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## Reactive Ductus Arteriosus in a Nineteen-Month-Old Patient

By Maria C. Yates, MD; Nischal K. Gautam, MD; P. Syamasundar Rao, MD

### Introduction

A hemodynamically-significant Patent Ductus Arteriosus (PDA) may be seen in up to 8 per 1000 live births of preterm infants.<sup>1</sup> Increased survival of preterm infants has resulted in the need for transcatheter closure for PDA, reviewed elsewhere.<sup>2-7</sup> Ductal spasm during cardiac catheterization and angiographic study may lead to inappropriate device selection and the potential for device embolization and procedure failure. Here we present a case of a reactive ductus in a 19-month-old female which resulted in device embolization.

### Case Report

A 19-month-old female was referred to us for consideration of transcatheter occlusion of PDA. She was born prematurely at approximately 32 weeks of gestation. She was discharged home from the Neonatal Intensive Care Unit (NICU)

at 2 months of age. She was followed by her primary pediatric cardiologist with a diagnosis of a moderate-sized PDA with left-to-right shunt. Parents reported no cardiac symptomatology and she was on no cardiac medications. At a routine follow-up visit with her primary pediatric cardiologist at 17 months of age, an echocardiogram revealed the patient had a mild left atrial and left ventricular enlargement, resulting in referral for transcatheter occlusion. Our evaluation revealed a Grade III/VI continuous machinery murmur typical for PDA, no signs of heart failure, and mild enlargement of the left atrium and left ventricle; an echocardiographic study displayed a moderate-sized ductus (Figure 1A and B). We agreed with primary cardiologist's diagnosis of PDA and the recommendation for transcatheter occlusion.

At age 19 months, cardiac catheterization and selective cineangiography were performed with intent to transcatheter occlude the ductus. On the morning of the procedure, a Grade III/VI continuous murmur of PDA was heard on

Table. Hemodynamic Data (All data were obtained while the patient was in room air)

Site	Prior to Ductal Pressures mmHg	Occlusion O <sub>2</sub> Saturation (%)	After Ductal Pressures mmHg	Occlusion O <sub>2</sub> Saturation (%)
Superior Vena Cava		72		
Right Atrium	m = 6	72	m = 5	
Right Ventricle	30/7	72	29/6	76
Main Pulmonary Artery	29/19, m=24	86	29/11, m = 20	76
Right Pulmonary Artery	25/13, m=17	78		
Left Pulmonary Artery	25/13, m=17	82		
Left Ventricle	90/6	96		
Ascending Aorta	90/55, m=75	96	88/50, m = 70	96
Descending Aorta	90/55, m=75	96	87/50, m = 70	

m, mean; O<sub>2</sub>, oxygen



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auscultation. The parents informed us that the patient may have a latex allergy. Therefore, diphenhydramine 10 mg (1.2mg/kg) was administered intravenously immediately prior to the procedure. Other medications used during the general endotracheal anesthesia included: fentanyl, rocuronium and inhaled sevoflurane. Right-and-left heart catheterization was performed percutaneously, hemodynamic data recorded and an aortic arch cineangiogram was obtained. Hemodynamic data revealed right heart pressures at the upper limits of normal and a significant left-to-right shunt with a Qp:Qs of 1.5:1 (Table). However, angiography revealed a very small

ductus, measuring less than 1mm in diameter (Figure 2). Based on the angiographic appearance, a 5-mm loop, 6-cm long Gianturco coil was selected for occlusion of the PDA. The coil was deployed across the PDA in a manner described in our previous publication.<sup>3,7-9</sup> However, the coil embolized into a small distal branch of the left pulmonary artery, requiring transcatheter retrieval. The PDA was then successfully closed with a 6/4 Amplatzer Duct Occluder (Figure 3A & B). Post device implantation angiography (Figure 3B) and O<sub>2</sub> saturation data (Table) revealed no residual shunt. Echocardiography the

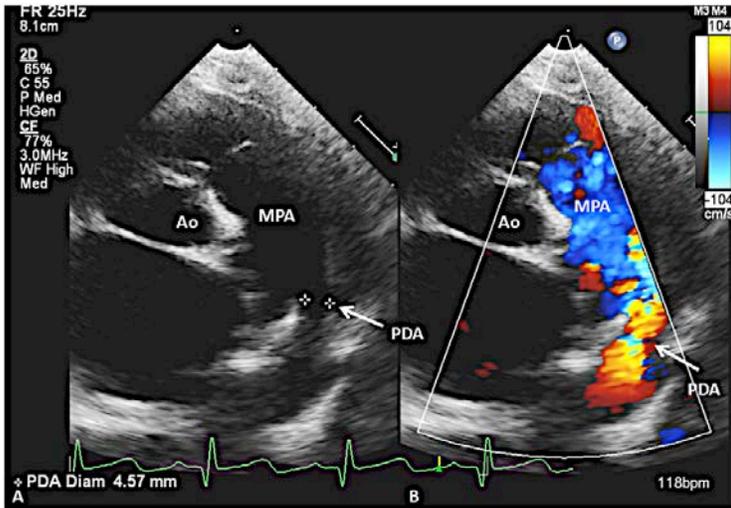


Figure 1. Selected video frames from precordial short axis views demonstrating a patent ductus arteriosus (PDA); 2D measurement of the minimal ductal diameter (A) with left to right shunt by color Doppler (B) are shown. AO, aorta; MPA, main pulmonary artery.

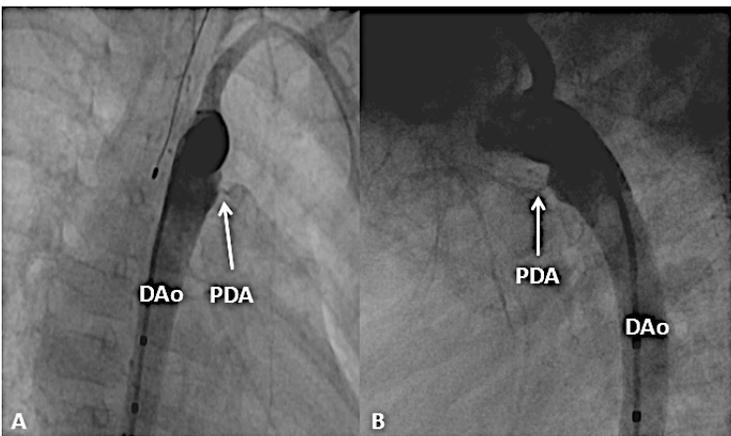


Figure 2. Selected aortic arch cineangiographic frames in right anterior oblique (A) and straight lateral (B) views demonstrating an extremely small (arrows in A and B) Patent Ductus Arteriosus (PDA). DAo, descending aorta.

