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BABIES BORN EARLY CAN HAVE BRAIN INJURY

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It is extremely common for babies to be born early. When babies are born too early, their normal brain development is interrupted, and they are more likely to have problems later on in their lives. Disrupting brain development results in various types of brain injury depending on how early the baby is born. Even babies who are born a little bit early can have brain injury. It is important to understand the differences in brain development between babies who are born at full term compared with those who are born early. Knowledge of these differences allows scientists and doctors to discover new treatments for babies who are born early. It is very important to minimize brain injury, so that these babies get off to a good start.

INTRODUCTION

It is really exciting when a family is making plans for a new baby. As the anticipation builds, it might seem like the sooner the baby arrives the better. However, babies need to complete important stages of brain development before they are born. Doctors consider babies born before they have

reached the normal 37–40 weeks of time inside the mother to be "preterm" (Figure 1A). Worldwide, about 11% of babies are born preterm [1]. Most of these babies are born just a few weeks early. A small group of these babies are born extremely preterm, meaning they are born before 28 weeks of development. The earlier a baby is born the more vulnerable their brain is to injury. Brain injury can happen when a baby is born early because the baby's brain development is disrupted. The brain injuries that babies experience can affect them for the rest of their lives. Doctors and neuroscientists are still trying to understand how to help the brains of preterm babies develop normally and reduce brain injury so that the babies do not have problems with their brains when they grow up.

TRIMESTER

Pregnancy is divided into three stages. Each of these stages is called a trimester.

PRETERM BABY

A normal baby is born between 37 and 40 weeks of development. If a baby is born early, before 37 weeks, then doctors call the baby "preterm."

BRAIN DEVELOPMENT

Pregnancy is divided into three separate stages called **trimesters**. Very specific developmental events occur in each trimester (Figure 1B). Understanding how a baby's brain develops during each stage is the first step in determining what kind of brain injury a **preterm baby** might have.

Brain development begins during the first trimester with the formation of something called the "neural tube." The neural tube is a group of cells that will eventually form the entire brain and spinal cord. The neural tube cells divide over and over again, to form the basic regions of the brain. It is crucial to understand that only the basic structure of these brain regions is established during this early time, and that it is only later in development, even into adolescence in some cases, that these regions stop growing.

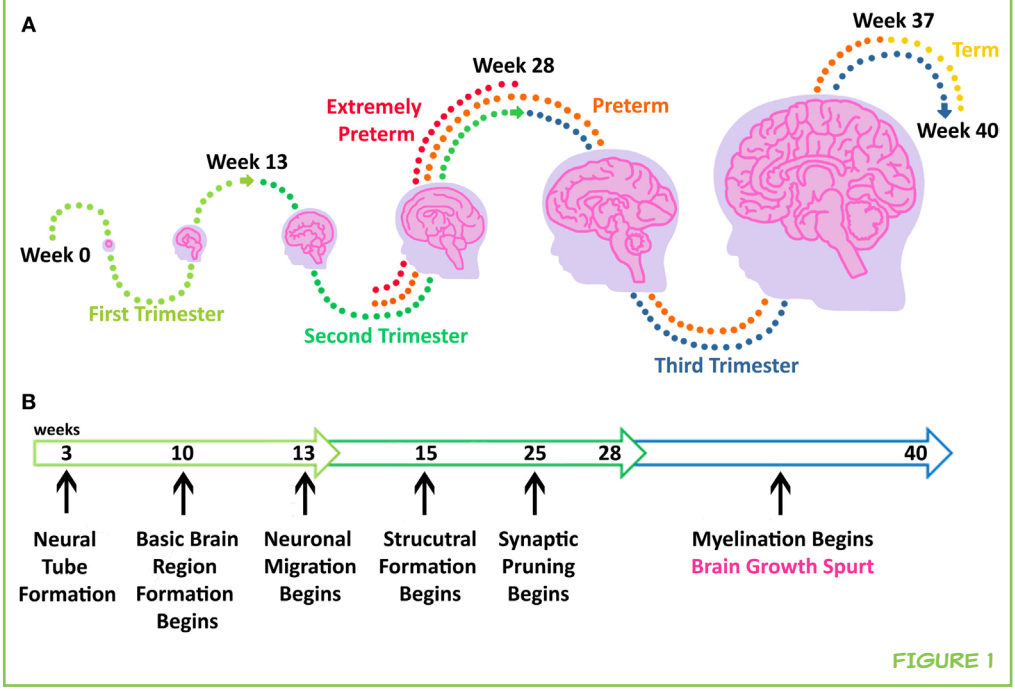

FIGURE 1

This figure shows the stages of pregnancy as well as the events in human brain development.
A. A timeline of the three trimesters of pregnancy. Babies who are born early, before 37 weeks, are called preterm (orange dots). Preterm babies who are born between week 22 and week 28 are called extremely preterm (red dots). Babies are born on time if they are born "at term," between week 37 and week 40 (yellow dots).
B. Brain development is a series of complex steps. Black arrows point to specific events in brain development that happen on certain weeks throughout a pregnancy. One of the first steps in brain development happens at week 3, when the neural tube forms. Myelination is one of the last steps of brain development that happens during the third trimester of pregnancy, when the brain undergoes a massive growth spurt.

