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Feeding methods and weight evolution in newborns with congenital microcephaly due for Zika Virus

Métodos de alimentação e evolução do peso de recém-nascidos com microcefalia congênita por Zika Vírus

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ABSTRACT

Purpose: Investigate the form of diet offer, according to the different feeding methods, and describe the weight gain in newborns with microcephaly related to Zika Virus, comparing them with newborns without microcephaly. **Methods**: Retrospective cohort with nested case-control study. Information on gestational age, weight and feeding methods (maternal breast, nasogastric/orogastric tube, bottle and cup) were collected from medical records of 43 newborns with microcephaly due to Zika Virus, matched according to gestational age with 43 newborns without involvement (control group), in a reference maternity hospital in northeastern Brazil. Data were collected from birth to hospital discharge. Outcome measures were weights (at birth and at discharge), weight gain speed, length of hospital stay and feeding methods. **Results:** The microcephaly group had lower weights at birth (D=-1.67; p<0.001), even more likely to be underweight (Phi=0.687; p<0.001), and at discharge (D=-0.87; p=0.006), than the control group. The microcephaly group also showed a higher rate of weight gain (D=0.77; p=0.006), although with eating methods similar to the control group, including acceptance of the mother's breast, exclusively (34.9%) or complemented (58.1%). **Conclusion:** Newborns with Zika Virus-related microcephaly used similar feeding methods, including maternal breast, to those in the non-affected group. As for weight, they showed lower values at birth and at discharge, despite having a faster postnatal early growth than those without microcephaly.

Keywords: Zika Virus; Microcephaly; Newborn; Weight gain; Feeding methods

RESUMO

Objetivo: investigar a forma de oferta de dieta, conforme os diversos métodos de alimentação, e descrever o ganho de peso em recém-nascidos com microcefalia relacionada ao Zika Vírus, comparando-os com recém-nascidos sem microcefalia. **Método:** estudo de coorte retrospectivo com caso controle aninhado. Informações sobre idade gestacional, peso e métodos de alimentação (seio materno, sonda nasogástrica/orogástrica, mamadeira e copo) foram coletadas em prontuários de 43 recém-nascidos com microcefalia por Zika Vírus, equiparados conforme idade gestacional com 43 recém-nascidos sem acometimentos (grupo controle), em uma maternidade de referência no Nordeste do Brasil. Os dados foram coletados desde o nascimento até a alta hospitalar. As medidas de desfecho foram pesos (ao nascer e na alta), velocidade de ganho de peso, tempo de internação e métodos de alimentação. **Resultados:** O grupo com microcefalia apresentou menores pesos ao nascer (D=-1,67; p<0,001), inclusive com maior probabilidade de serem baixo peso (Phi=0,687; p<0,001), e no momento da alta (D=-0,87; p=0,006), do que o controle. O grupo com microcefalia também apresentou maior velocidade de ganho de peso (D=0,77; p=0,006), embora com métodos alimentares semelhantes ao grupo controle, incluindo a aceitação do seio materno, de forma exclusiva (34,9%) ou complementada (58,1%). **Conclusão:** recém-nascidos com microcefalia relacionada ao Zika Vírus utilizaram métodos alimentares semelhantes, incluindo seio materno, aos do grupo sem acometimento. Quanto ao peso, apresentaram valores menores ao nascimento e na alta, apesar de terem um crescimento precoce pós-natal mais rápido que aqueles sem microcefalia.

Palavras-chave: Zika Vírus; Microcefalia; Recém-nascido; Ganho de peso; Métodos de alimentação

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INTRODUCTION

At the end of 2014, there was an increase in the number of newborns (NB) with microcephaly in Brazil, precisely in geographic areas where the Zika Virus (ZKV) had appeared. Epidemiological and cohort studies have established a strong relationship between ZKV and intrauterine infections[1,2]. With the ZKV outbreak a congenital syndrome initially poorly defined was characterized by microcephaly, encephalopathy, short stature, underweight and feeding problems[3,4].

