Zika Virus & Microcephaly
Update for Healthcare Providers
Of Pregnant Women and Infants

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Dr. Deborah Campbell, MD, FAAP
Professor of Clinical Pediatrics
Albert Einstein College of Medicine
Chief, Division of Neonatology
Children's Hospital at Montefiore

Deborah Fox, MPH
Director
Congenital Malformations Registry
Center for Environmental Health
New York State Department of Health
Objectives

At the conclusion of this webinar, healthcare providers will be able to:
• Describe what is known about maternal Zika virus infection and birth outcomes
• Discuss other factors that can cause microcephaly in a fetus
• Describe how to determine if a fetus or newborn is microcephalic
• Understand how your efforts and reporting to the Congenital Malformations Registry will improve knowledge about Zika virus infection and microcephaly
CDC Media Briefing on Wednesday 4/13/16

“It is now clear that Zika does cause microcephaly”

“An unprecedented association - Never before in history could a bite from a mosquito result in a devastating birth malformation”

“Still working to understand range of birth defects associated with Zika, and time of greatest risk”

Microcephaly in context of Zika virus (ZIKV) infection

What we know:

• Timing of ZIKV exposure associated with severe microcephaly appears to be in late 1\textsuperscript{st}/early 2\textsuperscript{nd} trimester, which would be consistent with the defects observed
  – Exposure determined by timing of symptoms or by travel to ZIKV infected area

• ZIKV infections later in pregnancy associated with poor intrauterine growth and fetal death

Brasil P. *NEJM*, March 4, 2016, DOI: 10.1056/NEJMoa1602412
Microcephaly in context of Zika virus (ZIKV) infection

What we know:

• Strong temporal and geographic association
  – Increased # of microcephaly cases in Brazil, French Polynesia and tentatively Columbia following outbreaks of ZIKV infections
  – ZIKV infection in mothers during pregnancy precedes findings of microcephaly and other brain anomalies in fetuses and infants
  – Confirmed ZIKV infection in pregnant women in the U.S. which have resulted in adverse pregnancy outcomes have all followed travel to a ZIKV infected region outside of the U.S.

Broutet N. NEJM 2016;374(16);1506-9. DOI: 10.1056/NEJMp1602708
Microcephaly in the context of Zika virus infection

What we know:

• Other viral infections (CMV) have had similar effects
• ZIKV is neurotrophic
  – Live ZIKV cultured from brain of fetus with severe anomalies after maternal infection
  – Identification of Zika virus RNA in brain tissue of affected fetuses and infants
  – ZIKV efficiently infects neural progenitor cells, producing cell death and abnormal growth

Petersen LR. *NEJM* March 30, 2016, DOI: 10.1056/NEJMra1602113
Microcephaly in the context of Zika virus infection

What we know:

• Fetuses/infants with presumed exposure have similar patterns
  – severe microcephaly, intracranial calcifications, & other brain anomalies
  – sometimes eye findings, redundant scalp skin, arthrogryposis and clubfoot

• Some infants with features consistent with fetal brain disruption sequence

Brasil P. NEJM, March 4, 2016, DOI: 10.1056/NEJMoia1602412
Some reported findings regarding what Zika virus does to the brain

- Brain atrophy with calcifications & enlarged cisterna magna
- Asymmetric hemispheres with severe unilateral ventriculomegaly
- Displacement of midline
- Thinning of parenchyma on dilated side
- Failure to visualize corpus callosum and thalami
- Thinning of pons and brainstem
- Asymmetric eyes with cataracts and intraocular calcifications
- Fetal Brain Disruption Sequence

Driggers RW et al. NEJM, March 30, 2016, DOI: 10.1056/NEJMoa1601824
Mlakar J et al. NEJM, 2016;374:951-8, DOI: 10.1056/NEJMoa1600651
MRI of fetal brain at 19 weeks gestation

Driggers RW et al. NEJM, March 30, 2016, DOI: 10.1056/NEJMoa1601824
Microcephaly in the context of Zika virus infection

What we don’t know

• Full spectrum of defects caused by prenatal Zika virus infection (ocular, hearing, heart, …)
• Relative and absolute risk among infants born to mothers infected at different times during pregnancy
• Other factors that might affect a woman’s risk of adverse pregnancy or birth outcomes
  – Co-infection with another virus
  – Preexisting immune response to another flavivirus
  – Genetic background of mother and fetus
  – Timing and/or severity of maternal infection
• Validated birth prevalence estimates of microcephaly in Brazil or other countries in recent outbreak
Estimation of Prevalence – Monitoring Change

• Prevalence of microcephaly in U.S. varies from 2 to 12 cases per 10,000 live births among state-based birth defects programs
• In NYS, 110-160 congenital microcephaly cases* reported annually (4.6 – 6.7 per 10,000 live births)
• Historically, microcephaly has been inconsistently measured and reported
• Our aim is to improve surveillance of microcephaly in NYS

*Does NOT exclude cases with other diagnoses associated with abnormal head size or with other causes (in utero infections, genetic causes, teratogenic exposures, maternal radiation, etc..)
Enhanced microcephaly surveillance will:

