

# Neonatal Respiratory Distress Syndrome and Its Treatment with Artificial Surfactant

Neonatal respiratory distress syndrome, previously called hyaline membrane disease, is a respiratory disease affecting premature newborns. Neonatal respiratory distress syndrome involves shallow breathing, pauses between breaths that last a few seconds, or apnea, and a bluish tinge to the infant's skin. The syndrome occurs when microscopic sacs called alveoli in infant lungs do not produce surfactant, a liquid that coats the inside of the lungs and helps them inflate during breathing. Respiratory distress syndrome is the leading cause of death among premature infants and, in rare cases, it can affect full-term infants. Physicians can administer artificial, animal-derived surfactant to treat respiratory distress syndrome. As of 2017, the treatment has decreased the mortality rate of respiratory distress syndrome from almost one hundred percent to less than ten percent.

Respiratory distress syndrome affects premature infants who are born before their lungs have developed enough to support breathing outside the uterus. At full-term birth, an infant's lungs contain millions of microscopic sacs called alveoli. In the alveoli, cells called Type II alveolar cells produce a liquid called surfactant. Surfactant is necessary for breathing. The lungs of premature infants, however, have not developed enough alveoli or Type II alveolar cells to produce the amount of surfactant needed to breathe properly. While respiratory distress syndrome usually affects premature infants, in rare cases the syndrome can also affect full-term infants. When respiratory distress syndrome affects full-term infants, it is the result of a genetic condition, rather than underdeveloped lungs.

In the 1920s, physiologist Kurt von Neergaard hypothesized that there was some sort of liquid in human lungs that allowed them to open during respiration. However, Neergaard did not find what that liquid was. In the 1950s physician John Clements observed surfactant, the liquid that Neergaard hypothesized coated the inside of the lungs. In 1959, researchers Mary Ellen Avery and Jeremiah Mead at Harvard University in Cambridge, Massachusetts, reported the absence of surfactant in the lungs of infants who died from hyaline membrane disease, later called respiratory distress syndrome. Avery and Mead hypothesized that the lack of surfactant was responsible for what was then called hyaline membrane disease. Once researchers established the existence and relevance of surfactant, they began researching the chemical makeup of the compound. Researchers found that surfactant is made up of fats and proteins, like the structure of a cell membrane.

Avery and Mead's hypothesis that the lack of surfactant in premature infants causes neonatal respiratory distress syndrome proved correct. Neonatal respiratory distress syndrome primarily affects premature infants, whose lungs are not developed enough to provide enough oxygen to their brain and other organs. While developing in the uterus, a fetus's lungs are unnecessary as a breathing organ because the pregnant woman provides oxygen to the fetus through the umbilical cord connecting them. However, lungs must be able to function immediately after birth to provide the newly independent fetus with oxygen. Lung development extends through both the embryological and fetal stages of development, from week three gestation until delivery. Initially, fetal lungs develop as a small bud from the endoderm, the innermost layer of cells in the developing embryo. The process occurs within the first few weeks of pregnancy. From the bud, the trachea, or the windpipe that transfers air to and from the lungs, develops. The trachea branches into two bronchi, one for each lung. By the fourteenth week of development, seventy percent of the airway has developed.

At around twenty-six weeks gestation, microscopic balloon-like sacs called primitive alveoli develop in the fetal lungs. Those primitive alveoli continue to develop after birth and throughout childhood, and they eventually become mature alveoli. Alveoli are the sites at which gases are exchanged

between the lungs and the bloodstream. During gas exchange, a person draws oxygen into their lungs, where the alveoli diffuse that oxygen into the person's bloodstream. Simultaneously, carbon dioxide diffuses out of the bloodstream into the alveoli, where the carbon dioxide is exhaled through the airway. At full-term birth, each one of an infant's lungs will contain about one hundred million alveoli. Throughout the first thirty-six months of life, alveoli continue to develop. Fully developed lungs contain approximately three hundred million alveoli each.

