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MAJOR ARTICLE

Early Clinical Infancy Outcomes for Microcephaly and/or Small for Gestational Age Zika-Exposed Infants

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(See the Editorial Commentary by Kovacs on pages 2673–4.)

Background. Zika-exposed infants with microcephaly (proportional or disproportional) and those who are small for gestational age without microcephaly should be closely followed, particularly their growth trajectories. They are at high risk of adverse outcomes in the first year of life.Antenatal Zika virus (ZIKV) exposure may lead to adverse infant outcomes including microcephaly and being small for gestational age (SGA). ZIKV-exposed infants with a diagnosis of microcephaly (proportional [PM] or disproportional [DM]) or SGA at birth were evaluated with anthropometric measurements and health outcomes.

Methods. Infants had laboratory-confirmed ZIKV exposure in Brazil. PM, DM, or SGA classification was based on head circumference and weight. First-year growth parameters and clinical outcomes were recorded with analyses performed.

Results. Among the 156 ZIKV-exposed infants, 14 (9.0%) were SGA, 13 (8.3%) PM, 13 (8.3%) DM, and 116 (74.4%) were neither SGA nor had microcephaly (NSNM). High rates of any neurologic, ophthalmologic, and hearing abnormalities were observed for PM (100%), DM (100%), and SGA (42.9%) vs NSNM infants (18.3%; P <.001); odds ratio [OR], 3.4 (95% confidence interval [CI], 1.1–10.7) for SGA vs NSNM. Neuroimaging abnormalities were seen in 100% of PM and DM and in 42.9% of SGA vs NSNM infants 16%; (P <.001); OR 3.9 (95% CI, 1.2–12.8) for SGA vs NSNM. Growth rates by z score, particularly for microcephaly infants, were poor after birth but showed improvement beyond 4 months of life.

Conclusions. ZIKV-exposed infants with microcephaly (PM and DM) had similarly high rates of adverse outcomes but showed improvement in growth measurements beyond 4 months of life. While SGA infants had fewer adverse outcomes compared with microcephaly infants, notable adverse outcomes were observed in some; their odds of having adverse outcomes were 3 to 4 times greater compared to NSNM infants.

Keywords. Zika; congenital Zika syndrome; microcephaly; proportional microcephaly; small for gestational age (SGA).

In utero Zika virus (ZIKV) exposure may lead to a spectrum of central nervous system (CNS) infant abnormalities. Congenital ZIKV syndrome (CZS) has been used to describe ZIKV-exposed infants with devastating manifestations including severe microcephaly, other brain and ocular abnormalities, contractures, and severe neurologic impairment [1]; the vast majority are in Brazil [2–4].

CZS infants with microcephaly were the primary focus during the global ZIKV epidemic, with less attention placed on other markers of infant growth and development or their relationship to microcephaly. No prior investigations have focused on outcomes for small for gestational age (SGA) infants, which is defined as an infant whose weight is less than −1.28 standard deviations (SDs) for gender and gestational age. This unstudied relationship of SGA and microcephaly may be of importance because it allows for a distinction between microcephaly that is either proportional or disproportional. Infants with disproportional microcephaly (DM) have microcephaly but are not SGA (head circumference and weight at birth are not proportional). Infants with proportional microcephaly (PM) have microcephaly and are also SGA (head circumference and weight at birth are proportional).

The purpose of the study was to evaluate ZIKV-exposed infants with either a diagnosis of microcephaly or SGA at birth and evaluate anthropometric measurements and health outcomes during the first year of life, particularly the relationships between SGA, proportional microcephaly, and disproportional microcephaly and infant health outcomes.

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METHODS

Study Population

The study was conducted at the Fernandes Figueira Institute (IFF), Oswaldo Cruz Foundation (FIOCRUZ), Rio de Janeiro, Brazil. The IFF maternity and children's hospital is a referral center for high-risk pregnancies and pediatrics, including infectious diseases such as ZIKV. This was a retrospective analysis focused on ZIKV-exposed infants with microcephaly and/or SGA at birth followed at IFF. All infants with laboratory-confirmed ZIKV exposure during pregnancy (positive maternal and/or infant ZIKV polymerase chain reaction [PCR]) and early infant outcomes available for review from IFF were included in this study (see the Supplementary Materials for details). Review board approvals for the study's retrospective review of medical records were obtained at the IFF/FIOCRUZ and the University of California–Los Angeles (see the Supplementary Materials for details).

Study Procedures

Laboratory confirmation of ZIKV infection via real-time reverse-transcriptase PCR (RT-PCR) assays with the ZIKV QuantiTect Probe RT-PCR kit (Qiagen) was performed on mothers during pregnancy and infants after birth, primarily from serum and urine specimens. As part of the enrollment criteria, all infants had laboratory-confirmed ZIKV exposure during pregnancy (positive maternal and/or infant ZIKV PCR). More specifically, all infants fulfilled at least 1 of the following criteria for enrollment: had mothers with documented positive ZIKV PCR during pregnancy from serum, urine, amniotic fluid, placenta, or breast milk or had themselves a documented positive ZIKV PCR at birth from serum, urine, or cerebrospinal fluid (Supplementary Methods; Supplementary Table 1). We used the real-time RT-PCR protocol described by Lanciotti et al [5]. Zika MAC-ELISA (IgM antibody capture enzyme-linked immunosorbent assay), provided by the Centers for Disease Control and Prevention, was also performed on all available infant serum specimens but was not used as an inclusionary criteria in this analysis; only positive PCR results were considered for selection of the 156 infants who participated in this analysis [6–9] (see Supplementary Methods for detail). Both tests were performed at the FIOCRUZ IFF.

