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News and Information for BC/BE Neonatologists and Perinatologists

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Neonatology Today (NT) is a monthly newsletter for BC/BE neonatologists and perinatologists that provides timely news and information regarding the care of newborns and the diagnosis and treatment of premature and/or sick infants.

THE LATE PRETERM INFANT

By Lucky Jain, MD

The Growing Problem of Late Prematurity!

There is hardly anything novel about being born at a late preterm gestation; yet, these infants are beginning to get a lot of attention, and have been the subject of much debate and writing recently[1,2]. Almost everyone, it seems, has a favorite story to tell of a perfectly healthy looking 35-36 week gestation infant, that started well, but went on to require ECMO or developed some other serious complication like kernicterus[3]. It is no wonder that this rather unpredictable behavior has earned them the infamous label of being "great imposters," since their near term status allows them to be passed off as mature infants even though they often manifest signs of physiologic immaturity and delayed transition in the neonatal period[4]. Births at > 34 and < 37 weeks gestation (referred to herein as "late preterm" births) account for a significant proportion (~75%) of preterm births in North America (Figure 1)[5]. Several studies have documented the high incidence of neonatal complications and NICU admissions in this population. These infants have a higher incidence of respiratory failure than term infants and can manifest signs of more global

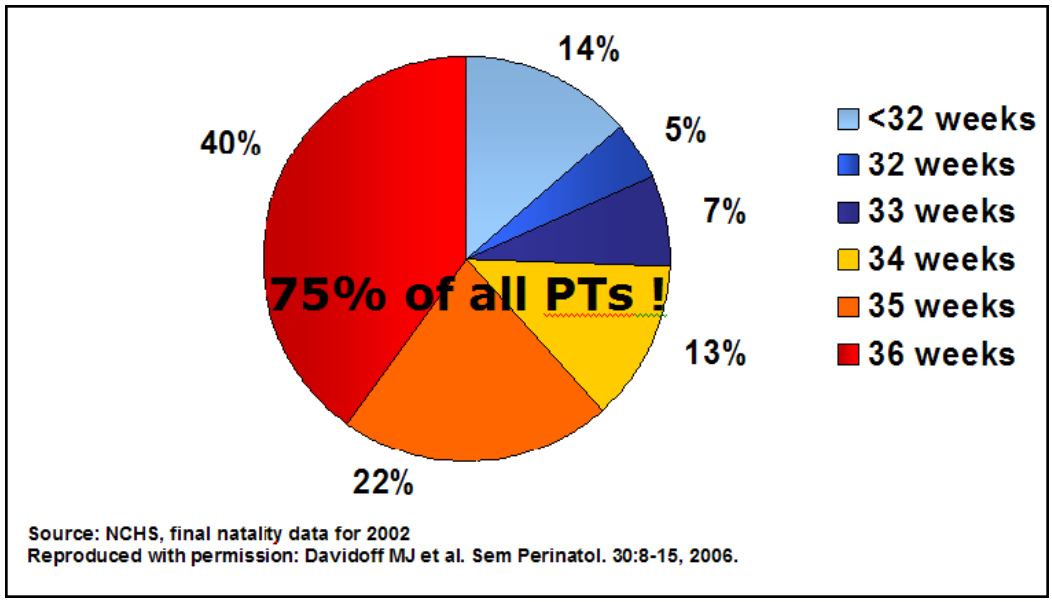

Figure 1. Preterm deliveries in the US and the contribution of births at late preterm gestations.

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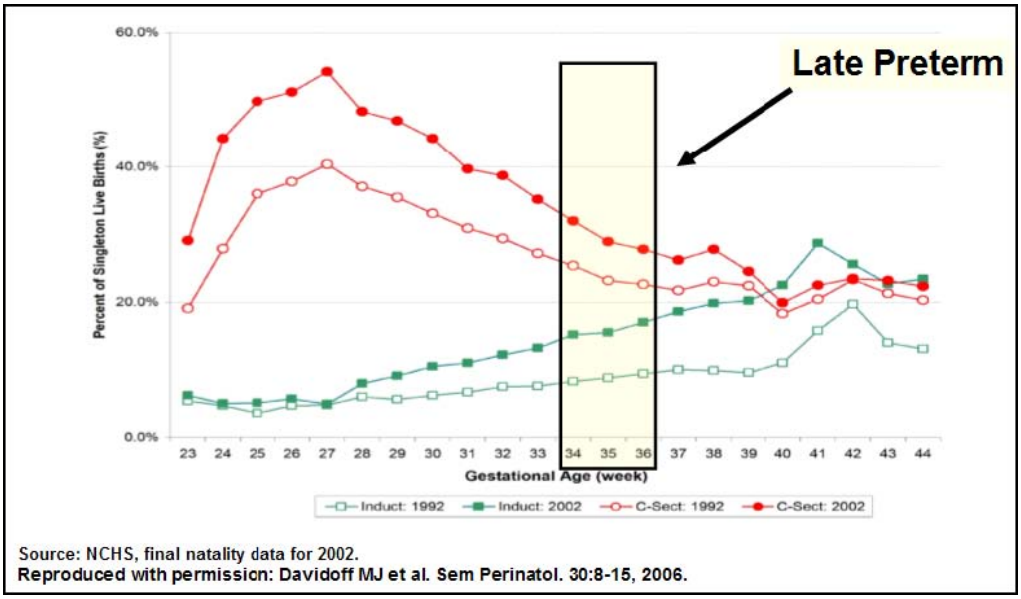

