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Catecholaminergic Polymorphic Ventricular Tachycardia Due to Ryanodine Receptor (RYR2) Gene Mutation Presenting as Recurrent Apparent Life-Threatening Event Followed by Sudden Death

By Nathanya Baez Hernandez, MD; Chetan Sharma, MD; Uzoma Okorie, MD; Elizabeth McPherson, MD

Keywords: Catecholaminergic Polymorphic Ventricular Tachycardia, RYR2 gene mutation.

Running Title: Catecholaminergic Polymorphic Ventricular Tachycardia.

Abstract

While the majority of infants with an apparent life-threatening event (ALTE) recover uneventfully, some may have underlying causes that place them at increased risk for recurrent events and sudden death.[1] Recurrent ALTEs warrant deeper evaluation with high suspicion for cardiac arrhythmias. We present a two-month-old infant with recurrent ALTE followed by sudden cardiac death that had essentially normal evaluation including electrocardiogram during admission for an ALTE, but postmortem genetic testing showed a rare pathogenic mutation in the *RYR2* gene leading to a retrospective diagnosis of catecholaminergic polymorphic ventricular tachycardia (CPVT). To our knowledge, this is the first case of CPVT presenting as recurrent ALTEs at this young age.

"While the majority of infants with an apparent life-threatening event (ALTE) recover uneventfully, some may have underlying causes that place them at increased risk for recurrent events and sudden death.[1]"

Case Presentation

The patient presented here is a female infant born at 38 weeks to a healthy gravida 3, para 2, mother. Delivery was by Caesarean-section for intrauterine growth retardation. Birth weight was 2470 g (<10%). Apgar scores were 9/9. Family history was notable for sudden death of a sibling at 2 months, which had been attributed to pneumonia despite a normal physical examination just 24 hours prior to his death. Both parents were healthy, but a maternal half aunt had also died suddenly during infancy.

At 7 weeks of age during a minor respiratory infection, our patient presented with an episode of rapid shallow breathing followed by apnea requiring 2 minutes of home cardiopulmonary resuscitation (CPR). On admission, her examination was normal except for mild nasal congestion. Initial work-up, including complete blood count, C-reactive protein, comprehensive metabolic panel, chest x-ray, EKG and urinalysis, was unremarkable. Electrocardiogram showed normal sinus rhythm and normal corrected QT interval (QTc) at 449 milliseconds. She was discharged home after 48 hours of observation, but presented again within 10 hours after discharge with a recurrence of apnea and unresponsiveness requiring brief CPR. During her second admission, she had a normal video electroencephalogram monitoring, ammonia, amino acids, and organic acids with mildly elevated lactate. Patient was discharged home with a home Apnea-Bradycardia monitor. Three days after hospital discharge, she had a third apneic episode, for which resuscitation was unsuccessful. Post-mortem genetic testing showed a pathogenic mutation Pro466Ala in the *RYR2* gene.

Discussion

An ALTE describes an acute, unexpected change in an infant's breathing, appearance,

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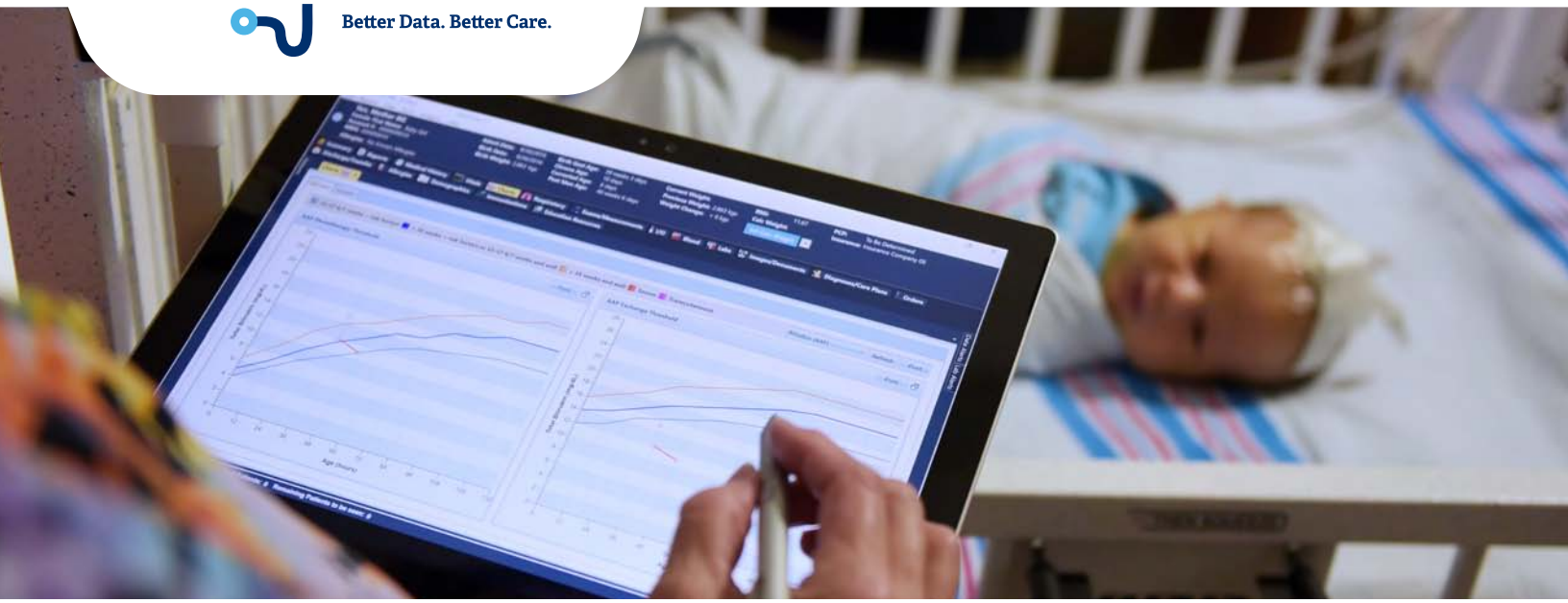

