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## IN THIS ISSUE




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# Health Risks of the Late-Preterm Infant

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## INTRODUCTION

The American Academy of Pediatrics (AAP) and the American College of Obstetricians and Gynecologists define a "preterm" infant as one who is born before the end of the 37th week (259th day; 36 6/7 weeks' gestation) of pregnancy, as determined from the first day of the last menstrual period (AAP, ACOG). Data from the Centers for Disease Control and Prevention indicate that preterm births have increased 21% since 1990 and in 2006 in the US account for nearly 13% of the birth total (Hamilton). Some previously used descriptors, such as "near term," were applied to those preterm infants born between approximately 34 and 36 weeks gestational age. Such a descriptor implied that such infants were almost term, could be managed as term infants, and downplayed the potential health risks to this cohort of physiologically immature infants (Engle). During a workshop sponsored in 2005 by the National Institutes of Health, it was recommended that the designation of near term be formally replaced by "late-preterm" to denote the period from the day after the end of the 34th completed week of gestation (239th day or 34 0/7 weeks' gestation after the mother's last menstrual period) to just prior to term

***"Preterm births have increased more than 20% since 1990 and the largest growth segment within this group consists of the late-preterm infant born between 34 and 36 weeks of gestation. The late preterm infant, as described by the AAP Committee of Fetus and Newborn, experience greater morbidity and mortality, and more frequent re-hospitalization after initial discharge and throughout the first year of life than term infants."***

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| Table 1. Accepted Definitions for Gestational Age Categories | |
|---|---|
| **Birth Category** | **Descriptor** |
| Post-term | Infant born from the beginning of the first day (295th day) of the 43rd week following the onset of the last menstrual period[a] |
| Term | Infant born on the first day (260th day) of the 38th week through the end of the last day of the 42nd week (294th day)[a] |
| Pre-term | Infant born before the end of the 37th week (259th day) of pregnancy, counting from the first day of the last menstrual period[a] |
| Late-Preterm | Infant born between the gestational ages of 34 weeks and 0/7 days through 36 weeks and 6/7 days (239th-259th day)[b] |
| Very Preterm | Infant born less than 32 completed weeks of gestation[c] |

*[a]=American Academy of Pediatrics, American College of Obstetricians and Gynecologists*
*[b]=National Institute of Child Health and Human Development of the National Institutes of Health*
*[c]=Centers for Disease Control, National Vital Statistics Reports*

| Table 2. Morbidity Related to Organ System Challenges Faced by Late-Preterm Infants | |
|---|---|
| **Organ System/Function** | **Potential Morbidity** |
| Cardiopulmonary | Respiratory Distress Syndrome<br>Apnea of prematurity<br>Sudden infant death system<br>Severe infection with respiratory syncytial virus |
| Immune | Inability to adequately fight infection<br>Sepsis<br>Severe infection with respiratory syncytial virus |
| Temperature regulation | Hypothermia |
| Endocrine | Hypoglycemia |
| Hepatic | Prolonged jaundice |
| Ability to feed | Failure to thrive<br>Feeding difficulties<br>Electrolyte disturbances, dehydration |

(259th day or 36 6/7 weeks' gestation) (Table 1) (Raju). The term late-preterm was also recommended by the Committee on Fetus and Newborn in 2007 and refers to those infants born between the gestational ages of 34 weeks and 0/7 days through 36 weeks and 6/7 days (239th-259th day) (Engle). This was done as a result of the growing evidence late preterm infants are physiologically immature in comparison to their term counterparts. The bottom cutoff point, although arbitrarily selected, was based on the acceptance as a maturational milestone for the fetus with respect to patient care decisions by obstetricians, including admission to a level 2 or 3 NICU (Engle; Raju). Late-preterm infants experience morbidity and infant mortality rates that are three times greater than for term infants (Matthews). Despite this, the health risks that this group faces are not fully appreciated by caregivers and parents (Table 2). Late-preterm infants often receive intermediate or level I care and are discharged from the hospital without specialized plans for follow-up.

