomes are the required transcription factors for cNK cells and not for uterine trNK cells [12]. When pregnancy occurs, trNK and cNK cells increase in the decidua, providing the tolerogenic model for a normal pregnancy [12,13]. The trNK are closer to the trophoblasts, and the cNK cells are in the periphery. Once labor starts, the cNK presence decreases in the endometrium, while the number of uterine trNK cells diminishes in the puerperium [12]. In this particular physiological event, the cooperation among different cell populations and the tissue involved is crucial for fetal survival. Nonetheless,
the tissue events in which NK cells are involved are not necessarily dependent on specific subpopulations circulating NK cells in the peripheral blood [6,8,10–13].

2. NK Cells in Pregnancy

Progestrone is essential in reproduction and pregnancy maintenance. The hormone induces the transcription and secretion of progesterone-induced blocking factor (PIBF) [14,15]. In turn, PIBF levels are increased in normal pregnancy and very low in recurrent pregnancy failure [16]. Moreover, the progesterone stimulates protein glycoligin A (GdA), or human placental protein-14 binds to NK cells CD16 low CD56 bright NK cells purified from peripheral blood and transforms them into dNK-like cells [17,18]. Sialylated glycans expressed on glycoligin A are critical for binding to the receptor [17]. In addition, Glycoligin A stimulated cells to control endothelial cell angiogenesis by secreting vascular endothelial growth factor (VEGF) and trophoblast invasion by secreting insulin-like growth factor-binding protein 1 (IGFBP-1) [17].

Studies in pregnancy loss and preeclampsia have raised important questions concerning the role of NK cells in embryo implantation [9–19]. Fetal expression of MHC-I and its recognition by KIR receptors on NK cells, along with NKG2A/CD94, are critical for dNK cells (Table 1). On the contrary, the role of cNK cells is not tolerogenic; it protects the decidua against pathogens and abnormal cells. The cytotoxic response of cNK cells depends on NKG2D/CD94 and KIR activating receptors, NKp30, NKp46, and not by NKG2A/CD94 and KIR inhibitory receptors and their ligands. Activation of cNK cells may lead to a robust cytotoxic response against the embryo leading to pregnancy termination [11,19–22]. However, cNK cells are also critical for vascular remodeling, an important event to maintain blood flow to the fetus, often impaired in preeclampsia. The tolerogenic response of dNK cells is dependent on TGFβ levels, while IFNγ activates cNK cells. Thus, a balance between TGFβ production inducing the tolerogenic response of NK cells or IFNγ inducing inflammatory responses is critical to determine pregnancy outcome [11,19–22].

Huhn and coworkers [23] were able to determine, in healthy human pregnancy, different cell populations in the decidua (Table 1). They identified three decidual NK cell subpopulations (d1, d2, and d3), ILC3, and a group of proliferating NK cells using mass cytometry [23]. When dNK cells were stimulated with PMA and ionomycin, dNK2 and dNK3 secreted more chemokines than dNK1. The secretion included the chemokine C motif ligand (XCL1), a cytokine able to activate maternal dendritic cells and fetal extravillous trophoblasts. The d2 and d3 NK cells express a high amount of KIR inhibitory receptors [23]. Nevertheless, KIR antigen expression in dNK1 cells correlates with granzyme B granule content in the cells suggesting that these cells are more prone to be cytotoxic. These results indicate that KIR receptors control fetal development and could be involved in eliminating abnormal trophoblasts [24]. These issues have also been discussed in a recent review [19].

In summary, uNK cells are similar to dNK cells in the expression of several antigens; however, some others are only present in dNK cells (Table 1).

The involvement of different dNK cell subpopulations in embryo implantation and maintaining pregnancy still requires more research. Guo et al. [24], analyzing single-cell NK by qPCR, reported that a subset of dNK cells, previously defined as a protective NK cell for embryo growth, is diminished in patients with spontaneous abortion. Even though the decrease of this subpopulation may be due to different events, their assessment may be critical for determining therapeutic success.

A shift in the control of tissue subpopulations can be observed in different stages of normal pregnancy. In the first trimester, NK cells are prone to protect the fetus from pathogens; however, this protection decreased in term pregnancies [19,22,23]. In term pregnancies, dNK cells, usually tolerogenic, have a higher cytotoxic response against K562 than those of the first trimester [22,23]. This effect may be due to an impaired inhibitory response due to a downregulated expression of inhibitory receptors recognizing HLA-C antigens or HLA E and G similarly as cNK cells [22,23]. Also, the dNK cells from the first trimester differ from that dNK obtained in term pregnancies based on proteomic data.
It is unclear if the cNK cells redistribute to other tissue or circulation after pregnancy termination and if the dNK cells transform into uNK cells to aid endometrial tissue repair after pregnancy.

