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Congenital Chylothorax Associated with 15q13.3 Microduplication Managed with Intrauterine Thoracentesis with Favorable Outcome

By Kathryn E. Patrick, MD; Anushka Chelliah, MD; Jessica Jackson, MD, MSBS; Anthony Greg, MD, MBA; Patrick Duff, MD

Background

Neonatal chylothorax is characterized by an accumulation of chyle in the pleural space and can be an acquired or congenital condition. Congenital Chylothorax is a relatively rare condition with a reported incidence of 0.004%, or 1 in 24,000 live births and is the result of aberrant or obstructed lymph drainage.⁴ Although rare, Congenital Chylothorax is the most common cause of congenital pleural effusions.¹⁸ Congenital Chylothorax may be idiopathic; or, it can be associated with fetal hydrops, lymph disorders such as congenital pulmonary lymphangiectasia and generalized lymphangiomatosis, bronchopulmonary sequestration, congenital diaphragmatic hernia, or chromosomal or other genetic abnormalities.^{2,7,11,21,22} In one study, nearly one third of the Congenital Chylothorax cases were associated with a genetic syndrome.⁴ Specifically, Congenital Chylothorax has been associated with Down Syndrome; Turner's Syndrome; and genetic disorders involving deletions and mutations in the RAS/MAPK pathway (RASopathies)

such as Noonan, Cardio-facio-cutaneous, and Costello Syndromes.^{10,17,19,24}

Fetal diagnosis of chylothorax is most often an ultrasound diagnosis.⁶ Postnatal diagnosis is usually made following a workup of neonatal respiratory distress immediately following delivery. It is important to diagnose pleural effusions prenatally, as they can be associated with extrathoracic fetal anomalies and can lead to polyhydramnios and subsequent preterm labor. Prenatal diagnosis of this condition can also aid with delivery planning. These neonates are at increased risk for respiratory distress secondary to mediastinal compression, pulmonary hypoplasia, pneumothorax, and pneumomediastinum. Characterizing the pleural effusion as chylous (versus serous) can be accomplished by thoracentesis pre or post natally. A predominance of lymphocytes (>80%) is seen on cell count of the pleural fluid.²⁶ However, clinical correlation must be made as a predominance of atypical lymphocytes can also be seen in the setting of viral infection.⁸ Characterizing a pleural effusion determines proper short- and long-term management of these neonates.

When diagnosed prenatally, management of fetal pleural effusion is controversial and depends on gestation age; severity of effusion; evidence of progression of the

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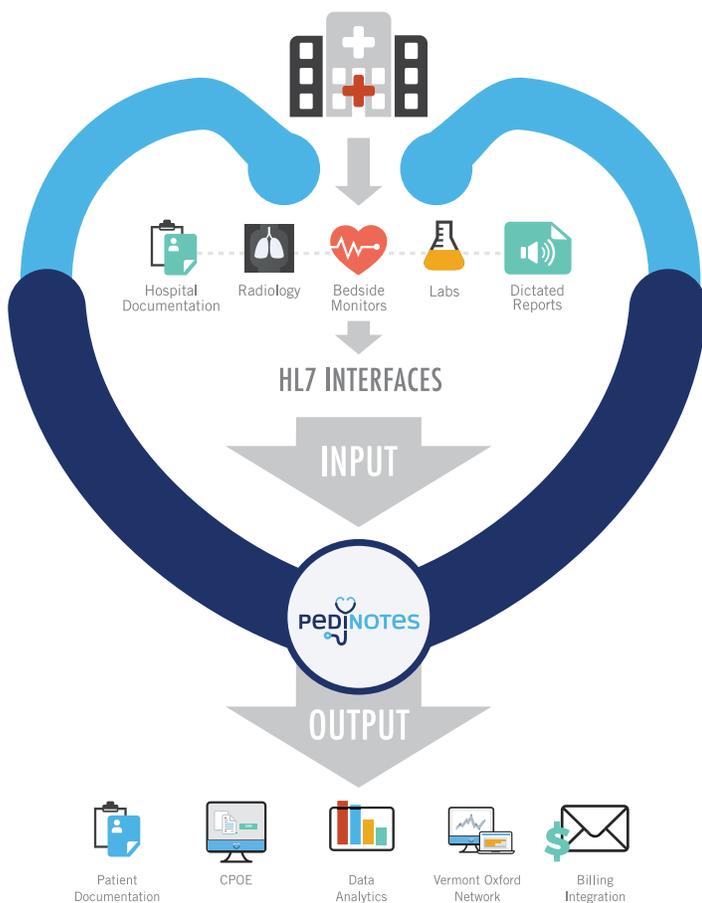
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effusion; and the presence or absence of mediastinal shift, hydrops, polyhydramnios, and other fetal anomalies. Pregnancy termination can be considered prior to viability, and observation with postnatal intervention can be considered after 32-34 weeks gestation. Observation for spontaneous resolution is often the first approach. If intervention is deemed necessary, diagnostic and therapeutic thoracentesis, thoracoamniotic shunting, and thoraco-maternal cutaneous drainage can be performed.⁵

Postnatally, neonates with congenital chylothorax are initially managed with diet modification including administration of a formula high in medium-chain triglycerides, which ultimately leads to decreased thoracic duct lymphatic flow.¹ Most cases of Congenital Chylothorax resolve with nonoperative management.¹³ When the response to diet modification is inadequate, or there is rapid reaccumulation of chylothorax after repeated thoracenteses, bowel rest with total parental nutrition, Octreotide, and tube thoracostomy can be considered. Thoracotomy with thoracic duct ligation and pleuroperitoneal shunts performed thoroscopically are effective, but should be used only after all other nonsurgical approaches have failed.^{15,16}

When Congenital Chylothorax does not resolve, perinatal morbidity and mortality can be significant. In a review of 29 cases, there was an overall three-year survival rate of 56%.⁶ It must be noted that 66% of these cases also involved fetal hydrops, and antenatal intrauterine interventions were performed in 38%. The presence of hydrops, large effusions, gestational age less than 34 weeks, and onset of pneumothorax within 12 hours of birth were found to be associated with an increased mortality rate. Of the survivors, most were asymptomatic at the time of childhood follow-up; however, 27% were found to have asthma in early infancy.⁶

Case

A 25-year-old, gravida 2 para 0-0-1-0, with a history of a first trimester spontaneous miscarriage, was referred to our Labor and Delivery at 36 0/7 weeks gestation with a newly-diagnosed large fetal right-pleural effusion, seen during a third trimester ultrasound for growth. There were no other abnormalities noted on the ultrasound, amniotic fluid was normal, and middle cerebral arterial peak velocity was 0.89 multiples of the median.