Adoption of new nomenclature was an important step to alert and encourage caregivers to study the problems particular to the late preterm population, a group that currently accounts for 71% (~390,000 births) of all premature births. The purpose of this review is to provide a broad overview of some of the key developmental challenges, morbidity, and mortality faced by late-preterm infants.

## LUNG AND IMMUNE SYSTEM DEVELOPMENT IN LATE-PRETERM INFANTS

### *Lung development*

Human lung development can be divided into six developmental stages—embryonic, pseudoglandular, canalicular, saccular, alveolar,

and microvascular maturation (Roth-Kleiner; Langston). The stages have flexible boundaries and vary in time of occurrence among individuals. The lungs of potentially viable preterm infants predominantly fall within the saccular stage and are generally consistent with gestational age. The canalicular stage, 16 to 26 weeks post conception, is marked by canalization of the interstitium by capillaries and appearance of surfactant, and signals the beginning of the future blood-air interface. The saccular stage is present from 26 to 36 weeks and is characterized by dilation of the terminal clusters of acinar tubules and buds and extension into thin, smooth-walled transitory ducts and saccules that later become the true alveolar ducts and alveoli of the adult. The alveolar stage represents the last phase of lung development, from 36 weeks to 3 years postnatal, and is distinguished by the formation of secondary alveolar septa (Moore and Persaud). The process of alveolarization further increases lung surface area available for gas exchange by tenfold. There is extreme variability in the onset of alveolar formation leading to a wide range in total alveolar number available at birth. Alveoli are not only important for gas exchange, but are also critical in maintaining airway patency of the terminal bronchioles which are not supported by cartilage. In addition, infants have very compliant chest walls which can also create a tendency for airway collapse. These mechanical stresses, especially due to the lack of alveoli, place all premature infants, including the late-preterm infant, at higher risk of morbidity.

Only recently has it been possible to adequately test lung function in infants. Compared to term infants, late-preterm infants even after the first year of life do not catch up with term infants with respect to alveolar growth or expiratory flow rates. Persistence of reduced expiratory flows in "healthy" late-preterm infants may contribute to their increased risk for recurrent respiratory illness early in life. It is understandable that children born during the late-preterm period will frequently have inadequate lung function and face many respiratory challenges such as acute respiratory distress, apnea of prematurity, and severe complications following infection with viral respiratory pathogens such as respiratory syncytial virus (Friedrich).

***Immune function***

The immune system of a newborn infant does not function to the same capacity as those of older children and adults. This immaturity may play a protective role in prevention of premature rejection of the fetus by the mother (Clapp). There is a paucity of information about the effect of premature birth on the functional status of the immune system with respect to host defense capabilities including the expression of humoral, cellular and other immune mediators. It is known, however, that the immune system of infants born prematurely is not capable of the same scope or magnitude of innate or adaptive protective response to invading organisms as demonstrated for term infants, and these children are at increased risk of infection. Recent studies suggest that innate and adaptive immunity in late preterm infants is often inadequate as well and that perinatal infection is significantly greater in this group of infants as compared with term infants (Engle; Escobar).

Age-related changes in various components of the immune system such as interferon-gamma levels, T-lymphocyte function and natural killer cell (NKC) activity have been compared in preterm and term neonates, children, and adults (Gasparoni; Bont). A correlation was observed between gestational age and immune function as demonstrated by a reduction in NKC activity, lower proliferative response of T cells, and reduced cytotoxic response and cytokine production during the neonatal period. The innate immune system plays a key role in host defense against infection, and immaturity of monocytes and granulocytes can lead to reduced cytokine production. Preterm infants have been shown to express considerably lower levels of innate immunity receptors (e.g., toll-like receptors, CD14) and this leads to an impaired response to invasion from infecting organisms in premature newborns (Sadeghi). Maternal gamma G-globulin (IgG) is transferred to the fetus during the last few months of pregnancy and a linear relationship between the logarithms of IgG levels at birth and gestational age has been demonstrated (Yeung). Yeung and Hobbs (Yeung) studied serum IgG levels of small-for-date, premature and term babies, from 24-40 weeks gestational age. Even IgG levels in the late- preterm infant were found to be suboptimal. The mean serum IgG concentration of 42 singleton babies who were born at 34-36 weeks gestation was roughly half that (i.e., mean, 522-656 mg/mL) of babies born at 40 weeks gestation (i.e., mean, 1100 mg/mL).

