AAP ZIKA ECHO
(EXTENSION FOR COMMUNITY HEALTHCARE OUTCOMES)
**HOUSEKEEPING ITEMS**

- For educational and quality improvement purposes, this ECHO session will be recorded.
- Project ECHO® collects participation data for each ECHO session. This data allows Project ECHO to measure, analyze, and report on the ECHO movement’s reach. Data is used in reports, on maps and visualizations, for research, for communications and surveys, for data quality assurance activities, and for decision-making related to new initiatives.
- To protect patient privacy, please do not provide any (PHI) protected health information.
- Please mute your microphone when not speaking. If you have video capability, please enable it.
- There is a chat function in Zoom that may be used to send messages to the group. For IT help, please chat to the AAP Admin and we will assist you.
TODAY’S LECTURE

Congenital Abnormalities

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**CASE DEFINITION – CONGENITAL ZIKA VIRUS DISEASE** (JUNE 2016)

**Clinical Criteria**

Liveborn infant with congenital microcephaly, or intracranial calcifications, or structural brain or eye abnormalities, or other congenital central nervous system-related abnormalities not explained by another etiology.

*Called Zika Virus Syndrome in some places and Zika Virus Disease others

CASE CLASSIFICATION: PROBABLE

A neonate meets clinical criteria for congenital disease; AND
The neonate’s mother has an epidemiologic linkage or meets laboratory criteria for recent ZIKV or flavivirus infection; AND
The neonate has laboratory evidence of ZIKV or flavivirus infection by:

• Positive ZIKV IgM antibody test of serum or CSF collected within 2 days of birth; AND
  – positive neutralizing antibody titers against ZIKV and dengue or other flaviviruses endemic to the region where exposure occurred; OR
  – negative dengue virus IgM antibody test and no neutralizing antibody testing performed.

CASE CLASSIFICATION: CONFIRMED

A neonate meets the clinical criteria for congenital disease AND meets one of the following laboratory criteria:

• ZIKV detection by culture, viral antigen, or viral RNA in fetal tissue, umbilical cord blood, or amniotic fluid; or neonatal serum, CSF, or urine collected within 2 days of birth; OR

• Positive ZIKV IgM antibody test of umbilical cord blood, neonatal serum or CSF collected within 2 days of birth with positive ZIKV neutralizing antibody titers and negative neutralizing antibody titers against dengue or other flaviviruses endemic to the region where exposure occurred.

Microcephaly: The Most Apparent Marker?

• Microcephaly is a very specific diagnosis, and typically unusual as an isolated finding: initially seen in newborns
  – On ultrasound, typically defined as HC < 3rd %ile for GA

• Microcephaly became an early trigger to search for Zika association, but spectrum of disease became apparent
  – Microcephaly can occur as a result of a fetal brain disruption sequence: this appears to be pathology of Zika infection
SEVERE MICROCEPHALY WITH PARTIALLY COLLAPSED SKULL

Microcephaly

- Symptoms include below-average head size
- Often caused by failure of brain to grow at normal rate
- Head circumference measuring less than 31.5-32cm at birth
- Affects 25,000 children in US each year

Source: ADAM, WHO

Zika virus intrauterine infection causes fetal brain abnormality and microcephaly: tip of the iceberg?

Source: Ultrasound in Obstetrics & Gynecology
Volume 47, Issue 1, pages 6-7, 5 JAN 2016 DOI: 10.1002/uog.15831
Fetal Brain Anomalies

- Microcephaly
- Hydrocephalus/hydranencephaly
- Absent structures: (CC, pons, cerebellar vermis)
- Neuronal migration disorders (lissencephaly)
- Fetal brain disruption sequence
- Cerebral calcifications
- Brain asymmetry

On June 8, this report was posted as an MMWR Early Release on the MMWR website (https://www.cdc.gov/mmwr).

Pregnant women living in or traveling to areas with local mosquito-borne Zika virus transmission are at risk for Zika virus infection, which can lead to severe fetal and infant brain abnormalities and microcephaly (1). In February 2016, CDC recommended 1) routine testing for Zika virus infection of asymptomatic pregnant women living in areas with ongoing local Zika virus transmission at the first prenatal care visit, 2) retesting during the second trimester for women who initially test negative, and 3) testing of pregnant women with signs or symptoms consistent with Zika virus disease (e.g., fever, rash, arthralgia, or conjunctivitis) at any time during pregnancy (2). 2,549 completed pregnancies (live births and pregnancy losses at any gestational age) with laboratory evidence of recent possible Zika virus infection; 5% of fetuses or infants resulting from these pregnancies had birth defects potentially associated with Zika virus infection (3, 4, 5). Among completed pregnancies with positive nucleic acid tests confirming Zika infection identified in the first, second, and third trimesters, the percentage of fetuses or infants with possible Zika-associated birth defects was 8%, 5%, and 4%, respectively. Among liveborn infants, 59% had Zika laboratory testing results reported to the pregnancy and infant registries. Identification and follow-up of infants born to women with laboratory evidence of recent possible Zika virus infection during pregnancy permits timely and appropriate

**STUDY RESULTS SUMMARY**

- Overall, about 5% of fetuses and infants born to women with lab evidence of Zika virus infection in the U.S. territories has possible Zika-associated birth defects
  - Same as percentage reported in 50 U.S. states during 2016
- Possible Zika-associated birth defects including brain abnormalities and/or microcephaly were reported following Zika virus infection during every trimester of pregnancy
- Among completed pregnancies with positive nucleic acid tests confirming Zika virus infection identified in first, second and third trimesters, the percentage of fetuses or infants with possible Zika-associated birth defects was 8%, 5% and 4%, respectively

