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Adverse outcomes of pregnancy-associated Zika virus infection

William J. Britt, MD

Department of Pediatrics, University of Alabama School of Medicine, Childrens Hospital Harbor Bldg 160, Birmingham, AL 35233

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ABSTRACT

The spread of Zika virus to the Americas was accompanied by surge in the number of infants with CNS abnormalities leading to a declaration of a health emergency by the WHO. This was accompanied by significant responses from governmental health agencies in the United States and Europe that resulted in significant new information described in the natural history of this perinatal infection in a very short period of time. Although much has been learned about Zika virus infection during pregnancy, limitations of current diagnostics and the challenges for accurate serologic diagnosis of acute Zika virus infection has restricted our understanding of the natural history of this perinatal infection to infants born to women with clinical disease during pregnancy and to Zika exposed infants with obvious clinical stigmata of disease. Thus, the spectrum of disease in infants exposed to Zika virus during pregnancy remains to be defined. In contrast, observations in informative animal models of Zika virus infections have provided rational pathways for vaccine development and existing antiviral drug development programs for other flaviviruses have resulted in accelerated development for potential antiviral therapies. This brief review will highlight some of the current concepts of the natural history of Zika virus during pregnancy.

Introduction

In late 2014, cases of an acute onset and self-limited, exanthematous illness characterized by arthralgias, pruritus, and less commonly, conjunctivitis were noted in Northeast Brazil in areas where Dengue virus (DENV) and Chikungunya virus (CHIKV) infections were endemic.[1–3] Shortly thereafter in the spring of 2015, the Brazilian Ministry of Health reported that Zika virus (ZIKV) was circulating in this region and in other regions of Brazil and potentially responsible for clusters of this newly recognized acute exanthematous illness.[1,3] Following these reports, a number of centers in Northeast Brazil reported ZIKV activity and in one report, attack rates of clinical illnesses consistent with ZIKV infection were reported to be as high as 8.2/1000 in children to as low as 3.8/1000 in adults.[3] Initially, the emergence of ZIKV infection in Brazil was also associated with an increase in cases of a Guillian-Barre like syndrome; however, by late summer in 2015 an increase in the number of infants born with microcephaly, including severely microcephalic infants (>3 SD below mean head circumference for age) with unusually severe decreased growth and development of the cerebrum, and redundant scalp skin.[1] Early case studies strongly suggested a link between ZIKV infection during early pregnancy and the delivery of an infant with severe microcephaly and neurological deficits.[4] In November of 2015, the Brazilian Ministry of Health, the Pan American Health Organization issued alerts about the possible association between ZIKV infections in

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E-mail address: wbritt@peds.uab.edu

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pregnancy and microcephaly in the offspring of affected pregnancies and in early 2016, the World Health Organization (WHO) declared ZIKV a health emergency. Amidst a flurry of international conferences and meetings, several large natural history studies of ZIKV infections were organized by the NIH and CDC to gather sufficient number of cases and controls to definitively address questions of causality of neurologic damage in offspring of women infected with ZIKV during pregnancy. Importantly, these studies were sufficiently powered to comprehensively define the spectrum of abnormalities in infants infected *in-utero*. These studies continue and with expected enrollment, should address key questions in the natural history of ZIKV during pregnancy in countries in South America and the Caribbean. In this brief overview, we will provide some of the key epidemiological characteristics of the ZIKV outbreak in South America and the Caribbean, the spectrum of disease in the infant infected in-utero, potential mechanisms of disease in the infected fetus, and the current approach to diagnosis of this infection in pregnant mothers and their offspring.

Epidemiological observations of the ZIKV outbreak in Brazil and northern South America