**MORTALITY, MORBIDITY AND RE-HOSPITALIZATION AMONG LATE-PRETERM INFANTS**

Late-preterm infants experience greater mortality, morbidity and more frequent re-hospitalization after initial discharge, and account for greater healthcare costs in the first year of life than term infants (Wang; Mathews; Young; McIntire; Raju; Tomashek; Shapiro-Mendoza; Underwood; Oddie; Escobar 2005, 2006).

***Mortality***

National statistics from the Centers for Disease Control and Prevention for calendar year 2004 indicate that one-third of infant deaths were due to preterm-related causes, and infant mortality rates for late-preterm infants were 3 times greater than for those born at term (Mathews). Data from birth and death certificates of infants born in Utah between 1999 and 2004 were reviewed to determine the relative risk for mortality and the causes and ages of death for late-preterm newborns compared with those born at term (Young). A total of 283,975 births occurred in those with a gestational age ≥34 to ≤42 weeks, of which 21,106 were in late-preterm infants. Significantly higher mortality rates were also noted for late-preterm newborns during the first year after birth. Each weekly increase in estimated gestational age from 34 through 36 weeks was associated with an approximate 30% decrease in mortality rates and risk ratios during the first year of life even adjusting for birth defects. The investigators noted that at their institution, newborns with an estimated gestational age ≥34 weeks who appear stable are usually admitted to the well-baby nursery where care was highly variable. A retrospective analysis of neonatal mortality and

morbidity rates at 34, 35, and 36 weeks of gestation compared with births at term over an 18 year period at a hospital in Texas revealed that late-preterm births accounted for 76% of all preterm births at that institution (McIntire). Late-preterm neonatal mortality rates were 1.1, 1.5, and 0.5 per 1,000 live births at 34, 35, and 36 weeks, respectively, compared with 0.2 per 1,000 live births at 39 weeks (P<0.001).

***Morbidity in initial hospitalization***

Medical records of 90 late-preterm (i.e., 35-36 6/7 weeks' gestation) and 95 full-term neonates were retrospectively analyzed to determine if late-preterm infants are prone to more medical problems, experience longer hospital stays, and incur greater costs for hospitalization than their older counterparts (Wang). Despite comparable birth weight (mean=2638 g), and comparable Apgar scores between groups, important differences in clinical outcomes were noted. Late-preterm infants were more apt to exhibit temperature instability, were seven times more likely to have respiratory distress (28.9% vs. 4.2%), were more prone to clinical jaundice (54.4% vs. 37.9%), were much more likely to have a clinical problem resulting in the assignment of one or more medical diagnoses, underwent 3 times more evaluations for sepsis (36.7% vs. 12.6%), and experienced more delays in discharge to home.