The role of cNK cells on pathogen has become more evident in the latest years. cNK cells have been involved in protecting the fetus against infections like Toxoplasma gondii [25,26]. During Toxoplasma infection, Tim-3 is involved in dNK impairment, and consequently, cNK may be involved in pregnancy termination by NK cells [25,26]. The response is dependent upon the production of IFN γ and the downregulation of KIR inhibitory receptors.

3. NK Cells and Endometrial Disease

A first approximation of the importance of the role of hormones in endometriosis was by Loverro and coworkers [27]. Mizumoto [28] and Eriksson et al. [29] contrasted previous reports demonstrating the presence of suppressive leukocytes in the endometrium, and Eriksson et al. [29] defined the phenotype of uNK cells and their response to TGFβ. One essential difference between NK cells from peripheral blood and uNK cells is the response to hypoxia [30–32]. Furthermore, the peripheral NK cells and uNK cells respond differently to TGFβ when the cells are incubated in hypoxic conditions ex vivo [31,32]. These results suggest a significant difference in hypoxia-inducing transcription factor 1 and, consequently, substantial changes in physiological responses.

In mouse endometriosis models, trNK cells express higher amounts of inhibitory KIR receptors [33]. This increased expression does not parallel with an increase in HLA E and HLA G molecules, physiological ligands of such receptors, suggesting that the inflammatory response is not physiologically controlled. Other MHC class I receptors and NKp46, CD103 (integrin alpha E), seem to be related to NK cell attraction and increased cytotoxic responses by cNK cells [33,34]. In aged mouse and humans, the resolution of endometriosis is delayed [34]. Chronic inflammation in endometrial tissue decreases the telomerase activity of several cells, impeding their optimal physiological response in mouse [34] and humans [21,35–39]. trNK cells could also be affected by the low telomerase response [34]. On the other hand, senescent cells may activate the cytotoxic response of cNK cells [34–39] against autologous cells and, in consequence, generate more cell death maintaining the local chronic inflammatory response.

In humans, NK cells, macrophages, and T cells are responsible for maintaining the local inflammatory response [35–40]. The role of TH17 and IFN γ has been widely discussed; however, the control of inflammation in the tissue is not achieved in many patients despite surgery or other therapeutic options raising the question of a wider variety of endometrial diseases [21,36–39]. One of the often-overlooked events is autoantibodies, which can play an essential role in maintaining the inflammatory response [40–42].

The frequency of endometrial cancer is high in developed countries as compared to other cancers [43]. The occurrence of this type of cancer has been associated with ageing and obesity [43]. Despite the solid statistical association between ageing and obesity to tumour incidence, little is known about the immune response in this type of tumour except for T CD8 cytotoxic cells [44]. The generation of a tumour in the endometrium associated with age and obesity has raised important questions concerning the pool of circulating and tissue-dependent NK cells [43–46]. The trNK cells do not represent a cell type able to induce a proper immune vigilant response [45,46]. In an analysis of menstrual blood, NK cells were shown to express CD103 [47], an antigen expressed in T regulatory cells [48]. Two populations were described based upon the CD103 marker [47,48]. The CD103 positive cells express inhibitory KIR, Tigit, and TIM3 proteins and inhibit local immune response [49,50]. The CD103 negative counterparts have low expression of those markers and high cytotoxic markers; they are cytotoxic against the tumour [49,50]. The number of inhibitory receptors and suppressive cells increases depending on the severity of the disease [49,50]. The production and secretion of chemokines and IL-1β and IL-6 by these cells are decreased, suggesting reduced cell recruitment to the tumour [49,50].
Several reports on the importance of KIR receptors in endometriosis [51,52] and the expression of NKG2D [53]. However, more analysis is required because of the contradictory reports on uNK cells in endometriosis and inflammatory events related to pregnancy loss [54,55].

4. NK Cells in Autoimmune Diseases

During the screening of possible causes of infertility or recurrent pregnancy loss, the presence of autoantibodies may be relevant. The presence of autoantibodies may be independent of peripheral lymphocyte or NK cell populations, but may be dependent on tissue subclinical inflammatory responses.

Women with autoimmune diseases with the proper therapeutic conditions may undergo pregnancy without major complications. The most common autoimmune disease is anti-thyroid antibodies [41,42,56–58]; however, the most difficult to treat is antiphospholipid antibody and lupus. The main issue depends upon the control of autoantibodies and thrombosis. Most patients with subtle inflammatory reactions may benefit from progesterone or anti-inflammatory therapy [40].

