Decision Making in the Face of Uncertainty: Perinatal Zika Virus Infection

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Received date: April 19, 2016; Accepted date: Apr 24, 2016; Published date: Apr 29, 2016

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Keywords: Zika virus; Microcephaly; Decision making; Uncertainty

Abstract

Zika virus is currently impacting the Americas with its third major global outbreak. Most notably, this outbreak, which began in 2015, has been temporally linked to cases of microcephaly within Brazil. Zika’s worrisome fetal outcomes have raised concern about perinatal Zika infection. There is little known about the virus’s impact on pregnancy in various trimesters, the timeline of the infection, the significance of immunity and the range of fetal outcomes. This uncertainty makes the physician’s role in counseling patients all the more challenging. As members of the medical field, it is important to provide the best available information to help patients make informed decisions, which is particularly challenging in the face of this emerging epidemic and evolving knowledge base.

Zika virus is an RNA virus that is a member of the flavivirus family closely related to dengue, yellow fever and West Nile virus. Currently the Aedes Aegypti mosquito is the only vector transmitting Zika to humans, thereby limiting the impact of Zika to warm climate areas where the mosquito inhabits. In fact, Zika was first discovered in 1947 as a virus impacting primates and transmitted by a mosquito vector within a forest in Uganda. However, arboviruses are continually evolving and there is concern that this virus could adapt to new vectors and expand to more northern environments as well.

Study

The Zika virus genome that was first identified in Uganda has evolved over the past seventy years as it spread from Africa to Southeast Asia, across the Pacific and now to the Americas. The first major outbreak documented in humans occurred in 2007 in the Yap Islands of Micronesia. During this outbreak, the virus caused non-specific flu-like symptoms including a maculopapular rash, arthralgia (joint pain), conjunctivitis (red eyes) and fever. These are the typical symptoms seen with Zika virus still today. However, only one out of five people affected by Zika develop symptoms, making the clinical diagnosis rather challenging. The second outbreak occurred in 2013 in French Polynesia. This outbreak was the first time Zika was linked to a more severe disease, as it was found to be associated with Guillain-Barre syndrome following infection [1,2]. Genomic sequencing has shown that the French Polynesian strain was similar to a strain originating in Southeast Asia, whereas the Yap Island outbreak was more closely linked to the genome originating in Africa. The particular strain impacting Brazil today has been closely linked to that from Southeast Asia, similar to the 2013 French Polynesian outbreak and associated with Guillain-Barre syndrome [3].

The maternal transmission of flaviviruses is not well understood, however there have been associations between other viruses in this family and fetal anomalies in the past. Between June and September of 1989 in Rohtak, India, there was a dramatic increase in newborns with neural tube defects (NTDs). This sudden rise in congenital abnormalities began about nine months after an epidemic of dengue fever, which plagued the region from September to December 1988. Women infected with dengue virus in the first trimester of pregnancy were found to be living in the area of Northern India which had the rise in NTDs in 1989, thus suggesting that the infection might have contributed [4]. From 1992 to 2006, a retrospective study of pregnant women in Saint Laurent du Maroni hospital in French Guiana, was conducted to observe the impact of dengue virus on pregnancy. Outcomes showed that dengue during pregnancy dramatically increased the risk of premature labor. However, only 5% of babies with mothers infected with dengue proved infected by dengue themselves, as per umbilical blood testing [5]. While dengue is in the same virus family as Zika, these studies do not provide guidance on how to deal with Zika in pregnancy nor do they shed light on the impact of Zika virus on infected fetuses.

The current outbreak in Brazil began in March 2015 [6]. Since Brazil’s first locally-acquired and confirmed case, the country has seen a dramatic rise in the incidence of microcephaly, more than 20 times that of the previous year [7]. By November 2015, the number of cases of microcephaly doubled within Brazil, just nine months after the first reported case [7]. In Paraiba, Brazil, studies showed that Zika virus is transmitted through the placenta and to the fetus, as PCR was used to isolate the virus from amniotic fluid in two patients after a diagnosis of microcephaly was confirmed [8]. In an early case report from the New England Journal of Medicine a 25 year old previously healthy European woman, who lived and worked in Northeastern Brazil since 2013, became pregnant in February 2015. At 13 weeks gestation, she reported symptoms of fever, musculoskeletal and retroocular pain and an itching generalized maculopapular rash, consistent with Zika virus infection. No testing was performed at the time. Ultrasounds performed at 14 and 20 weeks of gestation showed normal fetal growth and anatomy. The patient returned to Slovenia and at 29 weeks reported decreased fetal movement, at which time the first signs of fetal anomalies were seen on ultrasound. At 32 weeks, ultrasonography...
revealed intrauterine growth restriction (fetal weight at 3rd percentile), normal amniotic fluid, normal size placenta with calcifications, head circumference < 2nd percentile for gestation (consistent with a diagnosis of microcephaly), moderate ventriculomegaly, transcerebellar diameter < 2nd percentile and calcifications throughout the brain. No other obvious fetal structural abnormalities were noted and Doppler studies were normal. The pregnancy was terminated at 32 weeks and autopsy findings confirmed the strong neurotropism of the virus. Reverse transcription polymerase chain reaction (RT-PCR) was positive for Zika virus only in the fetal brain. The complete Zika virus genome sequence, consistent with the Asian lineage of the virus, was recovered from fetal brain tissue, the localization of the calcifications was consistent with destroyed neuronal structures and the autopsy suggested arrested development of the cerebral cortex at 20 weeks. Other studies were normal including a 46,XY karyotype, as well as tests for dengue, yellow fever, West Nile, tick-borne encephalitis, chikungunya, lymphocytic choriomeningitis, cytomegalovirus, rubella, varicella-zoster, herpes simples, parvovirus B19, entroviruses and toxoplasmosis [9].