Around 8 weeks into the first trimester, a massive movement of neurons begins. These neurons are considered the thinking cells of the brain. They originate from specific areas of the brain where new cells are formed and travel through the brain tissue to their final destinations. This movement of newly formed neurons, called "neuronal migration," continues for the rest of brain development.

Important stages in brain development also occur in the second trimester of pregnancy. Early in the second trimester, more advanced brain structures begin to form out of the general structures that were established during the first trimester. These structures form as more and more neurons migrate into the regions. When a neuron arrives at its destination, it makes connections with other neurons. These connections are called **synapses**, which is where one neuron passes a message to another neuron. In the middle of the second trimester, the important process of "synaptic pruning" begins. At this stage of brain development, neurons have made synaptic connections with as many other neurons as possible. But as development continues and as neurons start to send messages to one another, not all of the connections are necessary. Synaptic pruning is the process of removing the extra connections that are not being used. This removal makes the brain regions more organized, so that only the essential synapses remain. The process of synaptic pruning continues after a baby is born.

SYNAPSE

The place where messages are sent from one neuron to another neuron across a tiny space.

> ***DID YOU KNOW?*** *Neurons in the brain are one of the most unique cell types in the human body. Neurons are able to talk to each other using electricity and chemicals called "neurotransmitters". Neurons use electricity to carry a message to a different part of the brain where the message is then translated into a chemical package that is sent to other neurons!*

During the third trimester of pregnancy, a brain growth spurt occurs. From the beginning of the third trimester to the end of the third trimester, the baby's brain will nearly double in size [2]. The brain grows so quickly for two reasons. The first is that processes that started earlier in development are ongoing, such as the forming and migration of new neurons and other types of brain cells. The second reason for this rapid growth is that the process of "myelination" begins. Myelination is when a certain type of brain cell, called an "oligodendrocyte," wraps the axons of neurons with a substance called myelin (Figure 2). The axon is a skinny arm on the neuron that reaches to other parts of the brain. The myelin wrapping allows messages to travel down the length of the axon so that neurons can communicate with each other much more quickly than before the myelin was there. Myelin also provides the axon with materials it needs to stay healthy.

TERM BABY

A baby who is born on time, at 37–40 weeks of development.

When **term babies** are born, between 37 to 40 weeks, their brains have completed these complex stages of development and their brains are ready

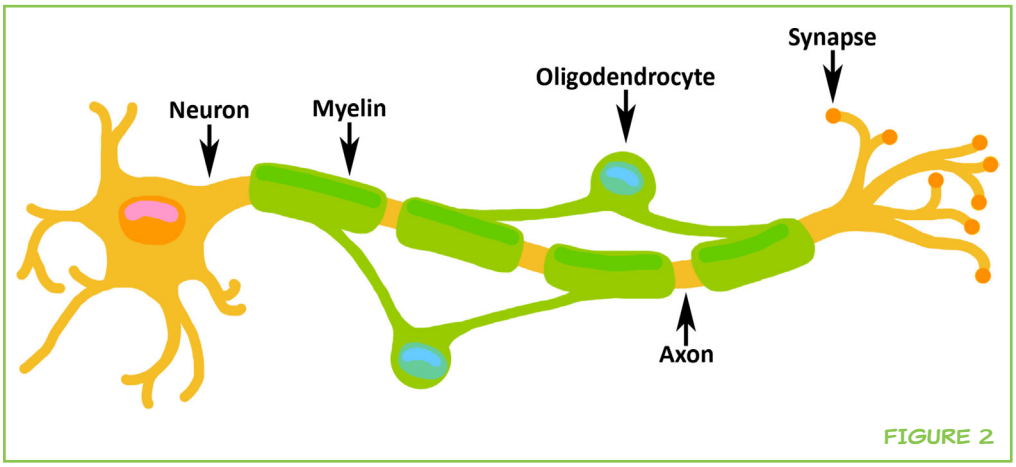

FIGURE 2

Oligodendrocytes make myelin, which wraps the axons of neurons during the third trimester of pregnancy. Myelin allows a message to be sent down the axon to the synapse, where the message is then passed on to another neuron. The neuron receiving the message, called the postsynaptic neuron, is not shown.

to encounter the world. If babies are born early, their brain development is interrupted.

