Impact of Postnatal Head Circumference Growth in Normocephalic Infants Prenatally exposed to Zika Virus in Puerto Rico

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Objective: We aimed to describe the head circumference (HC) growth trends for non-microcephalic infants exposed to the Zika virus (ZIKV) in utero.

Methods: This was a medical record review of non-microcephalic neonates exposed to ZIKV whose mothers received prenatal care at the fetal evaluation unit (2015–2017). The mean HC values of babies from prenatal age to 1 year old were compared with the standardized values on HC growth charts.

Results: Sixty-three mother–infant pairs were included, and 56 infants (boys, 30%; girls, 70%) were evaluated. The mothers tested positive for ZIKV; their babies had a mean gestational age of 38 weeks (32–42) and a mean birth weight of 3,150 grams (1,190–4,220). The mean HC growth of the fetuses (19–34 weeks gestational age) placed them in the 25th percentile, increasing to the 50th percentile (according to the World Health Organization [WHO]). Compared with other growth charts (INTERGROWTH-21st [International Fetal and Newborn Growth Consortium for the 21st Century] and Puerto Rico reference values), the mean HC grew in the 50th percentile at 18 to 30 weeks of gestational age, indicating normal growth in children from Zika-positive women. According to the WHO chart, the postnatal HCs of both the girls and boys reached the 75th and 50th percentiles, respectively.

Conclusions: Postnatal HC growth was normal. Results from this study suggest that infants exposed to ZIKV in utero can be normocephalic at birth. Therefore, the neurodevelopmental outcomes of such infants should be followed throughout childhood and adolescence, regardless of their HCs at birth.

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Key words: Congenital Zika virus, Head circumference, Zika virus exposure, Puerto Rico

The Zika virus (ZIKV) was originally identified in 1947 in the Zika Forest, which is located in Uganda, Africa. It is transmitted to humans primarily by the bite of an infected Aedes mosquito. These mosquitoes are found in tropical regions. They also spread the dengue and chikungunya viruses (1). From 2014 to 2016, the ZIKV epidemic taking place in the Americas became associated with a significant increase in congenital microcephaly cases; at this point, the World Health Organization (WHO) declared it a global public health emergency. The United States declared ZIKV a public health emergency in Puerto Rico in August 2016. On July 7, 2016, the Centers for Disease Control and Prevention (CDC) indicated that Puerto Rico had 5,582 confirmed ZIKV cases and that there might be many additional unconfirmed cases representing patients who were as yet asymptomatic (2). The number of confirmed cases rose to over 40,000 by May 20, 2017 (3), and of them, 3,703 were women who contracted the virus during their pregnancies, resulting in at least 38 instances of ZIKV-associated birth defects

In February 2016, the WHO declared the association of congenital microcephaly and ZIKV infection to be a Public Health Emergency of International Concern. The link between ZIKV infection during pregnancy and the occurrence in newborns of both congenital microcephaly and other neurological abnormalities is supported by scientific evidence (4). Neonates exposed to ZIKV infection during gestation have increased risk (ranging from 1% to 13%) of microcephaly (5). Recent studies suggest that microcephaly, although one of the more prominent clinical indicators of ZIKV, is only 1 in a spectrum of congenital infections that might be linked to the virus (3,4,5,6,7,8). Though the clinical manifestations of Zika (e.g., microcephaly, sensorineural hearing loss, visual impairments, arthrogryposis) can vary, the majority of fetuses that are exposed to prenatal ZIKV display no obvious signs of neurological issues when they are born (5,6).

At the moment, there are no reports in Puerto Rico on the head circumference (HC) growth of children born from pregnant women exposed to ZIKV.

This study aimed to present the prenatal and postnatal HC growth measures of a cohort of ZIKV-exposed children,

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comparing them with the WHO and INTERGROWTH-21st (International Fetal and Newborn Growth Consortium for the 21st Century) growth standards and Puerto Rico growth reference values.

Methods

Study Design

This retrospective observational study included a cohort of fetuses, neonates, and infants that all had intrauterine exposure to ZIKV and were born from January 1, 2015, to December 31, 2017, in Puerto Rico.

Study Population

This retrospective record review included neonates admitted to the neonatal intensive care unit of the University Pediatric Hospital (UPH-NICU) and mothers evaluated at the antenatal evaluation unit of the Obstetrics and Gynecology Department of the University Hospital.

