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# The Immune System of Preterm Infant: A Review for the Pediatrician

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**Abstract**

Preterm birth remains a significant global health challenge, contributing to high neonatal morbidity and mortality. Preterm newborns exhibit distinct immunological and inflammatory profiles compared to term infants, increasing their susceptibility to infections, oxidative stress, and inflammatory complications. This review explores the unique aspects of neonatal immunity, focusing on the immaturity of innate, humoral, and cellular immune responses in preterm infants. Key findings include impaired function of natural killer (NK) cells and monocytes, reduced transfer of maternal IgG, altered cytokine profiles, and imabalanced oxidative stress due to underdeveloped antioxidant defenses. Additionally, preterm infants display a Th2-skewed immune response with diminished Th1 and Th17 activity, further compromising antimicrobial defense. The interplay between immune dysregulation, oxidative damage, and infection susceptibility underscores the need for targeted interventions. Understanding these mechanisms is crucial for improving clinical outcomes in this vulnerable population.

## INTRODUCTION

A preterm newborn is defined, according to the World Health Organization (WHO), as a live-born infant before completing 37 weeks of gestational age (GA), or 259 days from the first day of the last menstrual period [1]. Considered a public health issue, prematurity affects approximately 1 in every 10 births worldwide [1,2]. Certain conditions are identified as risk factors for preterm birth, such as twin pregnancy, incomplete prenatal care, lower maternal education, maternal age of 40 years or older and Indigenous race [3].

Despite advances in understanding the pathophysiology of preterm infant diseases, new diagnostic methods, and therapeutic options [4], data indicate that approximately 1 million children still die annually due to direct and indirect complications of prematurity [1,5], representing about 35% of newborn deaths and 16% of deaths in children under 5 years of age worldwide [6,7]. The lower the GA, the higher the rates of complications and mortality [8].

One of the leading causes of death in newborns is neonatal sepsis [9,10]. Several factors appear to influence neonates' susceptibility to infections, including genetic factors, gut microbiome, maternal factors (such as maternal antibodies against group B Streptococci), and the virulence of the microorganism [9]. In particular, preterm births constitute one of the main risk factors for the development of neonatal sepsis [11], and respiratory tract infections [12]. In this context, the newborn's immune system plays a fundamental role in the increased infectious susceptibility.

The human immune system can be divided into the innate immune system and the adaptive immune system. Each of these systems comprises various cells, soluble peptides, and cellular receptors capable of directly or indirectly eliminating invading microorganisms. The main effector components of innate immunity are pattern recognition receptors, such as *Toll-like* receptors (TLR), phagocytes (neutrophils, monocytes, and dendritic cells), natural killer (NK) cells, innate lymphoid cells, cytokines, chemokines, epithelial antimicrobial peptides, and the complement system. In adaptive immunity, there is a more robust and specialized immune response to the initial antigenic stimulus. Adaptive immunity encompasses two main immune arms: 1) the humoral immune system, mediated by immunoglobulins (IG) and B lymphocytes; and 2) the cellular immune system, mediated by T cells. It is important to note that these subdivisions are merely didactic, as, *in vivo*, there is a continuous interrelationship between these immune mechanisms, which act synergistically and concomitantly during an infection [13].

Studies in the 1990s defined the term neonatal immune immaturity or neonatal immunodeficiency as the set of

characteristics of the immune system specific to this age group [14-17]. Over the years, other studies have further elucidated these unique characteristics of the neonatal period, describing the particularities of the innate and adaptive compartments in preterm infants [18,19]. Based on this knowledge, several theories have emerged to explain the higher occurrence of infections in preterm infants [9]; however, many genetic, epigenetic factors, and immunological phenotypes remain unclear.