Figure 2. Changes in gestational age specific Cesarean section rates and induction rates for singleton births in the United States over a ten year period from 1992 and 2002.

immaturity with temperature instability, apnea, hypoglycemia, and poor feeding[6]. Comprehensive data about neonatal complications and outcomes in late preterm infants are hard to obtain because of the lack of large databases such as those available for preterm infants. It is estimated that nearly 50% of infants born at 34 weeks gestation require intensive care; this number drops to 15% at 35 weeks and 8% at 36 weeks gestation[7]. In addition to respiratory distress, these infants often have other neonatal complications including hypoglycemia, hyperbilirubinemia, feeding difficulties, and difficulty in maintaining body temperature[6]. Long term morbidity information and outcomes are largely unknown since these infants are not followed by developmental continuity clinics, despite the growing concern that their brains may be prone to white matter injury (Kinney).

In obstetric and pediatric practice, late preterm infants are often considered functionally mature and are managed according to protocols developed for full term infants. Late preterm infants have also been consistently excluded from RCTs which focus on respiratory diseases of the more vulnerable, very preterm infant. Instead they have been included in large multicenter random controlled trials designed to assess the efficacy and safety of therapies for neonates born at 34 weeks gestation or more. Unlike studies in the preterm, studies in the term and the late preterm population uniformly fail to stratify by gestational age, or use gestational age as a major confounder when analyzing outcomes. As a result, the evidence that we use to treat the late preterm is often extrapolated from studies where the overwhelming majority of infants enrolled are either term or postdates and the mean gestational age is 39 ± 2 weeks. Gestational age continues to be a major determinant of survival, as has been shown in studies comparing late preterm and term infants with similar birth anomalies (diaphragmatic hernia); similar differences have also been observed in infants treated with other modalities such as ECMO[8].

Delayed Respiratory Transition in Late Preterm Infants

The last few weeks of gestation are critical for fetal development and maturation, gradually preparing the fetus for a safe landing[9]. Biochemical and hormonal changes that accompany spontaneous labor and vaginal delivery also play an important role in this transition. For effective gas exchange to occur, alveolar spaces must be cleared of excess fluid and ventilated, and pulmonary blood flow increased to match ventilation with perfusion. Failure of either of these events can jeopardize neonatal transition and cause the infant to develop respiratory distress. We are still far from a complete understanding of the mechanisms(s) by which fetal lungs are able to clear themselves of excessive fluid at birth. It is clear, though, that traditional explanations which relied on "Starling forces" and "vaginal squeeze" can only account for a fraction of the fluid absorbed. Amiloride-sensitive sodium transport by lung epithelia through epithelial sodium channels (ENaC) has emerged as a key event in the trans- epithelial movement of alveolar fluid, and appears to be a two-step process[8]. The first step is passive movement of Na+ from lumen across the apical membrane into the cell through Na+ permeable ion channels. The second step is active extrusion of Na+ from the cell across the basolateral membrane into the serosal space. The lung epithelium is believed to switch from a predominantly chloride-secreting membrane at birth to a predominantly Na+ absorbing membrane after birth. These changes have also been correlated with an increased production of the mRNA for amiloride-sensitive epithelial Na+ channels (ENaC) in the developing lung. Disruption of this process has been implicated in several disease states including TTNB. It is now known that the experience of vaginal delivery enhances respiratory performance, and this effect is greater than that achieved by simple reduction of lung liquid volume to half in fetuses delivered without enduring labor. Removal of lung fluid starts before birth and continues postnatally with fluid being carried away by several possible pathways including pulmonary lymphatics, blood vessels, upper airway, mediastinum, and pleural space[10-12]. In later life, pulmonary edema can result either from excessive movement of water and solute across the alveolar capillary membrane, or from failure of reabsorption of lung fluid.