There is a lack of consensus in the literature regarding the birth characteristics of children with ZKV-related microcephaly. While some authors state that low birth weight and prematurity are identified as the most frequent adverse outcomes of ZKV infection[5] others believe that although children with microcephaly are more likely to have low birth weight the frequency of prematurity is not high[6,7].

Children with ZKV-related microcephaly, even when they have normal weight and length at birth[8] present deterioration in their nutritional status with twice the prevalence of underweight for age in the second year of life when compared to uninfected children[9]. Clinical studies on the supply of complementary nutrition to high-risk newborns are necessary since inadequate growth may be related to unsatisfactory neurodevelopment[10].

The Brazilian Ministry of Health[11,12] and the World Health Organization[13] recommend exclusive breastfeeding up to 6 months of age and supplemented up to 2 years of age, including children born to mothers with suspected, probable or confirmed ZKV infection. The initiation and successful maintenance of breastfeeding depends on efficient skills which can be too complex task for subjects with microcephaly.

Speech therapy is concerned with the form of food supply, which may include the necessity of using an alternative feeding route (for example, feeding by cup, bottle or orogastric tube - SOG) in order that the newborn can receive the diet and achieve adequate growth[14,15]. Although eating difficulties are well documented in children with neurological disabilities, data are still scarce on populations affected by ZKV[16]. The nutritional management of these newborns has become a challenge for health professionals in endemic areas.

Studies have shown that children with ZKV-related microcephaly have difficulties in food intake, which may be related to both changes in the tone of the orofacial muscles, which interfere with adequate lip sealing, sucking and tongue movements[17], as well as adverse conditions associated with the texture of food, prolonged meals and disturbances in the mechanisms of hunger and satiety[3,4].

Studies on the growth pattern including initial weight gain are still missing according to the dietary methods used during hospitalization at the maternity hospital. The objective of the present study was to investigate the form of diet offer according to the different feeding methods and to describe the weight gain from birth to hospital discharge in newborns with ZKV-related microcephaly comparing them with newborns without involvement.

METHODS

This is a retrospective cohort study with a nested case-control of 86 newborns born between February 2015 and March 2017 during the period of the ZKV outbreak which caused births with microcephaly in the Northeast of Brazil. All NBs belonged to the same high risk reference public maternity hospital and their data were collected from hospital records.

43 NBs were identified who were suitable for the "Protocolo de Vigilância em Resposta à Ocorrência de Microcefalia relacionada à Infecção por ZKV"[18], being classified as belonging to the study group with microcephaly (GM), matched, according to gestational age at birth (GAB), with 43 newborns in the control group without microcephaly (CG).

It was considered as inclusion criteria in the GM head circumference measurement less than two standard deviations as expected for sex and gestational age (GA). Microcephaly was related to ZKV after excluding other etiologies (cytomegalovirus, rubella, toxoplasmosis, HIV, syphilis) and by evidence of fetal ZKV infection based on clinical and epidemiological criteria according to the Ministry of Health and international literature[11,12].

It was considered as inclusion criteria in the CG appropriate head circumference measurement according to gender and GA. GAB was also observed which should correspond to GM participants.

Exclusion criteria were considered for both groups (GM and CG) newborns with clinical instability characterized by dyspnea, cyanosis and/or tachycardia. The newborn in the CG could also not present evidence of fetal ZKV infection according to established parameters[11,12].

The data collected included GA, birth weight, diagnosis of microcephaly according to the tests performed (computed tomography, ultrasound and serology for ZKV), weight measurements and feeding methods (maternal breast - MB, nasogastric/orogastric tube (OGT), bottles with a common nipple or orthodontic and cup), throughout the hospital stay.