In addition to mortality from infections, preterm infants are at increased risk for developing pulmonary, metabolic diseases, neurodevelopmental delay, and malnutrition [4]. These factors directly influence the high rates of short-, medium-, and long-term morbidity compared to term newborns [20]. Many of these complications, such as retinopathy, chronic lung disease, intraventricular hemorrhage, periventricular leukomalacia, and necrotizing enterocolitis, are directly related to an imbalance in inflammation control mechanisms in preterm infants, involving oxidative stress and the production of inflammatory cytokines [21-25].

Oxidative stress is the condition caused by the excessive generation of reactive oxygen species (ROS), which accumulate in tissues and cause tissue damage. Physiologically, by the end of gestation, antioxidant enzymes are produced in the newborn to counteract the increased production of ROS induced by birth [23]. The imbalance between oxidative challenge and the body's antioxidant efficacy is called oxidative stress, and the preterm population is particularly susceptible to tissue damage caused by the excess of these substances [23,26,27].

Other important molecules in this process are cytokines. Cytokines are soluble proteins produced by immune and non-immune cells of the body and are responsible for mediating inflammatory responses locally and systemically in situations of tissue injury [13,28]. In general, they can be subdivided into primarily pro-inflammatory cytokines (such as IL-1, IL-6, TNF-α, IL-12, IL-17, and IFN-γ), or anti-inflammatory cytokines (such as IL-10 and TGF-β) [29]. However, it is now known that the pro-inflammatory and anti-inflammatory roles of cytokines vary depending on the kinetics involved and the target cell receptors [30].

An increase in pro-inflammatory cytokines or a reduction in anti-inflammatory cytokines are at the core of the etiopathogenesis of various inflammatory diseases, such as autoimmune diseases, inborn errors of immunity, and neoplasms [29]. Factors associated with preterm birth (such as maternal infection, premature rupture of membranes, and preterm labor), are related to inflammatory changes in newborns and contribute to a more abundant inflammatory reaction, with consequent manifestation of comorbidities in preterm infants [31,32]. However, studies evaluating the profile of these molecules in this population are scarce, leaving gaps in understanding the real role of these cytokines in preterm inflammation.

Greater efforts in elucidating the inflammatory and infectious processes in preterm infants are necessary, given the impact of the clinical consequences resulting from the imbalance of these processes in this population. The relationship between these immunological and inflammatory markers and clinical outcomes in these patients may help in the identification and development of earlier and targeted interventions. The present study provides a narrative review for pediatricians regarding the immunological and inflammatory mechanisms in term and preterm newborns.

## LITERATURE REVIEW

### Immune System in the Newborn and Preterm Newborn

**Innate Immunity:** The development of the immune system occurs progressively throughout gestation and continues in the postpartum period, in all immune compartments-innate, humoral, and cellular. The innate immune system is particularly important in this period, as it stimulates rapid, partially selective, and efficient responses to most antigenic stimuli [33], while the adaptive immune system remains immature until later stages of childhood [34]. Traditionally, the components of innate immunity are described as antigen-nonspecific and lacking immunological memory [35], however, more recent studies have demonstrated some degree of increased responsiveness to repeated antigenic stimuli. Hence, the term "trained innate immunity" was coined [36].

Dendritic cells (monocytes and tissue macrophages), are examples of innate immune cells specialized in capturing and presenting antigens to T cells, functioning as a link between the innate and acquired immune systems. These functions are performed through the expression of various surface molecules (recognition of foreign patterns and co-stimulatory molecules), production of chemokines and cytokines, and phagocytosis of microorganisms [13,37]. NK cells are also part of the innate immune arm and play a crucial role in immune responses against a range of pathogens through cytokine secretion (mainly interferon-gamma [IFN-γ]), and destruction of cells infected by intracellular organisms, such as viruses [38]. Additionally, they contribute to homeostasis in peripheral blood and secondary lymphoid tissues and actively participate in antitumor surveillance [13,39].

At birth, even in term newborns, several components of the innate immune compartment differs from adult responses, such as increased number and function of innate lymphoid cells [40], and reduced rolling, adhesion, transmigration, chemotaxis, and phagocytosis of neutrophils and monocytes [41], as well as significant alterations in the number and function of NK cells [38,42].

