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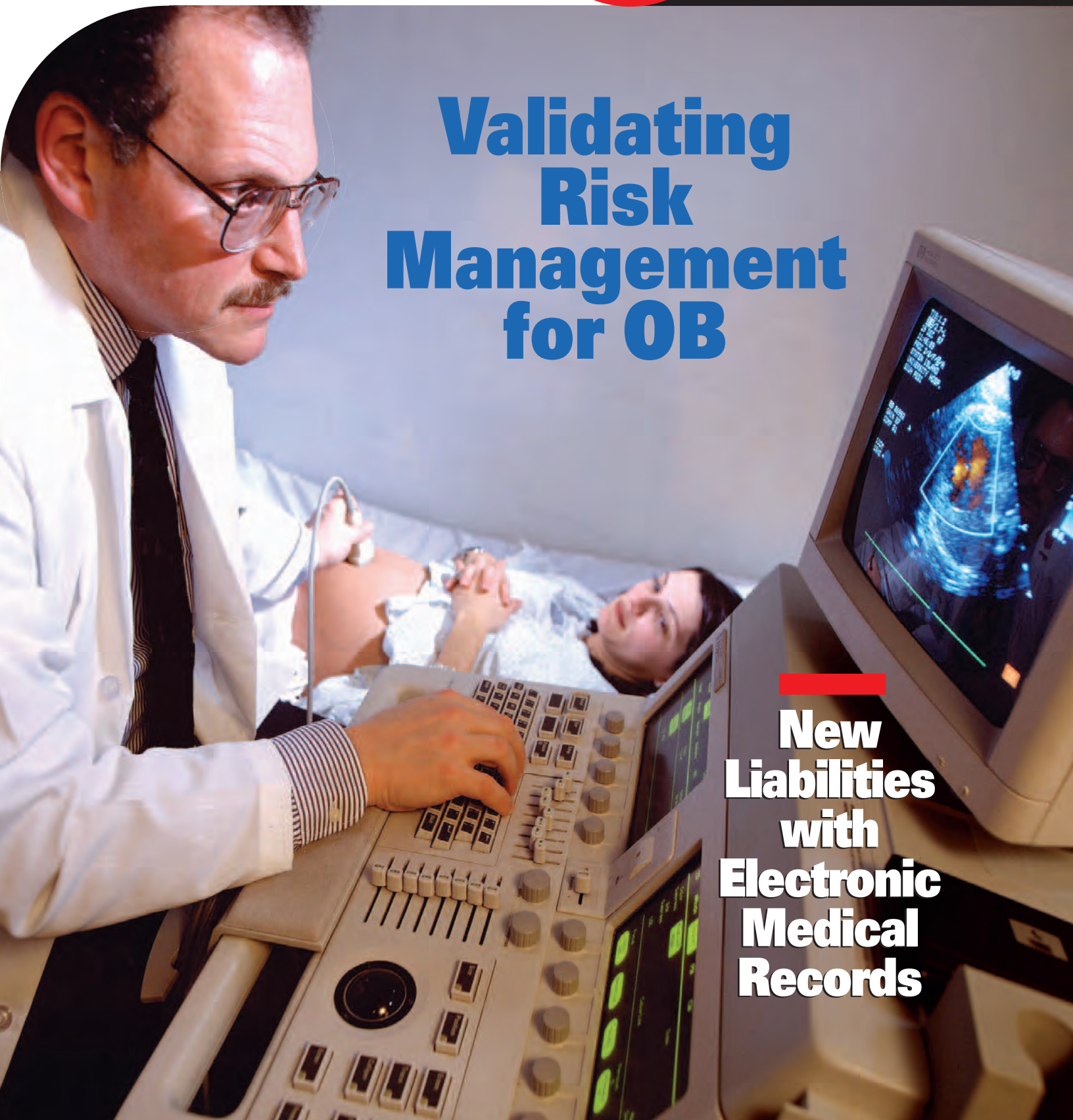
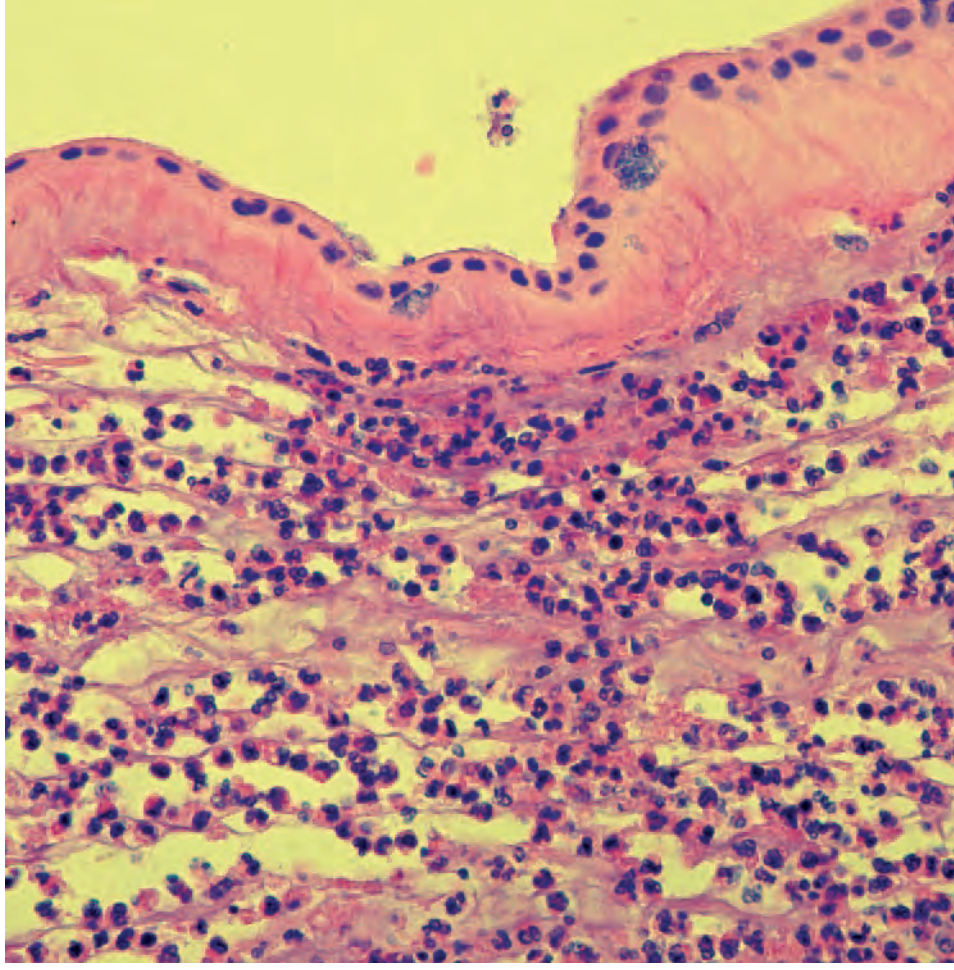


