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From Womb to World: Transplacental Immunity and HIV Response in Neonates

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Abstract

The neonatal period marks a critical stage of immune development, especially in infants exposed to HIV during gestation. While mother-to-child transmission (MTCT) has significantly declined with the use of antiretroviral therapy (ART), a considerable number of neonates remain vulnerable to infection. Interestingly, many HIV-exposed neonates remain uninfected, underscoring the vital role of transplacental immunity in modulating HIV susceptibility. This review explores the intricate immunohematological interactions between maternal and fetal systems, emphasizing how maternal antibodies, placental immune cells, and cytokine environments contribute to either protection or vulnerability against HIV. Key components of transplacental immunity include the selective transfer of maternal IgG antibodies, regulation of placental cytokine balance, and early activation of innate immune responses in the fetus. The placenta itself acts not only as a physical barrier but as an immune organ that shapes fetal immune education through interactions with maternal immune cells and pathogens. Neonatal natural killer (NK) cells, monocytes, and dendritic cells are influenced by intrauterine exposures, potentially priming them for heightened immune vigilance or dysregulation after birth. Furthermore, ART—while essential for maternal viral suppression—can influence neonatal immune development, with implications for hematological parameters and vaccine responsiveness.

Keywords: Transplacental immunity, HIV-exposed neonates, maternal antibodies, immune modulation, vertical transmission

Abbreviations

ADCC – Antibody-Dependent Cellular Cytotoxicity, **ART** – Antiretroviral Therapy, **BCR** – B Cell Receptor, **DC** – Dendritic Cell, **FcRn** – Neonatal Fc Receptor, **HEU** – HIV-Exposed , ninfected, **HIV** – Human Immunodeficiency Virus, **IgG** – Immunoglobulin G, **IL** – Interleukin
NK – Natural Killer (cell), **PCR** – Polymerase Chain Reaction, **TCR** – T Cell Receptor, **TGF-β** – Transforming Growth Factor Beta, **TLR** – Toll-Like Receptor, **TNF-α** – Tumor Necrosis, Factor Alpha, **WHO** – World Health Organization

Introduction

Human immunodeficiency virus (HIV) infection in neonates presents a unique immunological scenario, one in which the immature immune system must contend with a highly adaptive pathogen during a critical phase of development [1-2]. Despite high exposure rates in utero and during delivery, only a subset of infants born to HIV-positive mothers become infected. This observation points to the presence of protective immunological factors, many of which originate from the maternal-fetal interface. Among these, transplacental immunity plays a central role, enabling the fetus to receive immunoglobulins and other immune mediators from the mother, thus equipping the neonate with passive immunological defenses during early life [3-4].The placenta serves as the central conduit for transplacental immunity. Far from being a passive filter, it acts as a highly selective and dynamic immunological barrier. Through mechanisms such as Fc receptor–mediated antibody transfer and cytokine regulation, the placenta facilitates the delivery of maternal immunoglobulin G (IgG) antibodies and shapes the intrauterine immune environment. However, in HIV-infected pregnancies, placental function may be compromised due to inflammation, villitis, and altered expression of immunoregulatory molecules. These changes can affect both the quality and quantity of immune protection conferred to the fetus [5-6].

One of the most critical components of transplacental immunity is the maternal IgG antibody, which is transferred to the fetus beginning in the second trimester and peaking in the third. In the context of HIV, maternal antibodies may include HIV-specific neutralizing antibodies capable of inhibiting viral replication. However, the efficiency of this transfer is influenced by maternal viral load, ART status, gestational age, and placental integrity. Moreover, not all transferred antibodies are beneficial—some may enhance viral entry via antibody-dependent enhancement (ADE), thereby complicating the protective landscape [7].Beyond antibodies, the maternal immune environment—characterized by cytokines, chemokines, and regulatory cells—has a profound influence on fetal immune development. In a healthy pregnancy, anti-inflammatory cytokines such as interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β) dominate, promoting tolerance and protecting against immunopathology. HIV infection can disrupt this balance, increasing levels of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), which may compromise placental integrity and alter fetal immune programming. These cytokine shifts can predispose the fetus to both infection and immune dysregulation postnatally [8-9].

