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Children's National™
Fetal Medicine Institute
Part of the Children's National Health System

Fetal Connections

Dear Colleagues,

I hope this finds you well and enjoying the beginning of fall.

At the Fetal Medicine Institute, it certainly has been a busy summer! Our International Symposium on the Fetal Brain is almost upon us, and we are excited to delve deeper into important discussions with colleagues from all different backgrounds on September 15 and 16 at the W Hotel here in Washington, DC. Keep an eye out for our Winter Fetal Connections and a special session of our Topics in Fetal Medicine CME series, where we will highlight a few of our stimulating speakers and talk topics from the event.

In addition, the looming threat of a local Zika virus outbreak has kept us on high alert as we develop plans for any possible scenario that might unfold. We have seen a number of travel-related cases and are actively involved on the ground in Colombia, where we are partnering with local physicians in an exciting research collaboration. Following conversations with concerned physicians and anxious pregnant women, we also have developed a clinical **Congenital Zika Virus Program** in our Fetal Medicine Institute—one of the first in the country. This multidisciplinary program brings together specific strengths in the Institute, especially Fetal Neurology, Fetal Infectious Disease (led by our Infectious Disease Division Chief, Roberta DeBiasi, MD) and Fetal Imaging. Our Institute has a strong focus on the fetal brain, making us uniquely positioned to consult with pregnant women and provide comprehensive care. Being a part of Children's National Health System additionally allows us to provide continuous postnatal care for children born with complications related to the Zika virus throughout childhood.

Our case study on page 3 focuses on a case of microcephaly and provides insight into our clinical approach to a patient with a suspected Zika-related fetal abnormality.

Best wishes,

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

An Introduction to our Clinical Congenital Zika Virus Program

Children's National Health System recently launched a clinical Congenital Zika Virus Program based out of our Fetal Medicine Institute. This program is designed to provide advanced diagnostics and consultation for pregnant women and infants with suspected exposure to the Zika virus. Our program is a leader in international Zika-related research initiatives, giving us first-hand access to and knowledge of the latest Zika findings to help your patients.

Our Process

Our approach is multidisciplinary, headed by Roberta DeBiaisi, MD, Chief of Infectious Disease, and Adré du Plessis, MBChB, MPH, a fetal neurologist and our Director of the Fetal Medicine Institute. With so much new information continually coming to light about the Zika virus, we ensure that your patients are being consulted by top-tier physicians in each of their different specialties. These specialists combine the most current CDC recommendations with the newest developments in international Zika research to ensure each patient gets individually tailored services, counseling, and treatment plans.

(Continued on page 2.)

Our Clinical Congenital Zika Virus Program *(continued from page 1.)*

We work with you and your patient to address any Zika concerns, from answering questions and providing patients with an easily accessible contact in the program, to handling streamlined blood testing, to imaging and follow-up consultations. We have direct contacts at the Departments of Health in the surrounding jurisdictions, and we have established a standardized protocol for patients with each of them to ensure timely results. We strive to give expert guidance to provide referring physicians and patients an accurate and streamlined diagnosis and management plan personalized to the patient's unique situation.

In addition, our top-ranked neonatologists along with physicians from over 40 other subspecialty programs at Children's National care for Zika-affected patients post-delivery, providing smooth and continuous care for children of all ages.

If you suspect any of your pregnant or infant patients have been exposed to or infected with the Zika virus per the guidelines on our webpage, ChildrensNational.org/Zika, please **call the Congenital Zika Virus Program at 202-476-7409.** Our care is tailored to individual patients' gestational age needs, travel history, genetic background, personal concerns, and our experts are available to answer any questions or concerns you may have about the Zika virus. You can reach them by calling the number above or emailing fetalmedicine@childrensnational.org.

If your patients have any questions about the Zika virus and how it could affect them, visit our **Zika Resources Page** at ChildrensNational.org/Zika for information to pass on to them.