Study Site

Puerto Rico is a United States territory located in the Caribbean. The island's current (December 4, 2023) population is 3,193,694, and the current (ditto) birth rate is 6.554 per 1000 population (9). The NICU of the study group is located in the UPH, which is affiliated with the University of Puerto Rico School of Medicine, in San Juan. The UPH-NICU is part of this level-4 teaching hospital and has approximately 450 admissions, yearly. Our NICU serves as a referral center for critical newborns. The antenatal evaluation unit at the University Hospital screens thousands of pregnancies and provides antenatal care to high-risk cases.

During the Zika epidemic, this unit evaluated and followed over 700 pregnancies in which the mother had been determined to be positive for Zika immunoglobulin M antibodies.

Inclusion and Exclusion Criteria

In this study, we included infants born from January 1, 2015, to December 31, 2017, to pregnant women exposed to ZIKV who were evaluated at the antenatal evaluation unit at the University Hospital and followed at the UPH clinics. Information was gathered from mothers with documented ZIKV infection during their pregnancies. Their infants had 2 or more HC measurements. We excluded infants with microcephaly or brain abnormalities.

Data Collection and Procedures

The following variables were collected from medical records by trained data collectors.

a. Information regarding pregnancy and Zika infection. Maternal age and trimester of positive testing.
b. Sonographic findings. Weeks of gestational age (WGA), estimated fetal weight (percentile and Z-score), fetal HC measurement (percentile, and Z-score).
c. Using ultrasound, fetal measurements were made at different weeks of gestation, as recommended by the American Institute of Ultrasound in Medicine (AIUM), by a certified sonographer. The data measurements and estimations were made using Hadlock's formula.
d. Infant physical exam. WGA, birth weight (BW), birth HC, and HC at 3, 6, 9, and 12 months. Birth and later HC measures were taken by different nurses/physicians in the follow-up visits. No special or standardized protocol other than the HC measuring technique described by the CDC was followed.

We defined *normocephalic* as any infant with an HC measure no more than 2 SD above the mean for gestational age and sex or from the 3rd to the 97th percentiles for age. Infants were determined to be microcephalic if their HC measures were less than 2 SD below the mean (Z-score ≤ 2 SD) or the 3rd percentile for age, and macrocephalic if their HC measures were in the 98th or greater percentile for age.

The protocol was approved by the University of Puerto Rico Medical Sciences Campus Institutional Review Board.

Data Analysis

Descriptive analysis was used to evaluate the variables in this population. Continuous variables were described using means, percentages or medians, and percentiles and ranges. Categorical variables were described using frequencies and percentages. Unadjusted comparisons between variables were performed using the t-test or the chi-square test. A P value less than .05 was considered statistically significant.

To compare the HC results in fetuses exposed to ZIKV during pregnancy, we calculated the means, medians, and SDs of the HC values for each week of gestation using INTERGROWTH-21st, WHO, and Puerto Rico measures (10,11,12).

The INTERGROWTH-21st project was created in 2014 and is responsible for the development of an international, multiethnic, and multicountry sex-specific set of standards regarding weight, length, and HC based on gestational age at birth to evaluate fetuses, newborns, and infants as well as the postnatal growth of preterm infants.

We compared newborn and infant HC measurements in children exposed to ZIKV during pregnancy. We calculated the means and SDs of HC values at birth and at 3, 6, 9, and 12 months using the WHO standard growth chart for girls using the t-test or chi-square test. A P value less than .05 was considered statistically significant.

We chose the WHO standard for girls since using a threshold for microcephaly that is sex-independent (with a single cutoff based on the INTERGROWTH-21st sonographic standard for neonatal HC) will probably lead to the more frequent categorization of female infants as microcephalic, given the typical anatomical variance in which girls generally exhibit smaller head sizes than do boys (7).

A total of 244 measures were analyzed, with approximately 5 measures per subject. The fetal measures included measurements from 18 to 40 weeks of gestation at different weeks of gestation for a total of 174 measures (consisting of approximately 7 measures per week) during the fetal period. The infant measures were evaluated at 3, 6, 9, and 12 months (±4 weeks) for a total of 70 measures during the infant period. Approximately 17 measures per month were made.