***Early Re-hospitalization after initial discharge***

Oddie et al. studied the frequency and association of early postpartum discharge and infant hospital readmission rates during the first 28 days of life (Oddie). Early discharge was defined as discharge on the day of or immediately after the day of birth. Out of 32,015 births, 11,338 (42%) were discharged early and 907 (2.8%) were readmitted within the specified time period. When analyzed by gestational age, those born between 35-37 weeks had the highest rate of readmission of all ages studied. The American Academy of Pediatrics recommends that early postnatal discharge should be limited to infants who are of singleton birth between 38 and 42 weeks' gestation and who meet a variety of other criteria, yet late-preterm infants are frequently grouped with older counterparts and discharged <48 hours after delivery (Raju). A retrospective study was conducted, based on data from the Massachusetts Pregnancy to Early Life Longitudinal Data Project, to examine neonatal morbidity and postnatal re-hospitalization among late-preterm and term infants who were discharged early after vaginal delivery (Tomashek). Of 300,106 singleton deliveries, 16,825 (5.6%) occurred at 34-36 completed weeks' gestation. A total of 6.7% of late-preterm and 10.0% of term infants were discharged early with most of the infants from both groups being of normal birth weight (≥2500 g). Late-preterm infants were 1.5 times more likely to require subsequent hospital-related care, and were re-hospitalized at almost twice the rate during the first 28 days of life than term infants. Major reasons for early re-hospitalization included jaundice and infection. The investigators concluded that the optimal timing for hospital discharge of late-preterm infants has not been defined and these infants should not be treated according to discharge guidelines established for term infants. Further subset analyses by this same investigative group revealed that late-preterm infants were seven times (22% vs. 3%) more likely to experience newborn morbidity (i.e., temperature instability, hypoglycemia, respiratory distress, hyperbilirubinemia, prolonged hospitalization, and neonatal mortality) than term infants and the morbidity risk doubled in infants for each gestational week born earlier than 38 weeks (Shapiro-Mendoza). The risk of morbidity was further increased in late-preterm infants whose mothers had pre-existing medical conditions such as gestational diabetes.

***Re-hospitalization in the first year of life***

Data on hospitalizations during the first year of life in children <36 weeks gestation was analyzed to determine total costs, in-hospital days and average lengths of stay (Underwood). Of 263,000 infants born in California who qualified for study, 15% experienced at least one hospital readmission. Infants 34 and 35 weeks gestation constituted the largest segment of the study population (62%), had the highest proportion of infants readmitted (57%) and most total readmissions (52%), spent the greatest number of total days in the hospital (45%), and had the highest total costs ($157 million; 42%) per cohort. Respiratory Syncytial Virus (RSV) infection was the most common diagnosis leading to re-hospitalization of premature infants in the first year of life. The investigators concluded that late-preterm infants represent the largest segment of preterm infants who suffer re-hospitalization and these children incur a significant portion of associated hospital costs.

A retrospective study of re-hospitalizations at seven Kaiser Permanente Medical Care Program delivery services of newborns of all gestations was undertaken to determine patterns that could be useful to clinicians in charge of decisions governing newborn discharge practices (Escobar). A total of 33,374 live births occurred at the study sites and 11% of children were admitted to the NICU. Late-preterm infants who had not spent time in a NICU prior to initial discharge home constituted the largest cohort re-hospitalized. The investigators hypothesized that owing to general appearance, initial discharge decisions are more likely based on infant birth weight rather than gestational age.

***Respiratory Syncytial Virus in late preterm infants***

RSV is the most important cause of bronchiolitis and pneumonia requiring hospitalization in infants and young children (AAP 2006). Characteristics that increase the risk of severe disease and hospitalization include chronic lung disease, hemodynamically significant congenital heart disease, and birth ≤35 weeks of gestation (AAP 2006). Although prematurity is a recognized risk factor, RSV studies have not specifically assessed the burden of RSV for the late-preterm infants; rather they have reported outcomes for premature infants as a whole or have stratified results according to a limited number of specified gestational age groupings (e.g., ≤32 weeks' gestation; 33-35 weeks' gestation). However, extrapo-

lation from relevant trials indicate that late-preterm infants experience high rates of RSV-related hospitalizations, comparable hospital stays, and severe disease requiring ICU care that are comparable to preterm infants born at <33 weeks gestation (Boyce; Willson; Horn; Law 1998, 2004; Figueras-Aloy; Madhi).