Respiratory Morbidity in Late Preterm Neonates Born by Cesarean Section

A significant number of late preterm neonates are delivered by CS or after artificial induction of labor, and this number has been steadily increasing in North America[13] (Figure 2). Overall, cesarean births rose a seventh year in a row in 2005 to a record 30.1% of all deliveries (National Vital Statistics Report, 2005). This rate is 33% higher than the rate seen in 1996 and is accompanied by a large drop in women attempting vaginal birth after a previous CS. Among other reasons cited for this increase are more older women giving birth, a rise in multiple gestations, as well as physicians' concerns about risks of vaginal birth; predictions are that continued increases are inevitable. Rates of CS are considerably higher in some other parts of the world, especially in Latin America. While indications for the high rate of operative

deliveries can vary by regions and by maternal choice, up to 50% of these procedures may be performed because of a previous CS.

A higher occurrence of respiratory morbidity in late preterm and term infants delivered by ECS has been observed by many investigators. These infants have a higher incidence of TTNB, RDS resulting from iatrogenic prematurity, and severe PPHN and/or HRF. Some of these reports also show higher rates of NICU admissions, mechanical ventilation, oxygen therapy, ECMO, and death. Madar et al. [14] showed that infants born by ECS at 37-38 weeks are 120 times more likely to receive ventilatory support for RDS than those born at 39-41 weeks.

	Late Preterm (N=2062)	Term (N=12,336)	p
Birth Weight	2.82 ± 0.50 kg	3.42 ± 0.56 kg	<.0001
Gestation	35.4 ± 0.8 wks	39.7 ± 1.5 wks	<.0001
Male	66%	57%	<.0001
Median Apgar 1	6	5	<.0001
Median Apgar 5	8	7	<.0001

Table I. Demographic characteristics of the late preterm and term ECMO population. Data expressed as mean ± SD or percentage.

It is also important to remember that the bulk of deliveries in the US occur at community hospitals (3024 community hospitals and 241 academic medical centers that deliver babies) and many serve rural populations. Multiple factors contribute to less rigorous dating and timing of deliveries in these settings. Once born, late preterm infants are often cared for in term nurseries by pediatricians. However, transitional care in these infants often requires a higher level of monitoring and support.

Why do elective cesarean deliveries carry a higher risk for the neonate? Since ECS is commonly performed between 37 and 40 weeks gestation, it was believed that much of respiratory morbidity in newborns delivered by ECS is secondary to iatrogenic prematurity. Indeed, studies evaluating large series of patients have shown a higher rate of prematurity and surfactant deficiency in these patients. Morrison et al. [15] showed that respiratory morbidity in ECS is inversely related to gestational age at the time of ECS: 73.8/1000 in the 37th week, 42.3/1000 in the 38th week, and 17.8/1000 in the 39th week of gestation. To minimize the occurrence of iatrogenic RDS, fetal lung maturity testing was initially recommended prior to ECS, but this is seldom done, given the risks associated with amniocentesis. Delaying ECS to 38-40 weeks has been shown to decrease the risk of respiratory distress, but this carries the risk of the patient going into spontaneous labor. Further, it is clear that in addition to RDS, infants delivered by ECS are at higher risk of developing TTNB, and PPHN unrelated to their gestational age at the time of delivery[8]. While most of these neonates develop transient respiratory distress and recover without any long term consequences, a significant number progress to severe respiratory failure. These infants not only require prolonged hospitalization, but also are at

	Late Preterm (N=2062)	Term (N=12,336)	p
Age on ECMO	2.6 ± 3.3 days	2.2 ± 2.8 days	<.0001
Hours on ECMO	145 ± 102 hrs	136 ± 86 hrs	<.0001
% Lung Support	99%	99%	NS
Discontinuation or Death on ECMO	28.2%	15.5%	<.0001
Survival	74%	87%	<.0001

Table II. ECMO course in late preterm and term infants. Late preterm infants were older at cannulation, had a longer duration of ECMO support, and had a significantly lower survival rate when compared to term infants. Data expressed as mean ± SD or percentage.

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increased risk for chronic lung disease and death. In addition, there is a higher incidence of respiratory depression at birth (low Apgar scores), thought to be related to fluid -logged lungs, making the transition to air breathing more difficult.

In an effort to reduce the occurrence of iatrogenic prematurity associated with ECS deliveries, the American College of Obstetrics and Gynecology (Guidelines for Perinatal Care, 5th edition, p 148) recommends scheduling ECS at 39 weeks or later on the basis of menstrual dates, or waiting for the onset of spontaneous labor. It also lays down the criteria for establishing fetal maturity before ECS. However, as alluded to earlier, the safety of this approach in mothers with previous CS deliveries has not been established in rigorous trials. Some population based studies point to an increased risk of uterine rupture and perinatal death in mothers with previous CS who went into spontaneous labor after 39 weeks. Such findings, as well as factors related to the convenience of scheduled ECS deliveries for both families as well as the providers, will continue to influence the timing of ECS.

