Dear Colleagues,

Welcome to the fall issue of Fetal Connections. In this edition, we introduce you to a program that is at the heart of our mission in fetal and transitional medicine—the Critical Care Delivery Program. This program includes a team of highly skilled specialists who focus on the in utero identification of fetuses at high risk for catastrophic collapse immediately or soon after delivery. The goals of this team are to prevent neonatal demise, as well as serious injury including irreversible brain injury.

In this issue, we also introduce our new physician liaison and explain her role. Additionally, we begin a recurring newsletter feature article called the Quarterly Case Review. In these case studies, we will highlight interesting clinical findings from the prior quarter.

Lastly, we announce another educational opportunity from our institute. Specifically, we have secured Continuing Medical Education (CME) accreditation for a planned series of monthly videoconferences on Topics in Fetal Medicine. We would like to invite you, our colleagues in the maternal-fetal-neonatal community, to participate in this new CME opportunity once it begins. Please stay tuned for more details in future issues of Fetal Connections.

Sincerely,

Adrè J. du Plessis, MBChB, MPH
Director, Fetal Medicine Institute
Division Chief, Fetal and Transitional Medicine
Director, Fetal Brain Program

Dear Colleagues

Our New Fetal Medicine Physician Liaison

Recently, Jayne Garstecki, BSN, joined our team as the dedicated physician liaison for the Fetal Medicine Institute at Children’s National Health System. She has a nursing background in pediatric intensive care, open-heart surgery, and interventional cardiology, as well as clinical medical device sales experience.

Ms. Garstecki will assist your practice in many ways including:

- Communicating about our services, expertise, and referral process
- Addressing any outstanding concerns that affect your partnership with us

She will work with our assigned care coordinators to answer any questions you might have, facilitate the referral process, and make it easy for you and your patients to navigate the Fetal Medicine Institute. This frontline team will rapidly address the needs of you and your patients, while facilitating access for your patients to the state-of-the-art imaging, counseling, and care provided by the Fetal Medicine Institute at Children’s National.

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Quarterly Case Review

The Fetal Medicine Institute recently evaluated two fetal cases referred for suspected skeletal dysplasias. Both cases met radiologic criteria for thanatophoric dysplasia (TD); one was confirmed by genetic testing. Here we report the fetal MRI (magnetic resonance imaging) findings of associated cerebral malformations from both cases.

Clinical Findings

- Referred cases had markedly short long bones and small chest contours
- Both pregnancies ended before 20 weeks gestation (one spontaneously) and autopsies were declined
- Fetal MRI results for both cases showed the following striking and unusual temporal lobe abnormalities:
  - Bilateral temporal lobe hypertrophy (see Fig. 1)
  - Abnormal gyration (see Fig. 2) with deep transversely oriented sulci on the inferomedial aspects of the temporal and occipital lobes
- Other Case 1 fetal MRI findings (not shown) included dysmorphic calvarium, macrocephaly, elevation of the tentorium, cerebellar dysgenesis, and a thickened midbrain; both cases showed ventriculomegaly.

Several cases with similar cerebral findings have been described in other reports of skeletal dysplasia, including TD, hypochondroplasia, and recently a case of achondroplasia. TD is the most common type of lethal neonatal skeletal dysplasia. Anomalies associated with TD are attributed to gain of function (GOF) mutations in the fibroblast growth factor receptor 3 (FGFR3) gene that is located on the short arm of chromosome 4. Inheritance is autosomal dominant, but most probands have de novo FGFR3 mutations, with an empiric recurrence risk of about 2 percent. FGFR3 is a tyrosine kinase receptor that modulates cell proliferation and apoptosis signaling pathways. GOF FGFR3 mutations in TD cause constitutive activation of FGFR3. This results in enhanced cell proliferation and apoptosis inhibition, with the net effect of accelerated and abnormal cortical formation. FGFR3 is expressed in cartilage growth plates of the long bones during enchondral bone ossification and in the developing cerebral cortex. Accelerated cortical formation leads to increased cortical thickness and surface area, with premature and abnormal sulcation primarily in the inferomedial temporal regions. This topography of cortical overgrowth and malformation is thought to reflect the regional gradient expression of FGFR3 in the developing cortex, which is higher and lower in the caudomedial and rostrolateral areas, respectively.

These cases are fascinating examples of genotypic-phenotypic relationships across tissue types in the developing fetus. Further study to determine the genetic underpinnings of these detected pathogenic cerebral findings may be warranted.

In an era of major medical and technological advancement, fetal and neonatal care have become vibrant and exciting multidisciplinary fields that require the close collaboration of obstetrics, neonatology, pediatrics, surgery, and other medical subspecialties. As a result, we now view the fetus as a patient who requires individualized care that is distinct from the prenatal care provided to the pregnant mother. At the Fetal Medicine Institute, we embrace this changing medical landscape and advance the vision of fetal medicine as ‘prenatal pediatrics.’ Our Critical Care Delivery Program plays an important role in advancing this vision.