A large US study of preterm infants retrospectively analyzed rates of hospitalization associated with RSV infection among term and preterm children ≤36 weeks gestational age enrolled in the Tennessee Medicaid program from July 1989 through June 1993 (Boyce). During the first 6 months of life, the estimated number of RSV hospitalizations per 1000 child-years of RSV season was relatively similar regardless of gestational age (i.e., 187.5 for those ≤28 weeks' gestational age, 163.6 for those 29 to <33 weeks' gestational age, and 159.6 for those 33 to 36 weeks' gestational age). A prospective, two-year study of 1,516 children hospitalized with RSV lower respiratory tract infection was conducted in Canada to determine the relative impact of gestational age on morbidity (Law 1998). Otherwise healthy infants 33 through 36 weeks' gestational age comprised 12.9% of the study population and as a group were significantly younger (by chronological age) on admission than infants with a gestational age of either <33 weeks or >36 weeks. They had a statistically similar prevalence of intensive care admissions and requirement for mechanical ventilation compared with infants with a gestational age <33 weeks (28.4% and 12.2% vs. 31.2% and 21.9%, respectively), and a significantly greater incidence of apnea at presentation, requirement for supplemental oxygen and mechanical ventilation, and need for management in an ICU than infants born after 36 weeks' gestation (Law). Two fatalities were noted and both occurred in the 33 to 36 weeks' gestational age group.

RSV disease requiring ICU admission is also comparable in the late-preterm infant. Outcome data from a retrospective study of 684 infants hospitalized with non-specific bronchiolitis or RSV pneumonia across 10 institutions revealed that infants of 33 to 35 weeks' gestational age had the highest incidence of complications, spent the most days in the hospital, and incurred the greatest healthcare costs (Willson). Of note, infants born at 36 weeks gestation had the longest stays in the pediatric intensive care unit and the second highest rate of complications as compared with their smaller preterm counterparts. Further subset analyses of these infants with RSV-specific bronchiolitis were conducted to determine specific resource use and patient outcomes according to gestational age (Horn). After controlling for severity of illness and differences in standards of care among participating institutions, infants 33 to 35 weeks' gestational age were again found to require the longest hospital and intensive care unit stays, had significantly more hospitalizations for RSV, and incurred significantly higher intubation rates compared with all other gestational age groups.

### *Risk factors for severe RSV disease*

Risk factors for hospitalization due to RSV infection were prospectively analyzed in 1,860 infants born at 33 through 35 weeks of gestation in four Canadian provinces (Law). A total of 7.6% of the study population was hospitalized for respiratory tract illnesses and of this segment 3.6% were infected with RSV. Numerous host/environmental independent risk factors were identified (i.e., day-care attendance, birth during the months of November through January, pre-school age siblings, birth weight <10th percentile, male gender, ≥2 smokers in the home, households with >5 people) that increased the risk of hospitalization in these children. Risk factors linked to RSV infection in infants 33 to 35 weeks' gestational age necessitating hospitalization have been reported in other studies as well. In a trial in 1,158 infants of 29-35 weeks' gestational age that had not received RSV prophylaxis, 48 (4.2%) were hospitalized for RSV infection during the first year of life (Doering). The likelihood of hospitalization was related to identified risk factors (i.e., neurologic problems, male gender, presence of an older sibling, and discharge from birth hospital October to December). No significant differences concerning the risk of RSV hospitalization were found between children with a gestational age of 29 to 32 weeks and children with a gestational age of 33 to 35 weeks. Findings from a prospective study conducted in Spain of 186 preterm infants 33 to 35 weeks' gestational age who were prospectively studied indicated that 20.5% required admission to an ICU for RSV-related disease and 7.6% were mechanically ventilated (Figueras-Aloy). Compared with matched controls, those who were ≤10 weeks old at the start of the season, had a short history of breast feeding, lived with ≥4 people at home, had at least one school-aged sibling, and had a family history of wheezing were most likely to be hospitalized due to RSV.

## MANAGEMENT OF LATE-PRETERM INFANTS

Evidenced-based practice guidelines for the management of late-preterm infants are presently lacking and there are wide variations in the management of these infants among different care units (McCormick; Escobar). Late-preterm infants are often treated as term infants and are cared for in general maternity units and Level I nurseries by clinicians who are often unfamiliar with their special needs. Such infants are frequently discharged to home within 48 hours of birth with no plan for high-risk follow-up. In addition, parents are unlikely to be told that their infants are at high-risk for re-hospitalization for certain disorders such as jaundice, RSV and other infection and, therefore, are not taught preventive measures. Specific care with respect to service unit and length of hospital stay is all too often guided by policies set by insurance providers and/or is based on factors other than gestational age such as birth weight and general appearance on physical examination.