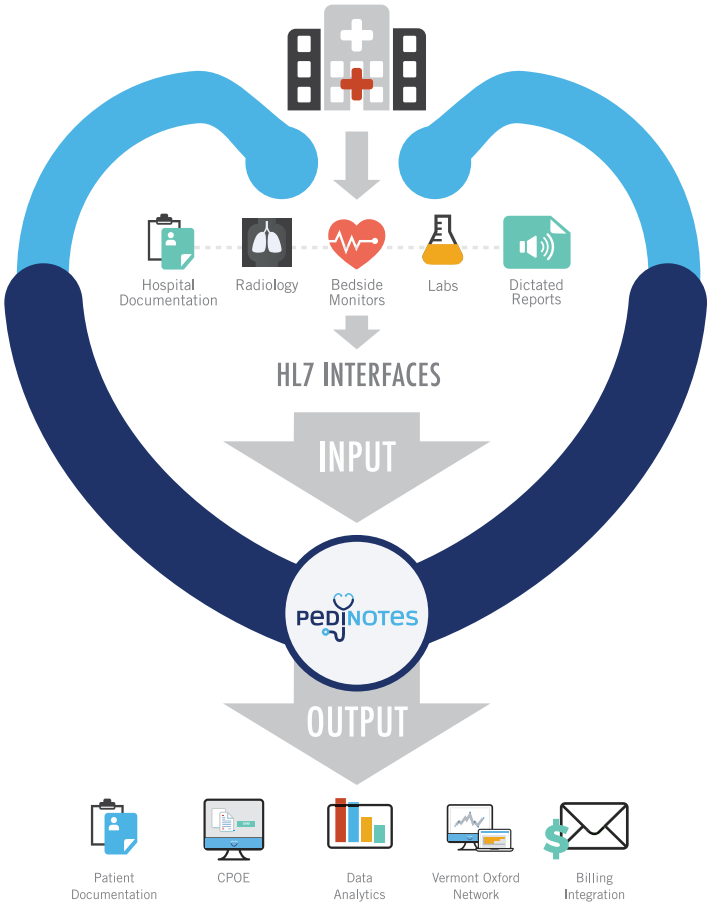

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or behavior that is frightening to the parent or caretaker. It is not a specific diagnosis, but rather a "chief complaint" that brings an infant to medical attention. The incidence is estimated to be 0.05 – 1% in population-based studies.[1-2]

ALTEs should not be considered a precursor to Sudden Infant Death Syndrome (SIDS) because the risk factors differ and only 7.4% of infants dying from SIDS had a previous ALTE.[3] Nevertheless, infants with a history of an ALTE are at increased risk for mortality ranging from 0.2% to 1.1%.[4,5] One study reported sudden unexpected death in 2% of ALTE survivors who had required CPR during their initial episode.[6]

There is no consensus regarding evaluation of infants following an ALTE. While the most frequently observed causes include gastroesophageal reflux, infection, and seizures, many of these diagnoses are apparent clinically and the yield for specific investigations such as esophageal pH probe, brain imaging (except when child abuse is suspected), and video electroencephalogram is low.[7] Cardiovascular disease may be a risk factor for subsequent death, but less than 50% of infants with ALTE undergo cardiac evaluation.[8] In those that do undergo cardiac evaluation, less than 5% have a cardiac disease identified, most commonly small Atrial or Ventricular Septal Defects; and only 1% has clinically significant arrhythmias that may explain the ALTE.[9-10]

In our index patient, the ALTE recurrence, as well as the family history of sudden infant death in an apparently healthy sibling and maternal half-aunt, suggested the possibility of an underlying hereditary disorder predisposing to cardiac arrhythmia. At the time of death, blood was obtained for the GeneDx Sudden Cardiac Arrest Arrhythmia Panel, which includes the following genes: KCNQ1, KCNH2, SCN5A, ANK2, KCNE1, KCNJ2, CAV3, RYR2, and CASQ2. No abnormality was found in any of the long QT-associated genes, but a pathogenic mutation, Pro466Ala, was found in RYR2. The *RYR*2 gene is associated with CPVT as well as arryhthmogenic right ventricular dysplasia. The specific amino acid change, Pro466Ala was previously reported in one individual with aborted cardiac arrest and a family history of multiple people with sudden cardiac death.[11]

Our index patient's mother tested negative for the same mutation, suggesting that the death of her half-sister was not related, but the father and surviving sibling tested positive for the same mutation. This suggests that the patient's deceased brother might also have had a genetic mutation that placed him at risk for cardiac arrhythmia. If his autopsy diagnosis of pneumonia was correct, respiratory infection could have been a trigger for arrhythmia rather than the major cause of his death.

CPVT is a life-threatening cardiac channelopathy that presents predominately in children and young adults. Patients with CPVT have normal heart structure and an entirely normal-appearing EKG at rest, but exertion may provoke ventricular ectopy. Patients with CPVT most often present in the first or second decade with syncope associated with physical effort or emotion, but cardiac arrest and sudden death can also be the first presentation.[12] CPVT has been reported as cause of sudden death in infants, but has not previously been reported as a cause of recurrent ALTE.[13-14] This is not surprising as the usual evaluation for ALTE would not be expected to identify infants with CPVT unless an EKG was obtained during the ALTE episode. In contrast to Long QT Syndrome in which the QTc is elevated, CPVT is not detectable on resting EKG because the baseline EKG, including QTc, is generally normal. Clinical work-up when CPVT is suspected should include: an evaluation of medical and family history, stress testing, holter monitoring, cardiac imaging, and targeted genetic testing.[15]

In 2007, Tester et al performed a study to assess the spectrum and prevalence of RYR2 mutations in a cohort of 134 SIDS cases. Overall, two distinct and novel RYR2 mutations (R2267H and S4565R) were identified in two cases of SIDS.[14] Subsequently, Larsen et al identified a higher prevalence of variants in the CPVT-associated gene *RYR2* with 7/74 persons aged 0-40 years with sudden unexplained death, including a cohort of infants who died of SIDS, found to be heterozygous for a rare sequence variant in the RYR2 gene.[13] In this study, the prevalence of SIDS-associated RYR2 mutation was 9.4%, much higher than the 1-2% previously reported.[13] No comparable genetic testing has been undertaken in patients with ALTEs.

Conclusion

We suggest that more attention should be given to the possibility of cardiac arrhythmias as a cause of ALTE, especially when ALTEs are recurrent and/or there is a family history of SIDS or sudden cardiac death in children and young adults. A thorough cardiac evaluation including genetic testing should be considered as part of the ALTE evaluation.

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"We suggest that more attention should be given to the possibility of cardiac arrhythmias as a cause of ALTE, especially when ALTEs are recurrent and/or there is a family history of SIDS or sudden cardiac death in children and young adults. A thorough cardiac evaluation including genetic testing should be considered as part of the ALTE evaluation."

