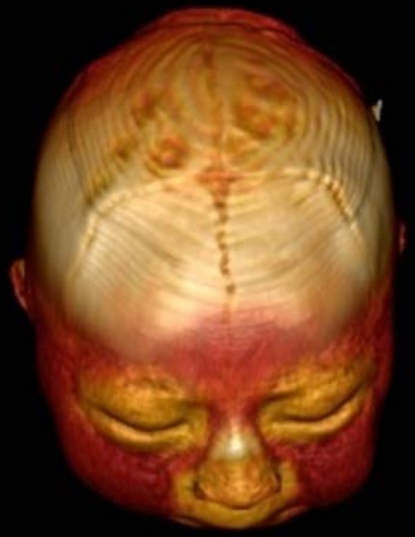
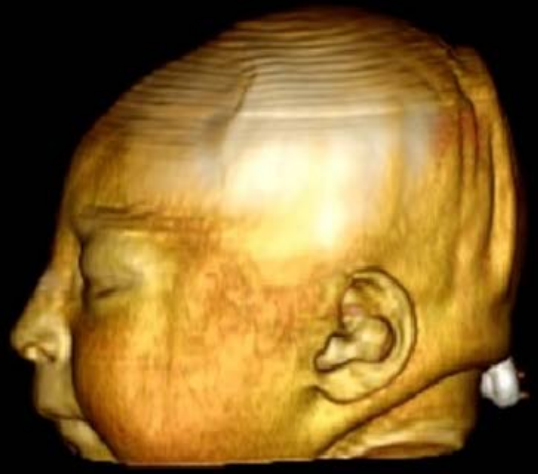
UPDATE: CONGENITAL ZIKA VIRUS SYNDROME





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What is Zika?

Zika virus timeline

- 1947 Zika virus identified in macaque in Uganda (Zika Forest): fortuitous discovery during a yellow fever study
- 1953 Zika virus recognized as cause of human illness in Nigeria
- 1953-2007 Sporadic cases of mild febrile illness attributed to Zika in Africa and Asia
- 2007 Large outbreak of Zika virus illness in the State of Yap, Federated States of Micronesia: 5000 infections occurred in a total population of 6700; Spectrum of Zika illness defined
- 2013-2014 Large outbreak of Zika virus infection in French Polynesia with 32,000 cases
- Mar 2015 Zika virus first identified in the Americas in Brazil

Zika virus timeline

- Sept 2015 Increased number of infants born with microcephaly noted in Brazil
- Early 2016 Increase in microcephaly retrospectively noted in French Polynesia following the 2013-2014 outbreak
- Jan 2016 CDC issues interim travel guidance for pregnant women for areas with ongoing Zika virus transmission
  - Feb 2016 WHO declared Public Health Emergency of International Concern
  - Nov 2016 Public health emergency status downgraded

What is Zika Virus?

- Single stranded RNA Virus
- Genus Flavivirus
- Closely related to dengue, yellow fever, Japanese encephalitis, and West Nile viruses
- Primarily transmitted by two *Aedes* species mosquitoes – *Aedes aegypti* and *Aedes albopictus*

***Aedes aegypti* mosquito**

***Aedes albopictus* mosquito**

What is Zika Virus?

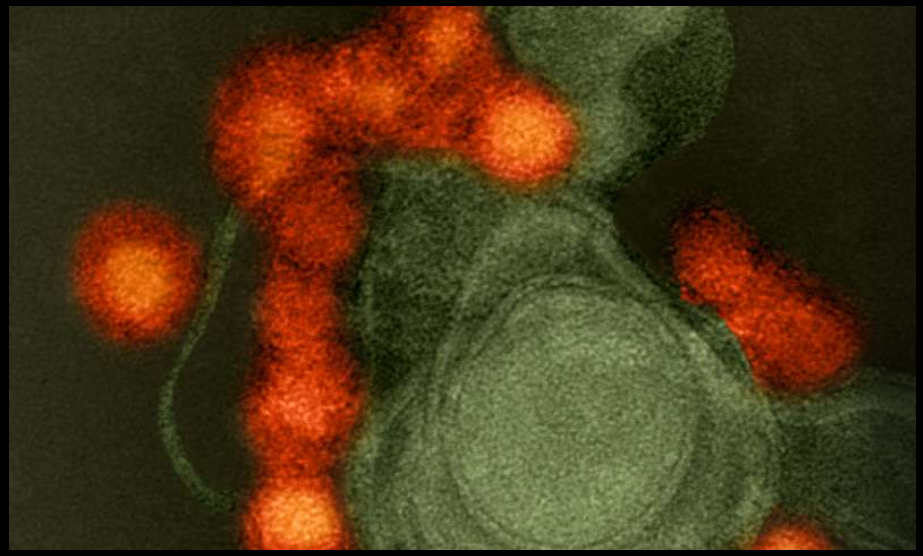
- *Aedes* species mosquitoes are aggressive daytime biters
- Live in and around households; lay eggs in domestic water holding containers
- Can also transmit dengue and chikungunya viruses

***Aedes aegypti* mosquito**

***Aedes albopictus* mosquito**

Additional modes of transmission

- Intrauterine transmission
- Intrapartum transmission from viremic mother
- Sexual transmission
- Blood transfusion
- Laboratory exposure



Zika virus infection

- Intrauterine viral infections may affect the fetal brain (neurotropic)
- TORCH infections (toxoplasmosis, rubella, CMV, herpes)
- West Nile encephalitis- rare cases of fetal brain abnormalities
- Zika goes a step further

Zika virus infection

- Infection is generally associated with a mild disease (fever, arthralgias, erythema, conjunctivitis)
- Often asymptomatic (80%)
- Cases of Guillain-Barré syndrome also reported, although rare

What happened in Brazil?