Innate immune cells in the fetus, such as natural killer (NK) cells, monocytes, and dendritic cells, exhibit distinctive developmental profiles that differ from their adult counterparts. While their cytotoxic activity is generally lower, these cells are primed to respond rapidly to infection. Exposure to HIV antigens in utero may modulate

their responsiveness, either enhancing vigilance or contributing to immune exhaustion. Toll-like receptors (TLRs), another component of innate immunity, are present in the fetus and may recognize viral components, initiating signaling cascades that shape the neonate's initial immune repertoire [10-11].The administration of maternal antiretroviral therapy has revolutionized the management of HIV in pregnancy, drastically reducing mother-to-child transmission rates. However, ART also crosses the placenta and may influence fetal immune development in unintended ways. Studies suggest alterations in T-cell subset distributions, delayed thymic maturation, and hematological abnormalities in ART-exposed but uninfected infants. These findings necessitate a closer examination of the long-term immunohematological impact of ART during gestation and its interplay with transplacental immune factors [12-14].

Additionally, neonates born to HIV-positive mothers often face challenges beyond infection itself. HIV-exposed but uninfected (HEU) infants show altered responses to vaccines, increased susceptibility to infections, and distinct immunological profiles compared to HIV-unexposed peers. These disparities highlight the need to understand how transplacental immunity and intrauterine exposures shape neonatal immune trajectories and inform clinical outcomes. Addressing these questions is essential for optimizing postnatal care and immunization strategies in this vulnerable population [15-16].

Aim

The aim of this review is to explore the intricate mechanisms underlying transplacental immunity in the context of HIV exposure during pregnancy, with a particular focus on the immunological responses of neonates.

Review Methods

This review article was conducted through a comprehensive examination of existing literature to understand the dynamics of transplacental immunity in neonates exposed to HIV, with a particular focus on the impact of maternal HIV infection and antiretroviral therapy (ART) on neonatal immune responses. The methodology for this review was structured to ensure a thorough analysis of both the immunological mechanisms at play and the therapeutic interventions available, particularly ART, which has significantly impacted the prevention of vertical HIV transmission. The review process was systematic, covering both primary research studies and relevant secondary sources, ensuring an evidence-based narrative on the topic.

Search Strategy and Data Sources

A structured search strategy was employed to identify relevant studies on transplacental immunity, maternal HIV infection, neonatal immune responses, and ART in the context of HIV prevention during pregnancy. The databases accessed included PubMed, Scopus, and Web of Science, which are comprehensive repositories of peer-reviewed scientific literature. The following keywords were used to guide the search: "transplacental immunity," "neonatal HIV exposure," "maternal HIV," "antiretroviral therapy and pregnancy," "maternal-fetal immune interactions," and "HIV vertical transmission." The inclusion criteria were set to prioritize studies published in English, peer-reviewed, and with relevance to the topic at hand, ensuring a focus on high-quality and recent research. The publication range was set from 2000 to the present to capture contemporary findings, although earlier pivotal studies were also included when necessary.

Inclusion and Exclusion Criteria

Studies were included based on the following criteria:

1. **Study Design**: Peer-reviewed original research articles, systematic reviews, clinical trials, cohort studies, and observational studies were considered.
2. **Population**: Studies focusing on pregnant women with HIV, their immune responses, and those addressing neonatal health outcomes, particularly those involving HIV-exposed neonates, were included.

3. **Intervention**: Studies that examined the impact of ART during pregnancy and its influence on maternal immune responses and neonatal health outcomes were prioritized.
4. **Outcome Measures**: Studies focusing on the effects of ART on maternal viral load, placental immunity, transfer of antibodies, and neonatal immune system responses were key.
5. **Language**: Only studies published in English were included.

Exclusion criteria included:

1. **Non-human Studies**: Studies not conducted on humans or not directly related to the maternal-fetal immune interaction in the context of HIV exposure were excluded.
2. **Irrelevant Articles**: Articles not addressing transplacental immunity, ART effects, or maternal HIV transmission dynamics were excluded.
3. **Outdated Sources**: Studies published before 2000 were excluded unless they were foundational works that provided critical context to newer findings.