Autoantibodies may be responsible for NK cell activation in the decidua; however, the mechanism is unclear [41,42,56–58]. Control of thyroid hormone can be achieved pharmacologically. Vitamin D appears to have a protective role in this process as human chorionic gonadotrophin [56–58]. Both induce a tolerogenic immune response [56–59]. However, anti-nuclear and antiphospholipid antibodies may require special medical treatment. Zhang and coworkers [41] were able to show a correlation of NKG2D expression with antiphospholipid antibodies in obstetric patients. These results support the hypothesis of downregulation of inhibitory KIR receptor expression in patients with autoimmune diseases. It would be interesting to study the possible role of small HLA molecules in modulating NK cell responses in these patients.

Jiang and coworkers showed the importance of NETosis and dNK cells in lupus pregnancies [60]. The critical issue seems to be related to the inflammatory burden based on cell death at the endometria [60]. In addition, NETs may induce dNK modulation depending on DAMP receptor signaling, which would downregulate KIR inhibitory receptors, enhancing KIR activating receptor [60]. Probably, impaired production of HLA E and G, ligands of inhibitory receptors, may also play a vital role in dNK activation.

5. NK Cells in Obesity

In adipose tissue, trNK cells seem to be important not only in maintaining adipose tissue control, but they may be involved in the subtle inflammatory activation that may lead to insulin resistance and metabolic syndrome [46,61–63]. In the breast mouse tumour model, adipose tissue increase and high-fat diet are related to more tumour growth, suggesting a skewed response of NK cells against the tumour [46,61–63]. In particular, Spielman and coworkers [63] injected mammary tumour 4T1-luc2 cells in the mammary adipose tissue of BALBc animals in which ovaries were surgically removed and showed that NK cells close to the tumour had a higher expression of NKG2D despite a decreased expression of Nkp46 and an increased amount of adipose tissue. These results propose that there is a link between adipokines and circulating and trNK cells [64]. Even though leptin and adiponectin do not alter peripheral blood NK cells cytotoxic response in vitro, there is evidence of the increased incidence of endometrial, ovary, and mammary tissues cancer in obese humans and animals [46,65].

Another alternative that has not been explored in detail is single or multiple genetic polymorphisms of critical proteins, receptors, or signal transduction pathways that may be relevant for NK cell modulation and tissue migration [46]. Studies with the NK cell line NK-92 suggest that several exciting analyses could be performed using migration and invasion [66–69]. For example, STAT 3 was involved in Tim-3 dysregulation of dNK, which involves immune response against pathogen and tissue rejection [27,67–69]. The migration of tissue-resident NK cells from obese individuals has not been studied thoroughly in
different metabolic disorders related to circulating hormone levels and could be relevant to understand the possible effect on uterine or decidual NK cells.

Pregravid and gravid obesity seem to alter the immune cells involved in the endometrium [70–72] and predispose women to gestational diabetes. Maternal obesity also alters uNK activity [70–72]. Even though in NK cells of gravid obese women, the expression of KIR2DS1 is increased over KIR2DL1, there is no increase in cytotoxic response. Yet, the interaction of the activating receptor HLAC2 induces the secretion of TNFα, which affects the local inflammatory milieu and may affect fetal development and may predispose to preeclampsia [70–72]. It is unclear whether nutritional restriction or diet modulation may affect uNK cells in obese pregnant women. Conversely, the effects may be assumed to be similar to those observed in mammary tumour-challenged mice [73].

6. NK Cells in Infectious Diseases in Pregnancy

Control of infectious diseases is essential during pregnancy since they can be life-threatening for the embryo and fetus [74–76]. The most dangerous pathogens in pregnancy are influenza, SARS CoV-2, malaria, toxoplasma, hepatitis, Zika virus, herpes simplex virus, human cytomegalovirus, Ebola, dengue, measles, and smallpox [74–76]. In addition, pregnant women may be more susceptible to pathogen infection, malaria infection, HIV infection, and listeriosis. The susceptibility may be due to the tolerogenic environment generated during pregnancy. For example, in SARS CoV2 infection, there seems to be an increased activation of NK and T cell in the maternal-fetal interface, despite the absence of virus in the tissue [77]. This effect may be due to inflammatory cytokines generated upon viral infection.

In Listeria monocytogenes, the role of uterine NK cells seems to protect from the infection, although it is not crucial for its response as observed in the mouse model [78]. However, other pathogens like mycobacteria have been barely studied. There has been a proposal for a BCG vaccine for endometriosis since it is known that BCG activates NK and NKT cells [79]; however, there have not been well-conducted trials to test that hypothesis.

