OPEN ACCESS

ARTIGO ORIGINAL

Radiological Evaluation of the Hip of Patients with Congenital Zika Syndrome

Avaliação Radiológica do Quadril de Pacientes com Síndrome da Zika Congênita

Mônica Alexandra Sampaio Torres[1], Cláudio Soares Conceição[1], Rogério Meira Bastos[2], Marcos Almeida Matos[2*]

[1]Post Graduation Student of Escola Bahiana de Medicina e Saúde Pública; [2]Preceptor of the Orthopedics Residency at Santa Izabel Hospital; Salvador, Bahia, Brasil

Introduction: Congenital Zika syndrome can generate microcephaly and spastic motor syndromes, limb deformities, and arthrogryposis. Hip dysplasia, associated with this syndrome, is frequent but poorly studied. Objective: To describe the radiographic alterations of the hip in patients with Congenital Zika Syndrome (CZS). Methods: Observational cross-sectional cohort study. We studied 25 patients with a serological diagnosis of CZS and a sample of 50 hips. Patients underwent evaluation, with lines and angles drawn on AP and P radiographs of the pelvis to assess the relationship between the femoral head and the acetabulum. The correlation was performed between radiographic changes of the hip in patients with SZC, gender, presence of arthrogryposis, spasticity, and microcephaly. Results: The mean age was 36 months (29-45 months), 15 patients were female (60%), with a predominance of blacks and browns (72%). The mean maternal age was 28 years (16-44 years), 11 (44%) had the disease before the 12th week of gestation, and all had clinical symptoms related to ZIKA virus infection. At birth, patients had an average head circumference of 26 cm (26-32 cm). Of the 50 hips evaluated in the study, 38 (76%) hips patients had orthopedic deformities, and 20 (40%) hips patients had arthrogryposis. In the radiographic changes of the hip, of the 50 hips, 12 (24%) hips were Tonnis grade I, 22 (44%) were subluxated (grade II), 9 (18%) were low dislocated (grade III), and 7 (14%) were high dislocated (grade IV). The RI was changed in 43 (86%) hips. ACD was valgus in 45 (90%) hips. ACEW was changed in 13 (26%) hips. The IA was changed in 18 (36%) of the evaluated hips. Conclusion: We found a high frequency of dysplastic changes in the hip in the patients of this study. So, we indicate radiological investigation of the hip in children with microcephaly and suspected CZS.

Keywords: Microcephaly; Zika Virus; Radiographic Evaluation; Congenital Abnormalities; Arthrogryposis.

Introdução: A síndrome da Zika Congênita pode gerar microcefalia e síndromes motoras espásticas, deformidades em membros e artrogripose. A displasia do quadril, associada a esta síndrome, embora frequênte, ainda é pouco estudada. Objetivo: Descrever as alterações radiográficas do quadril em pacientes com Síndrome da Zika Congênita (SZC). Métodos: Estudo observacional de coorte transversal. Foram estudados 25 pacientes com o diagnóstico sorológico da SZC e amostra composta por 50 quadris. Os pacientes realizaram avaliação, sendo traçadas linhas e ângulos nas radiografias em AP e P da bacia para avaliar a relação entre a cabeça femoral e o acetábulo. Foi realizada a correlação entre as alterações radiográficas do quadril

Correspondence addresses:
Dr. Marcos Almeida Matos
marcos.almeida@hotmail.com

Received: January 15, 2022

Revised: March 20, 2022

Accepted: March 25, 2022

Published: March 28, 2022

Data Availability Statement: All relevant data are within the paper and its Supporting Information files.

Funding: This work was the result of authors' initiative. There was no support of research or publication funds.