Some studies have evaluated alterations in innate immune components in preterm infants. Quinello et al., observed reduced expression of CD80 in dendritic cells of preterm infants compared to term newborns and adults [43]. More recently, De Biasi and colleagues demonstrated that preterm infants exhibit a particular innate immunological phenotype compared to term newborns, with: 1) higher concentrations of the alarmin S100A8, a protein that binds to TLR and activates monocytes and macrophages; 2) a higher number of immature monocytes; 3) a lower number of classical monocytes; and 4) reduced inflammasome activation after *in vitro* stimulation (33). Anderson and colleagues found, in preterm infants, a lower frequency of classical monocytes (CD14+CD16−), and myeloid dendritic cells compared to term newborns [44].

The number and function of NK cells are also altered in preterm infants compared to term infants. Perez and colleagues found lower absolute counts of these cells in newborns below 31 weeks of GA compared to preterm infants above 32 weeks of GA and term infants, with higher percentages in infants above 38 weeks of GA [45]. However, these findings were not replicated in other studies [46]. De Biasi and colleagues found a higher number of a specific NK cell subpopulation (CD56−CD16+), in cord blood of preterm infants. These cells exhibit less efficient cytolytic ability, with reduced cytokine production capacity [33]. Anderson and colleagues [44], also observed, in preterm infants, a reduced frequency of CD56 bright NK cells-a population of NK cells with high cytokine production capacity [47], and another NK cell subpopulation expressing NKG2A [44]. This surface molecule is an inhibitory marker whose function is to suppress cytokine secretion and cytotoxicity [48], which may partly explain this population's susceptibility to viral infections.

These and other evidence [49-51], show that preterm infants have a present but still immature innate immunity, with lower activity in response to antigenic stimuli.

**Humoral Immunity:** Humoral immunity is mediated by immunoglobulin (or antibody) molecules present in serum and mucosal secretions. It is important for: 1) neutralizing microorganisms before cellular infection; 2) opsonization for subsequent phagocytosis; and 3) activation of the complement system. Immunoglobulins are produced by B lymphocytes, which, when activated by an antigenic stimulus, transform into antibody-secreting plasma cells [13]. In this context, cells initially producing Immunoglobulin M (IgM), undergo a process called "class switching" and begin producing antibodies with higher antigen affinity, with distinct effector functions. Depending on the type of heavy chain in their molecular structure, Immunoglobulin A (IgA), Immunoglobulin E (IgE), and Immunoglobulin G (IgG), are produced [10,13]. IgG can be subclassified in 4 subtypes (IgG1, IgG2, IgG3, and IgG4), which, despite sharing 90% structural similarity, have different immunological functions *in vivo* [52,53].

In newborns, endogenous IgM production begins in utero and increases substantially in the first months of life [54]. After birth, exposure to external antigens increases significantly, stimulating isotype switching and leading to endogenous production of IgG and IgA, mainly after 6 months of life [54,55].

Unlike IgG, complement system proteins, IgA, IgM, and most IgE antibodies do not cross the placental barrier [10,56]. Additionally, newborn B lymphocytes primarily exhibit a *naïve* and transitional profile (B cells without prior antigen recognition), with few memory cells, as well as deficient maturation of germinal centers and marginal zones in lymphoid organs compared to older children and adults. There is also lower expression of BCR and co-stimulatory molecules [57]. These differences determine a diminished antigenic response to infections and vaccines [58]. Due to these factors, passive immunization becomes the primary form of humoral immunity in the neonatal period, both through the transplacental passage of IgG and secretory IgA present in breast milk.