The feeding methods used by each NB were extracted from the medical record and clinical evolution of the team since not all participants underwent speech therapy in order that specific data on oral motor development could be obtained. On the other hand, the methods used somehow could already demonstrate the oral ability of the newborn.

In addition, as it is an institution that advocates humanized neonatal care, according to the Baby Friendly Hospital Initiative (BFHI)[19], there was an effort by the entire health team including the speech therapist to prioritize when possible indication of breastfeeding which presupposes oral motor skills.

The data were analyzed using the R Core Team 2018 software, version 3.5.1. The variables were summarized using frequencies, percentages, 95% confidence intervals (95% CI) and means with standard deviation (SD). Associations between categorical variables were tested using Fisher's exact test, Pearson's chi-square test and relative risks with 95% CI. Phi coefficient effect size was calculated for proportions. The variables normally distributed were tested using the Student's t test and those that were not, with the Mann-Whitney test.

Cohen's Effect Size D was used to quantify the differences in measure of central tendency[20]. Linear regressions were used to estimate differences in weight gain speed (grams/day) between newborns with and without microcephaly, adjusted for the number of days until discharge, and feeding methods. The p values were adjusted using the Benjamini-Hochber method[21]. Values of $p<0.05$ were considered statistically significant.

The study was approved by the Research Ethics Committee of the Federal University of Sergipe, No. CAEE 53611316.0.0000.5546.

All guardians signed the Free and Informed Consent Form (FICF) for inclusion in the research.

RESULTS

All newborns included in the study were hospitalized for at least 4 days. NBs with microcephaly (MG) were admitted to the maternity hospital to follow the ZKV investigation protocol and those without microcephaly (CG), for various reasons, including gestational diabetes, to investigate possible infections after premature rupture of membranes and maternal urinary infections.

Table 1 shows the clinical characteristics of the neonates including GA and birth weight in addition to clinical complications. There were no differences between the MG and CG groups for GAB and clinical complications (use of respiratory support and antibiotic therapy) which guaranteed the participants' uniformity regarding these clinical parameters (Table 1).

About weight, Table 1 shows birth weight, weight gain and gain speed during hospitalization. There was a difference in body weight gain between the groups from birth to hospital discharge. The GM had lower weights at birth after 48 hours of life and at hospital discharge. However, there was a greater global weight gain and a higher daily rate of weight gain. Despite this, all NBs in the study (with and without microcephaly) had a similar hospitalization time (Table 1).

Table 2 shows the feeding methods used during hospitalization including exclusive BF, or not (complement by means of a glass, bottle or OGT), and absence of MS, comparing newborns with and without microcephaly. There were no differences between the groups regarding the supply of MS, the use of a nasogastric / orogastric tube, bottles or a cup. There was only a greater trend towards the use of SOG in GM, although not significant (Table 2).

In Figure 1, the prevalence of breastfeeding initiation is shown, according to the days (from birth to the 37th day of life). It was observed that 58% of the newborns in the GM and 70% of the newborns in the CG were taken to the MB as soon as they were born. However, 14% of the GM started breastfeeding only after 5 days of life specifically 5, 6, 7, 8, 13 and 37 days after birth, while no newborn in the CG started MB so late (Figure 1).

Table 3 shows the regression parameters adjusted for weight gain speed comparing newborns with and without microcephaly. As for feeding methods and length of hospital stay (days until discharge), there was a difference between the speed of neonatal weight gain and the presence of microcephaly with an average speed of weight gain of 81.3 g / day being higher in MG when compared to CG (p = 0.002), after adjustment of p values by the method of Benjamini-Hochber[21] (Table 3).