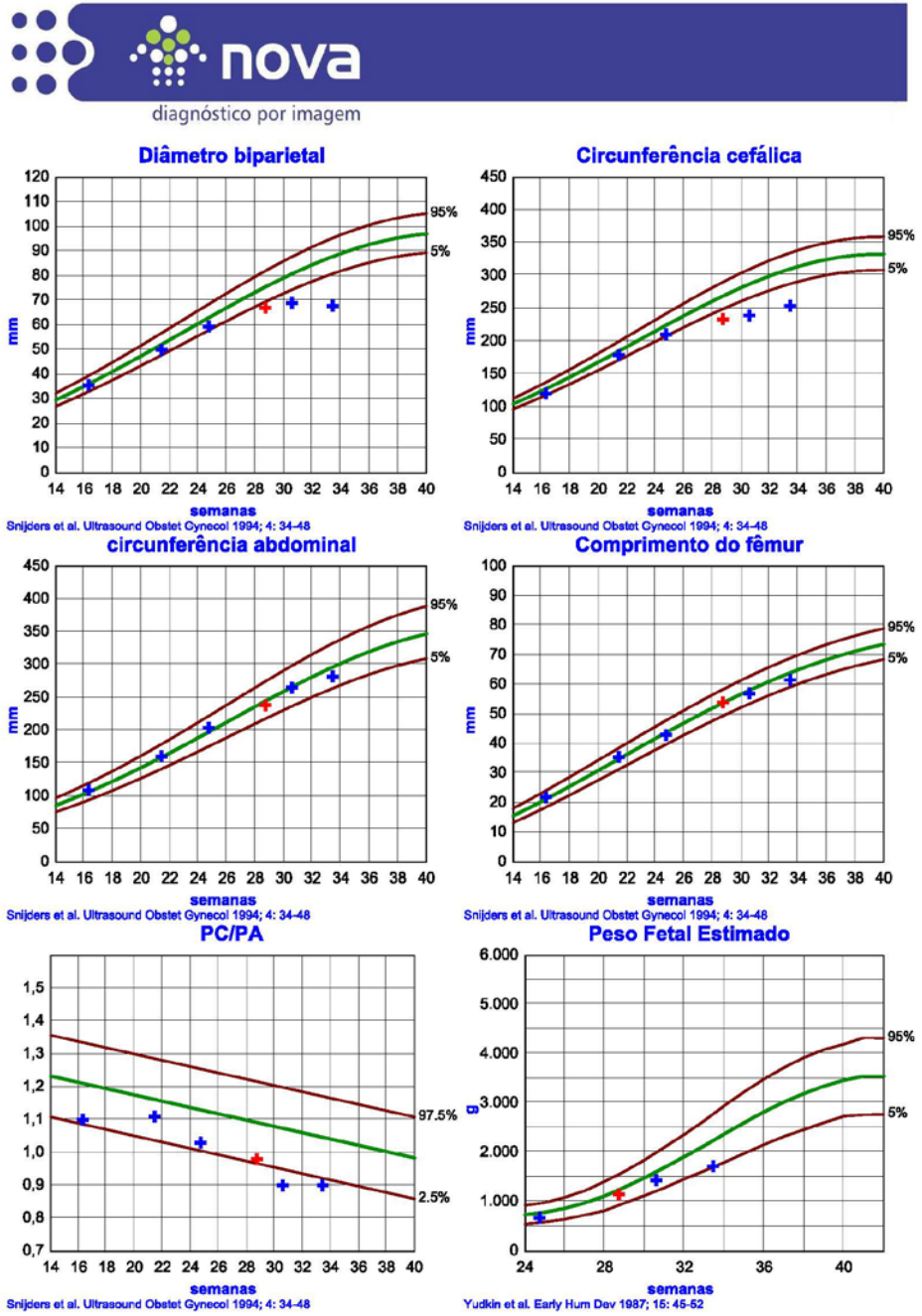
- Cluster of severe microcephaly cases in Brazil corresponding with outbreak of Zika virus in May 2015; incidence of microcephaly 20 times the baseline rate
- Case definition difficulties
  - Revised case definition in June 2016

Why no fetal cases until 2015?

- First identified in Uganda in 1947
- Underreporting of cases?
- Acquisition of immunity in endemic areas?
- Disease rare until recently?
- Genomic changes → more virulent strains?
- Possibly the severe cases represent the “tip of the iceberg” and that less severe cases are not recognized at birth → underreporting of cases….

Ultrasound findings suggestive of Zika virus infection

- Microcephaly
  - Onset often ~24-28 wk gestation
- Intracranial calcifications
  - Frequently subcortical rather than more common periventricular
- Ventriculomegaly
  - Often severe, asymmetric
- Brain destruction is significant and affects posterior fossa (cerebellum), brainstem, thalami
- Arthrogryposis- often atypical joint deformations

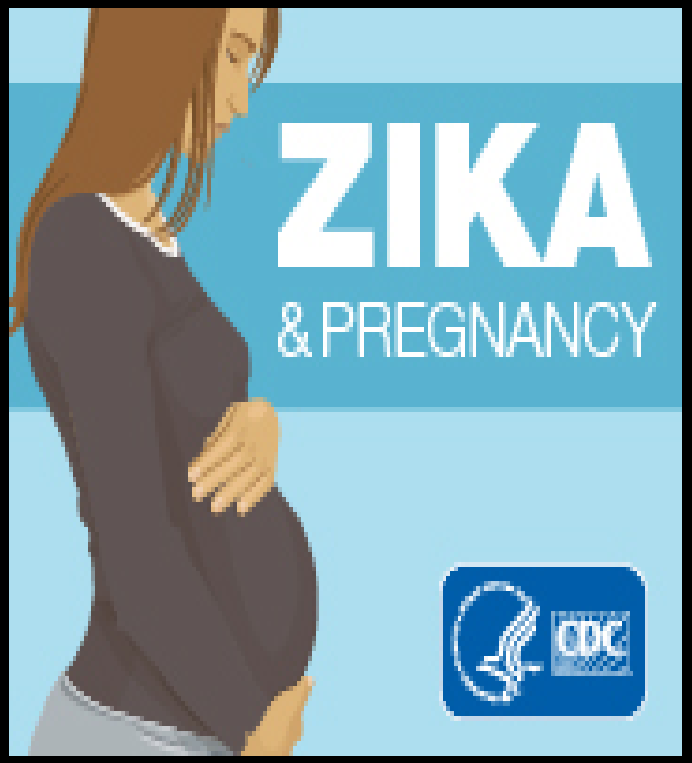


Página 1 de 1, impressa em 8 de Março de 2016 - LUDEMILA GEMELLI, examinada em 17 de Setembro de 2015.