Meet the Team

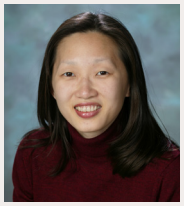
Lindsay Pesacreta, MS, FNP-BC
Nurse Practitioner

Dorothy Bulas, MD
Director, Fetal Imaging Program

Roberta DeBiasi, MD
Pediatric Infectious Disease Specialist

Sarah Mulkey, MD, PhD
Fetal Neurologist

André J. du Plessis, MBChB, MPH
Director, Fetal Medicine Institute



Taen Chang, MD
Neonatal Neurologist

Gilbert Vezina, MD
Director, Neuroradiology

Cara Biddle, MD, MPH
Children's Health Center Pediatrician

Welcome to the team, Dr. Mulkey!

Sarah Mulkey, MD, joins us from Arkansas Children's Hospital. A neurologist with clinical and research interests in neonatal neurology, Dr. Mulkey received her medical degree from Florida State University College of Medicine. We are excited to have her on board!

Quarterly Case Review

Fetal Microcephaly and Congenital Zika Virus Infection

We recently evaluated the fetus of a 28-year-old G2P1 woman referred for fetal microcephaly, ventriculomegaly, and talipes equinovarus noted on a routine fetal anatomy ultrasound (US) at 24 weeks' gestation. Dating of pregnancy was based on maternal last menstrual period and confirmed by a first trimester US. The patient declined amniocentesis and opted for non-invasive prenatal testing that indicated low risk for aneuploidy. Maternal serology testing for cytomegalovirus (CMV) infection showed positive IgG and negative IgM titers for CMV, Toxoplasma, and HSV-1. Toxoplasma and CMV avidity tests were negative for recent infections. A maternal serum alpha-fetoprotein level was normal. Review of her travel history revealed that the patient had spent four weeks in El Salvador from nine to 13 weeks' gestation She did not report insect bites or illness. The family history was negative for consanguinity, congenital defects, and genetic syndromic and childhood onset neurologic disorders.

Consultation Result

The patient was counseled by a multidisciplinary team composed of a genetic counselor, fetal neurologist, and a pediatric infectious disease specialist. Possible etiologies of the fetal anomalies, clinical implications, and pregnancy management were discussed extensively. Given the patient's travel history, Zika virus testing was ordered. Maternal serology was positive for Zika virus infection (positive IgM titer) and infection was confirmed by the plaque-reduction neutralization test. Zika PCR was negative, likely due to the duration of time from infection.

The patient continues to be closely followed by her maternal fetal medicine specialist. Postnatal testing is recommended, including collections of cord blood, umbilical cord, placenta, and fetal tissue (in case of fetal loss) for Zika testing. We recommend a non-sedated brain MRI and neurological evaluation in the newborn period, with ongoing neurologic follow-up in our Congenital Zika Virus Program.

(continued on page 4.)

References

1. Hadlock FP, Harrist RB, Martinez-Poyer J. In utero analysis of fetal growth: a sonographic weight standard. Radiology. 1991;181(1):129-33.

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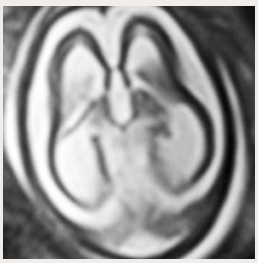
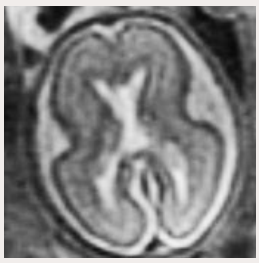
Fetal Imaging

- The patient underwent a fetal MRI (unenhanced fast T1, T2, and diffusion weighted MRI) and a detailed antenatal US evaluation at 25 weeks' gestation.
- The US confirmed the diagnosis of fetal microcephaly with a head circumference (HC) of 19.84 cm and a biparietal diameter (BPD) of 5.29 cm, both 2 standard deviation below the mean for gestational age. The rest of the fetal biometry was at the 30th percentile for gestational age.[1]
- On fetal brain MRI *(Fig 1-2)*, the lateral ventricles were mildly enlarged, measuring 11 mm at the level of the atria. The MRI also confirmed severe microcephaly; the fronto-occipital diameter (FOD) measured 50 mm, the cerebral BPD measured 43mm, and the bone BPD measured 48 mm, all 2 SD below the mean.[2]
- Other anomalies found on fetal MRI *(Fig. 1-3)* included contractures of the upper and lower extremities with muscular atrophy consistent with arthrogryposis *(Fig. 3)*, decreased fetal movements, and mild right pleural effusion with no evidence of ascites or hydrops.
- The fetal arterial and venous Doppler parameters were normal.