Competing interests: The authors have declared that no competing interests exist.

e-ISSN: 2764-2089
ISSN: 2526-5563

em pacientes com SZC, o sexo, a presença de artrogripose, espasticidade e microcefalia. Resultados: A média de idade foi de 36 meses (29-45 meses), 15 pacientes eram do sexo feminino (60%), com o predomínio de pretos e pardos (72%). A média de idade materna foi de 28 anos (16-44 anos), 11 (44%) delas apresentaram a doença antes das 12º semanas de gestação e todas apresentaram sintomas clínicos relacionados a infecção pelo ZIKA vírus. Ao nascer os pacientes apresentavam como média o perímetro cefálico de 26 cm (26-32 cm). Dos 50 quadris avaliados no estudo, em 38 (76%) quadris os pacientes apresentavam deformidades ortopédicas e em 20 (40%) quadris os pacientes apresentaram artrogripose. Nos pacientes com microcefalia, havia deformidade em 40 (80%) dos quadris. Nas alterações radiológicas do quadril, dos 50 quadris 12 (24%) quadris foram grau I de Tonnis, 22 (44%) subluxados (grau II), 9 (18%) luxados baixos (grau III) e 7 (14%) luxados altos (grau IV). O índice de Reimers (IR) estava anormal em 43 (86%) quadris. O ângulo cérvico-diafisário (ACD) estava valgo em 45 (90%) dos quadris. O ângulo Center-Edge de Wiberg (ACEW) estava anormal em 13 (26%) dos quadris.. O IA foi alterado em 18 (36%) dos quadris avaliados. Conclusão: Encontramos grande frequência de alterações displásicas no quadril nos pacientes da amostra e por isso recomendamos a investigação radiológica do quadril crianças com microcefalia e suspeitas de SZC.
Palavras-chaves: Microcefalia; Zika Vírus; Avaliação radiográfica; Anormalidades Congênitas; Artrogripose.

Introdução

The Zika virus (ZIKV) is an RNA arbovirus by the Flaviviridae family, transmitted to humans by the mosquitoes' bite of the genus Aedes.[1] Infection caused by this virus was designated a Public Health Emergency of International Concern in 2016 by the World Health Organization (WHO).[2-5] In Brazil, the Congenital Zika Syndrome (SZC) has been described as vertical transmission of the Zika virus (ZIKV) from mother to fetus.[6] This new syndrome was confirmed in early 2015 by the association of a significant increase in births of children with microcephaly with infection by this virus in 18 states, distributed in the 5 Brazilian regions.[6]

Symptoms of infection only develop in 20% of those infected and, when present, have an acute onset, including manifestations such as intermittent fever, pruritic maculopapular rash, non-purulent, and non-pruritus conjunctival hyperemia, arthralgia, myalgia, and headache. Symptomatic patients have a benign course, and the symptomatological picture usually disappears after 3 to 7 days.[3,4] However, in cases of CZS, Brazilian researchers confirmed the association between maternal infection and severe deformities in newborns.[7-9] Since then, evidence of this association has emerged, characterizing the Congenital Zika Syndrome (CZS).[5,7-9]

ZIKV infection can lead to pregnancy loss or severe comorbidities in the neonate, such as congenital microcephaly, brain and eye defects, spastic motor syndromes, limb deformities, and severe arthrogryposis in the extremities.[5,7,8,10] Among the musculoskeletal alterations related to arthrogryposis, hip dysplasia has been described in the literature, associated or not with a partial (subluxation) or complete dislocation (dislocation) of the femoral head.[5,7,8,10]

The diagnosis of hip dysplasia is effected by clinical examination and imaging methods such as X-rays.[9,10] Hip radiography becomes an essential complementary exam since the physical examination of the hip in babies with SZC is greatly limited by musculoskeletal deformities and associated spasticity.[9,10] Radiographic evaluation of the hip is a necessary propaedeutic complement for diagnosis and definition of therapeutic management.

Despite the possible high prevalence of hip dysplasia in SZC, no studies describe this prevalence or the clinical and radiographic characteristics of this severe deformity. Studies of this nature are necessary to create therapeutic protocols in children with CZS. This study aims to describe the hips' dysplasia in patients with CZS and characterize radiographic changes associated.

Materials and Methods

Study Design

This investigation is a descriptive and analytical observational study of radiographic findings of the

hip in patients with CZS. The study was carried out at the Orthopedics Service of Hospital Santa Izabel and the Radiology Service of the Centro Médico Saúde Bahiana from October 2018 to October 2019.

