



# Growth patterns among structurally normal fetuses with documented Zika virus infection during pregnancy

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# Zika Epidemic in Puerto Rico



- It is estimated that the Zika virus might infect 20% of the population in PR. The first case was documented in December 2015 but the peak of the epidemic was seen on 2016.
- Potentially, **6-7,000 pregnant women** would have been infected with Zika out of the **34,485** live births reported on 2014.  
<http://sp.rcm.upr.edu/demo/index.php/series-historicas-estadisticas-vitales/nacimientos-vivos>
- A significant proportion of the infants born to women with Zika could have the severe manifestation of CZS and perhaps a larger proportion might be affected by the spectrum of disease that includes ocular, hearing and other manifestations, growth and neurodevelopmental issues including disability.





# Zika Testing In Puerto Rico



- The PR Department of Health following CDC Guidelines started testing of all pregnant women during the 1<sup>st</sup> and 2<sup>nd</sup> trimester irrespective of symptoms and later offered routine testing in all trimesters (1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup>).
- Zika testing is also offered **anytime in pregnancy if symptoms appear.**
- The Trioplex Real-time RT-PCR Assay is used for detection and differentiation of RNA from **Dengue, Chikungunya and Zika** viruses in serum, whole blood (EDTA), cerebrospinal fluid (CSF) and for the detection of Zika virus RNA in urine, and amniotic fluid.
- Zika Virus Antibody (IgM), MAC-ELISA is also used

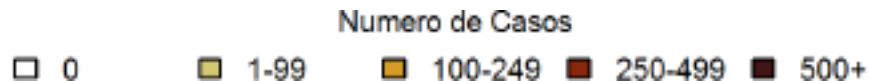
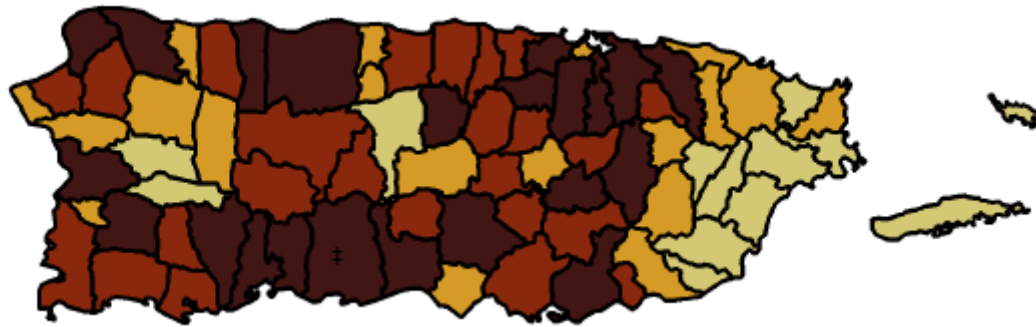


# Confirmed Zika cases, PR

Week 5, 2017 (January 29 to February 4, 2017)

<http://www.salud.gov.pr/Estadisticas-Registros-yPublicaciones/Pages/VigilanciadeZika.aspx>

## Confirmed cases (n = 38,733), week 5



### Other findings

68 Guillain–Barré (GBS).

51 Zika

17 flavivirus

2 deaths associated to GBS

12 congenital defects

### Cumulative ZIKV, 2015–2016

38,733 confirmed cases

3,076 pregnant women

1,766 (57%) symptomatic

1,310 (43%) asymptomatic

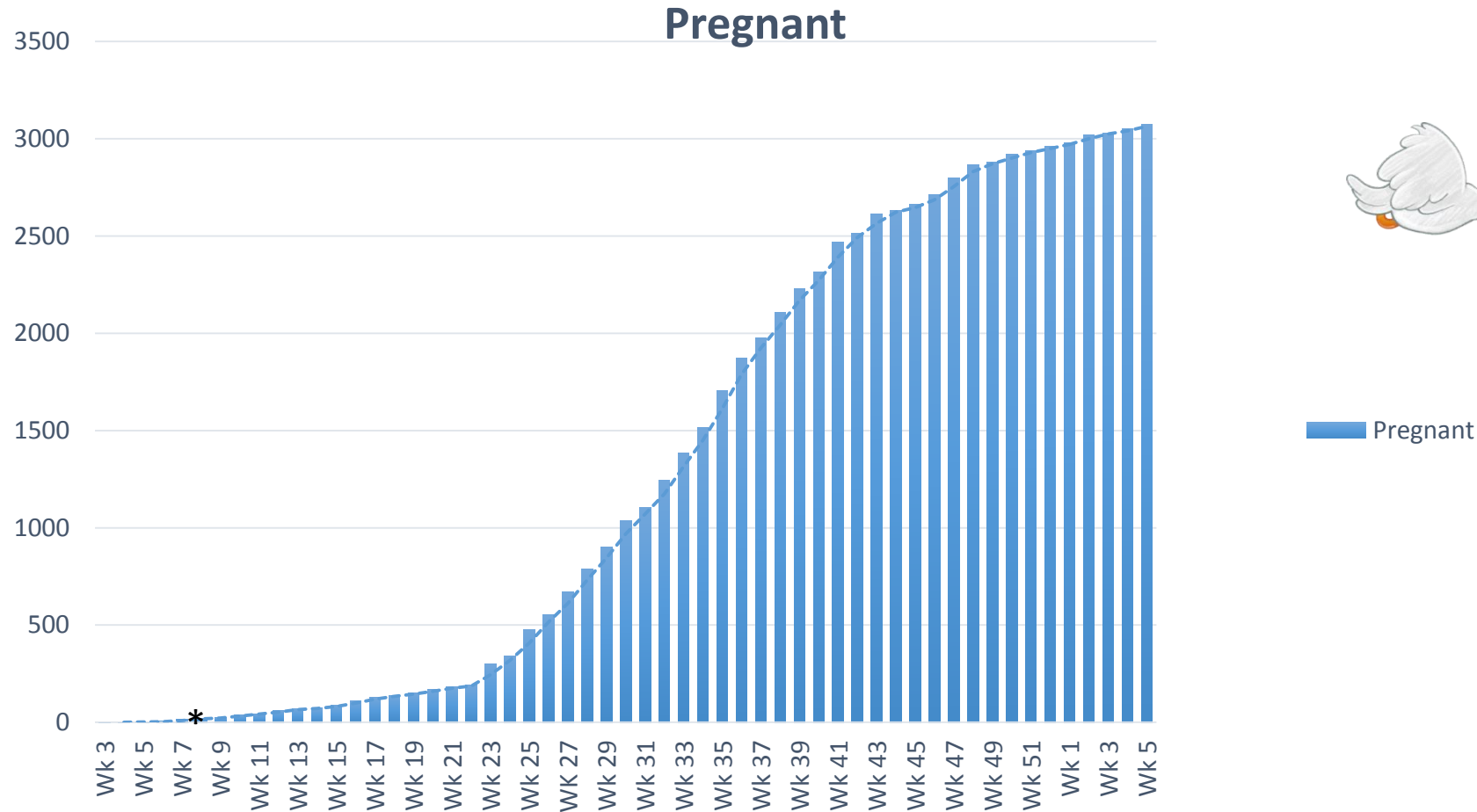
389 (<1%) hospitalized

5 deaths

# Confirmed Zika cases in pregnant women, PR

Up to week 5 (January 29 to February 4, 2017)

<http://www.salud.gov.pr/Estadisticas-Registros-y-Publicaciones/Pages/VigilanciadeZika.aspx>