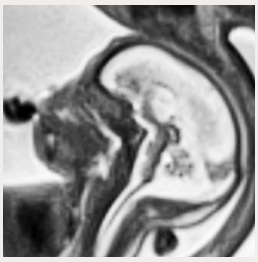


(Fig. 1a)



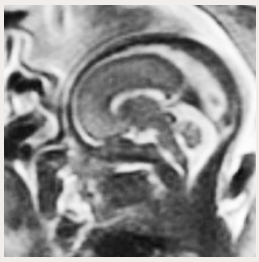
(Fig. 1b)

*Axial T2-weighted imaging of the fetal brain **(1a)** with maternal Zika virus infection showing severe diffuse thinning of the cerebral cortical mantle with evidence of small parenchymal cysts in the white matter adjacent to the frontal horns and mild ventriculomegaly compared to **(1b)** a normal fetal brain at 25 weeks' gestation.*

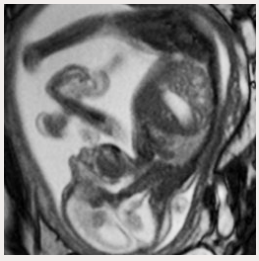


(Fig. 2a)

*Sagittal T2-weighted imaging of the brain of the **(1a)** affected fetus showing partial agenesis of the corpus callosum and a small anterior bulge of the pons compared to **(2b)** a normal 25 weeks fetus.*



(Fig. 2b)



(Fig. 3)

*T2-weighted imaging of the affected fetus showing multiple contractures of both upper and lower extremities with muscular atrophy. **(3)***

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Microcephaly Discussion

- Fetal microcephaly is defined as a HC < 2SD below the mean or < 3rd percentile for gestational age. There is controversy about the best standard for diagnosing microcephaly and whether this should be adapted for ethnicity.
- In many cases of fetal microcephaly, HC may improve postnatally or be normal at birth.[3-4]
- Fetal MRI may be able to better evaluate for other associated brain anomalies in cases of fetal microcephaly.

It is important to distinguish *primary* genetic (known or suspected) causes and *secondary* acquired-destructive forms. Cases with *secondary microcephaly* often have relatively moderate microcephaly but have severe intellectual disability, major neurologic abnormalities, and often a history of a preceding sentinel event/mechanism. Causes of *secondary microcephaly* include congenital infections (such as Zika), teratogenic agents, hypoxic, and ischemic injuries.

Primary microcephalies

- *Microcephaly vera* has an overall normal brain configuration but neurons in cortical layers II and III are severely depleted; it is a recessive inheritance, and intellectual disability is usually mild.
- *Microlissencephaly* is an extreme form of microcephaly, with a thick cortex and markedly decreased cortical sulci (agyria-pachygyria). Microlissencephaly is associated with gross neurologic abnormalities, profound intellectual disability, and epilepsy.
- *Radial microbrain* is an extreme form of microcephaly where the brain may weigh < 50 grams.

Prognosis of microcephaly

- HC between 2 - 3 SD < mean: outcome often favorable, especially in the absence of brain anomalies or syndromic conditions
- HC between 3 - 4 SD < mean: higher risk of intellectual disability
- HC < 4 SD < mean: poor intellectual outcome

Prenatal imaging findings previously described in Zika virus infection:[5-7] (*described in case)

- Microcephaly with atrophy of the cerebral mantle and enlarged extra-axial space*
- Abnormal lamination pattern of the cerebral mantle
- Intracranial and intraocular calcifications
- Cerebral ventriculomegaly*
- Parenchymal cysts*
- Prominence of the choroid plexus
- Absent or hypoplastic corpus callosum*
- Hypoplastic brain stem and/or cerebellum*

Conclusion

In the present case of microcephaly, fetal brain MRI findings and travel history raised the suspicion of congenital Zika virus infection and guided specific testing.

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Fetal Connections

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Fetal Connections is written for physicians and should be used for medical education purposes only.
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