One of the critical elements for the elimination of pathogens by NK cells is the presence of KIR. In an exciting analysis performed by Omosun and coworkers [80,81], KIR receptors’ role in placental malaria and perinatal transmission of HIV-1 was analyzed. Inhibitory KIR2DL2 and KIR2DL3, alleles of the same locus, negatively affect malaria and malaria/HIV co-infection. Furthermore, the maternal KIR genes KIR2DL2, KIR2DL5, KIR2DS5, and KIR2DS2, were associated with decreased HIV-1 transmission from mother to child [80,81].

KIR expression is crucial in protecting the fetus and may play a pivotal role also with preeclampsia associated with the inflammatory response generated by the pathogen [82–86]. An association between KIR/HLA class I mismatch and preeclampsia suggest that there may be more than one mechanism involved between NK cell activation upon pathogen-induced local inflammatory response and preeclampsia [85,86]. Future analysis should be directed towards understanding the phenomenon, and probably using small HLA inhibitory molecules HLA E/G could decrease the inflammatory burden. For example, soluble HLA-G induces apoptosis of dNK cells after Toxoplasma gondii infection [87].

Innate immune antiviral response plays a crucial role in the response. In cytomegalovirus infection, Tomac and coworkers [88] were able to show that low viral load and high viral load affect the corpus luteum differently in a murine model. There is local inflammatory activation at low viral load, but pregnancy continues; there is a massive immune response at high viral load, leading to pregnancy loss. Moreover, in Zika virus infection, there is evidence of memory-like NK cells, and the expression of CD27 characterizes it [89]. However, these experiments, carried in the mouse model of the disease, may not be parallel to the infection in humans since the viral escape, in humans, seems to be dependent upon upregulation of MHC class I [90]. Herpes simplex virus may induce embryo damage by decreasing the expression of HLA G, critical in local tolerogenic responses [91].
In patients with hepatitis B and recurrent pregnancy loss, the virus induces a decrease in NK cell function in peripheral cells [92]. A similar impairment in NK cell cytotoxicity was observed in hepatitis C virus-infected patients [93]. Furthermore, diminished NK responses are also observed in dengue viral infection and may play a role in the disease [94]. Thus, dysregulation of NK cells in these viral infections may be significant for peripheral NK cells and trNK cells.

NK cells are activated and can provide protecting memory responses in Ebola viral infections [95]. This protective response seems to be essential for liver NK cells, a target tissue. Thus, the protection against the virus may be critical also in uterine NK cells and decrease cell mortality.

Only a few reports have described the local immune response against measles and smallpox in pregnancy.

The differences in NK cell response to viral infection observed in the murine model cannot be assumed to occur in humans, reviewed recently [96, 97]. In particular, several assumptions based upon the response of trNK cells may not be extrapolated since ILC cells play an essential role in mice and a less prevalent role in humans.

7. Pharmacological Modulation of NK Cells

In general, normal pregnancy requires a tolerogenic response that is controlled at the tissue level. Pharmacologic modulation of this effect is essential in order to achieve that goal [98]. The therapy has been primarily based upon indirect knowledge from animal models and in the analysis performed in patients with recurrent abortions due to non-genetic or pathogenic events [98–100]. However, different medical conditions in which therapy may substantially affect pregnancy outcomes may be related to NK function.

One crucial analysis is based on the fact that peripheral blood NK cells may not be appropriate to determine treatment effect [98–100]. Variations, upon treatment, on circulating cell quantities, and a decrease in cytotoxic responses may be due either to changes in the activation markers or changes in subpopulations based upon cell maturation. Due to the variety of receptors and signals involved in NK physiology, it is challenging to determine which specific antigen or receptor could be a critical biomarker to ascertain treatment responses.

NK cells in recurrent spontaneous abortion have been several pharmacological therapies used [98–100]. Some therapies are based on a general anti-inflammatory rationale, screening peripheral blood NK cells subpopulations and cytotoxic activity [98–100]. However, treatment efficiency depends on pregnancy success and complete pregnancy with alive newborns [99, 100]. In some cases, therapeutic modulation has been shown to increase the number of genetic malformations and the possibility of preeclampsia, eclampsia, or HELLP syndrome [98–100]. Hence, the modulation of tissue-resident NK cells and conventional NK cells may alter the local biological response.

Table 2 summarizes different therapies involved in NK cells and their involvement in pregnancy.