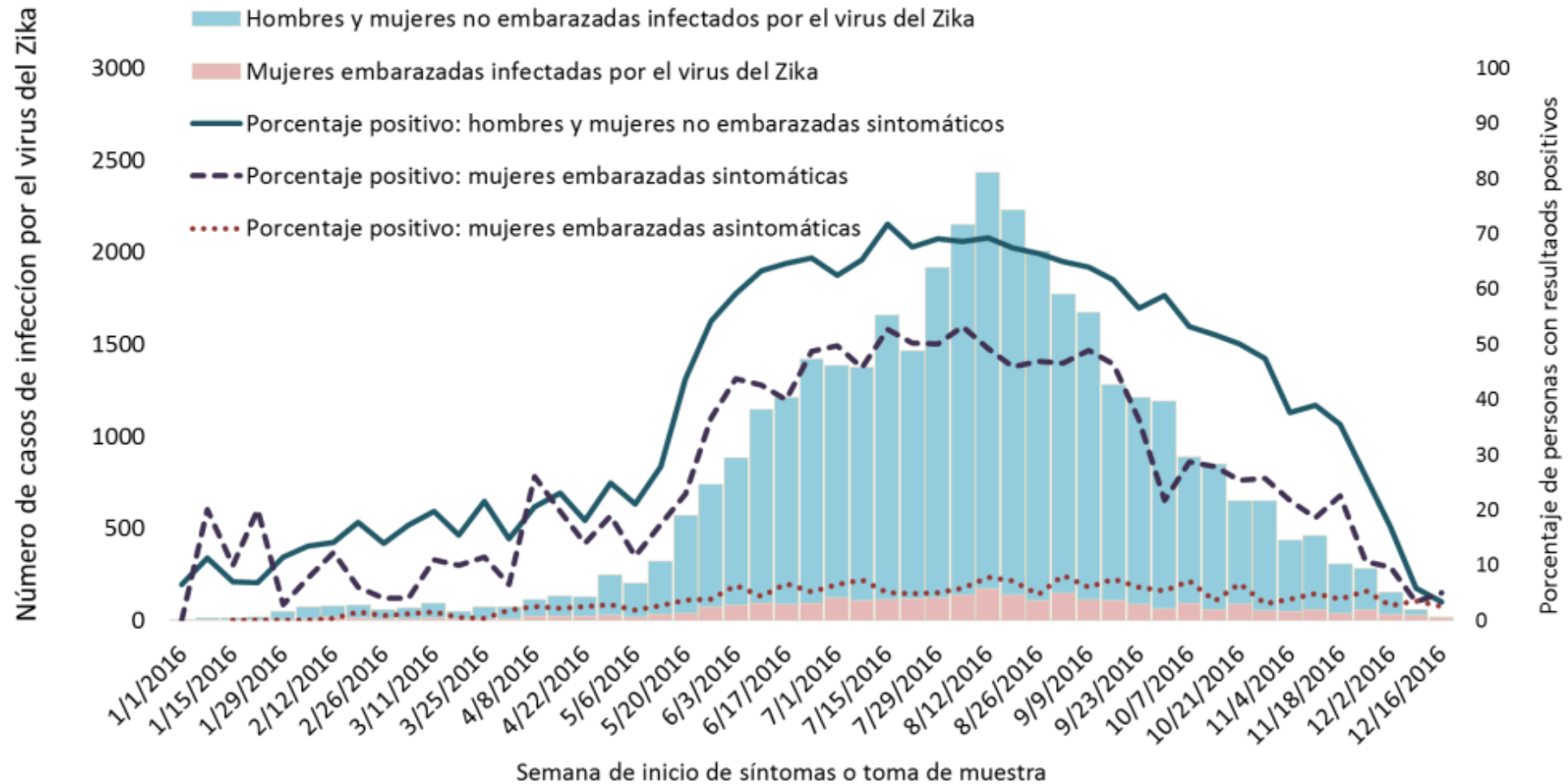


# Zika cases in Puerto Rico according to symptoms and pregnancy status

Source: PR health department/Up to December 22, 2016.

[https://www.salud.gov.pr/Estadisticas-Registros-y-Publicaciones/Documents/Sistema%20de%20Vigilancia%20Activa%20de%20Zika%20en%20Embarazos%20semana%201-51\\_2016.pdf](https://www.salud.gov.pr/Estadisticas-Registros-y-Publicaciones/Documents/Sistema%20de%20Vigilancia%20Activa%20de%20Zika%20en%20Embarazos%20semana%201-51_2016.pdf)

[https://www.salud.gov.pr/Estadisticas-Registros-y-Publicaciones/Documents/Sistema%20de%20Vigilancia%20Activa%20de%20Zika%20en%20Embarazos%20semana%201-51\\_2016.pdf](https://www.salud.gov.pr/Estadisticas-Registros-y-Publicaciones/Documents/Sistema%20de%20Vigilancia%20Activa%20de%20Zika%20en%20Embarazos%20semana%201-51_2016.pdf)





Severe Brain damage  
caused by Zika virus  
Infection has been  
well documented  
with rates of CZS of  
1-11%

Honein MA et al US Zika Pregnancy Registry ; Birth Defects Among Fetuses and Infants of US Women With Evidence of Possible Zika Virus Infection During Pregnancy. JAMA

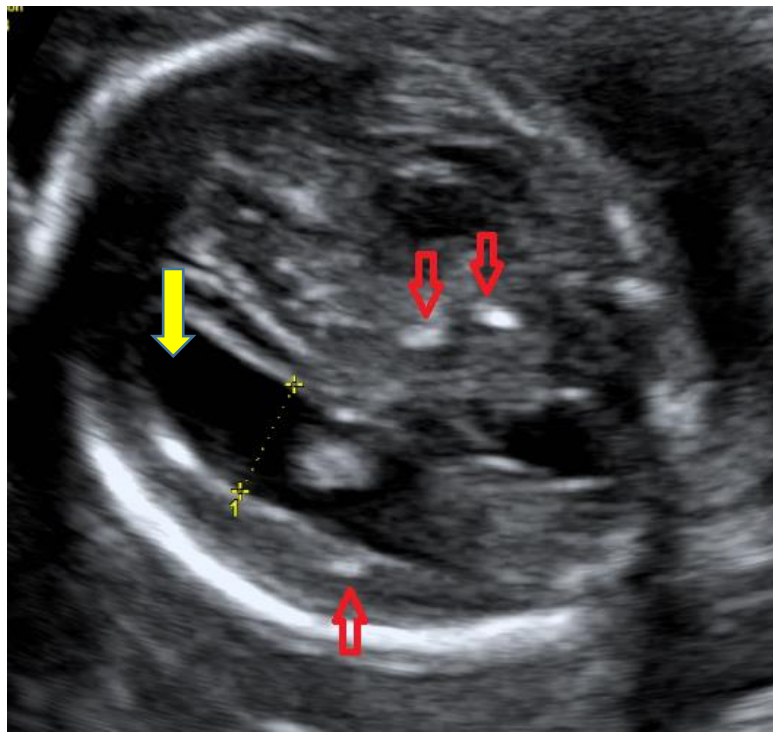
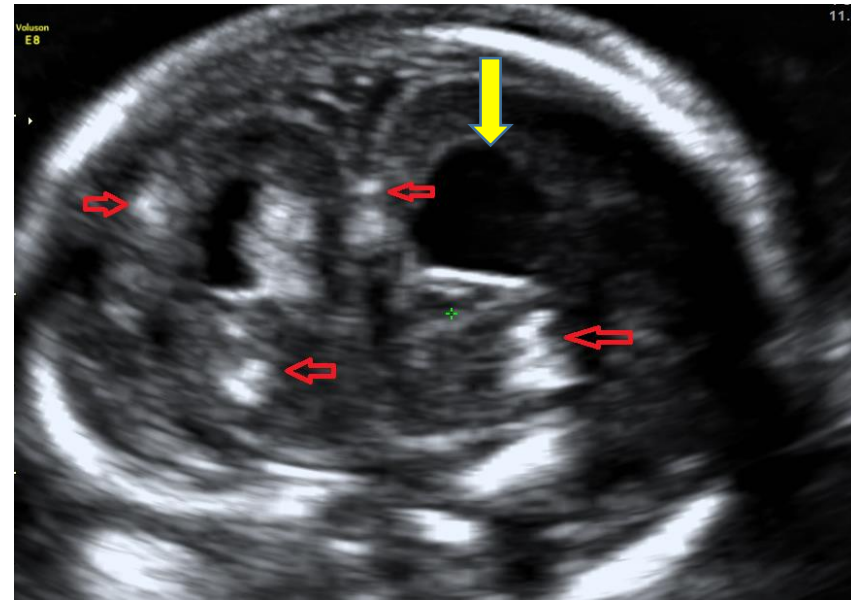
<http://jamanetwork.com/journals/jama/fullarticle/2593702>