Severe Hypoxic Respiratory Failure in Late Preterm Infants

The general impression among clinicians is that respiratory distress in late preterm infants constitutes a benign self limited illness that requires minimal intervention. While milder forms of respiratory distress due to TTNB and other causes are frequently seen in late preterm infants, it is not known how many of these infants become seriously ill and require clinical intervention. It is also not clear if the risk to benefit ratio of an intervention that is designed to reduce respiratory morbidity in infants delivered at late preterm gestations will justify its clinical application in a large number of mothers. One approach would be to evaluate the true occurrence of severe hypoxic respiratory failure in this population. Heritage and Cunningham[16] and Keszler et al[17] reported severe respiratory morbidity and resulting mortality in late preterm infants born by ECS who developed pulmonary hypertension, hence the term "malignant TTN." A significant number of these infants required ECMO. The etiology of pulmonary hypertension and HRF in late preterm is also not entirely clear. Many of these infants are asymptomatic immediately after birth or have mild respiratory distress, low oxygen requirements and radiographic findings suggestive of retained lung fluid or mild RDS. However, in a subset of infants, there is a gradual increase in oxygen requirement and subsequent evidence of PPHN. In large preterm infants, oxygen is often provided via oxyhoods. There are studies, especially in the adult anesthesia literature, that document a high incidence of alveolar collapse due to oxygen absorption and denitrogenation (nitrogen washout). Rothen et al.[18] have shown that in the post-operative period, atelectasis is twice more common in patients ventilated with 100% oxygen as compared to 30%. Detailed study of late preterm infants who required ECMO is warranted to better understand the pathophysiology of HRF and the influence of confounding variables.

We recently reviewed data from the ELSO Neonatal Registry to study the demographic characteristics, ECMO course, morbidity and mortality in late preterm infants[3]. Infants with congenital anomalies including congenital diaphragmatic hernia were excluded. From 1989 to 2006, a total of 15,590 neonates treated with ECMO were registered with ELSO. Of these, 2258 (14.5%) neonates were late preterm. Their demographic characteristics are shown in Table I. The mean gestational age and birth weight of late preterm infants were 35.3 + 0.9 weeks and 2.8 + 0.51 kg respectively. A greater number of late preterm infants treated with ECMO were non-Hispanic whites and were delivered by ECS. The primary etiology of hypoxic respiratory failure in late preterm infants was RDS or sepsis as compared to term infants who were more likely to have aspiration syndromes. Pulmonary hypertension was reported with equal frequency in both groups. Data related to the ECMO course are summarized in Table II. Late preterm infants were older at cannulation and had

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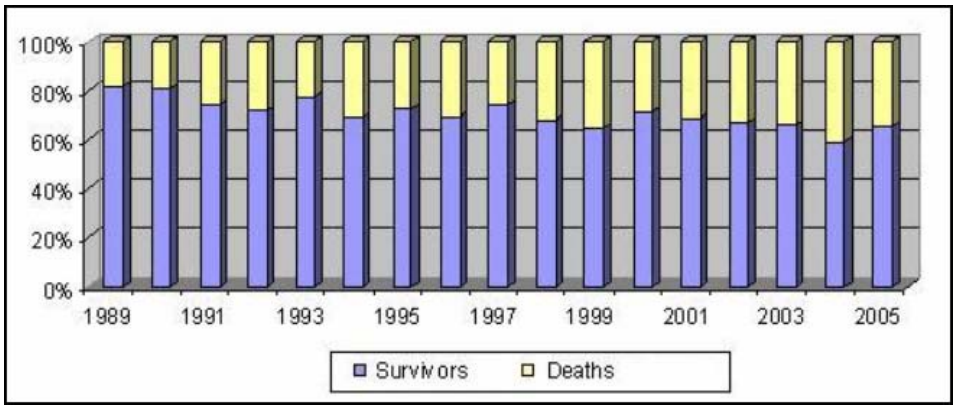

Figure 3. Change in survival of late preterm infants treated with ECMO since 1989. Survival in this population fell from 81.5% in 1989 to 65.2% in 2005 in spite of improvements in ECMO.

a longer duration of ECMO support. Table III compares the major complications reported in late preterm and term infants. Late preterm infants were more likely to have intraventricular hemorrhage and other neurologic complications than term infants. They were also more likely to die on ECMO or have ECMO support discontinued prior to lung recovery. The overall survival rate was 74% for late preterm infants as compared to 87% for term infants ($p<0.0001$). Survival in the late preterm neonatal ECMO population fell from 81.5% in 1989 to 65.2% in 2005 (Figure 3). Gestational age continued to be an independent risk factor for mortality in neonates treated with ECMO after correction for race, diagnosis, mode of delivery and 5 minute Apgar score.