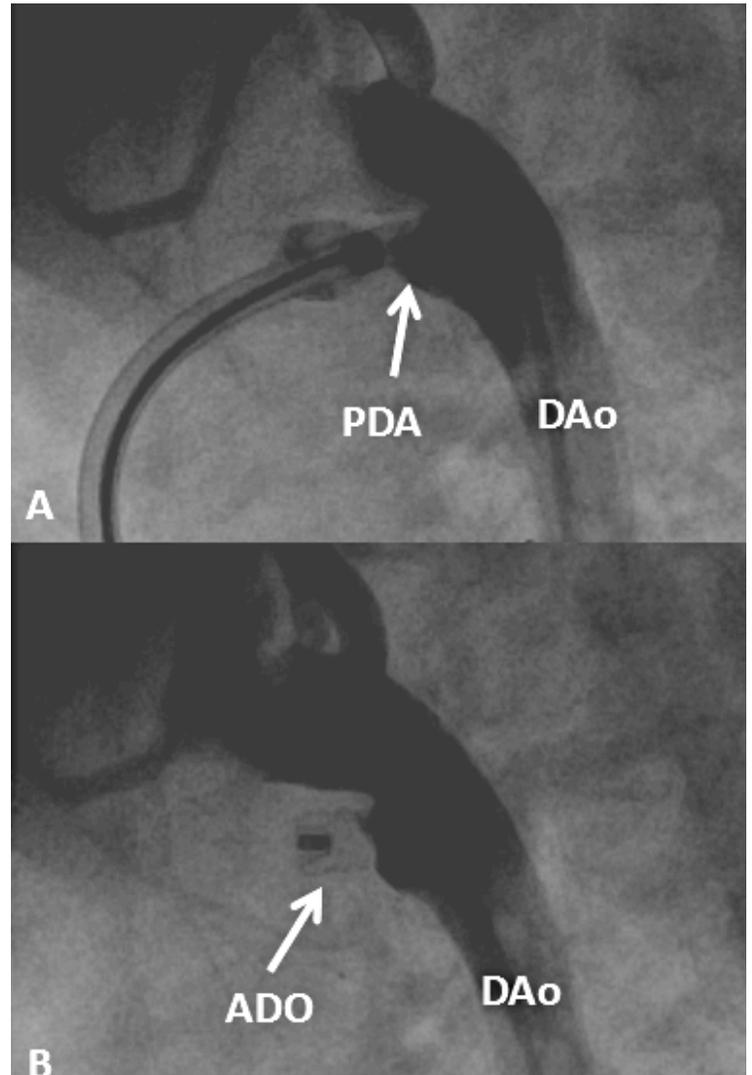


Figure 3. Selected aortic arch cineangiographic frames in straight lateral view demonstrating a moderate-sized Patent Ductus Arteriosus (PDA) in (A) prior to occlusion of the PDA and complete closure without residual shunt (B) following Amplatzer Duct Occluder (ADO) device closure. DAo, descending aorta.



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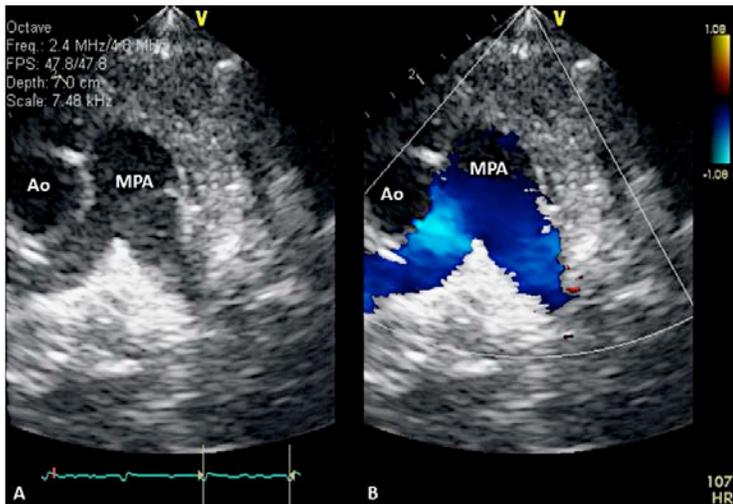


Figure 4. Selected video frames from precordial short axis views of an echocardiogram performed on the day following ductal closure demonstrating no residual shunt. AO, aorta; MPA, main pulmonary artery.

next morning revealed no residual shunting across the ductus arteriosus (Figure 4).

**Discussion**

Here we present a case of a hemodynamically-significant ductus arteriosus based on echocardiographic findings (Figure 1) and oxygen saturation data (Table) which on angiography was a very narrow ductus (Figure 2). The ampulla, however, was of good size. The data are indicative of intra-procedural ductal spasm, although the ductus was not crossed prior to angiography. However, inadvertent stimulation of the ductus while catheterizing right-and-left branch pulmonary arteries cannot be excluded. Because of the extremely small size of the PDA, we elected to use Gianturco coil for occlusion of PDA which spontaneously dislodged, requiring transcatheter retrieval. Subsequently, successful occlusion with an Amplatzer Duct Occluder was performed (Figures 3 & 4). It is not clear whether the ductal constriction that spontaneously occurred was secondary to inadvertent catheter stimulation or related to drugs administered immediately prior to or during the procedure.

**Literature Review and Potential Causes**

Prior reports suggesting reactive ducti with spasm of the ductal musculature have invoked: relative calmness (reopened by excitement),<sup>10</sup> ductal constriction in a formerly premature infant<sup>11</sup>, kinking of the ductus in upright position<sup>12</sup> and former prematurity<sup>13,14</sup> as contributory factors. Presence of a large proximal shunt<sup>15</sup> has also been suggested as a reason for

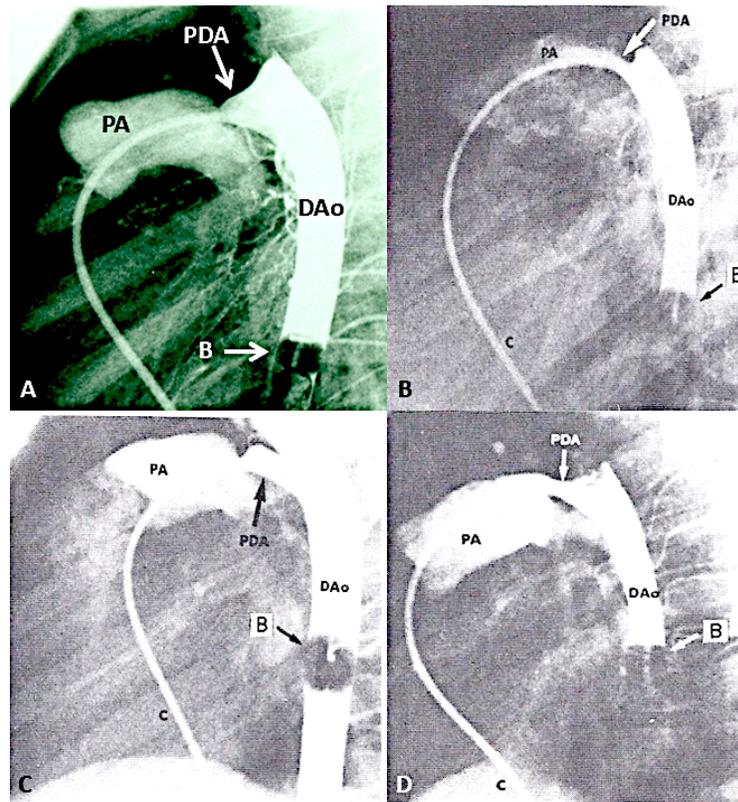


Figure 5. Balloon (B) occlusion aortography demonstrates good opacification of Patent Ductus Arteriosus (PDA) in four different patients. C, catheter; DAo, descending aorta; PA, pulmonary artery.

non-opacification of a ductus on angiography. Prematurity appears to be the predominant associated abnormality in the vast majority of the cases reported thus far,<sup>10,11,13,14</sup> including the present case.