A more recent publication is the preliminary report of testing and outcomes for 88 pregnant women enrolled in a study in Rio de Janeiro, Brazil, when they presented with a rash reported in the previous five days. Of the 88 women, 72 women (88%) tested positive for Zika virus. Two of the 72 women experienced miscarriage in the first trimester. Forty-two (60%) had a prenatal ultrasound exam and of those, the timing of exposure and infection with Zika virus ranged from 6 to 35 weeks. Twelve of these cases had abnormalities noted on ultrasound (29%), including five fetuses with intrauterine growth restriction, four fetuses with cerebral calcifications, and two fetuses with other CNS alterations. Four fetuses had abnormal Doppler studies and two had oligohydramnios or anhydramnios. There were two fetal deaths after 30 weeks in women who had been infected at 25 weeks and 32 weeks gestation. At the time of the publication, six live births had occurred revealing two normal appearing infants, one infant with severe microcephaly and global cerebral atrophy (identified prenatally), two small for gestational age infants, and one infant with prenatal anhydramnios who appeared normal at birth [10].

These studies represent the growing evidence base linking Zika virus infection with adverse perinatal outcomes including microcephaly. There are many questions that still remain, especially those concerning the timing of infection, the performance of various tests for Zika virus infection and the optimal way to follow an at-risk pregnancy.

Case studies from February 2016 suggested that the Zika virus is also spread via sexual transmission. There were two confirmed transmissions and four probable transmissions, all involving condomless vaginal intercourse while the male was symptomatic or shortly after the symptomatic period [11]. A report in MMWR confirmed that men can transmit the virus to their sexual partner via semen [12]. It is therefore highly recommended that pregnant females use condoms throughout their pregnancy to protect themselves from Zika. This is particularly important in endemic regions, where the male counterpart may be unaware of his Zika infection. The spread of Zika virus via sexual transmission raises further concern that the virus can be spread and impact pregnant females even in areas without the Aedes Aegypti.

As Zika virus continues to spread across the Americas and raise global medical concern, the obstetric community is facing challenging clinical scenarios. Although many questions are still unanswered, the CDC issued interim guidelines on January 22, 2016 for pregnant women during a Zika virus outbreak [13]. These guidelines were updated on February 12, 2016, taking into consideration what is known thus far regarding the virus and serving as a guideline for obstetricians to use to best advise their patients [14,15]. We present here composite cases that illustrate how the guidelines are being implemented in clinical practice.

Case 1

A 31 year old woman, gravida 3 para 2, presented at 12 weeks and 3 days concerned because she travelled to the Dominican Republic (DR) to visit her family five weeks ago, over the Christmas vacation. She was in the DR for almost a month. Her partner did not travel with her but rather stayed in New York with his family. She denied acute onset of fever, maculopapular rash, arthralgias or conjunctivitis during her time in the DR or since returning home. She had no other complaints at the time of the appointment, but wanted to pursue testing for Zika virus infection.

Plan

The patient was informed that since she travelled to an area with active Zika virus transmission, as noted on cdc.gov/zika, she would be eligible for testing for maternal Zika virus infection, as per CDC guidelines [14]. We discussed that four out of five women with Zika do not have symptoms. We also discussed that the test results could be inconclusive and that it could take some time for the results to come back. The patient understood and agreed to the testing. We ordered Zika virus testing in the form of reverse transcription polymerase chain reaction (RT-PCR) for virus in the blood and urine, as well as antibody testing. Testing was sent out to the New York State lab through the hospital laboratory. She was encouraged to continue with her scheduled routine anatomy ultrasound at 18-20 weeks and was advised that her obstetrician could consider serial ultrasounds to detect microcephaly or intracranial calcifications in the third trimester if she was still concerned.

Case 2

A 27 year old woman, gravida 1 para 0, presented at 24 weeks and 4 days, after returning from vacation in Puerto Rico a week ago. She explained that a few days after returning home she developed a fever, a rash that started on her face, and red itchy eyes. She initially did not think anything of her symptoms, but was now concerned about Zika infection and the health of her baby. The patient had an anatomy scan the day of the appointment and no structural anomalies were observed. The patient reported feeling very anxious about her baby and, after seeing the news reports, she wanted to be sure that the baby’s head is developing properly.