Management strategies for late preterm infants with hypoxic respiratory failure

For the most part, common principles applicable to the care of term infants with respiratory failure also hold true for the late preterm infant; however, certain differences exist and clinicians needs to be aware of them. Key issues are summarized below:

Developmental immaturity of the late preterm neonate requires greater attention to detail and efforts to prevent iatrogenic injury. This also requires accurate determination and documentation of gestational age.

Supportive care includes, among other things, continuous monitoring of oxygenation, blood pressure and perfusion. Fluid and electrolyte management can be tricky since adequate circulatory volume is critical to maintain right ventricular filling and cardiac output, and, excessive volume infusions (especially colloids) can cause pulmonary edema.

Respiratory management includes appropriate use of oxygen and ventilation support. In the late preterm and term infant, the pathophysiology of ventilator induced lung injury is similar to that seen in ARDS with activation of the inflammatory cascade, and injury from free oxygen radicals. Care should therefore be taken to avoid volutrauma and to use adequate distending pressure.

Surfactant use is currently underutilized in this population, since classic signs of RDS are often absent. There is evidence that surfactant deficiency in these infants contributes to decreased lung compliance and atelectasis, and that exogenous surfactant therapy can be a promising adjunctive therapy, especially if used early.

Pulmonary hypertension is common in these infants in spite of the lack of severe parenchymal lung disease. Since initial ventilator settings tend to be low, traditional criteria based on OI for initiation of inhaled nitric oxide may be misleading. There is urgent need for evaluation of use of inhaled nitric oxide early in late preterm infants to prevent severe hypoxic respiratory failure.

Discharge in late preterm infants should not be considered before 48 hours after birth. Vital signs should be within normal range for the 12 hours preceding discharge (respiratory rate <60/min; heart rate 100-160/bpm; axillary temperature 36.5-37.4 in an open crib with appropriate clothing).

There should be at least 24 hours of successful feeding, demonstrating the ability to coordinate sucking, swallowing and breathing while feeding. If weight loss is greater than 7%, the infant should not be discharged. There should be formal evaluation of breast feeding including observation of position,

	Late Preterm	Term	RR	95% CI
Hemorrhagic	6.4%	8.4%	0.76	0.68-0.84
Mechanical	1.4%	1.5%	0.94	0.87-1.00
Metabolic	8.8%	7.1%	1.25	1.14-1.37
Neurologic	12.4%	8.2%	1.51	1.40-1.63
IVH	4.4%	1.9%	2.33	2.02-2.69
Other	8.0%	6.3%	1.27	1.15-1.39
Hemofiltration/Dialysis	7.3%	5.6%	1.31	1.18-1.45
Culture Proven Infection	2.6%	2.4%	1.11	0.94-1.32
Major Cardiovascular	4.1%	3.7%	1.06	0.95-1.18
PDA	1.8%	1.9%	0.93	0.76-1.14
Other	4.1%	3.7%	1.12	0.98-1.21
Pulmonary Hemorrhage	1.5%	1.4%	1.12	0.90-1.40

Table III. ECMO complication rates in late preterm and term infants. Late preterm infants were more likely to have intraventricular hemorrhage and other neurologic complications than term infants.

IVH, intraventricular hemorrhage; PDA, patent ductus arteriosis; RR, relative risk; CI, confidence interval.

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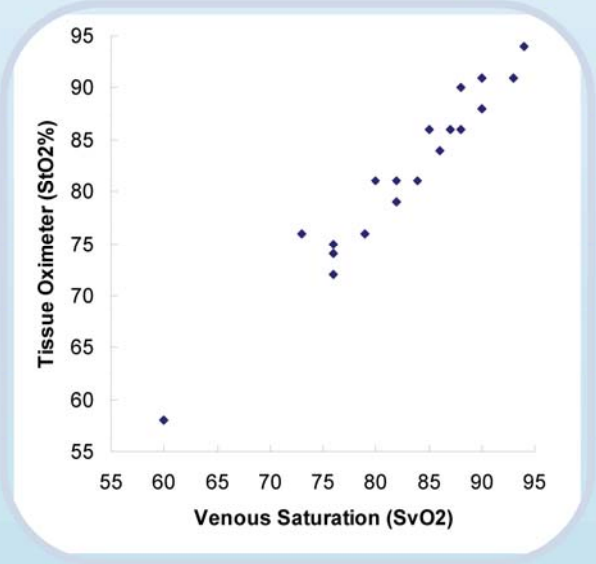

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latch, and milk transfer, with documentation in the record by trained caregivers at least twice daily after birth. A feeding plan should be developed, and there should be documentation of passage of at least one stool spontaneously prior to discharge.