Zika virus infection at 13 wk gestation

Courtesy of NOVA Diagnóstico por Imagem

Zika Virus in Pregnancy



- Incidence of Zika virus infection in pregnant women is not known
- Infection can occur in any trimester
- No evidence of more severe disease compared with non-pregnant women
- No evidence of increased susceptibility during pregnancy

Possible adverse reproductive outcomes due to Zika infection

- Fetal death- early and late pregnancy loss
- Infant with microcephaly and serious brain anomalies **
- Infant with other birth defects
- Infant with less severe brain anomalies and developmental disabilities
- Infant with developmental disabilities alone
- Other adverse pregnancy outcomes such as preterm birth

** causal relationship established

Risk stratification

- Consider Zika virus disease in patient with compatible clinical S/Sx and who traveled to or resides in areas with ongoing Zika transmission
- History of sex without condom with someone who traveled to or resides in areas with ongoing Zika transmission
- All pregnant women should be assessed for possible Zika virus exposure at each prenatal visit
  - Offer testing to those with symptoms or asymptomatic with risk factors

Risk stratification

- Offer testing to asymptomatic pregnant women who:
  - Traveled to or live in an area with active Zika virus transmission
  - Had sex without a condom with someone who traveled to or resides in an area with active Zika virus transmission

Maternal infection→ fetal infection?

- Many unanswered questions:
  - How often does maternal infection result in fetal infection?
  - What proportion of positive amniotic fluid tests will result in infected fetus/ infants?
  - What proportion of infected fetus / infants will be *severely* affected?
  - What proportion of asymptomatic infants will have sequelae?
  - What are those potential long-term sequelae?

Confirmed maternal infection

- Refer to maternal-fetal medicine
- Counsel about reproductive options
- Consider invasive testing (amniocentesis)
  - Zika virus RT-PCR can be performed on amniotic fluid, however it is not known how sensitive or specific this is for congenital infection
- Serial ultrasounds for growth, evaluation of the CNS
- Consider other imaging modalities (e.g. MRI)
  - MRI is ***NOT*** for screening
- Postnatal evaluation of neonate, placenta- coordinate with health department

Prenatal Zika virus infection → Congenital Zika Syndrome

Destruction of existing CNS tissue & Disruption of future developmental processes

Neurologic dysfunction

- -Hearing, vision, swallowing problems
- -Global developmental impairment
- -Limb contractures
- -Hypertonia, epilepsy, extreme irritability

Brain volume loss

- -Severe microcephaly
- -Misshapen skull with overlapping sutures
- -Redundant scalp

Recognizable pattern: Congenital Zika syndrome

Congenital Zika Syndrome: Unique Pattern of Malformations

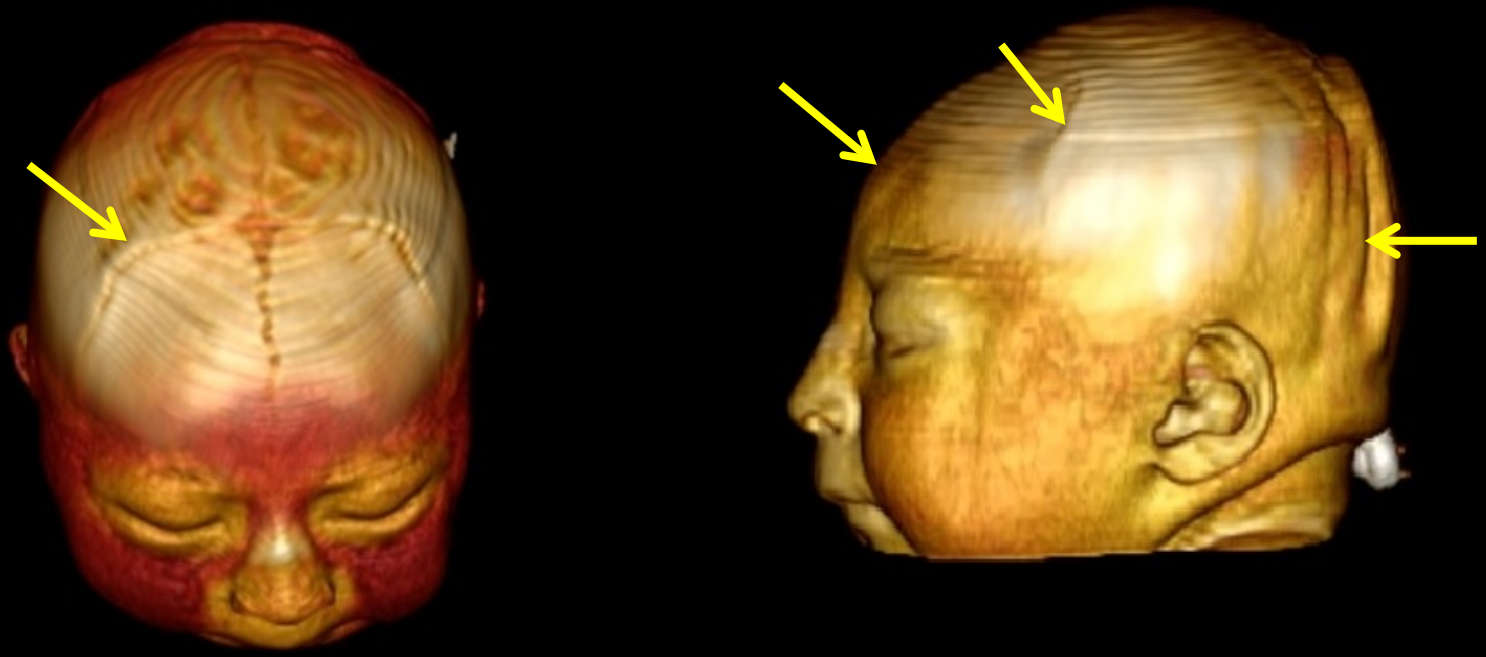
- Severe microcephaly with partial skull collapse
- Intracranial calcifications in the subcortical region
- Macular scarring and focal pigmentary retinal mottling
- Congenital contractures
- Neurologic abnormalities both pyramidal and extrapyramidal