ZIKV-exposed infants were evaluated from March 2016 to June 2017. Infant outcomes including head circumference (HC), weight, length, and clinical exams were documented by IFF pediatric infectious diseases specialists at all infant follow-up visits. Infants were evaluated by pediatric neurologists and geneticists at the time of birth. Preterm birth was defined as gestational age <37 weeks. Neuroimaging was performed on infants after birth. Transfontanelle ultrasound (TFUS) was done on infants, and those with abnormalities on TFUS or physical exam had computerized tomography (CT) or magnetic resonance brain imaging (MRI) performed. Infants were evaluated by a pediatric ophthalmologist at birth and every 3 months and had hearing evaluations including brainstem auditory evoked response tests.

Microcephaly and SGA Definitions

Ballard assessment was done on infants at the time of birth to confirm gestational age. Microcephaly was defined as HC z score of less than −2 for gestational age and gender at the time of birth. Severe microcephaly was defined as a HC z score of less than −3 for gestational age and gender at the time of birth. SGA was defined as a weight z score of less than −1.28 for gestational age and gender at the time of birth. This group included only those infants who were SGA without microcephaly at birth. PM was defined by both microcephaly and SGA at birth. DM was defined by only microcephaly but not SGA at birth. (The Supplementary Materials include CZS, abnormal neuroimaging, fundoscopic exam, hearing, and morphologic exam definitions).

We used Intergrowth 21st online software to calculate z scores for all birth measurements (weight, height, HC) based on gestational age and gender [10]. Growth curves were created by calculating postnatal values of weight, height, and HC z scores. For full-term infants, postnatal values were determined based on World Health Organization (WHO) growth standards software [11]. As recommended by Intergrowth 21st, for preterm infants, postnatal z scores were calculated using Intergrowth 21st software up until postmenstrual age (gestational age + postnatal age) of 64 weeks. Beyond this age, the WHO software was used to calculate postnatal z scores for growth measurements.

Statistical Analyses

The χ^2 test of association was used to examine the association between categorical variables and infant groups (PM, DM, SGA, and neither SGA nor microcephaly [NSNM]). Analysis of variance was conducted to study the difference in means of continuous variables among infant groups, and 95% confidence intervals (CIs) were reported to compare the difference in means of HC, length, and weight measurements at birth. Bonferroni adjustment was used when multiple pairwise comparisons between the infant groups were performed. The association between the grouped clinical outcomes and infant groups (SGA vs NSNM) were examined using bivariate and multivariable logistic regression. A stepwise model selection that included all clinically important variables was used to construct the final multivariable logistic models.

The change in growth measurement z scores for each infant group over time was modeled as the dependent variable of a mixed effect piecewise regression model for repeated measurements assuming a compound symmetry covariance structure. Several different mixed effect piecewise regression models were explored with different knots from 2 to 7 months in order to select the

best fitting model. Using the Bayesian information criterion and prior knowledge, we selected the model with a knot at 4 months [12]. Due to variability in the infants' follow-up schedules, time was included in the model as a continuous variable. Independent covariates in each model include time, infant group, and the interaction between time and infant group. To determine if the change in the expected mean *z* scores from 0 to 4 and/or from 4 to 12 months was significantly different, we conducted pairwise comparisons between the slope of the lines before and after 4 months among the 3 infant groups. We examined the difference in the slopes at 4 months within each infant group. Statistical analyses were conducted using SAS, version 9.4 (Cary, NC).

RESULTS

A total of 156 infants with laboratory-confirmed in utero ZIKV exposure were evaluated for microcephaly and/or SGA at birth. A total of 145 infants were born to mothers with ZIKV-positive PCR testing in pregnancy, and the other 11 infants had positive ZIKV PCRs from specimens collected after birth. There were 98 (62.8%) ZIKV-exposed infants who were asymptomatic at birth and during follow-up, whereas 22 (14.1%) were symptomatic with mild to moderate neurologic symptoms, and 36 (23.1%) had findings consistent with CZS.

Among the 156 ZIKV-exposed infants, 116 (74.4%) had NSNM at birth, whereas 14 (9.0%) had SGA without microcephaly, 13 (8.3%) had PM, and 13 (8.3%) had DM. All PM and DM infants were identified as CZS; 4 (28.6%) SGA infants were CZS, and 2 (14.3%) were symptomatic with additional neurologic findings.

Of the 40 infants with either microcephaly (PM, DM) or SGA without microcephaly, 24 (60%) demonstrated laboratory confirmation of ZIKV infection with either a positive infant ZIKV PCR and/or positive serum ZIKV IgM. For the PM infants, 10 (76.9%) had laboratory-confirmed ZIKV infection in contrast to 6 (46.2%) with DM, 8 (57.1%) with isolated SGA, and 39 (33.6%) with NSNM (Table 1).