The study was conducted according to the ethical criteria defined in Resolution 466/12 of the National Health Council by the Research Ethics Committee of Hospital Santa Izabel, and all participants completed an informed consent form (ICF).

Population Size

Patients were selected among those being followed up at the pediatric orthopedics outpatient clinic of Santa Izabel Hospital with clinical and laboratory diagnoses of SZC from March 2017 to March 2018. These patients were identified and referred for evaluation at the Radiology Service of the Medical Center Saúde Bahiana from October 2018 to October 2019.

The study population consisted of non-probabilistic sequential sampling. Patients with the serological diagnosis of congenital Zika Syndrome were included in the study. However, we excluded those who had not submitted to the standardized radiographic technique and those whose parents/guardians did not respond to the research questionnaires. There was no sample size calculation, given that we accepted all patients who attended the call from October 2018 to October 2019.

Procedures

The atients/guardians were submitted to a sociodemographic data collection questionnaire, with information on gender, age, skin color, family income, mother's education, and parents' marital status. The clinical-orthopedic characteristics of the patients were collected from medical records.

The individuals included in the study attended the Radiology Department of the Bahiana Saúde Medical Center for radiographic examinations. The following imaging tests were performed: radiography of the pelvis in two views, anteroposterior neutral and Von Rosen, using a standardized radiological technique. Image analysis was performed by a radiologist who is a member of the Brazilian College of Radiology, specializing in Pediatric Radiology.

Clinical-Orthopedic Evaluation

Maternal clinical characteristics considered for clinical-orthopedic evaluation were age, alcoholism, smoking, use of drugs or medication during pregnancy; gestational problems; type of delivery; complications at birth; maternal symptoms related to Zika virus infection in pregnancy; in which gestational week was affected by ZIKA.

The clinical characteristics for clinical-orthopedic evaluation were birth weight and head circumference, hypoxia at birth, Apgar at 1' and 5' minutes, osteoarticular deformities, and arthrogryposis.

For the present study, a case definition of microcephaly refers to those neonates with a head circumference smaller than the cut-off point of -2 standard deviations (SDs) below the mean value of the Fenton growth curves established according to sex and age of the pregnancy. So, we consider microcephaly in the neonate with a head circumference of up to 31 cm.[11]

A complete orthopedic examination was performed on all participants, including clinical assessment of primitive and acquired reflexes, range of motion, lower and upper limb deformities, motor development, and radiographic appraisal of the lower and upper limbs. The prevalent's patient characteristics - tone, reflex status, presence of contractures, and presence of stiffness - were used to differentiate spastic from non-spastic patients. The presence of contractures and stiffness associated with limb deformities were the criteria used to identify patients with arthrogryposis.[12]

Radiological Evaluation

We performed two views in the radiographic evaluation of the hip: neutral AP (antero-posterior) of the pelvis and Von Rosen. In the neutral AP radiograph of the pelvis, we considered the parameters of interest, namely, morphology and location of the proximal femoral epiphysis, Shenton's arch, acetabular index (AI), cervicodiaphyseal angle (CDA), femoral neck width, Wiberg's CE angle (WCEA), Reimers index (RI), classification of Tonnis for hip dysplasia. These characteristics were collected and measured from parameters recommended by the current literature (Figure 1).[13,14]