The patient was healthy without any medical co-morbidities. Pregnancy dating was established by an 8-week ultrasound, and she received regular prenatal care.

Her social history was unremarkable. Prenatal screening labs were normal. Her blood type was O positive, and antibody screen was negative. She had Non-Invasive Perinatal Screening (NIPS) for fetal aneuploidy, which was normal. There was a family history of Down Syndrome (sibling and cousin). She reported an upper respiratory illness about 1 week prior to presentation.

On exam, she was well-appearing with normal vital signs. The fetal nonstress test was reactive and reassuring. She was contracting without symptoms every 4 minutes. Her cervix was 1 cm dilated and uneffaced. There was no evidence of rupture of membranes or vaginal infection.

Ultrasound revealed a cephalic female fetus with an estimated fetal weight of 2993 grams (59%). Fetal heart rate and amniotic fluid volume were normal. She received a biophysical profile score of 8/8. There was forward flow throughout diastole in both umbilical arteries. A large right-pleural effusion was confirmed, as well as a possible Atrial Septal Defect (ASD) with an intracardiac echogenic focus. The rest of the anatomic survey was normal. Specifically, there was no evidence of extrathoracic anomalies or hydrops.

On Hospital Day 2, she was seen by the Neonatology and Pediatric Cardiology Teams, and underwent a fetal echocardiogram that showed a

right-pleural effusion, dilated superior vena cava and inferior vena cava, prominent coronary sinus ridge and Eustachian valve versus small right atrial mass, and possible dilated coronary sinus. Possible diagnoses were discussed with patient and a neonatal echocardiogram was recommended postnatally. She was discharged home with recommendations for weekly antenatal testing with her primary obstetrician and to return at 39 weeks for delivery.

She represented at 37 0/7 weeks gestation with worsening now bilateral pleural effusions, fetal hydrops, skin edema, ascites, and polyhydramnios. The fetal heart rate tracing was Category 2 with a baseline of 140, moderate variability, positive accelerations, and small spontaneous variable decelerations. There were asymptomatic contractions every 3-4 minutes. Cervical exam was unchanged. The decision was made to proceed with delivery via cesarean with fetal thoracentesis immediately prior to optimize postnatal resuscitation.

Fetal right thoracentesis was performed under ultrasound guidance (Figure 1) with removal of approximately 200 mL of clear, yellow pleural fluid. Cesarean delivery followed with delivery of a vigorous infant female weighing 3470 grams with Apgars of 7 and 9. There was clear amniotic fluid at the time of rupture, and neonatal cord blood arterial pH was 7.28 with a base deficit of 1.8.



Figure 1. Transverse view of the fetal thorax and spine (SP) with large right-pleural effusion (EF) and small, collapsed right-fetal lung (LU).

On initial exam, the infant was active with decreased, but audible breath sounds. Initial resuscitation in the operating room was with mask CPAP (Continuous Positive Airway Pressure). The neonate was noted to have edema over the right jawline, neck, abdomen, and back. There was no rash, petechiae, or jaundice. There were no obvious dysmorphic features. The infant quickly required increasing FiO₂ due to desaturations and was intubated shortly after birth. There was reaccumulation of right pleural effusion on chest X-ray, therefore, a chest tube was placed with a return of significant amount of blood-tinged fluid. This fluid was sent for cell count, glucose, protein, viral studies, and gram stain. Fluid was consistent with chyle, and was negative for bacteria or virus. Abdominal ultrasound showed a moderate amount of ascites and bilateral pleural effusions, but was otherwise normal.

The infant was initially started on total parenteral nutrition (TPN) and antibiotics. She was extubated successfully on the second Day of Life (DOL). Echocardiogram performed on the second day of life revealed a Patent Foramen Ovale versus an Atrial Septal Defect, a normal finding for an infant this age. The initial chest tube was self-removed on the fourth DOL; however, two subsequent chest tubes were placed on the fifth day of life for re-accumulation of right pleural fluid and right pneumothorax with associated respiratory decompensation.

The infant was slowly transitioned to full breast feeds on the third DOL. After the diagnosis of chylothorax was confirmed based on pleural fluid analysis, the infant was transitioned to formula containing a high amount of medium chain triglyceride oil with plans to transition to spun breastmilk as an outpatient. Drainage of the pleural space and antibiotics were discontinued after one week. The infant was discharged from the NICU (Neonatal Intensive Care Unit) in stable condition on DOL 16.

Given non-immune hydrops of otherwise unknown etiology, genetics consultation was requested and chromosome analysis revealed a normal 46, XX karyotype. CHG microarray identified a microduplication of uncertain significance on the long arm of chromosome 15 [15q13.3(32,037,769-32,509,926)x3].

Discussion

Here we report a case of a fetus with a unilateral pleural effusion first identified late in the third trimester that quickly progressed into hydrops. A fetal thoracentesis was performed immediately prior to delivery. The neonate was phenotypically normal, and there were no birth defects identified. The pleural fluid was consistent with chyle, and the neonate was diagnosed with Congenital Chylothorax with associated hydrops. Her hospital course was complicated by multiple chest tubes for pleural fluid re-accumulation and pneumothorax, as well as special feeding considerations secondary to chylothorax. She was discharged home from the NICU on DOL 16. Shortly after discharge, postnatal genetic testing identified a normal female karyotype, 46 XX, with a variant of uncertain significance on array CGH. There is no record of paternal genetic testing.