**Prematurity**

Normal postnatal closure of the ductus arteriosus occurs in two phases: functional and anatomical closure.<sup>1,16-18</sup> Functional closure typically occurs within hours of birth in full-term infants, and is characterized, in part, by cellular migration of the medial smooth muscle within the ductus, which results in the intima protruding into the lumen of the ductus and functional closure. Anatomic closure is completed within 2-3 weeks and consists of necrosis of the ductal tissue and connective tissue formation to form the ligamentum arteriosum.<sup>1,16-19</sup> Disruption of this process can be caused by prematurity, lung disease, sepsis, hypoxia, or other stress-induced factors. In the premature infant the effect of the factors that lead to ductal occlusion may be blunted.<sup>20,21</sup> The mechanism by which such altered ductal muscle constriction takes place may be related to persistence of



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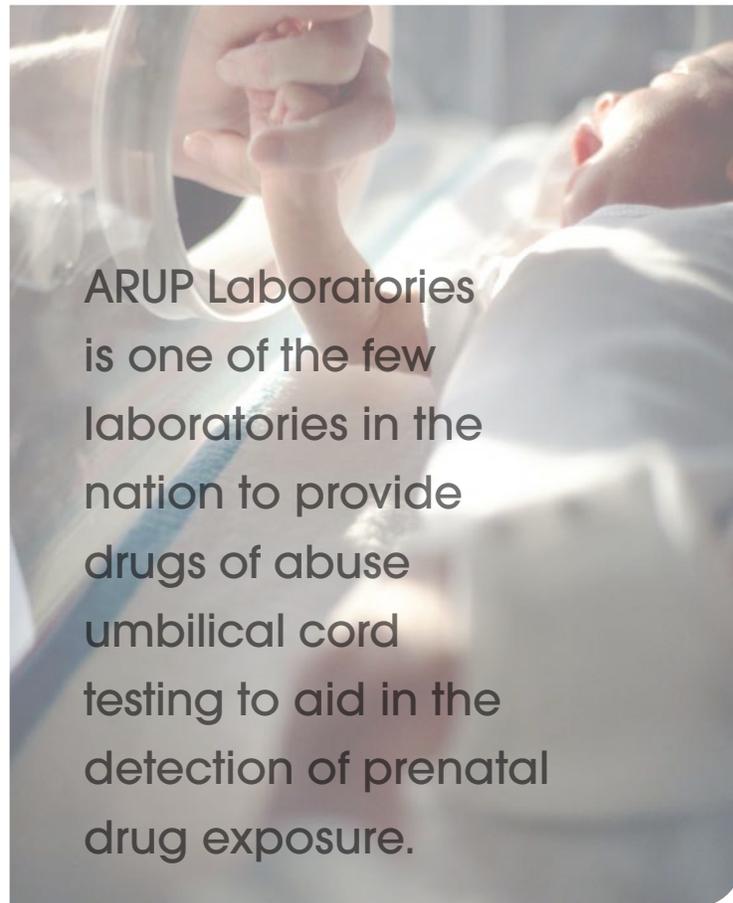
biochemical profiles of fetal ductal smooth muscle cells in the premature<sup>21,22</sup> and of vasomotion.<sup>23,24</sup> However, it is not established that such abnormalities persist into late infancy. The ductal reactivity demonstrated in our case, as well those of Shapiro,<sup>10</sup> DuBrow,<sup>11</sup> Lozier<sup>13</sup> and Batlivala<sup>14</sup> and their colleagues, would indicate the presence of ductal muscular reactivity way beyond the neonatal period, into late and even past infancy.

### **Drugs and Pharmacologic Agents Producing Ductal Constriction.**

The ductus is known to be reactive in response to multiple medications, including: prostaglandins, oxygen, catecholamines, bradykinin, acetylcholine and other kinins.<sup>25</sup> Nonsteroidal anti-inflammatory drugs such as indomethacin and ibuprofen have been administered for both prophylactic and therapeutic management of PDA; however, it is less effective after 14 Days of Life. Cotton and colleagues showed that cimetidine, a selective H<sub>2</sub> blocker, had vasoactive properties on the ductus arteriosus.<sup>26</sup> Their studies indicated that histamine may have both vasodilatory and vasoconstrictive effects upon the ductus arteriosus; however, in their study the patients were receiving long-term cimetidine, but more importantly, the observation in their study was ductal patency, not ductal constriction. The proposed mechanism for the observed association between cimetidine and PDA in preterm infants is via a cytochrome P450 (CYP) mechanism. Multiple CYPs were expressed within the ductus arteriosus, however the study was limited to specimens from mice. Diphenhydramine is metabolized via CYP pathways, but it is unknown if this mechanism would be involved in ductal vasoreactivity or if a single intravenous dose of diphenhydramine in the setting of general anesthesia would have any significant vasoactive effect. We were unable to identify any cases in the literature reporting ductal constriction secondary to diphenhydramine.

### **Prevalence**

The prevalence of clinically-identified reactive ductus appears low. This is the only case the senior author has witnessed among nearly 330 consecutive cases of transcatheter closure of PDAs (50 button device closures,<sup>27,28 80</sup> published<sup>29</sup> and unpublished Gianturco coil occlusions and 200 published<sup>30</sup> and unpublished Amplatzer Duct Occluder device deployments) that the senior author was involved with, giving a prevalence of 0.3%. However, Batlivala and his associates<sup>14</sup> found seven cases out of 331, giving a prevalence of 2.1%; much greater than that seen in our experience. The true incidence is probably somewhere in between these two figures. However, there are no data on what percentage of formerly premature babies will have reactive PDAs.



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## Therapeutic implications

Medium- and large-sized PDAs are closed to prevent further volume overloading of the left heart and to treat congestive heart failure and small PDAs are closed to eliminate the risk of bacterial endocarditis. Successful ligation of PDA was first performed by Gross and Hubbard in 1939.<sup>31</sup> Since that time, surgery was the mainstay in the management of PDA until transcatheter methods were developed. The first transcatheter method was developed by Porstman and his associates in 1967;<sup>32,33</sup> this is followed by that described by Rashkind and his colleagues.<sup>34,35</sup> A number of other devices have since been designed and tried in animal models followed by use in human subjects; and these were reviewed elsewhere.<sup>2-7</sup>

At the present time, Gianturco coils, Amplatzer Duct Occluder I and II, Gianturco-Grifka Vascular Occlusion Device and Duct-Occluder pfm are the only devices approved by FDA for transcatheter occlusion; of these, Gianturco coils and Amplatzer Duct Occluder-I are most commonly used. The criteria for selection of the type and size of the device are based on minimal ductal diameter and shape of the ductus.<sup>6,7</sup> Both of these require assessment of PDA on angiography. The case presented in this report and the previous publications by DuBrow,<sup>11</sup> Lozier<sup>13</sup> and Batlivala<sup>14</sup> and their associates suggest that ductal constriction may occur in infants who were premature and the embolization of the device may occur with consequent failure of the procedure. This is largely related to misjudgment of the size of the ductus. Several suggestions to avoid the problem will be offered:

1. If the patient is formerly a premature infant, the potential for development of ductal constriction should be kept in mind during the process of transcatheter closure of PDA.
2. Because the ductus is known to constrict by increased arterial oxygen tension, supplemental oxygen should be avoided until after aortic arch cineangiography is performed.
3. Catheter positioned in the ductal ampulla via an anterogradely positioned catheter (Figure 3A) or balloon occlusion aortography,<sup>35</sup> as illustrated in Figure 5, may help complete opacification of the ductus.

We suggest that in the event a patient requires intraprocedural diphenhydramine for latex sensitivity or other allergy, extreme care should be taken to evaluate physical findings and echocardiographic data in the assessment of the degree of left-to-right shunting. However, it seems most likely that the ductal spasm observed in our case occurred as a result of the procedure itself and the patient's former prematurity. In such cases it may be prudent to obtain angiography prior to any



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hemodynamic measurements in an attempt to minimize any chance of ductal spasm.