7.1. Progesterone

Progesterone is an essential hormone that may be given orally or applied topically for pregnancy maintenance [101–103]. NK cells do not have receptors for this hormone; however, T cells do [102–104]. The factor induced by progesterone, PIBF, generates a tolerogenic TH2 response in the endometrium and consequently may affect NK cell migration and response [105]. Miko et al. [106] reported an inverse correlation between PIBF levels and local leptin levels and leptin receptors involved in local progesterone production and trophoblast growth. These results parallel that described blocking PIBF in an experimental mouse model. PIBF inhibition significantly increased miscarriages despite successful implantation. The increase in miscarriage was associated with an increase in NK activity [104–106]. In the equine model, an exciting interaction between galectin and PIBF has been observed protecting pregnancy [107]. Thus, the effect of progesterone is dependent upon glycolelin.
A and PIBF transcription and secretion. They, in turn, provide the critical tolerogenic milieu for embryo implantation and pregnancy.

In the presence of progesterone, stromal and dendritic cells secrete IL-15 and IL-18 critical for NK cells [105,108]. A significant increase in IL-15 level is observed in the secretory phase compared to the proliferative phase of the hormonal cycle and then during early pregnancy in parallel to progesterone levels [105,108]. A negative correlation was also found between IL-18 and the number of uNK [109]. Murata H and coworkers [110] recently reported the importance of the heart- and neural crest derivatives-expressed transcript 2 (HAND2) and inductor of IL-15 secretion by human endometrial stromal cells induced by synthetic progesterone. Then, it is assumed that this IL-15 produced is critical in the role of NK in the decidua.

In an interesting study involving in vitro fertilization, it was found that serum progesterone levels are critical for pregnancy success and termination, suggesting that modulation of decidual cells by progesterone is crucial [111]. Furthermore, progesterone is required to induce a tolerogenic milieu in the endometrium and the decidua.

The hormone is generally used as an immunosuppressor. There are therapeutic guidelines to use in endometriosis, and it has been used to prevent abortion and preterm delivery [112]. In general, there are three pharmacological approaches: oral formulation, injections, and micronized hormone. It was hypothesized that progesterone absorption through the vagina may downregulate the endometrium’s inflammatory milieu [112]. However, there are differences in pharmacodynamics depending on the hormone preparation. The use of progesterone regulates glucose transport, enhancing endometrial receptivity to the embryo [101].

Progesterone’s effect on different cell types and trophoblast, like the newly described variety of trophoblast expressing HLA-G, is unknown [113]. However, in this case, the critical element modulates inhibitory signals through the KIR receptors, which can be crucial for embryo implantation and successful pregnancy.

7.2. Low Molecular Weight Heparin

Experiments ex vivo performed many years ago highlighted the role of heparin decreasing cytotoxic response [114]. Heparin was also shown to increase fetus stability, diminishing pregnancy loss. The effect of heparin is attributed to modulation of endothelial cell responses, relaxing the vasculature, decreasing resistance, and hence protecting the patient from preeclampsia [114–116]. However, ex vivo experiments using macrophages and helper T cells stimulated with heparin were more inflammatory than tolerogenic [117]. This unanticipated result may be due to the lack of other cells that contribute to the cell response. A recent report reveals that the effect of heparin as the antitumor drug does not involve NK cell activation, suggesting that heparin instead activates Th1 and hence NK cells are more cytotoxic against the tumour [118]. More research is required to ascertain the importance of this drug on in vivo NK cell modulation in pregnancy.

Patients with antiphospholipid antibodies and with thrombotic pathologies are treated with heparin during pregnancy. There are several hypotheses on the possible mechanisms of heparin; however, none of them involved NK cell response [118,119]. Thus, heparin’s role in preventing thrombotic events may be crucial for the embryo or fetal survival. The use of heparin as an immunomodulator is complicated to envision; however, the effect of heparin binding to receptors on different cell types and modulating cellular processes may, in turn, affect NK cell response [118,119]. Therefore, more research should be performed to ascertain the possible effect of this and other glycosaminoglycans on NK cell function.

7.3. Corticosteroids

Corticosteroids have been found to modulate the NK cell response [120]. Prednisolone treatment of NK in vitro suppressed NK cells cytolytic activity against K562 cells [121]. This suppressive effect of steroids was observed on the cytotoxic CD16+ NK cells [121]. Before pregnancy, the effect of corticosteroids has been related to a decrease in the subclinical
pro-inflammatory burden [122,123], and it may favor embryo implantation. However, it is unclear what corticosteroids may affect local trNK cells or the migration of cNK cells.

A recent review by Li and coworkers [124] revised the PD1/PD1 L axis and pregnancy role. When there is an increase in the expression of PD1 in endometriosis [125], there is less probability of pregnancy maintenance. In cancer therapy, the difference in response is clear using dexamethasone or prednisone involving PD1/PDL1 L axis [126]. Therefore, this axis should be studied in more extensive trials. On the other hand, if steroids down modulate PD1 and decrease the cytotoxic or pro-inflammatory responses of stimulated NK cells, then embryo anidation and pregnancy will be successful.