DNA copy number variants (CNVs) are changes in the amount of DNA in a particular genomic region. Although they arise through a different mechanism, they can be considered small segments of

chromosome aneuploidy. Similar to whole chromosome aneuploidy, phenotypic changes come about from alterations in gene dosage; too much in the case of duplications, and too little in the case of deletions.²⁷ Whereas whole chromosome aneuploidy arises from abnormalities of segregation during meiosis or mitosis, aberrant recombination between homologous chromosomes causes CNVs.

Genomic regions involving flanking low-copy repeats (LCRs) are particularly prone to CNVs through non-allelic homologous recombination (NAHR).¹⁴ The proximal region of chromosome 15 (15q11-q14) is one such unstable genomic region that contains many complex sets of LCRs, identified as BP1-BP6.¹² CNVs in this region include: deletions, duplications, triplications, inversions, translocations, and supernumerary derivative chromosome. As such, aberrations in this genomic region are common in the general population and are associated with variable pathogenicity, phenotypic, and clinical significance.

Deletions involving the proximal region of chromosome 15 are better described in the literature than the reciprocal duplications of the same region. Specifically, Sharp et al described a 15q13.3 Microdeletion Syndrome in 2008 that involves deletions within BP4-BP5, which encompasses the CHRNA7 gene.²⁰ The CHRNA7 gene encodes the alpha-7 nicotinic acetylcholine receptor, a synaptic ion channel protein, involved in mediating neuronal signal transmission and dopamine regulation. 15q13.3 Microdeletion Syndrome involves a spectrum of neuropsychiatric disorders including developmental delay/intellectual disability (DD/ID), epilepsy, autism, and schizophrenia.^{3,25}

Duplications in this genomic region are less well-understood. The estimated frequency of microduplications of 15q13.3 is common in the general population, and has been reported as 1 in 180 (0.6%).⁹ Recent case reports have shown possible associations between duplications of 15q13.3 and a variety of cognitive impairment and neuropsychiatric phenotypes, including attention hyperactivity disorder albeit with high variability of expressivity and reduced penetrance.^{23,25,27} After thorough review of the literature, there seems to be no association of CNVs involving 15q13.3 with fetal pleural effusion or hydrops.

It has been well-described in the literature that fetal pleural effusion, fetal hydrops, and Congenital Chylothorax are common perinatal findings in a class of genetic disorders called "RASopathies." These autosomal dominant disorders are caused by germline mutations, the genes involved in the RAS/mitogen activated protein kinase (MAPK) pathway, which plays a major role in cell cycle control and differentiation. Often, these mutations lead to abnormal or aberrant lymphatic development or drainage.²⁴

To date, there are over 10 known genes involved in the RAS/MAPK pathway (with more genes continuing to be discovered.), and thus, implicated in causing disease when mutated.²⁸ Perinatal abnormalities described in these disorders include: increased nuchal translucency, fetal hydrops, pleural effusion, chylothorax, and congenital cardiac defects. Phenotypic features of these disorders include: craniofacial, cardiac, cutaneous, musculoskeletal, and ocular abnormalities;



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short stature, a spectrum of neurocognitive impairment, and increased risk for malignancy. Noonan Syndrome is the most common of these disorders with an incidence of 1/1000-1/2500, but other disorders included in "Rasopathies" include: Neurofibromatosis Type 1, Costello Syndrome, Cardio-facio-cutaneous Syndrome, and Autoimmune Lymphoproliferative Syndrome.²⁴

This case highlights Neonatal Congenital Chylothorax identified in the third trimester and treated antenatally with fetal thoracentesis for improved neonatal resuscitation. Postnatal genetic testing was non-diagnostic. However, a microduplication that is associated with a spectrum of cognitive impairment and neuropsychiatric disorders was identified. If this case report is supported by others with similar molecular findings, perhaps the genetic etiology of fetal pleural effusion, fetal hydrops, and congenital chylothorax can be expanded beyond RAS/MAPK pathway genes.

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Psychosocial Support for Perinatal Substance Use Mothers and Their Newborns

By Cheryl A. Milford, EdS

The use of prescription pain relievers has increased significantly in the last 15 years, with 4.3 million people in the United States using opioid medications in 2014. While there will always be a place for the appropriate use of prescription pain relievers, the use of opioid medications as a substance of abuse has become a major public health concern.¹ Chronic Opioid Substance Use Disorder does not impact just the person using, but also their family, friends and community.¹ Use of opioids during the perinatal period is also on the rise. The Substance Abuse and Mental Health Services Administration noted in its 2016 literature review that maternal opioid use in the U.S. increased from 1.9 per 1000 births per year in 2000 to 5.63 per 1000 births per year in 2009. Not surprisingly, Neonatal Abstinence Syndrome increased as well, from 3.4 per 1000 hospital live births in 2009 to 5.8 per hospital live births in 2012.¹ Medication-assisted management and counseling are the current standards of treatment, but it is imperative that perinatal healthcare providers be aware of the psychosocial needs of mothers and their newborns in this population in order to effectively support maternal-infant attachment and bonding during the critical period surrounding birth and also to assist in providing needed resources for the mother and child.²

In 2015, the National Perinatal Association convened a national workgroup of professionals and parents to develop interdisciplinary, evidence-based recommendations for family-centered interventions and management of substance use disorder during pregnancy and the perinatal period. *The Workgroup on Perinatal Substance Use Disorder* is currently undertaking a comprehensive literature review in order to develop evidence-based recommendations for providing service to this high-risk population. In the context of the literature review, it has become apparent that consideration of the psychosocial needs for these mothers and their newborns has only become an emphasis in the last 5 years. Addressing these issues is essential to ongoing recovery and decreasing the risk of relapse.²

