Pharmacotherapy of Meconium Aspiration Syndrome (MAS)

By Rama Bhat, MD

Introduction

Meconium Aspiration Syndrome (MAS) occurs in 2 to 5% (about 1/3rd) of infants born through meconium stained amniotic fluid. Even though the incidence of MAS has decreased in the developed world, it is still a major cause of mortality and morbidity in the developing countries. Major risk factors for meconium stained amniotic fluid (MSAF) and MAS include post maturity, presence of fetal heart rate abnormalities in the intrapartum period, Cesarean birth and maternal ethnicity (African American, Pacific Islanders). The reduction in post maturity and better intrapartum management in recent years have led to the reduction in MAS in the Western world. Several recent publications have enhanced our understanding of the pathophysiology of MAS. In brief, meconium-induced lung damage is multifactorial and manifests soon after birth with respiratory distress and persistent pulmonary hypertension. The pathophysiologic changes in MAS can be from: mechanical obstruction due to high viscosity and tenacity of meconium, chemical pneumonitis from neutrophil and macrophage infiltration, cytokine release and subsequent inflammatory response, surfactant inactivation and release of various vasoconstrictors. Further, ante-partum, intrapartum and post partum hypoxia adds insult to the injury by increased pulmonary vasoconstriction. Management of MAS in the NICU has also undergone significant changes based on better diagnostic approaches available today. Readers are referred to recent publications on ventilatory management of infants with MAS. The objective of this review is to focus on some of the currently available pharmacological agents and some promising new agents in the management of infants with MAS admitted to NICU.

Pharmacotherapy

While most infants born through MSAF do well after birth and are discharged home, about one third (30%) of them require additional respiratory and pharmacological support. Pharmacotherapy of infants with MAS can be described under general and specific treatment strategies. General pharmacological treatment strategies include the use of sedatives, alkali and muscle relaxants. Specific treatment strategies include pharmacological agents used to reduce lung injury, surfactant, anti-inflammatory agents and pulmonary vasodilators. These are described in detail below.

General Management

Drugs used in the general management of MAS include sedatives, sodium bicarbonate and muscle relaxants.

Sedation

Approximately 30 to 50% of MAS infants may need respiratory assistance in the form of continuous positive airway pressure (CPAP) or mechanical ventilation. The majority of these infants are term gestation, get easily agitated, and demonstrate frequent desaturations with handling. In infants on mechanical ventilation these desaturations can be minimized with the use of analgesic/sedatives.
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Alkalization

The rationale for the use of alkali is based on the principle that alkalosis decreases pulmonary vascular resistance. Increasing the pH from 7.45 to 7.5 either by hyperventilation or by sodium bicarbonate infusion (0.5 to 1.0 meq/kg/h) has been shown to produce pulmonary vasodilatation in both experimental animal models and human newborns with pulmonary hypertension. Sodium bicarbonate can increase intracellular acidosis and decrease cardiac output and coronary perfusion; hyperventilation, on the other hand, can increase the risk of chronic lung disease from barotrauma and hearing loss from injury to hair cells. Walsh-Sukys et al reported that treatment with sodium bicarbonate was associated with increased need for extra corporeal membrane oxygenation (ECMO) and oxygen requirement at 28 days. Neither hyperventilation nor alkali infusion therapies have been vigorously tested in a randomized controlled trial in human newborns. Use of bicarbonate is on the decline since the advent of inhaled nitric oxide therapy (iNO).

Muscle Relaxants

Prior to iNO therapy muscle relaxants were frequently used (mean 73%, range 33-98%) in conjunction with sedatives in intubated infants. Short acting non-depolarizing, competitive neuromuscular agents like pancuronium bromide (Pavulon) or Vecuronium bromide are the drugs of choice. Walsh-Sukys et al showed that in babies with pulmonary hypertension from all causes those who received muscle relaxants had more than twice the risk of death when compared to other therapies, even those on HFV/OR =2.84, 1.12-7.16. Again prospective randomized studies regarding the safety and efficacy of muscle relaxants in MAS are not available. Prolonged use of muscle relaxants along with sedation can lead to hypotension, prolonged ventilatory support, feeding intolerance, urinary stasis, tolerance and drug withdrawal. While controlling pain and discomfort in the newborn is the goal of every physician, a randomized controlled study to assess the cost-benefit analysis of such a therapy seems prudent.