DISCUSSION

In the population with microcephaly studied here, there was a statistically similar acceptance although not significant regarding the feeding methods used in newborns without involvement despite the greater use of OGT in newborns of the GM. The literature also referred to the installation of OGT in specific situations, such as persistent choking[17]. Several factors are reported in the diet, depending on the degree of neurological impairment, including conditions related to the texture of food, the prolonged time of meals, with stress and

Table 1. Clinical characteristics and weight gain of newborns with and without microcephaly

	Microcephaly	Without Microcephaly	p-value	Adjusted p-value	Effect Size
	43 (50)	43 (50)			
Conditions in hospitalization					
Gestational Age at Birth, mean (SD)	38.6 (1.2)	38.8 (1.4)	0.359^{W}	0.380	-0.205^{D}
Corrected gestational age at discharge, mean (SD)	39.5 (1.2)	39.4 (1.5)	0.872^{T}	0.872	-0.035^{D}
Birth weight, mean (SD)	2376.6 (435.2)	3168.0 (459.7)	<0.001^{T}	<0.001	-1.667^{D}
Weight at 48 hours, mean (SD)	2647.8 (547.0)	3118.3 (674.5)	0.003^{W}	0.006	-0.695^{D}
Weight at hospital discharge, mean (SD)	2675.1 (599.9)	3224.3 (576.1)	<0.001^{W}	0.006	-0.874^{D}
Weight gain, mean (SD)	191.4 (375.9)	-58.7 (264.0)	0.009^{W}	0.013	0.578^{D}
Weight gain speed (g/day), mean (SD)	47.1 (94.3)	-35.3 (64.4)	0.003^{W}	0.006	0.769^{D}
Birth weight					
<2500 g	14 (73.7)	3 (8.3)	<0.001^{QM}	<0.001	0.687^{P}
2500-2999 g	3 (15.8)	9 (25.0)			
> 3000 g	2 (10.5)	24 (66.7)			
Days until hospital discharge, mean (SD)	6.4 (6.7)	4.9 (4.5)	0.380^{W}	0.380	0.268^{D}
≤ 3 days	21 (48.8)	22 (51.2)	0.829^{Q}	0.829	0.023^{P}
> 3 days	22 (51.2)	21 (48.8)			
Treatment n (%)					
Halo	6 (14.0)	3 (7.9)	0.490^{F}	1.000	0.096^{P}
Mechanical pulmonary ventilation	3 (7.0)	1 (2.6)	0.618^{F}	1.000	0.100^{P}
Continuous positive airway pressure	2 (4.7)	1 (2.6)	1.000^{F}	1.000	0.053^{P}
Antibiotics	2 (4.7)	3 (7.9)	0.661^{F}	1.000	0.067^{P}

n – absolute frequency; ^{W} Mann-Whitney Test; ^{T} Unpaired T Teste; ^{F} Fisher Exact Test; ^{Q} Pearson Chi-square Test; ^{QM} Monte-Carlo Pearson Chi-square Test; ^{D} Cohen's D; ^{P} Phi Coefficient; The p-values were adjusted for the false discovery rate by the Benjamini-Hochberg method.

Subtitle: SD = Standard Deviation; g = grams; g/day = grams per day; n = absolute frequency; % = percentages

Table 2. Feeding methods used during hospitalization of newborns with and without microcephaly

Feeding methods n (%)	Group		p-value	Adjusted p-value	Effect Size	RR (95%CI)
	Microcephaly	Without Microcephaly				
	43 (53)	38 (47)				
Excluxive BF	15 (34.9)	18 (47.4)	0.268	1.000	0.130	0.74 (0.43-1.25)
BF+ cup or bottle or OGT	25 (58.1)	18 (47.4)	0.377	1.000	0.110	1.23 (0.81-1.87)
Cup	20 (46.5)	18 (47.4)	1.000	1.000	0.009	0.98 (0.62-1.56)
Bottle	4 (9.3)	2 (5.3)	0.679	1.000	0.077	1.76 (0.34-9.11)
OGT	10 (23.3)	3 (7.9)	0.074	1.000	0.209	2.95 (0.87-9.92)
Without BF	3 (7.0)	2 (5.3)	1.000	1.000	0.032	1.32 (0.23-7.52)

n – absolute frequency. Fisher Exact Test; RR – Relative Risk. Phi Coefficient. The p-values were adjusted for the false discovery rate by the Benjamini-Hochberg method
Subtitle: BF = Breastfeeding, OGT = Orogastric Tube; CI = Confidence Interval