Women with substance use disorders have higher rates of childhood trauma, sexual assault, lack of education, poverty and mental illness than non-use women.³ Many of these factors began early in the lives of these women and are the lens through which they view the world.³ Substance use disorders in pregnant and postpartum women often lead to feelings of guilt and shame and fears about Child Protective Services (CPS) involvement.² All of these factors have the potential to impact the ability to transition to motherhood and can affect the attachment process for the mother-infant dyad.³

An understanding of Substance Use Disorder as not only a physiological disease, but as a behavioral disorder, is essential for providing health care to these women and their newborns.⁴ While medication is the foundation of the treatment protocol, counseling and the psychosocial aspects of treatment require professionals to assist women affected by substance use disorders in altering their behaviors. This includes supporting women in adjusting their thought processes, values and attitudes as well as changing her external milieu to develop behaviors, thoughts and attitudes that are incompatible with substance use behaviors.⁴ Treatment for substance use disorders requires not only medication and counseling, but also major lifestyle and behavioral changes to decrease the risk for relapse.⁴ Perinatal healthcare providers have an important role in encouraging and facilitating the intensive therapy protocols needed to support wellness in their interactions with pregnant and postpartum women affected by substance abuse disorder.³

The birth of the baby in this setting brings additional challenges. Neonatal Abstinence Syndrome (NAS) results in neonatal symptoms that can be barriers to interaction and attachment. Infant irritability, poor feeding and increased muscle tone are stressful and painful for mothers to observe.³ Mothers report feeling shame and incompetence when they cannot comfort or feed their babies.³ In addition to their own negative emotions, women in several studies reported that they felt stigmatized and treated with a negative bias by healthcare providers because of their substance use disorder.^{2, 3} These attitudes and behaviors have significant impact on the mother's view of herself and her ability to care for her infant.² If CPS involvement is mandated by the state, mothers have the additional fears and concerns of their infant being removed from their custody and placed in foster care.²

It is important to recognize that the strengths the pregnant or postpartum woman with Substance Use Disorder brings to treatment during her pregnancy and postpartum care are her love for her child and a strong motivation to be a good mother.³ This motivation can aid women in reaching out for treatment in spite of their fear, shame and guilt.³ Women with substance use disorder have reported that they viewed their pregnancy as giving their lives a higher meaning and acknowledged that a prerequisite to being a good mother was sobriety.³ Pregnancy and impending motherhood can be a stressful time for some women, but this time period can be even more stressful for women with substance use disorders and their psychosocial needs are often significantly increased. Every healthcare provider has a significant impact on how the woman views herself as a person and a mother.²

Addressing the Psychosocial Needs of Women with Substance Use Disorder and Their Newborns

The most important aspect of providing psychosocial support for women with substance use disorder and their newborns is that their health care professionals have a complete understanding about the nature of their physiological disease and behavioral disorder. Up-to-date education and training about substance use disorders will provide clinicians with the understanding and competence to engage in a positive, supportive relationship with mothers and their babies.² Encouraging positive and ongoing maternal-newborn attachment by supporting maternal and infant care together, can reduce shame, guilt and maternal self-doubt.² It is critically important for CPS professionals to receive such training with an emphasis on the resource and treatment needs of the dyad towards a goal of recovery and wellness. The dyad should be viewed in the context of public health approaches rather than a punitive or judgemental approach.² Health care providers are in a crucial role to

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educate the justice system and the general public on substance use disorder as a disease, not a choice.

At a foundational level, basic resources are essential to any mother-infant dyad. Accessing adequate housing, food, clothing and health care resources are often a significant challenge to women with substance use disorders. Perinatal social workers can assess each dyad's resource needs and assist the family in obtaining needed resources.² In addition, assessing physical and emotional safety for the dyad in their home environment is necessary. A safe environment is critical to the well being of both mother and baby and to development of a secure attachment.³ Perinatal social workers can aid mothers in obtaining a safe home for themselves and their children.³ They are also key players in the communication between mothers and health care providers. Perinatal social workers can facilitate the mother's understanding of the healthcare system, at the same time help healthcare providers understand the mother's life circumstances in the context of her environment.² Perinatal healthcare professionals offering psychosocial assistance to the pregnant woman and postpartum mother can decrease the psychosocial stressors of her substance use disorder, her resource limitations and her parenting concerns.³

Bedside professionals are key to educating and assisting mothers in learning how to care for their infants experiencing NAS in the hospital setting. Calming and feeding techniques can facilitate maternal feelings of confidence and competence. Discussing and modeling stress reduction behaviors and self-care can support pregnant women and postpartum mothers in their own wellness and secure attachment to their baby.³

Mothers in several studies reported great concerns about relapsing. Perinatal healthcare professionals can encourage and support mothers in continuing their substance use disorder treatment.^{2,3} Women are more open and vulnerable to education and interactions with their health care professionals during pregnancy and postpartum periods. Encouragement and praise for their recovery from their caregivers may have greater impact on maternal motivation and behavior during this time.³

Peer-to-peer support groups for pregnant and postpartum women may be helpful in decreasing feeling of isolation, shame and guilt.² In addition, perinatal healthcare professional groups can support other providers in engaging in supportive and positive caregiving practices.² Perinatal social workers or other trained mental health professionals can facilitate support groups and offer additional treatment services as needed.²

Several recent care provision approaches appear to support the psychosocial needs of this population more effectively. Providing obstetrical care, medication-assisted treatment and counseling in one center is being explored.⁵ Conversion to buprenorphine, prenatal care and weekly behavioral counseling are provided in the same center with highly trained substance use disorder specialists. The goal of such programs is ongoing recovery with maternal wellness and secure attachment of the maternal-infant dyad. Research is being conducted and such an approach appears to be both clinically appropriate and cost-effective.⁵ Postpartum hospital services are also being evaluated. Rooming-in for the mother-newborn dyad has been initiated in Canada with encouraging results. Having the mother be the infant's primary caregiver during the postpartum hospital stay encourages secure attachment. Mothers are taught how to comfort their infants, how to evaluate their symptoms of NAS and how to breastfeed. The study results indicated decreased requirements for pharmacologic treatment of NAS and decreased length of hospitalization.⁶ Approaches that utilize highly trained healthcare professionals and continuity of care have the potential to mitigate many of the psychosocial stressors for the pregnant woman and the maternal-infant dyad. Further research is required to determine the short- and long-term efficacy of these treatment approaches.

