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# White Matter Injury in Preterm Infants

## *Could Human Milk Play a Role in Its Prevention?*

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**ABSTRACT**

Human milk has been found to be beneficial for the development of all newborns. It is protective during the development of the gastrointestinal tract, important in neurologic development, immune system function, and nourishment. Human milk has a number of components that aid in the anti-inflammatory process and free radical reduction and is a building block for neurologic development. Cerebral white matter injury is a common occurrence in preterm infants. Results of this injury can be seen into early childhood and throughout the life of the individual. White matter injury most frequently occurs because of hypoxia and the inflammatory process, which often results in the injury of myelinating oligodendrites. This article proposes the potential importance of human milk in slowing and preventing cerebral white matter injury because of the components in human milk that affect the inflammatory and free radical reduction processes. It also proposes its ability to provide nutrients essential to myelin development.

**Key Words:** cerebral white matter, cerebral white matter injury, human milk, periventricular leukomalacia, periventricular white matter, preterm infant, white matter, white matter injury

The benefits of human milk are extensive. Human milk has components that are important in immunologic and neurologic development, the absorption of nutrients, and gastrointestinal function.[1] These components allow infants, both healthy and vulnerable, to receive both nourishment and protection. Exclusive breastfeeding for at least 6 months has been a standing recommendation of the World Health Organization due to its numerous benefits.[2] In addition, breastfeeding provides a cost-effective way for mothers to provide for their infants.[3]

As beneficial as breastfeeding is to a healthy infant, human milk is even more beneficial to preterm infants who go through their last weeks, and sometimes months, of development outside of the womb. For the sake of this article, a preterm infant will be defined as any infant born before 37 weeks of gestation. Extensive research has demonstrated the benefits of human milk on the developing gastrointestinal tract of preterm infants. Human milk provides a protective coating and aids in proper tight junction function in the growing preterm infant, which explains the role of human milk in protection against necrotizing enterocolitis.[4]

Necrotizing enterocolitis is the leading gastrointestinal cause of death in preterm infants, but these infants are also highly susceptible to neurologic injuries.[4,5] Although much of fetal neocortical neurologic development is completed before 22 weeks of gestation, the neocortex continues to develop through 36 weeks of gestation and even after birth.[5] There is a second wave of neurologic development in the third trimester.[5] During this time, myelination and organization of various tracts of the brain occur.[5] When an infant is born preterm, this third-trimester burst of brain development is done in the less-protective extrauterine environment.

In preterm infants, cerebral white matter injury (related to the myelination occurring during the third trimester) is a common neurologic injury.[6] This injury has been found to have lasting effects into early childhood and beyond.[7] As scientific advances

*Author Affiliations:* *University of Pennsylvania School of Nursing, Philadelphia.*

*This study was written with the resources and support of School of Nursing at the University of Pennsylvania.*

*The authors and CE planners have disclosed that they have no financial relationships related to this article.*

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*DOI: 10.1097/ANC.0b013e31827bfead*

have increased, the survival rates of preterm infants have also increased.[6] In 2007, 85% of preterm infants were surviving after discharge, a number that will only increase as more advances are made in medicine.[6] Therefore, it can be assumed that as the number of surviving preterm infants increases, so will the number of children with problems related to cerebral white matter injury.

This study explains how components of human milk may aid in protecting preterm infants from white matter injury, thus protecting the child from further injury to the brain and developmental delays later on in life. Although much work has been done on cerebral white matter injury in the preterm infant, little work has been done to suggest how infant nutrition, and more specifically human milk, may be protective against such injuries. Human milk may well have a role in improving the outcomes and prognoses of individuals with cerebral white matter injury as infants.