The transplacental transfer of antigen-specific IgG antibodies is an adaptive mechanism that, at least in part, minimizes the effects of an immature humoral immunity. Since IgG is a high molecular weight structure, its transport across the placenta occurs through an active mechanism mediated by the neonatal Fc receptor (FcRn), which binds to IgG molecules and prevents their lysosomal degradation in the syncytiotrophoblast [59-61]. Even after the neonatal period, FcRn is essential in prolonging the half-life of IgG, as well as contributing to the modulation of cellular and humoral immune responses [13,62]. Moreover, recent studies have demonstrated the participation of other Fc receptors in the IgG transfer process in preterm infants [63], and alterations in the galactosylation and sialylation of these proteins confer a pro-inflammatory status to preterm infants [64], which may partly compensate for the quantitative reduction in total antibodies.

Transplacental IgG transfer begins around the 13th week of gestation, initially with low efficiency. In general, the transfer rate is mainly determined by maternal serum IgG concentration—the higher the maternal IgG, the greater the transfer to the newborn, up to a saturation level of FcRn receptors (around 1500 mg/dL). However, other factors also influence IgG transfer efficiency in newborns, such as IgG subclass (with IgG1 being the most efficient and IgG2 the least efficient), maternal nutritional status, infant gender (male > female), and higher GA [60,65,66].

The influence of GA on serum immunoglobulin levels in preterm infants is well described. Studies since the 1960s have shown very low concentrations of IgM and IgA in preterm infants (provided there is no intrauterine infection), and IgG levels directly proportional to GA [67-69]. In the first trimester, there is almost no maternal-fetal IgG transfer; in the second trimester, the fetal IgG concentration transferred increases, reaching 10% of maternal concentration by the 22nd week and about 50% by the 32nd week [70]. Only after the 35th week of gestation do fetal IgG levels exceed maternal levels [71]. The majority of this antibody is thus transferred transplacentally during the third trimester of gestation, when the increase in fetal IgG doubles compared to the second trimester [72]; this explains the lower IgG levels found in preterm infants, as addressed in several studies [46,63,64,73-75].

Other studies also show differences in transplacental transfer and concentrations of IgG subclasses in preterm infants. A systematic review demonstrated no consensus on the hierarchy of transfer among different IgG subclasses, but there was agreement among the included studies regarding a lower maternal-fetal transfer rate of IgG2 in preterm infants [65]. IgG2 levels in preterm infants are typically about 60% of maternal levels [61], and these alterations may, at least in part, explain the susceptibility of preterm infants to bacteria such as *Streptococcus pneumoniae* and *Nesseria meningitides*, as this subclass is important in recognizing polysaccharide antigens present in the cell wall of these bacteria. Finally, in addition to low transplacental IgG transfer, the reduced endogenous production of this immunoglobulin by preterm infants is also determined by low expression of co-stimulatory molecules (TACI, BCMA, BAFF-R, and CD40L)-involved in the immunoglobulin isotype switching process-compared to term newborns [76]. As a result, there is a slower increase in IgG repertoire diversity throughout gestation in preterm infants compared to term newborns [77].

**Cellular Immunity:** T lymphocytes are the main mediators of cellular immunity. The effector mechanisms by which these cells act in host defense include: 1) recognition of peptides derived from foreign proteins bound to major histocompatibility complex (MHC) molecules of other immune cells; 2) direct apoptosis of cells infected by intracellular microorganisms through cytolytic mechanisms; and 3) production of cytokines that orchestrate the activation of other effector cells, such as macrophages, to enhance their phagocytic capacity. Unlike innate immune cells, which directly recognize microbial "pattern" molecules, T lymphocytes are activated by exposure to pathogen peptides previously processed by antigen-presenting cells, such as dendritic cells. This antigen processing confers adaptive immunity with some important differences compared to innate immunity, such as greater specificity (ability to recognize a much larger number of different antigens, even with subtle differences between them) and greater immunological memory (ability to react in an amplified manner to previous antigenic stimuli, even many years after primary infection) [13,57].