Plan

Current recommendations include Zika virus testing of maternal serum and urine via reverse transcription polymerase chain reaction (RT-PCR) in symptomatic women [14,15]. Antibody testing for Immunoglobulin M (IgM) and neutralizing antibody can be performed on specimens collected greater than or equal to four days after the onset of symptoms. If it is positive or inconclusive, the patient will be offered amniocentesis to test the amniotic fluid for Zika virus infection. While the patient’s anatomy scan was reassuring, she was offered serial ultrasounds to assess for calcifications and microcephaly,
which are typically seen in the third trimester of pregnancy. The patient was counselled on the uncertainty of the antibody test and the options for diagnostic testing via amniocentesis. The patient opted for maternal Zika RT-PCR testing, followed by antibody testing if the result was negative. At the time of the appointment she declined amniocentesis due to the 1% risk of pregnancy loss. She opted to pursue serial ultrasounds instead. She is also going to follow up with her counselor regarding anxiety.

**Case 3**

A 22 year old gravida 2 para 1 woman presented at 6 weeks and 1 day having just returned from a trip to Buenos Aires, Argentina, with her friends a week ago. She denied any fever, rash, red eyes or joint pain. She had been following the news on Zika and was concerned about possible Zika infection, as she got many mosquito bites on the beach. She presented to her obstetrician’s office to discuss testing options for Zika virus.

**Plan**

The patient was reassured that Argentina was not currently a country where Zika virus was circulating, based on the CDC surveillance which is presented on cdc.gov/zika. She was advised to continue with her routine prenatal care. After understanding her lack of exposure to Zika, she agreed with this plan.

**Case 4**

A 32 year old gravida 3 Para 2 woman was found on routine ultrasound at 20 weeks and 3 days, to have a fetus with a head circumference of the 2nd percentile on anatomy scan. She was given the diagnosis of microcephaly and sent to genetics for counseling. The patient was very worried, as she had seen many pictures of microcephaly on the news recently about Zika. The patient lived in the Bronx and had not travelled within the past year, nor had her partner.

**Plan**

The patient was reassured that she was not at risk for Zika infection since neither she, nor her current partner, had travelled to a country where the virus was circulating. She was advised about the various causes of microcephaly and offered an amniocentesis to test for genetic etiologies as well as other causative infections including toxoplasmosis, rubella, cytomegalovirus (CMV), herpes and HIV. After receiving counseling about her testing options, the patient decided to return home and speak to her partner further before making a decision.

**Case 5**

A 29 year old gravida 1 para 0, presented for her initial prenatal care visit. Her last menstrual period was about 10 weeks ago and she had no complaints at the time of the appointment. She was concerned, as her husband returned home from a trip to Central America the previous week and was experiencing vomiting, fever, a rash and muscle pain. While the patient herself had not travelled, she was worried her husband had Zika virus and was unclear if she should stay away from him. Since his return, they have had condomless vaginal intercourse four times.

**Plan**

The spread of Zika virus through semen was discussed with the patient and we alerted her of her increased risk of Zika. The patient was offered and agreed to testing since her husband traveled to an area where he might have been exposed and he was symptomatic. Despite her lack of travel history, her partner’s symptoms following his travels to an endemic region put her at high risk, as Zika can be spread via semen [12]. She was advised to follow up and be sure to have her 18-week anatomy ultrasound.

**Discussion**

Shared decision-making is engrained into medical education and practice. However the amount of direction that patients are given when making medical decisions may vary based on how strongly the clinician feels on a given topic. Studies suggest that physicians tend to leave more of the decision-making in the hands of their patients when data and information are unclear and they do not feel as confident about the risk-benefit assessment [16]. However, it is in these times of uncertainty that patients and the general public tend to rely on those in the medical field the most. Medical students, who are already coping with uncertainty as they build their knowledge base, may feel this uncertainty acutely as friends and family turn to them for advice about an issue so prominently publicized in the media. This inability to deal with uncertainty is linked to significant distress in medical students [17]. Although uncertainty is a part of every medical decision, it is not at the forefront of medical education and therefore, physicians learn how to deal with it during their years in practice by putting more onus on the patient [16,18].

It is important to recognize the uncertainty that exists around Zika virus and to use guidelines issued by organizations such as the Centres for Disease Control and Prevention (CDC) and the American College of Obstetricians and Gynaecologists (ACOG) as a template for providing patient care within this context. In order to preserve patient autonomy in a situation with risk and uncertainty, shared-decision-making is the best legal and ethical approach [18]. In order to carry this out appropriately in the setting of the Zika outbreak, a patient must be fully informed with the most up-to-date information with regards to what is known, what is unknown and the potential impact of Zika exposure on pregnancy. To empower women to take part in the shared-decision-making process, they must also be counseled about the continually changing practice guidelines and what expert opinions say on the matter. In the face of uncertainty it is important to follow current published guidelines so that as a medical professional you can provide the most empowering tool for your patients, knowledge.

**References**