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Indication

INOMAX is indicated to improve oxygenation and reduce the need for extracorporeal membrane oxygenation in term and near-term (>34 weeks gestation) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension in conjunction with ventilatory support and other appropriate agents.

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- Abrupt discontinuation of INOMAX may lead to increasing pulmonary artery pressure and worsening oxygenation.
- Methemoglobinemia and NO_2 levels are dose dependent. Nitric oxide donor compounds may have an additive effect with INOMAX on the risk of developing methemoglobinemia. Nitrogen dioxide may cause airway inflammation and damage to lung tissues.
- In patients with pre-existing left ventricular dysfunction, INOMAX may increase pulmonary capillary wedge pressure leading to pulmonary edema.
- Monitor for PaO_2, inspired NO_2, and methemoglobin during INOMAX administration.
- INOMAX must be administered using a calibrated INOmax DS_{IR}® Nitric Oxide Delivery System operated by trained personnel. Only validated ventilator systems should be used in conjunction with INOMAX.

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Brief Summary of Prescribing Information

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INOmax® is indicated to improve oxygenation and reduce the need for extracorporeal membrane oxygenation in term and near-term (>34 weeks) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension in conjunction with ventilator support and other appropriate agents.

CONTRAINDICATIONS

INOmax is contraindicated in neonates dependent on right-to-left shunting of blood.

WARNINGS AND PRECAUTIONS

Rebound Pulmonary Hypertension Syndrome following Abrupt Discontinuation

Wean from INOmax. Abrupt discontinuation of INOmax may lead to worsening oxygenation and increasing pulmonary artery pressure, i.e., Rebound Pulmonary Hypertension Syndrome. Signs and symptoms of Rebound Pulmonary Hypertension Syndrome include hypoxemia, systemic hypotension, bradycardia, and decreased cardiac output. If Rebound Pulmonary Hypertension occurs, reinstate INOmax therapy immediately.

Hypoxemia from Methemoglobinemia

Nitric oxide combines with hemoglobin to form methemoglobin, which does not transport oxygen. Methemoglobin levels increase with the dose of INOmax; it can take 8 hours or more before steady-state methemoglobin levels are attained. Monitor methemoglobin and adjust the dose of INOmax to optimize oxygenation.

If methemoglobin levels do not resolve with decrease in dose or discontinuation of INOmax, additional therapy may be warranted to treat methemoglobinemia.

Airway Injury from Nitrogen Dioxide

Nitrogen dioxide (NO_2) forms in gas mixtures containing NO and O_2. Nitrogen dioxide may cause airway inflammation and damage to lung tissues.

If there is an unexpected change in NO_2 concentration, or if the NO_2 concentration reaches 3 ppm when measured in the breathing circuit, then the delivery system should be assessed in accordance with the Nitric Oxide Delivery System O&M Manual troubleshooting section, and the NO_2 analyzer should be recalibrated. The dose of INOmax and/or FiO_2 should be adjusted as appropriate.

Worsening Heart Failure

Patients with left ventricular dysfunction treated with INOmax may experience pulmonary edema, increased pulmonary capillary wedge pressure, worsening of left ventricular dysfunction, systemic hypotension, bradycardia and cardiac arrest. Discontinue INOmax while providing symptomatic care.

ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from the clinical studies does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

Controlled studies have included 325 patients on INOmax doses of 5 to 80 ppm and 251 patients on placebo. Total mortality in the pooled trials was 11% on placebo and 9% on INOmax, a result adequate to exclude INOmax mortality being more than 40% worse than placebo.

In both the NINOS and CINRGI studies, the duration of hospitalization was similar in INOmax and placebo-treated groups.

From all controlled studies, at least 6 months of follow-up is available for 278 patients who received INOmax and 212 patients who received placebo. Among these patients, there was no evidence of an adverse effect of treatment on the need for rehospitalization, special medical services, pulmonary disease, or neurological sequelae.

In the NINOS study, treatment groups were similar with respect to the incidence and severity of intracranial hemorrhage, Grade IV hemorrhage, periventricular leukomalacia, cerebral infarction, seizures requiring anticonvulsant therapy, pulmonary hemorrhage, or gastrointestinal hemorrhage.

In CINRGI, the only adverse reaction (>2% higher incidence on INOmax than on placebo) was hypotension (14% vs. 11%).

Based upon post-marketing experience, accidental exposure to nitric oxide for inhalation in hospital staff has been associated with chest discomfort, dizziness, dry throat, dyspnea, and headache.

DRUG INTERACTIONS

Nitric Oxide Donor Agents

Nitric oxide donor agents such as prilocaine, sodium nitroprusside and nitroglycerine may increase the risk of developing methemoglobinemia.

OVERDOSAGE

Overdosage with INOmax is manifest by elevations in methemoglobin and pulmonary toxicities associated with inspired NO_2. Elevated NO_2 may cause acute lung injury. Elevations in methemoglobin reduce the oxygen delivery capacity of the circulation. In clinical studies, NO_2 levels >3 ppm or methemoglobin levels >7% were treated by reducing the dose of, or discontinuing, INOmax.

Methemoglobinemia that does not resolve after reduction or discontinuation of therapy can be treated with intravenous vitamin C, intravenous methylene blue, or blood transfusion, based upon the clinical situation.

 IMK111-01540 R2 January 2016

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Upcoming Medical Meetings

Innovations in Neonatal Care
Aug. 7-9, 2017; Austin, TX USA
www.innovationsconference.com

2017 AAP National Conference & Exhibition
Sep. 15-19, 2017; Chicago, IL USA
https://shop.aap.org/2017-national-conference-exhibition/

6th National Neonatal Simulation Conference
Sep. 26-27, 2017; Southampton, UK
www.mproveonline.com/conference

7th International Arab Neonatal Care Conference
Sep. 29-Oct. 1, 2017; Dubai Festival City
http://ancc2017.info

8th Phoenix Fetal Cardiology Symposium
Oct. 27-31, 2017; Phoenix, AZ USA
www.fetalcardio.com

20th International Conference on Neonatology and Perinatology
Dec. 4-6, 2017; Madrid, Spain
http://neonatology.conferenceseries.com

Hot Topics in Neonatology
Dec. 10-13, 2017; Washington, DC USA
https://neonatalcareacademy.com/events/hot-topics-in-neonatology/