Validating Risk Management for OB

New Liabilities with Electronic Medical Records

BY JAMES ROSENBLUM, ESQ.



Breaking down a liability case: understanding the medicine

Placental Pathology and Fetal Inflammatory Response to Infection

WHEN NEONATAL ENCEPHALOPATHY OCCURS AND A BABY DEVELOPS CEREBRAL PALSY, PLAINTIFFS' ATTORNEYS ATTRIBUTE THESE CONDITIONS TO MISMANAGEMENT DURING LABOR AND DELIVERY, AND SEEK MULTI-MILLION-DOLLAR AWARDS.

People involved in obstetric liability litigation know that maternal infection ("chorio-amnionitis") can cause brain damage, but may not appreciate how the inflammatory response to infection manifests itself and causes brain damage. Even neonatologists label brain damage as "hypoxic ischemic encephalopathy," without regard to the pathology, and placental pathologists may not fully understand the clinical significance of abnormal pathology. Placental pathology is also a narrow field, with only a handful of well-versed experts, because placental disease, in general, plays a small role in the determination of clinical care.

Good experts in court require an appreciation of all these subjects, including perinatal hematology, perinatal immunology, pediatric neuro-pathophysiology, and pediatric neuro-radiology. The jargon of placental pathology is also difficult for non-pathologists. Pathologists use vague terms like a "robust" inflammatory response and use different terms for the same things. Thus, granulocytes, neutrophils, polymorhonuclear leukocytes (PMLs), "polys," refer to similar cells. The term "pathology" refers to abnormal tissue or disease, but pathologists need to know what "normal" looks like to understand when conditions are abnormal.

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Anatomy, physiology of placenta

Some may think the placenta is a maternal organ and that the fetus "begins" with the umbilical cord. Medical books refer to a "maternal" side and a "fetal" side of the placenta, suggesting "co-ownership." In fact, the placenta is a fetal organ that receives maternal blood and acts as the fetus' lung, with exchange of gases, and GI tract, with absorption of nutrients from the mother. There is an interplay between the two circulations, and damage or injury to one may affect the other, but this does not necessarily occur because they are separate.