There are several groups of T lymphocytes with distinct effector functions *in vivo*. The main groups are CD4-expressing cells, also called helper T lymphocytes; and CD8-expressing cells, also called cytotoxic T lymphocytes. CD4 T cells are the main producers of a wide variety of cytokines for B lymphocyte activation, with consequent stimulation of IgA, IgG, and IgE production (through isotype switching), and destruction of extracellular pathogens; and macrophage activation to eliminate intracellular pathogens such as mycobacteria, protozoa, and fungi [57]. CD8 T cells also produce cytokines (though in smaller quantities and less diversity than CD4 cells), but their primary effector function is cytotoxicity in target cells altered by intracellular infection or neoplasia [57,78]. Other cells of utmost importance in the adaptive immune system are regulatory T lymphocytes (Treg). Unlike classical CD4 and CD8 lymphocytes, Treg act in immune contraction, reducing the initial activation response and actively participating in immune tolerance processes [13].

At birth, the number of T lymphocytes is high. This population consists mostly of *naïve* cells and recent thymic emigrants [55,79]. By school age, the number of T cells decreases to levels approximating those of an adult [80]. Despite being numerically superior early in life, their functionality is low due to various factors: a low repertoire of T-cell receptors (TCR), with consequent production of short-lived effector cells [81], low IL-2 production (a pro-inflammatory cytokine essential for the proliferation and differentiation of effector and memory cells) [82], low inflammatory response when exposed to superantigens [83], limited polarization of *naïve* T lymphocytes to the Th1 subtype and consequent reduced IFN-γ production [54],

and high regulatory T cell activity [84-86]. Additionally, neonatal CD8 cells exhibit slower responses than adults [57]. However, recent studies show that this "deficient" immunity is, at least in part, compensated by "bystander activation" of *naïve* neonatal CD8-specific cells. In this newly discovered type of activation, this subgroup of CD8 cells is stimulated by innate inflammatory cytokines, not by the canonical TCR-mediated pathway. Therefore, they can also be considered part of innate immunity, along with other similarly activated immune cells, such as NK cells, innate lymphoid cells, mucosa-associated invariant T cells, NKT cells, and *γδ* T cells [81].

Although most studies use cord blood for lymphocyte subset analyses at birth, there are significant changes in these markers within the first weeks of life, likely related to the constant maturation of the immune system in response to antigenic stimuli such as infections, vaccines, nutrition, and microbiome [87-89]. These recent analyses show that newborns with different immunological phenotypes in cord blood converge toward the same immune development trajectory, demonstrating the importance of environmental factors throughout life [79].

There are conflicting data regarding the cellular immunity of preterm infants. Some studies show a higher number of T lymphocytes compared to term newborns [43], others show no difference between the groups [46,90], or even higher numbers in term newborns [91]. When studying the subpopulations of these lymphocytes, some differences are found: the regulatory immune system, mainly composed of regulatory T cells (Treg), develops early in the fetus, conferring a more tolerogenic and less inflammatory environment to preterm infants [85,91], and a higher number of CD4 lymphocytes relative to CD8 (higher CD4/CD8 ratio) in preterm infants than in term newborns [91].

Another difference is the polarization of CD4 T lymphocytes into Th2 lymphocytes, relative to a lower proliferation of Th1 lymphocytes, which occurs in newborns [10]. Th1 and Th17 lymphocytes are even more reduced in preterm infants than in term newborns, resulting in deficient production of Th1 (IFN-γ, IL-2, and TNF-α), and Th17 (IL-17), cytokines [13,54,57,91-93].

**Cytokines in the Preterm Newborn**

One of the earliest phases of immune system activation is the secretion of cytokines by tissue cells. In adaptive immunity, when presented with a specific antigenic stimulus, CD4 T lymphocytes produce inflammatory cytokines that induce specific immune effector mechanisms for that agent. This mechanism of "specialization" of CD4 T lymphocytes to a specific stimulus is called polarization, where each type of "polarized" T lymphocyte can produce specific cytokines and express transcription factors. The main subgroups of activated T cells are Th1, Th2, and Th17 cells [13,57,93].