## HUMAN MILK AND ITS CONSTITUENTS

Human milk has a number of constituents making it both nutritive and protective for the newborn. Although the components of human milk are universal, differences in composition have been noted on the basis of the infant's gestational age.[8] Some minerals noted to be in human milk are calcium, phosphorus, magnesium, copper, zinc, and iron.[1,9] Human milk also has vitamins D, E, K, $B_{12}$, $B_6$, and C.[1,9] Vitamins and minerals have a number of functions. Vitamins $B_{12}$ and $B_6$, for example, are important in cellular respiration, whereas vitamin K is important in clotting and gastrointestinal function.[10] Vitamin $B_{12}$ also has a role in maintaining neuronal function.[10] Vitamin D, calcium, phosphorus, and magnesium are important in bone growth and development.[10] Vitamins E and C are known for their antioxidant properties.[11]

Macronutrients such as proteins, carbohydrates, and fatty acids are also found in human milk.[8] A study of 102 mothers of preterm infants demonstrated that protein, carbohydrate, and fat contents were significantly higher in the milk of mothers who had preterm infants than in the milk from mothers of term infants.[8] In addition, these researchers found a gestational age effect; the more preterm the delivery, the higher concentrations of these macronutrients.[8] Furthermore, the amount of fat in milk changes on the basis of the degree of breast fullness or emptiness.[1] As the breast is emptied, the milk (ie, hind milk) has increased fat and calories.[1] Fat content not only adds calories to the milk, but some fatty acids are beneficial in the anti-inflammatory response, thus aiding in the immune response of the developing infant.[10]

Protein content is inversely proportional to the volume of milk expressed[1]: Smaller volumes of milk have higher protein contents than larger volumes. Some proteins known to be in human milk are $B_{12}$ binding protein, cytokine receptors (which aids in the anti-inflammatory response), and peroxidase, catalase, and superoxide dismutase (all antioxidants that aid in the reduction of free radicals).[12,11] κ-Casein, lactoferrin, lactoalbumin, and immunoglobulin A are all proteins that have immunologic functions in human milk.[13,10] κ-Casein and lactoferrin have also been found to have anti-inflammatory actions in the newborn, further aiding in the immune function of the newborn and baby.[13]

Other compounds found in human milk are cytokines, interleukin 1, interleukin 6, and tumor necrotic factor–α. All of these compounds play a role in the inflammatory and immune response.[14] Nucleotides are another macronutrient present in human milk.[15] Some nucleotides such as adenosine and guanine are key components of energy, cellular signaling, and second messenger proteins involved in cellular communication.[15] Free nucleotides have been found to aid in the anti-inflammatory response.[16] Higher concentrations of nucleotides have been found in mature milk (15 days postpartum) than in colostrum.[15]

Numerous components of human milk play a role in the inflammatory process and more specifically the anti-inflammatory process. The function of these components may prove to be important in protection against cerebral white matter damage, where the inflammatory response is a key factor in the damage done to the cells.[17] Human milk also has components that are important in the reduction of reactive oxygen species (ROS), thus acting as an antioxidant.[11]

Similar to the inflammatory process, damage by ROS has been implicated in the pathogenesis of cerebral white matter injury.[17] Furthermore, components such as cholesterol and fatty acids (which have been associated with neurologic development) may aid in myelin formation, thus serving as building blocks to white matter.[10,18]

## CEREBRAL WHITE MATTER INJURY IN PRETERM INFANTS

The brain consists of white and gray matter. White matter receives its name from its white appearance.[19] The tissue appears to be white because of the presence of myelinated axons.[19] Gray matter is so named for its gray appearance, resulting from the darker cell bodies of which it is composed.[19] Myelin provides a protective sheath allowing axonal transmission to be protected and propagated between the soma and its target location.[19] Cerebral white matter injury is one of the most common neural injuries faced by preterm infants.[5] This injury is often the result of damage caused by ischemia, infection, and the inflammatory process.[5] Neuroanatomy of the preterm infant may also increase vulnerability to such injuries.[20]

## CAUSES OF ISCHEMIA AND HEMORRHAGE

The germinal matrix is an area that generally develops between 34 and 35 weeks of gestation and is absent in a term infant.[20] This is an area that is especially vulnerable to intraventricular and periventricular hemorrhage.[20] The hemorrhage risk is related to the nature of the area's blood flow. In this area, blood flow is high; however, the vessels are large and irregularly shaped.[20] This anatomy makes it easy for a rupture to occur, which then leads to ischemia to the connecting areas.[20] Hemorrhage of the germinal matrix often occurs concurrently with periventricular leukomalacia (PVL) and is most often seen in infants born prior to 32 weeks of gestation.[21]