Significant differences were noted among groups with regard to gestational age at ZIKV infection ($P < .001$). For PM infants, all maternal ZIKV infections occurred during the first trimester; 83.3% occurred in the first trimester for DM infants. For SGA infants, the majority of ZIKV maternal infections occurred in the second trimester (61.5%) and among NSNM infants in the second or third trimesters (77%; Table 2).

Birth Cohort Characteristics and Growth Measurements

Mean gestational age was 268.8 days for all infants, with a similar gestational age at birth noted among groups. Mean HC at birth was 34.8 cm for NSNM infants, with lower mean HCs for the PM (27.1 cm), DM (29.1 cm), and SGA (32.6 cm) groups. Comparison of the mean HCs for infants with PM and DM revealed that PM infants had statistically significantly smaller mean HCs compared to DM infants ($P = .031$). The mean birth weight for NSNM infants was 3.3 kg and was similarly low for the PM (2.1 kg) and SGA (2.2 kg) groups, in contrast to 2.9 kg for the DM group (Table 1).

First-year Growth Curve Evaluations

Infant growth measurements including HC, weight, and length were taken at birth and during monthly follow-up visits during the first 7 months of life, with additional measurements taken until 13 months. Mean *z* scores for infant length, weight, and HC from birth to 13 months are shown in Figure 1. To further elucidate growth changes, piecewise regression (prediction) lines of mean *z* scores were created for HC, weight, and length for each infant group.

Prior to 4 months of age, the rate of HC *z* score changes (slope) was not significantly different among PM and DM infants but was significantly different between SGA and PM infants ($P = .002$) and between SGA and DM infants ($P = .005$). At 4 months, HC *z* scores improved with significant changes noted in the slope for PM ($P < .001$) and DM ($P = .002$) infants. No significant changes were noted in HC growth (slope) for the SGA group after 4 months of age. The rate of weight *z* score changes (slope) showed significant differences among SGA and DM infants until 4 months of age ($P = .01$). Improvement in infant weight *z* scores was also significant for PM ($P = .04$) and DM ($P = .04$) groups at 4 months. In contrast, no significant differences were observed in the rate of length *z* score changes (slope) among the 3 groups in the period before or after 4 months of age. However, at 4 months, the change in length *z* score (slope) showed significant improvement for PM and DM infants (PM, $P = .005$; DM, $P = .007$; Figure 1).

First-year Clinical Outcomes

Significant differences were observed in the frequency of adverse outcomes among ZIKV-exposed infant groups. Rates of seizures were significantly different among groups, with seizures more frequent in PM (84.6%) and DM (84.6%) groups in comparison to the SGA (21.4%) and NSNM (4.3%) groups ($P < .001$). Rates of dysphagia were significantly higher among PM (53.8%) and DM (38.5%) compared to SGA (14.4%) and NSNM (1.7%) infants ($P < .001$). Ten percent of infants (PM, DM, SGA) required placement of ventriculo-peritoneal shunts compared to only 1.7% of NSNM infants; 12.5% required gastric tube placement, which was not necessary for NSNM infants (Table 3).

Morphologic clinical evaluation was frequently abnormal in PM (100%), DM (100%), and SGA (28.7%) infants compared to NSNM infants (3.5%), with significant differences noted among groups ($P < .001$). Similarly, neurologic evaluation was abnormal for PM (100%), DM (100%), and SGA (42.9%) groups compared to NSNM infants (11.2%; $P < .001$). Differences existed in the

Table 1. Zika Virus (ZIKV)–Exposed Infant Cohort Characteristics at Birth Including Infant/Maternal Laboratory Results and Maternal Health/Pregnancy Issues by Infant ZIKV Group

