White Matter Injury in Preterm Infants
Could Human Milk Play a Role in Its Prevention?
Francesca O. Kotey, BA, BSN; Diane L. Spatz, PhD, RN-BC, FAAN

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
have increased, the survival rates of preterm infants
have also increased. In 2007, 85% of preterm infants
were surviving after discharge, a number that will
only increase as more advances are made in
medicine. 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. Some minerals
noted to be in human milk are calcium, phosphorus,
magnesium, copper, zinc, and iron. Human milk
also has vitamins D, E, K, B₁₂, B₁₅, and C. Vitamins
and minerals have a number of functions. Vitamins
B₁₂ and B₁₅ are important in maintaining neuronal
function. Vitamin D, calcium, phosphorus, and magnesium are important
in bone growth and development. Vitamins E and C
are known for their antioxidant properties.

Macronutrients such as proteins, carbohydrates,
and fatty acids are also found in human milk. 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. In addition, these researchers found a gestational age effect; the more preterm the delivery,
the higher concentrations of these macronutrients.
Furthermore, the amount of fat in milk changes on the basis of the degree of breast fullness
or emptiness. As the breast is emptied, the milk
(ie, hind milk) has increased fat and calories. 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.

Protein content is inversely proportional to the
volume of milk expressed: Smaller volumes of milk
have higher protein contents than larger volumes.
Some proteins known to be in human milk are B₁₂
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). κ-Casein,
lactoferrin, lactoalbunin, and immunoglobulin A are all proteins that have immunologic
functions in human milk. 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.

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

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. Human milk also has components
that are important in the reduction of reactive oxygen
species (ROS), thus acting as an antioxidant.

Similar to the inflammatory process, damage by
ROS has been implicated in the pathogenesis of
cerebral white matter injury. 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.

**CEREBRAL WHITE MATTER INJURY IN
PRETERM INFANTS**

The brain consists of white and gray matter. White
matter receives its name from its white appearance. The
tissue appears to be white because of the presence
of myelinated axons. Gray matter is so named for its gray appearance, resulting from the darker cell bodies of which it is composed. Myelin provides a protective sheath allowing axonal transmission to be protected and propagated between the soma and its
target location. Cerebral white matter injury is one
of the most common neural injuries faced by preterm
infants. This injury is often the result of damage
caused by ischemia, infection, and the inflammatory
process. Neuroanatomy of the preterm infant may
also increase vulnerability to such injuries.
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.3 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.7 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.7 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. There were also significant differences between males and females, with females overall having higher scores than males.

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. 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. It is proposed that the presence of long-chain polyunsaturated fatty acids in colostrums is a key influence on neurodevelopmental outcomes.

White matter distribution has been directly linked to the neurodevelopmental ability of preterm infant survivors. White matter injury that occurred in infancy was directly related to developmental impairments (cognition, coordination, behavioral problems, and lower academic performances) at age 2. 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. 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. 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. 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. Conditions such as NICU environment and caregiving affect neurologic cues (and thus development) in the preterm infant’s brain, showing how important environment and care are to the neurologic development of the newborn. 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. This further suggests the multifactor influences of cerebral white matter injury and the importance of protecting the preterm infant from damage done by ROS. Damage to immature oligodendrites is known to be caused by proinflammatory cytokotks, thus increasing the pathogenesis of PVL. Furthermore, microglia are known to have an abundance of nucleotide receptors that aid in the inflammatory response. 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 cytokotks, κ-casein, lactoferrin, anti-inflammatory fatty acids, and nucleotides that can aid in the anti-inflammatory response. 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. Interleukin 6 and tumor necrotic factor–α are both produced by T-helper cells directly affecting plasma cells and antigen presenting cells, respectively. Soluble cytokine receptors prevent anti-inflammatory cytokotks from exerting their effect. Specifically, lactoferrin affects the production of cytokotks, suppresses complement activation, and acts as an antioxidant. Fatty acids serve as a precursor to prostaglandins, which are mediators of the inflammatory process. Nucleotides act on purinergic receptors that are present on microglia.

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. Vitamin C, vitamin E, catalase, superoxide dismutate, glutathione, and β-carotene protect against free radical damage done by ROS. 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. Examples of these factors are inflammation,
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.

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. 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.

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

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Anti-inflammatory</th>
<th>Inflammatory</th>
<th>Antioxidant</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interleukin 1</td>
<td>X</td>
<td></td>
<td>Blackburn5</td>
<td></td>
</tr>
<tr>
<td>Interleukin 6</td>
<td>X</td>
<td></td>
<td>Blackburn5</td>
<td></td>
</tr>
<tr>
<td>Tumor necrotic factor-α</td>
<td>X</td>
<td></td>
<td>Blackburn5</td>
<td></td>
</tr>
<tr>
<td>Cytokines</td>
<td>X</td>
<td>X</td>
<td>Blackburn5</td>
<td></td>
</tr>
<tr>
<td>Fatty acids</td>
<td>X</td>
<td>X</td>
<td>Rolffs et al10</td>
<td></td>
</tr>
<tr>
<td>Nucleotides</td>
<td>X</td>
<td>X</td>
<td>Di Virgilio et al16</td>
<td></td>
</tr>
<tr>
<td>Peroxidase</td>
<td></td>
<td>X</td>
<td>Lopez12</td>
<td></td>
</tr>
<tr>
<td>Soluble cytokine receptors</td>
<td>X</td>
<td>X</td>
<td>Lopez12</td>
<td></td>
</tr>
<tr>
<td>Lactoferrin</td>
<td>X</td>
<td>X</td>
<td>Venter and Dean13 and Lopez12</td>
<td></td>
</tr>
<tr>
<td>κ-Casein</td>
<td>X</td>
<td>X</td>
<td>Venter and Dean13</td>
<td></td>
</tr>
<tr>
<td>Vitamin C</td>
<td></td>
<td>X</td>
<td>Zarban et al11</td>
<td></td>
</tr>
<tr>
<td>Vitamin E</td>
<td></td>
<td>X</td>
<td>Zarban et al11</td>
<td></td>
</tr>
<tr>
<td>Catalase</td>
<td></td>
<td>X</td>
<td>Zarban et al11</td>
<td></td>
</tr>
<tr>
<td>Superoxide dismutate</td>
<td></td>
<td>X</td>
<td>Zarban et al11</td>
<td></td>
</tr>
<tr>
<td>Glutathione</td>
<td></td>
<td>X</td>
<td>Zarban et al11</td>
<td></td>
</tr>
<tr>
<td>β-Carotene</td>
<td></td>
<td>X</td>
<td>Zarban et al11</td>
<td></td>
</tr>
</tbody>
</table>
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.

References

For more than 69 additional continuing education articles related to neonatal, go to NursingCenter.com/CE.

www.advancesinneonatalcare.org

Copyright © 2013 National Association of Neonatal Nurses. Unauthorized reproduction of this article is prohibited.