## Summary and Conclusions

We present a 19-month-old infant who developed spontaneous ductal constriction which resulted in the selection of a Gianturco coil for occluding the ductus which embolized. Immediately thereafter successful occlusion of the PDA with an Amplatzer device was undertaken. Extensive review of the literature resulted in identification of only a few cases of reactive ductus beyond the neonatal period. Prevalence of ductal constriction is very low (less than 2%), and it would appear that the reactive ductus causing ductal constriction is related to the premature birth of the infant. Preservation fetal ductal muscular characteristics may be responsible for this problem. When transcatheter occlusion of PDA is planned in a formerly premature infant, appropriate precaution should be undertaken to avoid inappropriate selection of the type and size of the closure device in order to prevent embolization.

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***“When transcatheter occlusion of PDA is planned in a formerly premature infant, appropriate precaution should be undertaken to avoid inappropriate selection of the type and size of the closure device in order to prevent embolization.”***

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# The 29th Annual Gravens Conference

on the Physical & Developmental Environment of the High Risk Infant, in collaboration with the March of Dimes



Photo by Jessica Storm NICU Photography

**T**he 29<sup>th</sup> year of the Gravens Conference provides us with an opportunity to explore the current state of neonatal care and envision a future that best supports the high-risk infant, the family and the team of professionals assisting in the baby's care.

Over the past quarter century, neonatal care providers have worked tirelessly to mitigate the stress experienced by neonates, parents and providers. Doing so has involved change and its inherent struggles, but eventually we have come through the process by adapting our NICU culture, policies and approach. With the promotion of evidence-based knowledge in neurodevelopmental science, developmental care, healthcare design, and family support at the annual Gravens Conference, we endeavor to nurture the developmental needs of babies and the emotional and informational needs of their parents.

Join us at the **Sheraton Sand Key** in **Clearwater Beach, Florida**, to continue our research, learning and practice as we examine 'Neuroscience, Neuroprotection, and Nurturing'. The most current science, state-of-the-art research and leading practices will be presented in three key conference tracks: developmental care, healthcare architecture and design, and family support.

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# Highlights from the Second Fetal Cardiac Symposium at Rush University in Chicago - September 10<sup>th</sup>-12<sup>th</sup>, 2015

By Karim Diab, MD

The Second Fetal Cardiac Symposium took place in the amazing summertime that the windy city offers. The meeting was held at Rush University Medical Center in Chicago and was expanded from last year to two-and-a-half days, and included a total of 15 faculty members from various institutions. With the persistence of the low national prenatal detection rate of congenital cardiac defects despite universal screening during pregnancy, the main goal of the conference was to boost the education in the field in

order help improve the status of prenatal diagnosis of congenital heart disease. This was done through a series of didactic lectures, as well as by focusing on improving the technical skills in scanning the fetal heart through hands-on sessions.

As was the case with the first year of launching the meeting, the symposium continued to be a tremendous success and was nearly sold-out with an audience of 140 registrants who came from 10 different countries and more than 19 states within the U.S. Fifteen percent of the registrants came from overseas, including countries such as

Canada, Japan, Brazil, Mexico, China, Columbia, Netherlands, Iran, Qatar and Saudi Arabia.

Most of the attendees (~65%), however, came from the Midwest states, highlighting the need for such a conference focusing on the fetal heart in this region. Although more than 50% of the attendees were physicians, there were about 30% sonographers attending the meeting, likely reflecting the attractiveness of hands-on workshops included in the meeting and that provide the attendees with practical scanning opportunities rather than only didactic lectures. The attendees came from various specialties including: Pediatric Cardiology, OB and MFM as well as other specialties such as neonatology and radiology.

The conference featured a two-and-a-half day meeting that offered thorough and updated presentations on scanning the fetal heart and diagnosing and managing various common fetal congenital heart disease malformations. The activity was designated for a maximum of 19.25 AMA PRA Category 1 continuing medical education credit, 19.25 continuing Nursing Education credits and 19.25 CME credits in medical sonography (SDMS). Lectures, given by an internationally acclaimed faculty in pediatric cardiology and maternal-fetal medicine specialists, emphasized the basics of fetal cardiac scanning coupled with live case





demonstrations and tips for diagnosing various anomalies. There was intensive focus on anomalies of the four-chamber and outflow-tracts views, reflecting the recently published guidelines for screening for fetal heart disease. In addition, there was specific focus on the 3-vessel and tracheal view that Dr. Alfred Abuhamad lectured on very extensively with ample video clips and examples to the point that he almost called it the most important view and likely the only view needed for

screening for Critical Congenital Heart Disease (CCHD)! The symposium featured a unique two-hour workshop on both days of the meeting, which gave the attendees a unique opportunity to scan pregnant volunteers with both normal hearts and cardiac pathology. The pathologies included: right-sided and-left sided critical lesions that helped attendees practice scanning fetuses with anomalies. This provided an excellent opportunity for becoming more familiar with the

required cardiac views including the 4-chamber, the outflow tracts and the three-vessel views. It also allowed participants to experiment scanning using various technological instruments and machines that are currently on the market. All this was done under the supervision of expert faculty in the field of fetal cardiology and maternal fetal medicine.

The first day of the meeting started with an overview on the basics of fetal cardiovascular physiology and the current guidelines and indications for performing fetal echocardiography by Drs. Abdulla and Young. Then, Dr. Mark Sklansky from UCLA went over the impact of prenatal diagnosis of CHD on the outcome in these patients. This was followed by a live scanning demonstration of a complete fetal echocardiographic study. It then sequentially focused on the essential screening views of the fetal heart including the four-chamber and the outflow tract views as well as the three-vessel view. This demonstrated the normal findings, as well as typical cardiac lesions diagnosed with the particular view which helped give the audience practical tips for scanning and diagnosing various cardiac malformations. Additional lectures focused on specific lesions. Dr. E. Alboliras went over Ventricular Septal Defect (VSD) and AVC lesions, Dr. W. Tworetzky talked about Ebstein's Anomaly and some of the newly suggested in-utero treatment modalities in some cases using NSAIDs to close the ductus. He also talked about HLHS with the skinny LV vs. the fat and globular LV. Dr. E. Jaeggi went over Total Anomalous Pulmonary Venous Return (TAPVR), which continues to be tricky to diagnose and missed on prenatal screens, as well as DILV and MV anomalies. Other lesions that were discussed included D-TGA and cc-TGA (Dr. Sklansky), ductal anomalies and conotruncal anomalies, as well as coarctation and arch anomalies. The first day ended with the first hands-on session of the symposium with 6 stations for hands-on scanning on fetuses with normal hearts as well as cardiac pathologies.

The second day of the symposium started with a session focusing on the national guidelines for screening for

CHD by Dr. Abuhamad. Additional lectures went over various cases and tips in imaging (Dr. Awad), 3D and 4D imaging by Dr. Sklansky, cardiomegaly and CM (Dr. Young), fetal cardiac tumors (Dr. Jaeggi) and hydrops and its management (Dr. Hornberger).

Dr. Abuhamad lectured extensively on the three-vessel and tracheal view and Dr. Tworetzky talked about the various heterotaxy lesions.

Midday on the second day of the meeting there was another hands-on session with an additional 6 stations for scanning and practice.

There was also a session on the "Most Interesting Case I've Seen," where the audience presented interesting, and unusual fetal cases with cardiac pathology that included cases such as fetal aortic-LV tunnel, critical PS, aneurysm of the intervalvular fibrosa and AVC, Ebstein's Anomaly, fetal AF, and a case of a giant LA pseudoaneurysm.