Characteristic	Total	NSNM	PM	DM	Isolated SGA	*P* Value
Number of participants (%)	156	116 (74.4)	13 (8.3)	13 (8.3)	14 (9)	…
Gender						
Male	76 (48.7%)	55 (47.4%)	6 (46.2%)	7 (53.9%)	8 (57.1%)	.911
Female	80 (51.3%)	61 (52.6%)	7 (53.9%)	6 (46.2%)	6 (42.9%)	…
Gestational age (days)						
Mean (SD)	268.8 (±14.4)	270.2 (±12.5)	263.3 (±24.9)	268.2 (±16.6)	263.8 (±14.5)	.197
Birth HC (cm)						
Mean (SD)	33.5 (±3.1)	34.8 (±1.8)	27.1 (±2.8)	29.1 (±1.6)	32.6 (±2.2)	…
Mean difference (95% CI)[c] PM–DM	−2.0 (−3.9, −0.2)	…	…	…	…	.031
Mean *z* score (SD)	0.2 (±2.1)	1.1 (±1.1)	−4.0 (±1.0)	−3.3 (±0.6)	−0.4 (±1.2)	…
Mean difference (95% CI) z score[c] (PM–DM)	−0.7 (−1.4, −0.1)	…	…	…	…	.028
Birth weight (kg)						
Mean (SD)	3.0 (±0.7)	3.3 (±0.5)	2.1 (±0.7)	2.9 (±0.4)	2.2 (±0.4)	…
Mean difference (95% CI)[c] SGA–PM	0.1 (−0.3, 0.5)	…	…	…	…	.679
Mean *z* score (SD)	−0.1 (±1.2)	0.40 (±0.9)	−2.2 (±0.6)	−0.3 (±0.7)	−1.9 (±0.4)	…
Mean difference (95% CI) z score[c] SGA–PM	0.3 (−0.2, 0.7)	…	…	…	…	.217
Birth length (cm)						
Mean (SD)	48.3 (±3.7)	49.0 (±2.8)	44.1 (±5.7)	49.3 (±2.9)	45.3 (±4.8)	<.001
Mean difference (95% CI)[d]						
SGA–DM	−3.9 (−7.4, −0.5)	…	…	…	…	…
SGA–PM	1.2 (−2.2, 4.7)	…	…	…	…	…
PM–DM	−5.2 (−8.7, −1.6)	…	…	…	…	…
Mean *z* score (SD)	−0.1 (±1.7)	0.1 (±1.6)	−1.8 (±1.1)	0.50 (±1.5)	−1.3 (±1.6)	<.001
Mean difference (95% CI) z score[d]						
SGA–DM	−1.8 (−3.4, −0.2)	…	…	…	…	…
SGA–PM	0.5 (−1.1, 2.1)	…	…	…	…	…
PM–DM	−2.3 (−3.9, −0.6)	…	…	…	…	…
Infant ZIKV laboratory results						
Any laboratory-confirmed infant ZIKV (+PCR and/or +IgM)						
Yes	63 (40.4%)	39 (33.6%)	10 (76.9%)	6 (46.2%)	8 (57.1%)	…
No	93 (59.6%)	77 (66.4%)	3 (23.1%)	7 (53.8%)	6 (42.9%)	…
Infant ZIKV IgM positive						
Yes	42 (26.9%)	25 (21.6%)	5 (38.5%)	5 (38.5%)	7 (50%)	…
No[e]	56 (35.9%)	44 (37.9%)	3 (23.1%)	5 (38.5%)	4 (28.6%)	…
Any infant ZIKV PCR positive						
Yes	35 (22.4%)	18 (15.5%)	10 (76.9%)	4 (30.8%)	3 (21.4%)	…
No[f]	121 (77.6%)	98 (84.5%)	3 (23.1%)	9 (69.2%)	11 (78.6%)	…

Table 1. Continued

Characteristic	Total	NSNM	PM	DM	Isolated SGA	*P* Value
Any maternal PCR positive						
Yes	145 (92.9%)	112 (96.6%)	8 (61.5%)	12 (92.3%)	13 (92.9%)	…
No[g]	11 (7.1%)	4 (3.4%)	5 (38.5%)	1 (7.7%)	1 (7.1%)	…
Timing of maternal ZIKV infection						
First trimester	48	27 (56.3%)	8 (16.7%)	10 (20.8%)	3 (6.3%)	…
Second trimester	68	58 (85.3%)	0 (0%)	2 (2.9%)	8 (11.8%)	…
Third trimester	32	30 (93.8%)	0 (0%)	0 (0%)	2 (6.3%)	…
History of prior maternal health issues and/or pregnancy issues[h]						
Yes	10 (6.4%)	1 (0.9%)	2 (15.4%)	1 (7.7%)	6 (42.9%)	<.001
No	146 (93.6%)	115 (99.1%)	11 (84.6%)	12 (92.3%)	8 (57.1%)	
Other congenital infections[i]						
Yes	0 (0%)	0 (0%)	0 (0%)	0 0%)	0 (0%)	NA
No	156 (100%)	116 (100%)	13 (100%)	0 (100%)	14 (100%)	
Maternal drug use during pregnancy						
Yes	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	NA
No	156 (100%)	116 (100%)	13 (100%)	13 (100%)	14 (100%)	

Due to infant classification criteria, only specific groups in which the infants were not grouped based on the outcome were compared for statistically significant differences: HC *z* score was compared among DM and PM infants; weight *z* score was compared among PM and SGA infants; and length *z* score was compared among all groups. For maternal/infant ZIKV lab testing, note that some infants did not receive testing after birth (IgM or ZIKV PCR) because they were referred from outside hospitals. Thus, some columns may not add up to 100%. For maternal/infant PCRs, some mother–infant pairs were PCR-positive from both maternal and infant specimens. The Fisher exact test was used for *P* values for maternal health/pregnancy issues. For maternal trimester of infection, trimester of ZIKV infection was not available for all mothers.

Abbreviations: CI, confidence interval; DM, disproportional microcephaly; HC, head circumference; IgM, immunoglobulin M; NA, not applicable; NSNM, neither SGA nor microcephaly; PCR, polymerase chain reaction; PM, proportional microcephaly; SD, standard deviation; SGA, small for gestational age; ZIKV, Zika virus.

[a]For infant growth measurements, *P* value performing a χ^2 test of association.