As shown on the diagram of the placenta, the fetus is surrounded by amniotic fluid encased in the amniotic sac. The amniotic cavity (containing the amniotic fluid in which the fetus floats) is lined by two membranes, the amnion (inner membrane), and chorion (outer membrane). The placenta lies between the endometrium and amnion, occupying a variable percentage of this junction, depending on the gestational age. The portion of the endometrium next to the placenta is the parietal decidua, (the decidua basalis, or basal plate), which contains maternal blood vessels.

The fetal side of the placenta is the chorionic plate (an extension of the chorion) and the amnion, where the umbilical cord carrying fetal blood vessels enters the placenta.

Between the decidua basalis and chorionic plate are the lacunae or inter-villous spaces, containing maternal blood and the beginning of the fetal circulation, i.e., tiny capillaries, in villi, like branches of a tree. These capillaries are ensheathed in thin membranes (trophoblasts) and a small amount of connective tissue. Oxygen and other nutrients diffuse across the villous membrane from the mother's blood to fetal circulation and are carried back to the fetus in succession through larger and larger veins in the villi, to the chorionic plate, to the umbilical vein, and finally to the fetal heart where it is distributed to fetal tissues by the fetal circulatory system. In reverse, waste and CO_2 from the fetal circulation travel from the umbilical arteries into successively smaller arteries in the placental villi and finally diffuse into the maternal blood in the placenta.

The umbilical cord connects the fetus to the placenta. It contains a fetal vein that brings oxygenated blood and nutrients from the placenta to the infant, and two fetal arteries that return de-oxygenated blood to the placenta. These vessels are surrounded by connective tissue called Wharton's jelly, which cushion the blood vessels, protecting them from coiling around each other during fetal movements.

Infection

Infection can occur in maternal tissues (the chorion, amnion, or maternal circulation), the amniotic fluid, or fetal tissues. Different organisms (most commonly bacteria such as Group B Streptococcus and E. coli) preferentially infect different parts of the feto-placental unit. Some infections are more virulent and therefore more dangerous. Infections typically enter the vagina and ascend into the uterus (ascending infection). Organisms pass through membranes (the chorion and amnion), into the amniotic fluid, causing an intra-amniotic infection (IAI). Since the fetus floats in the amniotic fluid, swallows and breathes this fluid, infectious organisms may enter fetal lungs and stomach and infect the fetus (sepsis), provoking a fetal response. A less frequent mechanism of spread of infection to the fetus is hematogenous, wherein infection spreads from maternal blood into the placenta and then through villi and capillaries to the fetus.

Maternal infection may be clinically evident (fever, chills, etc.) or silent and limited to the placenta (i.e., seen only on histological examination). Newborn sepsis is usually diagnosed by blood or spinal fluid cultures. However, blood and spinal fluid cultures may be negative, because antibiotics given before delivery may artificially sterilize fluids, but not eradicate, infection.

Inflammatory response: the role of blood cells

Blood cells ("cytes") include white cells (leukocytes), red cells (erythrocytes) and platelets (thrombocytes), which are usually made in bone marrow. White cells respond to infections by recognizing specific components called antigens on the infectious agent, followed by ingesting and digesting infectious/foreign material. They also "clean up" the cellular debris generated from the infection. They can squeeze out of blood vessels, through vessel walls, into surrounding connective tissue to attack infection. One might picture soldiers who organize and march out of the fort. White cells also secrete chemicals to destroy bacteria that can disrupt vessel walls and block vessels (to wall off the infection). Although this process is therapeutic in fighting infection, it can also damage tissues. Minor damage heals, but major tissue damage causes scar tissue and possible loss of function.