While the primitive alveoli are developing, cells called Type II alveolar cells begin to form in the developing lungs. The main role of those cells is to secrete surfactant. Surfactant plays two roles in the lungs. First, surfactant decreases the pressure of the atmosphere on alveoli. During inhalation, the alveoli expand, and during exhalation, they collapse inwards. Without surfactant, the inner tissue of the alveoli sticks together during exhalation, causing the alveoli to collapse and preventing gas exchange. If gas exchange does not occur at the alveoli, oxygen will not reach the bloodstream or tissues throughout the body, including the brain and other organs. The second role surfactant plays in the lungs is that it increases the compliance, or expandability, of the lungs. Lungs expand during respiration as they take in oxygen-rich air from the atmosphere. Without that expandability, the lungs do not take in enough oxygen. Infants born before thirty-five weeks gestation are at risk for respiratory distress syndrome because their Type II alveolar cells are not producing enough surfactant for sufficient breathing.

When a premature infant whose lungs are not producing enough surfactant is born, those lungs are unable to provide the infant with enough oxygen, which results in respiratory distress syndrome. Rarely, some very premature infants are unable to take a first breath because their lungs are stiff and unable to expand and contract as needed to breathe. Usually, however, affected infants can breathe, but display obvious signs of distress, such as flared nostrils during inhalation and grunting during exhalation. After a few hours, whatever small amount of surfactant present in the lungs at birth gets used up, making treatment necessary.

Because labored breathing can be caused by conditions other than respiratory distress syndrome, physicians must first diagnose respiratory distress syndrome before deciding on a treatment plan. Physicians diagnose respiratory distress syndrome using chest x-rays, blood tests, and echocardiography. If the infant has respiratory distress syndrome, their chest x-ray will show a bell-shaped thorax, or chest cavity, and small, underdeveloped lungs. Physicians use blood tests and echocardiography to rule out other diagnoses. If a blood test shows low amounts of oxygen in an infant's blood, the physician can diagnose respiratory distress syndrome. An infection in the blood, however, indicates that an infant's breathing problems are caused by something other than respiratory distress syndrome. Physicians use echocardiography, a diagnostic technique that examines the heart, to rule out a heart condition that may be causing the infant's respiratory distress.

Once physicians diagnose an infant with respiratory distress syndrome, they can treat the infant by administering artificial surfactant. In the US, artificial surfactant used for surfactant replacement therapy is extracted from the lung of a cow or a pig. Physicians use two strategies for administering surfactant. First, using a preventative strategy, physicians administer artificial surfactant to premature infants who are at risk for developing respiratory distress. Second, using a therapeutic strategy, physicians administer surfactant to infants who have been ventilated after their respiratory distress syndrome has been diagnosed. Physicians administer artificial surfactant through a tube they insert through the infant's trachea, the passageway that brings air to and from the lungs.

Physicians can choose to administer one or two doses of surfactant. In 2009, Roger Soll and Eren Özek conducted a meta-analysis that showed that multiple doses of artificial surfactant lowered the risk of complications and death associated with a single dose of surfactant. That is because while a single dose of surfactant rapidly improves an infant's breathing, the surfactant can become ineffective, causing the infant's symptoms to return. In infants with respiratory distress syndrome, excess pressure is exerted on the alveoli by attempts to open them during respiration. That excess pressure can either come from the infant's attempts to breathe or from a mechanical respirator placed by a physician. The excess pressure ruptures the alveoli, allowing air to flood out of the lungs into the surrounding chest. However, the risk of rupture decreases if a physician uses two doses of surfactant rather than one dose. Using two doses can also decrease the risk of sepsis, or bloodstream infection, and infant death. Generally, physicians do not administer more than two

doses of surfactant.

In the first decade of the twenty-first century, cases of neonatal respiratory distress syndrome grew because of an increase in pre-term deliveries. However, the mortality rate of neonatal respiratory distress syndrome has decreased due to surfactant replacement therapy.

## Sources

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