[b]For infant growth measurements, *P* value performing 1-way analysis of variance.

[c]For infant growth measurements, 95% CI using a *t* test.

[d]For infant growth measurements, pairwise comparison of 95% CIs with Bonferroni adjustment.

[e]IgM tested and negative.

[f]PCR not done or unknown as opposed to negative PCR.

[g]PCR not done or unknown as opposed to negative PCR.

[h]For maternal health issues/pregnancy complications, pregnancy complications included hypothyroidism, obesity, premature rupture of membranes, preeclampsia/eclampsia, and hypertension.

[i]For maternal health issues/pregnancy complications, there was 1 case of maternal cytomegalovirus (CMV) IgM positive in the first and second trimester, but the DM infant did not have congenital CMV.

Table 2. Zika Virus (ZIKV)–Exposed Infant Group and Trimester of ZIKV Infection

Infant Group	Infants with Laboratory-Confirmed ZIKV	Trimester of ZIKV Infection[a]			*P* Value[b,c]
		First	Second	Third	
Neither SGA nor microcephaly, N = 115		27 (56.3%)	58 (85.3%)	30 (93.8%)	
	Yes	16 (59.3%)	14(24.1%)	8 (26.7%)	.004
	No	11 (40.7%)	44(75.9%)	22 (73.3%)	
Proportional microcephaly, N = 8		8 (16.7%)	0 (0%)	0 (0%)	
	Yes	5 (62.5%)	0 (0%)	0 (0%)	.231
	No	3 (37.5%)	0 (0%)	0 (0%)	
Disproportional microcephaly, N = 12		10 (20.8%)	2 (2.9%)	0 (0%)	
	Yes	6 (60.0%)	0 (0%)	0 (0%)	.315
	No	4 (40.0%)	2 (100%)	0 (0%)	
SGA, N = 13		3 (6.3%)	8 (11.8%)	2 (6.3%)	
	Yes	2 (66.7%)	4 (50.0%)	1 (50.0%)	>.999
	No	1 (33.3%)	4 (50.0%)	1 (50.0%)	
Total		48	68	32	
	Yes	29 (60.4%)	18 (26.5%)	9 (28.1%)	
	No	19 (39.6%)	50 (73.5%)	23 (71.9%)	<.001

Abbreviations: SGA, small for gestational age; ZIKA, Zika virus.

[a]Trimester of infection was unknown for 8 infants

[b]Fisher exact test examining association between laboratory-confirmed ZIKV and trimester of infection within each infant group.

[c]Fischer exact test was used to determine *P* value.

rates of any neurologic, ophthalmologic, or hearing abnormalities among PM (100%), DM (100%), and SGA (42.9%) groups compared to NSNM infants (18.3%; $P < .001$), with differences also seen when evaluated independently for each of the 4 groups. Significant differences among groups existed in the rates of neuroimaging abnormalities, including any abnormality seen on TFUS, CT, or MRI; 100% of PM and DM infants had abnormalities in contrast to 42.9% of SGA and 16% of NSNM infants (P <.001). When isolated SGA and NSNM infants were compared directly, the odds of having abnormal neuroimaging were nearly 4 times greater (odds ratio [OR], 3.9; 95% CI, 1.2–12.8) and the odds of having an abnormal ophthalmologic, hearing, or neurologic exam (OR, 3.4; 95% CI, 1.1–10.7) were more than 3 times greater for SGA infants compared to NSNM infants. These findings remained even after controlling for infant gender, prematurity (<37 weeks), maternal health and pregnancy issues, and infant infections (Table 3; Supplementary Table 3). Significant differences among infant groups were also noted with respect to rates of infections, neonatal intensive care unit (NICU) admissions, and mean number of days spent in the NICU.

DISCUSSION

We are the first to investigate differences in anthropomorphic measurements and outcomes for in utero ZIKV-exposed infants with respect to categorization at birth as PM, DM, or SGA. PM and DM infants had similarly high rates of adverse outcomes and were primarily exposed to ZIKV infection during the first trimester compared to SGA and NSNM infants who were primarily exposed in later trimesters. While infants with SGA without microcephaly had lower rates of adverse infant outcomes compared to those with microcephaly, notable adverse outcomes were observed in a subset of infants. The odds of adverse outcomes for SGA infants were 3 to nearly 4 times greater in comparison to NSNM infants. Mean *z* score growth measures for microcephaly infants (PM, DM) were poor after birth but began to show significant improvement beyond 4 months of life.

Mean HCs for PM and DM infants were similar to those seen in prior studies of CZS infants (28.1 cm ± 1.8 cm), and mean birth weights were within the range seen in other studies of microcephaly infants (2577 g ± 260 g) [13]. One study of 87 Brazilian CZS infants found that 40% were low birth weight and 29% were SGA at birth [13]. The SGA infants also had lower HC *z* scores compared to those who were not SGA [13]. Although not specifically stated, it is likely that many of those infants would have been classified as PM as the majority of the infants had microcephaly [13]. Similarly, we found that PM infants had smaller HC *z* scores compared to DM infants.