Categorization of the late preterm infant into well-defined subgroups is important for identification and prevention of potential health risks and for development and adoption of appropriate care plans (Table 3). Discharge guidelines need to be initiated in the hospital where late preterm infants are typically cared for (i.e., term nursery or step-down nursery) including the establishment of standards for discharge planning. Strategies to prevent against early breastfeeding cessation and lactation-associated morbidities (Meier), better educational initiatives for parents of these infants

**Table 3. Checklist of Discharge Criteria for Late-preterm Infants[a]**

- Gestational age has been accurately determined
- Observation for at least 48 hours to determine basic competencies (e.g., feeding, temperature regulation, hearing)
- A period of at least 24 hours of successful feeding and a formal evaluation of breastfeeding ability
- Follow-up medical care planned and appropriate immunizations administered/scheduled
- No abnormalities on physical examination
- Appropriate blood tests reviewed including metabolic and genetic screenings
- Family, environmental, and social risk factors assessed
- Education of parents/caregivers regarding basic infant care and potential warning signs/symptoms of illness

[a]*Adapted from Engle 2007; not all inclusive*

regarding potential disease risks, growth and development and child follow-up procedures, and further research to gain a better understanding of the specific physiological challenges faced by these infants should all be developed and included in discharge and care of the late preterm infant, particularly in the first year of life (Escobar; Engle; Raju).

## SUMMARY AND CONCLUSIONS

Preterm births have increased more than 20% since 1990 and the largest growth segment within this group consists of the late-preterm infant born between 34 and 36 weeks of gestation. The late preterm infant, as described by the AAP Committee of Fetus and Newborn, experience greater morbidity and mortality, and more frequent re-hospitalization after initial discharge and throughout the first year of life than term infants. They are especially prone to high rates of respiratory disorders, including severe RSV disease, and other infection due to their physiologically immature pulmonary and immune systems and limited compensatory mechanisms and account for greater healthcare costs than term infants. Additional initiatives aimed at establishing evidence-based discharge and follow-up practice guidelines, educational programs and identification tools, and further research into the various issues that relate to late-preterm birth are clearly needed.

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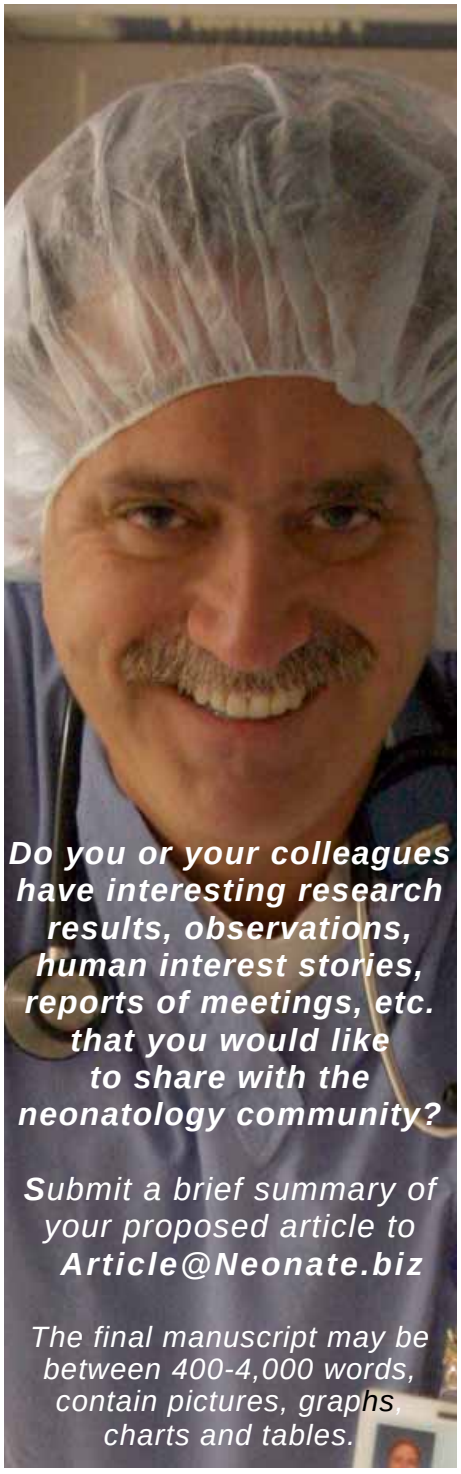

