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REVIEW ARTICLE

Study of increased cases of embryonic and fetal deaths diagnosed by ultrasound during the Zika virus outbreak

Estudio del aumento de casos de muertes embrionarias y fetales diagnosticadas por ecografía durante el brote del virus Zika

Estudo de aumento de casos de óbitos embrionários e fetais diagnosticados por ultrassonografia durante o surto de Zika vírus

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Abstract

The aim of the research was to describe the main causes of fetal death to improve the quality of care for pregnant women. The Zika virus is a virus of the Flavoviridae family, the Dengue and Chikungunya viruses also belong to this family and are transmitted by the Aedes mosquito. There is a concern of the World Health Organization and the Ministry of Health with the increase in cases of Zika virus in pregnant women, since infection with this virus can lead to the presence of neurological changes, such as microcephaly and fetal loss diagnosed by pelvic or transvaginal obstetric ultrasound. . During the period of outbreak of Zika virus infection, there was an increase in cases of deaths diagnosed by ultrasound examination, in the period from 2005 to 2020. Conclusion: The survey identified the socioeconomic level, the obstetric background, the lack of adequate medical monitoring during prenatal care and difficulty in reporting, which are factors that are directly involved with the difficulty of investigating the causes of fetal/embryonic deaths.

Descriptors: Obstetric Ultrasound; Fetal Death; Embryonic Death; Zika Virus.

Resumén

El objetivo de la investigación fue describir las principales causas de muerte fetal para mejorar la calidad de la atención a las mujeres embarazadas. El virus Zika es un virus de la familia Flavoviridae, los virus Dengue y Chikungunya también pertenecen a esta familia y son transmitidos por el mosquito Aedes. La Organización Mundial de la Salud y el Ministerio de Salud están preocupados por el aumento de los casos de virus Zika en mujeres embarazadas, ya que la infección con este virus puede conducir a la presencia de cambios neurológicos, como microcefalia y pérdida fetal diagnosticada por ultrasonido obstétrico pélvico o transvaginal. . Durante el período de brote de infección por el virus del Zika, hubo un aumento en los casos de muertes diagnosticadas por ecografía, en el período comprendido entre 2005 y 2020. Conclusión: La encuesta identificó el nivel socioeconómico, los antecedentes obstétricos, la falta de un control médico adecuado. durante la atención prenatal y la dificultad para informar, que son factores directamente relacionados con la dificultad de investigar las causas de las muertes fetales/embrionarias.

Descriptores: Ecografía Obstétrica; Muerte Fetal; Muerte Embrionaria; Virus Zika.

Resumo

O objetivo da pesquisa foi descrever as principais causas de óbito fetal para melhorar a qualidade de atendimento as gestantes. O Zika vírus é um vírus da família Flavoviridae, também pertencem a essa família os vírus da Dengue e Chikungunya, e são transmitidos pelo mosquito Aedes. Há uma preocupação da Organização Mundial de Saúde e do Ministério da Saúde com o aumento de casos de Zika vírus em gestantes, pois a infecção por esse vírus pode levar à presença de alterações neurológicas, como microcefalia e perda fetal diagnosticada pela ultrassonografia obstétrica pélvica ou transvaginal. Durante o período de surto da infecção por Zika vírus, houve um aumento dos casos de óbitos diagnosticados pelo exame de ultrassom, no período de 2005 a 2020. Conclusão: A pesquisa identificou o nível socioeconômico, os antecedentes obstétricos, a falta de acompanhamento médico adequado durante o pré-natal e dificuldade de notificação, os quais são fatores que estão envolvidos diretamente com a dificuldade de investigação das causas dos óbitos fetais/embrionários.

Descritores: Ultrassonografia Obstétrica; Óbito Fetal; Óbito Embrionário; Zika Vírus.

Introduction

The Zika virus is a virus of the Flavoviridae family, the Dengue and Chikungunya viruses also belong to this family and are transmitted by the Aedes mosquito. In the years 2013 and 2015 there were outbreaks of the disease caused by him in French Polynesia and in Brazil, respectively, since then, national authorities have reported potential neurological and autoimmune complications of the disease. Some of the complications for the fetus that are being studied are: microcephaly, the association with Guillain-Barré syndrome, spontaneous abortion, and other neurological complications. The diagnosis of Zika is made by confirming the presence of viral material in the method of polymerase chain reaction by reverse transcriptase in blood serum, within five days after the onset of symptoms; this material can also be found in the urine, with a longer time, for up to three weeks after the onset of symptomatic symptoms[1-9].