Anti-inflammatory Agents

Antibiotics

The use of antibiotics in MAS has been controversial. Initial use of antibiotics was advocated as it was believed that stress caused the passage of meconium and the most likely reason for perinatal stress was an infection. This was substantiated in 1967 by Bryan who showed that even though sterile meconium was never fatal on its own; when given intratracheally along with E. coli it reduced the number of organisms needed to cause death. It was hypothesized that meconium reduced innate host resistance. Eidelman et al recently reported that a clear amniotic fluid was inhibitory for bacterial growth but in the presence of meconium, bacteria (Beta-Strep) grew much faster. Whether every infant with a diagnosis of meconium aspiration should be treated with antibiotics still remains a controversy. A recent controlled study by Lin et al reported that in non-intubated MAS infants, antibiotic treatment did not decrease duration of tachypnea, oxygen requirement, and the need for nasal continuous positive pressure support. Two other controlled trials from India also concluded that routine antibiotic therapy provides no advantage. From the available data it is appropriate not to give antibiotics to newborns with MAS without any known risk factors (prolonged rupture of membranes, chorioamnionitis, positive antenatal group B beta strep culture and need for ventilator support)

Steroids

Pneumonitis is the second cardinal finding in Meconium Aspiration Syndrome. Studies from our own laboratory have shown an increased expression of cytokine levels, especially TNF-α, IL-1β, IL-8 and lung cell apoptosis in newborn rabbits exposed to meconium. Since inflammation is one of the major findings in MAS, anti-inflammatory agents have been tried both in animal and human newborns as an adjunct therapy following meconium aspiration. Steroids in particular glucocorticoids (Dexamethasone) have been used to quell the inflammatory response. Animal studies and a small series of uncontrolled human trials did show definite clinical improvement in oxygenation and lung function. Recent meta-analysis of the available two randomized controlled studies failed to show any difference in mortality, chronic lung disease and length of hospital stay. At present, with the existing evidence of lack of efficacy and the real risk of developmental delay including cerebral palsy, use of dexamethasone can not be recommended.

Other anti-inflammatory agents like cromolyn, pentoxifylline, Clara cell protein and recombinant super oxide dismutase may have some beneficial effects via the inhibition of neutrophil migration and gen-
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Surfactant Therapy and Lavage

Meconium is shown to alter the surfactant function in the lung. The inhibitory effect of meconium on surfactant function has been well documented and was attributed to: (a) free fatty acids, (b) protein fractions and bilirubin present in the meconium. Administration of bolus doses of surfactant has been shown to improve oxygenation and lung function and decrease the need for ECMO in newborn infants. Few randomized controlled studies have shown improvement in oxygenation and reduction in barotraumas while others have shown only reduction in the need for ECMO. Most patients with MAS need higher doses of surfactant (150 mg/kg/dose) to overcome the inhibitory effects of meconium. Recently, surfactant lavage was tried in place of bolus doses in animal models of MAS and human newborns. The goal here was to remove the tenacious meconium adhered to tracheal mucous membrane and also to replace the inactivated surfactant. Both synthetic (Surfaxin 5 mg/ml) and natural surfactants, (Survanta 15 mg/ml) have been used for bronchoalveolar lavage. Only one small controlled study is published so far. This procedure involves administration of large volumes (15 ml to 48ml/ kg) of diluted surfactant mixture into the lungs followed by aspiration. The procedure can be risky and can result in acute clinical deterioration. At present, surfactant lavage in MAS is still considered experimental and a large controlled study is needed to determine its efficacy.