# Medical News, Products and Information

**Discovery Labs' Surfaxin® Phase 2 BPD Clinical Trial Results Published in *Pediatrics***

Discovery Laboratories, Inc. announced the publication of results from its Phase 2 clinical trial of Surfaxin® for the prevention and treatment of Bronchopulmonary Dysplasia (BPD) in the January 2009 issue of *Pediatrics*. BPD is a chronic, debilitating lung disease typically affecting premature infants who received treatment for Respiratory Distress Syndrome (RDS). The results from the study indicated that administration of additional doses of Surfaxin following standard SRT treatment for acute RDS may represent a novel therapeutic option for infants at risk for developing BPD. Presently, there are no approved pharmaceutical therapies for BPD.

Robert J. Capetola, President and CEO of Discovery Labs commented, "We are extremely pleased that *Pediatrics* has published these data and made them available to the medical community. We believe that these data further validate the pharmacology of our KL-4 surfactant, and support our continued development of our technology platform to address a broad range of unmet medical needs in pulmonary medicine."

Discovery Labs conducted a Phase 2 clinical trial to evaluate the safety and potential efficacy of Surfaxin in infants at risk for BPD. The clinical trial enrolled 136 premature infants that were randomized to receive, in addition to standard of care, either Surfaxin standard dose (175 mg/kg), Surfaxin low dose (90 mg/kg), or sham air as a control. In this pilot estimation study, infants treated with the Surfaxin standard dose, as compared to those in the control group experienced a lower incidence of death or BPD (58% vs. 66%), a higher survival rate through 36 weeks post-menstrual age (89% vs. 84%), and fewer days on mechanical ventilation. No meaningful conclusions could be drawn from the Surfaxin low dose treatment group, likely due to this group containing infants with more pre-existing medical risk conditions.

Dr. Matthew Laughon, Assistant Professor, Department of Pediatrics, Division of Neonatal-Perinatal Medicine, The University of North Carolina at Chapel Hill, commented, "The data from this Phase 2 estimation trial support additional trials to evaluate the potential of Surfaxin as a therapeutic option for the prevention of BPD. BPD represents one of the most challenging clinical problems we face in neonatology. Extremely low birth weight infants, particularly those that require mechanical ventilation, are at risk for this debilitating disorder."

BPD is associated with surfactant deficiency and is diagnosed when premature infants require mechanical ventilation or supplemental oxygen at 36 weeks post-menstrual age. Premature infants are often born with a lack of natural lung surfactant and are unable to absorb sufficient oxygen to survive, resulting in RDS. These infants often require endotracheal intubation to administer one of the currently-available, animal-derived surfactants (usually within the first hours of birth) and to provide respiratory support via mechanical ventilation. Unfortunately, many infants relapse following initial SRT and require reintubation and prolonged mechanical ventilation as well as supplemental oxygen, which increases the risk of developing BPD. Discovery Labs believes that BPD may be prevented with repeated doses of Surfaxin administered after the initial RDS SRT treatment (on day 1 or 2 of life) to improve the clinical outcome of these infants.

Surfaxin®, an investigational drug, is the subject of an Approvable Letter from the US Food and Drug Administration (FDA) for the prevention of Respiratory Distress Syndrome in premature infants. The publication listed above includes information that may be of interest to healthcare practitioners; however, the clinical relevance of this information has not been established.