7.4. Intravenous Immunoglobulins (IVIg)

The pharmacological mechanisms of IVIg enhancing embryo implantation and successful pregnancy have not been studied thoroughly. In peripheral blood, it was reported: a decrease in NK cytotoxic activity, a decreased amount of activated T and B cells, an increase in tolerogenic T cells, along with a reduction of activated antigen-presenting cells [127]. A decrease of autologous antigens upon treatment is suspected [127–129]. In a meta-analysis of 13 trials, Christiansen et al. [129] were unable to determine the impact of IVIg on live births. However, if the treatment started before conception, the results were better. Similar outcomes were encountered by Abdolmohammadi-Vahid et al. [130] in four clinical trials. More well designed clinical trials, including monitoring NK cell cytotoxic and tolerogenic responses, are required.

Two exciting issues have not been well described in this treatment. First, it is believed that intravenous immunoglobulins would decrease the number of antibodies against their own ligands and decrease autoimmune responses [127–131]. Yet, it is unclear if IVIg may enhance antibody-dependent cellular cytotoxicity on NK cells. Second, ADCC may increase the elimination of unwanted cells in different tissues and consequently decrease the inflammatory burden detrimental to embryo implantation and pregnancy maintenance.

7.5. Lipid Infusions

Lipid infusions, particularly Intralipid, have been suggested as alternative therapy for recurrent abortions since these lipids seem to modulate NK cell function and promote trophoblast invasiveness [132,133]. In mouse models and ex vivo studies, intralipid suppressed abnormal NK cytotoxic [132–135]. However, the results of the meta-analysis have not been conclusive. On the other hand, omega-3 fatty acid infusions decreased inflammatory burden (TNF-α, IL-1, IL-6 or IL-8 [133–136]. However, again, the lack of adequately designed trials has limited this therapy in recurrent abortions.

Our group reported an increase in NK proliferative and cytotoxic responses when human NK cells were stimulated in vitro with chylomicrons [137]. In addition, the supplementation with fatty acids modulated the expression of different receptors on the NK membrane [138]. Probably, the use of intravenous intralipid would modulate NK subpopulations and consequently favor NK maturation and migration.

7.6. Vitamin D

Several years ago, Evans and coworkers [139] reported that decidual cells could synthesize 1,25-dihydroxy vitamin D3 and that this production is higher in the first trimester of pregnancy. These results raised essential questions on local cell tolerance and the importance of vitamin D in tolerogenic responses. Tamblyn and coworkers [140] showed significant differences in vitamin D3 between uNK and peripheral blood NK cells, suggesting different overall signal transduction responses. Even though the authors concluded that uNK cells and peripheral blood NK cells are not the direct targets of vitamin D, the difference in cell responses suggests that the uptake of vitamin D3 can be an accessory signal for local uNK tolerogenic responses.

Vitamin D3 was shown to modulate NK cytotoxic response [141], an event that has been linked to an increased success rate of pregnancy [142]. Ota and coworker [143] per-
formed a gene polymorphism of methylenetetrahydrofolate reductase C677T in patients with recurrent abortion [144]. Patients with the TT polymorphism had higher homocysteinemia levels, lower vitamin D3 levels, nevertheless, higher NK cell cytotoxic responses against K562 cells [144]. These results suggest a relationship between folate metabolism with vitamin D3 levels and NK cytotoxic responses. Supplementation of vitamin D3 and methyl folate in these patients will probably increase pregnancy success.

In a recent review on vitamin D and pregnancy, Zhao et al. [144] discussed the importance of this vitamin on pregnancy loss associated with antiphospholipid syndrome and modulation of Th1/Th17 axis in recurrent pregnancy loss. It is suggested that the effect of vitamin D disrupting this pro-inflammatory Th1/Th17 axis affect NK responses and hence pregnancy maintenance. More research has to be done to verify this hypothesis.

7.7. Exosomes

Exosomes are extracellular vesicles that originate from the endosomal compartment of cells. The structures contain protein, DNA, RNA, and/or miRNA of the cells that secrete them. Exosomes have been used as biomarkers in different reproductive diseases [145–151]. Wu and coworkers [149] analyzed the miRNA in samples from patients with varying types of endometriosis to understand the regulation of different pathways. They then were able to explore the most relevant miRNA in endometriosis [148–150]. This information is critical since directed therapies depending on endometriosis may provide new elements to control the inflammatory disease and aid in fertilization [148–166]. In addition, exosomes contain miRNA and other proteins. These miRNAs decrease the inflammatory burden by blocking the transcription of inflammatory cytokines and, consequently, induce tissue repair crucial for embryo annidation and pregnancy survival [149–151].

