Identifying possible inaccuracy in reported birth head circumference measurements among infants in the US Zika Pregnancy and Infant Registry

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Abstract

The US Zika Pregnancy and Infant Registry (USZPIR) monitors infants born to mothers with confirmed or possible Zika virus (ZIKV) infection during pregnancy. The surveillance case definition for Zika-associated birth defects includes microcephaly based on head circumference (HC). We assessed birth and follow-up data from infants with birth HC measurements <3rd percentile and birthweight ≥10th percentile to determine possible misclassification of microcephaly.

We developed a schema informed by literature review and expert opinion to identify possible HC measurement inaccuracy using HC growth velocity and neuroimaging results. Two or more HC measurements between 2-12 months of age were required for assessment. Inaccuracy in birth HC measurement was suspected if growth velocity was >3 centimeters/month in the first three months or HC was consistently >25th percentile during follow-up. Normal neuroimaging was considered supportive of HC measurement inaccuracy.

Of 6,799 infants, 351 (5.2%) had Zika-associated birth defects, of which 111 had birth HC measurements <3rd percentile and birthweight ≥10th percentile. Of 84/111 infants with sufficient follow-up, 38/84 (45%) were classified as having possible inaccuracy of birth HC measurement, 19/84 (23%) had HC ≥3rd percentile on follow-up without meeting criteria for possible inaccuracy, and 27/84 (32%) had continued HC <3rd percentile. After excluding possible inaccuracies, the proportion of infants with Zika-associated birth defects including microcephaly decreased from 5.2% to 4.6%.

About one-third of infants with Zika-associated birth defects had only microcephaly, but indications of possible measurement inaccuracy were common. Implementation of this schema in ZIKV infection during pregnancy studies can reduce misclassification of microcephaly.

Full Text

In November 2015, Brazil reported an association between Zika virus (ZIKV) infection during pregnancy and an increase in the number of infants born with microcephaly (Newton Sérgio De Carvalho, 2016). Very little was known about the potential harm ZIKV infection during pregnancy would have on pregnancy and infant outcomes. To better understand and define the spectrum of outcomes and provide guidance for pregnant women and their infants, the Centers for Disease Control and Prevention (CDC) collaborated with jurisdictional health department partners to establish the US Zika Pregnancy and Infant Registry (USZPIR) to prospectively follow pregnant women with laboratory evidence of confirmed or possible ZIKV infection and their infants born from December 1, 2015 through March 31, 2018 in the US states, District of Columbia, and US territories and freely associated states (Simeone, 2016; NCBDDD, 2019).

The USZPIR collects information from prenatal, birth hospitalization and delivery, and infant follow-up information up to ages 2-5 years from medical records. The surveillance case definition has been revised

over time as our understanding of congenital ZIKV infection improved and now includes brain anomalies and/or microcephaly, eye abnormalities, and neurodevelopmental abnormalities (Rice, 2018; Olson, 2019). The surveillance case definition for microcephaly was defined as birth head circumference (HC) measurement less than the third percentile (<3rd percentile) for gestational age and sex based on INTERGROWTH-21ST standards (INTERGROWTH-21st, 2020) and has been in place since the inception (Honein, 2017).

The longitudinal surveillance structure of USZPIR allows information about infant health and developmental outcomes to accumulate over time, providing an opportunity for increased clinical detail, and presumably a more accurate clinical assessment. As additional infant follow-up visits were reported to USZPIR, the inherent challenges in conducting surveillance of microcephaly became more evident. Some infants with reported birth HC <3rd percentile had follow-up HC measurements that suggested the birth measurements were inaccurate. This analysis aimed to determine the possible inaccuracy of HC measurements among infants with birth HC <3rd percentile and birthweight ≥10th percentile who have additional follow-up data reported to USZPIR.