Results

Sixty-three mother–infant pairs were included in the analysis, yielding a total of 56 infants. Seven were excluded due to their having fewer than 2 measures. Of the evaluated children, 19 (30%) were boys and 44 (70%) were girls. They had a mean gestational age of 38 weeks (range: 32 to 42 weeks) and a mean BW of 3,150 grams (range: 1,190 to 4,220 grams). The mean maternal age was 25 years (range: 16 to 43 years). All the mothers tested positive for ZIKV—48% in the first trimester, 36% in the second, and 16% in the third. Table 1 describes the study population.

During the fetal period (19–34 WGA), the mean HC tended to reach the 25th percentile, reaching the 50th percentile after 35 weeks and maintaining its growth compared to the WHO's standardized growth charts. The HCs of infants exposed to the virus in the first trimester reached the 25th percentile at 21 to 27 WGA. Infants exposed in the second trimester reached approximately the 25th percentile at 24 to 30 WGA. The infants who were exposed in the third trimester were not evaluated because there were not enough measurements (Figure 1).

According to the INTERGROWTH-21st standard growth charts, the mean HC growth rate was in the 50th percentile during the fetal period (18–30 WGA) but never reached the 90th percentile (Figure 2).

During the fetal period, the mean HC reached the 50th percentile but remained below the 90th percentile, according to the Puerto Rico growth charts. The mean HC grew similarly to that detailed in the INTERGROWTH-21st standard growth charts (Figure 3).

After birth (3, 6, 9, and 12 months), the girls' mean HCs nearly reached the 75th percentile and the boys' reached almost the 50th percentile, both according to the WHO's mean HC growth chart for girls (Figures 4 and 5).

Table 1. Demographic characteristics of 63 mother–infant pairs, the Zika virus–exposed cohort

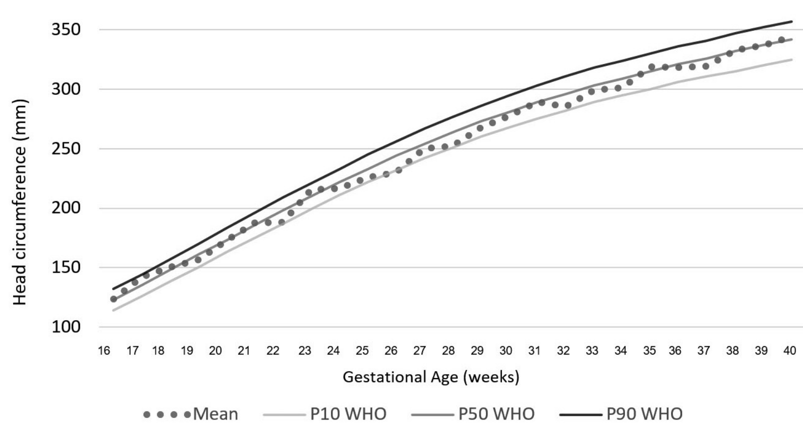
General characteristics	Frequency
MOTHERS	
Age (years)	
13–24	33 (52%)
25–34	24 (38%)
≥35	6 (10%)
Trimester of exposure	
First	30 (48%)
Second	23 (36%)
Third	10 (16%)
NEONATES	
Sex	
Female	44 (70%)
Male	19 (30%)
Gestational age (weeks)	
Term (≥37)	54 (86%)
Preterm (≤36)	9 (14%)
Birth weight (grams)	
>2,500	55 (87%)
1,500–2,499	6 (10%)
<1,500	2 (3%)
Weight (size based on gestational age)	
Small	2 (3%)
Adequate	45 (71%)
Large	16 (26%)
Head circumference	
Normocephalic	63 (100%)
Microcephalic	0 (0%)

Discussion

For decades, children's cranial growth and brain development have been assessed by measuring HC (13). In the initial 2 years of life, a child's cranium undergoes significant transformation of a structural and geometric nature: The skull's volume doubles within the initial 6 to 9 months after birth, increasing by an additional 20% over the course of the next 6 months (13). The efficacy of monitoring infant health is significantly enhanced when serial HC measurements are compared with normative growth curves (13). Findings in the available literature strongly indicate that there is a robust correlation between early postnatal head growth—particularly that occurring before 12 to 24 months of chronological age—and long-term neurological and cognitive outcomes in preterm children. It is evident that such outcomes are predominantly influenced by this head growth rather than by weight or length (14). The American Academy of Pediatrics recommends that all children have an HC measurement at each well-child visit until reaching 2 years of age (15).