P Brasil, J Pereira, C Raja, et al., "Zika Virus Infection in Pregnant Women in Rio de Janeiro – Preliminary Report," NEJM

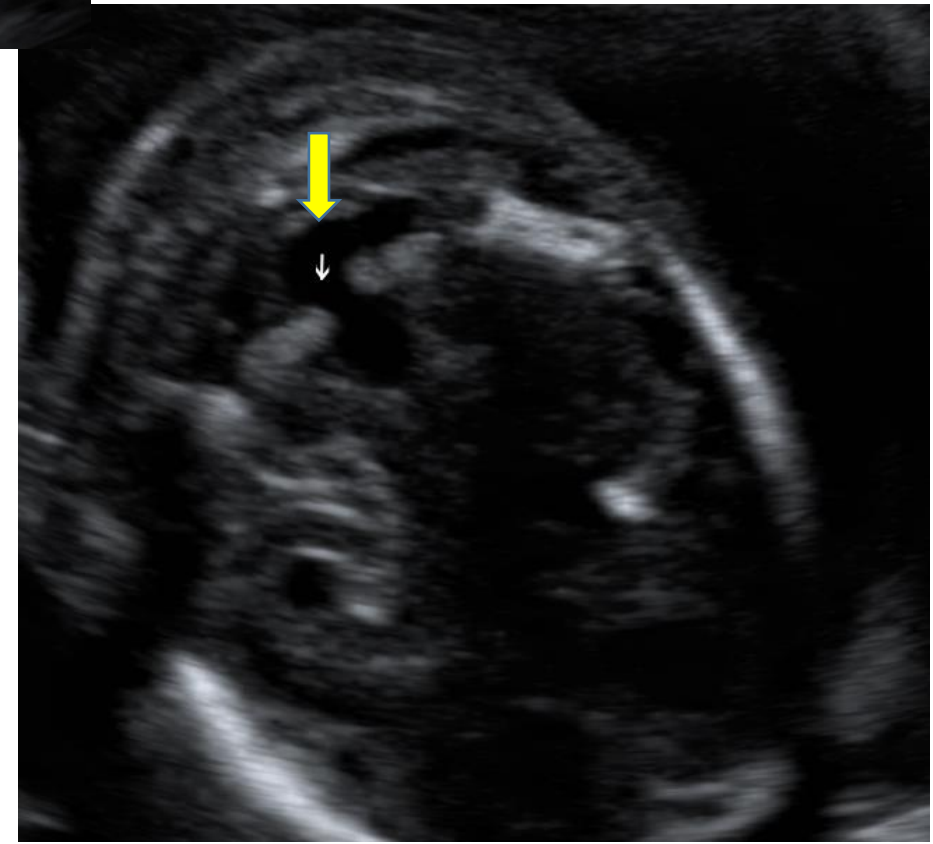
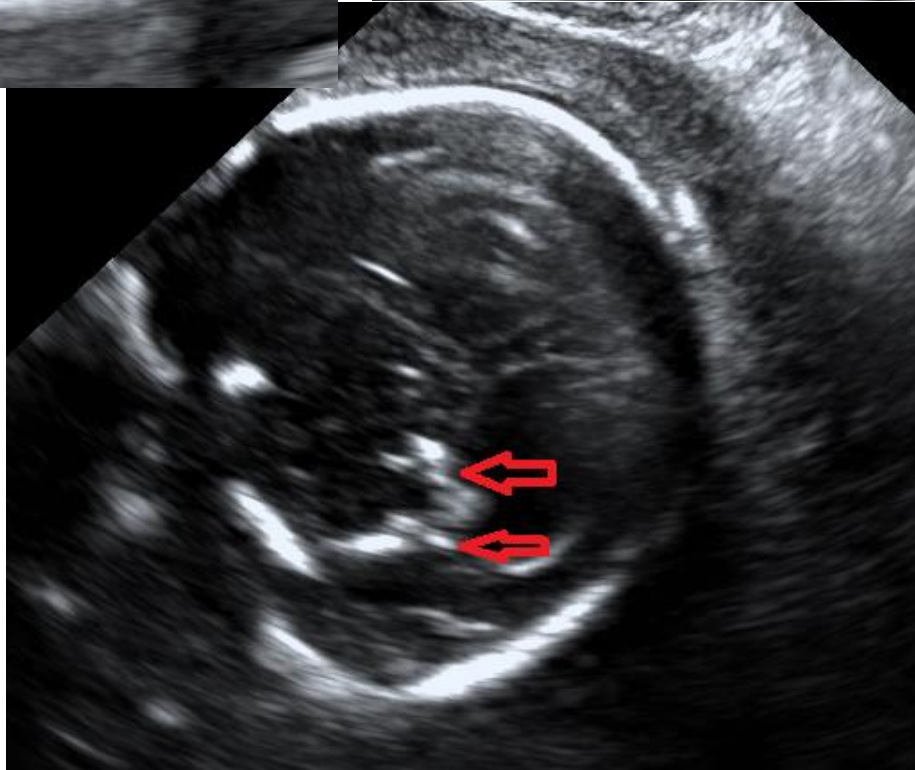
<http://www.nejm.org/doi/full/10.1056/NEJMoa1602412>



Ventricular dilatation and abnormal cerebellar development (yellow arrows)



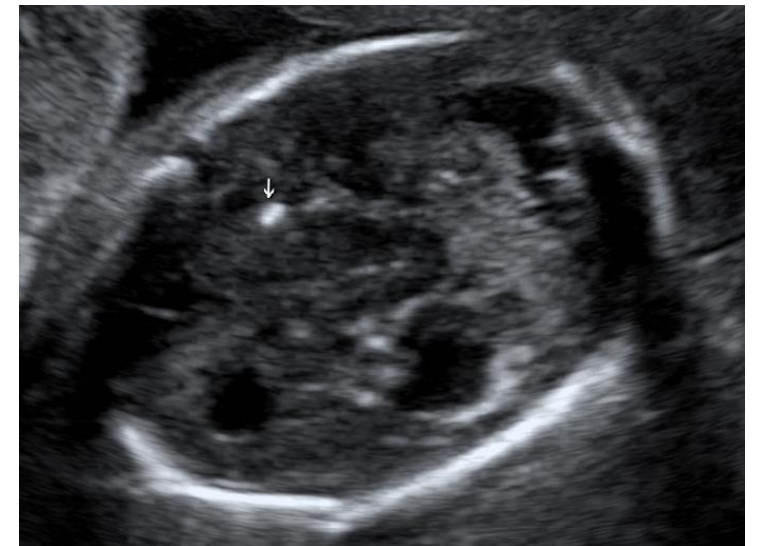
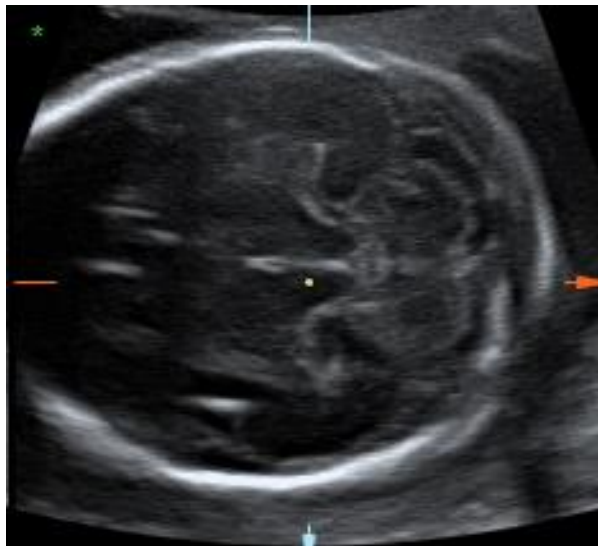
Intracranial calcifications (red arrows) in fetuses affected with Zika during the first trimester of pregnancy





# The full spectrum of materno-fetal Zika Virus Infection is yet to be defined:

- Hypothesis: A condition that can cause devastating effects in the fetus such as the Congenital Zika Syndrome (CZS) and microcephaly secondary to brain tissue damage, is capable of producing a full range of disease **from normal to severe**.