Statistical Analysis

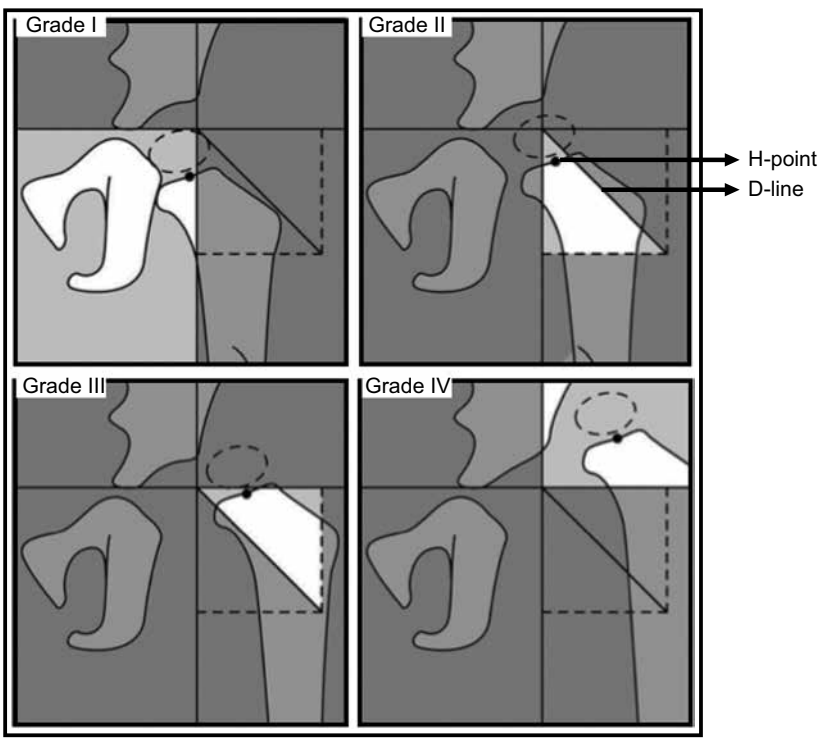
Patient data were analyzed using the SPSS database program, version 25. Data were presented in distribution tables by frequency of radiographic changes in the basin incidences. In the case of numerical variables, such as angle measurements, mean/median and standard deviation were considered. In the case of categorical variables, we presented tables for groups with and without changes in imaging tests. Chi-square (or Fisher when applicable) was used for categorical variables and Student's T-test for continuous variables. In the statistical analysis of the data, the probability value (p) lower than 0.05 (5%) for the type I error was considered significant.

Results

In this study, 25 patients were evaluated, with a mean age of 36 months (29-45 months), 15 were female (60%), with a predominance of blacks and browns (72%). The average maternal age was 28 years (16-44 years), 18 of them (72%) had partners, and 15 had completed high school or higher education (62.5%).

Regarding prenatal care, the average number of consultations was 7. Eleven mothers (44%) had

Figure 1. The Tonnis radiographic classification of developmental dysplasia of the hip (DDH).[23]



the disease before the 12th week of pregnancy. All mothers had clinical symptoms related to ZIKA virus infection - rash, fever, arthralgia, headache, eye pain - and in only two cases, the parents presented the symptoms. There was no history of alcoholism, smoking, or drug use in any of them. Among the pregnant women, 24 (96%) reported only using folic acid or ferrous sulfate, the pregnancy was uneventful in 18 (72%), there was eclampsia/preeclampsia in 2 (8%), and oligo/polyhydramnios occurred in 2 (8%).

Normal delivery was the most frequent, occurring in 14 of the mothers (56%); in 4 of them (16%) were complications in the delivery, 2 cases of perinatal hypoxia (8%), and 2 cases of fetal distress (8%). At birth, the patients had a mean head circumference of 29 cm (26-32 cm), birth weight of 2614 g (1490-3900 g) and length of 46 cm (36-54 cm).

Of the 25 patients analyzed (50 hips), the presence of orthopedic deformities was observed in 19 (76%), and 10 of them (40%) had arthrogryposis in the upper and lower limbs. Microcephaly, characterized by a head circumference of 31 centimeters or less (33), was present in 20 patients (80%).

According to the Tonnes classification, of the 50 hips in our sample, 12 hips (24%) were normal (Tonnis I), 22 (44%) were subluxated (Tonnis II), 9 (18%) were low dislocated (Tonnis III) and 7 (14%) had high dislocations (Tonnis IV). The IR was changed in 43 hips (86%). ACD was valgus in 45 hips (90%). ACEW was changed in 13 hips (26%). The IA was changed in 18 of the hips (36%).