Few previous studies have investigated growth rates of ZIKV-exposed infants, and none have made distinctions between PM, DM, and SGA groups. However, 1 study of 48 Brazilian infants with probable CZS did report infant growth measurements over the first 8 months; the majority (87%) had microcephaly, mostly severe [12]. Nearly 20% of those infants had birth weights ≥2 SDs below the mean (SGA based on our criteria) [12]. In that study,

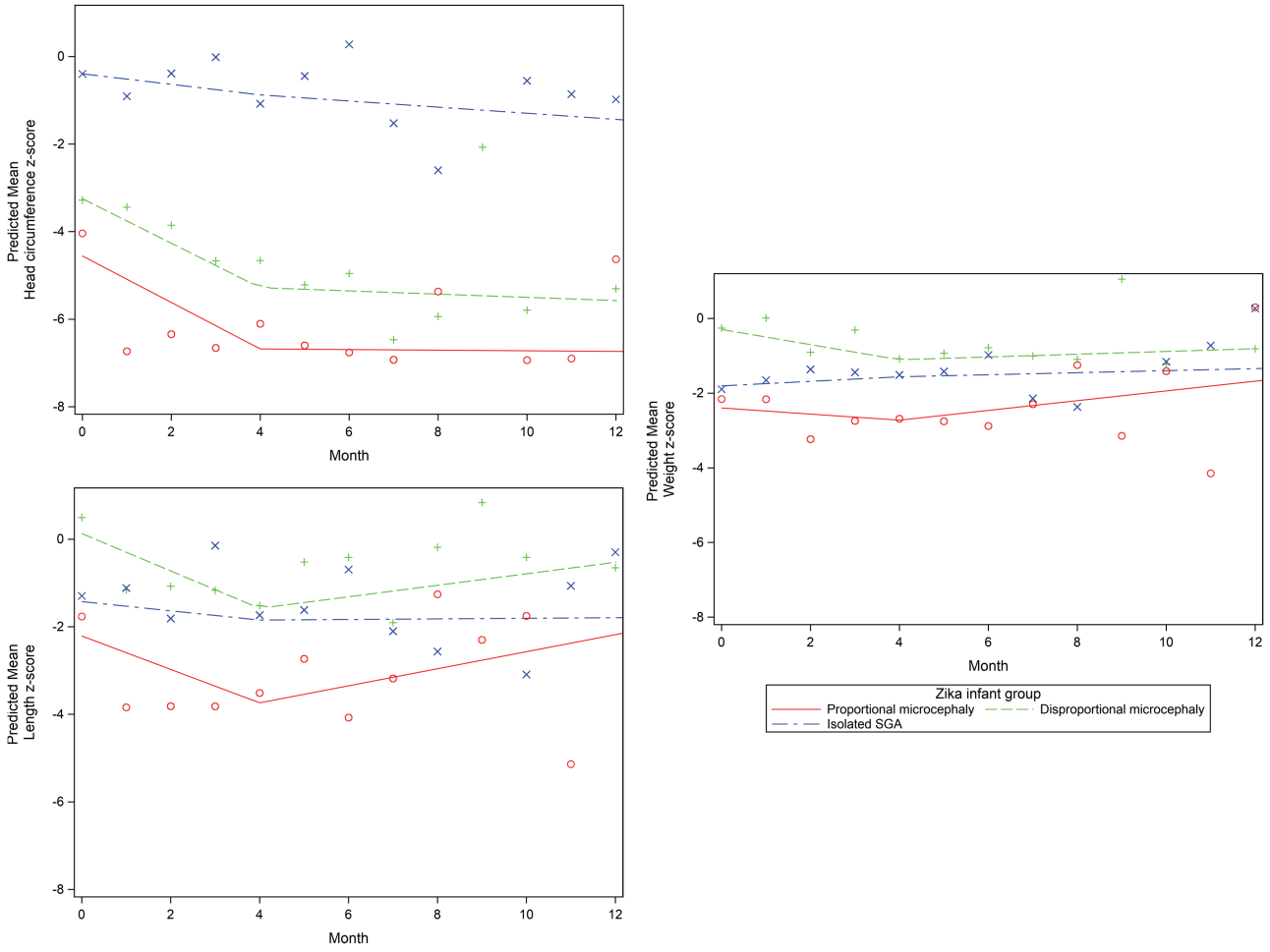

Figure 1. Piecewise regression lines for head circumference, weight, and length z scores over 12 months for proportional microcephaly, disproportional microcephaly, and Zika virus–infected infants, knot at 4 months. The figure shows mean z scores and piecewise regression (prediction) lines of mean z scores for head circumference, weight, and length during the first year of life for each of the 3 ZIKV-exposed infant groups (PM, DM, SGA). Abbreviations: DM, disproportional; PM, proportional; SGA, small for gestational age.

HC decreased to a *z* score of −5.5 by 4 months [12]. Likewise, for the microcephaly infants (PM, DM) in our study, decreased mean *z* scores for weight, length, and HC were observed, especially in the initial months after birth. Our findings were most prominent for head growth over time, which is likely due to the severe CNS damage characteristic of in utero ZIKV [12, 14]. Mean HC *z* scores for microcephaly infants (PM, DM) in our study similarly declined by the fourth month. Our modeled predicted lines based on microcephaly infant growth measures also suggested improvement in *z* score growth beyond 4 months of age.