Specialty Review in Neonatology
Feb. 20 - 25, 2018; Orlando, FL USA
www.specialtyreview.com

NEO: The Conference on Neonatology
Feb. 22-25, 2018; Orlando, FL USA
www.neoconference.com

39th Annual NPA Conference
Mar. 14-16, 2018; Loma Linda, CA USA
http://nationalperinatal.org/annualconference2018

Workshop on Neonatal-Perinatal Practice Strategies
Apr. 13-15, 2018; Scottsdale AZ, USA
https://shop.aap.org/2018-workshop-on-neonatal-perinatal-practice-strategies/

NeoHeart 2017 - Abstract Title: Transcatheter Echocardiographic-Guided Closure of Patent Ductus Arteriosus in Extremely Premature Newborns: Early Results and Mid-Term Follow-up

Evan Zahn, MD; Dan Peck, MD; Ruchira Garg, MD; Marion McRae, NP; Phillip Nevin, RN; Kaylan Basaker; Alistair Phillips, MD; Charles Simmons, MD

Neonatology Today is publishing selected abstracts from **NeoHeart 2017** with permission. This abstract is from **"NeoHeart: Cardiovascular Management of the Neonate.**" March 22-25, 2017; Manchester Grand Hyatt, San Diego, CA USA

Objectives: The goal of this study was to describe early and mid-term outcomes of extremely premature newborns (EPN) who underwent transcatheter echocardiographic-guided Patent Ductus Arteriosus (PDA) closure.

Background: The treatment of hemodynamically significant PDA in EPN is controversial. Treatment with cyclooxygenase inhibitors induces ductal constriction and closure in some EPN; however, this therapy is only successful in an estimated 50-60% of cases and carries a risk of pharmacologic complications, such as renal insufficiency and bleeding. Surgical ligation of PDA in EPN confers significant risk of procedural morbidity, including Post-Ligation Syndrome (PLS) and may adversely affect long-term outcomes. This has led to an era of conservative expectant management of these EPN despite the obvious ill effects PDA can have on their clinical course and outcomes.

Methods: A retrospective review of all EPN who underwent transcatheter echocardiographic-guided closure of PDA at our institution between 3/13 and 10/16 was performed. Pre-procedural clinical variables, imaging data, procedural elements and clinical follow-up data were collected to evaluate acute, early- and mid-term results. Post-Ligation Syndrome (PLS) was defined using previously published parameters. Patients were followed at pre-specified intervals and prospectively collected data was reviewed retrospectively.

Results: Transcatheter closure was attempted in 36 EPN (median gestational age/birth weight = 27 (24-33) weeks /848 (480-2480)g; procedural age/weight = 22 (5-80) days/1153 (755-2380)g and successful in 33/36 (92%). The three procedural failures were all related to the potential development of left pulmonary artery stenosis caused by the device and all devices were removed uneventfully during the implant procedure. Complications included two instances of device malposition, resolved with device repositioning (no long-term sequelae), and one instance of left pulmonary artery stenosis, requiring a left pulmonary artery stent at a later date.

There were no procedural deaths, residual PDA or device embolization. While most patients exhibited a transient decrease in LV systolic function, there were no clinical cases of PLS. One baby, who required a complex device repositioning (noted above), had an increase in ventilatory requirements for 24 hours and prolonged diminished LV function believed secondary to the complexity of the procedure. Survival to discharge was 97% (35/36) with a single late death (3 months post-procedure) unrelated to the procedure. At a median time from the procedure of 2.1 years all patients were alive and well, with no patients exhibiting residual PDA flow or the development of pulmonary artery stenosis or aortic coarctation of the aorta.

Conclusions: This newly described technique can be performed safely with a high success rate and minimal procedural morbidity in EPN. Early and mid-term follow-up is encouraging. Future efforts should be directed towards developing specific devices for this unique population and determining if this new treatment option results in better long-term outcomes than traditional medical and surgical therapies.

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All other authors: No disclosures

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"This newly described technique can be performed safely with a high success rate and minimal procedural morbidity in EPN. Early and mid-term follow-up is encouraging. Future efforts should be directed towards developing specific devices for this unique population and determining if this new treatment option results in better long-term outcomes than traditional medical and surgical therapies."

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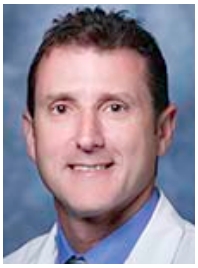

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The National Perinatal Association and Perinatal Substance Use Disorder

By Cheryl A. Milford, EdS; Erika Goyer, BA; Joelle Puccio, BSN, RN

Members of the NPA write a regular column in *Neonatology Today*.

As Americans, we find ourselves in the midst of what is understandably being called an opioid epidemic. Public health data describe rising rates of opioid use and misuse (SAMHSA, 2014). A dramatic increase in overdoses associated with opioid use has focused our attention on the risks of substance use and dependence (CDC, 2016). Those risks are of special concern during the perinatal period when the effects of substance use can be amplified. While we know that pregnant women use illicit substances at half the rate of their nonpregnant peers - and use less during their third trimester - the rates of substance use and, therefore, infants exposed to substances is still high with more than 400 000 infants exposed to alcohol or illicit drugs in utero each year (SAMHSA, 2014).

While the perinatal period presents unique risks for mothers who are substance dependent and their babies, it is also a time when there are unique opportunities for positive intervention. As clinicians and health care providers it is imperative that we understand the nature of women's substance use disorders and provide care that preserves the mother-infant dyad, promotes a mother's parenting potential, and supports the baby.

Substance use disorders seldom begin during a pregnancy (Cleveland, Bonugli, McGlothen 2016). Women typically have long histories of problematic substance use that also include periods of abstinence that predate their pregnancy (Forray, Merry, Lin, et al., 2015). So the subset of women who continue substance misuse during pregnancy are most likely those who qualify for diagnosis of a substance use disorder (Forray, 2016).

Some factors that correlate with perinatal substance use disorder include depression, intimate partner violence, sexual abuse and childhood trauma (Cleveland, Bonugli & McGlothen, 2016, Torchalla et al 2015). In many cases, women began their substance use as a coping mechanism to deal with these factors. For women without a history of trauma, substance use can increase risk of structural violence, imbalance of power in intimate relationships, and involvement with the criminal justice system, all of which can contribute to new experiences of trauma. (Torchalla et al., 2015)

The National Perinatal Association (NPA) views perinatal substance use as a major health care concern for perinatal providers, advocates, women and their families.