Pulmonary Vasodilators

Nitric Oxide

Introduction of inhaled nitric oxide (iNO) as a pulmonary vasodilator was a major breakthrough in Neonatal Medicine. With its introduction the management of MAS with pulmonary hypertension underwent a major change. INO was approved by FDA in December 1999 for the treatment persistent pulmonary hypertension (PPHN). Inhaled nitric oxide can be considered as an ideal pulmonary vasodilator because of its rapid effect on pulmonary vasculature causing pulmonary vasodilation with minimal systemic vascular effects. Inhaled nitric oxide is rapidly removed from circulation. The mechanism of action of iNO is by activation of soluble guanylate cyclase which increases the cGMP-dependent kinase which, in turn, decreases intracellular calcium in the vascular smooth muscle cell resulting in smooth muscle relaxation. Several large randomized clinical trials have shown that INO therapy is associated with significant reduction in ECMO use. The current recommendation is to start iNO in infants more than 34 weeks gestation diagnosed with hypoxemic respiratory failure and evidence of pulmonary hypertension by clinical and echocardiographic examination. Most of the published studies recommend INO when oxygenation index is >25 after surfactant therapy and adequate ventilatory support. The recommended starting dose of INO is 20 ppm. Weaning from iNO starts as oxygenation improves. It is recommended that iNO should be weaned by 5 ppm initially and once the dose of 5 ppm is reached further weaning should be by 1 ppm. Slow weaning is preferable to avert rebound hypoxemia. During iNO therapy infants should be monitored for adverse effects such as methemoglobinemia, and hypotension. High inspired iNO can lead to prolonged bleeding time and inhibit platelet aggregation, however, none of the randomized studies in term newborns have reported increased bleeding tendency. Some NICU have used INO via nasal cannula; however, available information is limited.

Phosphodiesterase (PDEs) Inhibitors

PDEs are a family of enzymes that hydrolyze cyclic nucleotides and regulate their intra-cellular levels. Both cyclic AMP and cyclic GMP play an important role in cell signaling. PDE inhibitors block the hydrolysis of cyclic nucleotides and increase GMP levels which help to maintain low intracellular calcium concentration and relax vascular smooth muscle. Several of the PDE inhibitors are approved for use in adults but not in newborns. Table 1 below shows...

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<thead>
<tr>
<th>Drug</th>
<th>Route of Administration</th>
<th>Dosage</th>
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<tbody>
<tr>
<td>Milrinone</td>
<td>IV</td>
<td>Loading 75 mcg/kg X 60 minutes Maintenance 0.5 – 0.75 mcg/kg/min</td>
</tr>
<tr>
<td>PDE-3 Inhibitor</td>
<td>IV</td>
<td>0.3 to 0.6 mg/kg</td>
</tr>
<tr>
<td>Dipyridamol</td>
<td>IV</td>
<td>0.25 – 1 mg/kg/dose every 6 hours till oxygenation index is &lt; 20</td>
</tr>
<tr>
<td>PDE-5 Inhibitor</td>
<td>IV/PO/NG</td>
<td>Magnesium Sulfate</td>
</tr>
<tr>
<td>Sildenafil</td>
<td>IV/PO/NG</td>
<td>Bolus of 200 mg/kg, followed by 20-150 mg/kg/h</td>
</tr>
<tr>
<td>ET Receptor Blocker</td>
<td>PO/NG</td>
<td>Bosentan</td>
</tr>
<tr>
<td>Magnesium Sulfate</td>
<td>IV</td>
<td>1 mg/kg/dose every 12h, X 24 h 0.5 mg/kg twice a day and then once a day at 0.5 mg/kg</td>
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Table 1. Pulmonary Vasodilators
the different PDE inhibitors and their dosages used in the newborns. Of the various PDE inhibitors only milrinone, dipyridamole, zaprinast and sildenafil have been tried in newborns with persistent pulmonary hypertension and in infants following cardiac surgery. Of the 4 PDE inhibitors only sildenafil can be given both by intravenous and oral route. Intravenous sildenafil is undergoing clinical trial in newborns at this time.

In the developed countries PDE inhibitors are used for weaning infants from nitric oxide. Milrinone is a specific PDE-3 inhibitor; whereas, dipyridamole, zaprinast and sildenafil are PDE-5 inhibitors. Sildenafil is the most popular drug used either in combination with INO or as the only pulmonary vasodilator. This latter mode is popular in developing countries because of ease of administration via nasogastric tube. A recent study reported improvement in pO2 following intra tracheal administration of sildenafil in a piglets. The table above describes the dose and mode of administration of various pulmonary vasodilators including sildenafil. While sildenafil use has definitely increased across the world, there is very little information regarding its pharmacokinetics and metabolism in neonates. Both sildenafil and dipyridamole have been approved for clinical use in adults with pulmonary hypertension. Sildenafil use intravenously or by oral route may exaggerate hypotension in infants. Other side effects reported include rapid progression of retinopathy in preterm infants.

