Congenital CMV Infection
Cytomegalovirus (CMV) is a member of the herpes viridae family. Humans are the main reservoir of human CMV (HHV-5). Primary infection of the host occurs when a previously uninfected individual acquires the disease for the first time. In addition to primary infection, there can also be latent and reactivated viral infection. The virus is shed in bodily fluids such as saliva, urine, breast milk, semen and blood. Seroprevalence rate in women of reproductive age is 40-83%. Factors associated with seropositivity include young maternal age, multiple sexual partners and early sexual debut. Primary infection cannot be clinically distinguished from Epstein Barr virus (EBV) infection and presents with symptoms that include fever, malaise, headache, pharyngitis, lymphadenopathy, hepatosplenomegaly and arthralgias. An important risk for primary infection during pregnancy is prolonged exposure to young children. CMV infected children under 2 years of age secrete the virus in their urine and saliva for about 24 months.

Congenital CMV infection is the most common intrauterine infection in the U.S. and the most common cause of non-genetic sensorineural hearing loss in children. The live birth prevalence rate in developed countries is 0.6-0.7%, resulting in approximately 40,000 cases annually in the U.S. However, only about 10% are symptomatic as neonates. The most common symptoms of congenital CMV infection are jaundice, petechiae and hepatosplenomegaly. The risk of long-term neurological sequelae increases even further in symptomatic babies. Over 90% of symptomatic babies develop sequelae such as sensorineural hearing loss, ophthalmological deficits and central nervous system (CNS) malformations compared to 10-25% of asymptomatic babies. Mortality in congenital CMV is disproportionately greater in infants from lower socioeconomic groups.

Surfactant Protein Deficiencies and Secondary Surfactant Deficiency
Surfactant administration is used in premature infants with respiratory distress syndrome (RDS). The major function of pulmonary surfactant is the reduction of surface tension at the air-water interface of terminal airways, resulting in a decreased tendency for alveolar collapse. Pulmonary surfactant is a complex mixture of lipids and proteins that reduces alveolar surface tension and prevents atelectasis. Without surfactant, forces as great as 70 dynes/cm² are generated at the air-liquid interfaces in alveoli, and would quickly lead to alveolar collapse and respiratory failure if unopposed. Pulmonary surfactant is a lipoprotein complex, which coats the luminal surface of alveoli to reduce surface tension to near 0 dynes/cm² at the air-liquid interface and to prevent alveolar collapse at end-expiration. Maintenance of alveolar patency is critical for effective gas exchange.

Surfactant has secondary functions that are equally important. It enhances macrophage activity as well as mucociliary clearance, both of which enhance the lungs’ defenses against bacteria and viruses. Four surfactant-associated proteins (SP) have been identified and designated as SP-A, SP-B, SP-C, and SP-D. They are produced by and secreted from type II alveolar cells and Clara cells of the respiratory epithelium. Surfactant contains two types of proteins, hydrophilic (SP-A, SP-D) and hydrophobic (SP-B, SP-C). Low molecular weight SP-B and SP-C decrease surface tension and are “responsible” for spreading, adsorption and stability of phospholipids. High molecular weight SP-A and SP-D are “responsible” for surfactant homeostasis as well as host defense.

SP-A-deficient mice have normal survival without changes in surfactant composition, function, secretion, reuptake, or stability; however, they lack tubular myelin in their alveoli. Despite relatively normal lung function, SP-A-deficient mice are highly susceptible to certain bacterial (Group B Streptococci, H. influenza, Pseudomonas) and viral (RSV, influenza A) pathogens. SP-B deficiency demonstrates the critical role of SP-B in surfactant function, homeostasis, and lung function. Targeted disruption of the mouse SP-B gene causes respiratory failure at birth. Although the lung structure in newborn SP-B-deficient mice is normal, their lungs fail to inflate postnatally. Most human infants with hereditary SP-B deficiency die from RDS early in the neonatal period, although mutations leading to partial SP-B function have been identified and are associated with the development of chronic lung disease. SP-C-deficient mice survive postnatally, but physiologic studies demonstrate abnormalities in lung function—specifically low...
Shedding of CMV in urine and cervicovaginal secretions increases in pregnancy with increasing gestational age (GA), thus, transmission of disease is more likely as pregnancy advances (58–78% in third trimester vs. 30 – 45% in first trimester). However, long-term sequelae are less likely to occur if the fetus is infected later in pregnancy (24 – 26% if infected in first trimester vs. 2.5 – 6% if infected after 20 weeks). Hormonal changes associated with pregnancy and lactation may stimulate reactivation of CMV.

Screening for CMV in pregnancy is controversial owing to a lack of tests with a sufficient level of sensitivity and specificity and also because of limited options for intervention. However, in certain circumstances, screening is advisable. These include mononucleosis-like illness in pregnancy, exposure to an individual with CMV infection, occupational exposure (health or childcare worker) or fetal ultrasound suggestive of congenital CMV infection such as the presence of ventriculomegaly, hyperechogenic bowel, intracranial calcifications and hydrops. In cases of suspected primary CMV infection, both maternal and fetal testing should be performed.