Summary

Perinatal substance use disorder has been increasing since the beginning of the twenty-first century.¹ Its impact on mothers, infants, families and communities is significant. Substance Use Disorder is both a physiological disease and a behavioral disorder. While medication is the basis for initiation of treatment, counseling and addressing psychosocial stressors are crucial to sustaining recovery.³ Perinatal health care providers are key in supporting pregnant and postpartum women in their recovery. Providers need education and training in caring for this population, decreasing stigmatization and negative caregiver attitudes in both the outpatient and hospital settings. Understanding the resource limitations, feelings of shame, guilt and fear, and motivation for recovery to become a competent mother are all skills that perinatal healthcare professionals must exhibit. Positive, non-judgmental and supportive care encourages pregnant and postpartum women to feel confident and competent in their transition to motherhood.² Developing a relationship of trust with each woman, acknowledging her disease and supporting her work in recovery have a great impact during this wondrous and stressful time in her life.³ It is clear from the literature that judgmental and negative attitudes on the part of perinatal

Upcoming Medical Meetings

Specialty Review in Neonatology
Feb. 21-26, 2017; Orlando, FL USA
www.specialtyreview.com

NEO - The Conference for Neonatology
Feb. 23-26, 2017; Orlando, FL USA
www.neoconference.com

30th Annual Gravens Conference on the Physical and Developmental Environment of the High Risk Infant, in Collaboration with the March of Dimes
Mar. 1-4, 2017; Clearwater Beach, FL USA
www.tinyurl.com/GravensConference

NPA 38th Annual Conference - Perinatal Mental Health: Advocating for the Health and Wellbeing of Families
Mar. 9-11, 2017; Atlanta, GA USA
www.nationalperinatal.org

NeoHeart: Cardiovascular Management of the Neonate
Mar. 22-25, 2017; San Diego, CA USA
choc.org/neoheart

Annual Convention of the American Institute of Ultrasound in Medicine
Mar. 25 - 29, 2017; Orlando, FL USA
www.aium.org/annualConvention

2017 Workshop on Perinatal Practice Strategies
Mar. 31 - April 2, 2017; Scottsdale, AZ USA
<https://shop.aap.org/2017-workshop-on-perinatal-practice-strategies/>

14th National Advanced Practice Neonatal Nurses Conference
Apr. 19-27, 2017; Waikiki Beach, HI USA
www.academyonline.org

1st World Congress on Maternal Fetal Neonatal Medicine
Apr. 23 - 26, 2017; London, UK
www.worldmfm.eu

healthcare providers can both traumatize and alienate women from their caregivers and children.³ It is an essential aspect of our practice to provide care to all women and their infants that is compassionate, that nurtures wellness and is free of judgmental attitudes.³ Such practice has the potential to decrease



Support, Advocacy and Research



Dr. Alan Spitzer Joins the Board of Graham's Foundation

Alan R. Spitzer, M.D., a prominent neonatal researcher and academician, recently accepted a position on the Graham's Foundation board. Dr. Spitzer was a practicing neonatologist for more than 25 years, and served as Chief of the Division of Neonatology at the State University of New York at Stony Brook, and as Professor of Pediatrics at Stony Brook. Most recently, he oversaw clinical research as well as continuing medical education and clinical quality initiatives at the Pediatrix Medical Group. He also authored the popular neonatal textbook, *Intensive Care of the Fetus and Newborn*, and collaborated on more than 200 peer-reviewed research articles and textbook chapters

Dr. Spitzer's experience, both hands-on and in the research space will be a valuable asset to Graham's Foundation, which has delivered support, advocacy and research to improve outcomes for preemies and their families since 2009. With help from advisors and thought leaders like Dr. Spitzer, Graham's Foundation has not only supported tens of thousands of families affected by premature birth, but has also given those families a stronger voice in the evolution of neonatal care.

Dr. Spitzer's appointment to the board will be formally announced at the foundation's upcoming 'Tinis for Preemies fundraiser on March 3 at the Carranor Hunt & Polo Club in Perrysburg, OH.

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psychosocial stressors and facilitate secure attachment for women with substance use disorder and their newborns.

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Neonatologist and Neonatal ARNP Opportunities in Miami, Florida

Nicklaus Children's Hospital (formerly Miami Children's Hospital), a 289-bed freestanding children's hospital and Level III trauma center, and Pediatric Specialists of America (PSA), the physician-led multispecialty group practice of Miami Children's Health System, have two exceptional opportunities for a board-certified or board-eligible (BC/BE) fellowship-trained neonatologist, and a neonatal ARNP with at least three years of experience.

Both positions will be part of a comprehensive high-risk fetal and newborn medicine program to care for healthy mothers who are expecting a baby with complex medical issues. The labor and delivery unit, consisting of 16 private rooms, is located at The Miami Medical Center (TMMC). Opened as a joint venture between Miami Children's Health System and other collaborators, TMMC is a hospital with 67 luxury suites located near West Miami that offers world-class healthcare services, personalized hospitality and premium amenities. The unit is currently supported by three physicians and five ARNPs, with a projected volume of more than 500 deliveries for 2017.

The BC/BE neonatologist will be responsible for attending deliveries, resuscitating and stabilizing newborns in the delivery room, as well as provide leadership, oversight and supervision in the Level I nursery. The neonatologist would also be operationally involved in the 10-bed, high-risk delivery unit at Nicklaus Children's Hospital. The neonatal ARNP candidate should possess at least three years of experience and be proficient in newborn resuscitation, including neonatal intubation, umbilical line placement and peripheral cannulation, lumbar punctures and circumcision. Both roles are based in Miami and offer salaries that are competitive and commensurate with experience.