The Placenta as an Immunological Barrier and Conduit

The placenta occupies a dual role in fetal development—as a structural barrier protecting the fetus from maternal pathogens, and as a conduit for the regulated transfer of immune mediators, nutrients, gases, and waste products. In the context of HIV exposure, the placenta assumes added importance, orchestrating a delicate immunological balance between tolerance and defense. This unique organ facilitates maternal-fetal crosstalk through a tightly regulated network of cellular interactions, cytokine gradients, and receptor-mediated transport mechanisms that determine the degree of immune protection or vulnerability afforded to the neonate [17-19].Histologically, the placenta comprises several layers, with the syncytiotrophoblast acting as the first and primary interface between maternal blood and fetal circulation. This multinucleated barrier is devoid of intercellular gaps, thereby minimizing direct viral passage. However, HIV has demonstrated the ability to cross this barrier under specific pathological or inflammatory conditions, such as chorioamnionitis or placental villitis. Transmigration may occur via infected maternal immune cells (trojan horse mechanism), direct transcytosis, or breaches in placental architecture. The expression of chemokine receptors such as CCR5 and CXCR4 on placental trophoblasts and fetal macrophages (Hofbauer cells) further implicates this tissue in potential HIV interaction and transmission dynamics [20-22].

Functionally, the placenta actively transfers maternal immunoglobulin G (IgG) antibodies to the fetus via the neonatal Fc receptor (FcRn), which is abundantly expressed on syncytiotrophoblasts. This process intensifies in the third trimester and ensures passive immunization of the fetus against a broad spectrum of pathogens. In HIV-infected pregnancies, the efficiency of IgG transfer may be diminished due to maternal hypergammaglobulinemia, placental inflammation, or ART-induced changes in FcRn expression. Despite these limitations, HIV-specific neutralizing antibodies have been detected in the cord blood of some exposed neonates, suggesting partial protection. However, concerns remain regarding the potential for non-neutralizing or enhancing antibodies to facilitate viral entry through mechanisms such as antibody-dependent enhancement (ADE) [23-25].

Beyond antibodies, the placenta modulates cytokine profiles at the maternal-fetal interface, which directly influences fetal immune development. Under physiologic conditions, a predominance of anti-inflammatory cytokines (e.g., IL-10, TGF-β) supports fetal tolerance. HIV infection disrupts this milieu, upregulating pro-inflammatory mediators such as TNF-α, IL-6, and interferon-gamma (IFN-γ), which may compromise placental integrity, promote immune activation, and increase the risk of in utero HIV transmission. Moreover, placental immune cells—particularly Hofbauer cells—serve as both sentinels and reservoirs. Their role in HIV pathogenesis remains complex: while they can

phagocytose viral particles and produce antiviral cytokines, they may also support viral replication under permissive conditions [26-27].The influence of maternal ART on placental immunology adds another layer of complexity. Certain antiretroviral drugs have been associated with mitochondrial toxicity, altered angiogenesis, and disruptions in cytokine balance, potentially affecting the placental transfer of immune components and fetal hematopoiesis. While ART remains essential for viral suppression and transmission prevention, its implications for transplacental immune function and long-term neonatal immunity warrant continued investigation [27-28].

Maternal Antibodies: Double-Edged Swords in Neonatal HIV Defense

Maternal antibodies, particularly immunoglobulin G (IgG), are critical to neonatal immunity, providing essential protection against a variety of infections during the early months of life. These antibodies are transferred across the placenta via the neonatal Fc receptor (FcRn), ensuring that the fetus is equipped with passive immunity prior to birth. In HIV-exposed pregnancies, the role of maternal antibodies takes on an additional layer of complexity, as they may either provide protection against HIV infection or, conversely, enhance the risk of viral transmission. This dual nature of maternal antibodies as both protective and potentially harmful is reminiscent of a double-edged sword, where their capacity to defend against pathogens may simultaneously leave the neonate vulnerable to HIV [29].

On the one hand, maternal HIV-specific antibodies can offer the neonate a certain degree of passive protection against HIV infection. These antibodies are capable of neutralizing the virus by binding to HIV envelope glycoproteins and preventing viral entry into host cells. Neutralizing antibodies can also prevent viral replication in the neonate, reducing the likelihood of infection despite exposure during delivery or breastfeeding. In fact, several studies have demonstrated the presence of HIV-specific IgG in the blood of uninfected neonates born to HIV-positive mothers, suggesting that maternal immunity may delay or prevent HIV acquisition in some cases. The transfer of these antibodies plays a central role in vertical transmission prevention strategies, especially when ART is administered to the mother during pregnancy [30-31].