Table 1 correlates the types of radiographic changes in the hip in patients in the sample with the presence or absence of arthrogryposis. We correlate the changes with the presence or absence of microcephaly in Table 2. In Table 3, we correlate the Tonnes classification between microcephalic and arthrogrypotic patients. Table 4 shows the intragroup relationship of IA among microcephalic patients and arthrogryposis.

We observed that altered hips (Tonnis II, III, and IV) were the most prevalent presentations among arthrogrypotic and microcephalic patients. Twenty hips was clinically diagnosed with arthrogryposis, 16 hips (80%) had dysplastic alterations (Tonnis II, III, and IV). Among the 40 hips of microcephalic patients, 30 (75%) had alterations.

Table 1. Correlation between the radiological parameter of the hip and the presence of arthrogryposis.

Radiological Parameter	Arthrogrypotic	Not-Arthrogrypotic	*p*	*n*
IR (>10 %) *n* = 37	19 (51.4%)	18 (48.6%)	0.20*	42****
ACD (>140°) *n* = 40	20 (50%)	20 (50%)	0.26*	42
ACEW (<20°) *n* =13	6 (46.2%)	7 (46.2%)	0.28**	40***
IA (>30°) *n* = 15	9 (60%)	6 (40%)	0.48**	42
Tonnis II a IV *n* =32	16 (50%)	16 (50%)	0.30**	42

* Fisher test; ** Pearson's chi square; *** ACEW was immeasurable in two hips; **** Clinical data regarding the presence or absence of arthrogryposis were not described for 8 hips.

Table 2. Correlation between the radiological parameter and the presence of microcephaly.

Radiological Parameter	Microcephalic	Not-Microcephalic	*p*	*n*
IR (>10 %) *n* = 43	35 (81.4%)	8 (18.6%)	0.42*	50
ACD (>140°) *n* = 45	35 (77.8%)	10 (22.2%)	0.31*	50
ACEW (<20°) *n* =13	10 (76.9%)	3 (23.1%)	0.08**	48***
IA (>30°) *n* = 18	15 (83.3%)	3 (16.7%)	0.64**	50
Tonnis II a IV *n* =38	30 (78.9%)	8 (21.1%)	0.11**	50

* Fisher test; ** Pearson's chi square; *** ACEW was immeansurable in two hips.

Table 3. Hip dysplasia (Tonnis classification) intragroup correlation among microcephalics and among arthrogrypotics.

IHDI	Microcephalic *p* = 0.2*	Arthrogrypotic *p* = 0.3*
Normal (Tonnis I)	10 (25%)	4 (20%)
Subluxury (Tonnis II)	15 (37.5%)	7 (35%)
Low luxury (Tonnis III)	8 (20%)	6 (30%)
High luxury (Tonnis IV)	7 (17.5%)	3 (15%)
***n* válidos**	**40**	**20**

* Pearson's chi square.

A similar trend was observed for IA. The 20 hips with arthrogrypotic, in 16 (80%), the IA was greater than 20º. Among the 40 hips of microcephalic patients, 30 (75%) had an IA greater than 20º.

Regarding gender, women showed greater severity of hip changes, both in the IA and for the IHDI classification (Tables 5 and 6).

Discussion

In the analysis of sociodemographic variables, we noticed that of the 25 patients evaluated there was a slight predominance of females (60%) and blacks and browns (72%). As for maternal variables, the mean age was 28 years, with an

Table 4. Acetabular index intragroup correlation among among microcephalics and among arthrogrypotics.

Acetabular Index	Microcephalic *p* = 0.64*	Arthrogrypotic *p* = 0.48*
Normal (< 20º)	10 (25%)	4 (20%)
Borderline (20º-30º)	15 (37.5%)	7 (35%)
Changed (> 30º)	15 (37.5%)	9 (45%)
***n* (valid)**	**40**	**20**

* Pearson's chi square.

Table 5. Intragroup correlation between Tonnis classification and gender.

IHDI Classification	Male *p* = 0.03*	Female *p* = 0.03*
Normal (Tonnis I)	9 (45%)	3 (10%)
Subluxury (Tonnis II)	10 (50%)	12 (40%)
Low luxury (Tonnis III)	1 (5%)	8 (26.7%)
High luxury (Tonnis IV)	0 (0%)	7 (23.3%)
***n* (valid)**	**20**	**30**

* Pearson's chi square.