ZIKV was first isolated in 1947 from a Rhesus macaque monkey that served as a sentinel monkey in a Rockefeller Foundation supported field station that was established for studies of Yellow Fever in the Zika forest in Gambia.[5] Subsequently, additional ZIKV isolates were collected from mosquitos in the same area. In 1954, the first ZIKV infection in humans was reported in a patient in Nigeria.[6] There appeared to be only limited ZIKV activity outside of Africa such that the first case of human ZIKV infection occurring outside of Africa was described in a patient in Indonesia.[7] Serological studies carried out in the 1950s and 1960s suggested that ZIKV was endemic in all of Africa as well as in several Asian countries, although the quantifying the seroprevalence of ZIKV infection is problematic because of the cross-reactivity between antibodies to other Flaviviruses and ZIKV. This remains an ongoing technical issue in the serodiagnosis of ZIKV infections in areas of the world where other Flavivirus infections are endemic.[2] Definitive information detailing the emergence of ZIKV infection in a population was first reported from studies carried out in Yap, an island in Micronesia located in the Western Pacific.[2] Although DENV infection was initially suspected as the etiology of this acute febrile illness associated with rash and arthralgias, local physicians viewed the presenting symptomatology of this infection as atypical for DENV infections and studies carried out on specimens sent to the CDC demonstrated ZIKV in about 14% of those specimens tested by PCR.[8,9] It was estimated that over 70% of the population was infected with ZIKV during the 3-month period of the outbreak, and of ZIKV-infected individuals, about 18% exhibited clinical symptoms compatible with ZIKV infection.[8,9] Subsequently, in 2013 in French Polynesia, an outbreak of ZIKV resulted in an estimated 39,000 cases of ZIKV infection, although this is likely an underestimate of the number of cases as many infected individuals with mild or asymptomatic infections were not tested for ZIKV infection.[2,10,11] Interestingly the duration of this outbreak was also finite and reported to be about 21 weeks.[2] After this outbreak, ZIKV infections were reported throughout the Pacific Islands, including the Chilean Easter Islands.[10] The origin(s) of ZIKV that was associated with the initial outbreak of ZIKV infections in Pacific Islands are uncertain but phylogenetic analysis of isolates from patients infected with ZIKV in YAP revealed a lineage that was most consistent with ZIKV isolates from Cambodia.[12]

Although the first descriptions of the acute exanthematous illness in Brazil in 2014 were likely ZIKV infections, it was not until the spring of 2015 when the first case of ZIKV infection was confirmed in the northeastern Brazilian state of Bahia.[1] Subsequently, ZIKV infections were reported in almost all states in Brazil and by December 2015, it was estimated that between 500,000 and 1,000,000 people had been infected.[13] In late 2015, ZIKV infections were confirmed in Colombia and in the Caribbean, including Puerto Rico (Pan American Health Organization, 2015. Epidemiological update. Zika virus infection. 16 October 2015. Pan American Health Organization, Washington, DC). Although the source of ZIKV that resulted in the Brazilian outbreak has not been definitively identified, some authorities suggest that ZIKV was imported into Brazil following international sporting competitions in 2014 that included participating teams from Polynesia.[14–18] Brazil represented an ideal environment for the emergence of ZIKV as both species of mosquito vectors, *Aedes aegypti* and *Aedes albopictus* were present throughout Brazil and mosquito control was limited in many areas of the Northeast of the country.[17] Shortly after its emergence in Brazil, this newly introduced arbovirus spread rapidly through South America and the Caribbean. Imported cases of ZIKV infection were also reported in several European countries and the United States in travelers returning from endemic areas.[19] ZIKV infections continue to be reported in Puerto Rico, albeit at a lower rate than during 2016, and 3 cases of ZIKV infection presumably acquired through mosquito exposure have occurred in the United States mainland[20] (cdc.gov/zika/reporting/Nov2017). In addition, cases of presumed sexually transmitted ZIKV virus infection have been reported in the United States.[21,22]

Significant interest developed in ZIKV as a cause of birth defects following reports from Brazil of the sudden increase in infants born with microcephaly, many with seemingly stereotypic cranial abnormalities not commonly seen following other causes of microcephaly, including typical findings associated with congenital infections. The spike in the incidence of microcephaly was first reported by healthcare workers in the early fall 2015 in the Northeast region of Brazil and by November of 2015 the Brazilian Ministry of Health suggested a possible association between ZIKV infections secondary to an estimated 20-fold increase in the incidence of microcephaly in this region.[23,13] Shortly thereafter a number of governmental health agencies including the Pan American Health Organization, the CDC, and the European Center for Disease Prevention and Control also posted alerts describing the association between ZIKV infection during pregnancy and microcephaly. Since this time there has been considerable effort by several health agencies to organize natural history studies of ZIKV infections during pregnancy to define and quantify relationship(s) between ZIKV during