NPA's mission is to educate, advocate and integrate for optimal perinatal care in the United States. To this end, NPA is continuing its commitment to the understanding of perinatal substance use disorder. NPA convened a symposium in collaboration with the National Advocates for Pregnant Women in Nashville, TN in October of 2015. The result of the interdisciplinary discussion, which included all stakeholders, including pregnant women and parenting women with substance use disorder, was to organize a perinatal substance disorder workgroup. This workgroup is also interdisciplinary and includes women, families, and advocates. It is developing a family toolkit to educate women and their families on available resources and their rights, clinical recommendations for providing trauma-informed care with harm reduction practices and legal recommendations and guidelines for supporting decriminalization and decreasing incarceration for pregnant people with substance use disorder. The products being produced by the workgroup are evidence-based and grounded in the tenets of meeting people where they're at, celebrating any positive change, and respect for client agency as the foundation for all disciplines and especially women experiencing perinatal substance abuse disorder.

"While the perinatal period presents unique risks for mothers who are substance dependent and their babies, it is also a time when there are unique opportunities for positive intervention. As clinicians and health care providers it is imperative that we understand the nature of women's substance use disorders and provide care that preserves the mother-infant dyad, promotes a mother's parenting potential, and supports the baby."

The National Perinatal Association supports comprehensive treatment programs for women with perinatal substance use disorder. Such programs must incorporate gender specific, developmentally appropriate, trauma informed care. It is essential to work from a harm reduction model, promoting "Any Positive Change" as determined by the client, including plans ranging from abstinence, to safer use, to decreased use. Client abandonment in the case of continued use is unacceptable. Options for treatment should include, at minimum, medication assisted treatment, group and/or individual counseling, crisis intervention, mental health assessment and treatment, dental care, parenting classes and support, and social services such as housing, employment assistance, WIC, etc. (Paltrow & Flavin, 2013; SAMSHA, 2016; Cleveland, Bonugli & McGlothen, 2016; Patrick, Schiff et. al., 2017).

The National Perinatal Association opposes legal measures that criminalize pregnant people for substance use. The classification of these crimes, which can only be committed by pregnant people, are inherently gender discriminatory, in addition to being

counterproductive to the goal of improving maternal and neonatal outcomes. (Paltrow and Flavin, 2013) Criminalization and incarceration are ineffective and harmful to the health of the pregnant woman and her infant (Patrick, Schiff et. al., 2017).

In March of 2018, *the National Perinatal Association's annual conference: Perinatal Substance Use: Evidence-based Solutions and Support for the Family* will convene at Loma Linda University Children's Hospital in Loma Linda, California. Nationally and internationally recognized experts, parents, women, clinicians and advocates will meet from March 14th to 16th to discuss practices and approaches that support optimal outcomes for women, their infants and their families. Experts in legal issues, pharmacology, mental health, medicine, nursing and family advocacy will provide participants with specific practices and philosophies of care that they can take back to their community and implement immediately. The NPA Perinatal Substance Use Disorder Workgroup will present the results of their work, with recommendations for ongoing and future solutions to this significant health care issue.

Please join us in Loma Linda, California for evidence-based solutions and practices that support women, their families, and health care professionals working with families experiencing perinatal substance use disorder. We also invite you to join NPA and share in our passion and commitment to providing optimal perinatal care to mothers, infants and their families. See the NPA website at: www.nationalperinatal.org.

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"In March of 2018, the National Perinatal Association's annual conference: Perinatal Substance Use: Evidence-based Solutions and Support for the Family will convene at Loma Linda University Children's Hospital in Loma Linda, California. Nationally and internationally recognized experts, parents, women, clinicians and advocates will meet from March 14th to 16th to discuss practices and approaches that support optimal outcomes for women, their infants and their families."

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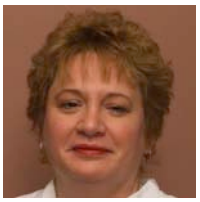

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Children's Health System

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This position is responsible for oversight of the delivery of all clinical services for Nemours Children's hospital partnership locations throughout Florida. This will include functioning as a patient and physician advocate, while providing clinical input into operational and management decisions related to the organization. Furthermore, this position will work to make certain the clinical activities are congruent with and support the mission of the Nemours Children's Health System.

The Medical Director will work in hospital partnership locations with the Administrator to ensure proper functioning of the day-to-day operations of the hospital partnerships. As an active practicing Neonatologist, the Medical Director will provide medical services to patients at Nemours Children's hospital partnership locations. This position is based in Orlando, Florida. Some travel is required.

For confidential consideration, please forward your formal CV to:
Brian Richardson, Physician Recruiter,
The Nemours Foundation
brichard@nemours.org
or
for more information and to submit CV online, please visit
http://careers.nemours.org/jobs/138000

Primary duties include:

- Reporting directly to the CMO of Network Operations and, along with the Administrator, being directly accountable for the clinical and operational processes supporting the Nemours programs at hospital partnership locations.
- Working with Administrators to engage, recruit, hire and orient qualified providers to become part of the Nemours Children's hospital partnerships.
- Developing and implementing policies, guidelines and clinical standards for patient care.
- Providing oversight and input to ensure clinical standards required for accreditation are met.
- Investigating and addressing clinical or quality issues and concerns.
- Working collaboratively with CMOs and specialty physician leaders to develop, optimize and/or expand specialty programs at hospital partnership locations.
- Providing oversight and input to evaluate and advance key health care initiatives.
- Developing and supporting programs for clinical quality improvement and patient safety, including initial and ongoing competency assessment and training.
- Providing administrative support and physician leadership, serving as an advocate for physicians and patients.
- Serving as a liaison to administration for clinical and provider-related issues. Serving as a liaison between physicians and between physicians and patients.
- Working with administration to develop annual operating and capital budgets.
- Collaborating with business development to cultivate new partnerships, and being an active participant in the strategic planning process.
- Building internal and external relationships, expanding the sphere of influence, and advocating for improvements and change within the enterprise and Florida. Promoting Nemours Children's hospital partnerships and serving as liaison to Nemours Children's Specialty Care/Nemours Children's Hospital and the pediatric community, ensuring an integrated approach to patient care.
- Having an active clinical practice in Neonatology.

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Our Associates enjoy comprehensive benefits, including our unique "Bridge to a Healthy Future" pediatric health plan, an integrated wellness program, opportunities for professional growth, and much more. As an equal opportunity employer, Nemours focuses on the best-qualified applicants for our openings.