Congenital Zika Syndrome – Cranial Morphology

- Features
  - Severe microcephaly (most more than 3 SD below the mean)
  - Partial collapse of the skull with overlapping sutures
  - Occipital bone prominence
  - Small or absent anterior fontanel
  - Scalp rugae
- Consistent with fetal brain disruption sequence (FBDS)
- Not all with severe microcephaly have FBDS phenotype
- FBDS is rare but not unique to congenital Zika syndrome

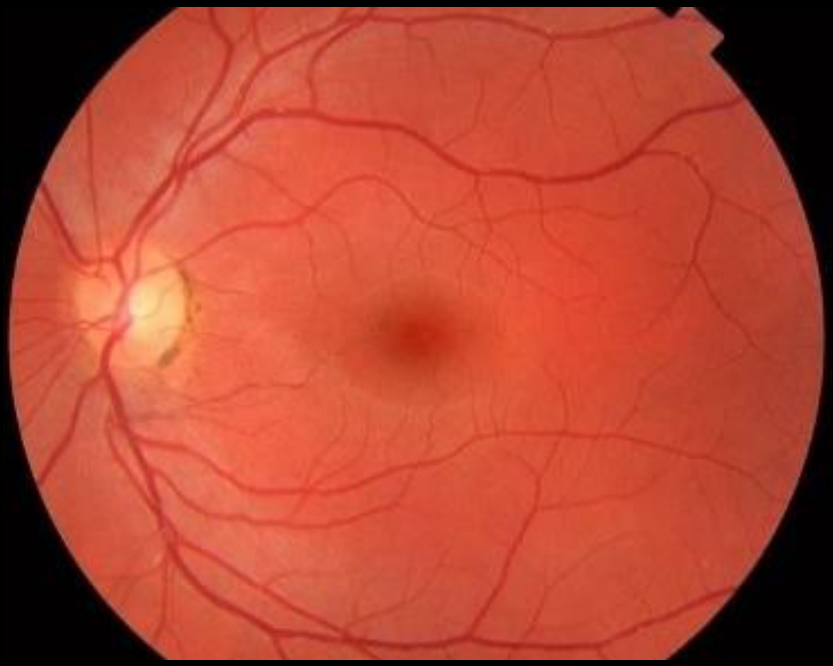
Newborn with microcephaly

CT reconstruction



Cortesia Maisa Wanderley

Congenital Zika Syndrome- Ocular findings



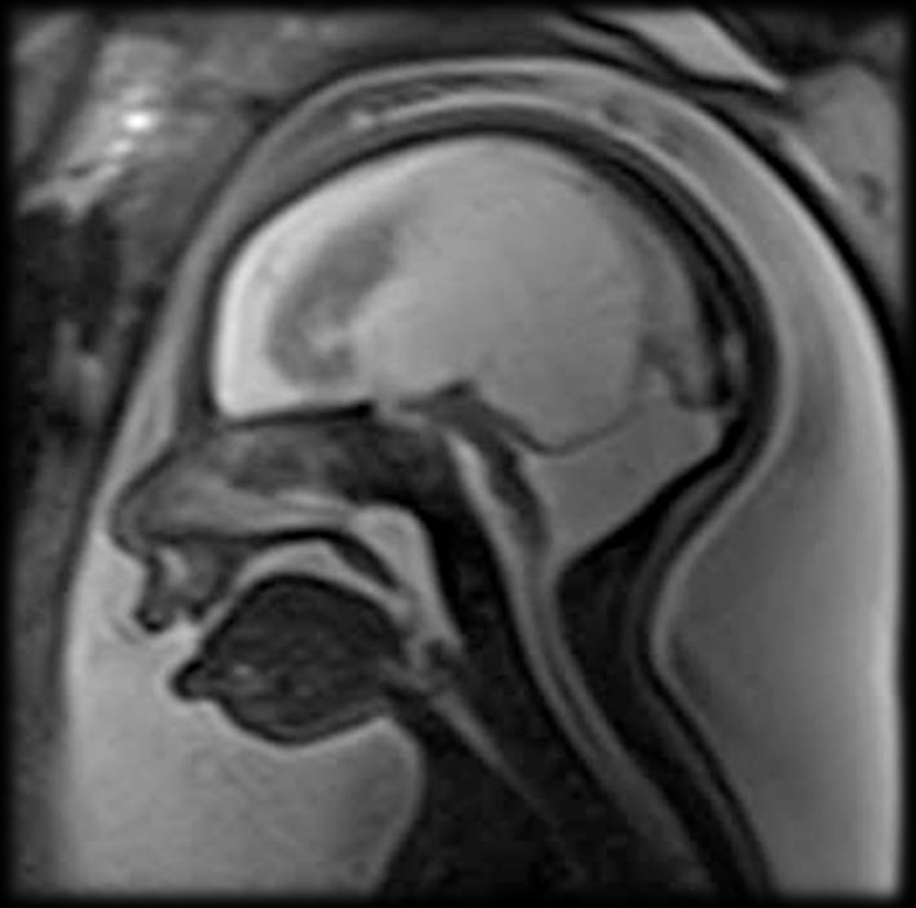
Normal fundus

Fundus of presumed Zika infection
Ventura, et.al. 2016

Congenital Zika Syndrome-Arthrogryposis

Imaging in Congenital Zika Syndrome

29 wk gestation



Zika affected

Normal

Adriana Melo-