The use of endosomes for therapy has raised the interest of several groups in recent years [145–149]. In addition, the experience with other disease has provided new tools for generating individual and targeted analysis to decrease the inflammatory response and provide the critical tissue milieu for implantation and pregnancy [145–151].

7.8. Other Therapies

A recent review by Busnelli et al. [104] revisited several procedures regarding recurrent pregnancy loss. The intruterine infusion of autologous peripheral blood mononuclear cells (PBMC) seems to reduce endometriosis [105]. Also, platelets infusion can increase local progesterone production, probably by releasing TGFβ [152]. Thus, the infused cells provide a tolerogenic milieu for embryo implantation. Also, a mild positive effect of subcutaneous G-CSF injection inducing clinical pregnancy post embryo implantation was observed [104]. One possible mechanism of tolerance induced by G-CSF is the inhibition of NK cytotoxicity activity [104]. It is nevertheless unclear why the beneficial effect of G-CSF is subcutaneous and not intrauterine.

Other therapies involve platelet-rich plasma in the uterine cavity and the use of different stem cells [149–155]. The goal of the platelet-rich plasma is related to local TGFβ release and consequently promote NK differentiation [149–155]. There have not been conclusive studies using this therapy and other therapies involving various stem cells and allostimulation [155]. There is still room for more directed treatments, which would increase the recruitment and modulation of NK cells. However, it is essential to recognize that a balance of NK subpopulations, cNK, uNK, and dNK, is required for normal physiological responses. The immune vigilant role of NK cells is also crucial for eliminating pathogens and abnormal cells, and non-viable embryos.

Modulation of PD1/PDL1 is also essential in understanding NK responses in the endometrium and the possible role of this diad in preeclampsia [156–160]. This diad’s mechanism may depend upon the inflammatory burden and the expression of markers of downregulation on NK cells. The inflammatory response generated by pathogens of tumour cells in the endometrium involves NfkB, which also seems vital in uterine artery remodeling [160].
Treatment like medroxyprogesterone acetate was shown to increase NK cell activity in menopause [161]. This modulation may also be relevant in other conditions like polycystic ovary syndrome, in which hormonal dysregulation may affect endometrial NK cell responses [158]. Waiyaput and coworkers [162] reported that treatment with combined contraceptive pills increased the migration of NK cells, suppressive macrophages, and tolerogenic T cells to the inflamed endometrium of menopause women. In addition, protoanaxadiol, an antioxidant ginsenoside compound, was reported to induce the expression of tolerogenic antigens on NK cells [163]. Thus, hormone therapy radical scavenging causes a protective response in the endometrium.

Interestingly, new therapeutic uses essentially for antitumor responses as LAIR-2 (LAIR-1 inhibitor) and P4H shRNA (collagen inhibitor) modulate NK cytotoxic responses and may provide exciting options in the future for peripheral and trNK cells [164]. JAK kinase inhibitors were shown to modulate peripheral NK and ILC1 cells with stimulating effects on immune response regulation [165]. New studies may focus on the use of therapy usually used for treating tumors. Aromatase inhibitors may also be relevant for combined therapies in endometriosis.

The immunomodulatory effect of Mesenchymal Stem Cells (MSCs) on NK cells has been a matter of discussion for several years [145,146]. In a mouse model of recurrent abortion, when MSC cells were co-cultured with primed, inflammatory NK cells, MSC induced a shift in cytokine production and tolerogenic responses [145]. This result suggests that MSC cells may influence a tolerogenic microenvironment in early pregnancy. This effect has to be assessed in clinical studies. It is unclear if another type of stem cell could also be involved in the treatment.

Another promising target for therapy is G-CSF since the cytokine is modulated in the endometrium and may facilitate the endometrial repair and NK cell migration. Studies of the role of this cytokine in pregnancy and endometrial cancer are underway.

It can be concluded that the different therapeutic schemes should be concentrated on the signal transduction responses of NK cells. Directed therapies would enhance the expression and functions of tolerogenic molecules rather than activating molecules, promoting embryo rejection and pregnancy termination. Figure 1 illustrates the crucial pathways that should be modulated with new types of directed therapy. The role of cytokines or other soluble factors may not be as effective as other factors, considering the difference in peripheral NK cells compared with tissue NK cells. In addition, the reduction of the inflammatory milieu has to be achieved, most probably with complementary therapy. The effect of cytokines and fatty acids may depend on the NK cell type and the type of fatty acid involved. Future research should be directed to study the mechanism of NK modulation by using small molecules that would control specific signal transduction pathways. Several therapies employed nowadays still require proper validation.
Figure 1. This figure summarizes the general aspects discussed in the review. Some of the most relevant receptors in human NK cells are represented along with the mechanism of the different therapies reviewed. The inhibitory effects are depicted in red, and the activating effects in blue. The receptors described in yellow represent an effect that can induce activation or inhibition. In the case of fatty acids, the effect encountered depends on the type of fatty acid, and in the case of the cytokines, G-CSF and IL-15, it depends on the NK cell type.