However, maternal antibodies may not always offer the anticipated protection. A key concern arises with non-neutralizing antibodies or antibodies that inadvertently enhance viral entry. This phenomenon, known as antibody-dependent enhancement (ADE), occurs when antibodies bind to HIV without neutralizing the virus, and instead, promote viral uptake into host cells through Fc receptor-mediated mechanisms. ADE can be particularly problematic in the context of HIV, as maternal antibodies might facilitate the very transmission they are supposed to prevent, especially in the presence of high maternal viral load or an ineffective immune response. This paradoxical effect can increase the risk of HIV infection in the neonate, particularly when antibody titers are high, or the antibodies present are not sufficiently potent to neutralize the virus [32-33].

The affinity of maternal antibodies for specific HIV epitopes also plays a role in determining their protective or harmful effects. The diversity of the HIV virus—particularly in its ability to mutate rapidly—poses a challenge for maternal antibody responses. Antibodies targeting conserved regions of the virus are more likely to provide effective neutralization, while those targeting variable regions may be less efficient or even harmful. Furthermore, the immune landscape in HIV-infected pregnancies is often skewed by chronic inflammation, altered cytokine profiles, and immune exhaustion, which can affect the quality of the antibodies produced. Consequently, the maternal antibody response may be less robust in certain individuals, limiting the potential for protection and exacerbating the risk of vertical transmission [34].

In addition to direct antiviral activity, maternal antibodies influence the neonatal immune system by shaping the development of the infant's own

immune responses. The presence of maternal antibodies at birth can affect the maturation of neonatal immune cells, particularly B cells, by modulating their activation and differentiation. While maternal antibodies help prevent infections early in life, they may also interfere with the infant's ability to mount an independent immune response, especially in the case of persistent antibody-mediated suppression. This phenomenon is particularly important for vaccines, where the presence of maternal antibodies can attenuate the infant's response to vaccination. This interference can complicate the establishment of effective long-term immunity in HIV-exposed but uninfected (HEU) infants [36].

The timing and efficiency of maternal antibody transfer are also crucial determinants of neonatal HIV outcomes. In HIV-infected pregnancies, factors such as maternal viral load, ART adherence, and the presence of placental inflammation can significantly impact the quantity and quality of antibodies transferred to the fetus. High maternal viral loads or inadequate ART regimens can result in suboptimal antibody transfer, leaving the neonate more susceptible to infection. Conversely, well-controlled maternal viral loads and effective ART can facilitate the transfer of protective antibodies, enhancing the chances of neonatal protection against HIV. Thus, understanding the interplay between these factors is key to optimizing prevention of mother-to-child transmission (PMTCT) strategies [37-38].

Neonatal Innate Immunity and Response to HIV Exposure

The neonatal immune system is functionally immature at birth, with innate immune responses playing a critical role in providing initial defense against pathogens, including HIV. Unlike adults, neonates rely heavily on innate immune mechanisms for pathogen recognition and elimination, as their adaptive immune system is still developing. This phase of immune development is particularly important in HIV-exposed neonates, as the innate immune response often represents the first line of defense against viral invasion. However, the efficiency and functionality of this early immune response can be compromised in HIV-exposed infants, especially those who are HIV-infected or HIV-exposed but uninfected (HEU), thus influencing their susceptibility to both HIV infection and other infections [39-40].

One of the key components of the neonatal innate immune system is the pattern recognition receptor (PRR)-mediated detection of pathogens, including viral pathogens like HIV. Toll-like receptors (TLRs) are central to the activation of the innate immune response, recognizing pathogen-associated molecular patterns (PAMPs) such as viral RNA or glycoproteins. In neonates, the expression and functionality of TLRs are distinct from those of adults, with certain TLRs showing reduced responsiveness, particularly in the early stages of life. This altered TLR profile in neonates could impact their ability to mount a robust antiviral response against HIV. Studies suggest that neonatal TLRs, especially TLR3, TLR7, and TLR8, are capable of detecting HIV and initiating immune responses; however, their suboptimal activation may contribute to the impaired response to HIV and other infections in neonates [41-42].