Hemorrhage risk is further increased because of the lack of cerebellum development.[20] The cerebellum is important in motor function and coordination.[20] Its critical developmental period is between 30 and 32 weeks of gestation.[20] This is an area of the brain that detects changes in serum levels of chemicals such as potassium, prostaglandins, hydrogen ions, and serum osmolarity.[20] The amount of gray and white matter in the cerebellum is directly related to length of gestation.[20] Therefore, the longer the gestation, the higher the density of white and gray matter.[20] When an infant is born preterm, the cerebellum is unable to properly autoregulate the brain, thus allowing damage due to changes in blood pressure and serum chemical concentrations.[20] This risk is further increased because of the permeability of the blood-brain barrier.[20] A healthy and well-developed blood-brain barrier has tight junctions between cells serving as a barrier between the capillary beds feeding the brain and the epithelial tissue.[20] In a preterm infant, the tight junctions are more permeable, allowing substances into brain tissue that would not normally be present.[20] Preterm infants have decreased autoregulation of their arteries; therefore, their blood vessels do not always respond to changes by dilating or constricting.[21] This lack of autoregulation can lead to problems with cerebral profusion. An example of this is when sepsis occurs.[21] Sepsis causes the blood pressure to decrease.[21] When blood pressure decreases in a preterm infant, the blood vessels of the brain fail to compensate for the pressure change, leading to ischemia.[21] Periventricular white matter is particularly susceptible to ischemic injury due to its meager vasculature: vasculature that is especially sparse during the third trimester.[21]

## EFFECTS OF WHITE MATTER INJURY IN PRETERM INFANTS

White matter injury is commonly the result of ischemia related to hypoxia, periventricular hemorrhage, intraventricular hemorrhage, hypotension, hypercapnia, and/or inflammatory damage from cytokine release.[5] The result is damage to oligodendrites—cells whose primary function is to produce myelin.[5] Specifically, cytokines, interleukin 1, interleukin 6, and tumor necrosis factor–α have been attributed as primary causes of damage to oligodendrites.[5] Periventricular white matter is a common site of injury.[22] This area goes through its greatest amount of development between 23 and 32 weeks of gestation.[22] Damage to this area can be classified as either cystic (PVL) or noncystic.[22] Noncystic damage leads to retardation of myelination and damage to gray matter.[22] Periventricular leukomalacia results in white matter, decreasing along with alterations in glia cells.[5] Examples of glia cells are astroglia, microglia, and premyelinating oligodendrites.[5] More specifically, PVL causes microglia to become activated leading to the production of proinflammatory cytokines and the destruction of premyelinating oligodendrites.[22] These cells are highly susceptible to injury from free radicals, glutamate, and proinflammatory cytokines, leading to the death of oligodendrocytes.[22]

The effects of microglia activation can present as soon as 3 hours after the initial injury.[22] When this injury is not corrected, damaged axons in and around the injury site become swollen and degraded and have a buildup of iron.[22] This damage can be seen as early as 1 to 2 weeks following the initial injury.[22] By the time PVL reaches a chronic stage, the initial damages are generally no longer apparent; however, the damages cause coagulation necrosis in all brain tissues.[22] This damage is present in axons from the superior occipitofrontal fasciculus, superior longitudinal fasciculus, corticospinal tract, optic radiation, and thalamocortical fibers, leading to motor, visual, and sensory problems, and higher cortical function.[22]

Research has demonstrated changes in white matter distribution, presence, and microstructure in preterm infants.[23] One group of researchers focused on the initial damages with additional research examining neurologic function later in life.[23] These researchers noted changes in white matter distribution in preterm infants, showing that some areas have greater amounts of white matter than others.[23] Increased white matter was noted in the temporal, parietal, and frontal lobes, while decreased white matter was noted in the brainstem and internal capsule; however, functionality of these various areas of white matter was not measured.[23]

Damage to white matter, however, is not transient but can last into childhood.[7] Differences in white matter were examined in 12-year-old children born prematurely.[7] This study noted that even in individuals without brain injury, there were significant differences in white matter distribution.[7] This same study noted that children who had suffered white matter injury as preterm infants had significantly

lower verbal and full IQ and vocabulary scores.[7] There were also significant differences between males and females, with females overall having higher scores than males.[7]