Serological tests can be performed with IgM antibodies detected by enzyme-linked immunosorbent or immunofluorescence assays from the fifth day after the onset of symptoms, however, if the patient has a previous history of infection by viruses of the same family, such as dengue virus, cross reaction, obtaining a false positive result. The ultrasound examination began to be implanted for the diagnosis of serious fetal anomalies around 1978, with the evolution of technology, the images provided by him improved and, in 1983, a correlation between ultrasound diagnosis and prognosis was observed for the first time. fetal. The exam must be performed by a specialist doctor, and it is done through a transducer that captures the images of the different organs or different structures of the fetus according to the tissue composition, and passes to the monitor, where the person responsible for carrying out the exam interprets. During the examination it is considered that there was early embryonic death when the embryo has a head-buttock length of less than five millimeters and does not present cardiac activity, according to the American College of Radiologists[2,3,10-16].

There is a concern of the World Health Organization and the Ministry of Health with the increase in cases of Zika virus in pregnant women, as several studies have shown an important relationship of neurological changes and fetal and embryonic deaths in patients with positive serology and/or RNA detection in the blood and urine of pregnant women diagnosed with microcephaly and some other changes in the central nervous system identified by ultrasound[16-21].

Methodology

This is an integrative literature review. Data collection was performed through computerized mechanical consultation in the VHL (Virtual Health Library) and SciELO (Scientific Electronic Library Online) databases.

The descriptors used in this research were consulted in the list of Health Science Descriptors (DeCS) to use the appropriate keywords for the research. In the next stage, the articles of interest for this study were selected, considering as criteria: articles in the health field, being work developed at the national level; to be available in full in Portuguese online, the sample consists of scientific articles centered on the theme of research in periodicals published from 2005 to 2020. The descriptors used were: “Obstetric ultrasound”, “Fetal death”, “Embryonic death” and “Zika virus”.

Results and Discussion

Regarding the results of this study, the search in the databases resulted in 20 articles, in which 8 excluded publications were submitted to the inclusion and exclusion criteria. Chart 1 presents the articles that were read in full, as they were relevant to the objectives of this study.

Chart 1. Distribution of publications on Palliative Care: Attention to Cancer Patients. São Paulo, SP, Brazil, 2020

N°	Author	Year	Method	Title	Results
1	SCHULER-FACCINI L. *et al*	2015	Literature review	Possível associação entre a infecção pelo vírus Zika e a microcefalia — Brasil, 2015	As of January 2016, indigenous Zika virus transmission has been confirmed in 19 countries in the Americas, in addition to Brazil. Although other countries in the Americas, such as Uruguay and Argentina, have not registered the indigenous transmission of the Zika virus, the presence of a competent vector, Aedes aegypti, in these countries presents a potential risk of spreading the virus.
2	ORGANIZAÇÃO MUNDIAL DA SAÚDE (OMS)	2005	Descriptive study	WHO statement at the first meeting of the International Health Regulatory Emergency Committee (2005) (RSI 2005) on the Zika virus and the observed increase in neurological disorders and neonatal malformations	Based on this opinion, the Director General declared Public Health Emergency of International Interest (PHEIC) on February 1, 2016. The Director General endorsed the Committee's opinion and issued them as Temporary Recommendations under the IHR (2005). The Director General thanked the members and advisers of the Committee for their advice.
3	MINISTERIO DA SAÚDE (MS)	2016	Exploratory study	Epidemiological Bulletin, Monitoring of dengue cases, Chikungunya fever and Zika virus fever until Epidemiological Week 49, 2016	Notified cases and deaths can be excluded at any time, after registration in the notification system, by the State and Municipal Health Services. This can cause differences in numbers from one epidemiological week to another. This information applies both to dengue fever and to Chikungunya fever and Zika virus fever.