Nicklaus Children's neonatology program is consecutively ranked among the best in the nation by U.S. News & World Report. The 40-bed Level III and Level II neonatal intensive care unit (NICU) was the first of its kind in South Florida and receives referrals of the most critically ill neonates from hospitals throughout Florida, Latin America and the Caribbean.

Founded in 1950, the rebranded Nicklaus Children's Hospital is renowned for excellence in all aspects of pediatric medicine and has numerous subspecialty programs that are routinely ranked among the best in the nation. It is also home to the largest pediatric teaching program in the southeastern U.S. Many of our physicians have trained or worked at other leading medical institutions. Join a phenomenal team that brings lifelong health and hope to children and their families through innovative and compassionate care.

Nicklaus Children's Hospital is located in Miami, Florida, and offers all of the advantages of a tropical, diverse, metropolitan community. Enjoy abundant sunshine and warm weather year-round with easy access to beaches, golf courses, two international airports and sporting events such as the Miami Dolphins, Heat, Marlins and Panthers.

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Medical News, Products & Information

Compiled and Reviewed by Tony Carlson, Senior Editor

Emergency Video Telemedicine Positively Impacts Newborn Resuscitation



Newswise — Approximately 10% of newborns require help breathing after birth, and 1 in 1,000 newborns require more intensive resuscitation measures. These infrequent, high-risk deliveries may present challenges to community hospitals less familiar with advanced newborn resuscitation interventions. Telemedicine consultations are a good option to help meet these challenges and positively impact patient care, according to a study published in *Mayo Clinic Proceedings*.

“Following a complicated delivery, a newborn’s outcome is associated with the quality of care provided during the first minutes of life,” says Jennifer Fang, MD, a Mayo Clinic fellow in Neonatal-Perinatal Medicine and one of the study’s authors. “For this reason, it is critical to understand how Telemedicine can be used to positively impact those outcomes.”

During a 20-month study, Mayo Clinic’s Division of Neonatal Medicine worked with six health system sites to provide newborn telemedicine consultations. During the study, 84 telemedicine consultations were conducted.

“The enhanced access to neonatologists, who could remotely assess the newborn and guide the local care team through the resuscitation, allowed one-third of the babies to stay with their families in the local hospital,” says Dr. Fang. “This allowed the patients to receive the correct level of care in the right location — increasing the value of care. Also, the potential cost savings can be substantial.”

This study also looked at how the local care team and neonatologist collaborated. “Other research has shown that teamwork and communication are critical during neonatal emergencies. We wanted to assess how telemedicine affected teamwork and communication,” according to Dr. Fang.

Providers responded positively to surveys that assessed teamwork and the impact of the telemedicine consult on patient safety and quality of care. “These results speak to the acceptability and

clinical impact of this type of telemedicine project in community hospitals,” says Dr. Fang.

In addition to Dr. Fang, the paper’s co-authors are:

- Christopher Collura, MD, Mayo Clinic
- Robert V. Johnson, MD, Mayo Clinic
- Garth Asay, MD, Mayo Clinic
- William Carey, MD, Mayo Clinic
- Douglas Derleth, MD, Mayo Clinic
- Tara Lang, MD, Gundersen Health System
- Beth Kreofsky, Mayo Clinic
- Christopher Colby, MD, Mayo Clinic

Mayo Clinic Proceedings is a monthly peer-reviewed medical journal that publishes original articles and reviews dealing with clinical and laboratory medicine, clinical research, basic science research and clinical epidemiology. *Mayo Clinic Proceedings* is sponsored by the Mayo Foundation for Medical Education and Research as part of its commitment to physician education. It publishes submissions from authors worldwide. The journal has been published for more than 80 years and has a circulation of 130,000. Articles are available at mayoclinicproceedings.org.

Controlling Risk of C. Diff Saves Lives, Prevents Infection and Reduces Health Care Costs

Newswise — The constant fear of having an embarrassing bathroom accident paralyzed Judy Post. Mental, physical and emotional stress consumed her. She wondered if her life would ever return to normal.

“It was very difficult on me. I kept thinking nothing was going to help me,” Post said. “I was really scared.”

She was diagnosed with a *Clostridium difficile* infection and was treated for it with vancomycin and got better. However, a few days after she stopped the vancomycin, the diarrhea would come back as the infection relapsed. After talking with several doctors she was directed to Matthew Sims, MD, PhD, Director of Infectious Disease Research at Beaumont Hospital, Royal Oak, who enrolled her in a research study and broke the cycle of relapses.

“I had no idea what *C. difficile* was. My family members hadn’t heard of it, either,” she said.

C. difficile is an infection that causes life-threatening diarrhea. According to an article published in the *New England Journal of Medicine*, nearly 30,000 people die from *C. difficile* every year in the United States. Doctors say more than 450,000 are battling the infection. Twelve percent of all hospital-acquired infections are *C. difficile*.

The Agency for Healthcare Research and Quality recently awarded Dr. Sims with a \$2.4 million grant to study a theory that could prevent thousands of *C. difficile* infections and deaths all over the world. This is one of the largest grants Beaumont Health has ever received.

Some people carry *C. diff* spores in their colon, but don’t get sick because their good bacteria keeps it in check. However, when *C. diff* carriers take antibiotics to treat an infection elsewhere in the body, those antibiotics can also kill off the good bacteria.

When good bacteria dies, this removes the restraints on the *C. diff* and allows it to grow out of control, which causes the person to become sick.

Dr. Sims believes oral vancomycin can keep the *C. diff* in check when the good bacteria is killed by other antibiotics and should prevent the patient from becoming sick. Participants in the study will be given vancomycin or a placebo along with the antibiotics treating the original infection.