Dendritic cells (DCs), another cornerstone of innate immunity, also play a significant role in detecting HIV and initiating immune responses. In neonates, DCs are present but functionally distinct from those in adults. They are more prone to inducing tolerogenic responses, which may hinder the development of protective immunity to HIV. HIV exposure can further alter the functionality of these cells, potentially leading to an increased risk of viral persistence and immune dysregulation. The compromised dendritic cell function in neonates may also impair their ability to effectively present HIV antigens to T cells, which is essential for generating an adaptive immune response. Additionally, the presence of HIV in utero may alter the programming of these cells, leaving the infant more susceptible to chronic immune activation and inflammation [43-44].Natural killer (NK) cells, essential effector cells of the innate immune system, are another critical player in the response to HIV. NK cells

exert their antiviral effects by recognizing and killing infected cells through the release of cytotoxic molecules and the production of cytokines. While NK cells in neonates are present and capable of recognizing HIV-infected cells, their cytotoxic activity is generally weaker than in adults. The immaturity of neonatal NK cells, combined with potential exposure to HIV in utero, may contribute to a suboptimal antiviral response. In some cases, HIV-exposed but uninfected infants may demonstrate alterations in NK cell function, possibly due to chronic low-level exposure to the virus. This may lead to an impaired ability to control early HIV replication, especially during the perinatal period when viral exposure is most likely [45-46].

Monocytes and macrophages, which serve as both sentinel cells and reservoirs for HIV, are also pivotal in the neonatal response to HIV exposure. In neonates, these cells demonstrate a developmental immaturity that can impair their ability to mount an efficient inflammatory response to HIV. Additionally, monocytes in HIV-exposed neonates have been shown to exhibit altered activation and cytokine production, potentially leading to an increased susceptibility to viral replication and dissemination. This altered macrophage function may also play a role in the establishment of HIV reservoirs in neonates, allowing the virus to persist in tissues despite antiretroviral therapy. Moreover, maternal HIV-specific antibodies can influence monocyte and macrophage function in neonates, either enhancing or inhibiting viral replication depending on the type of antibody present [47-48].

While the innate immune system in neonates offers essential defense against HIV, it is not without limitations. The innate immune response in neonates is characterized by a bias toward tolerance rather than inflammation, which is thought to protect the fetus from immune-mediated damage during pregnancy. However, this bias can be detrimental when the immune system encounters pathogens like HIV, as it may hinder the establishment of a robust antiviral response. Chronic immune activation due to persistent low-level viral exposure can also impair the function of innate immune cells, contributing to immune exhaustion and promoting the persistence of HIV in neonates [49-50].Neonatal responses to HIV exposure are further complicated by maternal factors, including viral load and ART use during pregnancy. High maternal viral loads may result in increased exposure of the fetus to HIV, potentially overwhelming the neonatal immune system. Conversely, maternal ART reduces viral transmission but can also influence the neonate's immune system in ways that are still not fully understood. ART drugs can cross the placenta, and while their primary function is to prevent viral transmission, they may also affect the development and function of neonatal innate immune cells, particularly those involved in antiviral responses [51].

Cytokine Milieu and Immune Modulation at the Maternal-Fetal Interface

The maternal-fetal interface represents a complex immunological environment where maternal immune responses must be carefully modulated to protect the fetus while simultaneously preventing maternal immune rejection of the semi-allogeneic fetus. This delicate balance is facilitated by a specific cytokine milieu, which is shaped by both maternal and fetal factors, and plays a critical role in the immune modulation that occurs during pregnancy. The cytokines present at the maternal-fetal interface not only influence the development of the fetus but also dictate how the maternal immune system responds to pathogens such as HIV. Understanding the cytokine profile at this interface is pivotal in comprehending how maternal immunity may either enhance or diminish the neonate's ability to mount an effective immune response to HIV exposure [52].Cytokines are signaling molecules that regulate immune cell activity, and their expression at the maternal-fetal interface is intricately regulated to prevent fetal rejection while maintaining immune surveillance against infections. The predominant cytokines in this environment include pro-inflammatory cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6),

and tumor necrosis factor-alpha (TNF-α), which are involved in immune activation and defense, as well as anti-inflammatory cytokines such as interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β), which promote immune tolerance. The balance between these cytokines determines the success of pregnancy and the fetus's ability to develop immune competence while avoiding immune-mediated damage [53].

In the context of HIV infection, maternal cytokine profiles are altered in response to both the virus and the chronic immune activation that is often seen in HIV-infected individuals. Maternal HIV infection can increase the production of pro-inflammatory cytokines such as IL-6, TNF-α, and interferon-gamma (IFN-γ), which can lead to persistent low-level inflammation. This inflammation at the maternal-fetal interface may have significant implications for fetal immune development, potentially altering the capacity of the neonate's immune system to respond effectively to HIV exposure. Elevated levels of these pro-inflammatory cytokines may also contribute to the disruption of the placental barrier, facilitating HIV transmission to the fetus. Chronic inflammation associated with maternal HIV may further skew the immune balance, leading to immune activation in the fetus, which could predispose neonates to immune dysregulation and chronic inflammatory conditions [54-55].