Additional things that need attention include: a) a risk assessment plan for jaundice, b) lack of active bleeding at circumcision site for at least two hours, c) maternal and infant blood test results should be available and have been reviewed, d) initial hepatitis B vaccine should have been administered or an appointment scheduled for its administration, e) metabolic and genetic screening tests performed in accordance with local requirements, f) a successful car seat safety test, g) hearing assessment performed and results documented in the medical records and follow-up accomplished or planned, where necessary.

Family, environmental, and social risk factors should have been assessed. When risk factors are present, discharge should be delayed until they are resolved. Identification of a primary physician, with a follow up visit arranged for 24-48 hours after discharge is also recommended.

Summary

In the United States, a significant number of babies each year are delivered at late preterm gestations, and up to 50% of these deliveries occur by cesarean section. Of these, a significant number of infants develop severe hypoxic respiratory failure resulting in need for additional treatments like ventilation, surfactant, inhaled nitric oxide, and ECMO. There is an urgent need for preventive and therapeutic interventions that can help in optimizing the outcome of this vulnerable population.

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ANNUAL NEONATAL PRACTICES CONFERENCE SCHEDULED FOR JUNE 22-27 IN CHICAGO

The Fourth Annual **Evidence vs. Experience in Neonatal Practices**™ CME conference will be held in Chicago on June 22-23, 2007, providing physicians and other health-care professionals with state-of-the-art information on the specialized management of preterm infants. A faculty of international thought leaders will participate in this exciting and informative program, describing and discussing the latest developments in the field, including cutting-edge treatments and their practical applications.

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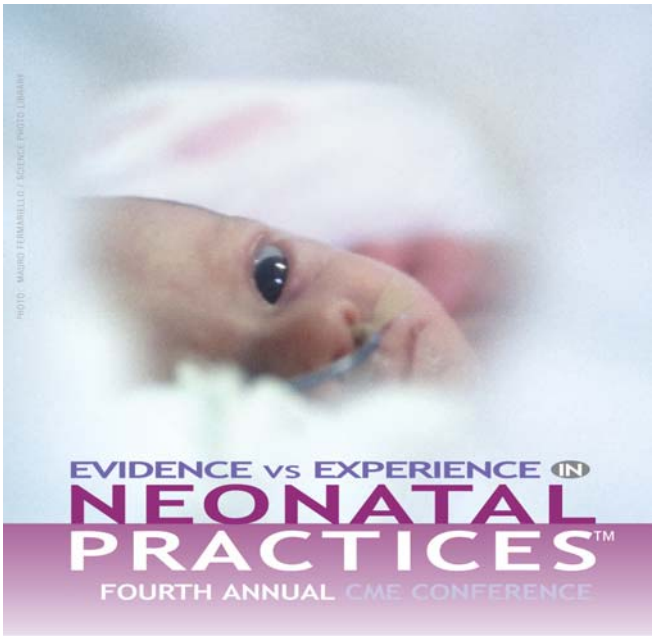
Rangasamy Ramanathan, MD
Program Chair

Rangasamy Ramanathan, MD, of the Keck School of Medicine of the University of Southern California, will serve as chair of this stimulating program. In addition to the symposium's other organizing committee members – Jatinder Bhatia, MBBS (Medical College of Georgia), Kris Sekar, MD (University of Oklahoma Health Sciences Center) and Istvan Seri, MD, PhD (Childrens Hospital Los Angeles) – the faculty will include leading neonatologists from the U.S. and Europe. The keynote address on the topic of "Surfactants: Past, Present and Future" will be delivered by Henry L. Halliday, MD (Queen's University of Belfast, Northern Ireland).

The conference, which is returning this year to the city of its inaugural meeting, will take place at the InterContinental Chicago. The target audience for the event includes physicians, nurse practitioners, nurses and others caring for preterm infants. As in previous years, attendees will be encouraged to participate actively in the program, interacting with the expert faculty, offering their own clinical and research insights, and using an Audience Response System to help ascertain what they've learned.



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MEDICAL NEWS, PRODUCTS AND INFORMATION

New Placenta Screening for High-Risk Pregnancies

For the first time ever, a team of Toronto researchers are using a combination of ultrasound and blood tests to screen high-risk pregnant mothers for placental damage. By completing these non-invasive tests, most high-risk mothers can be reassured that their placenta is formed and functioning properly, so they can expect a healthy pregnancy. The tests are done early enough, at 16 to 23 weeks gestation, so if results are abnormal, physicians have time to improve pregnancy outcomes. "Close to 40% of high-risk mothers we see in our clinic experience placental damage," says Dr. John Kingdom, Principal Investigator of the study and Maternal-Fetal Medicine Specialist at Mount Sinai Hospital. The research is among the first to look at placenta health – a vital life line between mother and fetus through which nutrients, oxygen, antibodies and hormones pass.