Table 3. Adjusted regression model for weight gain speed in newborns with microcephaly compared to those without microcephaly

	B (95%CI)	p-value	B_{adj} (95%CI)	p-value
Group				
MG	82.4 (35.9; 129.0)	0.001	81.3 (31.9; 130.7)	0.002
CG	1		1	
Feeding methods				
Excluxive BF	-124.1 (-255.0; 6.72)	0.062	-114.6 (-233.3; 4.1)	0.058
BF+ cup or bottle or OGT	-68.0 (-195.0; 59.0)	0.286	-62.6 (-177.9; 52.7)	0.278
Without BF	1		1	
Days until hospital discharge				
> 3 days	-28.0 (-79.2; 23.2)	0.276	9.7 (-44.5; 63.9)	0.719
≤ 3 days	1		1	

B – Linear regression parameter estimates. B_{adj} – Multiple linear regression parameter estimates. 95%CI – 95% confidence interval for linear regression parameter estimate.
Subtitle: MG = ZKV-related Microcephaly Group; CG = Control Group; BF = Breastfeeding, OGT = Orogastric Tube

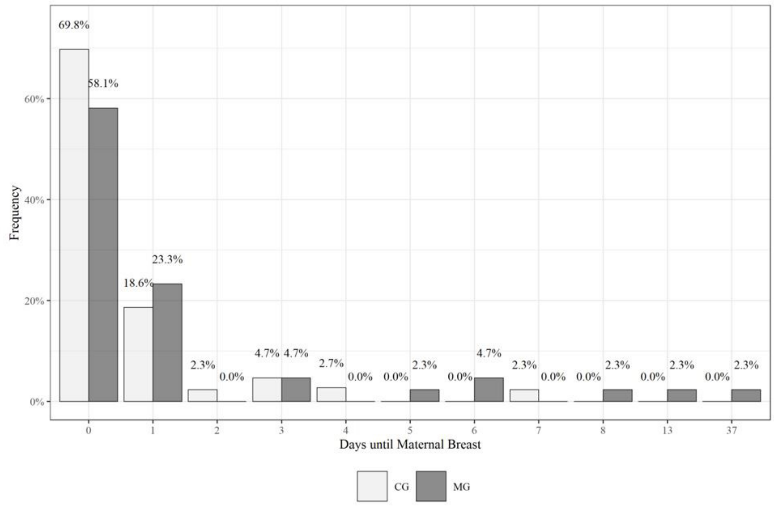

Figure 1. Prevalence of breastfeeding initiation, in days (0 to 37 after birth)
Subtitle: MG = ZKV-related Microcephaly Group; CG = Control Group

fatigue, disturbances in the mechanisms of hunger and satiety, among others[3,4].

The similarity in the acceptance of MS in both groups, despite the later initiation and to a lesser extent in some participants with microcephaly, could be attributed to the fact that the reference institution of the study follows the guidelines of the National Microcephaly Coping Policy[11,18], which in line with other entities instituted practices to encourage breastfeeding even in the presence of the ZKV scenario. There were also no differences between groups for the other methods of feeding: cup, bottle and OGT.

Regarding oral diet offer to complement MB, it is worth mentioning that institutions that follow the BFHI guidelines[19] avoid the prescription of artificial nipples, which probably can explain the greater use of the glass than the bottle for newborns in both groups. Despite this practice, a longitudinal study showed a high incidence of bottle feeding (89.9%) at older ages in the population affected by ZKV[17]. It is recommended that there be speech therapy intervention to monitor the different feeding methods[15].