Conversely, anti-inflammatory cytokines such as IL-10 and TGF-β are essential in maintaining immune tolerance at the maternal-fetal interface and preventing rejection of the fetus. These cytokines promote a state of immune quiescence, ensuring that the maternal immune system does not mount an attack against the developing fetus. In HIV-infected pregnancies, however, the regulation of these cytokines can be disrupted, leading to an imbalance that may favor immune activation rather than tolerance. An exaggerated inflammatory response can increase the likelihood of preterm birth, placental damage, and fetal growth restriction, all of which can complicate pregnancy outcomes. Moreover, persistent inflammation may create an environment conducive to the transmission of HIV from mother to fetus, as inflammatory cytokines may enhance the permeability of the placental barrier or facilitate the entry of the virus into fetal tissues [56-57].

The cytokine milieu at the maternal-fetal interface also affects the development of fetal immune responses, particularly in the context of HIV exposure. Early exposure to cytokines such as IL-6 and TNF-α can influence the development of the fetal immune system, particularly T cell differentiation and the balance between T helper cell (Th) 1 and Th2 responses. In HIV-exposed but uninfected (HEU) infants, this early exposure may lead to skewed immune development, with a tendency toward a Th1-biased response. This bias may enhance susceptibility to chronic inflammatory diseases and autoimmune conditions later in life. Furthermore, maternal immune responses during pregnancy can affect the expression of fetal immunoregulatory molecules, influencing the development of immune tolerance or immune activation in the neonate. These subtle shifts in immune programming can have long-term effects on the neonate's ability to respond to infections, including HIV, and could impact the overall immune health of the child [58-59].

In addition to cytokines, placental cells themselves, including trophoblasts, decidual cells, and immune cells, contribute to the modulation of immune responses at the maternal-fetal interface. Trophoblasts, which form the outer layer of the placenta, play a key role in regulating immune interactions with maternal cells. These cells express various cytokines and chemokines that help to establish a tolerogenic environment at the interface, preventing maternal immune cells from attacking the fetus. In the presence of HIV, however, this delicate balance can be disrupted, with trophoblast cells potentially becoming more permissive to HIV entry. This altered placental function may facilitate vertical transmission of the virus, particularly in cases where the maternal immune response is suboptimal or the placental barrier is compromised by chronic inflammation [60-62].

The modulation of the immune environment at the maternal-fetal interface is also influenced by maternal antiretroviral therapy (ART). ART is designed to reduce maternal viral load, thereby decreasing the risk of vertical transmission. However, the impact of ART on the cytokine milieu at the maternal-fetal interface is not fully understood. Some studies suggest that ART may reduce inflammatory cytokine production and restore a more balanced immune response, potentially enhancing the protective effects of maternal immunity against HIV. On the other hand, ART drugs may also have immunomodulatory effects that alter the expression of certain cytokines, potentially influencing the development of the neonatal immune system. The long-term consequences of these changes are still being investigated, but they highlight the complexity of immune interactions during pregnancy and the need for more research to optimize ART regimens for both maternal and fetal health [63-64].

Impact of Antiretroviral Therapy on Transplacental Immunity

Antiretroviral therapy (ART) has revolutionized the management of HIV-infected pregnant women, significantly reducing the risk of vertical transmission to the neonate. By lowering maternal viral load to undetectable levels, ART plays a pivotal role in preventing in utero HIV infection, offering both direct and indirect benefits to the neonate. While the primary goal of ART in pregnant women is to reduce the risk of transmission, it is essential to understand how ART impacts the immunological environment at the maternal-fetal interface, particularly in relation to transplacental immunity. The effects of ART on maternal and fetal immune responses can have important implications for both the success of pregnancy and the immune development of the neonate [65].

ART can alter the cytokine and immune cell profile in the maternal circulation, which may, in turn, affect the immune environment at the placental interface. Maternal HIV infection is typically associated with a pro-inflammatory cytokine milieu, characterized by elevated levels of cytokines such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interferon-gamma (IFN-γ). These cytokines contribute to immune activation and chronic inflammation, which may disrupt placental function and increase the risk of HIV transmission. ART, particularly when administered effectively to achieve viral suppression, can reduce the systemic levels of these pro-inflammatory cytokines, thereby decreasing maternal immune activation. This reduction in immune activation may have beneficial effects on the placental environment, potentially decreasing the permeability of the placental barrier and minimizing the risk of HIV transmission [66-68].