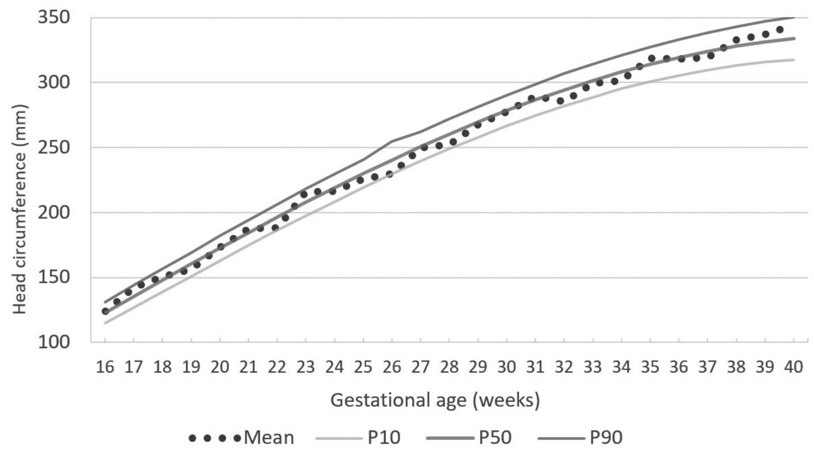
Although microcephaly has been associated with ZIKV infection, the spectrum of organ

Figure 1. Our cohort's measures compared to those of the WHO growth charts



At 19 to 34 weeks of gestational age, the mean head circumference (HC) growth of the fetuses placed them in the 25th percentile, increasing to the 50th percentile (according to the growth chart of the World Health Organization [WHO]) at 35 weeks.

Figure 2. Our cohort's head circumference measures compared to those of the INTERGROWTH-21st growth charts



Comparing the mean HC growth of our study subjects during the fetal period with the INTERGROWTH-21st (International Fetal and Newborn Growth Consortium for the 21st Century) standardized growth charts, we observed that the HCs of our subjects reached the 50th percentile at 18 to 30 weeks gestational age but never reached the 90th percentile.

injury associated with this virus is likely to be even greater than is currently known. A key contributor to the induction of congenital anomalies lies in the virus's capacity to circumvent the initial (innate) immune response, which evasion enables the virus to replicate and subsequently invade numerous cells within the human placenta and fetal brain, including neural progenitor and stem cells that are not yet mature (7).

It is also possible that any neurological injury beginning with ZIKV exposure as a fetus will, in the first year of life, continue developing, becoming more pronounced with time (7). Extending throughout adolescence, hippocampal neurogenesis is crucial to the development of both learning and memory. Such conditions as depression, schizophrenia, and Alzheimer's may be linked to the impaired development of neural stem cells (16).

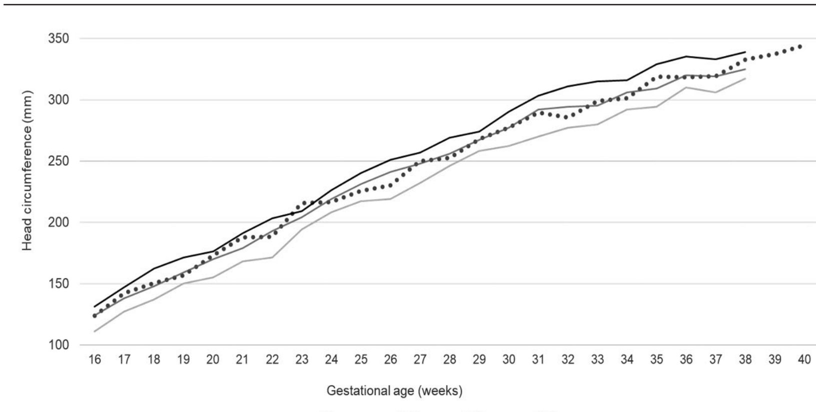
Brain dysfunction associated with ZIKV is not only evident in clear instances of microcephaly (often linked to maternal ZIKV infection occurring in the first trimester of gestation) but is also observed in newborns with typical head sizes and who were born to mothers infected late in their pregnancies. The likelihood that a fetus will suffer from microcephaly if its mother is infected with the virus varies (1%–13%), but there is a worry that other, less conspicuous, nervous-system problems may be more prevalent (17). The literature has shown that the interval between maternal infection and the emergence of sonographic evidence of fetal abnormality can range from 2 to 29 weeks (18). In a 2018 study, 19 normocephalic children from Brazil exposed in utero to ZIKV were evaluated and found to have high rates of ataxia, dyskinesia, irritability, and hypertonia or hypotonia, either of which final pair could be a warning sign for a central nervous system disorder; this study reported on 11 (of 13) patients with laboratory evidence of congenital Zika infection but who had normal-sized heads at birth (19).