4	GULLAND, A.	2016	Research	O vírus Zika é uma emergência de saúde pública global, declara a OMS	Public Health England said that despite limited evidence of sexual transmission of the virus, men returning from a country where the virus is endemic must use a condom for 28 days if their partner is pregnant or at risk of becoming pregnant. Men who suspect they have been exposed to the virus should use a condom for six months after recovery.
5	WEAVER, S.C	2014	Literature review	Chegada do vírus Chikungunya ao novo mundo: perspectivas de disseminação e impacto na saúde pública.	It is critical that public health authorities implement robust surveillance based on existing dengue programs, establish local diagnostic capacity to test mosquitoes and sera from suspected cases and develop outbreak response plans, including educational efforts to reduce contact with vectors. Healthcare professionals should also be trained to include CHIK in their differential diagnoses for dengue-like illnesses and to use the drugs available optimally to alleviate severe CHIK symptoms.
6	BESNARD, M; LASTÈRE, S; TEISSIER, A; CAO-ORMEAU V.M, MUSSO D.	2012	Clinical case	Evidências de transmissão perinatal do vírus Zika, Polinésia Francesa, dezembro de 2013 e fevereiro de 2014	For all serious neonatal diseases reported with other arbovirus infections, such as Chikungunya and dengue, we recommend close monitoring of perinatal ZIKAV infections. Due to the high RNA load of ZIKAV detected in breast milk, and even if replicative ZIKAV particles have not been detected, transmission of ZIKAV through breastfeeding should be considered.
7	LENGLET Y	2006	Quantitative study	Infecção por Chikungunya na gravidez: evidências de infecção intrauterina em mulheres grávidas e transmissão vertical no parto. Levantamento do surto da ilha da reunião.	Although the risks of fetal contamination appear to be rare before 22 weeks of gestation, they are potentially dangerous. After 22 weeks of gestation, the newborn's infection occurs if the mother has a positive viremia at delivery. Transplacental transmission is suspected, but the pathogenic mechanism remains unknown.
8	FRITEL, X; *et al*	2010	Qualitative and quantitative research	Infecção pelo vírus Chikungunya durante a gravidez, Reunião, França, 2006	In this comparative study, we observed no effect of Chikungunya infection on pregnancy outcomes, except for the number of prenatal maternal hospitalizations for Chikungunya symptoms. Our study involved a high proportion of maternities and births in Réunion. Systematic determination of serological status by identifying specific IgM and confirmed IgG infection status.
9	NETO, C. N; *et al*	2009	Exploratory-descriptive study	Importância da ultrassonografia de rotina na prática obstétrica segundo as evidências científicas	Estimation of weight by ultrasonography is important to assess the evolution of growth during pregnancy, as well as to reduce the morbidity and mortality associated with deviations in intrauterine growth by following and adopting specific protocols for monitoring fetal vitality.
10	JEVE, Y. *et al*	2011	Literature review	Acurácia do ultrassom de primeiro trimestre no diagnóstico de morte embrionária precoce: uma revisão sistemática	The findings are limited by the small number of studies and patients, age of studies, inclusion of symptomatic and asymptomatic women and variable reference standards for the diagnosis of early pregnancy death. Before guidelines for the safe management of threatened abortion can be formulated, there is an urgent need for a prospective study with adequate nutrition, using current ultrasound technology and an agreed reference standard for the success or loss of pregnancy.
11	FORMIGLI, V.L. A. *et al*	1996	Literature review	Avaliação da atenção à saúde através da investigação de óbitos infantis	The survey of medical records in health units recorded a loss of 58.3%, revealing the low degree of organization of hospital statistics; care classified as inadequate and inadequate prevailed, especially in the item's physical examination and treatment. Despite the study's operational limitations, the results point to problems of access, effectiveness, and adequacy of the health care process.
12	DATASUS	2018	Descriptive study	Óbitos fetais	1 Northern Region 3,608 2 Northeast Region 10,371 3 Southeast Region 11,245 4 South Region 3,098 5 Central-West Region 2,368 TOTAL 30,690
13	EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL.	2015	Exploratory-descriptive study	Avaliação rápida dos riscos: epidemia do vírus Zika nas Américas: potencial associação com microcefalia e síndrome de Guillain-Barré - 4a atualização, 10 de dezembro de 2015	Paralelamente, estão em andamento investigações no Brasil e na Polinésia Francesa para estabelecer se existe uma ligação entre a infecção pelo vírus Zika e outras síndromes neurológicas, em particular a síndrome de Guillain-Barré. Durante o surto de vírus Zika na Polinésia Francesa, 74 pacientes que apresentaram sintomas de Zika desenvolveram mais tarde síndromes neurológicas ou autoimunes - dentre eles, 42 foram diagnosticados como síndrome de Guillain-Barré. No Brasil, foram relatados 121 casos de manifestações neurológicas e síndrome de Guillain-Barré (SGB), todos com história de sintomas semelhantes ao Zika.
14	CUEVAS E.L. *et al*	2016	Qualitative and quantitative research	Relatório preliminar de microcefalia potencialmente associada à infecção pelo vírus Zika durante a gravidez - Colômbia, janeiro a novembro de 2016	Based on an average term pregnancy, the 24-week period between the peak of the Zika virus outbreak and the peak in the reported occurrence of microcephaly suggests that the greatest risk of microcephaly is associated with Zika virus infection during the first trimester and the beginning of the second trimester of pregnancy. During epidemiological weeks 5–45, there was a more than four-fold increase in reported cases of microcephaly in Colombia in 2016, compared to the previous year.
15	POMAR, L. *et al*	2017	Prospective cohort study	Associação entre vírus Zika e fetopatia: um estudo	ZIKV infection during pregnancy is associated with a significant risk of fetal CNS involvement and intrauterine death, especially when the