# Methods

- Growth patterns of FETUSES WHOSE MOTHERS CONTRACTED Zika Virus infection during pregnancy and showed **no prenatal intracranial anomalies** were evaluated prospectively.
- In all cases, the diagnosis of Zika was based on patient symptomatology suggestive of Arboviral disease and confirmed by a positive Zika PCR.
- Patients were grouped based on the timing of the infection during pregnancy and followed prospectively with Level II sonographic evaluations performed by an experienced sonographer.
- We chose one study performed more than 6 weeks after the documented ZIKA to allow time to identify any impact on growth.
- Their biometric data was compared to a reference population of normal fetuses from the years 2014 and 2015 prior to the onset of the ZIKA epidemic in P.R.

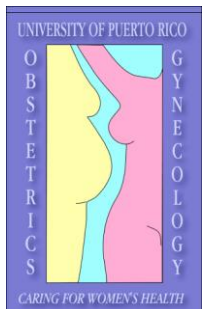
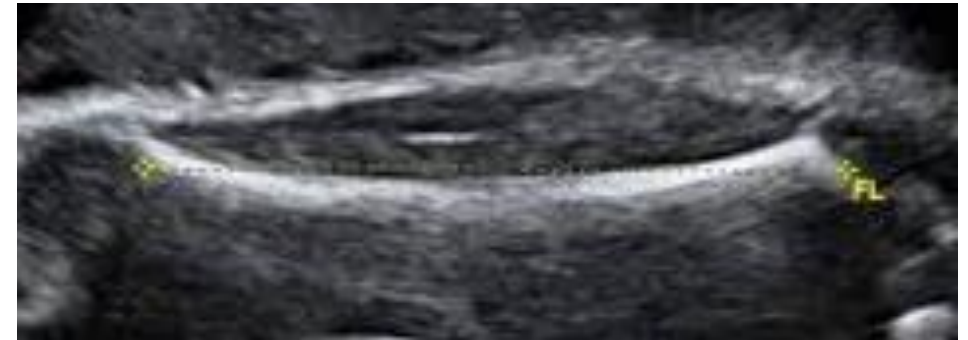


# Exclusion Criteria



- For both the reference population and the Zika affected cases, exclusion criteria included:
  - Any maternal condition judged to be capable of producing abnormal fetal growth
  - Maternal drug use or exposure to medications that could affect fetal growth
  - Uncertain gestational age
  - Multiple gestation
  - Fetal structural anomalies identified on the examination
  - Documented fetal genetic abnormalities
  - Abnormal placentation
  - Abnormal amniotic fluid volume at the time of examination
  - A single umbilical artery
- For the Zika affected pregnancies, uncertainty as to when the infection occurred was also an exclusion criteria.

Biometry was obtained using standard sonographic criteria established by the AIUM (American Institute of Ultrasound in Medicine)



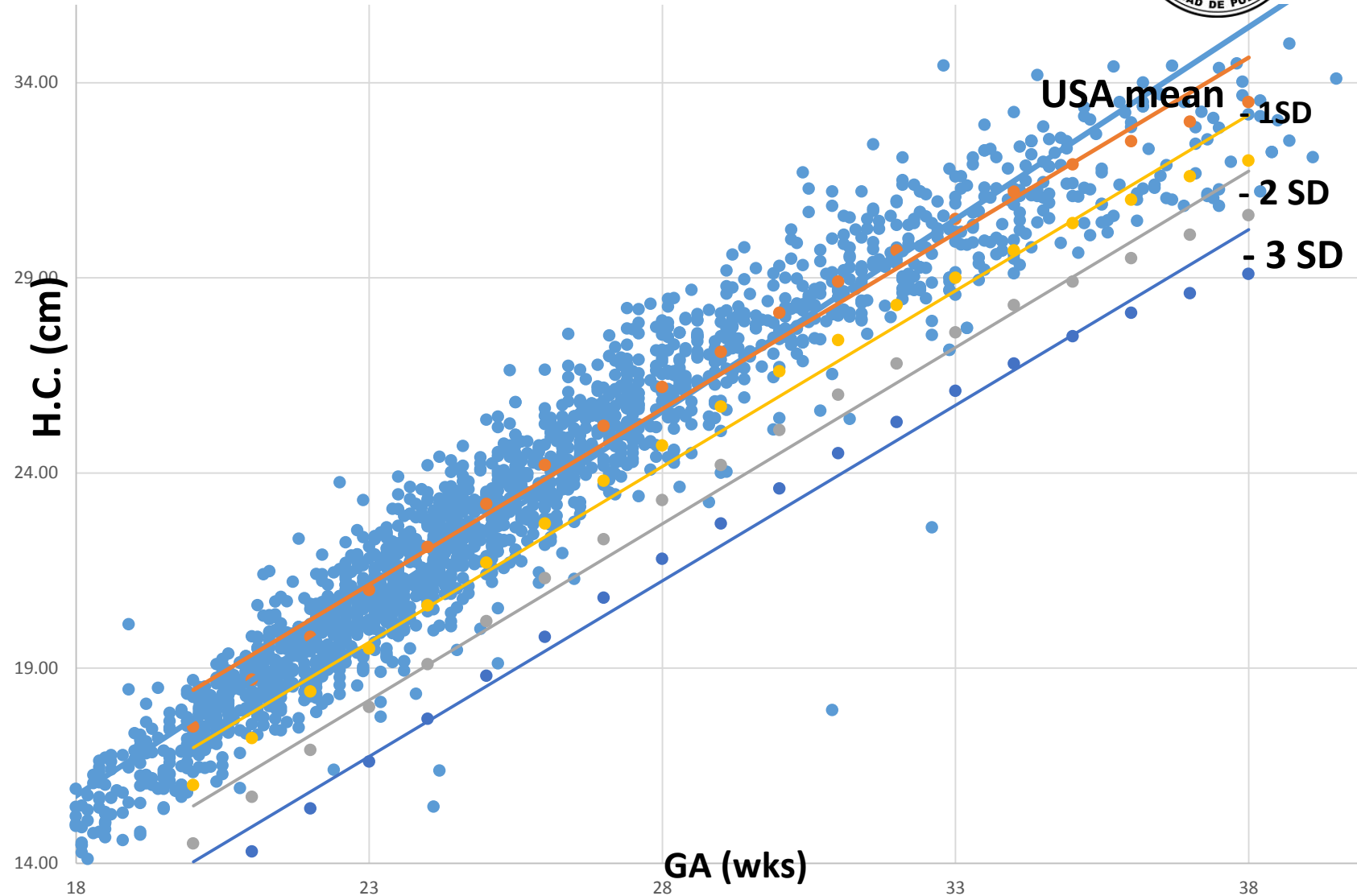


Reference population from 2014 and 2015 prior to the onset of the Zika epidemic in Puerto Rico:

(N = 2016)



- The mean, -1, -2, and -3 SD for our population are equivalent to the standards reported in the U.S.A.