Clinical ZIKV subject matter experts developed a schema for reviewing microcephaly classification at birth among infants in USZPIR based on a review of the scientific literature and expert opinion (Box). Infants born small-for-gestational-age (SGA) (birthweight <10th percentile by age and sex based on INTERGROWTH-21ST standards) were excluded from assessment due to differences in growth trajectory from infants born appropriate for gestational age (Karlberg, 1995). Birth HC <3rd percentile was evaluated for possible inaccuracy if two or more follow-up HC measurements were reported to USZPIR between two and twelve months of age with at least one measurement prior to six months of age; otherwise, infants were deemed to have insufficient data to assess. HC <3rd percentile was suspected to be inaccurate if either of two criteria was met: 1) greater than expected head growth velocity (>3 cm/month) between birth and three months of age (WHO, n.d.); or 2) all HCs above 25th percentile between two and twelve months of age. Normal neuroimaging reported from birth or infant follow-up was considered supportive evidence of possible birth HC measurement inaccuracy.

HCs at birth and throughout follow-up were reviewed and classified based on USZPIR data reported to CDC by December 2020. Eligible infants with birth HC <3rd percentile were categorized into one of four mutually exclusive categories based on follow-up HC measurements: 1) HC remains <3rd percentile, 2) all follow-up HCs ≥3rd percentile and <10th percentile, 3) all follow-up HCs ≥10th percentile, and 4) suspected birth HC measurement inaccuracy. The proportion of infants in the USZPIR with Zika-associated birth defects was calculated with and without infants suspected to have HC measurement inaccuracy at birth.

Among 6,799 liveborn infants in USZPIR with reported follow-up data, 252 infants had birth HC measurements <3rd percentile (Figure 1). Of these, 141 (56%) infants had HC <3rd percentile and a birthweight <10th percentile (i.e., SGA). Among the remaining 111 infants with birthweight ≥10th percentile, 27 (24%) infants had insufficient follow-up data to be assessed for birth HC inaccuracy.

Among 84/111 infants with sufficient follow-up data (e.g., two or more reported HC measurements in follow-up), 27/84 (32%) infants had HC measurements that remained <3rd percentile, 6/84 (7%) infants had all follow-up HCs >3rd percentile and <10th percentile, 13/84 (15%) infants had all follow-up HCs ≥10th percentile, and 38/84 (45%) were suspected to have inaccuracy in the reported birth HC. Among infants with a suspected birth HC inaccuracy, none had reported brain abnormalities, and two had reported Zika-associated eye abnormalities. The proportion of infants with Zika-associated birth defects was 5.2% (351/6,799), and after accounting for the 36 infants with possible inaccuracy of birth HC measurement and no other reportable Zika-associated birth defect, the proportion of infants with Zika-associated birth defects decreased to 4.6% (315/6,799).

Use of this schema for possible inaccuracy in reported birth HC measurement addresses misclassification and refines the prevalence estimate of Zika-associated birth defects in USZPIR. However, we were only able to apply this classification schema to a third (33%, 84/252) of infants in USZPIR with a reported birth HC <3rd percentile, which demonstrates the challenges of defining and conducting surveillance of microcephaly.

Although microcephaly is often defined as birth HC <3rd percentile for gestational age and sex, a previous report reviewing the use of HC measurement alone for identification of microcephaly noted this criterion as practical for surveillance but found that when this cut-off-based definition was applied to populations, the observed prevalence contradicted the expected prevalence of microcephaly reported in the literature (Kalmin, 2019). Rounding of HC measurements to the whole centimeter, in addition to using only the number of completed weeks for gestational age, can introduce error and impact microcephaly prevalence both in routine surveillance prior to the Zika epidemic and even in situations during the Zika epidemic when staff are trained and insertion tapes are used for HC measurement (Harville, 2019; Harville, 2020). In the United States, birth defects surveillance programs use a variety of case ascertainment methods for identifying infants with microcephaly and typically use additional criteria beyond a HC measurement <3rd percentile, such as documentation of a diagnosis of microcephaly in a medical record (Cragan, 2016).