All ZIKV-exposed infants (PM, DM, SGA) experienced high rates of health problems in comparison to NSNM infants. Not surprisingly, clinical abnormalities and adverse outcomes were most prominent in microcephalic infants compared to SGA infants. However, initial expectations that PM infants may fare better than DM infants were not validated; both groups demonstrated equally high poor-outcome rates. Microcephaly infants had extremely high rates of seizures; abnormal neurologic, morphologic, and ophthalmologic exams; and abnormal neuroimaging studies. The findings for microcephaly infants appear largely consistent with reported literature. All PM and DM patients had neuroimaging abnormalities, which is consistent with prior studies of Brazilian ZIKV microcephaly infants, where nearly all had calcifications and many had cortical malformations and ventriculomegaly [13, 15]. Eye abnormalities in microcephaly infants ranged from 69% to 77%, while others have reported 35% to 100% among infants with microcephaly and intracerebral calcifications [13, 16–22]. The microcephaly infants had higher rates of hearing abnormalities (23–33%) than previously reported (6%) [23, 24]. Chronic issues including seizures and dysphagia appeared more frequently in microcephaly infants (seizures, 85%; dysphagia, 39%–54%) compared to previous reports (seizures, 50%; dysphagia 15%) [1, 12, 25, 26].

The relatively high rates of adverse outcomes among SGA infants were also of interest and were higher than those seen among NSNM infants. No other studies of ZIKV-exposed infants have

Table 3. Frequency of Adverse Infant Outcomes by Zika Virus Infant Groups

Type of Infant Outcome	NSNM n = 116	Proportional Microcephaly n = 13	Disproportional Microcephaly n = 13	SGA n = 14	*P* Value	Odds Ratio[a,b] (95% Confidence Interval); *P* Value for SGA vs NSNM Groups
NICU (days)	2.1 (4.7)	21.8 (30.0)	9.8 (11.9)	28.8 (78.9)	<.001	…
Mean (standard deviation) range[c]	(0 –30)	(0–100)	(0–47)	(0–300)		
Median (interquartile range)	0 (0 –0)	4.0 (0 –35.0)	8.0 (5.0–10.0)	0 (0.0–18.0)		
NICU stay						
Yes	25 (21.7%)	7 (53.9%)	10 (76.9%)	6 (42.9%)	<.001	…
No	90 (78.3%)	6 (46.2%)	3 (23.1%)	8 (57.1%)		
TFUS						
Abnormal	5 (5.0%)	11 (100%)	11 (100%)	5 (35.7%)	<.001	…
Normal	106 (95.0%)	0 (0%)	0 (0%)	9 (64.3%)		
Head CT scan						
Abnormal	7 (63.6 %)	13 (100%)	13 (100%)	5 (83.3%)	.010	…
Normal	4 (36.4%)	0 (0%)	0 (0%)	1 (16.7%)		
Head MRI scan						
Abnormal	18 (60%)	4 (100%)	9 (100%)	1 (50%)	.056	…
Normal	12 (40%)	0 (0%)	0 (0%)	1 (50%)		
Ophthalmologic exam						
Abnormal	6 (5.2%)	10 (77.9%)	9 (69.2%)	4 (28.6%)	<.001	…
Normal	109 (94.8%)	3 (23.1%)	4 (30.8%)	10 (71.4%)		
Hearing exam						
Abnormal	2 (1.9%)	4 (33.3%)	3 (23.1%)	1 (7.7%)	<.001	…
Normal	103 (98.1%)	8 (66.7%)	10 (76.9%)	12 (92.3%)		
Morphologic evaluation						
Abnormal	4 (3.5%)	13 (100%)	13 (100%)	4 (28.6%)	<.001	…
Normal	112 (96.5%)	0 (0%)	0 (0%)	10 (71.4%)		
Neurologic evaluation						
Abnormal	13 (11.2%)	13 (100%)	13 (100%)	6 (42.9%)	<.001	…
Normal	103 (88.8%)	0 (0%)	0 (0%)	8 (57.1%)		
Infections[d]						
Yes	43 (37.1%)	6 (46.2%)	1 (7.7%)	2 (14.3%)	.045	…
No	73 (62.9%)	7 (53.8%)	12 (92.3%)	12 (85.7%)		
Seizures						
Yes	5 (4.3%)	11 (84.6%)	11 (84.6%)	3 (21.4%)	<.001	…
No	111 (95.7%)	2 (15.4%)	2 (15.4%)	11 (78.6%)		
Dysphagia						
Yes	2 (1.7%)	7 (53.8%)	5 (38.5%)	2 (14.4%)	<.001	…
No	114 (98.3%)	6 (46.2%)	8 (61.5%)	12 (85.7%)		
Gastrostomy tube						
Yes	0 (0%)	2 (15.4%)	1 (7.7%)	2 (14.3%)	.001	…
No	116 (100%)	11 (84.6%)	12 (92.3%)	12 (85.7%)		
Ventriculoperitoneal shunt						
Yes	2 (1.7%)	1 (7.7%)	1 (7.7%)	2 (14.3%)	.051	…
No	114 (98.3%)	12 (92.3%)	12 (92.3%)	12 (85.7%)		
Grouped infant outcomes						
Any abnormal neuroimaging (TFUS, head CT, head MRI)						
Yes	17 (16.0%)	13 (100%)	13 (100%)	6 (42.9%)	<.001	3.9 (1.2–12.8)[e]; *P* = .023
No	89 (84.0%)	0 (0%)	0 (0%)	8 (57.1%)		
Any abnormal ophthalmologic, hearing, or neurologic exam						
Yes	21(18.3%)	13 (100%)	13 (100%)	6 (42.9%)	<.001	3.4 (1.1–10.7)[e]; *P* = .041
No	94 (81.7%)	0 (0%)	0 (0%)	8 (57.1%)		
Any abnormality except NICU stay or infection						
Yes	33 (28.5%)	13 (100%)	13 (100%)	6 (42.9%)	<.001	1.9 (0.6–5.9)[e]; *P* = .272
No	83(71.5%)	0 (0%)	0 (0%)	8 (57.1%)		