Van der Linden et al. (2016) followed up on a series of 13 infants proven to have congenital ZIKV and found that their head growth had slowed to the point of microcephaly and that they displayed evidence of neurologic sequelae (20).

In our study, HC growth during fetal life was observed to be within the 25 to the 50th percentile compared with the WHO and INTERGROWTH-21st growth standards. The viral complexity of ZIKV aids in its targeting of the central nervous system; in addition, the virus may affect various cells when the infected individual is at different stages of cerebral development (17). If a fetus is exceptionally large at birth or if infection with ZIKV occurs late in the pregnancy, the slowing of biparietal diameter growth may not be considered clinically abnormal (16).

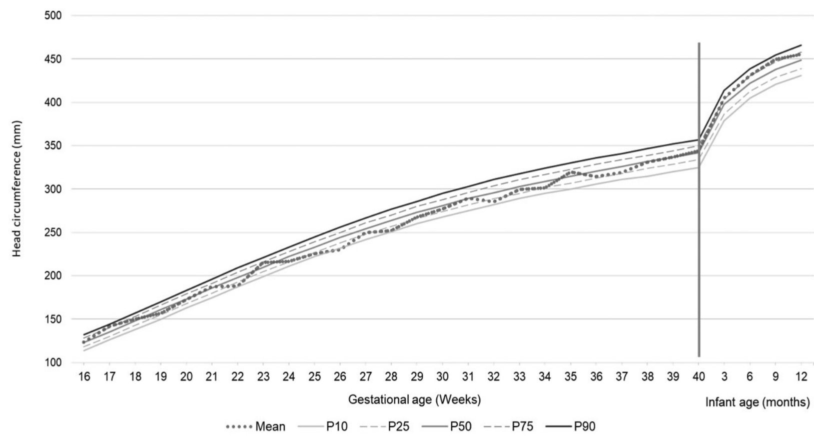
In a 2017 study (Nguyen et al., 2017), 4 healthy, pregnant monkeys were inoculated with the virus at 31, 38, 104, or 119 days of gestation (term: 165 ± 10 days). According to Nguyen and team, fetal infection correlated with an observable decrease in fetal HC during the final month of gestation, though without constraining overall fetal growth (21).

Figure 3. Our cohort's head circumferences measures compared to those of the Puerto Rico growth charts



Comparing the mean HC growth of our study subjects during the fetal period with Puerto Rico growth charts, we observed that the HCs of our subjects reached the 50th percentile but never reached the 90th percentile. The HCs of our subjects grew at a rate that conformed with that set by the INTERGROWTH-21st standardized growth charts.

Figure 4. Our cohort's measures (girls only) compared to the those of the WHO growth chart



Comparing the mean HC measures of our female study subjects after birth (at 3, 6, 9, and 12 months) with those of the WHO growth chart, we observed that the HCs of those subjects nearly reached the 75th percentile.

Puerto Ricans are a heterogenous group with mainly European, African, and Indigenous Taino ancestry; they can be considered a mixed population. A study published by De La Vega et al. (2008) validated the use of mixed United States population growth charts to evaluate the Puerto Rican population (12). In 2012, forensic anthropologists at the University of Tennessee in Knoxville examined 1,500 skulls dating back to the mid-1800s and extending into the mid-1980s (22). The research team determined that, viewed from the front, human skulls in the United States have lengthened, narrowed, and grown in size, while facial features have also narrowed—significantly—and become higher (22).