In addition to reducing maternal viral load, ART also has direct effects on immune cells at the maternal-fetal interface. The use of ART during pregnancy has been shown to influence the function of maternal immune cells, including T cells, monocytes, and dendritic cells. These changes in immune cell function may enhance immune tolerance at the maternal-fetal interface, which is critical for preventing maternal rejection of the fetus. Moreover, ART can reduce the activation of maternal immune cells, which may help to maintain a more balanced immune response that favors fetal protection. In HIV-infected women, ART may promote a more favorable cytokine balance, shifting the immune response from a pro-inflammatory to a more regulatory and anti-inflammatory phenotype. This shift is essential for preserving the integrity of the placental barrier and preventing fetal harm [69-71].

The impact of ART on transplacental immunity is also reflected in the transfer of maternal antibodies to the fetus. Maternal antibodies play a crucial role in providing passive immunity to the neonate, particularly in the early months of life before the infant's immune system is fully mature. ART can influence the profile of antibodies that are transferred across the placenta, as the reduction in maternal viral load may alter the concentration of HIV-specific antibodies, such as anti-HIV IgG. Some studies suggest that ART

may enhance the transfer of protective antibodies, not only against HIV but also against other pathogens. This enhanced antibody transfer could provide the neonate with an additional layer of protection, particularly in the first few months of life when the infant's immune system is still developing. However, it is also important to note that the transfer of antibodies may be influenced by the timing and efficacy of ART during pregnancy, as well as by the maternal immune status [72-74].

The effects of ART on the fetal immune system itself are less well understood, particularly in relation to the development of neonatal immunity. ART has been shown to reduce maternal viral load and prevent HIV transmission to the fetus, but it may also influence the fetal immune system in ways that are still under investigation. One area of concern is the potential impact of in utero ART exposure on the neonatal immune system's ability to develop a robust adaptive immune response. While ART prevents fetal HIV infection, it is possible that prolonged exposure to ART in utero could alter the normal development of immune tolerance and immune cell maturation in the neonate. Some studies suggest that ART-exposed neonates may have a different immune profile compared to those born to HIV-negative mothers, potentially leading to immune system alterations that could affect the infant's long-term health [75-77].

In addition to its effects on the immune system, ART during pregnancy also influences the placental microenvironment. The placental barrier serves as both a protective and selective interface between the maternal and fetal circulations, and its integrity is crucial for the exchange of nutrients, gases, and immune cells. ART, particularly with certain drug regimens, may influence placental function, either by reducing inflammation or by altering the permeability of the placental barrier. This could affect the ability of the placenta to transfer immune cells or cytokines, which in turn may influence the development of the fetal immune system. While ART effectively reduces the risk of HIV transmission, its effects on placental function and fetal immune development require further exploration to fully understand the long-term consequences for the neonate [78].

Conclusion

The complex interplay between maternal immunity, placental function, and fetal development is central to understanding the mechanisms of HIV transmission and immune responses during pregnancy. Transplacental immunity, which includes the transfer of maternal antibodies and immune modulation at the maternal-fetal interface, plays a critical role in protecting the neonate from infections, including HIV. While the placenta serves as a vital immunological barrier, it is also susceptible to disruption by maternal HIV infection and associated chronic inflammation. The introduction of antiretroviral therapy (ART) has significantly altered the trajectory of HIV transmission, offering a powerful tool to reduce maternal viral load and prevent vertical transmission to the fetus. However, ART's effects on maternal and fetal immune systems are complex and require careful consideration, as they can influence the cytokine milieu, immune cell function, and the integrity of the placental barrier.

Antiretroviral therapy has proven to be effective in reducing the risk of HIV transmission from mother to child, but its impact on the broader immune landscape, including both maternal immunity and fetal immune development, is multifaceted. ART can alleviate maternal immune activation and promote a more tolerogenic environment at the maternal-fetal interface, reducing inflammation that could otherwise compromise fetal health. Additionally, ART enhances the transfer of protective maternal antibodies to the fetus, offering the neonate passive immunity during the early months of life. However, the long-term effects of in utero ART exposure on neonatal immune programming remain an area of active investigation. While ART protects the fetus from HIV infection, it may also influence the neonate's ability to mount an effective immune response to other pathogens.

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