Medical News, Products & Information

Compiled and Reviewed by Tony Carlson, Senior Editor

Study Finds Infant Sucking Performance May Facilitate Early Detection of Adverse Neurodevelopmental Outcomes

Newswise — A new study published in *Thieme's Seminars in Speech and Language* indicates that an infant's ability to feed, or sucking performance, may correlate with neurodevelopmental outcomes. The article, "Quantifying Neonatal Sucking Performance: Promise of New Methods," features the use of NFANT Labs' flagship product, nfant® Feeding Solution.

The study highlights the value of neonatal sucking assessment as a part of routine clinical care in the Neonatal Intensive Care Unit (NICU) and the potential it holds for early detection of preterm infants at risk for adverse neurodevelopmental outcomes.

The paper was published as part of the Journal's 20th anniversary special edition highlighting the state of the science in the field of Pediatric Dysphagia. It was conducted at the University of Kentucky and led by NFANT Labs' co-founder Dr. Gilson Capilouto.

"Safe and efficient feeding is the most complex skill of the newborn and a criteria for hospital discharge," said Dr. Capilouto. "Our results reinforce the idea that a baby's ability to suck safely and efficiently may be a window into the brain that can give us insight into how a baby is developing. Early detection of feeding difficulties means better developmental outcomes and cost savings for healthcare providers and families."

The paper demonstrates that metrics generated from feeding patterns collected at hospital discharge using nfant® Feeding Solution accurately differentiated full-term infants, preterm infants at high risk for poor neurodevelopmental outcomes, and preterm infants at low risk.

The study followed preterm infants in the hospital as they matured – from initiation of feeding through discharge and follow-up visits several months out. Full-term infants were also included to establish a standard of sucking performance for comparison. The goal was to find distinguishing traits in sucking patterns that would help clinicians identify those infants at risk for feeding issues and/or long-term neurodevelopmental problems.

Findings from the study highlight the need to include objective neonatal sucking assessment as part of routine clinical care and the need to examine the relationship neurodevelopment may have with feeding performance. The study is ongoing and will continue to follow infants until they are one year of age in order to correlate early sucking ability and scores on standardized tests of development. This study is one of several ongoing studies investigating the use of nfant Feeding Solution with other at-risk populations such as infants born with opioid addiction, infants of diabetic mothers, and infants at risk for developmental disabilities such as autism and cerebral palsy.

NFANT Labs is an emerging digital health and medical device company based in Atlanta, Georgia, dedicated to infant feeding. Its first product, nfant® Feeding Solution, is the first FDA-cleared "Internet of Things" (IoT) medical device for the NICU. Improving the standard of feeding care by collecting objective data and tracking feeding progression has the potential to shorten NICU stays, reduce readmissions and deliver substantial savings. For more information, visit www.nfant.com.

Largest Survey to Date of Patient and Family Experience at US Children's Hospitals

A survey of more than 17,000 parents of hospitalized children, conducted by the Center of Excellence for Pediatric Quality Measurement at Boston Children's Hospital, gives mixed responses about the quality of the inpatient experience at 69 U.S. children's hospitals. The analysis, the largest to date in pediatrics, found much variability from hospital to hospital. The findings are reported online today in the journal Pediatrics.

"Patient and family experience is one of the core aspects of quality healthcare, and has been associated with improved health outcomes," says lead author Sara Toomey, MD, MPhil, MPH, MSc, Medical Director of Patient Experience at Boston Children's and Assistant Professor of Pediatrics at Harvard Medical School. "This large data set gives us a much-needed overview of how well hospitals are doing in providing positive pediatric patient and family care experiences."

Although adult patients have been surveyed through the Adult Hospital Consumer Assessment of Healthcare Providers and Systems (Adult HCAHPS) Survey for more than 10 years, this is the first large-scale survey in the U.S. capturing the hospital care experience of children and their families.

Parents of hospitalized children completed the Child HCAHPS survey from December 2012 to February 2014. The survey asked about 18 measures of patient experience in five categories: communication with the parent, communication with the child, attention to safety and comfort, hospital environment and overall experience during the hospital stay.

The average hospital rating was 73% overall, but scores varied from measure to measure. For example, the average hospital scores were lowest for "preventing mistakes and helping you report concerns" (55%) and highest for "keeping you informed about your child's care in the emergency room" (84%).

There was substantial variability among hospitals on each of the 18 measures. For example, scores on "involving teens in their care," ranged from 53% to 96%; "how well doctors communicate with your child," 55% to 91%; "communication about your child's medicines," 70 to 96% and "paying attention to your child's pain," 59% to 94%.

"These ranges suggest that we can do better at involving families in patient safety and empowering them to speak up when safety concerns present themselves," says Toomey.

Dedicated children's hospitals tended to score somewhat better than children's wards within general hospitals. Teaching hospitals performed better than non-teaching hospitals in most categories, but got lower scores for quietness.

"The fact that we see variation across participating hospitals, with some doing very well and some lagging, suggests that there is an opportunity to try to help hospitals improve and learn from each other how they can do better," says senior author Mark Schuster, MD, PhD, Chief of the Division of General Pediatrics at Boston Children's and Professor of Pediatrics at Harvard.

The study was supported by the Agency for Healthcare Research and Quality, the Centers for Medicare & Medicaid Services and Harvard Catalyst/Harvard Clinical and Translational Science Center.

Boston Children's Hospital is home to the world's largest research enterprise based at a pediatric medical center, where its discoveries have benefited both children and adults since 1869. More than 1,100 scientists, including seven members of the National Academy of Sciences, 11 members of the Institute of Medicine and 10 members of the Howard Hughes Medical Institute comprise Boston Children's research community. Boston Children's is also the primary pediatric teaching affiliate of Harvard Medical School. For more information, visit @BostonChildrens, @BCH_Innovation.

Study Suggests New Way to Prevent Vision Loss in Diabetics and Premature Babies

Researchers at Bascom Palmer Eye Institute, part of the University of Miami Miller School of Medicine, have identified a new molecule that induces the formation of abnormal blood vessels in the eyes of diabetic mice. The study, "Secretogranin III as a disease-associated ligand for antiangiogenic therapy of diabetic retinopathy," which was published March 22nd in *The Journal of Experimental Medicine*, suggests that inhibiting this molecule may prevent similarly aberrant blood vessels from damaging the vision of not only diabetics, but also premature infants.