Magnesium Sulfate

Magnesium is a non-specific vasodilator as well as a muscle relaxant a property very useful in infants with MAS and pulmonary hypertension. It has sedative and anti-thrombotic activity too. Magnesium sulfate has been used in the developing countries to treat pulmonary hypertension in newborns because of easy availability and low cost. It is administered intravenously with a loading dose (200 mg/kg) followed by a maintenance dose of 20 to 150 mg/kg/h. Small case series have shown significant improvement in oxygenation and oxygenation index. Hypotension, hypotonia are some of the side effects with its use. Large randomized trials have not been carried out so far.

Prostacyclins

Both prostacyclin and prostaglandin lower pulmonary vascular resistance. PGE-1 has been approved by the FDA for use in newborns to keep the ductus open. PGE2 is a weak pulmonary vasodilator when compared to Prostacyclin (PGI2) which has been approved by the FDA to treat pulmonary hypertension in adults. Prostacyclin has a short half-life (~ 1 min) and it is a potent systemic and pulmonary vasodilator. It needs to be given by IV route only. Newer synthetic analogues of PGI2 with longer half-life are available for clinical use and these can be given orally as well as by aerosol. Aerosolized PGI2 has been tried in newborns who failed INO therapy. Large multi-center randomized controlled studies in newborns are lacking so far.

Endothelin Antagonist

Endothelins play a major role in maintaining high pulmonary vascular resistance in utero. Endothelin levels are elevated in adults and newborns with pulmonary hypertension. Endothelin (ET-1) mediates vasoconstriction and smooth muscle cell proliferation through ET-A receptors. Bosentan, a non-specific ET-a and ET-B receptor antagonist, has been approved by the FDA for clinical use in adults with pulmonary hypertension, but only recently has it been tried animals and in human newborns with PPHN. The drug is given orally. Safety and efficacy studies are not available in newborns.

Other pharmacological agents being investigated at this time include: super oxide dismutase, arginine, vasoactive intestinal peptide and adrenomedullin. Many of these may be used in the future as adjuncts to wean the infants from inhaled nitric oxide.

In summary, management of infants with severe MAS requires a multi-pronged approach. In addition to various ventilatory strategies, these infants need various pharmacologic agents to support pulmonary vasculature as well as myocardium.

References

15. Shankar V, Paul VK, Deorari AK, Singh M. Do neonates with meconium aspira-


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Experimental Treatment Stops Newborn Brain Injury

Newswise — Inhibiting an enzyme in the brains of newborns suffering from oxygen and blood flow deprivation stops a type of brain damage that is a leading cause of cerebral palsy, mental retardation and death, according to researchers at Cincinnati Children’s Hospital Medical Center.

Reporting their results in the Journal of Neuroscience, the scientists show blocking the brain enzyme, tissue-type plasminogen activator (tPA), prevents progressive brain damage triggered by the lack of oxygen and blood supply. The experimental preclinical treatment involved putting a naturally occurring substance called plasminogen activator inhibitor-1 (PAI-1) into the brains of newborn rats, said Chia-Yi Kuan, MD, PhD, senior investigator on the study, and a researcher in the divisions of Developmental Biology and Neurology at Cincinnati Children’s.

Besides demonstrating the brain’s plasminogen activator system plays a pivotal role in neonatal cerebral hypoxic-ischemic brain injury, Dr. Kuan said the study also shows this system may be a promising therapeutic target in infants suffering hypoxic-ischemic encephalopathy (HIE). Identification of a treatment target is a vital step to finding better ways to treat newborns with HIE.

“Not only is hypoxic-ischemic encephalopathy an important cause of perinatal mortality and permanent neurological morbidity, but there are no specific medications against HIE in current medical practice,” explained Ton J. DeGrauw, MD, PhD, Director of Neurology at Cincinnati Children’s. “This is why the findings of this study may have important clinical implications because, in a rodent model of HIE, they show that inhibiting plasminogen activators in functional areas of the brain is a powerful strategy for brain protection.”