"Treatment with oral vancomycin will not kill the spores. It will not cure people. Patients will still carry the spores in their body. However, the drug should prevent those spores from turning into a full blown *C. difficile* infection, holding them at bay like the good bacteria would have, and thus prevent the patient from becoming sick," Dr. Sims said.

The StoP CDI study will test this idea in a randomized, double-blinded, placebo-controlled trial. If successful in demonstrating that vancomycin can prevent the disease, the research could save thousands of lives, stop tens of thousands of infections, and save millions of health care dollars.

Post is not part of the StoP CDI study, but she says the research study she participated in with Dr. Sims was like a miracle that changed her life and she's eager to see what the new study will find.

"Every day, I become more positive about my life. I still carry a bottle of vancomycin with me, just in case I might need it," Post said.

Dr. Barbara Stonestreet Receives Additional Funding to Evaluate Treatment Strategies for Perinatal Brain Injury

Researcher from Women & Infants Hospital receives grant from Eunice Kennedy Shriver National Institute of Child Health and Human Development.

Barbara Stonestreet, MD, a Neonatal-Perinatal specialist at Women & Infants Hospital of Rhode Island, a Care New England hospital, and Professor of Pediatrics at The Warren Alpert Medical School of Brown University, has received a five-year, nearly \$2.8 million grant from the Eunice Kennedy Shriver National Institute of Child Health and Human Development for her research into determining the most effective strategies for the treatment of perinatal brain injury in full-term and premature infants. Last month it was announced that Dr. Stonestreet received two two-year grants totaling \$881,100 from the National Institutes of Health for this research.

Perinatal brain injury often results in severe developmental disabilities, including neurodevelopmental delay and cerebral palsy. The resulting neurodevelopmental disabilities can place a lifelong burden on parents and society.

Dr. Stonestreet explained, "We are looking at a novel approach to prevent and treat perinatal brain injury by targeting brain blood vessels with antibodies to preserve their function, to protect the brain, and to improve outcomes. This study has significant translational potential to provide new insights into novel therapies to prevent brain injury in the human fetus and/or premature and full-term infant."

Uterine Microbiota Play a Key Role in Implantation and Pregnancy Success in In Vitro Fertilization

Endometrial microbiota (bacteria in the uterine cavity) play an important role in determining whether women are able to get pregnant via in vitro fertilization (IVF), according to a new study

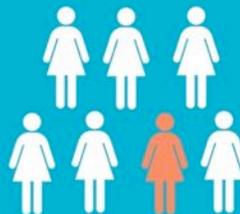
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published in the *American Journal of Obstetrics and Gynecology*.

"The uterine cavity has been considered sterile," explained lead investigator Carlos Simón, MD, PhD, of Igenomix Spain, and the Department of Obstetrics and Gynecology of the University of Valencia, Spain. "Our team sought to test the existence of endometrial microbiota that differs from that of the vagina. We assessed its hormonal regulation and analyzed the impact of the endometrial microbial community on reproductive outcome in patients undergoing IVF."

To identify the existence of an endometrial microbiota, investigators evaluated paired samples of endometrial and vaginal fluid obtained from 13 fertile women in pre-receptive and receptive phases within the same menstrual cycle. To investigate the hormonal regulation of the endometrial microbiota during the acquisition of endometrial receptivity, endometrial fluid was collected at pre-receptive and receptive phases within the same cycle from 22 fertile women. Finally, the reproductive impact of an altered endometrial microbiota in endometrial fluid was assessed by implantation, ongoing pregnancy, and live birth rates in 35 infertile patients undergoing IVF with a receptive endometrium diagnosed using the endometrial receptivity array based on gene expression.

When paired endometrial fluid and vaginal fluid samples from the same patients were examined, different bacterial communities were detected between the two sites in some women. The microbiota in the endometrial fluid was classified as Lactobacillus-dominated or non-Lactobacillus-dominated microbiota. There was no evidence that steroid hormones played a role in determining the composition of the microbial community in the endometrium. On the other hand, women with a non-Lactobacillus-dominated microbiota and a receptive endometrium had a significantly lower rate of implantation, pregnancy, and live birth than patients with a Lactobacillus-dominated microbiota.

In an accompanying commentary, Linda C. Giudice, MD, PhD, Distinguished Professor and Reproductive Endocrinologist at the University of California San Francisco, noted that reproductive success is clearly not solely defined by endometrial histology and gene expression. The ongoing revolution in technology, multiple -omics, and multidimensional data analysis has opened the window of implantation to a greater level of scrutiny. It is time to investigate the endometrial microbiome and expand research to its virome, fungome, epigenome, and metabolome, she wrote.

Putting the significance of this study into perspective, Roberto Romero, MD, DMedSci, Chief of the Perinatology Research Branch of NICHD/NIH and Editor-in-Chief for Obstetrics of the *American Journal of Obstetrics and Gynecology*, commented that "the endometrial cavity is not sterile and normally contains bacteria; however, whether bacteria within the cavity play a role in successful reproduction has been unknown to this point. The pioneering work of the team of Professor Simón now shows, for the first time, that colonization of the uterine cavity with some bacteria (non Lactobacillus-dominated) affects the success of in vitro fertilization, pregnancy rates, and live births. This brings hope that diagnostic tests to examine the microbial composition of the uterine cavity may be valuable in assessing the likelihood of success of IVF. Moreover, it raises the question of whether targeted treatment with antimicrobial agents or probiotics may be useful in

MEDICAL MEETING PROFILE

AAP 2017 Workshop on Perinatal Practice Strategies

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- Create a professional network to enhance career development
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- Explain basic quality improvement methodologies, identify opportunities for improvement, and apply evidence-based change

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Contributing Faculty: Wanda Barfield, MD, MPH, FAAP; Karen Puopolo, MD, PhD, FAAP; Ann R. Stark, MD, FAAP; John A. F. Zupancic, MD, ScD, FAAP

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improving reproductive success, and suggests that successful reproduction may depend on a host-microbial relationship in the endometrial cavity, unknown before this time."