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; NICU, neonatal intensive care unit; NSNM, neither SGA nor microcephaly; SGA, small for gestational age; TFUS, transfontanelle ultrasound.

[a]Odds ratio (OR) comparing SGA and NSNM groups only (reference group NSNM).

[b]Refer to Supplementary Table 3 for multivariate logistic regression with adjusted ORs for grouped infant outcomes shown above adjusted for infant gender, prematurity, maternal health and pregnancy issues, and infection.

[c]Please note that regarding NICU stay (days) for the SGA group, mean length of stay (days) was longest because 1 SGA infant with congenital Zika syndrome was never discharged from the hospital following 300 days. Further details are available in Supplementary Table 2 for infant 3.

[d]Infections (including pneumonias, urinary tract infections, skin infections, and bronchiolitis) among Zika virus–exposed infants primarily occurred beyond the immediate postnatal period during follow-up.

[e]Fischer exact test was performed to determine *P* values comparing the 4 infant groups.

focused on SGA as a risk factor for adverse infant outcomes. In other congenital infections, little has been published about SGA as a risk factor for adverse outcomes [27–29]. Approximately 43% of SGA infants were found to have a neurologic, ophthalmologic, or hearing abnormality in comparison to only 18% of NSNM infants (OR, 3.4; 95% CI, 1.1–10.7); 21% had seizures and 43% had abnormal neuroimaging compared to only 16% of NSNM infants (OR, 3.9; 95% CI, 1.2–12.8). While these SGA infants were not microcephalic at birth, it appears that the majority of adverse outcomes can be attributed to a subset of 6 infants who were not only SGA at birth but also had other severe manifestations of congenital ZIKV infection. Of these 6 infants, laboratory confirmation of ZIKV infection was observed among 4 (67%); only 1 mother had notable prior health issues or problems during pregnancy (hypothyroidism and hypertension; see Supplementary Table 2; Table 1). For ZIKV-exposed infants, our findings suggest that SGA may be another important but less emphasized manifestation of CZS.

While the rates of abnormalities in NSNM infants was lower than for microcephaly (100%) or SGA (43%) infant groups, nearly 29% of children had some type of adverse outcome. This likely reflects CNS ZIKV complications in children without microcephaly or other forms of growth restriction. It is curious that 37% of NSNM infants had some sort of infection after birth or during follow-up, which was higher than for DM or SGA infants. This finding warrants further investigation.

Primary study limitations include the relatively small sample size, which limited the power to determine differences between growth curve changes for PM, DM, and SGA groups and generalizability of additional multivariate analyses related to maternal and infant factors. This issue impacted our study primarily beyond 7 months of age when there was decreased frequency of growth measurements for each of the 3 groups. In addition, while all infants had laboratory-confirmed ZIKV exposure, many of the SGA and/or microcephaly infants did not have laboratory-confirmed ZIKV infection at the time of birth, which included 23% of PM and 54% of DM infants. This underscores inherent limitations in reliance on laboratory diagnosis of ZIKV at birth from infant ZIKV IgM and PCR. While differences were observed in timing of maternal ZIKV infection during pregnancy, women typically were tested at the time of clinical symptoms or at the time of referral for further evaluation but did not undergo ZIKV testing in each semester. It is also important to note that our study was a retrospective review of clinical data from a referral center for ZIKV-exposed infants. Thus, frequency data does not reflect incidence data.

CONCLUSIONS

We conducted this analysis to determine if distinctions between proportional and disproportional microcephaly and SGA at birth are important in determining the prognosis of ZIKV-exposed infants with respect to growth and adverse outcomes in the first year of life. ZIKV-exposed infants with PM, DM, and even SGA had high rates of adverse outcomes. In addition, notable rates of adverse outcomes were observed among ZIKV-exposed infants who were not microcephalic or SGA at birth. Our preliminary findings highlight the need for further long-term outcome studies for all ZIKV-exposed infants, especially those who have microcephaly (both PM and DM) or SGA at birth.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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