Earlier studies have pointed to the role certain brain proteases, or enzymes, play in adult brain injury following stroke, but very little has been known about what these enzymes do in neonatal cerebral hypoxic-ischemia, according to the researchers. The enzyme in this case, tPA, normally breaks down proteins and other molecules to eliminate blood clots.

The current study, posted on the journal’s website this month, included one-week-old rats in which brain hypoxia-ischemia was induced. The researchers found that hypoxia-ischemia leads to increased tPA activity. The enzyme then damages the brain blood vessels and the blood-brain barrier. The blood-brain barrier is a protective system designed to prevent invasions of blood-borne materials, in particular inflammatory cells or potential contaminants, into the central nervous system.

Dr. Kuan and his colleagues report that elevated tPA activity is triggered earlier in brain hypoxia than other proteases, particularly matrix metalloproteinases, in the progressive molecular process that leads to brain injury. This makes it a better target for therapeutic intervention to shut down the injury process early.

To test the importance of plasminogen activator in HIE, the research team examined the therapeutic effect of injecting PAI-1 into newborn rats suffering from the brain blood flow reduction and systemic hypoxia. The enzyme inhibitor was injected into the intracerebroventricular region of the brain, which includes a system of canals that distribute cerebrospinal fluid throughout the organ.

The researchers found that injection of PAI-1 greatly reduced the activity of both tPA and another brain enzyme, urokinase-type plasminogen activator. It also blocked hypoxic-ischemia-induced activation of matrix metalloproteinases and damage to the blood-brain barrier. The researchers also applied magnetic resonance imaging tests and microscopic analysis of brain tissues, which showed that PAI-1 treatment greatly reduced brain edema, axonal degeneration and the loss of brain tissue.

Dr. Kuan said additional studies are needed to test the effectiveness and safety of PAI-1 therapy in other experimental animal models. The researcher team also recommends studies to determine whether infants diagnosed with HIE, or who are at high risk for cerebral palsy, have elevated levels of tPA and plasmin in their brains or cerebrospinal fluid.

In human newborns, hypoxic brain injury usually occurs right before, during or shortly after birth, affecting two to four of every 1,000 births. The causes are mostly unknown, although some studies point to the possibility of problems with the placenta, maternal blood pressure or complications related to the umbilical cord. Close to 20 percent of newborn children with hypoxic-ischemia die and 25 percent of those who survive suffer from lifelong neurological problems.

Funding for the study came from the National Institutes of Health and the Alzheimer’s Association. The first author of the study is Dianer Yang, PhD, a research associate in Dr. Kuan’s laboratory. Also collaborating on the study were the Imaging Research Center/Department of Radiology at Cincinnati Children’s and the Department of Internal Medicine/Division of Cardiovascular Medicine at the University of Michigan Medical School.

Cincinnati Children’s Hospital Medical Center is one of 10 children’s hospitals in the United States to make the Honor Roll in US News and World Reports 2009-10 America’s Best Children’s Hospitals issue. It is highly ranked for its expertise in neonatal care and heart care. One of the three largest children’s hospitals in the US, Cincinnati Children’s is affiliated with the University of Cincinnati College of Medicine and is one of the top two recipients of pediatric research grants from the National Institutes of Health.

Additional information can be found at www.cincinnatichildrens.org.

Prenatal Payments Could Improve Birth Outcomes

Newswise — While most health care professionals tout the importance of regular
prenatal care throughout pregnancy, many women still do not get the care they need. Could providing financial incentives to patients or health care providers help improve compliance and —ultimately — outcomes?

That was the question raised by the authors of a new study, which appears in the journal Health Services Research online. They found that using incentives might not only improve the use of recommended care, but that it also could improve outcomes, especially for low-income women.

Examples of financial incentives were payments of $100 to patients and health care providers for “timely and comprehensive prenatal care.”

The researchers looked at administrative data and used information gleaned before and after the introduction of the Healthy Pregnancy Program — a program sponsored by the Culinary Health Fund of Las Vegas — to look at three maternal outcomes: rates of low birth weight, neonatal ICU (NICU) admission and spending in the first 18 years of life.