The regulations of the Ministry of Health[11,12] which recommend breastfeeding in newborns suspected of having congenital ZKV infection were followed in the population with microcephaly in the present study being considered in this context an important health promotion strategy and disease prevention both childhood and adult life. In addition, the data obtained here showed satisfactory results regarding weight gain in this initial period of life.

The pairing between the MG and CG groups, in terms of GAB and the profile of clinical complications ensured uniformity for comparison purposes. All NBs in the study had an GAB greater than 37 weeks, and were not considered premature[22]. These results reaffirm the report of the Brazilian Society of Medical Genetics, which, after reviewing 35 cases of microcephaly due to probable ZKV infection, found that most of the babies in its sample were born at term[23]. Full-term birth favors the maturity of orofacial functions and the ability to coordinate sucking/swallowing/breathing[9], for acceptance of a full and safe oral route.

Despite the favorable GAB in the present study, newborns in the MG were almost nine times more likely to have low birth weight (74%) than those in the CG. This index is higher than the prevalence of 30% reported by the literature[24], which reflects the restriction of intrauterine growth to ZKV[6,7] and other congenital infections such as dengue[25] and TORCH (toxoplasmosis, rubella, cytomegalovirus and herpes simple)[26]. Thus, newborns in the MG showed a higher speed of weight gain than the newborns in the CG although they were lighter at birth and at discharge suggesting the presence of weight recovery.

A study reported that the rapid rate of postnatal weight gain in newborns with low birth weight can result in better neurological results[27]. Perhaps the stimulus for weight recovery can alleviate possible future malnutrition, precisely in a population that usually presents eating difficulties related to mastication and swallowing skills associated with progressive developmental, motor and neurological abnormalities[9,28,29]. However, more studies still need to be carried out in this regard.

It is worth mentioning that the rapid weight gain occurred regardless of the food methods used since there were no differences between the groups regarding the mode of food supply. In this sense, it is important to highlight the institutional reality which follows the principles of BFHI[19], advocates and encourages breastfeeding, in addition to having the speech therapist in the interdisciplinary team, which could justify the conduct of appropriate early intervention.

On the other hand, MG's rapid weight gain speed suggests the presence of adaptive changes in metabolic patterns (hypothesis of the economic phenotype) which may increase the risk of overweight and future comorbidities[10] and deserves to be further investigated in longitudinal studies with this population.

Above all, in view of the findings of the present study on the rapid speed of weight gain in the affected population, breastfeeding and good dietary practices could contribute with an important positive repercussion for growth and good postnatal nutrition in which increasing difficulties to feed these children are reported[17,30]. Thus, breast suction should be promoted regardless of the pathology of the NB provided that there are clinical conditions and that all multidisciplinary support is given to the mother-baby binomial especially speech therapy.

Evidence of the acceptance of the various methods of oral feeding in newborns with microcephaly, with emphasis on MB, can be considered an important differential of this research, contributing to the reflection on early behaviors among the affected population. There was a limitation in relation to the few cases followed due to the diagnosis of microcephaly with suspected etiology by the ZKV - according to criteria established in national and international literature[11,12] - having been raised only at the time of birth of the affected population given the unprecedented nature of the epidemic.

Another limiting factor of the present study is that the participants were only followed up until hospital discharge and it is not possible to elucidate the subsequent food development. It is worth remembering that the literature has described that at older ages children with microcephaly present weaning before the age of 6 months[17], eating problems such as dysphagia from the third month of life and deterioration of the nutritional status in the second year of life[9]. New studies should be proposed in this regard.

CONCLUSION

NBs with microcephaly had a high prevalence of low birth weight and experienced rapid postnatal growth despite having feeding methods similar to those established for NBs in the control group.

The lack of knowledge of the effects of ZKV in the medium and long term hinders the prognosis and clinical and nutritional management and requires for further studies on the outcome of feeding in early childhood including involving speech-language aspects especially in the orofacial motricity issues of the population with microcephaly. by ZKV.

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