8. Conclusions

There are several populations of NK cells that may play an essential role in immune response in pregnancy. The presence of different subpopulations of NK cells in tissues and its possible migration, dependent on hormonal stimulus, has raised important questions concerning pregnancy’s physiological and pathological responses. However, screening the peripheral blood NK cells number and cytotoxic function provides only partial information concerning the tissue-specific effect. More research should be performed to identify potential markers of therapy response that could be reliable and easily detectable.

Pathogens can activate local NK cell responses and can jeopardize the pregnancy. Different viral, parasitic, and bacterial infections affect local NK cells, essential for the embryo or fetal survival. Most of the responses can be modulated by KIR receptors, KIR ligands, and small tolerogenic small HLA molecules. However, most of the studies have been carried out either in the animal model with few cases in human counterparts, which have to be analyzed carefully. More research should be focused on exploring the effect of pathogens and therapy. In the current pandemic, new concepts of viral response, clearance and use of vaccines have been achieved in the emergency. Some of this knowledge can be extrapolated in other infectious.

Local hormones and other therapies seem to provide essential insights into pregnancy outcome rather than lipid emulsions. Steroids are vital compounds for decreasing the inflammatory burden and consequently modulate NK cell activity. However, new formulations of steroids should be designed to enhance treatment efficiency and reduce unwanted responses. Based on the analysis of endometrial biopsies, genetic and molecular analysis, and NK cell populations, the categorization of patients may enhance treatment responses.

Further research should be performed to increase therapy efficiency. Exosomes and mesenchymal stem cells could be essential for individualized therapy. Other strategies may soon be available and will provide more insights into the role of NK in pregnancy outcome.
Table 2. Pharmacologic modulation of NK cells. The table represents the significant finding with the different described treatment for modulation of NK cell populations and functions.

| Treatment Type                 | Effect on Peripheral NK Cells (Humans)                                                                 | Local Cells                                           | Animal Model                          | References                      |
|--------------------------------|--------------------------------------------------------------------------------------------------------|-------------------------------------------------------|---------------------------------------|----------------------------------|
| Progesterone                   | Inhibition on NK cytotoxicity by the progesterone-induced blocking factor                              | The indirect effect through T lymphocyte and stromal cell–cell cytokine secretion | Increase tolerogenic response. There is an indirect effect of T cells and stromal cells. | [103–113]                      |
| Low molecular weight heparin   | No direct effect                                                                                        | The indirect effect through T cell?                   | No direct reports                     | [114–119]                      |
| Corticosteroids                | Decrease in cell number and decrease in cytotoxic response.                                            | Downregulation of PD1/PD1L expression                | Increase in tolerogenic responses     | [120–126]                      |
| IVIg                            | Decrease in TH1 autoimmune cells. Modulation of NK cells                                               | Reduction of deficient stromal cells.                | Not reported                          | [127–131]                      |
| Lipid infusion                 | Decrease of the inflammatory burden and reduction in NK cytotoxic activity                             | Reduction of local transcription and secretion of IL15 and IL18 | Suppression cytotoxicity in vitro     | [132–138]                      |
| Vitamin D                      | Decrease of in vitro cytotoxic response.                                                               | Increase in tolerogenic responses                    | Modulation of iNKT cells which may affect NK cells | [139–144]                      |
| Exosomes                       | Increase in cytotoxic response against tumour cells                                                  | Decrease inflammatory burden increase tolerance      | Increase tolerogenic NK cell responses | [145–151]                      |
| Intrauterine PBMC Platelets    | Increase in NK cell activity                                                                           | Increase tolerogenic response via TGFβ               | Increase in local tolerogenic response | [152–155]                      |
| Medroxyprogesterone acetate    | Increase in NK cell activity                                                                           | Local decrease of IL-15                              | Not described                         | [161,162]                      |
| Other small molecule therapy   | Decrease peripheral NK cytotoxic response                                                              | Regulation of dNK                                     | Not described                         | [164,165]                      |
| G-CSF                          | There is an indirect effect on NK cytotoxic response                                                  | Increase in tolerogenic response                      | Increase in tolerogenic response Tim-3 dependent | [166]                           |

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