Patient adherence to recommended prenatal care topped off at 76%, five times more than it was when the program began, according to estimates by medical managers. The researchers also found significant associations between participation in the incentive program and lower odds of admission to the NICU and lower spending in the first year of life. They found no significant association with low birth weight.

“Findings from the evaluation of this program suggest the potential value to health benefit sponsors (like the Culinary Health Fund) of employing incentives to encourage the use of comprehensive prenatal care and perhaps other preventive care measures,” said lead author Meredith Rosenthal, PhD.

Rosenthal is an Associate Professor of Health Economics and Policy in the Department of Health Policy and Management at the Harvard School of Public Health.

“The study was unable to control for many of the behavioral risk factors and demographic factors that influence birth outcomes,” said Diane Ashton, Deputy Medical Director of the March of Dimes. “Therefore it is difficult to definitively conclude that the incentives strongly influenced the outcomes and not underlying differences in the two groups.”

Such risk factors could include things like smoking and obesity.

“It is always possible in a non-experimental study that other factors were changing that caused the results and we are incorrectly attributing the improvements to the incentives,” Rosenthal said. However, “in light of the overall strengths and limitations of the study, I believe these results provide moderately strong evidence that incentives for patients and doctors — we can’t separate out which mattered more — are effective in improving prenatal care adherence and the associated birth outcomes.”

Health Services Research is the official journal of the Academy of Health, and is published by John Wiley & Sons, Inc. on behalf of the Health Research and Educational Trust.


Maternal Immunity Not All Good for a Fetus

As a fetus does not mount an immune response to maternal proteins that cross the placenta, it has been assumed that a fetus would not reject non–genetically matched blood cells (specifically allogeneic blood cells) if they were transplanted while the fetus was in utero. The hope is that this procedure, which is known as IUHCT, could provide a viable approach for treating congenital blood disorders. However, studies using a mouse model of IUHCT indicate that most fetal recipients of allogeneic blood cells lose their transplanted cells 3-5 weeks after transplantation. Alan Flake and colleagues, at Children’s Hospital of Philadelphia, have now identified an immune mechanism responsible for graft failure in this model of IUHCT. Surprisingly, although fetal immune cells eliminated the transplanted allogeneic blood cells, they were triggered to do so by immune molecules known as alloantibodies that they obtained from their mother’s breast milk. The maternal alloantibodies were produced in response to IUHCT and so the authors conclude that in the absence of either a maternal immune response or transmission of the maternal alloantibodies to the fetus, transplanted blood cells should not be rejected, leaving open the door for IUHCT as a potential clinical strategy.

Title: Maternal alloantibodies induce a postnatal immune response that limits engraftment following in utero hematopoietic cell transplantation in mice

View the PDF of this article at: https://www.the-jci.org/article.php?id=38979.

Parents Fear Errors During Children’s Hospitalization

Newswise — Nearly two-thirds of parents reported they felt the need to watch over their child’s care to ensure that medical errors are not made during their hospital stay, according to a study led by Beth A. Tarini, MD, MS, Assistant Professor of Pediatrics at the University of Michigan Medical School.

In particular, parents whose first language is not English were more likely to report the need to be vigilant about their child’s care.

This is the first study to document parental concerns about medical errors during a child’s hospitalization.

Researchers also found that parents who were more confident in communicating with physicians were less likely to be concerned about medical mistakes.

“We need to address parents’ concerns about errors and find ways to make them feel comfortable talking to us about their child’s care,” Tarini says. “Parents are an underutilized resource in our efforts to prevent medical errors.”

This study, which appeared July 30 in the Journal of Hospital Medicine (Vol. 4, issue no. 9), surveyed 278 parents of children who were hospitalized at the Children’s Hospital & Regional Medical Center in Seattle, WA, in 2005.

Medical errors are linked to between 48,000 and 98,000 deaths a year, according to the Institute of Medicine, and are linked to increases in length of stay, health care costs and death. Doctors and hospitals have focused on processes and hospital systems as a way to prevent medical errors, but little work has been done in investigating the experiences of parents and their potential role in preventing errors.
Seizures During Pregnancy Associated with Risk of Pre-term and Small Babies

Women with epilepsy who have seizures during pregnancy appear more likely to give birth to pre-term, small or low-birth-weight babies than women without epilepsy, according to a report in the August issue of Archives of Neurology, one of the JAMA/Archives journals.