IPESQ

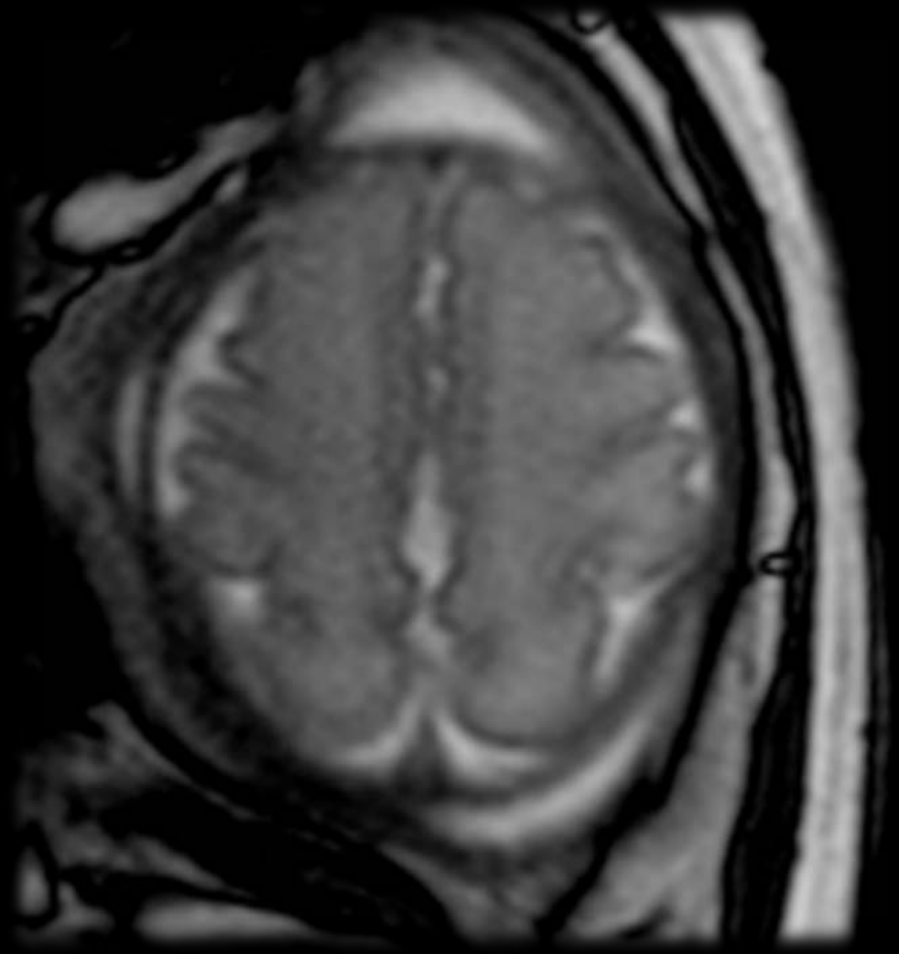
29 wk gestation

Zika affected

Normal

Adriana Melo-
IPESQ

30 wk gestation

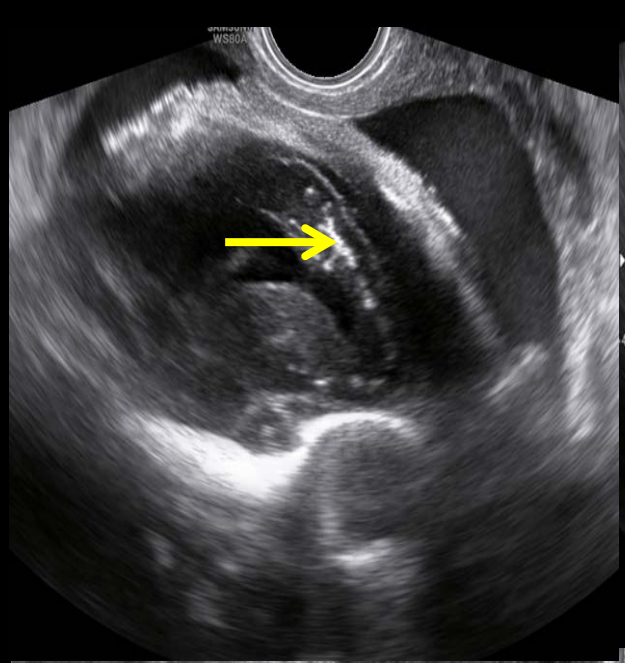


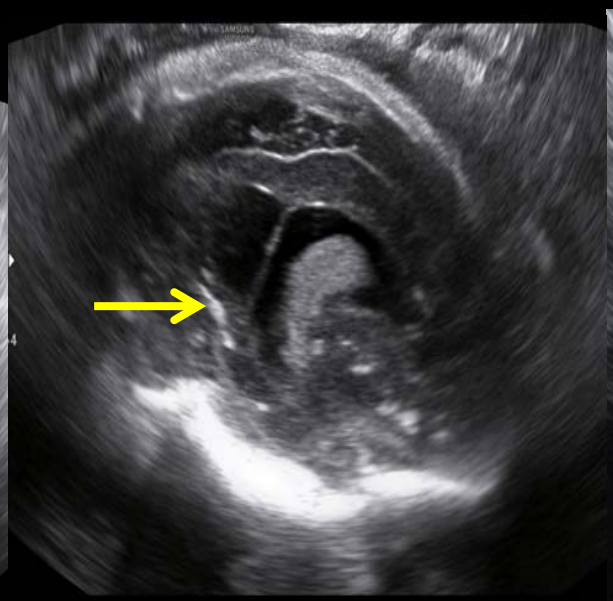
Zika affected

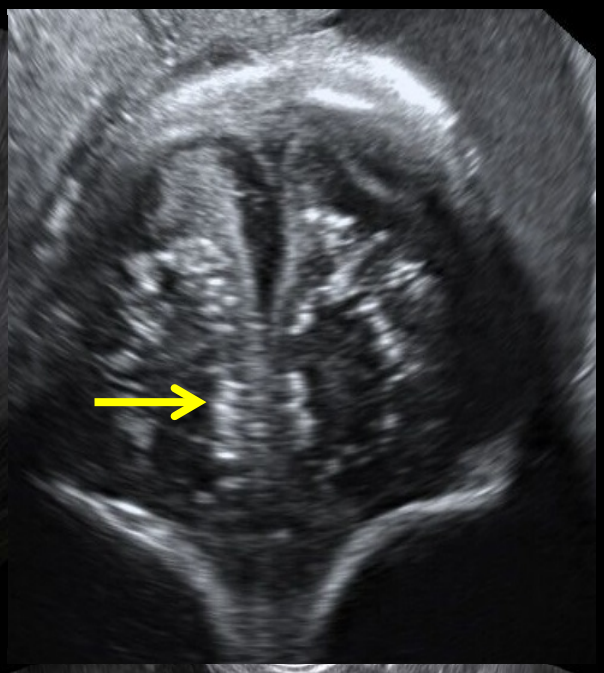
Normal

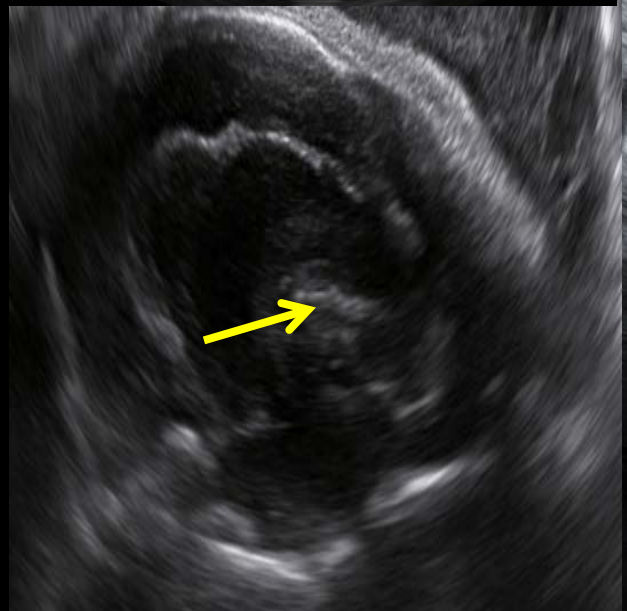
Adriana Melo-
IPESQ

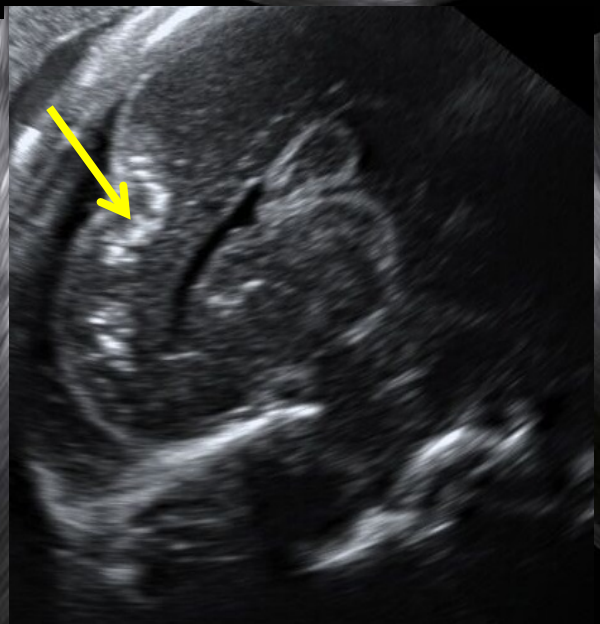
Calcifications - transvaginal ultrasound