This study showed that most Black Americans would have larger craniums as well, but believes that Hispanic skulls might be smaller as increased calories, nutritional adequacy and decreased activity have probably been important growth factors (22).

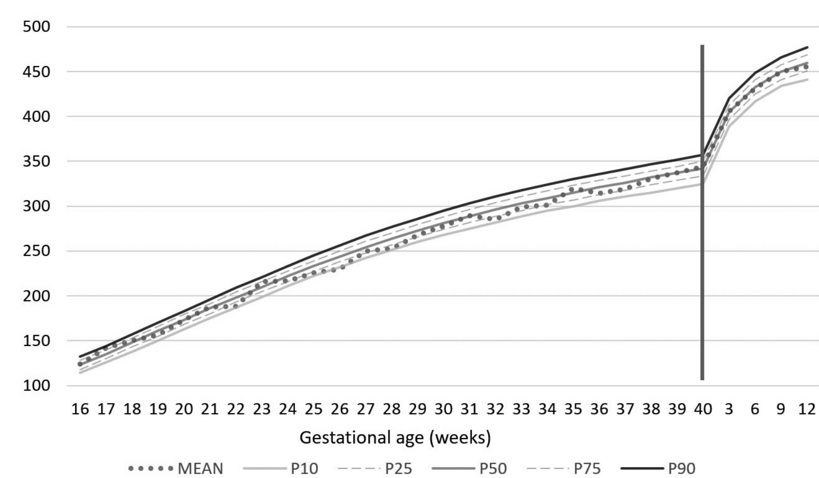
After birth (3, 6, 9, and 12 months), the HCs of the girls reached nearly the 75th percentile, and those of the boys, nearly the 50th percentile, according to the WHO's growth charts (for girls and boys, respectively). This suggests that despite the HC growth of girls being above the 50th percentile, the HC growth of both boys and girls is within the normocephalic range. The first meta-analysis of typical sex differences in global brain volume reported differences between males and females in said volume, from newborns to individuals over 80 years old (8).

Several characteristics of the study's method warrant attention. We based our study on a review of medical records. The data were limited to information found in the clinical reports, which sometimes lacked important information. Sonographic data were located in medical records of several formats–electronic and paper, primarily, and infant data were located in written medical records. Since the children whose records were reviewed were seen in various outpatient settings, the standardization of the measurement procedures was challenging. There was no standardized method for taking or a single person to take HC measures of infants at follow-up clinics.

However, there are some strengths in our study. Clinical measurements undoubtedly have a higher degree of error than more systematically obtained measurements for research. However, the majority of the measures that were analyzed were fetal and were taken by the same certified, experienced sonographer using the AIUM guidelines. Because ours is a referral center, this cohort might be a representative sample.

The American Academy of Pediatrics recommends following up these patients for further HC measures until they reach 2 years of age, but the Puerto Rico Health Department protocol will be followed for at least 5 years because of the unknown effects of ZIKV on child development and the local mosquito-borne transmission of ZIKV. The attenuation or loss of neural stem cells during neurogenesis elevates concerns regarding the long-term effects of congenital ZIKV exposure, not only on neonates but also on children and young adults who acquire ZIKV after birth (16).

Figure 5. Our cohort's measures (boys only) compared to the those of the WHO growth chart



Comparing the mean HC measures of our male study subjects after birth (at 3, 6, 9, and 12 months) with those of the WHO growth chart, we observed that the HCs of those subjects nearly reached the 50th percentile.

Conclusions

Even though we expected that the HC growth of the children for whom we had medical records would reach the 50th percentile—since they had no anomalies or risk factors except for their having been exposed to Zika—their fetal HC growth was between the 25th and the 50th percentiles and then, after birth, between the 50th and 75th percentiles.