Infants who are breastfed for at least 4 months demonstrate higher scores in fine and gross motor function, ability to adapt, communication, and socialization at ages 1, 2, and 3 years.[24] Furthermore, there is a positive correlation between the amount of human milk infants received and mental developmental outcomes in individuals at 12 to 17 months of age.[18] It is proposed that the presence of long-chain polyunsaturated fatty acids in colostrums is a key influence on neurodevelopmental outcomes.[18]

White matter distribution has been directly linked to the neurodevelopmental ability of preterm infant suvivors.[25] White matter injury that occurred in infancy was directly related to developmental impairments (cognition, coordination, behavioral problems, and lower academic performances) at age 2.[25] Thus, human milk may play an important role in improving the neurodevelopmental outcomes of affected individuals.

## PRETERM BRAIN DEVELOPMENT

Preterm infant neurologic development is not a linear process. It is impossible to determine infant outcomes from one specific event.[19] To better understand preterm neurologic development, a more chaotic theory of development needs to be taken into account, acknowledging the random behavior of preterm births.[19] It is better to think of preterm neurologic development as a situation in which a number of outcomes could happen as a result of multiple factors in the infant's development.[19] These authors, who suggest multiple coexisting events, also suggest that prebirth behaviors (ie, prenatal conditions, perinatal conditions, genetics, and maternal immunologic function) affect neurologic development, behavior, and function. This is not, however, a direct cause-effect relationship.[19] Conditions such as NICU environment and caregiving affect neurologic cues (and thus development) in the preterm infant's brain,[19] showing how important environment and care are to the neurologic development of the newborn.[19] Controlling for nutrition with human milk in such a chaotic environment may be crucial for proper neurologic development.

A second model, specific to cerebral white matter development, suggests that both hypoxia and infection can activate microglia. The microglia then release ROS, cytokines, and glutamate, which all ultimately lead to the death of oligodendrites.[17] This further suggests the multifactor influences of cerebral white matter injury and the importance of protecting the preterm infant from damage done by ROS.[17] Damage to immature oligodendrites is known to be caused by proinflammatory cytokines, thus increasing the pathogenesis of PVL.[26] Furthermore, microglia are known to have an abundance of nucleotide receptors that aid in the inflammatory response.[16] Thus, protecting against these 2 assaults may be key in preventing and/or decreasing the amount of damage done to cerebral white matter.

## IMPLICATIONS OF HUMAN MILK AND WHITE MATTER INJURY

Although there are many factors in the preterm infant's life that cannot be controlled for, one factor that can be controlled is nutrition. Nutrition is crucial for all newborns, and even more so for preterm infants. Human milk provides not only nourishment but also substances that may aid to protect the newborn against white matter injury through the reduction of ROS and the inflammatory process (see Table).

Human milk has a number of anti-inflammatory components such as soluble cytokine receptors, anti-inflammatory cytokines, κ-casein, lactoferrin, anti-inflammatory fatty acids, and nucleotides that can all aid in the anti-inflammatory response.[12,16,27] Cytokines such as interleukin 1, interleukin 6, and tumor necrotic factor–α are all mediators in the inflammatory process and are produced as a response to immune system stimulation.[5,28] Interleukin 6 and tumor necrotic factor–α are both produced by T-helper cells directly affecting plasma cells and antigen presenting cells, respectively.[28] Soluble cytokine receptors prevent anti-inflammatory cytokines from exerting their effect.[13] κ-Casein and lactoferrin have antimicrobial effects.[13] Specifically, lactoferrin affects the production of cytokines, suppresses complement activation, and acts as an antioxidant.[28] Fatty acids serve as a precursor to prostaglandins, which are mediators of the inflammatory process.[28] Nucleotides act on purinergic receptors that are present on microglia.[16]

Human milk is a rich source of antioxidants (peroxidase, catalase, superoxide dismutate, glutathione, vitamins E and C, and β-carotene) that are known to aid in neutralizing ROS.[11] Vitamin C, vitamin E, catalase, superoxide dismutate, glutathione, and β-carotene protect against free radical damage done by ROS.[11] Thus, human milk may have an important role in decreasing the amount of damage done when cerebral white matter injury is a threat.