Th1 lymphocytes are induced by microorganisms ingested by phagocytes and are the main cells responsible for host defense against intracellular germs, such as mycobacteria. Th1 lymphocytes are stimulated by IL-12 to produce IFN-γ, a key cytokine in macrophage activation. Th2 lymphocytes, on the other hand, are stimulated by antigens from helminths and allergens to produce IL-4, which stimulates mast cell degranulation, isotype switching to IgE, mucus secretion by the gastrointestinal epithelium, and eosinophil activation. Finally, Th17 lymphocytes are involved in neutrophil recruitment to infection sites and produce IL-17, which mediates inflammation against extracellular bacteria and fungi [13,57,93]. There are other subgroups of activator T lymphocytes, such as Th22 lymphocytes (stimulate innate immune responses in mucosal barriers), Th9 lymphocytes (involved in immune responses to helminths), and follicular helper T cells (Thf) (induce germinal center formation and immunological memory) [57].

In addition to these activator lymphocytes, after inflammation activation, there must be an "immune contraction": a reduction in activator responses to return to the basal state of immune homeostasis. In this context, TReg cells play a crucial role by secreting IL-10, which can inhibit the production of various inflammatory cytokines such as TNF-α, IL-1, and IL-12. Conditions with reduced TReg cells and/or their products (such as IL-10), lead to autoimmunity and exacerbated inflammation.

TNF-α plays a central role in this acute inflammatory response, being produced by macrophages and dendritic cells. This cytokine mediates the recruitment of phagocytes to infection sites, acts on the hypothalamus to increase body temperature, stimulates body catabolism, and induces acute-phase protein production [13,57].

In addition to TNF-α, IL-6 (produced by phagocytes, vascular endothelial cells, and fibroblasts in response to tissue damage) also participates in the acute inflammatory response. It induces the synthesis of a variety of other inflammatory mediators in the liver, stimulates neutrophil production in the bone marrow, and promotes the differentiation of *naïve* T lymphocytes into Th17 effector T lymphocytes [13].

The literature is not yet unanimous regarding cytokine concentrations in preterm infants compared to

term newborns. In a systematic review by Lyon et al., an increase in pro-inflammatory cytokines IL-8, IL-1, and IL-6 in preterm infants compared to term newborns was demonstrated in most included studies; TNF-α and IL-10 levels had conflicting results (half of the studies showed higher levels of these cytokines in preterm infants, and the other half showed higher levels in term newborns) [29]. Another systematic review shows an increase in pro-inflammatory mediators (such as IL-1, IL-6, IL-8, TNF-α, INF-γ) and a reduction in anti-inflammatory mediators, such as IL-10 and IL-4 [94]. Anderson et al., found lower levels of IL-1 and IL-6 in preterm infants compared to term newborns; moreover, there was no difference between the two groups regarding TNF-α and IL-10 levels [44]. A study by De Biasi and colleagues also showed no differences in IFN-γ, IL-2, IL-8, IL-6, IL-10, and TNF-α levels between term and preterm newborns [33]. Furthermore, when stimulated with antigens, preterm infants exhibit significantly reduced pro-inflammatory responses (IL-1, IL-6, and TNFα), and high anti-inflammatory responses (IL-10 and TGF-β), especially in extremely preterm infants [34]. These discrepancies among different studies are likely related to small sample sizes, different measurements, and antigenic stimuli used.

## Oxidative Stress in the Preterm Newborn

Reactive oxygen species (ROS), are a group of molecules produced from oxygen through a reduction-oxidation (redox) reaction or electron excitation and are extremely unstable particles that react with most substances found in living tissues, such as lipids, proteins, nucleic acids, and polysaccharides [24,95]. Today, it is recognized that ROS are fundamentally important for maintaining organism homeostasis, serving as key signaling substances for tissue damage and consequent activation and recruitment of immune cells such as neutrophils, macrophages, and T lymphocytes [95,96]. From a methodological perspective, ROS are difficult to quantify due to their extremely short half-life. Thus, a more practical approach is measuring the products of damage caused by oxidative stress. Malondialdehyde (MDA), is the main and most studied compound derived from lipid peroxidation of polyunsaturated fatty acids by ROS [96,97].