The ZIKV outbreak showed the importance of conducting surveillance to describe the impact of congenital infections on the frequency of birth defects, including microcephaly. The USZPIR used a sensitive surveillance case definition for microcephaly enabling a greater detection of possible adverse outcomes associated with ZIKV infection during pregnancy, which was particularly important early in the outbreak when little was known about the effect of ZIKV infection during pregnancy. Surveillance case definitions for microcephaly that are sensitive and specific will help increase the likelihood of accurately describing these outcomes.

There are several limitations to this reclassification schema. First, almost a quarter of infants with birth HC <3rd percentile did not have enough follow-up information reported to reassess microcephaly classification at birth. Second, this reclassification schema fails to consider the timing of HC measurement after birth, which can influence the measurement. One study of 499 infants at birth found statistically significant differences between HC measurements taken at one and three days of life, as well

as differences in HC dependent on the mode of delivery (Šimič Klaric´, 2014). Finally, these criteria are not applicable to SGA infants since there are recognized differences in their growth trajectory. A considerable proportion of infants (56%) in USZPIR meeting the case definition for birth HC <3rd percentile are proportionately SGA (head circumference <3rd percentile and birth weight <10th percentile). Future analyses will help investigate a possible association between prenatal exposure to ZIKV and SGA.

As additional information has become available, the USZPIR case definition for Zika-associated birth defects has adapted. The USZPIR surveillance case definition for microcephaly will continue to be defined as HC <3rd percentile for gestational age and sex reported during birth hospitalization. Infants in USZPIR that meet criteria for possible inaccuracy in birth HC will no longer be reported as having Zika-associated birth defects if that is the only reportable abnormality. Infants without sufficient follow-up data to be assessed for inaccuracy will remain categorized as having a reported Zika-associated birth defect. Despite limitations and challenges, the USZPIR continues to provide surveillance data to inform pregnant women, families, healthcare providers, and public health professionals regarding the impact of ZIKV in pregnancy and the importance of recommended follow-up for timely referral to services.

Box. Schema for possible inaccuracy of head circumference (HC) measurement among live born infants with birth HC <3rd percentile and birthweight ≥10th percentile reported to the US Zika Pregnancy and Infant Registry (USZPIR) [†,‡]

Infants must have two or more HC measurements reported between two and twelve months of age with the first measurement occurring prior to six months of age. A microcephaly HC measurement (HC <3rd percentile) at birth is suspected to be inaccurate if either of the following criteria were met: o Greater than expected head growth velocity (>3 cm/month) before three months of age[§] o Normal postnatal HC percentiles and consistently normal HC growth trajectory defined as postnatal HC consistently >25th percentile during the first year of life An infant with data that met either of the criteria is suspected to have an inaccurate HC reported at birth and no longer meets USZPIR surveillance criteria for microcephaly. Normal neuroimaging was considered supportive evidence of birth HC measurement inaccuracy.
[†]Infants with birthweight <10th percentile, or small-for-gestational-age, typically have a growth trajectory different than infants with birthweight ≥10th percentile and thus were not evaluated using these criteria for possible HC measurement inaccuracy.
[‡]Percentiles by infant sex and gestational age based on INTERGROWTH-21st online percentile calculator.
[§]Infants with >3 centimeters per month of growth velocity would be in the 95th percentile for HC growth velocity, regardless of sex (WHO, n.d.).