White cells are divided into two groups, one with granular

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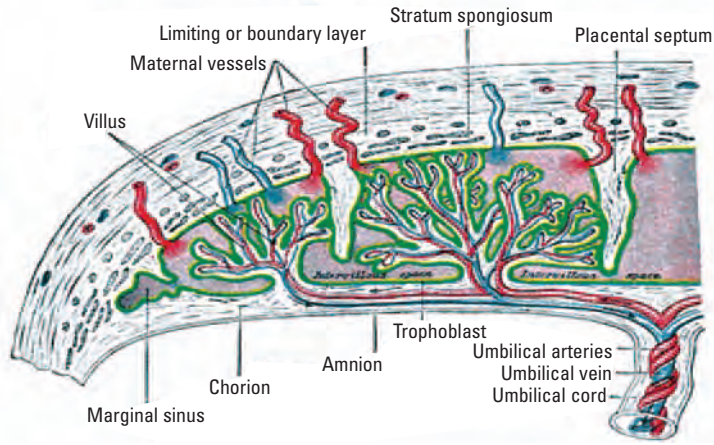
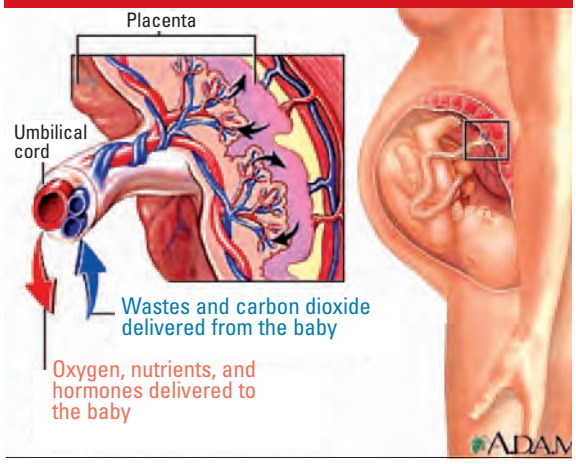


Placental Anatomy and Circulation



cytoplasm (granulocytes) and the other without granular cytoplasm (agranulocytes). Granulocytes have multi-lobed nuclei and hence are called polymorphonuclear leukocytes (PMLs), or "polys." These are further sub-classified into neutrophils (the most numerous PMLs), eosinophils, and basophils. When pathology slides are treated with special chemicals (stained), eosinophils have pink-red granular cytoplasm; basophils have blue granular cytoplasm, and neutrophils have pink-blue cytoplasm. Agranulocytes include lymphocytes (small cells) and monocytes/macrophages (larger cells). All have nuclei that stain dark blue.

Neutrophils are the primary line of defense for most acute infections. As neutrophils mature, their nuclei develop greater segmentations or lobations. Immature neutrophils have a less segmented nucleus, and are called bands, or "stabs" (German for "sword"). Many immature neutrophils compared to mature cells (the immature to total neutrophils ratio) reflects a longer duration of the inflammatory response to infection, because the body releases more cells quickly to fight infection and recruit "younger," more immature cells.

In chorioamnionitis, two immune systems (fetal and maternal) respond to infection. The fetal response is relatively slow and less predictable since the fetal immune system is immature and less well developed. This is evidenced by neutrophils traversing vessel walls to reach the offending agent in surrounding tissues, and this "apparent inflammation of the vessels" is referred to as vasculitis. However, it is not true vasculitis, in that the vessels themselves do not cause inflammation. Rather, inflammatory cells traveling through vessel walls give the appearance of vasculitis. This can occur in villi, chorionic plate vessels, umbilical cord vessels, or all those areas. Inflammation in the umbilical cord is called funisitis.

The mother's blood is in the lacunar spaces, and does not have to traverse a vessel wall to attack the infectious agent. Rather, the maternal immune response traverses the membranes to reach the amniotic cavity (the most common site of infection); hence, the term chorio-amnionitis.

Location and distance of inflammatory cells in the connective tissue reflects the duration and/or virulence of the infection. Hence, one can "time" (or "stage") the sequence of events. Early inflammation is Stage 1, when inflammatory cells have reached only the chorion. More prolonged inflammation is Stage 2 or chorio-amnionitis, in which inflammation has traveled farther and reached the amnion. White cells in connective tissue of the chorionic plate, or in Wharton's jelly (connective tissue around vessels in the umbilical cord), have also penetrated blood vessels and are Stage 2.

Grading refers to the severity or potency of the inflammatory response. It may be measured by the number of inflammatory cells per high power field (magnification by the microscope) or by the extent of damage caused to tissues (including disruption of endothelial lining of capillaries, necrosis, etc.)

Red cells (erythrocytes) do not fight infection directly, but they play an important role in keeping the tissues alive. They contain hemoglobin, which binds, transports, and delivers oxygen to vital tissues. They respond to stress by providing increased oxygen to tissues. As red cells mature, they lose their nucleus—to allow the cell to have more hemoglobin and hence carry more oxygen. The presence of nucleated red cells (reticulocytes) in the circulation suggests oxygen starvation, with the body releasing younger cells because of an insufficient number of older cells to deliver needed oxygen. Therefore, an increased number of immature (nucleated) red blood cells (NRBCs, reticulocytes) is a separate indicator of the body's response to infection and the duration of the infection. Estimates vary, but many articles indicate that it takes several hours for NRBCs to be released into the blood.