An estimated 0.2% to 0.7% of pregnant women have epilepsy, the most common major neurologic complication in pregnancy, according to background information in the article. "While approximately 40% of the 18 million women with epilepsy in the world are of childbearing age, managing maternal epilepsy and monitoring the health of the developing fetus remain some of the most perplexing and engaging issues in the fields of neurology and obstetrics," the authors write.

Yi-Hua Chen, PhD, of Tai Pei Medical University, Taiwan, and colleagues used data from the Taiwan National Health Insurance Research Data set and analyzed records from 1,016 women with epilepsy who gave birth between 2001 and 2003. Of these, 503 had seizures during pregnancy and 513 did not. A control group of 8,128 women who were the same age and gave birth during the same years but did not have epilepsy or any other chronic disease were selected for comparison.

Compared to women without epilepsy, women who had seizures during pregnancy had a 1.36-fold greater risk of having a low-birth-weight baby (weighing less than 2,500 grams), a 1.63-fold increased risk of giving birth pre-term (before 37 weeks) and a 1.37-fold increased risk of having a baby who was small for gestational age (having a birth weight below the 10th percentile for age). In addition, when compared with women who had epilepsy but did not have seizures, the odds of women who had seizures during pregnancy having a baby who was small for gestational age were 1.34 times greater.

Some previous studies had reported a link between adverse pregnancy outcomes and mothers’ epilepsy, but others found no association, the authors note. “Our study further illuminates these conflicting data to suggest that it is the seizures themselves that seem to contribute greatly to the increased risk of infants being delivered pre-term, of low birth weight and small for gestational age. For women who remained seizure-free throughout pregnancy, null or mild risk was identified compared with unaffected women.”

Several mechanisms might explain the association between seizures and adverse pregnancy outcomes. Trauma caused by a woman’s seizures could rupture fetal membranes, increasing risk of infection and early delivery. Tension and acute injury may result from contractions in the uterus that occur during seizures. However, additional research is needed to understand how seizures interfere with fetal development.

“Neonates born pre-term, of low birth weight and small for gestational age may be predisposed to diseases during infancy and later life, highlighting the significance of proper intervention strategies for prevention,” the authors write. These could include helping women control seizures for a period of time before pregnancy, assisting them in sleeping better, providing education about the risks of seizures while pregnant and teaching improved strategies for coping with stress.
"We found that interventions aimed at one outcome may affect other outcomes," wrote the authors. "We speculate that the decrease in the incidence of nosocomial infections in the pulmonary group was related to improved lung status and a reduced need for assisted respiration, invasive interventions, improved feeding and growth, and better overall health."

The method used in the study may be applicable in other areas of health care and may increase efficiency and reduce the costs.

In a related commentary
www.cmaj.ca/press/cmaj091243.pdf, Dr. William McGuire of the Hull York Medical School in York, UK, and coauthor writes that variations in practice contribute to uneven outcomes for premature infants. "Benchmarking and audit studies in neonatal networks have revealed marked variation in practice even when good evidence exists for specific interventions." They conclude that this study "adds to the accumulating evidence that multifaceted interventions may change practice and outcomes in neonatal intensive care settings," although more analysis is needed to ensure the best use of resources to help infants and their families.

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Ikaria hopes that this additional information supports the use of INOMAX while helping better identify appropriate candidates for INOMAX.

See updated full prescribing information: www.inomax.com/pdf/prescribing_information.pdf

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The updated label now reads: “When inhaled, nitric oxide selectively dilates the pulmonary vasculature, and because of efficient scavenging by hemoglobin, has minimal effect on the systemic vasculature.”

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  - > 2.5 kg: real-time data accuracy
  - < 2.5 kg: trend monitoring
- Noninvasive indication of O₂ changes in the cerebral and peripheral circulatory systems
  - Often providing an early warning of O₂ deficits associated with impending shock and anaerobiosis

INVOS® CEREBRAL/SOMATIC OXIMETER

Reflecting the Color of Life®

Labeling claims not applicable to other devices as data was derived using the INVOS System and its proprietary algorithm.

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