# Results

- A total of 620 patients were referred for evaluation due to Zika Infection during pregnancy
  - Evidence of brain damage: 14 (2.3%)
  - Meeting exclusion criteria 298 (48%)\*
- \* Most excluded cases were because of asymptomatic Zika infection



Of 620 patients referred to our institution for evaluation due to Zika infection during pregnancy, 322 (52%) met the **inclusion** criteria

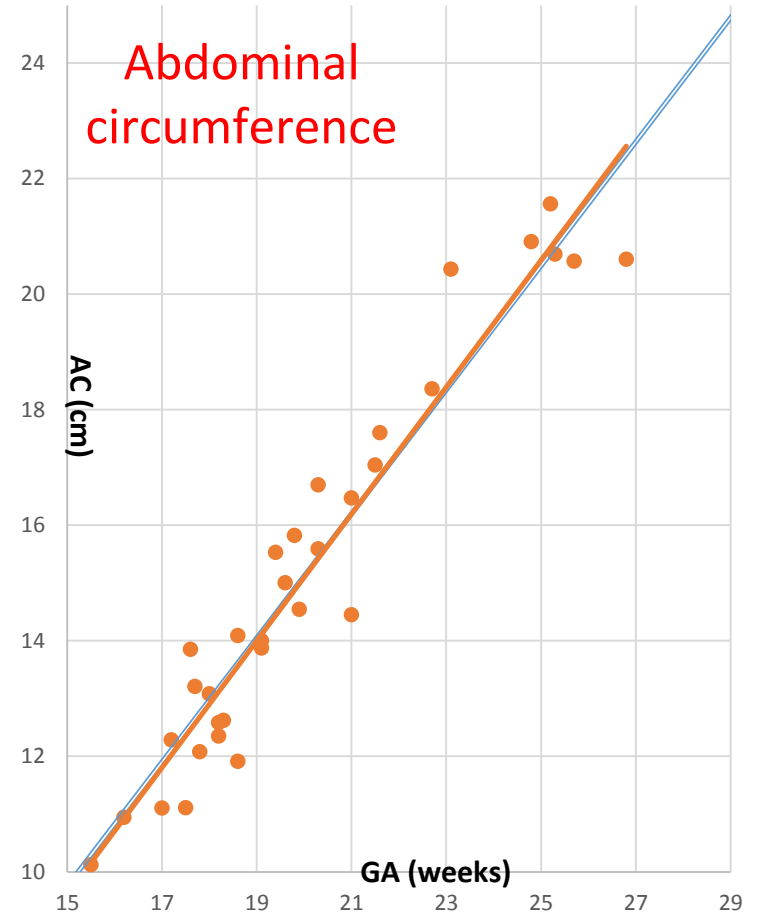
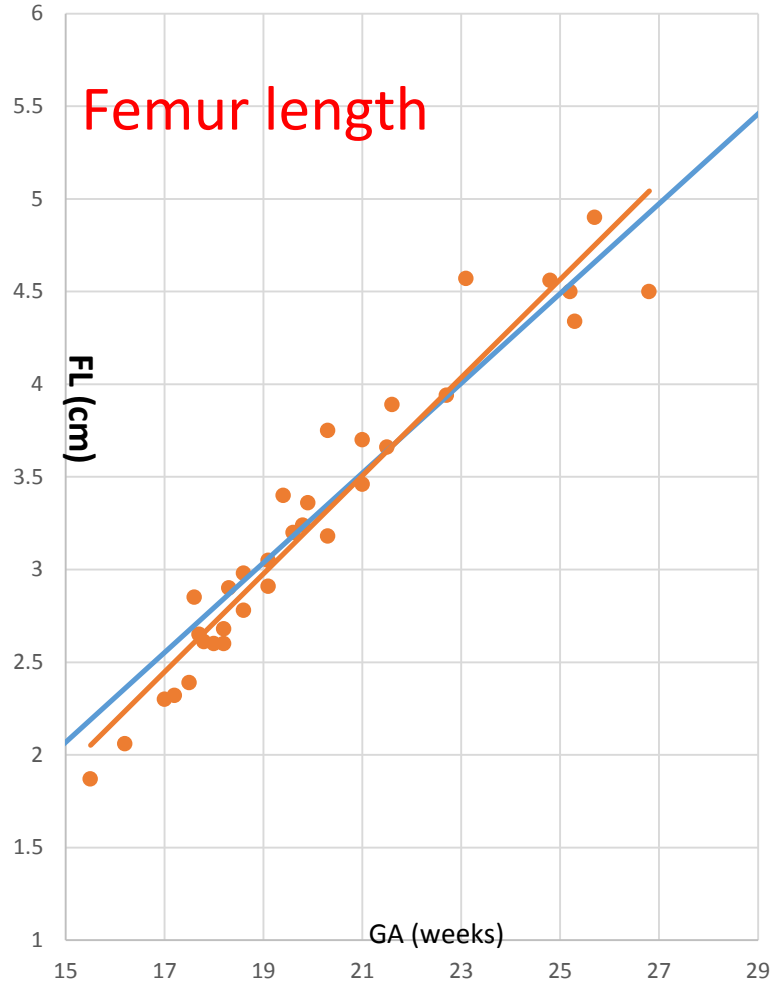
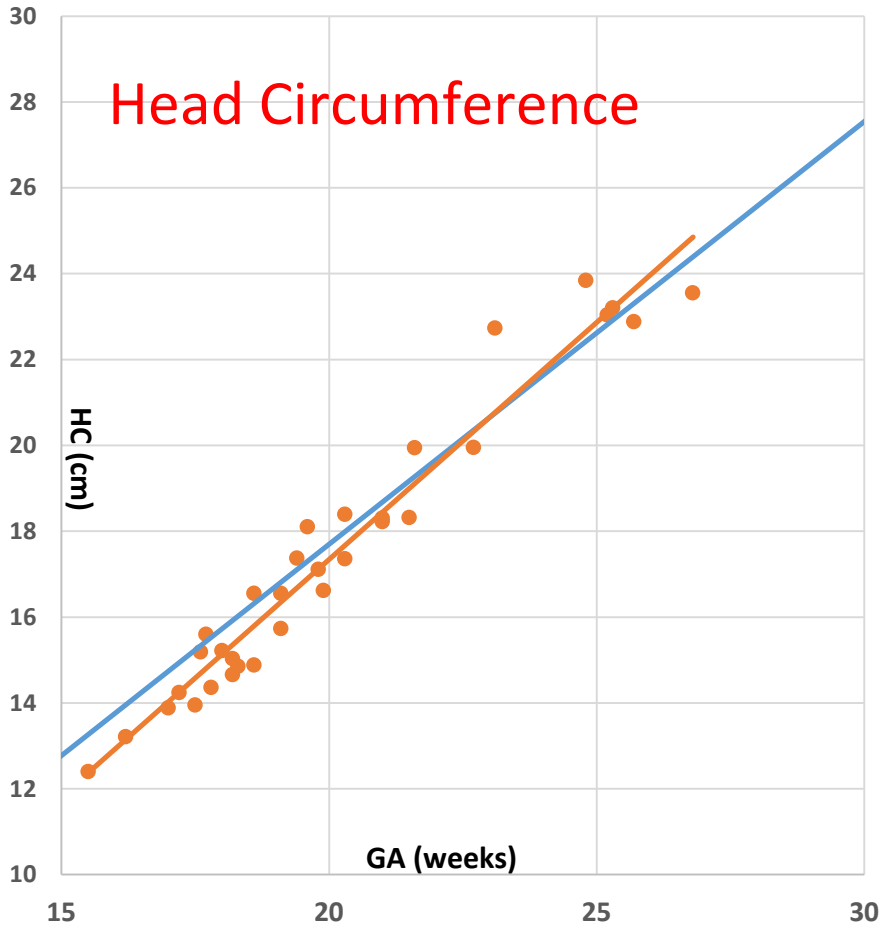