## DISCUSSION

It is clear that white matter damage is affected by multiple factors. The "multiple-hit hypothesis" suggests that factors during the antenatal, perinatal, and postnatal periods affect infant neurologic outcomes.[22] Examples of these factors are inflammation,

TABLE. Human Milk Constituents That May Protect Against White Matter Injury

| | Anti-inflammatory | Inflammatory Process | Antioxidant | Source |
|---|---|---|---|---|
| Interleukin 1 | | X | | Blackburn[5] |
| Interleukin 6 | | X | | Blackburn[5] |
| Tumor necrotic factor–α | | X | | Blackburn[5] |
| Cytokines | X | X | | Blackburn[5] |
| Fatty acids | X | X | | Rolfes et al[10] |
| Nucleotides | X | X | | Di Virgilio et al[16] |
| Peroxidase | | | X | Lopez[12] |
| Soluble cytokine receptors | X | X | | Lopez[12] |
| Lactoferrin | X | X | X | Venter and Dean[13] and Lopez[12] |
| κ-Casein | X | X | | Venter and Dean[13] |
| Vitamin C | | | X | Zarban et al[11] |
| Vitamin E | | | X | Zarban et al[11] |
| Catalase | | | X | Zarban et al[11] |
| Superoxide dismutate | | | X | Zarban et al[11] |
| Glutathione | | | X | Zarban et al[11] |
| β-Carotene | | | X | Zarban et al[11] |

hypoxia-ischemia, stress, drugs, exit toxicity, oxidative stress, and toxin exposure.[22]

Studies have been done showing how maternal medications and supplementation can affect neurologic outcomes of infants known to be at risk for adverse outcomes. An animal model intervention study using rats examined maternal supplementation of omega-3 fatty acid during pregnancy.[29] Omega-3 fatty acids inhibit nuclear factor κB signaling in the inflammatory pathway.[29] This research demonstrated that intervention rat pups had higher amounts of omega-3 fatty acid than control rat pups at birth.[29] The intervention rat pups also had long-term neurologic protection as a result of maternal omega-3 fatty acid supplementation.[29] A different study looking at maternal administration of magnesium sulfate found it to be neuroprotective, especially with respect to cerebral palsy, of which PVL is a leading cause.[21,30]

Neurologic outcomes (including PVL) can be protected against pre- and immediately postpartum. It is known that magnesium sulfate, cooling of the head (and sometimes body), and careful monitoring of blood gases are effective tools for PVL prevention.[21] Furthermore, the mechanisms of white matter injury, and more specifically PVL, have been well-studied, allowing room for hypotheses on mechanisms that may affect its progression.

A logical next step would be to study postnatal factors and their effects on neurologic development and more specifically white matter injury. Human milk may play a critical role due to the many nutritive and nonnutritive components that are anti-inflammatory and aid in ROS reduction. At this point, the exact mechanisms of how human milk may protect the preterm infant's brain are largely unknown. However, the importance of nutrition in proper visual development, involving both the brain and optic tissues, has been documented, proving substance to this hypothesis.[27]

Human milk may have a vital role in improving outcomes for infants with cerebral white matter injury. Human milk may also play a crucial role in providing building blocks to form myelin and various neurons. Human milk/breastfeeding exclusivity and duration are positively correlated with neurologic development in healthy infants.[24] Thus, human milk should be viewed as an additional treatment, because it may have a synergistic effect in slowing the progression of white matter injury.

Future research should examine the correlation between human milk and white matter damage in preterm infants. In addition, the exclusivity, timing, and duration (dose) of human milk exposure may be of critical importance when considering short- and long-term neurologic and development outcomes. There are many aspects of human milk that aid in the inflammatory process (both inflammatory and anti-inflammatory), ROS reduction, and nutrition. Research on the effects of white matter injury and the role of human milk should follow survivors through childhood and on to adulthood.

Given the current state of the science, there is no harm in promoting the use of human milk for preterm infants as human milk may indeed have a vital role in infants' neurodevelopmental outcomes. The provision of human milk could be a low-cost and effective way to minimize both the incidence of injury and the long-term sequelae. If the use of human milk is promoted for preterm infants, mothers will be empowered and understand that they are making an important contribution to their children's care.

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