The spectrum of clinical outcomes for infants and children with prenatal Zika virus (ZIKV) exposure continues to widen. When the ZIKV epidemic emerged in 2015, we were struck by the severe congenital malformations that occurred in utero. The constellation of microcephaly, abnormal neurologic tone, vision and hearing abnormalities, and arthrogryposis was given the term congenital Zika syndrome (CZS).\(^1,2\) The severity and frequency of brain damage were alarming and included findings of fetal brain disruption sequence and arthrogryposis, which were unique to congenital infection associated with ZIKV.\(^2\) However, for the 90% to 95% of ZIKV-exposed infants who were not born with severe abnormalities at birth and were normocephalic, our hope was that these children would have normal neurodevelopmental outcomes. Unfortunately, this has not been the case.\(^3,4\)

Cranston et al\(^5\) provide detailed clinical follow-up of a large cohort of children from Rio de Janeiro, Brazil, with antenatal ZIKV exposure. To assess whether birth head circumference (HC) was associated with a difference in neurodevelopmental outcomes, the authors stratified infants as having normocephaly or microcephaly by their birth HC. Not surprisingly, there was a high burden of neurologic and other clinical abnormalities, including failure to thrive, ophthalmologic and audiologic abnormalities, and congenital heart defects in the children born with microcephaly, and none of the children with microcephaly at birth were able to complete the Bayley Scales of Infant and Toddler Development, Third Edition, (Bayley-III) assessment owing to their level of disability.\(^5\) However, of considerable concern was the 68% of infants who had normocephaly at birth and had neurologic abnormalities on follow-up examination.\(^5\) This high rate, in part, reflects the initial reason for referral and is higher than would be expected in a general ZIKV-exposed child cohort. Nevertheless, this study describes a wide range of clinical outcomes for ZIKV-exposed children and supports the recommendation for continued longitudinal neurodevelopmental follow-up for all ZIKV-exposed infants.\(^3\)

An important finding by Cranston et al\(^5\) was that birth HC among infants who had normocephaly with in utero ZIKV exposure was associated with neurodevelopmental scores at follow-up evaluation. Infants with a larger birth HC, within the normocephalic range (±2 SDs), had higher overall neurodevelopmental scores on the Bayley-III assessment, whereas infants with a smaller birth HC within the normocephalic range had lower scores in the domains of cognitive and language functions. Although the authors did not report a specific HC \(z\) score that increased this risk, having a \(z\) score lower than 0 may be a way to stratify infants into high- and low-risk categories among infants with normal birth HC \(z\) scores. Combining HC with other early clinical data, such as the results of neuroimaging or a neurologic examination, can then further stratify infants for risk of subsequent abnormal neurologic outcomes. This finding of HC has not been shown in other ZIKV-exposed cohorts, possibly owing to the higher burden of abnormal neurologic outcomes in this cohort. However, this finding provides a practical tool to help determine risk for adverse clinical outcomes in a ZIKV-exposed infant at birth that can be widely used in a variety of follow-up settings.

Although birth HC is an important initial measurement, the HC growth trajectory is key. Cranston et al\(^5\) stratified outcomes based only on HC at birth, not on HC at follow-up. Of 162 infants with normocephaly at birth, 17 (10.5%) developed postnatal microcephaly;\(^5\) thus, the trajectory of head growth is critical. The neurologic outcome of a child who develops postnatal microcephaly would be very concerning compared with an infant who is born with normocephaly and maintains a steady HC percentile over time. Occipital frontal circumference correlates with intracranial volume. A small head size can be familial, but evaluations for genetic, infectious, or other etiologies are often
warranted and should be performed in cases in which ZIKV infection is not certain. Because early head growth trajectory is associated with cognitive outcomes in early childhood, following the HC percentile over time can enable recognition of a child with increased risk for poor outcome who could benefit from early intervention therapies. When used at birth and in follow-up, a simple measurement tape to measure HC should be a part of all infant and child assessments. Individual child growth charts should be accessible to clinicians so that the HC percentile can be accurately tracked over time because a single measurement may not enable recognition of abnormal head growth. This is important for public health surveillance and for clinicians who follow up with children who were exposed to ZIKV or who may have had other early infectious or noninfectious exposures that could be associated with child neurodevelopment.

Another way to stratify ZIKV-exposed infants is to combine HC and neuroimaging. Infants born with microcephaly can have brain calcifications, cerebral atrophy, ventriculomegaly, and a smooth gyral pattern (lissencephaly). However, in the cohort examined by Cranston et al., even some infants with normocephaly had brain calcifications and cerebral atrophy, and some developed postnatal microcephaly. Araujo and colleagues described 3 groups of ZIKV-exposed infants based on brain abnormalities and timing of microcephaly: infants with microcephaly at birth, infants with postnatal microcephaly, and infants with normocephaly. A simplified gyral pattern was observed only in infants with prenatal onset microcephaly, whereas polymicrogyria was a pattern seen only in infants with postnatal microcephaly or infants with normocephaly following prenatal ZIKV exposure.

Lissencephaly in ZIKV-exposed cases is a simplified gyral pattern because of neuronal injury, reduced cell proliferation, and increased apoptosis; this is different from the genetic-mediated lissencephalies that result in primary microcephaly. Thus, based on neuroimaging, the pattern and severity of brain structural abnormalities relate to the timing of onset of microcephaly and clinical outcomes. Postnatal development of microcephaly, failure to thrive, or developmental delay are important reasons to obtain neuroimaging at follow-up evaluation, especially if imaging was not previously performed.

Collectively, studies of antenatal ZIKV-exposed cohorts of children support the need for longitudinal follow-up over time for all children. A range of mild neurodevelopmental abnormalities to severe global developmental delay can be seen in children with or without microcephaly. Infant neurodevelopment occurs rapidly during the first year of life, and the trajectory of early development can foreshadow how an individual child will develop in the future. In the study by Cranston et al., children were evaluated monthly for the first 6 months of life and then every 3 months. This frequency of assessment may not be possible for most clinics. Neurodevelopmental assessments performed every 2 to 3 months for the first 6 months, then every 6 months to 2 years of age, and then yearly would provide the opportunity to observe changes in the developmental trajectory that warrant referral and in-depth evaluation. Infants and children displaying abnormal neurodevelopment at any time should have more frequent assessments. Novel approaches to care using telemedicine, video, and mailed or online questionnaires can improve follow-up rates and bring clinicians to remote areas. Follow-up of a ZIKV-exposed child may also require a multidisciplinary approach to address other clinical outcomes, such as failure to thrive, congenital heart disease, and ophthalmologic or audiologic problems. As children prepare to enter school, neurodevelopmental follow-up should continue because new challenges may emerge at more advanced ages, and these challenges may further widen the spectrum of abnormal neurologic and clinical outcomes following antenatal ZIKV exposure.
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REFERENCES