Known Abnormalities Unique to Zika Virus Syndrome

‘Characterizing the Pattern of Anomalies in Congenital Zika Syndrome for Pediatric Clinicians’
JAMA Pediatrics, October 2016

- Severe microcephaly with partially collapsed skull
- Thin cerebral cortices with subcortical calcifications
- Macular scarring and focal pigmentary retinal mottling
- Congenital contractures
- Marked early hypertonia and symptoms of extrapyramidal involvement

Source: http://jamanetwork.com/journals/jamapediatrics/fullarticle/2579543
Fig 3 Severe microcephaly.
VENTRICULAR CALCIFICATION OR OTHER CENTRAL NERVOUS SYSTEM LESIONS
CT Scans Reveal Extensive Abnormalities
23 infants with microcephaly in Pernambuco, Brazil

- Intracranial calcifications
- Global cortical hypogyration
- Ventriculomegaly
- Global cerebellar hypoplasia

Source: Hazin et al, NEJM April 6, 2016
**OPHTHO CRITERIA FOR CZS**

- First ophthalmological examination has to be performed within 30 days of birth.

- **SIGNS:** Focal pigment mottling of the retina and circular lesions of chorioretinal atrophy including the macula, along with optic nerve abnormalities
  - Identified in 30% of newborns with microcephaly (Frietas et al, JAMA Ophtho 2/16)
MACULAR SCARRING AND FOCAL PIGMENTARY RETINAL MOTTLING

Fundus Photographs of a 2-Month-Old Girl
The right eye has granular, pigmentary mottling in the macula (A), and the left eye has a chorioretinal lobulated atrophic lesion and slight pigmentary mottling (B).

Source: http://jamanetwork.com/journals/jamaophthalmology/fullarticle/2491896
CONGENITAL CONTRACTURES (ARTHROGRYPOSIS)

Arthrogryposis multiplex congenita (AMC), or simply arthrogryposis, describes **congenital joint contractures** in two or more areas of the body. It derives its name from Greek, literally meaning "curving of joints" (arthron, "joint"; grῦpōsis, late Latin form of late Greek grūpōsis, "hooking").

Source: [https://en.wikipedia.org/wiki/Arthrogryposis](https://en.wikipedia.org/wiki/Arthrogryposis)
CONGENITAL CONTRACTURES (ARTHROGRYPOSIS)

(A) Contracture in flexion of knee;
(B) hyperextension of knee (knee dislocation);
(C) clubfeet;
(D) deformities in 2nd, 3rd, and 4th fingers;
(E) joint contractures in legs and arms, without involvement of trunk

Source: [http://www.bmj.com/content/354/bmj.i3899](http://www.bmj.com/content/354/bmj.i3899)
MARKED EARLY HYPERTONIA AND SYMPTOMS OF EXTRAPYRAMIDAL INVOLVEMENT

• Loss of upper motor and alpha motor neurons can result in hypertonia, or increase in muscle tone.
• Increased resistance is apparent when the arms and legs are extended.
• Hyperextension of the back and tightly clenched fists are often seen.

Sources: [http://neuroscience.uth.tmc.edu/s3/chapter06.html](http://neuroscience.uth.tmc.edu/s3/chapter06.html) and [http://www.slideshare.net/peso88888/neonatal-examination-45813957](http://www.slideshare.net/peso88888/neonatal-examination-45813957)
OTHER KNOWN ABNORMALITIES ASSOCIATED WITH ZIKA VIRUS SYNDROME

- Strabismus
- Cutis Gyrata
- Hypotonia
- Hyperreflexia
- Glaucoma
- Irritability
- Seizures
OTHER OCULAR FINDINGS: STRABISMUS

Increased occurrence of strabismus (crossed eyes)

• 14% in babies with congenital Zika virus syndrome in the first year of life, versus 3-5% in the general population.

Source: Study by Marcia Tartarella, MD, PhD, et al, under review
Cutis verticis gyrata (CVG) is a descriptive term for a condition of the scalp manifesting as convoluted folds and furrows formed from thickened skin of the scalp resembling cerebriform pattern.

HYPOTONIA

Hypotonia (decreased muscle tone)

Source: https://englishforphysio.wordpress.com/tag/spasticity/
Hyperreflexia, or over-activity of the Autonomic Nervous System is defined as overactive or overresponsive reflexes. Examples of this can include twitching or spastic tendencies, which are indicative of upper motor neuron disease as well as the lessening or loss of control ordinarily exerted by higher brain centers of lower neural pathways (disinhibition).
SEIZURES

Study in Brazil showed children with CZS presented a high incidence of epileptic seizures before the end of the first year of life.

- In a case series of Brazilian infants with CZS or +Zika-IgM:
  - 38% (n=40) had epileptic seizures
    - 43.3% characterized as spasms
    - 22.7% as generalized tonic-clonic seizures
    - 20.5% as partial seizures
    - 4.5% as other types of seizures

SUMMARY: ZIKA- ASSOCIATED ADVERSE PREGNANCY OUTCOMES

- Fetal loss/miscarriage, stillbirth
- Fetal brain anomalies
  - Microcephaly
  - Ventriculomegaly
  - Intracranial calcifications
- Eye abnormalities
- Neurologic
  - Hypertonia
  - Arthrogryposis
  - Seizures