- These Patients were grouped according to the timing of infection during pregnancy:
  - **Group I:** prior to 7 weeks of gestation: **33**
  - **Group II:** between 7 and 14 weeks of gestation: **85**
  - **Group III:** between 14 and 26 weeks of gestation: **170**
  - **Group IV:** after 26 weeks of gestation: **34**

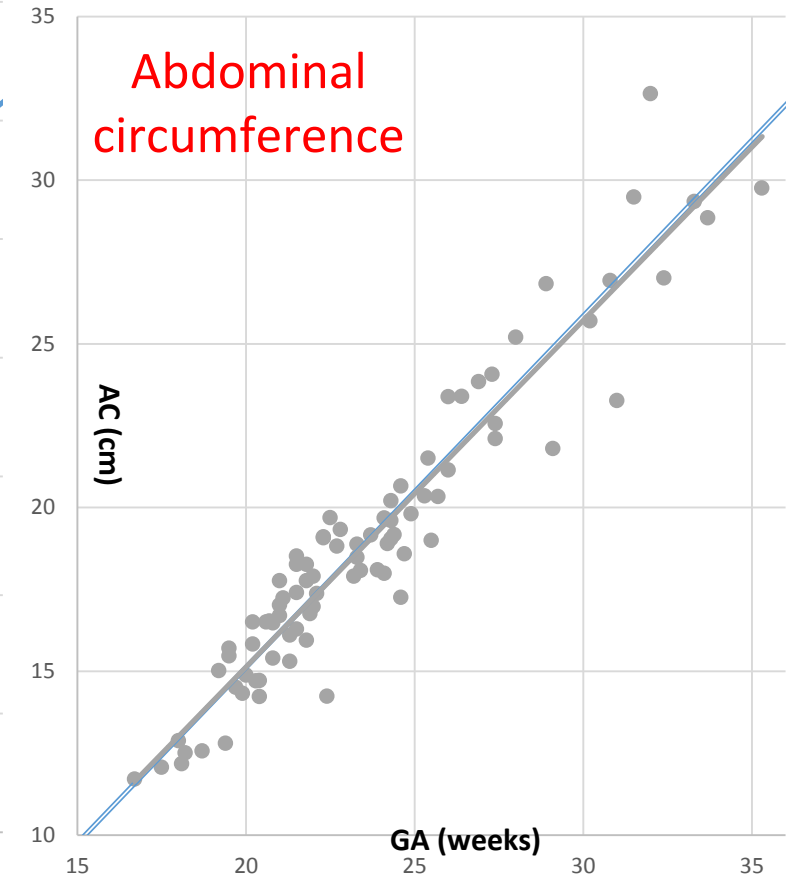
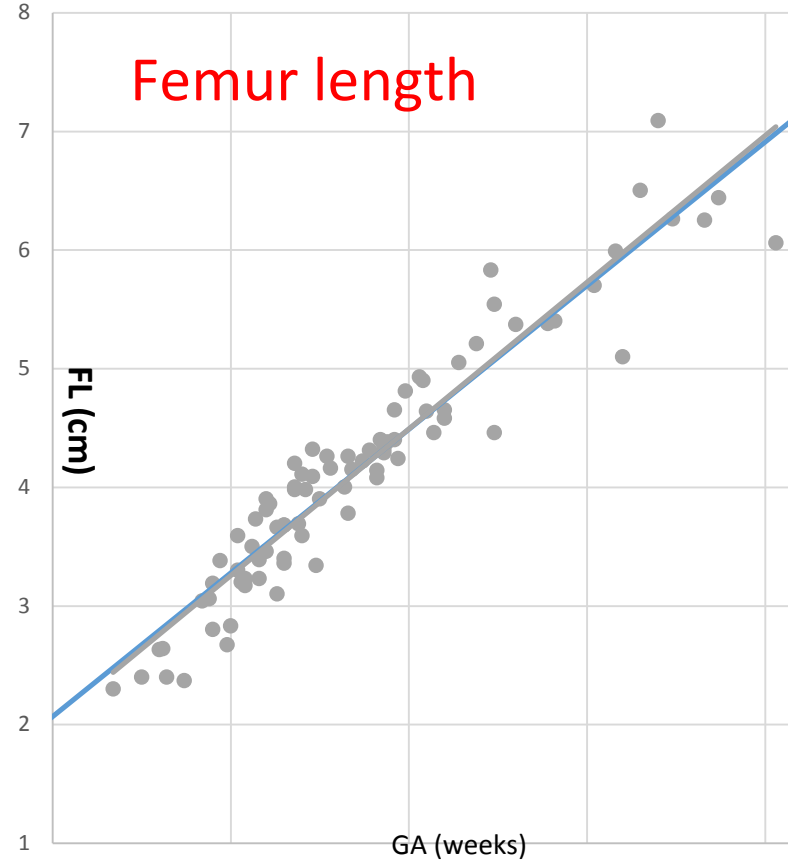
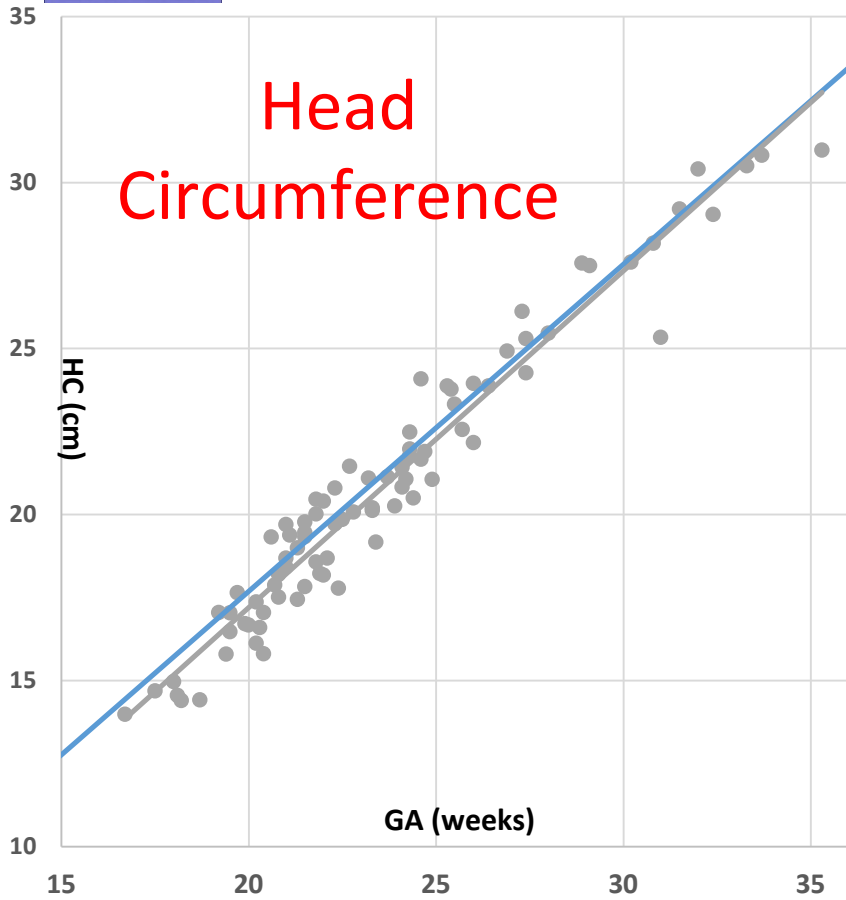