In addition to Igenomix and Valencia University, Lifesequencing and Biopolis (Scientific Park of Valencia University) contributed to this study. Endometrial samples were obtained from patients from IVI Valencia.

Vitamin D Status in Newborns and Risk of MS in Later Life

Newswise – Babies born with low levels of Vitamin D may be more likely to develop Multiple Sclerosis (MS) later in life than babies with higher levels of Vitamin D, according to a study published in the November 30th, 2016, online issue of *Neurology*[®], the medical journal of the American Academy of Neurology.

"More research is needed to confirm these results, but our results may provide important information to the ongoing debate about Vitamin D for pregnant women," said study author Nete Munk Nielsen, MD, MSc, PhD, of the State Serum Institute in Copenhagen, Denmark.

In Denmark, dried blood spots samples from newborn screening tests are stored in the Danish National Biobank. Researchers identified everyone in Denmark who was born since April 30, 1981, had onset of MS by 2012 and whose dried blood spots samples were included in the biobank. The blood from those 521 people was then compared to that of 972 people of the same sex and birthday who did not have MS. In this study, newborns with levels of Vitamin D less than 30 nanomoles per liter (nmol/L) were considered born with deficient levels. Levels of 30 to less than 50 nmol/L were considered insufficient and levels higher than or equal to 50 nmol/L were considered sufficient.

The study participants were divided into five groups based on Vitamin D level, with the bottom group having levels of less than 21 nmol/L and the top group with levels higher than or equal to 49 nmol/L. There were 136 people with MS and 193 people without MS in the bottom group. In the top group, there were 89 people with MS and 198 people without the disease. Those in the top group appeared to be 47% less likely to develop MS later in life than those in the bottom group.

Nielsen emphasizes that the study does not prove that increasing Vitamin D levels reduces the risk of MS.

The study has several limitations. Dried blood spots samples were only available for Vitamin D analysis for 67% of people with MS born during the time period. Vitamin D levels were based on one measurement. Study participants were 30 years old or younger, so the study does not include people who developed MS at an older age. In addition, the Danish population is predominantly white, so the results may not be generalizable to other populations. Furthermore, it cannot be excluded that this apparent beneficial effect could be mediated through other factors in later life such as Vitamin D levels, in which case a possible maternal Vitamin D supplementation would not reduce the MS risk in the offspring.

Reader's Comments

We encourage comments from our readers on articles they have read in *Neonatology Today*, and when given permission, we publish them.

The following was a comment from a reader on our lead article in our January 2017 issue, "Are IVF Doctors Exempt from the Hippocratic Oath?" by Janet Farrell Leontiou, PhD. You may read this issue at: www.neonatologytoday.net/newsletters/nt-jan17.pdf

"I, too, have concerns over the non-regulation of the fertility business. As a neonatologist, I am well-aware of the risks of multiples. The NICUs are filled with multiples.

I believe some of the problem is the desperation the couples have in trying to conceive. They may actually be told the risks, but feel desperate when conservative approaches have not worked. Some is a cultural view that twins, etc. are to be wished for. But I think the OB and fertility specialists have a responsibility to refuse requests for multiple embryo implants.

"...I think the OB and fertility specialists have a responsibility to refuse requests for multiple embryo implants."

Unfortunately, the media encourages the opposite, by featuring shows about families with multiples, and also families trying to conceive (couples calmly sitting there and discussing the benefit of implanting two or three embryos). I have also cared for multiple families that had one or two embryos split in utero to become twins, triplets etc., which may be related to the fertility medications the mom's take."

~ Ann Hilmo, MD



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Sources of vitamin D are diet, supplements and the sun. Dietary Vitamin D is primarily found in fatty fish such as salmon or mackerel. Levels of Vitamin D should be within the recommended levels, neither too low nor too high.

The study was supported by the Danish Society of Multiple Sclerosis, Aase & Ejnar Danielsen's Foundation, the U.S. National Institutes of Health and U.S. National Multiple Sclerosis Society.

The American Academy of Neurology is the world's largest association of neurologists and neuroscience professionals, with 30,000 members. The AAN is dedicated to promoting the highest quality patient-centered neurologic care. A neurologist is a doctor with specialized training in diagnosing, treating and managing disorders of the brain and nervous system such as Alzheimer's disease, stroke, migraine, multiple sclerosis, concussion, Parkinson's disease and epilepsy.

For more information about the American Academy of Neurology, visit www.aan.com.

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The National Perinatal Association (NPA) is an interdisciplinary organization that gives voice to the needs of parents, babies and families and all those interested in their health and wellbeing. Within NPA, parents and professionals work together to create positive change in perinatal care through education, parent programs, professional guidelines and events.

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3 BIG THINGS



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In nearly 20 years of successfully matching great physicians with great opportunities, I've learned that the right physician placement depends on three primary factors – location, work life and money!

LOCATION: Believe it or not, location drives most physician job opportunity decisions, but people often end up in the wrong places for the wrong reasons – the placement doesn't last and they must start their search all over again after a year or so. Conversely, often the best locations are places that people rarely think of, but which offer the lifestyle and family considerations that are at the core of what people are truly looking for.

WORK LIFE: Work life is arguably the most complex consideration to evaluate. Do you like the people you are (or will be) working with? Do they inspire you to do your best? Does the organization appreciate you and your contribution? Are you happy there? Do you look forward to starting work each day?

MONEY: Contrary to popular belief, money should never be the primary consideration. Money is always important and if it isn't sufficient it will kill the deal – but money is too often used by employers to mask weakness in other areas of consideration. That might be alright if it offsets location, for example - but money alone is a poor trade-off for the ongoing misery of a bad work life.

Of course, this is just a summary of these three considerations – there is more to it as you drill down on each of these areas and evaluate opportunities. If you would like some personalized help finding a great physician practice, please contact me at mike@hathawayhealthcare.com or 954-603-1192.

I look forward to helping you!

Sincerely,

Mike Hathaway

Hathaway Healthcare Executives

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