Changes in the vasculature of diabetes patients can cause long-term complications such as diabetic retinopathy, which affects around 93 million people worldwide. Many of these patients suffer a dramatic loss of vision as the blood vessels supplying the retina become leaky and new, abnormal blood vessels are formed to replace them. A molecule called vascular endothelial growth factor (VEGF) regulates blood vessel growth and leakiness, and two VEGF inhibitors, ranibizumab (Lucentis) and aflibercept (Eylea), have been approved to treat retinal vascular leakage, though they are only successful in about a third of patients.

The growth of abnormal new blood vessels also causes retinopathy of prematurity (ROP), the most common cause of vision loss in children. ROP affects up to 16,000 premature infants per year in the US. VEGF inhibitors are not approved for use in these patients because VEGF is crucial for vascular development in newborn children.

Study lead-author Wei Li, PhD, Research Associate Professor, and his colleagues at Bascom Palmer developed a technique called "comparative ligandomics" to identify additional molecules that regulate the behavior of blood vessels in diabetic mice. The approach allows the researchers to compare the signaling molecules that selectively bind to the surface of retinal blood vessel cells in diabetic but not healthy animals.

"It is estimated that between one third and one half of all marketed drugs act by binding to cell surface signaling molecules or their receptors," says Li. "Our ligandomics approach can be applied to any type of cell or disease to efficiently identify signaling molecules with pathogenic roles and therapeutic potential."

Using this technique, Li and colleagues discovered that a protein called Secretogranin III (Scg3) efficiently binds to the surface of retinal blood vessel cells in diabetic, but not healthy, mice. Though Scg3 promotes the secretion of hormones and other signaling factors, it wasn't thought to have a signaling function itself. Nevertheless, the researchers found that Scg3 increased vascular leakage, and, when administered to mice, it stimulated blood vessel growth in diabetic, but not healthy, animals.

VEGF, in contrast, stimulates blood vessel growth in both diabetic and healthy mice. Li and colleagues think that Scg3 binds to a distinct cell surface receptor that is specifically up-regulated in diabetes.

Treating diabetic mice with Scg3-neutralizing antibodies dramatically reduced the leakiness of their retinal blood vessels. Moreover, the

antibodies significantly inhibited the growth of new blood vessels in mice with oxygen-induced retinopathy, a well-established animal model of human ROP.

Though the researchers still need to confirm the role of Scg3 in humans, inhibiting this protein could be an effective treatment for both diabetic retinopathy and ROP, especially as it appears to have no role in normal vascular development. "Scg3 inhibitors may offer advantages, such as disease selectivity, high efficacy, and minimal side effects," Li says. "Because they target a distinct signaling pathway, anti-Scg3 therapies could be used in combination with, or as an alternative to, VEGF inhibitors."

The Journal of Experimental Medicine (*JEM*) features peer-reviewed research on immunology, cancer biology, stem cell biology, microbial pathogenesis, vascular biology, and neurobiology. For more information, visit http://jem.rupress.org/jem.org.

From the Classroom to the NICU: Real-World Neuroscience Opening New Avenues

When going to the movies with a group of friends, one small action can make a big difference when it comes to being on the same page after the movie: eye contact. A simple conversation before the movie sets you up to be more in sync with your friends after the movie.

These findings come from an unlikely place -- not the lab, or even a movie theater, but a classroom. Using portable EEG to measure brain activity among groups of students, researchers were able to record from multiple people simultaneously to study social interactions in real life.

"The goal of our research is to understand the neurodynamics of real-world social interactions, and we used the classroom as a real-world social neuroscience lab," says Suzanne Dikker of NYU and Utrecht University, who presented this new research at the *Cognitive Neuroscience Society (CNS) Annual Conference* in March. "The set-up we developed allows us to investigate aspects of human social interaction that are difficult or even impossible to study in a canonical laboratory setting."

While Dikker's work focuses on brain synchrony, she is but one of a growing number of neuroscientists both taking their work to more naturalistic settings and using more multisensory stimuli. From classrooms to museums to the Neonatal Intensive Care Unit (NICU), real-world settings are now possible research sites due to the advent of new neuroimaging techniques and advanced computational power, combined with a better understanding of the multisensory nature of our brains.

"The last 10 years are special in that they witnessed a confluence of advances in technology and in theoretical models that now are mature enough to take into consideration the full breadth of the complexity of the sensory environment and how we interact with it," says Pawel Matusz of the University of Lausanne in Switzerland and chair of the *CNS Ssymposium* on real-world neuroscience. Work in multiple settings is yielding unique insights into social interactions, attention, and neurodevelopment for the young and old alike.

Brains in sync

Conducting studies on brain synchrony - neural activity that is in sync among people - in real-world settings offers a great opportunity for new types of data, Dikker says. But with this opportunity comes a major challenge: adapting technologies and techniques for rapid deployment outside the lab. Most lab-grade neuroimaging equipment is expensive and not mobile. It is not possible, for example, to bring 10 fMRI scanners into a classroom or museum. Dikker and colleagues instead have adapted a low-grade EEG system for use in experiments, one that they can set up in only 5 minutes.

This adaptation comes with some sacrifices, she says. "It is unrealistic to expect the same level of data quality and experimental control from real-world neuroscience studies as we demand from laboratory

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experiments," Dikker says. "And we would never argue that efforts like ours move the field in a direction where the lab will become obsolete. Instead, we think of real-world research as a complementary approach that can inform, enrich, and inspire lab research, and vice versa."

In her latest work, Dikker and colleagues measured how much students are thinking about the same thing at the same time. They measured electrical brain activity with portable EEG and took survey data on social relationships and personality.

They found that the more a student felt part of the group, the more that student was engaged and in sync with the rest of the group. They also found that how much the students liked each other influenced brain synchrony during class - but, interestingly, it only mattered for those students who had eye contact at the beginning of class. "How much you like someone only matters if you have some actual interaction with that person," Dikker says.

In another study for which she will be presenting preliminary results at the CNS meeting, Dikker and colleagues measured brain synchrony in a museum installation. Collecting data from more than 2,000 people in the "Mutual Wave Machine," they also explored the role of eye contact in establishing synchrony.