# Group I: Zika onset prior to 7 weeks

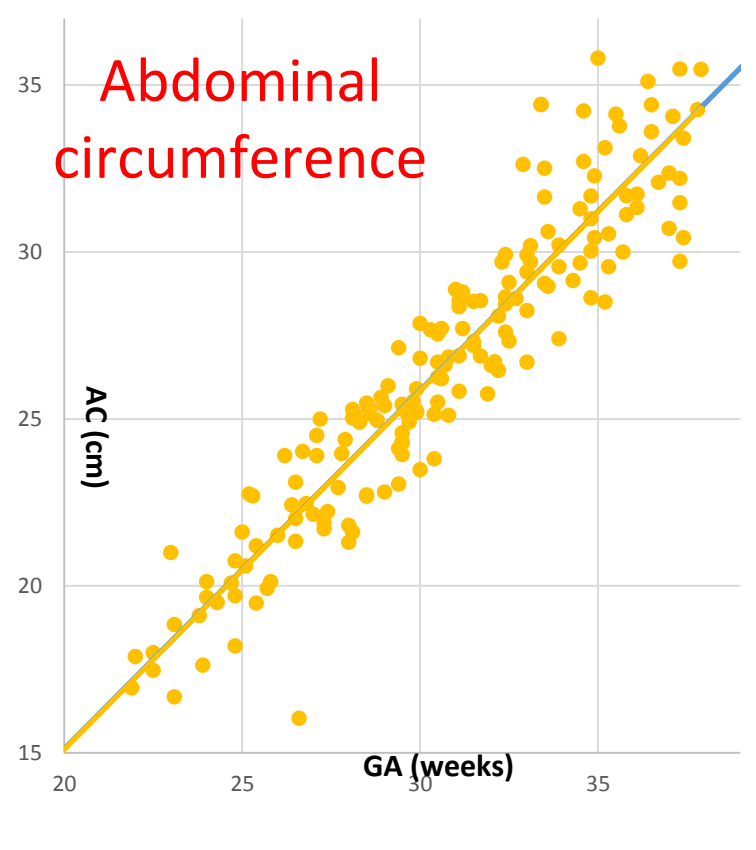
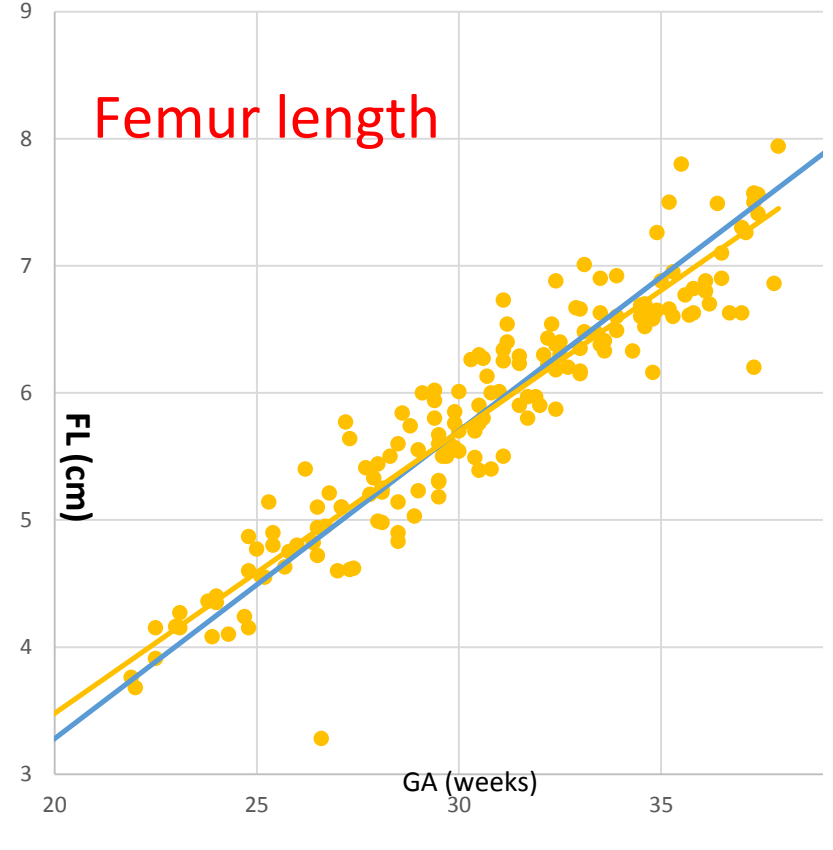
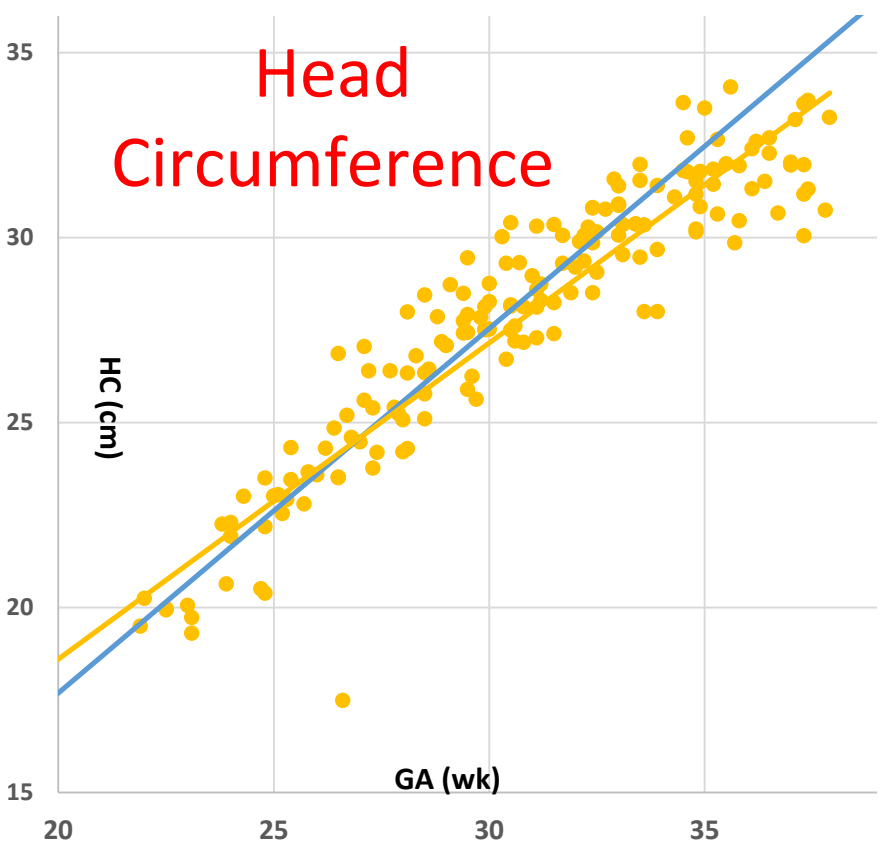
N = 33