There were two winners for a special prize and a free registration to next year's symposium was awarded to two of the presenters. This gave the audience ample opportunity to present challenging fetal cardiac cases and discuss them with the faculty.

The third day of the meeting focused on fetal rhythm abnormalities with lectures on the techniques to evaluate the fetal rhythm by echo and by fetal magnetocardiography, as well as diagnosing and managing fetal tachy and brady-arrhythmias and heart block. The last session of the meeting focused on fetal cardiac imaging in early gestation, genetic evaluation of the fetus with CHD and neurologic development of the fetus with CHD.

In addition to an extensive series of didactic presentations and live-scanning sessions, the symposium offered a variety of exhibitors that showcased the latest in ultrasound technology. The symposium also offered an exceptional opportunity for fellows and attendees to network and meet

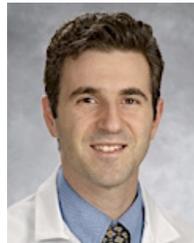
with pioneers in the field, as well as an opportunity to catch up with colleagues and meet new friends.

Given the recent updates and revisions to the North American guidelines, as well as the International Society of Ultrasound in Obstetrics and Gynecology (IUSOG) practice guidelines on sonographic screening examination of the fetal heart, the need for such annual fetal symposia in different regions is a must without any doubt in order to improve the skills of various practitioners in the field and ultimately improve the prenatal detection of CHD!

Keep an eye out for next year's meeting information as the registration sold out this year!! Dates for next year's symposium will be announced in the near future; for more information, you can reach Dr. Diab at [Karim\\_Diab@rush.edu](mailto:Karim_Diab@rush.edu) or visit the meeting website at [www.FetalCardiacSymposium.com](http://www.FetalCardiacSymposium.com).

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# NEONATOLOGY TODAY

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- No abstract should be submitted.
- The main text of the article should be written in informal style using correct English. The final manuscript may be between 400-4,000 words, and contain pictures, graphs, charts and tables. Accepted manuscripts will be published within 1-3 months of receipt. Abbreviations which are commonplace in pediatric cardiology or in the lay literature may be used.
- Comprehensive references are not required. We recommend that you provide only the most important and relevant references using the standard format.
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# NICU Discharge Readiness and Preparation: Part 2: Discharge Preparation

By Vincent C. Smith, MD, MPH

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



The American Academy of Pediatrics (AAP) recommends the transition to home occur when the infant achieves physiologic maturity and there is an active program for parental involvement and preparation for care of the infant at home. The timing of a Newborn Intensive Care Unit (NICU) discharge is mostly based on the physiologic maturity of the infant. Secondary factors are discharge planning and include the assurance that arrangements for outpatient follow-up have been completed and that the family has received the necessary teaching and demonstrated mastery of the essential knowledge and skills needed to care for their babies.

## Discharge Preparation

NICU discharge preparation is the process of facilitating comfort and confidence as well as the acquisition of knowledge and proficiencies to successfully make the transition from the NICU to home. Suggested content for a NICU discharge preparation program would include all of the following:

1. well-defined discharge teaching philosophy;
2. structured education program;
3. defined curriculum;
4. family assessment of discharge readiness; and
5. process for the transition of care to a medical home.

A well-defined discharge teaching philosophy refers to the approach that a NICU takes to all discharge preparation including identifying the discharge planning team, understanding the importance of partnering with the family, and having a willingness to accommodate different types of families. The discharge planning team typically consists of a combination of clinical nurses, physicians, neonatal advance practice nurses, physician assistants, case managers, and social workers. It is also imperative to remember that the infant's parents or primary caregivers are also an integral part of the discharge planning team. Families are able to build on their strengths, if given the opportunity to participate in the care early and be active participants in the discharge process. To embrace the concept of parents as part of the team, it is recommended that a NICU follow the four central tenets of family-centered care (i.e. dignity and respect, information sharing, family participation in care, and family collaboration). It is also important for a NICU to recognize that some families may have limited English proficiency and/or functional health literacy, and may have varied developmental needs (as in teen parents or parents with mental limitations) and will need support and special accommodation during their discharge preparation. All these are factors to consider when developing a discharge teaching philosophy.

The discharge teaching philosophy should be manifest throughout a structured education program. The target audience of the program should be a minimum of two people who are anticipated to be the main caregivers at home. The education program should be structured to begin early and be distributed throughout the NICU hospitalization. This approach may help prevent the family from being overwhelmed with a large volume of content near the end of the hospitalization. The program ought to also accomplish all of the following: include all the skills and knowledge the caregivers are expected to master; be tailored to their specific circumstance;

contain repetition and frequent opportunities to evaluate progress with the capacity for adjustment as necessary; and have a component of skill demonstration that takes advantage of the teach-back technique (i.e. repetition and return demonstrations). To reinforce the teaching and improve retention, bedside discharge teaching should be supplemented with written, video, photographic, and/or other multimedia materials whenever possible.

The structured education program needs to contain a defined curriculum of all the discharge teaching content. Although parts of the curriculum may need to be amended or modified to meet a family's specific needs or to match their situation, there are some general topics with which all families will need to be proficient. These general topics include: technical infant care skills (i.e. breast/bottle feeding and mixing formula; bathing and dressing an infant; caring for the infant's skin, umbilical cord and genitalia; placing the infant in a safe sleeping position and environment; and cardiopulmonary resuscitation (CPR). Caregivers should be familiar with normal and abnormal preterm infant behavior, and how to prepare the home environment for the addition of a newborn. Some families will need instruction on administering and storing medications properly, as well as using medical equipment. Finally, most families would benefit from some anticipatory guidance that gives them a realistic idea of what their homelife will be like during the immediate and long-term period following discharge. It is important for any anticipatory guidance to include: the number and type of routine infant health maintenance physician visits, the infant will need after discharge and helpful to estimate the possible illness-related physician visits to be expected. Anticipated or potential infant developmental or growth-related issues should be included.

Assessing family needs is an ongoing process; however, after a NICU family has completed the structured



educational program (with its well-defined curriculum) is a potentially optimal time to have a formal family assessment (a key component of a successful discharge process). The goal of a family assessment would be to better understand a family's specific needs and circumstance. A family assessment could include some of the following questions: what is family structure and what are the social support systems; what does the family think of its social support systems; are they adequate; what potential barriers to learning does the family have; what is their home environment like; are there financial or transportation challenges; how much previous experience does the family have; what are their coping habits and styles; and how equipped are they to handle their infant at home. These questions will complement the discharge readiness assessment and should be a standard part of the discharge process.

After all of this is complete and it is time for the family to transition from the NICU to home, the AAP recommends that arrangements be in place for health care of the infant after discharge in a medical home by a physician or other health care professional who is experienced in the care of high-risk infants, and that an organized program of tracking and surveillance to monitor growth and development also be in place. Finally, effective communication between the NICU and primary care providers in the medical home is a crucial piece of a successful transition.

Each NICU should make every effort to make sure that parents are prepared for discharge to prevent untoward events after discharge. Each NICU should also conduct regular evaluations of their discharge program to allow improvement over time. When discharge planning begins shortly after admission and includes structured education with a defined curriculum, attention to the family's needs, circumstances, and resources, as well as a plan in place for transfer of care to a medical home, the transition from NICU to home can be smooth, even in the most complex cases.

### Take Home Points

- NICU discharge preparation should begin shortly after admission and

continue until families are prepared to take their infants home.

- A NICU discharge preparation program should include all of the following: 1) well-defined discharge teaching philosophy; 2) structured education program; 3) defined curriculum; 4) family assessment of discharge readiness; and 5) process for the transition of care to a medical home.
- The family should be included as team members in the discharge planning process by following the tenets of family-centered care as much as possible.
- The structured family education program should be tailored to the family's specific needs and circumstances.