Declarations

CDC Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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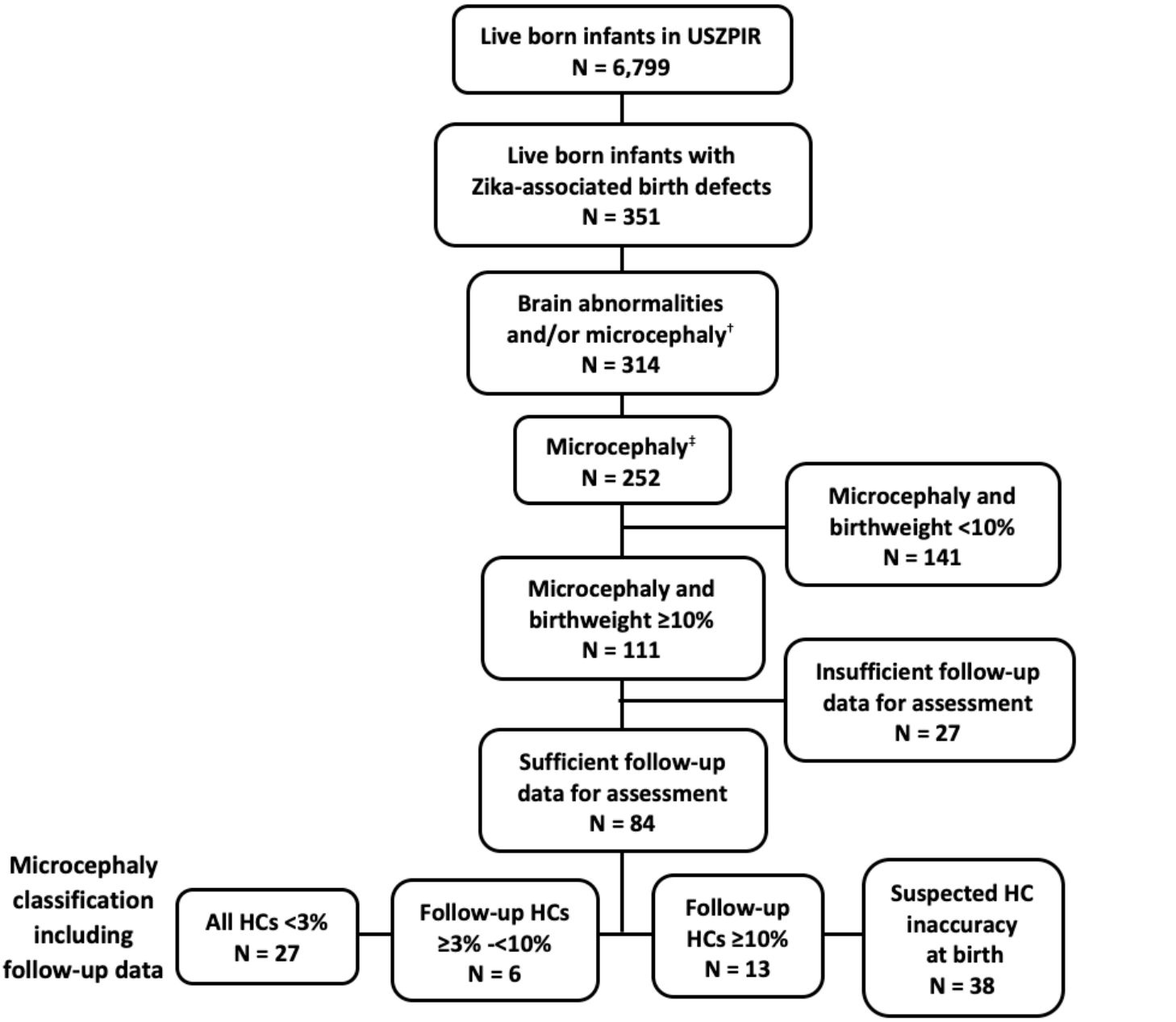
Figures



† 38 infants with brain abnormalities and/or microcephaly also have reported eye abnormalities.
‡ Microcephaly is defined as head circumference (HC) measurement at birth less than the 3rd percentile for gestational age and sex based on INTERGROWTH-21ST standards (INTERGROWTH-21st, 2020).

Figure 1

Live born infants in the US Zika Pregnancy and Infant Registry (USZPIR) with Zika-associated birth defects and classification of microcephaly using reported follow-up data