To arrive at a diagnosis of normocephaly, we considered only HC measurements, comparing them (by sex) to the WHO standard growth charts; we did not expect to find any neurodevelopmental problems in our cohort. However, this cohort was exposed to intrauterine ZIKV, which virus affects neurogenesis, explaining why there is an increased risk that their neurodevelopmental outcomes will be negatively affected beyond what could be predicted via their HC measurements. A 2019 study from Faiçal et al. reported on a group of normocephalic infants who had been exposed in utero to ZIKV. When assessed with the Bayley Scales of Infant and Toddler Development, third edition, almost 50% of the children were found to have experienced some form of neurodevelopmental delay (hindrances in language, cognitive, and motor development) (6). The overall neurodevelopment of ZIKV-exposed children whose HCs at birth and whose head growth in their first 2 years of life are both normal is unlikely to be affected; however, these children may nevertheless suffer from visual impairment, and they should be tested when they reach about 3 years of age (5). The infants of an entire generation suffered prenatal exposure to ZIKV, signifying that a wide range of consequences may affect the growth and development of thousands of children (23).

A cross-sectional study of infants who were prenatally exposed to ZIKV was performed in Puerto Rico (2018–2019); it showed unaffected motor and visually mediated cognitive development, but the children manifested deficits in their receptive language scores. By describing the head growth of exposed infants, our findings add to the literature, containing information for primary care physicians who follow these kinds of patients, enabling such physicians to be aware of what the head growth of these children should be. Also, this study highlights the importance of exploring the more subtle cognitive impairments that may appear in ZIKV-exposed infants (3).

In Puerto Rico, with the endemic presence of ZIKV and the majority of ZIKV cases being asymptomatic, a fetus can be exposed to the virus without any sign of the infection being present. The health department's current strategy of testing pregnant women for the presence of Zika RNA once every trimester will not likely identify most of the affected cases since viral RNA is detectable in the blood for a relatively short time. Measuring HC growth might very well be the first step in suspecting the presence of a neurological disorder, leading the relevant healthcare professional to make a referral to a pediatric specialist, potentially resulting in the provision of family-centered early-intervention services, if needed.

We recognize that head growth assessment is a very crude way to measure brain and (future) neurocognitive development. Other assessment methods may be needed to identify neonates that are at potential risk after having been exposed to Zika infection during pregnancy.

Monitoring the diverse clinical manifestations observed after an infant's prenatal exposure to ZIKV (including assessing HC as a continuous measure) might contribute to early intervention, thorough cross-disciplinary assessment, and comprehensive therapeutic care (24).

From both the quality-of-life and societal-cost perspectives, continued monitoring of non-microcephalic infants exposed to ZIKV is a public-health imperative and is essential for directing care (16).

Resumen

Objetivo: Nuestro objetivo fue describir las tendencias de crecimiento de la perimetro cefálico (PC) de bebés no microcefálicos expuestos al virus del Zika (ZIKV) en el útero. Métodos: Se realizó una revisión de las historias clínicas de recién nacidos no microcefálicos expuestos al ZIKV cuyas madres recibieron atención prenatal en la unidad de evaluación fetal (2015-2017). Los valores medios de PC de los bebés desde la edad prenatal hasta el año de edad se compararon con los valores estandarizados en las tablas de crecimiento de PC. Resultados: Se incluyeron sesenta y tres parejas de madre e hijo y se evaluaron 56 bebés (niños, 30%; niñas, 70%). Las madres dieron positivo a ZIKV; sus bebés tenían una edad gestacional promedio de 38 semanas (32–42) y un peso promedio al nacer de 3150 gramos (1190–4220). El crecimiento medio de PC de los fetos (19 a 34 semanas de edad gestacional) los colocó en el percentil 25, aumentando hasta el percentil 50 (según la Organización Mundial de la Salud [OMS]). En comparación con otras tablas de crecimiento (INTERGROWTH-21st [Consorcio Internacional de Crecimiento Fetal y Recién Nacido para el Siglo XXI] y valores de referencia de Puerto Rico), el PC promedio creció en el percentil 50 entre las 18 y 30 semanas de edad gestacional, lo que indica un crecimiento normal en los niños de mujeres con pruebas de Zika positivas. Según la gráfica de la OMS, el PC posnatal tanto de niñas como de niños alcanzaron los percentiles 75 y 50, respectivamente. Conclusiones: El crecimiento posnatal de PC fue normal. Los resultados de este estudio sugieren que los bebés expuestos al ZIKV en el útero pueden ser normocefálicos al nacer. Por lo tanto, los resultados del desarrollo neurológico de estos bebés deben seguirse durante la niñez y la adolescencia, independientemente de sus PC al nacer.

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