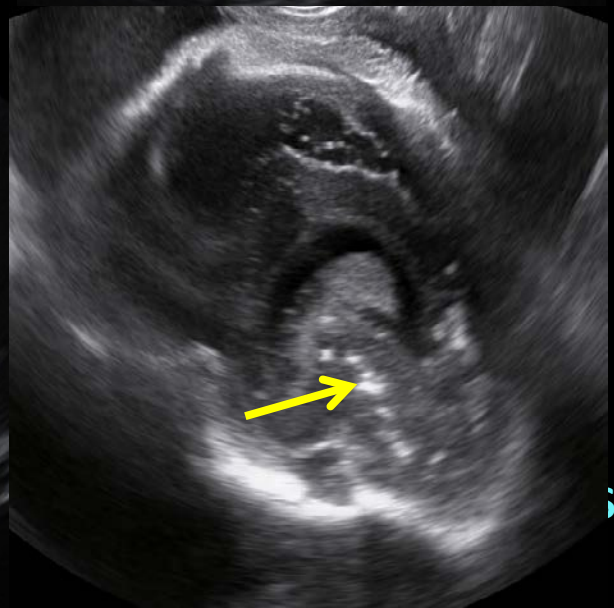




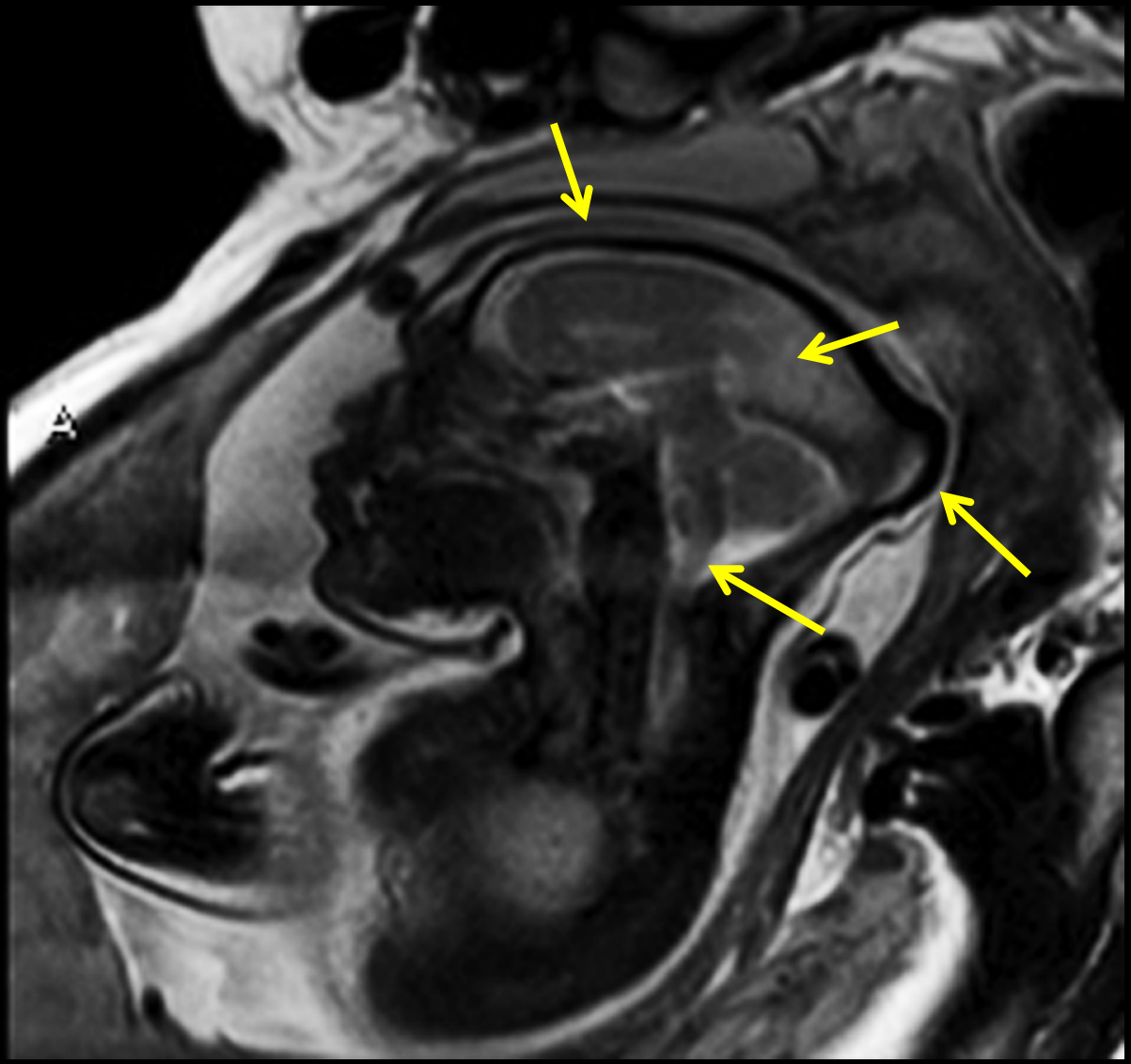








Zika MRI- sagittal

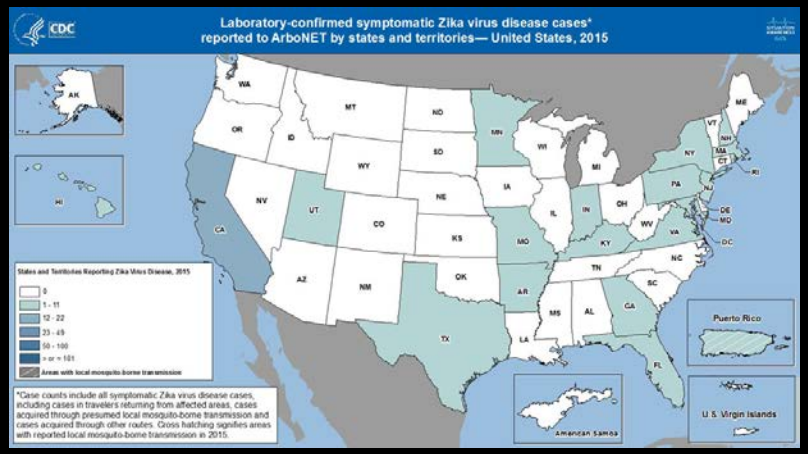


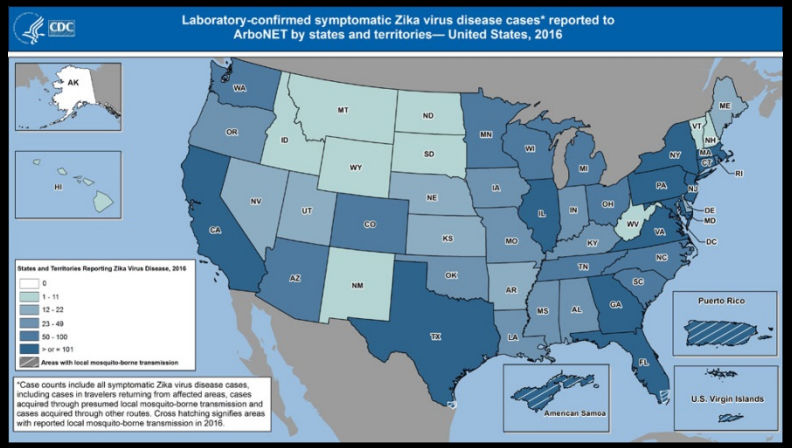
Courtesy of NOVA Diagnostico por Imagen

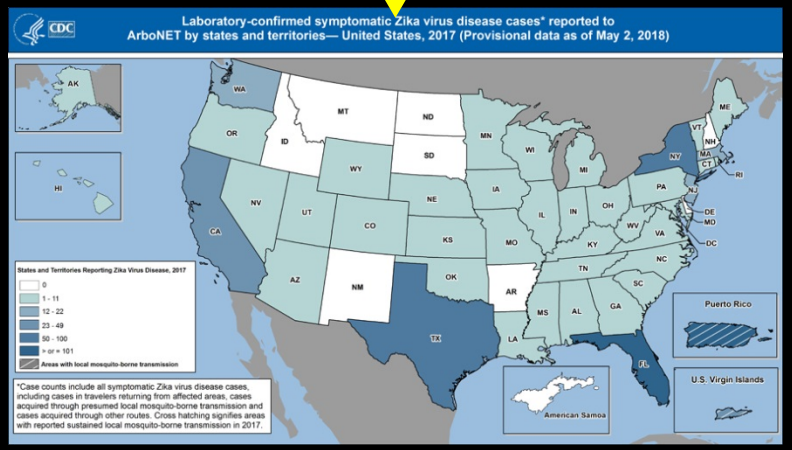
Scope of the problem in the US

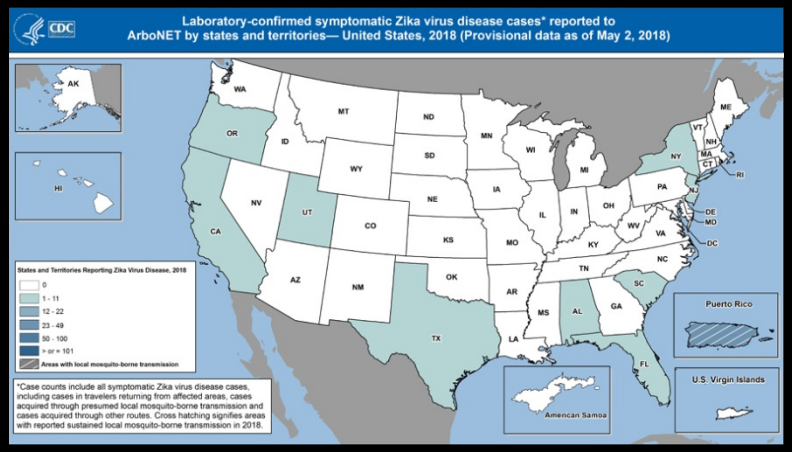
- US Zika Pregnancy Registry (CDC)
  - Preliminary data by Honein et.al. (JAMA 2017)
  - 442 completed pregnancies with +lab evidence Zika
  - Zika related birth defects found in 6% of infants of symptomatic women; 6% of infants of asymptomatic women
  - Primarily microcephaly and brain abnormalities
  - With exclusive first trimester exposure, birth defects in 11% of infants

Lab confirmed symptomatic Zika cases U.S. and territories 2015-2018









Utah experience as of 5/2018*

- Total positive moms to date: 21
- All travel related:
  - Mexico 47.62%
  - Marshall Islands 14.29%
  - Venezuela 14.29%
  - Honduras 9.52%
  - Guatemala 4.76%
  - Dominican Repub. 4.76%
  - El Salvador 4.76%

* Data from Utah Birth Defect Network/ Utah Public Health Laboratory

Utah experience as of 5/2018

- Total positive moms to date: 21
- Infants born to positive moms who then tested positive: 0
- 2 SABs tested positive for Zika- both 1st trimester
- Infants born to positive moms with microcephaly or “typical” Zika related birth defects: 0
- 1 infant not meeting milestones at 18 months

Utah experience as of 5/2018

- No major updates with testing
- Utah Public Health Laboratory
  - Symptomatic persons and exposed pregnant women tested free of charge
- Many commercial labs also conduct Zika testing for a fee

Zika Travel Information-
Areas with Risk of Zika Transmission

- Africa
- Asia
- The Caribbean
- North America
- Pacific Islands
- South America

Visit CDC's Zika website: http://www.cdc.gov/zika

Page last reviewed 5/24/18

"We're going to Puerto Rico for a wedding- is that ok?"

- Pregnant women or those trying/ capable of becoming pregnant should be counseled against travel to endemic areas
- If travel unavoidable, extreme caution to avoid exposure
  - Insect repellent (DEET, picaridin, IR3535, oil of lemon eucalyptus, para-menthane-diol, 2-undecanon)
  - Long sleeves, long pants
  - Screens on windows
  - Air conditioning

“We’re going to Puerto Rico for a wedding- is that ok?”