INTERRUPTED BRAIN DEVELOPMENT

Doctors who take care of preterm babies are worried about these babies developing brain injury. One way that brain injury can occur in babies born early is by interrupting brain development, causing their brains to develop in a way that is different from that of babies born at term. The amount of brain injury depends on how early a baby is born and on how healthy the baby is. Overall, babies who are born only a little early have a better chance of avoiding brain injury. Extremely preterm babies have not completed as many steps in brain development and thus have more problems with brain injury. Depending on how early a baby is born and which steps in brain development were interrupted, doctors and scientists can make predictions about the kind of brain injuries the preterm babies could have and how these brain injuries could affect these babies when they grow up.

Extremely preterm babies are born during the second trimester when the structures and regions of their brains are still in the process of forming. On the outside of the brain, a bumpy texture made up of grooves and ridges is formed during this time. The grooves are called sulci and the ridges are called gyri. When the formation of the sulci and gyri is interrupted, and they do not develop normally, these babies are at risk of developing a condition called epilepsy as they get older, which is when seizures occur multiple times. There are also regions on the inside of the brain that undergo important developmental milestones during the second trimester. The corpus callosum is one of these regions. The corpus callosum is a group of axons wrapped in myelin that carries messages from neurons on one side of the brain to neurons on the other side of the brain. In extremely preterm babies, the formation of the corpus callosum is interrupted and the axons crossing the bridge from one

side of the brain to the other side are disorganized and are not able to send messages as well [3].

> ***DID YOU KNOW?*** *In a normal human brain, there are more than 200 million axons that cross the corpus callosum to send messages from one side of the brain to the other. Recently, scientists examining the brain of the famous physicist, Albert Einstein, discovered that his corpus callosum was much larger than normal [4]! Could this mean that more connectivity between the two sides of the brain contributed to how smart Einstein was?*

Even when a baby is born just a little bit early, there is still a chance that the baby could have brain injury from abnormal brain development. During the third trimester, the process of myelination starts. If this process is interrupted, the myelin that supports axons might not develop normally. When these babies grow up, they could have trouble focusing in school and difficulty in learning certain subjects.

Brain injury in preterm babies not only comes from interrupting brain development before the babies are born but also happens after birth. Preterm babies are at risk of brain injury resulting from sudden changes in their surroundings. For example, being inside the mother is a very different environment compared with being in the neonatal intensive care unit (the place in a hospital where doctors take care of sick babies).

SENSORY OVERLOAD

When a preterm baby is born, the environment that the baby's brain is developing in is very different from what it is supposed to be. The change in environment can cause brain injury because the developing brain must now

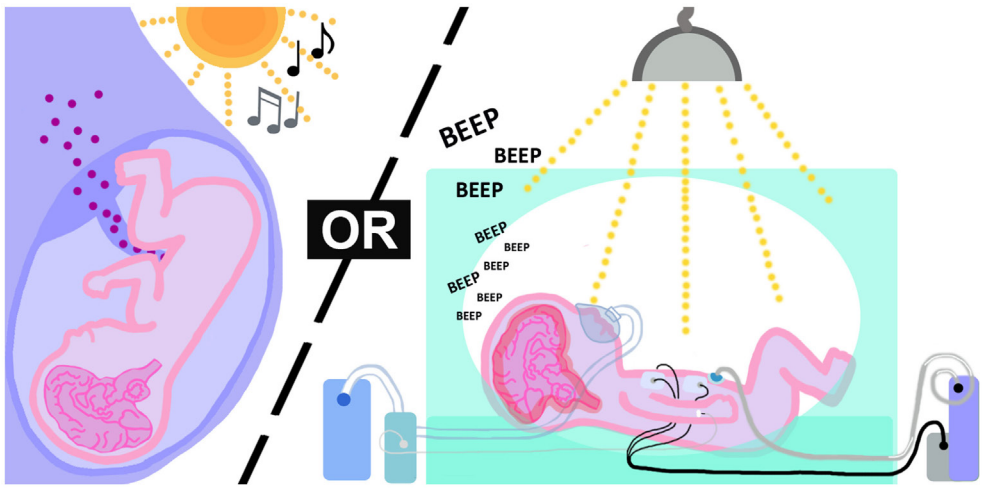

FIGURE 3

FIGURE 3

This figure shows some of the differences in the environment that preterm babies live in while they go through brain development, compared with babies who have not been born yet.
A preterm baby experiences different kinds of sensory input from the environment (sounds, lights and touch) that can hurt the baby's brain.

process all the information from the new environment before it is ready to do so. To make things even more complicated, babies who are born early can be really sick in other ways, which can also impact brain development.