Discovery Laboratories, Inc. is a biotechnology company developing Surfactant Replacement Therapies (SRT) for respiratory diseases. Surfactants are produced naturally in the lungs and are essential for breathing. Discovery Labs' technology produces a peptide-containing synthetic surfactant that is structurally similar to pulmonary surfactant. Discovery Labs believes that, with its proprietary technology, SRT has the potential, for the first time, to address a variety of respiratory diseases affecting neonatal, pediatric and adult patients.

Discovery Labs' lead product from its SRT pipeline is Surfaxin® for the prevention of Respiratory Distress Syndrome in premature infants. The FDA has established April 17, 2009 as its target date to complete its review of this new drug application (NDA), and potentially grant marketing approval for this product. Surfaxin® is also being developed for other neonatal and pediatric indications. Aerosurf®, Discovery Labs' aerosolized SRT, is being developed to potentially obviate the need for intubation and conventional mechanical ventilation and holds the promise to significantly expand the use of surfactants in respiratory medicine. For more information, visit: www.Discoverylabs.com.

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**Increased Rate of Hemangiomas Linked to Rise in Number of Low Birth Weight Infants in US**

Newswise - Low birth weight is the most significant factor for the development of infantile hemangiomas, a common birthmark, according to a new study by researchers at The Medical College of Wisconsin and Children's Research Institute.

The study, led by Beth Drolet, MD, Professor of Dermatology and Pediatrics at the Medical College and Medical Director of pediatricdermatology and birthmarks and vascular anomalies clinic at Children's Hospital of Wisconsin, was published in the November 2008 issue of *The Journal of Pediatrics.*

"Hemangiomas are benign tumors composed of blood vessels. Our institution has seen a dramatic increase in the number of infants presenting for care with hemangiomas. We believe the results of this study provide an explanation for this emerging pediatric health issue," said Dr. Drolet.

While factors such as being female, Caucasian and premature birth have been previously identified as risk factors for hemangiomas, Dr. Drolet's study found that low birth weight was the most statistically significant risk factor.

"For every 1.1 pound decrease in birth weight, the risk of hemangioma increased by nine-fold," said Dr. Drolet.

Recently, there has been an increase in the US of infants born under 5.5 pounds. In 2005, 8.2% of infants born in the US weighed less than 5.5 pounds. This is the highest percentage recorded since 1968 and is higher than the rate in most industrialized countries.

Additionally, a dramatic increase in low birth weight has been found in white, non-Hispanic infants. Low birth weight has increased 38% since 1990 in this group.

The researchers compared 420 children who had been diagnosed with infantile hemangiomas at Children's Hospital of Wisconsin and the University of California - San Francisco Medical Center (UCSF) with 353 children less than two years old who had been diagnosed with skin anomalies other than infantile hemangioma.

Dr. Drolet and co-investigator Dr. Ilona Frieden, Professor of Dermatology and Pediatrics at UCSF, formed a 10-member research consortium to better study ways to prevent and treat infantile hemangiomas.

Earlier studies by the research consortium identified other risk factors for developing hemangiomas, including increased maternal age, maternal history of infertility, and assisted reproductive technologies. Children born to women who had experienced a miscarriage are also more likely to develop hemangiomas. Additionally, 33% of infants with hemangiomas had the disorder in their family histories.

While hemangiomas are amongst the most common birthmarks, their cause is not known. Infantile hemangiomas are not visible at birth, but become evident within the first few weeks of life. Because of this, they are less likely to be recorded in typical birth defect registries. Hemangiomas may result in permanent scarring or other medical issues that require treatment.

"The finding that a significantly higher percentage of children with infantile hemangiomas had a positive family history suggests at least some genetic predisposition," said Dr. Drolet.

There are currently no FDA-approved medical therapies for the treatment of infantile hemangiomas. Most treatments are limited, due to increasing the potential risk of scarring.

"We urgently need further research to evaluate existing medications so that more evidence-based approaches to management can be established," said Dr. Drolet.

"Our study also underscores the need for continuing education of providers caring for children in distinguishing benign hemangiomas from those with the greatest potential for complications and need for treatment."

The study was funded by the Dermatology Foundation, The American Skin Association, and Children's Research Institute.



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