Maternal testing involves determining maternal antibody status. A definitive diagnosis of primary CMV infection is obtained if there is seroconversion from a previously antibody negative status to an antibody positive status. Since routine screening is not currently the standard of care, this conversion is often missed. The presence of IgM antibodies suggests primary infection; however, IgM antibodies can persist for several months. More complex testing such as IgG antibody avidity testing is therefore useful for sorting out the timing of infection. The avidity index is low with recent infections, thus the presence of IgM levels along with a low IgG avidity index is highly suggestive of a recent primary infection.

Fetal diagnosis is done via amniocentesis for viral culture with or without polymerase chain reaction (PCR). Replication of the virus in the fetal kidney, and thus shedding in the urine, occurs at least 5-7 weeks after infection. Thus, the optimal time for performing this test is 5-7 weeks after maternal infection occurred and after 21 weeks gestation. Sensitivity of amniocentesis after 21 weeks is about 71% compared to 30% if done before 21 weeks. A fetal sonogram is also recommended, however the possible findings are not specific for CMV and are present in <25% of infected fetuses. Cordocentesis for fetal IgM testing is not recommended due to poor sensitivity of the test and risk involved. Studies have been done in which both amniocenteses and cordocenteses were performed in women with suspected maternal infection. No baby was found to have a positive test on cordocentesis with negative amniocentesis suggesting that amniocentesis without cord blood testing is sufficient for diagnosing fetal CMV infection. Viral load of CMV in the amniotic fluid may be determined for prognostic value. CMV DNA load >103 genome equivalents/ml correlates with fetal infection while viral load > 105 GE/ml is associated with symptoms in the newborn.

For fetuses with positive isolation of virus, termination of the pregnancy may be offered to parents. This must be accompanied with thorough counseling to enable the parents make an informed decision. If the parents opt to continue the pregnancy, close follow up with regular ultrasound scans should be done. At birth, the newborn must be tested within 3 weeks of delivery using saliva or urine PCR/culture. A symptomatic newborn should be treated with Gancicovir, the use of which has been shown to prevent the progression of hearing loss. The most common side effects are bone marrow suppression and gonadal toxicity. If due to side effects or drug resistance Gancicovir cannot be used, Forscarnet is an option.

References:

Surfactant Proteins: Hydrophilic SP-A (blue, 650kDa) and SP-D (gold, 600kDa) have immune functions; Hydrophobic SP-B (green, 18kDa) and SP-C (blue, 5-6kDa) have 'stability' functions.

The premature infant has developmental deficiencies of pulmonary surfactant—both in composition—a relative deficiency of both saturated phosphatidylcholine, which forms the surface-active film, and SPs, which are essential for formation and stability of this film—and consequently in surfactant function. Additional mechanisms for surfactant dysfunction involve surfactant inactivation following interactions with meconium, blood, amniotic fluid, or plasma proteins, as well as altered surfactant function during mechanical ventilation. In premature ventilated infants, the latter surfactant dysfunction is typically manifested at 7-10 days of life, resulting in respiratory decompensation, and characterized by an inability to wean from the ventilator. Such premature infants may benefit from 'booster' doses of surfactant by temporarily augmenting the composition and function of their endogenous surfactant, yielding an improved respiratory status.

Several studies have found that as many as 20-25% of infants weighing less than 1000 g at birth, who have RDS and who were treated initially with surfactant, will develop respiratory deterioration after 7-10 days of life. Over 70% of these patients had short-term improvements in the severity of lung disease—with a significant reduction of oxygen support and/or ventilator settings—after additional surfactant. The investigators found an apparent benefit of treating this secondary surfactant deficiency by 'booster' surfactant administration, without any increase in morbidity or mortality.

Booster doses of surfactant appear to be safe for premature infants with RDS. However, infants with high ventilator settings (pressure or volume) should be excluded, due to the potential risk of air leak. In addition, infants with pre-existing air leak syndrome—e.g., pulmonary interstitial emphysema (PIE) or pneumothorax—may be susceptible to a deterioration in their respiratory status following surfactant administration.
Michel Slim, MD

It is with great sadness that we inform you of the passing away of Retiree, Professor Emeritus Michel Slim, MD, on Saturday, January 12, 2013.

Dr. Slim was a Professor in the Surgery Department at New York Medical College for 20 years prior to his retirement in September of 2006. As a testament to his devotion to medicine, Dr. Slim continued to hold lectures and grand rounds with residents until he had his stroke in 2011.

Dr. Michel Slim served at Westchester Medical Center as Chief of Pediatric Surgery and Director of Pediatric Trauma Service.

He was one of the founders of Maria Fareri Children's Hospital in New York and performed the first surgical procedure there upon its opening. His career of excellence culminated in New York Medical College honoring Dr. Slim with the title of Professor Emeritus in Pediatric Surgery and Pediatrics.

Dr. Slim’s family would like to extend their heartfelt gratitude to those who cared for him so well after his stroke.

They would also like to thank the many people around the world who have sent their prayers and best wishes.

We extend our sincerest sympathy to his Beloved wife, Norma and his daughters Julie, Lina, and Nayla And to his family, colleagues and students, Who will truly miss him.

We are interested in providing you with a newsletter that is relevant and of interest to you. Please contact us with perinatal topics you would like to see addressed. For a copy of our newsletter or to be placed on our mailing list, contact us by phone or e-mail. Please visit www.westchestermedicalcenter.com/RPC for information about the Regional Perinatal Center at the Maria Fareri Children's Hospital at Westchester Medical Center and to locate previous issues of The Perinatal Gazette.

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