"By identifying early on if there is a potential risk of complications, we can do everything possible to ensure the safety of both the mother and fetus," says Dr. Kingdom, who is also a Professor in the Department of Obstetrics and Gynaecology at the University of Toronto. "We can reassure those with normal test results that their placentas are functioning well and they can expect a healthy pregnancy and birth."

If the placenta is not functioning properly it could be a potential danger to the health of the mother and fetus. Abnormalities can lead to conditions such as preeclampsia (which is maternal high blood pressure), stillbirth or the need for a pre-term delivery.

The screening tests include: a maternal serum screening test used to detect Down's syndrome, which measures the hormone levels in the mother's blood; a uterine artery Doppler blood flow test, which checks the maternal blood flow in the placenta; and an ultrasound of the placental shape. Of the 212 high-risk women in the study, 19 delivered early due to poor fetal growth. None of these women had normal placental function test results. Likewise, only two of 22 stillbirths occurred in women with normal tests, and these losses were not related to abnormal placental function. This data demonstrates that the placenta screening tests can provide a good indication of which women may experience complications during pregnancy.

"This is an important first step in identifying placental abnormalities in early pregnancy, at a time when a number of interventions can be used to improve outcomes for those with the highest risk" says Dr. Kingdom. "This study will lead the way for future research in placenta screening and help us provide quality care for all mothers."

The research was published in the April 2007 *American Journal of Obstetrics and Gynecology*.

Mount Sinai Hospital is affiliated with the University of Toronto. For more information about Mount Sinai Hospital, please visit www.mtsinai.on.ca.

Mutation in HNF4A Associated with an Increase in Birthweight and Macrosomia

A mutation in one gene HNF4A, associated with diabetes in the young, has been shown to be associated with an average increase in birthweight of 790g. In the current issue of *PLoS Medicine* (http://medicine.plosjournals.org/perlserv/?request=get-document&doi=10.1371/journal.pmed.0040148), Andrew Hattersley and colleagues from the Peninsular Medical School, report the findings from a study of 108 individuals from 15 families where the mutation was present. Overall more than half of the babies who carried the mutation were defined as macrosomic compared with 13% of those with no mutations.

Macrosomia (birthweight more than 4000g) is associated with complications for both mothers and babies; one cause of macrosomia is diabetes in the mother. The particular type of diabetes investigated in this study is known as maturity-onset diabetes of the young (MODY) genes; two of the genes known to be involved in this disease are HNF4A and HNF1A/TCF1, both of which have a key role in the regulation of the secretion of insulin by the pancreas.

In addition to increased birthweight the researchers also found that low blood-sugar levels at birth were also more common in babies carrying the HNF4A mutation as compared to those who did not. In mice that lacked the equivalent mouse gene (Hnf4a) the researchers were able to show that there was high insulin during development and low blood sugar at birth.

Although this study is in patients with an unusual mutation, these results have wider implications as they establish that HNF4A is important in determining birthweight. However, the mechanism by which the same mutation also causes diabetes (ie with decreased insulin) in later life remains to be determined in view of the increased insulin shown to be present at birth that causes the low glucose. Nonetheless, the authors con-

clude that "in addition to maternal factors, paternal factors (including history of diabetes) should be considered when assessing macrosomia risk." A related perspective by Benjamin Glaser from the Hadassah-Hebrew University Medical Center, discusses the paper's implications further.

PLoS Medicine is an open access, freely available international medical journal. It publishes original research that enhances our understanding of human health and disease, together with commentary and analysis of important global health issues. For more information, visit www.plosmedicine.org.

Prenatal Nicotine Exposure Can Lead to Cardiac Function Reprogramming in Adult Offspring; Females More Likely to be Impacted

Description

New study using laboratory rats provides strong evidence that the effects of maternal smoking during the prenatal period of life can lead to cardiac vascular dysfunction beyond the formative years -- and into adulthood. The effect of nicotine shows a gender dichotomy with females being more susceptible than males.

At least 115 of American women smoke during pregnancy. The negative effects of nicotine exposure to their fetuses and newborns are significant. A 2004 report by the Surgeon General, for example, found that women who smoked during pregnancy had children who were at a three times higher risk for SIDS than were the offspring of non-smokers. Now, a new study using laboratory rats, provides strong evidence that the effects of maternal smoking during the prenatal period of life can lead to cardiac vascular dysfunction beyond the formative years -- and into adulthood.