Table 6. Intragroup correlation between acetabular intex and gender.

Acetabular Index	Male *p* = 0.02*	Female *p* = 0.02*
Normal (<20º)	9 (45%)	5 (16,7%)
Borderline (20º-30º)	8 (40%)	10 (33,3%)
Changed (> 30º)	3 (15%)	15 (50%)
***n* (valid)**	**20**	**30**

* Pearson's chi square.

average of seven prenatal consultations (minimum recommended number). The disease manifested itself before the 12th week of gestation in 11 cases (44%), all mothers presented clinical symptoms related to ZIKV infection (rash, fever, arthralgia, headache, eye pain), and, in two cases, only the fathers presented the symptoms of the infection. Normal birth was the most frequent (56%), against 16% with complications.

Congenital microcephaly can be associated with several changes, the most frequent being an intellectual disability, cerebral palsy, epilepsy, swallowing difficulties, visual and auditory system abnormalities, and behavioral disorders (ADHD and autism).[15] The severity of complications from Zika virus infection during pregnancy and the degree of involvement of the nervous system and its structures depend on several factors, such as stage of conceptus development, dose-response relationship, maternal-fetal genotype, and specific pathogenic mechanism of infection. each etiologic agent.[15] The identification of suspected cases and the differential diagnosis with genetic causes and other environmental teratogens, such as prenatal infections, alcohol, prenatal exposure to RX, and some medications, must be done since we observed microcephaly in all these conditions.[15]

For the analysis of radiographic variables, the sample consisted of evaluating the 50 hips of the 25 patients selected for the study. Orthopedic deformities were observed in 38 (76%). In 20 of the hips analyzed (40%), patients had arthrogryposis, presumably associated with congenital infection caused by ZIKV.

In this study, arthrogryposis did not result from the direct action of ZIKV on the joints but probably had a neurogenic origin, with chronic involvement of central and peripheral motor neurons, leading to fixed postures in the uterus and, consequently, deformities.[16]

In a study published in 2020,[12] a high prevalence of musculoskeletal alterations in patients with CZS was evidenced, mainly arthrogryposis and spasticity. Hip problems were seen in nearly 30% of patients, and foot abnormalities in around 20%. It has been suggested that joint contractures are likely caused by decreased activation of the corticospinal tract or by direct injury to spinal cord motor neurons, contributing to fetal hypomotility.[12,16,17]

At the time of radiographic diagnosis, we noticed that 76% of the 50 evaluated hips had alterations (Tonnis II, III, or IV). In cases of arthrogryposis, dysplasia had a prevalence of 80%; in microcephalic patients, the alterations were 75%. Among the other radiographic parameters of this study, the IR was changed in 43 (86%) hips. ACD was valgus in 45 (90%) hips. ACEW was changed in 13 (26%) hips. The IA was changed in 18 (36%) of the evaluated hips.

One of the possible limitations of this study would be the sample size, which does not allow the evaluation of secondary variables, and as it is a cross-sectional study, incapable of predicting the evolution of the patients' clinical condition with increasing age. However, these findings emphasize the need for both: a more vigilant assessment in the neonatal diagnosis of CZS, and the early inclusion of radiographic diagnosis, to allow the institution of treatment as soon as the condition is identified. We recommend radiographic investigation of the hip, still in the maternity ward, for neonates with microcephaly and suspected SZC, regardless of other risk factors for hip dysplasia.

Our findings demonstrated a high frequency of orthopedic complications associated with arthrogryposis and microcephaly in patients with SCZV. We observed a high prevalence of alterations in radiographic parameters of the hip, especially high dislocations whose prognosis and treatment are known to be worse. There was no significant difference in radiographic changes when comparing arthrogrypotic or microcephalic patients. Only females had significantly more hip changes than males.