• Provide better estimates of baseline risk of microcephaly
• Permit observation of temporal and spatial patterns
• Allow identification of ZIKV associated cases and other emerging public health threats
What is microcephaly

• Microcephaly is the clinical finding of a small head compared with infants of the same sex and age, or gestational age if measured at birth

• Head circumference (HC) is considered a reliable assessment of volume of the underlying brain
  • HC is also known as occipital-frontal circumference (OFC)

** Special thanks to Dr. Jan Cragan (CDC) for sharing slides on microcephaly and head circumference measurement
Congenital vs. acquired microcephaly

- Congenital microcephaly is usually present prenatally or at the time of birth/delivery
  - Abnormal development of the brain (often genetic)
  - Arrest or destruction of normally-forming brain (e.g., infection, vascular disruption)
- Acquired microcephaly develops as a result of late onset infection/insult (e.g., perinatal stroke), or after birth due to delivery complications or postnatal insult, trauma or infection
  - HC is normal at birth
  - As the baby grows in length, the head becomes comparatively smaller

AP Photo/Felipe Dana
Types of microcephaly

• Disproportionate – Head is small out of proportion to the weight and length, which may be normal for age and sex
• Proportionate – Head size, weight and length are all small for age and sex but proportional to each other
• “Relative” microcephaly – Head size measures within the normal range for age and sex, but is small out of proportion to the weight and length
Causes of Congenital Microcephaly

- *In utero* infections
  
  - Toxoplasmosis
  - Rubella
  - Cytomegalovirus (CMV)
  - Herpes
  - Human Immunodeficiency Virus (HIV)
  - Syphilis
  - Zika virus
Causes of Congenital Microcephaly

- Genetic causes
  - Single gene disorders (syndromes)
  - Chromosomal abnormalities, microdeletions, microduplications
  - Mitochondrial mutations
- In utero ischemia/hypoxia (e.g., placental insufficiency or abruption)
- Teratogens (e.g., maternal alcohol, hydantoin)
- Radiation
- Mercury (e.g., fish and seafood)
- Maternal conditions (e.g., poorly controlled diabetes, hyperphenylalaninemia)
Other birth defects with abnormal head size

• Anencephaly
  – Failure of the neural tube to close resulting in failure of the brain and skull to form

• Spina bifida
  – Failure of neural tube closure resulting in an opening in the spine
  – Can occur anywhere along the spine
Other birth defects with abnormal head size

- **Encephalocele**
  - A sac-like protrusion of the brain and membranes that cover it through an opening in the skull
  - Can have other brain and face defects

- **Holoprosencephaly/Arrhinencephaly**
  - Failure of the brain to fully divide into two cerebral hemispheres and other parts

- **Hydrocephalus**
  - Accumulation of fluid in the brain
  - Enlarged ventricles and skull
Brain abnormalities that can occur with microcephaly

- Intracranial calcifications
- Hydrocephalus ex-vacuo (extra axial fluid collection)
  - Damaged brain matter shrinks and is surrounded by fluid
  - Cerebral atrophy
- Hydranencephaly
  - Damaged brain matter replaced by pockets of fluid
- Pachygyria, lissencephaly
  - Abnormal ridges and folds (gyri) in the brain
Measuring HC (per World Health Organization [WHO])

- Use tape measure that cannot be stretched
- Securely wrap tape around widest possible circumference of head
  - 1-2 finger-widths above eyebrow on forehead
  - At the most prominent part of back of head
- Take measurement 3 times and select the largest measurement to nearest 0.1 cm
- Optimal measurement at 24-36 hours after birth when molding of head has subsided
  - Head shape can affect the accuracy of HC estimate of brain volume
Measuring Head Circumference

Baby with Typical Head Size

Baby with Microcephaly

Baby with Severe Microcephaly
Useful teaching video on how to measuring head circumference
https://www.youtube.com/watch?v=LW38bgQ9vVY

The following video clip is taken from a McMaster Neonatal Research Lab presentation, “Standardized Measurement Techniques for Growth” made available to us by Dr. Christopher Fusch.
From a McMaster Neonatal Research Lab presentation, “Standardized Measurement Techniques for Growth” made available to us by Dr. Christopher Fusch
Interim guidelines for the evaluation and testing of infants whose mothers traveled to or resided in an area with ongoing Zika virus transmission during pregnancy

Prenatal diagnosis of microcephaly is more challenging

• Can be detected during mid-pregnancy anomaly scan (ultrasound) at 18-20 weeks
• May not be evident until the late 2\textsuperscript{nd} or into the 3\textsuperscript{rd} trimester
• Usually present by 36 weeks
• Serial prenatal ultrasounds may be needed to detect the development of microcephaly \textit{in utero}
• Fetal MRI can be another useful imaging tool
Case definition for microcephaly after birth for purposes of Zika virus response

• HC measurements should be compared to age and sex matched controls for term births
  – Gestational age matched controls for preterm infants

• Recommended HC measures for microcephaly
  • Below the 3rd percentile for age and sex
  • Z score greater than 2 standard deviations (SDs) below the mean ($z<-2.00$) for age and sex