We invite you to join the NPA in supporting mothers, babies, and families during the perinatal period. As an interdisciplinary team, we can work together to improve the care we are committed to provide.

More information can be found at [www.nationalperinatal.org](http://www.nationalperinatal.org).

"NICU Discharge Readiness and Preparation: Part 1: Discharge Readiness" was published in the October 2015 edition of *Neonatology Today*.

### Selected Resources

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# Conference Report – Brain Monitoring and Neuroprotection 2015 in the Newborn, Oct. 1<sup>st</sup>-3<sup>rd</sup>, 2015

By Robert White, MD

The 9<sup>th</sup> International Conference on Brain Monitoring and Neuroprotection in the Newborn was held October 1<sup>st</sup>-3<sup>rd</sup> in Cork, Ireland. Attendees and faculty came from 26 countries on five continents. Topics spanned many research and clinical issues; some highlights are summarized in this article.

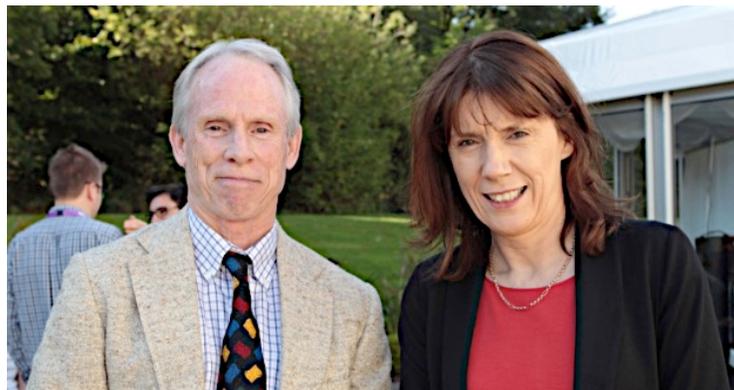
Dr. Solomon Moshe (New York) presented evidence that seizures were more common in newborns than at any other stage of life, both because of the increased risk for insults in the perinatal period, and because of the newborn's increased susceptibility, especially in prematures. Among other factors, this increased susceptibility arises from the incomplete myelination and immaturity of the endogenous systems involved in seizure control. Dr. Moshe introduced a theme touched on by other speakers throughout the meeting when he noted that the adverse changes seen in the brain of infant rats who were separated from their mothers were substantially greater than those caused by the seizures themselves.

Dr. Sampsa Vanhatalo (Helsinki) described how early endogenous brain activity was important to subsequent brain growth. Dr. Lena Hellstrom-Westas (Uppsala) emphasized the predictive value of early amplitude-integrated EEG (aEEG) monitoring, especially when paired with MRI scanning at term equivalent. She also showed examples of how abnormal pCO<sub>2</sub> or blood glucose levels could be reflected in the aEEG tracing, demonstrating that continuous cerebral monitoring can be useful in revealing the immediate impact on the brain of many of our clinical interventions, not just as a tool to detect and monitor seizures.

Dr. Bob Clancy (Philadelphia) reviewed a recent transition in the definition of "seizure", which is now no longer primarily a clinical diagnosis but an electrophysiologic one, since the majority of seizures in newborns, even status epilepticus, have no obvious clinical manifestation. He also noted that seizure frequency is

probably not the ideal metric to use to describe the severity of a seizure disorder, but rather "seizure burden", which describes the percentage or proportion of a given period of time during which seizures are present. Dr. Courtney Wusthoff (Palo Alto) provided evidence that 12% of infants <30 weeks gestation had clinical seizures, but that a much higher number had subclinical (electrographic) seizures. These were most commonly seen in the first 72 hours of life, and in most cases, were brief and limited in number. Some of these were only detected on conventional EEG since most aEEG machines filter out seizures that occur with a frequency of less than 2 per second, a frequency that is common in preterm infants.

Dr. Ronit Pressler (London) presented data showing that only half of newborns with seizures have a satisfactory response to phenobarbital, and second-line drugs add little benefit. No other drug has been shown to be as effective as phenobarbital, and it is not likely that current studies will shed further light on this problem. Dr. Nicholas Abend (Philadelphia) extended these observations to children in the Pediatric Intensive Care Unit (PICU), in whom those with encephalopathic conditions have a seizure incidence of at least 30%. Like newborns, seizures in children are frequently subclinical, usually occur in the first two days after admission, often meet criteria for status epilepticus,





and often don't respond to phenobarbital. Newer drugs do not appear to be more effective, though patients treated earlier in their course did seem to respond better. Finally, Dr. Linda de Vries (Utrecht) proposed that every newborn with seizures should have an MRI as part of their evaluation, since this showed a previously undetected etiology for the seizures or provided additional useful information in half of all infants.

The second session addressed neuroprotection. Dr. Manon Benders (Utrecht) reviewed evidence that increased spontaneous brain activity predicted enhanced brain growth and development, and identified several methods of intervention that have been shown to enhance brain development including developmental care, infant massage, and parents reading to their babies, whereas decreased infant stimulation, including: morphine drips or placing infants in private rooms without regular parental presence led to impaired brain growth. Dr. Kurt Albertine (Salt Lake City) reviewed his evidence from preterm sheep that inflammatory changes induced by high tidal volume ventilation, and mediated by systemic increases in IL-6 and IL-8, as well as elevated monocyte chemotaxis in the brain caused white matter injury and also increased the risk for necrotizing enterocolitis.

Dr. Alistair Gunn (Auckland) discussed ways to enhance our current practice of therapeutic hypothermia (TH) based on his studies in lambs. Hyperglycemia and hypocarbia are complicating factors in some infants with hypoxic-ischemic encephalopathy (HIE), and should be corrected aggressively since both can exacerbate the HIE injury. Erythropoietin and melatonin are promising adjuncts to TH, but remain under investigation. Premature infants perhaps suffer cerebral ischemia more frequently than term infants, but are not eligible for TH; fortunately, they seem to be more resilient to HIE insults than do term infants. Dr. John Barks (Ann Arbor) provided further insight on TH, presenting evidence that passive hypothermia is not very effective in reaching target temperatures, especially on transport, and that overcooling is a significant risk. A National Institute of Child Health and Human Development (NICHD) trial on late (>6 hours of age) initiation of TH has



been completed with data analysis ongoing; a trial of TH in late preterm infants is underway, but enrollment has been slow thus far, so this data will not be available in the near future. Several trials on pharmacologic adjuncts to TH are in progress, including: xenon (Phase III), erythropoietin (Phase II trial completed with data report expected soon), and darbepoetin, for which a Phase I trial has established safety.

Dr. Renee Shellhaas (Ann Arbor) reviewed the literature on sleep in the high-risk newborn by pointing out that sleep is not the absence of neurologic activity, but rather a crucial time for neurodevelopment. Ill infants have impaired sleep entropy and efficiency, spending more time in quiet sleep, which can be viewed as a recovery phase, and less time in REM sleep when synaptic formation and pruning occurs most actively.

Dr. Frank van Bel (Utrecht) presented data from a large study of infants monitored with near-infrared spectroscopy (NIRS). Normal cerebral saturation in the high-risk infant can be impaired by hypotension or patent ductus arteriosus (PDA), so the hemodynamic significance of both conditions may be better defined by their impact on cerebral saturation than by current metrics. Poor cerebral oxygen saturation can also be caused by conditions that interfere with cerebral autoregulation including pCO<sub>2</sub> values <30 or use of inotropic agents, by high mean airway pressures that reduce venous return to the heart; and by

hypoglycemia. Even with this knowledge, though, a randomized trial using NIRS to reduce the periods of time infants spent outside the optimal range for cerebral oxygen saturation did not lead to improved outcomes, so the clinical value of this technology remains somewhat elusive.