- Sexual transmission is well documented
- If pregnant, recommendation is for avoidance of unprotected intercourse for up to 6 months (or for duration of pregnancy) after travel to an endemic area

"I was in a place with risk of Zika recently (I went to a wedding in Puerto Rico). How long do I need to wait after returning to get pregnant?"

- Women: Women who have traveled to a place with a CDC travel notice should wait at least 8 weeks after travel (or 8 weeks after symptoms started if they get sick) before trying to conceive.

"I was in a place with risk of Zika recently (I went to a wedding in Puerto Rico). How long do I need to wait after returning to get pregnant?"

- Men: Men who have traveled to a place with a CDC travel notice should wait at least 6 months after travel (or 6 months after symptoms started if they get sick) before trying to conceive with their partner.
- The waiting period is longer for men because Zika stays in semen longer than in other body fluids.

Congenital Zika Syndrome: Longer term medical sequelae

- Longer term sequelae reported to date include the following:
  - Motor and cognitive disabilities (French Polynesia)
  - Hydrocephaly – some requiring a VP shunt
  - Worsening epilepsy
  - Feeding problems and severe reflux – some requiring a G-tube
  - Respiratory problems – diaphragmatic paralysis
  - Glaucoma
  - Potential cerebral palsy
  - Potential endocrine abnormalities
  - Microcephaly onset after birth

Many questions remain….

- What is the full range of potential reproductive health problems that Zika virus infection may cause?
- How long does the virus persist in various tissues after infection?
- What are other factors (e.g., co-occurring infection, nutrition, presence of symptoms) that might affect the risk for birth defects?
- Is there a way to predict who is at risk for long term sequelae?

Thanks to my CDC friends

- Cynthia Moore, PhD, MD
  - Director of the Division of Congenital and Developmental Disorders
  - Zika Virus Response Team
- Jan Cragan, MD, MPH
  - Medical officer with the National Center on Birth Defects and Developmental Disabilities
- Sonja Rasmussen, MD, MS
  - Director, Division of Public Health Information Dissemination, Center for Surveillance, Epidemiology, and Laboratory Services
  - Editor-in-chief, *Morbidity and Mortality Weekly Report*

Questions?