Depending on the intricate interplay of all of these factors (the duration of infection, virulence of the organisms, the maternal response to infection and the fetal response to infection), infection may or may not be contained. Hence, inflammation may be "local" (confined to a particular area), or systemic. Systemic responses may occur even where the infection is "local."

Fetal inflammatory response syndrome

Fetal inflammatory response syndrome (FIRS) refers to a systemic response that causes neurological and vascular injury. It may occur in response to infection in mother or fetus. It occurs in term and preterm infants. Some authors (e.g., Redline) have concluded that severe (high grade, high stage) inflammation is associated with, and predictive of, brain damage. Others (e.g., Benirschke et al.) suggest that that the relationship between inflammation and brain damage is multi-factorial, dependant not only on the grade or stage of the inflammatory response, but also the virulence of the infecting organism. Metaphorically, it is like a hurricane that produces different forces, causing different types of damage. Wind blows down trees, which can damage buildings. Rain can destroy structures in different ways. Movement of people, vehicles, and equipment, can be obstructed. Unlike a hurricane, however, the fetal response can be silent until birth.

As noted above, cells can seriously injure vascular walls. When the process is systemic, it means that the same process can occur in the fetal brain. Inflammation can also provoke a cascade

of biochemical responses causing brain damage. This involves pro-inflammatory cytokines (cyto, cell, "kinetic," movement), which signal molecules, like neuro-transmitters used in cellular communication, including proteins, peptides, or glycoproteins. Cytokines are immuno-modulating agents, including interleukins (referred to as IL, with a number, e.g., IL-6). Cytokines can be measured in the blood, but are not routinely measured. Therefore, their presence can be inferred from the presence of an inflammatory response and tissue damage, which varies from tissue to tissue, with some tissues (such as the underdeveloped brain of the fetus) being more sensitive to this injury. Cytokines released as a part of an inflammatory cascade are often selectively neuro-toxic, sparing other organ systems, leading to preferential damage to the central nervous system without a more global injury. However, in contrast to intra-partum asphyxia/ischemia, which causes brain damage by deep gray matter damage (basal ganglia and thalami), 24 to 48 hours after birth, FIRS in term infants may exhibit delayed radiological appearance of damage, including white matter damage (swelling, ventricular atrophy), as well as deep gray matter injury, reflecting a continuing process of cell injury and damage. Imaging in pre-term infants is likely to show intra-ventricular hemorrhage.

The cascade involves damage to glial cells and oligodendrites, which are necessary for forming myelin sheaths, the protective coating of nerves, which is essential to enhance conductivity of electrical impulses from neurons to other portions of the body. The cascade also activates glutamine, which produces neuro-toxic glutamic acid. It also produces tumor necrosis factor (TNF), which causes brain cell damage and death. It also leads to release of destructive oxygen free radicals. It can lead to two types of cell death, i.e., apoptosis (programmed cell death), and degeneration of cells.

Conclusion

Just as infection can cause brain damage, the inflammatory response to infection may cause brain damage. It can result from infection in the mother or the fetus. It may be silent and unpreventable, with no clinical evidence. Meanwhile, clinical evidence of maternal infection does not necessarily mean that the fetus will develop an inflammatory response. The response is complex, and involves an understanding of hematology, infectious diseases, neurobiology, and neuro-pathophysiology. It is evidenced by organization and movement of white blood cells, particularly neutrophils, through blood vessels into surrounding tissue. The presence of a significant number of immature white cells and immature red cells may also evidence the inflammatory response. Damage to vessel walls may be minor and local, but significant damage, with impaired blood flow, may occur. The response may also trigger a biochemical cascade of so-called pro-inflammatory cytokines, among other processes, which hinder the formation of myelin sheaths necessary for conduction of electrical impulses in the brain.

This article was written to clarify technical aspects of this process, because it involves complex, evolving medical research and principles not readily appreciated by many people involved in obstetric liability litigation. The complexity of issues requires the involvement of specialists in neonatology, pediatric neurology, pediatric infectious diseases, and placental pathology to explain why neonatal encephalopathy and cerebral palsy did not result from improper obstetrical care. PIAA

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