An offshoot of a project with performance artist Marina Abramovic, the Mutual Wave Machine invites two people at a time to sit in a dome-like structure and gaze at each other while seeing a simplified visualization of their brain activity with lights all around them. They had to greatly simplify the EEG data being collected (using only canonical frequency bands) to come up with an intuitive way to visualize the neural activity. "There are only small light sources when your brainwaves are not in sync, and when your brainwaves are perfectly in sync, the dome fills up with light," Dikker says.

They found that brain synchrony was higher for more empathetic individuals. Furthermore, people felt more connected and their brain activity was more in-sync with each other at the end of the experience than at the beginning. This occurred only for people who didn't know each other to start, however, and for those who were explicitly told that what they were seeing was feedback from the brain; some were not told.

The research has potential applications in therapeutic work -- for example, Dikker's team would like to test game-like neurofeedback in high-functioning autistic teens, to see if the method can help them respond better to social cues. But above those applications, the studies lay groundwork for future investigations to establish crosstalk between the lab and real world. For example, Dikker wants to further investigate in the lab what it is about eye contact that sets up the joint attention and brain synchrony.

Our multisensory brains

"Experiments that are conducted in naturalistic settings, such as those, for example, conducted by Suzanne Dikker, are informative as they explore new dimensions characterizing information processing in the real world," says Matusz of the University of Lausanne. "These technology-inspired neuroscientific investigations, using advanced signal processing methods, push the frontier on what we know about functional brain organization and the mind."

But he says that naturalistic studies should ideally be well-controlled lab experiments that aim to emulate the characteristics of information processing in everyday environments, while controlling for confounding factors. One of the most striking realizations of the past decade of work has been that information processing follows somewhat different principles than those established with traditional research involving just visual or just auditory stimuli.

"Information across different senses is exchanged and integrated at much earlier stages of brain processing than previously thought," Matusz says. "This has profound implications for our understanding of perception, attention, learning and memory processes."

For example, recognizing and finding a friend at a cocktail party full of people will be much easier if you not only see the person but also hear him/her. However, you will be also more easily distracted during this task than predicted by traditional models because multisensory objects are more distracting than just visual or auditory ones. A person next to you shouting and waving to someone else across the room, or someone bumping into you and saying sorry, will make it harder to locate your friend. These are tradeoffs that control our "selective attention" -- our ability to process important information and suppress distracting information -- in real-world environments.

In the work presented at the CNS meeting, Matusz's team used multisensory, audiovisual distractors to reveal that children can actually be less distracted than adults or older children. These results, published in *Cognition* in 2015, Matusz says "go against traditional models of brain and attention development, according to which there is a mature, adult state of attention that we gradually reach as we grow older from 'distractful youth.'"

In novel results building on that finding, he and colleagues explored how experience interacts with our selective attention as we grow. They asked young and adult participants to search for numerical digits, a category of objects where school-entering children are more familiar first with their sounds than their shapes. While the younger children benefited from having the audio, the sounds proved a distraction for the older children and adults. "These results echo recent voices in the neuroscience community suggesting that neuroscientific research provides meaningful knowledge when it is based on well-conceptualized studies of behavior," he says.

Clinically, this growing body of knowledge on the multisensory brain is opening novel avenues for addressing sensory and learning disorders. For example, in a collaborative project with Nathalie Maitre from Nationwide Children's Hospital in Ohio and Micah Murray from the University of Lausanne, Matusz worked with pre-term babies and their sense of touch. Every year, 15 million children worldwide are born prematurely, but the existing interventions are unclear in terms of their actual effects on sensory and brain processing. As published this month in Current Biology, the researchers recorded EEG in premature babies in the NICU and demonstrated a direct role of both negative and positive touch in shaping their somatosensory brain responses.

Dikker and Matusz are two speakers who presented in the symposium "Are we ready for real-world neuroscience research?" at the CNS annual meeting in San Francisco.

CNS is committed to the development of mind and brain research aimed at investigating the psychological, computational, and neuroscientific bases of cognition.

Very Premature Babies Benefit Most from Corticosteroids Before Birth

Giving corticosteroid drugs to mothers at risk of preterm delivery - from as early as 23 weeks of pregnancy - is associated with a lower rate of death and serious illness for their babies, finds a study published by *The BMJ Today.*

Very premature babies seem to benefit the most, even those born at 23 weeks, the findings show.

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Babies born early carry a greater risk of death and serious complications after birth such as breathing problems, bleeding into the brain or infection, compared with babies born at term. These problems tend to be more severe the earlier the baby is born.

Corticosteroids have been shown to help with a baby's development, and therefore, increase the chance of the baby surviving, once born.

Current guidelines recommend giving corticosteroids to at risk women from 23 to 34 weeks of pregnancy (gestation). However, the benefits for reducing ill health (morbidity) during the 23rd week had been less clear.

So a team of US researchers analysed data for 117,941 infants born between 23 and 34 weeks of gestation from 2009 to 2013 at 300 Neonatal Intensive Care Units across the US.

Death or major illness was analysed by gestational age and exposure to antenatal corticosteroids, adjusting for factors such as: birth weight, sex, mode of delivery and multiple births.

The researchers found that exposure to antenatal corticosteroids was associated with a significantly lower rate of death before discharge from hospital at each gestation compared with infants without exposure.

They also found that the number of infants needed to treat with antenatal corticosteroids to prevent one death before discharge increased from six at 23 and 24 weeks of gestation to 798 at 34 weeks of gestation, suggesting that infants born at the lowest gestational ages benefit most, even those born at 23 weeks.

The rate of survival without major illness while in hospital was also higher among infants exposed to antenatal corticosteroids at the lowest gestations.

"Among infants born from 23 to 34 weeks' gestation, antenatal exposure to corticosteroids compared with no exposure was associated with lower mortality and morbidity at most gestations," say the authors.

"This study highlights for the first time that infants at the lowest gestations seem to benefit the most from exposure to antenatal corticosteroids," they add.

The authors point out that this is an observational study, so no firm conclusions can be drawn about cause and effect, and they outline some limitations could have introduced bias.

Nevertheless, they conclude that this study "supports the administration of antenatal corticosteroids in women with threatened preterm labour from 23 to 34 weeks' gestation."

In a linked editorial, Professor Sarah McDonald at McMaster University in Canada agrees that the administration of antenatal corticosteroids to women at risk of early preterm birth "has been one of the most effective interventions to improve premature infants' outcomes."

However, she points out that that timing is critical in maximising benefits for very premature babies. Ideally corticosteroids should be administered within approximately one week of birth, she explains, and this remains the biggest challenge for clinicians.

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