Oxidative stress can be defined as an imbalance between oxidative damage caused by ROS and an antioxidant system [22]. These antioxidant substances protect cells from peroxidation reactions, reducing cellular damage and maintaining cell membrane integrity. They are produced endogenously or acquired through diet and can act in various ways to directly neutralize ROS or repair the tissue damage caused by them [98]. The most common antioxidants include the enzymes superoxide dismutase (SOD), catalase (CAT), glutathione (GSH), and bioactive molecules such as vitamins C and E.

It is known that this system is vitally important during the perinatal period. At birth, the transition from the intrauterine environment to extrauterine life involves rapid adaptation to relative hyperoxia and the consequent generation of a large amount of ROS. This must be controlled by the antioxidant system, whose maturation progresses during gestation and is completed in the last intrauterine weeks. Additionally, a higher transplacental transfer of these substances (beta-carotenes, vitamins C and E, ubiquinones), is observed in the final days of pregnancy. Therefore, healthy term newborns can tolerate this "physiological oxidative stress" secondary to increased oxygen concentration in the postpartum period [23,26,27,99-101].

In this context, preterm infants are at increased risk of experiencing consequences of an unbalanced oxidative system. Additionally, tissue damage in this population is exacerbated by the presence of certain perinatal conditions (such as preeclampsia, hypoxia, respiratory stress), or treatments (use of supplemental oxygen), which further reduce endogenous antioxidant production or increase ROS release [99]. In preterm infants, diseases such as early neonatal sepsis, bronchopulmonary dysplasia, retinopathy, necrotizing enterocolitis, intraventricular hemorrhage, and periventricular leukomalacia appear to be related to oxidative damage. Moreover, mortality and morbidity in these patients may also be influenced by the imbalance between ROS and the antioxidant system [102]. Another factor that hypothetically could lead to increased ROS production or reduced antioxidants is maternal age. However, the literature remains conflicting on this topic; a recent case-control study evaluated levels of total antioxidant capacity, total oxidative capacity, and clinical outcomes in groups of mothers of different ages but found no significant differences [103].

## Neonatal Sepsis

Few studies evaluate the relationship between the onset of neonatal sepsis and immunological markers and oxidative stress. There is still no consensus in the literature regarding a higher risk of sepsis in preterm infants with low IgG levels or detected lymphopenia at birth [46,104-106]. Nevertheless, systematic reviews and meta-analyses indicate that immunoglobulin replacement has no significant influence on the clinical outcome of these patients [107-109], suggesting non-exclusively immunological mechanisms in the development of neonatal sepsis.

## CONCLUSIONS

Preterm newborns face significant immunological challenges due to the immaturity of their innate and adaptive immune systems. Key alterations include reduced transplacental IgG transfer, impaired NK cell and monocyte function, and a cytokine profile favoring anti-inflammatory responses, which collectively increase susceptibility to infections. Additionally, preterm infants are particularly vulnerable to oxidative stress due to insufficient antioxidant defenses, contributing to complications such as bronchopulmonary dysplasia, necrotizing enterocolitis, and sepsis. Despite advances in understanding neonatal immunity, gaps remain in translating these findings into clinical interventions. Future research should focus on strategies to enhance immune protection, such as optimizing maternal immunization, developing targeted cytokine therapies, and mitigating oxidative damage. A deeper understanding of these mechanisms will be essential for improving survival and long-term outcomes in preterm infants. Addressing these challenges requires a multidisciplinary approach, integrating immunology, neonatology, and translational research to bridge the gap between scientific knowledge and clinical practice.

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