Preterm babies experience brain development in a very different environment (a hospital room) compared with babies who are born at full-term, whose brains develop inside of the mother (Figure 3). Scientists think that when the brain of a preterm baby develops outside of the mother, it receives inappropriate signals from the environment that affect how the neurons are organized. The preterm baby's brain is forced to process information coming in from the ears (sounds), eyes (light), nose (smells), mouth (tastes) and skin (touch) before the baby is ready to receive that sensory information. Scientists think that this kind of sensory overload might lead to the abnormal brain connections and brain structure in kids who were born extremely preterm [5]. Because we have learned that this early sensory overload might contribute to brain injury and abnormal development in preterm babies, doctors now recommend certain techniques to control the environment that these babies develop in, so that their brain injuries are not made worse. Most of these techniques try to mimic what the touches, sounds and lights would be like if the baby had not been born early.

When a baby is born early, the baby leaves the mother's body and enters the world before they are ready. Not only is the baby's brain not ready to process information but also the baby's body is not prepared to handle all of the challenges that come with living outside of the mother. Preterm babies are likely to become sick, which can cause further brain injury. Even though both term and preterm babies can get sick after being born, preterm babies are at a disadvantage, because their body systems and organs are at an earlier stage of development.

Outside of the mother, a baby can become sick from bacterial, viral or fungal infections. **Inflammation** is a normal and important process carried out by the body's immune system that helps fight off infection. However, when a preterm baby is sick with an infection, the inflammatory response can actually harm the baby's developing brain. Other challenges that preterm babies face include problems with blood flow to the brain and nutrition for the brain cells. Blood flow delivers oxygen to the brain. Preterm babies have trouble breathing and getting oxygen into their blood, because their lungs are not fully developed. If a baby's brain does not get enough oxygen, the neurons in the brain cannot survive. Before a baby is born, the nutrition it receives from its mother is perfectly adjusted for the baby's specific needs during each timepoint in development. For example, during the third trimester, oligodendrocytes need certain kinds of fats to make myelin. If a baby is born before the third trimester ends, the baby could develop brain injury if it doesn't have the right nutrients to make myelin. Doctors who take care of preterm babies work to

INFLAMMATION

When the body detects an injury or infection, it makes a protective response to help itself heal. This inflammation response involves the release of certain molecules that can contribute to brain injury.

provide the nutrition that the baby would be receiving if they had not been born early, to help with healthy brain development.

CONCLUSION

Together, all the changes that a baby experiences when they are born early can impact how the baby's brain develops. If the brain is not able to develop normally, the baby may grow up to have trouble in school or may have serious health problems. Although scientists and doctors are working on figuring out the best way to take care of preterm babies, there is still a lot work to be done. It is essential to continue researching how a baby's brain develops and what happens when brain development is interrupted when a baby is born early, so that we can find different ways to minimize the brain injury that these babies can have.

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CONFLICT OF INTEREST STATEMENT: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ISABELLE, AGE: 10

My name is Isabelle and I'm 10 years old. I love to draw and my favorite animal is a dolphin. I also play the piano and my favorite lesson at school is music.

LINCOLN, AGE: 10

Hi, my name is Lincoln and I am 10 years old. I love mountain biking, scootering and food! My favorite animals are sloths, chickens and llamas. I am passionate about rock music and love playing the drums.

AUTHORS

JESSIE NEWVILLE

I am a researcher in the Neurosciences Department at the University of New Mexico. I love learning about all things related to oligodendrocyte. My current research investigates how exposure to alcohol during development results in acute and long-lasting white matter injury in the brain. Through my research, I hope to contribute to the larger effort in the development of therapeutics that help people who have fetal alcohol spectrum disorder. When I have free time, I explore New Mexico, garden and appreciate poetry.

MARIA C. ORTEGA

I graduated from the University of New Mexico (UNM) with a B.S. in Psychology. I have contributed to the research efforts of Dr. Lauren Jantzie at UNM, who investigates perinatal brain injury. I am interested in prenatal health and the effects of abnormal brain development in infants. I hope to better understand how to best support moms and their infants, especially when they are struggling with preterm health effects.

JESSIE R. MAXWELL

I am a doctor and a scientist who is dedicated to improving the long-term outcomes of infants born preterm or ill. During my fellowship training, I realized how many infants are born with prenatal alcohol exposure and have related problems, such as inflammation during development. These newborns are at high risk of developmental delays, and as a clinician, the support I can offer is limited. However, in the laboratory, I am able to work toward expanding the current information known about these infants, with the ultimate goal of finding therapies that can help the infants. *jrmaxwell@salud.unm.edu