Program Overview
Our Critical Care Delivery Program draws upon the rich multidisciplinary resources of the Fetal Medicine Institute to provide expertise and state-of-the-art transitional care for patients with the highest risk fetal diagnoses. The program’s directors include Medical Director, Mary Donofrio, MD, who is a national expert in this field and has directed delivery room coordination of care at Children’s National for 10 years; and Surgical Director, Andrea Badillo, MD, a pediatric surgeon with fetal surgery training.

Our multidisciplinary Critical Care Delivery Program translates, integrates, and implements our research advances and best clinical practices to decrease neonatal mortality and minimize the risk of injury to the brain and other organs. This risk is particularly high for medical conditions that preclude normal cardiovascular transition. Such conditions include instances of structural or functional fetal heart disease, as well as upper or lower airway lesions that obstruct independent neonatal ventilation.

For these and other high-risk cases, the program’s expert pediatric and surgical subspecialists perform the following steps to strategically and effectively care for high-risk fetal patients.
1. Carefully assess the anticipated expertise that will be needed to deal effectively with the hazards of each individualized case
2. Assemble a team to identify all potential complications that may occur immediately at delivery
3. Assign team leaders to oversee the formulation of interventions that counter all possible complications
4. Perform real-time simulations in the operating room to prepare for the upcoming delivery, using specialty-specific checklists to organize and coordinate the teams

Program Care Recommendations
When our Fetal Medicine Institute team diagnoses a fetus with a congenital abnormality, we provide the pregnant mother with individualized recommendations for ongoing fetal follow-up and/or specialty treatment (when indicated), delivery room care (routine or specialized), and post-delivery care (from the need for routine outpatient follow up to possible transfer to Children’s National for subspecialty care).

In most cases, specialized in-utero or immediate post-delivery intervention is not necessary. Should specialized delivery care be required to improve the infant’s outcome, the team will collaborate with the referring doctors, obstetricians, and other Fetal Medicine Institute subspecialists to formulate a management plan. Delivery planning is determined by the anticipated Level of Care (LOC) that will be required at delivery and in the first few days of life (see table below).

(Continued on page 4.)

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<th>Level of Care (LOC) Definitions</th>
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<td><strong>LOC I:</strong> Delivery occurs at the patient’s local hospital; immediate post-birth specialist care not required; follow-up specialty outpatient care plans are made as needed.</td>
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<td><strong>LOC II:</strong> Delivery occurs at the patient’s local hospital with subsequent transfer to Children’s National for surgery or subspecialty intervention. Because on-site stabilization may be needed, this LOC requires an on-site neonatologist. Specialty care recommendations for stabilization are made to the neonatologist prior to transport.</td>
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<td><strong>LOC III:</strong> Delivery occurs at a hospital in close proximity to Children’s National because immediate subspecialty expertise to stabilize the infant is expected to be required at delivery. Delivery planning provides Children’s specialists with quick access to babies in the delivery room and ensures rapid transport to our specialist teams at Children’s National for immediate intervention or surgery.</td>
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<td><strong>LOC IV:</strong> Delivery is planned at Children’s National because it is expected that interventional subspecialty care (e.g., catheter intervention or surgery) will be required in the delivery room.</td>
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Our Critical Care Delivery Program (cont.)

Dr. Donofrio developed the LOC system in 2004 at Children’s National to care for high-risk cardiac patients; this system has now been adapted to accommodate all high-risk deliveries. Each LOC has its own care recommendations that are formulated from evidence-based medicine data. Our Critical Care Delivery Program team individualizes these standard LOC management plans to each patient, ultimately attaining a multidisciplinary expert consensus on the recommended care plan.

Most newborns can be stabilized and cared for in their local delivery hospital, even if transport to Children’s National for surgery or intervention is subsequently necessary. In these instances, the local neonatologist will stabilize the infant, sometimes in consultation with Children’s National specialists. LOC IV delivery recommendations are rare because they are only warranted for fetal conditions that require the following immediate neonatal procedures.

- Circulatory stabilization by cardiac specialists or interventionists with or without extracorporeal membrane oxygenation (ECMO) and anticipated surgical support
- Airway stabilization at delivery, most often using the EXIT (ex-utero intrapartum treatment) procedure

Children’s National has successfully managed delivery of these LOC IV patients since 2004, with 100 percent delivery room survival and good outcomes in these highest risk patients.

Including You
Our Critical Care Delivery Program aims to collaborate with you, our referring colleagues in the obstetric and perinatology community, to provide the best outcome for mother and baby. To this end, our Critical Care Delivery Program plans to capitalize on new videoconferencing capabilities offered by the Fetal Medicine Institute. Videoconferencing will allow you, the referring physician, to be involved in management discussions with your patient and our specialists throughout the process of planning for a complex delivery.

For more information about our Critical Care Delivery Program, visit www.ChildrensNational.org/fetal-high-risk
For more information about its Program Directors, visit www.ChildrensNational.org/findaprovider

Sign up for Fetal Connections

Fetal Connections is a quarterly newsletter from the Fetal Medicine Institute at Children’s National Health System. To sign up for our digital version, visit www.ChildrensNational.org/Fetal-Connections or call 202-476-4500.