Dr. Terrie Inder (Boston) summarized evidence that brain injury occurs predominantly in the first 3 days of life (exceptions being late sepsis and necrotizing enterocolitis), but that vulnerability to impaired brain development occurs over a much longer period. The temporal lobe is the area most often underdeveloped in preterm infants, with delayed language skills as the most common manifestation. She reviewed studies showing that auditory deprivation in private rooms where parents were largely absent led to impaired language development, whereas parental presence, especially in the form of kangaroo care, led to enhanced language development.

Dr. Gunnar Naulaers (Leuven) presented data from their new single-family room Neonatal Intensive Care Unit (NICU) showing positive benefits to parents in several respects; data on infant outcomes is also being collected and analyzed from their unit. Other studies confirm that the presence of parents in a private room is the key factor for improved infant outcomes.

Presentations by Dr. Gene Dempsey (Cork), Dr. Jeff Neil (Boston), and several abstract presentations showed that the science of brain care in the newborn is advancing rapidly, yet many important questions remain. These will be discussed at the next meeting on *Brain Monitoring and Neuroprotection in the Newborn*, which will also be held in Cork, Ireland in September 2017. Information on the 2015 meeting and previews of the 2017 meeting can be found at [www.newbornbrain2015.com](http://www.newbornbrain2015.com).

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# Medical News, Products & Information

Compiled and Reviewed by Tony Carlson, Senior Editor

## Capnia Announces Publication of CoSense® Clinical Data in the Journal Neonatology - Study Demonstrates Superiority of CoSense in Detecting Hemolysis and Reducing Jaundice-Related Readmissions

GLOBE NEWSWIRE -- Capnia, Inc., focused on the development of novel products based on its proprietary technologies for precision metering of gas flow, today announced a paper, titled "Measuring End-Tidal Carbon Monoxide of Jaundiced Neonates in the Birth Hospital to Identify Those with Hemolysis," has been published online in *Neonatology* (2016;109:1-5 [DOI:10.1159/000438482]). This peer-reviewed paper, which is expected to appear in the January 2016 print issue, discusses recent clinical research demonstrating the superiority of CoSense® End-Tidal Carbon Monoxide (ETCO) Monitor at detecting hemolysis in jaundiced newborns.

The results of the study conducted in neonates with bilirubin above the 75<sup>th</sup> percentile show that CoSense is more effective at identifying hemolysis than traditional measures, such as the Coombs test. Of the 100 high-risk neonates studied at three hospitals in the Intermountain Healthcare System, CoSense showed evidence of hemolysis in 37%, while Coombs testing showed several false negative results. None of the neonates studied with CoSense were readmitted to the hospital. In the same period of time, approximately 3% of the 3,535 neonates on whom CoSense was not used prior to discharge from the hospital, were readmitted for jaundice.

"Since 2004 the American Academy of Pediatrics (AAP) has recommended the use of ETCO measurement to confirm the presence or absence of hemolysis in neonates and CoSense is the only commercially available device that can accomplish this," said Dr. Robert Christensen, Director of Neonatology Research at Intermountain Healthcare and Chief, Division of Neonatology at the University of Utah School of Medicine. "Jaundice is the number one cause of re-hospitalization during the first weeks after birth. It is an outcome that is highly preventable and innovative technologies, such as CoSense, are much needed."

"We are pleased to see this data published in a highly-respected, peer-reviewed medical journal," said Anish Bhatnagar, MD, Chief Executive Officer of Capnia. "The effective detection of hemolysis in neonates represents a significant unmet medical need, and these data demonstrate that CoSense is a highly effective solution. This data further underscores the significant market for CoSense and we remain focused on our goal of making this important product widely available."

Capnia, Inc. develops and commercializes novel products based on its proprietary technologies for precision metering of gas flow. Capnia's lead product CoSense is based on the Sensalyze™ Technology Platform. It is a portable, non-invasive device that rapidly and accurately measures carbon monoxide (CO) in exhaled breath. CoSense has 510(k) clearance for sale in the U.S. and has received CE Mark certification for sale in the European Union. CoSense is used for the monitoring of CO from internal

sources (such as hemolysis, a dangerous condition in which red blood cells degrade rapidly), as well as external sources (such as CO poisoning and smoke inhalation). The initial target market is newborns with jaundice that are at risk for hemolysis, comprising approximately three million births in the U.S. and European Union. The Company's commercial, neonatology-focused product line also includes innovative pulmonary resuscitation solutions, including the NeoPIP™ Infant T-Piece Resuscitator and Universal T-Piece Circuit consumables. Capnia's proprietary therapeutic technology uses nasal, non-inhaled CO<sub>2</sub> and is being evaluated to treat the symptoms of allergies, as well as the trigeminally-mediated pain conditions such as cluster headache, trigeminal neuralgia and migraine.

## Study Finds Little Improvement in Mortality Rate for Extremely Preterm Infants Since 2000

About 500,000 babies are born premature in the United States each year, according to the U.S. National Library of Medicine. Those infants, born before 37 weeks of gestation, will likely deal with the threat of numerous complications or even death.

Accurate data on how those infants fare is important as doctors and parents face difficult decisions. Dr. Michael Malloy, a neonatologist and professor at the University of Texas Medical Branch at Galveston, recently took a closer look at the infant mortality rates of extremely preterm infants.

What Malloy found and described in a paper in *Journal of Perinatology* was that while there were significant improvements in the infant mortality rate among extremely preterm infants before 2000, there has been little improvement since the turn of the century.

Previous studies of extremely preterm infants - babies born after only 22 to 28 weeks of gestation - typically only focus on short periods of time and often use data from specialized centers with the latest technology and treatments, Malloy said.

But to get a broader view Malloy looked at infant birth and death certificates from the National Center for Health Statistics and compared the mortality rates from 1990 to 2000 and then from 2000 to 2010. He looked at more than 47,000 records and tracked the infant mortality rate for each week of gestation from 22 to 28.

What Malloy found was that there was a 40% to 50% reduction in death for each gestational week from 1990 to 2000. For example, the mortality rate of preterm infants born after 23 weeks of gestation decreased from 81.4% in 1990 to 67.8% in 2000. For babies born after 28 weeks, the mortality rate dropped from 9.5% in 1990 to 6% in 2000.

"We see a marked improvement across all these gestation ages," Malloy said.

But from 2000 to 2010, there was little to no improvement in the mortality rate, he said.



The difference may be related in part to the advances made in the 1990s. Advances such as the use of synthetic surfactant to prevent breathing disorders and the antenatal steroids likely helped reduce the mortality rate, Malloy said.

But while improvements to techniques and technology have been made since 2000, there have been no great breakthroughs or new discoveries, and the mortality rate from 2000 to 2010 has not improved dramatically, Malloy said.

Malloy said he points out these trends to help both doctors and expecting parents have realistic information when it comes to extremely preterm infants.

"It is an attempt to temper public expectations," Malloy said. "We just can't work complete miracles. We have to accept the fact that there is a biology that we are running up against."

### Birth Factors May Predict Schizophrenia in Genetic Subtype of Schizophrenia

Low birth weight (LBW) and preterm birth appear to increase the risk of schizophrenia among individuals with a genetic condition called the 22q11.2 Deletion Syndrome, a new study from the Centre for Addiction and Mental Health (CAMH) shows.