				prospectivo de coorte na Guiana Francesa	infection occurs during the first or second trimester. Microcephaly was not present in all cases of congenital ZIKV syndrome that we observed. Until more is known about this disease, it is essential to evaluate suspected cases monthly by detailed neurosonography, paying special attention to the corpus callosum and the presence of hyperechogenic foci.
16	BRASIL, P. *et al*	2016	Exploratory-descriptive study	Infecção pelo vírus Zika em mulheres grávidas no Rio de Janeiro	Despite mild clinical symptoms in the mother, ZIKV infection during pregnancy is harmful to the fetus and is associated with fetal death, fetal growth restriction and a spectrum of central nervous system abnormalities.
17	Nunes, M.L; *et al*.	2016	Literature review	Microcefalia e vírus Zika: uma análise clínica e epidemiológica do atual surto no Brasil.	The development of diagnostic techniques that confirm a cause-effect association and studies on the pathophysiology of central nervous system involvement should be prioritized. It is also necessary to strictly define the criteria for the diagnosis of microcephaly to identify the cases that must be submitted to an etiological investigation.
18	MENEZZ, A.M.D. *et al*	2016	Descriptive and cross-sectional study	Vigilância do óbito fetal: estudo das principais causas	Other studies associate fetal death with the use of drugs, alcohol, and tobacco, but these habits were not included in any of the records of the pregnant women evaluated. As for age, extreme ranges are risk factors for fetal death. In the studied population, 35% of pregnant women were at risk ages.
19	BARBEIRO, F.M.S, *et al*	2015	Systematic review	Óbitos fetais no Brasil: revisão sistemática	Prenatal care must prioritize more vulnerable women, socially or in relation to reproductive history and morbidities, to decrease the fetal mortality rate in Brazil. It is necessary to qualify to fill out the death certificate and invest in the fetal and infant death investigation committees.
20	SCHWARTZ, A.D. *et al*	2017	Retrospectiv e analysis of clinical, autopsy, pathological and post-mortem studies	Estudos de autópsia e post-mortem são concordantes: a patologia da infecção pelo vírus Zika é neurotrópica em fetos e bebês com microcefalia após transmissão transplacentária	There is agreement on the spectrum of brain damage, reinforcing previous data indicating that the Zika virus has a strong predilection for fetal central nervous system cells after vertical transmission. The occurrence of additional congenital abnormalities suggests that intrauterine brain damage caused by the Zika virus interferes with normal fetal development, resulting in fetal akinesia. Experimental in vitro and in vivo studies of Zika virus infection corroborate the findings of human autopsy of neural specificity.
21	KRAUER, F. *et al*	2017	Systematic review	Infecção pelo vírus Zika como causa de anormalidades cerebrais congênitas e síndrome de Guillain-Barré: revisão sistemática	The panel of experts acknowledged that the Zika virus alone may not be enough to cause congenital brain abnormalities or GBS but agreed that the evidence was sufficient to recommend increasing public health measures. The weaknesses are the limited assessment of the role of the dengue virus and other possible cofactors, the small number of comparative epidemiological studies.
22	JOÃO, E. C, *et al*	2017	Descriptive study	Infecção pelo vírus Zika associada a defeitos congênitos em mulheres grávidas infectadas pelo HIV	Case of Zika virus infection acquired during the first trimester in an HIV-infected pregnant woman that led to multiple fetal malformations and fetal death in Rio de Janeiro.
23	SOUZA, B.S.F, *et al*	2016	Quantitative and qualitative study	A infecção pelo vírus Zika induz anormalidades na mitose e morte celular apoptótica de células progenitoras neurais humanas	We show here that ZIKV causes massive death of neural stem cells, which is, at least in part, caused by abnormalities in cell division, including the presence of supernumerary centrosomes. Our results reinforce the link between ZIKV infection and reported defects in the development of the central nervous system.
24	CALVET, G. *et al*	2016	Case study	Detecção e Sequenciamento do Vírus Zika do Líquido Amniótico de Fetos com Microcefalia no Brasil: Um Estudo de Caso.	After sequencing the complete genome of the Brazilian Zika virus isolated from patient 1, phylogenetic analyzes showed that the virus shares 97-100% of its genomic identity with strains isolated during an outbreak in French Polynesia in 2013, and in the envelope and NS5 genomic regions , was grouped with sequences from North and South America, Southeast Asia and the Pacific.
25	MELO, A.S.O. *et al*	2016	Case study	Infecção intra-uterina pelo vírus Zika causa anormalidade cerebral fetal e microcefalia: ponta do iceberg?	As in other intrauterine infections, it is possible that the reported cases of microcephaly represent only the most affected children and that newborns with less serious diseases, affecting not only the brain, but also other organs, have not yet been diagnosed.
26	CUGOLA, F. R, *et al*.	2016	Case study	A cepa brasileira do vírus Zika causa defeitos congênitos em modelos experimentais	Our data reinforce the growing body of evidence that links the ZIKV (BR) outbreak to the alarming number of cases of congenital brain malformations. Our model can be used to determine the effectiveness of therapeutic approaches to combat the harmful impact of ZIKV (BR) on human neurodevelopment.