# Group II Zika onset between 7 and 14 weeks (N= 85)

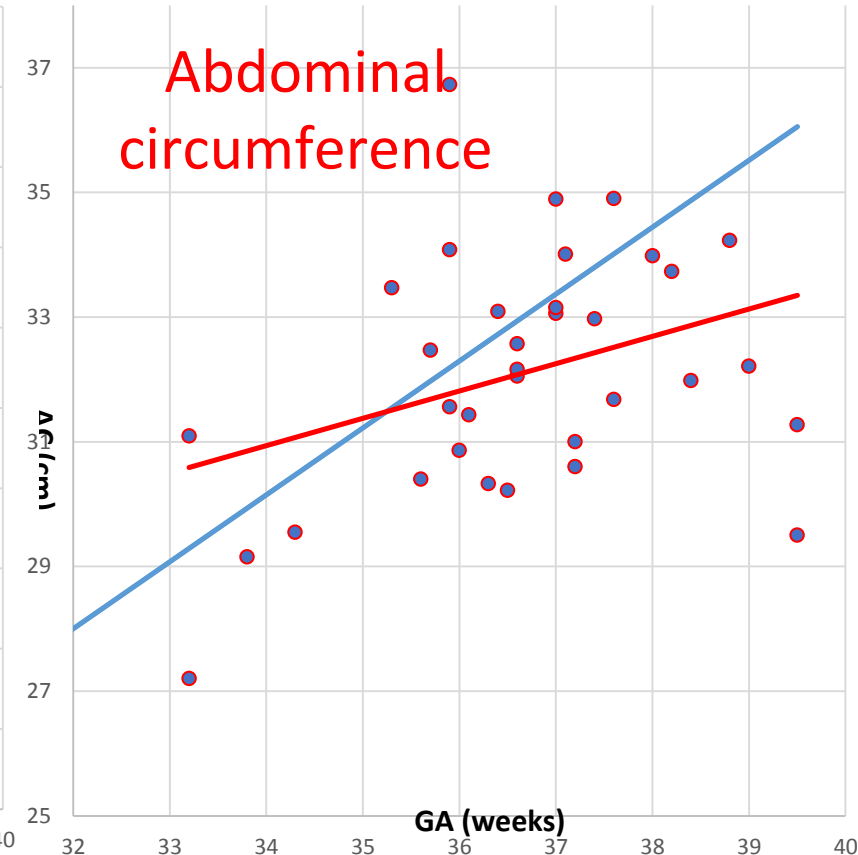
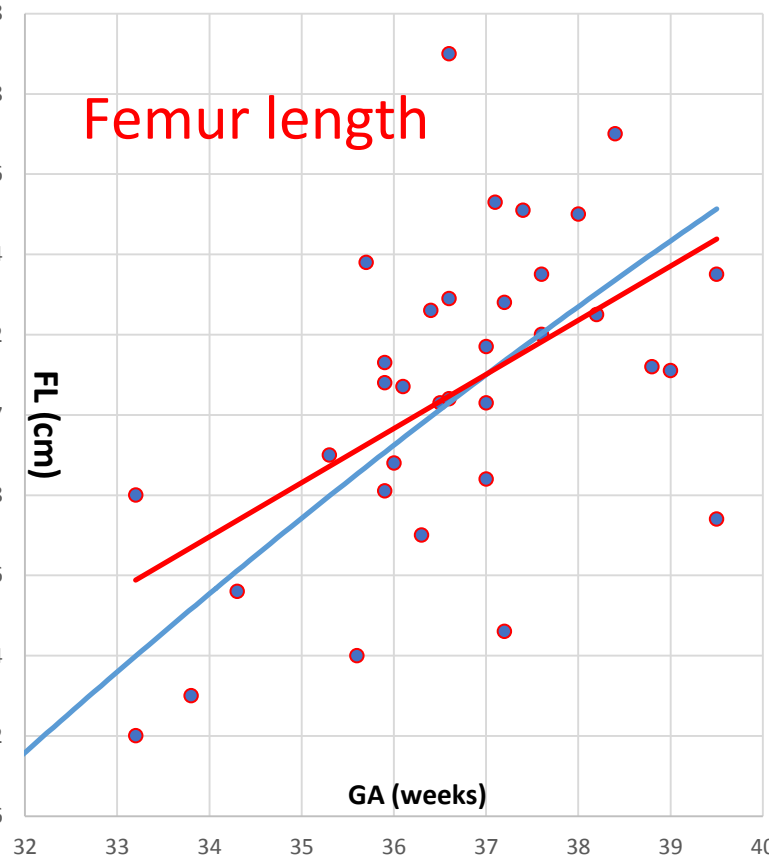
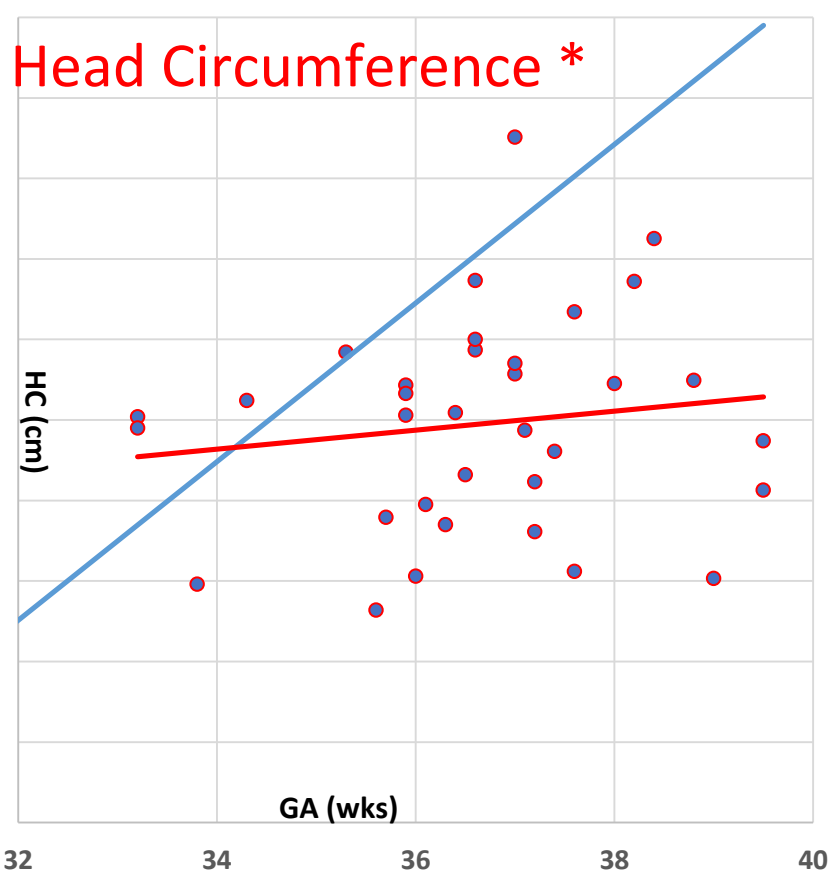


# Group III: Zika onset between 14 and 26 weeks (N=170)





# Group IV: Zika onset later than 26 weeks (N=34)\*



- Fisher's test ( $p=0.0175$ )
- TWO WAY ANOVA ( $p= 0.01776$ )

- Fisher's Test ( $p= 0.0463$ )
- TWO WAY ANOVA ( $p= 0.065$ )



# Findings:



- Fetuses with normal brain imaging whose mothers were affected with Zika infection during pregnancy have **smaller head circumferences than controls** ( $P = .0000154$ ).
- Fetuses whose mothers are affected by Zika Infection during pregnancy **prior to 26 weeks** of gestation that show no evidence of brain damage on sonography **appear to have a normal growth pattern throughout the rest of the pregnancy.**



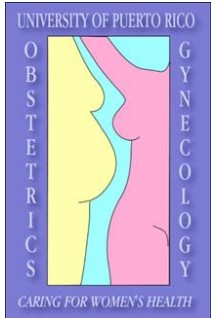
## Findings (2)

- Infection **after 26 weeks** of gestation produces a tendency towards **smaller head size** ( $p = 0.0175$ ) while other biometric parameters grow within the expected range.
- These findings require close attention and follow up since they may be a marker for future developmental anomalies that cannot be prenatally detected.
- The finding of “postnatal microcephaly” may be the result of such infections occurring late in pregnancy.



# Conclusions

- Zika infection during pregnancy can affect fetal brain growth, as measured by head circumference, even in the presence of normal sonographic imaging.
- This effect over the growth of the brain is not manifested in other biometric measures such as the femur or abdomen.
- The significance of such growth patterns on the infants future neurologic development is uncertain but definitively worrisome.
- This data suggests a spectrum of disease that is yet to be properly defined



# Thanks



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