The research, published in *Genetics in Medicine*, is "...part of ongoing efforts among schizophrenia researchers to predict and prevent illness at the earliest stages possible," says senior author Dr. Anne Bassett, Clinician-Scientist in CAMH's Campbell Family Mental Health Research Institute and Canada Research Chair in Schizophrenia Genetics and Genomic Disorders.

"Low birth weight and preterm birth have been proposed as risk factors in schizophrenia in general, but past studies have not shown a large effect on risk," says Dr. Bassett, who is also the Director of the Clinical Genetics Research Program at CAMH. "We've focused our lens on these risks in a small population with a specific genetic subtype of schizophrenia, where the connection between birth factors and risk of developing schizophrenia is noticeably stronger."

The risk of schizophrenia is known to be high in individuals with 22q11.2 Deletion Syndrome, as about one in four develops schizophrenia. This study found the risk was even higher - nearly one in two - among those who were born with a low birth weight or prematurely, based on standard measures.

The syndrome is caused by a small deletion on chromosome 22. It can lead to heart or palate abnormalities, developmental delays and other physical health problems, and in one in four cases, a schizophrenia diagnosis in late adolescence or early adulthood.

The research, led by medical student and first author Lily Van, included 123 adults with 22q11.2 Deletion Syndrome. After completing genetic tests to confirm this deletion, the researchers did a comprehensive review of participants' medical records to capture details on birth weight and prematurity and on through development. Psychiatrists on the study team also assessed all participants for the presence of major psychiatric illnesses, including schizophrenia.

In total, 51 patients were diagnosed with schizophrenia or schizoaffective disorder. The risk of developing schizophrenia, based on birth factors, was compared against those who did not have schizophrenia. In addition, researchers ruled out other factors, besides the genetic deletion in the baby, that could lead to prematurity or LBW, such as high blood pressure, gestational diabetes, smoking and substance use.

"The results needs to be replicated, but do have important clinical implications," says Dr. Bassett.

For instance, there are now prenatal tests that can signal the possibility of a 22q11.2 deletion as early as the first trimester of pregnancy. While such screening requires further confirmation through additional testing, it raises the idea of intervening, in cases where the deletion exists, during pregnancy or immediately after birth.

"The big-picture question is: Whether there is a way to support the developing fetal brain to improve outcomes, and lower the risk of schizophrenia?" says Dr. Bassett.

The Centre for Addiction and Mental Health (CAMH) is Canada's largest mental health and addiction teaching hospital, and one of the world's leading research centres in its field.

## Upcoming Medical Meetings

### Hot Topics in Neonatology 2015

Dec. 6-9, 2015; Washington, DC USA  
[www.hottopicsinneonatology.org](http://www.hottopicsinneonatology.org)

### 2016 NeoPREP - An Intensive Review and Update of Neonatal-Perinatal Medicine

Jan. 23-29, 2016; Atlanta, GA USA  
[shop.aap.org/2016-NeoPREP-An-Intensive-Review-and-Update-of-Neonatal-Perinatal-Medicine](http://shop.aap.org/2016-NeoPREP-An-Intensive-Review-and-Update-of-Neonatal-Perinatal-Medicine)

### Specialty Review in Neonatology

Feb. 23-28, 2016; Orlando, FL USA  
[www.specialtyreview.com](http://www.specialtyreview.com)

### CQI Symposium

Feb. 24, 2016; Orlando, FL USA  
[www.neoconference.com](http://www.neoconference.com)

### NEO: The Conference for Neonatology 2016

Feb. 25-28, 2016; Orlando, FL USA  
[www.neoconference.com](http://www.neoconference.com)

### 33<sup>rd</sup> Annual Conference on High Frequency Ventilation And Critical Care of Infants, Children & Adults

Mar. 29-Apr. 2, 2016; Snowbird, UT USA  
[paclac.org/event/33rd-annual-conference-on-high-frequency-ventilation/](http://paclac.org/event/33rd-annual-conference-on-high-frequency-ventilation/)

### The 2<sup>nd</sup> International Neonatology Association Conference (INAC 2016)

Jul. 15-17, 2016; Vienna, Austria  
[2016.worldneonatology.com](http://2016.worldneonatology.com)



## Cervical Pessary Doesn't Reduce Rate of Preterm Birth or Neonatal Complications in Twin Gestations

Having twins accounts for only 1.5% of all births, but 25% of preterm births, the leading cause of infant mortality worldwide. Successful strategies for reducing singleton preterm births include: prophylactic use of progesterone and cervical cerclage in patients with a prior history of preterm birth. To investigate whether the use of a cervical pessary might reduce premature births of twins, an international team of researchers conducted a large, multicenter, international randomized clinical trial (RCT) of approximately 1200 twin pregnancies. They report in the *American Journal of Obstetrics & Gynecology* that placement of a cervical pessary did not reduce spontaneous preterm births or reduce neonatal complications.

The rates of preterm birth (defined as <37, <34, or <32 weeks) are 5-6 times higher in twin than in singleton gestations. A cervical pessary is a plastic device that can be placed around the cervix in order to keep it closed and "long" in the hope that it will prevent preterm delivery.

"Twin pregnancies are at substantially higher risk of early preterm birth than singleton pregnancies and this risk is inversely related to sonographically measured cervical length at 20-24 weeks' gestation," explained lead investigator Kypros H Nicolaides, MD, Harris Birthright Research Centre for Fetal Medicine, King's College Hospital, London. "Our research indicates that insertion of cervical pessary at around 22 weeks in both randomly selected women pregnant with twins and in patients with a short cervix of less than 25 millimeters does not reduce the rate of spontaneous early preterm birth, perinatal death, adverse neonatal outcome, or need for neonatal therapy."

One-thousand-one-hundred-eighty women pregnant with twins participated in this multicenter RTC (centers in Europe, Asia, and South America), one of the largest studies ever conducted in twin gestations. Five hundred-ninety patients received cervical pessaries while 590 had expectant management. There were no significant differences between the pessary and control group in rates of spontaneous birth at less than 34 weeks (13.6% vs. 12.9%), perinatal death (2.5%

vs. 2.7%), adverse neonatal outcome (10.0% vs. 9.2%), or neonatal therapy (17.9% vs. 17.2%).

Two RCTs published after the start of this study provided contradictory results on the effect of cervical pessary on the rate of spontaneous birth at <34 weeks in singleton pregnancies with short cervix. Dr. Nicolaides and co-investigators conducted a post hoc subgroup analysis of 214 women with short cervix (<25 mm), which also showed no benefit from the insertion of a cervical pessary.

"This is a major international study examining an important clinical question - namely, whether a cervical pessary



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can reduce the rate of preterm delivery in twin gestations," commented Roberto Romero, MD, DMedSci, Editor-in-Chief for *Obstetrics of the American Journal of Obstetrics and Gynecology*, and Chief of the Perinatology Research Branch of NICHD/NIH. "Importantly, a cervical pessary did not reduce the rate of preterm delivery in women with either a short or long cervix. The report is key because many had hope that placement of this doughnut-like device would prevent preterm delivery. The results can be used to focus research on other therapeutic interventions that may be more effective in preventing preterm delivery in twin gestations."

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# NEONATOLOGY TODAY

News and Information for BC/BE Neonatologists and Perinatologists

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Neonatology Today (NT) is the leading monthly publication that goes to over 4,000 BC/BE neonatologists, Perinatologists, Fellows, NNPs, and their NICU teams. Neonatology Today provides timely news and information regarding the care of newborns, and the diagnosis and treatment of premature and/or sick infants. In addition, NT publishes special issues, directories, meeting agendas and meeting dailies around key meetings.

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