The diagnosis of fetal and embryonic death is carried out mainly by obstetric ultrasound, where it is considered fetal death when diagnosed after 10 weeks of gestation, before this period it is considered as embryonic death. The factors associated with the causes of fetal/embryonic death in Brazil have been widely published. About fetal death surveillance, whose objective was to understand the main causes of fetal death to improve the quality of care for pregnant women[22-24].

Prenatal care should prioritize more vulnerable women, socially or in relation to reproductive history and morbidities, to decrease the fetal mortality rate in Brazil. There was an increase in cases of fetal/embryonic deaths during the outbreak of Zika virus infection. Many studies were published in the years 2015 and 2016 regarding the relationship between Zika virus infection and spontaneous abortion, however due to the inadequate completion of the death notification form, it is difficult to assess its main causes, according to data from DATASUS 1,776 occurred cases of fetal deaths in the greater São Paulo region and 1,205 of these cases have not been investigated[24-26].

In the systematic review study on fetal deaths in Brazil between 2003 and 2013, in which 27 articles from different approaches were analyzed, to analyze the frequency and factors associated with fetal death, it was noticed that the deficiency in filling out the fetal death declaration impairs the identification of the causes of fetal deaths, especially when it comes to sociodemographic variables, however, it is noted that the causes were related to inadequate or absent prenatal care, low education, maternal morbidities and unfavorable reproductive history. When relating the number of cases in 2014 to those occurred in 2015, a slight decrease is noted, adding the category of cause of deaths affected by maternal factors, which can range from gestational hypertensive disease to spontaneous abortion without an apparent cause, this number went to 297 in 2014 and 274 in 2015, however when researching the investigation of these deaths, the result was 1,246 cases not investigated in 2014 and 1,205 in 2015, reaching the conclusion that despite having a small reduction in the number of reported cases between the years cited, there is no adequate investigation regarding the causes of these deaths[12-19].

Conclusion

Ultrasonography is the standardized exam by the Ministry of Health for the diagnosis of fetal / embryonic death. During the outbreak of Zika virus infection, there was an increase in the number of deaths diagnosed by ultrasound. According to the study, socioeconomic status, obstetric history, lack of adequate medical care during prenatal care and difficulty in notification are factors that are directly involved with the difficulty in investigating the causes of fetal/embryonic deaths.

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