• CDC suggests using INTERGROWTH 21st curves

http://intergrowth21.ndog.ox.ac.uk/en/ManualEntry
## Suggested Reference Charts for Head Circumference at Birth by Gestational Age and additional resources for growth charts

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<tr>
<th>Gestational Age at Birth</th>
<th>Reference Chart</th>
<th>Web Link</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>A tool for calculating percentiles for head circumference for infants 24-32 weeks is also available from this site.</td>
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<tr>
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<td></td>
<td>A tool for calculating z-scores for fetal growth standards is also available from this site.</td>
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Intergrowth-21st Fetal Growth Standards are based on measurements *in utero* only. International standards for birth measurements in infants less than 24 weeks gestation are not available. For most elective pregnancy terminations and many stillbirths, accurate postnatal head circumference measurements are not possible.

For a study comparing head circumference measurements in utero to those obtained after birth, see: Melamed N, Yoge Y, Danon D, et al. Sonographic estimation of fetal head circumference: how accurate are we? Ultrasound Obstet Gynecol 2011
Additional Resources for Growth Charts


- World Health Organization Child Growth Standards for birth to 5 years are available at: http://www.who.int/childgrowth/standards/en/

- Tools to calculate percentiles for weight, length, and head circumference by sex and gestational age or postnatal age based on several of these data are available at: http://peditools.org/
CDC establishing the US Zika Pregnancy Registry

Purpose:
- To understand more about ZIKV infection during pregnancy
- To update recommendations for clinical care of pregnant women with ZIKV infection

Who should be reported:
- All pregnant women in the US with laboratory evidence of ZIKV infection
- Infants with congenital ZIKV infection

CMR Background

- CMR established under Environmental Disease Surveillance Program in 1982, as a result of the Love Canal disaster in Niagara Falls, NY.

- Included children diagnosed up to 2 years of age, born or residing in NY, with a major birth defect, chromosomal anomaly or persistent metabolic defect. Required reporting by hospitals and physicians within ten days of diagnosis.

- In New York State, there are nearly 240,000 births every year. About 12,000 of these infants will have a major birth defect.
Several CMR Regulatory Changes Effective May 2016

• In addition to reporting by hospitals and physicians, require reporting by nurse practitioners authorized to diagnose congenital anomalies, physicians assistants authorized to diagnose congenital anomalies and midwives

• Require reporting of prenatal diagnosis of birth defects

• Extend the case capture periods for certain defects, including fetal alcohol syndrome (FAS), muscular dystrophies, genetic conditions and heart defects
Reporting congenital microcephaly in newborns

- Hospitals will report congenital microcephaly diagnosed at birth
- CMR is seeking reports from other health facilities/practices:
  - Birthing centers/Midwifery practices
  - Home births
  - Subspecialty clinics (neurology, genetics)
  - Other healthcare providers
- To request forms or get additional information, email: cmr@health.ny.gov

Currently not requesting reporting of prenatally diagnosed microcephaly
From CDC: For Health Care Providers

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4/28/2016
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• Dr. Peer Dar, Director, Division of Fetal Medicine and OBGYN Ultrasound, Montefiore Medical Center
• McMaster Neonatal Research Lab and Dr. Christopher Fusch
NYSDOH Zika Testing Eligibility

Identify a patient presenting for care who meets the following criteria:

1. Pregnant woman who had possible exposure (travel to an area with Zika virus transmission while pregnant or unprotected sex with partner who traveled) OR
2. Non-pregnant woman, man, or child who develops (or developed) compatible symptoms during or within 4 weeks of travel to an area with Zika virus transmission OR
3. A person who traveled to an area with active Zika virus transmission and who presents with Guillain-Barré syndrome OR
4. Infant with microcephaly, intracranial calcifications or other abnormality whose mother had exposure during pregnancy (or born to mothers with positive or inconclusive test results)
NYSDOH Zika Testing Procedures

Patient needs three things:

1. Lab order (PROVIDER)
   Order “Zika blood and urine PCR and Zika blood for serology”
2. Infectious Disease Requisition Form (IDR) (PROVIDER)
3. LHD authorization form (Local Health Department)
NYSDOH Zika Testing Results

• Results of Zika virus testing will be made available to providers

• Providers can access public health consultation for assistance with interpretation of results by calling the NYSDOH Zika Information Line at:

  1-888-364-4723

  Weekdays between 9AM and 5PM
NYC- Process for Ordering Zika Virus Testing as of March 21, 2016

• Healthcare providers must now call the NYC Health Department’s Provider Access Line (PAL) to request Zika testing
  
  PAL: 1-866-692-3641

• This is to ensure that appropriate tests are ordered and specimens are correctly collected, labeled, processed, packaged and transported
NYC- What to Expect When You Call

- Health Department representative will review case with you to ensure testing criteria are met
- If testing is appropriate then the representative on the phone will:
  - Collect the information needed to order the correct testing
  - Complete the required laboratory submission form
  - Advise on the type(s) of specimen(s) to collect
- The completed lab submission form(s) for your patient(s) and instructions for specimen collection and handling will be sent to you within 30 minutes via email or fax