References

1. Heukelbach J, Alencar CH, Kelvin AA, de Oliveira WK, Pamplona de Góes Cavalcanti L. Zika virus outbreak in Brazil. J Infect Dev Ctries. 2016;10:116-120. doi: 10.3855/jidc.8217.

2. Ayres CF. Identification of Zika virus vectors and implications for control. Lancet Infect Dis. 2016;16: 278-279.
3. Brasileira S, Tropical DM, Marcondes CB, Fátima M De, Melo F De. Zika virus in Brazil and the danger of infestation by Aedes (Stegomyia) mosquitoes.Rev Soc. Bras Med Trop. 2016;49:4–10.
4. Petersen E, Wilson ME, Touch S, Mccloskey B, Mwaba P, Bates M, et al. Rapid Spread of Zika virus in the Americas - Implications for public health preparedness for mass gatherings at the 2016 Brazil Olympic Games. Int J Infect Dis 2016;44:11–5.
5. Driggers RW, Ho CY, Korhonen EM, et al. Zika virus infection with prolonged maternal viremia and fetal brain abnormalities. N Engl J Med. 2016;374 (22):2142-2151.
6. MacDonald PDM, Holden EW. Zika and public health: Understanding the epidemiology and information environment. Pediatrics 2018 Feb;141(Suppl 2):S137-S145. doi: 10.1542/peds.2017-2038B. PMID: 29437046.
7. World Health Organization. WHO statement on the first meeting of International Health Regulations [2005] [IHR 2005] Emergency Committee on Zika virus and observed increase in neurological disorders and neonatal malformations. [Online] Available from: http://who.int/mediacentre/news/statements/2016/1st-emergencycommittee-zika/en/ [Accessed on 28 February 2016].
8. Ventura CV, Maia M, Bravo-Filho V, Góis AL, Belfort R Jr. Zika virus in Brazil and macular atrophy in a child with microcephaly. Lancet 2016;387 (10015):228.
9. Ministério da Saúde – Brasil. Ministério da Saúde confirma relação entre vírus Zika e microcefalia. Brasília: Ministério da Saúde. Available from:http://portalsaude.saude.gov.br/index.php/cidadao/principal/agência - saúde/21014 – Ministerio da Saúde confirma relação entre vírus zika e microcefalia. 2015. Accessed on February 03, 2016.
10. Paixão ES, Rodrigues LC. What we need to know about Zika virus. Br J Hosp Med (Lond). 2016 Mar;77(3):124-5. doi: 10.12968/hmed.2016.77.3.124.
11. Souza WV, Albuquerque MFPM, Vazquez E, Bezerra LCA, Mendes ADCG, Lyra TM, et al. Microcephaly epidemic related to the Zika virus and living conditions in Recife, Northeast Brazil. BMC Public Health. 2018;18(1):130.
12. Matos MA, Nascimento MAST, Merriman JW. Orthopaedic approach to the congenital Zika syndrome. Int Orthop. 2020 Nov 16. doi: 10.1007/s00264-020-04521-0.
13. Reimers J. The stability of the hip in children: A radiological study of the results of muscle surgery in Cerebral Palsy. Acta Orthop Scand (Suppl.). 1980;184:1-100.
14. Goiano EO, Akkari M, Pupin JP, Santili C. The Epidemiology of developmental dysplasia of the hip in males. Acta Ortop Bras. 2020;28(1):26-30.
15. Raymuno RT, Moreira A de SS. Microcefalia associada ao zika vírus: um relato de caso. Revista da Faculdade de Medicina de Teresópolis 2018;2(1).
16. Linden VVD, Rolim Filho EL, Lins OG, Linden AVD, Aragão MFVV, Brainer-Lima AM, et al. Congenital Zika syndrome with arthrogryposis: retrospective case series study. BMJ 2016;354:i3899. doi: 10.1136 / bmj.i3899.
17. Kalampokas E, Kalampokas T, Sofoudis C, Deligeoroglou E, Botsis D. Diagnosing arthrogryposis multiplex congenita: A review. ISRN Obstet Gynecol. 2012; 2012:264918. doi:10.5402/2012/264918.