The finding is part of a new study entitled *Effect of Prenatal Nicotine Exposure on Coronary Flow in Adult Offspring: A Gender Dichotomy*. It was conducted by Daliao Xiao, Jennifer Lawrence, Shumei Yang, and Lubo Zhang, all of the Center for Perinatal Biology, Loma Linda University, School of Medicine, Loma Linda, and the Department of Chemistry and Biochemistry, California State University, San Bernardino, CA Dr. Zhang lead a discussion of the findings at the 120th annual meeting of the American Physiological Society (APS; www.the-APS.org), was held as part of the Experimental Biology (EB '07) meeting. More than 12,000 scientists and researchers attended the conference, which was held April 28-May 2, 2007 at the Washington, DC Convention Center.

Summary of Methodology

Nicotine (2.1 mg/d) was administered via osmotic minipumps placed under the skin throughout gestation and up to ten days after delivery. Hearts were isolated from three month old male and female offspring, and subjected to 25-minutes of mechanical obstruction of blood flow ischemia followed by 60-minutes of myocardial impairment caused by opening of the blockage. Pulmonary artery discharge was collected as an index of coronary flow (ml/min/g heart wet weight).

Summary of Results

- The researchers found: that nicotine significantly decreased coronary flow in female (10.4±0.8 vs. 7.1±0.7, P< 0.05) but not in male (9.1± 0.5 vs. 9.0±0.7, P>0.05) hearts at baseline;

- nicotine treatment significantly decreased coronary flow during reperfusion up to 60-minutes in female, but not in male, hearts.
- prenatal nicotine exposure significantly increased ischemia and reperfusion-induced infarct size in left ventricles and significantly affected post-ischemic recovery of left ventricular function in both male and female offspring. However, the effect of nicotine was significantly more pronounced in females than in males.

Conclusions

The results suggest that prenatal nicotine exposure selectively decreases coronary flow in adult female offspring. The findings suggest that prenatal nicotine exposure causes a reprogramming of cardiac function resulting in an increase in heart susceptibility to ischemia and reperfusion injury in adult offspring. In addition, the effect of nicotine shows a gender dichotomy with females being more susceptible than males.

The selective effect of nicotine on coronary flow in the female heart may contribute to the increased susceptibility of female vs. male hearts, in response to ischemia and reperfusion-induced cardiac damage in animals exposed to prenatal nicotine treatment. Additional study is thus required.

Physiology is the study of how molecules, cells, tissues and organs function to create health or disease. The American Physiological Society (APS) has been an integral part of the scientific discovery process since it was established in 1887.

Study Recommends Universal Newborn Screening for Cystic Fibrosis

Newborn screening for cystic fibrosis saves on treatment costs and would offset the actual costs of the screening program. This new economic evidence suggests that universal newborn screening programs for cystic fibrosis should be adopted internationally, according to a recent article in *The Lancet.*

The study also showed that newborn cystic fibrosis screening reduced hospital admissions for invasive therapy.

Cystic fibrosis is a life-shortening hereditary lung disease, but treatments are available. In some regions newborn babies have been screened for cystic fibrosis for more than 25 years, and early diagnosis is associated with improvements in some clinical outcomes*. Furthermore, the clinical benefit of those

screened as newborn babies is associated with a lower treatment burden compared with clinically diagnosed groups. Whether these potential cost savings attributed to reduced therapeutic requirements would offset the cost of a newborn screening program had not previously been studied.

Cystic Fibrosis screening hit the headlines in November 2006, when it was announced that UK Chancellor Gordon Brown's baby son Fraser had been diagnosed. Babies are routinely screened for the condition in Scotland (since 2003), Wales and Northern Ireland, but this is not yet the case for all areas of England including London.

Dr Erika Sims (University of East Anglia, Norwich, UK) and colleagues from the University of Dundee, UK, used data from the UK cystic fibrosis database for 2002 to compare the treatment costs of 184 children aged 1 - 9 years who had cystic fibrosis that was identified by newborn screening with those of 950 children in the same age-group, who were identified after clinical presentation of the disease. Patients diagnosed by newborn screening cost significantly less to treat than those who were diagnosed clinically. Patients diagnosed on the basis of clinical presentation alone received therapy costing an estimated 60–400% more than patients diagnosed by newborn screening.

The authors concluded, "Newborn screening is associated with lower estimated treatment costs and reduced hospital admissions for invasive therapy, which suggests that indirect costs and disruption to family life will also be less. Furthermore, the potential cost savings to the yearly treatment budget could offset some, if not all, of the costs of a newborn screening service."

JUNE SYMPOSIUM FOCUS

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Keynote Presentation: Surfactants: Past, Present, and Future - Henry L. Halliday, MD; Queen's University of Belfast

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