ORIGINAL ARTICLE: ASSISTED REPRODUCTION

Zika virus detected in amniotic fluid and umbilical cord blood in an in vitro fertilization-conceived pregnancy in Venezuela

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Objective: To describe the consequences of Zika virus infection at 10 weeks of gestation in an IVF-conceived pregnancy in Venezuela.
Design: A case report.
Setting: Private assisted reproduction unit.
Patient(s): A 36-year-old patient who conceived her first pregnancy through IVF and became infected with Zika virus at 10 weeks' gestation in Venezuela.
Intervention(s): In vitro fertilization with fresh ET. Clinical, laboratory, and imaging Zika diagnostic methods.
Main Outcome Measure(s): Zika virus detection by real-time polymerase chain reaction (PCR) in maternal plasma, PCR in amniotic fluid and umbilical cord blood. Ultrasonography findings of anatomic abnormalities.
Result(s): Zika infection was confirmed at 10 weeks' gestation by real-time PCR; ultrasound results appeared normal. At 19 weeks' gestation, an ultrasound revealed biometry on three SDs below the means for all parameters but with no apparent anatomic abnormality. Zika virus was positive in maternal urine and amniotic fluid by PCR at 19 weeks' gestation. Ultrasound at 21 weeks + 4 days of gestation showed fetal cerebellar hypoplasia with ventricular dysmorphia, particularly marked on the left, consistent with microcephaly and ventriculomegaly. Because of the poor prognosis, pregnancy was interrupted at 24 weeks' gestation, in France. The PCR in umbilical cord blood taken in this procedure was positive for Zika virus.
Conclusion(s): Initial ultrasound findings in pregnancy may not be informative. Only at 21 weeks + 4 days of gestation did an ultrasound reveal fetal microcephaly and ventriculomegaly. Combined clinical, laboratory, and imaging findings provided a complete picture of the severe damage caused by Zika infection. (Fertil Steril® 2017;■:■–■. ©2017 The Authors. Published by Elsevier Inc. on behalf of the American Society for Reproductive Medicine. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
Key Words: Zika virus, microcephaly, congenital malformations, ventriculomegaly, amniotic fluid

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Recently, an epidemic of Zika virus (ZIKV) occurred in South and Central America. ZIKV, an arbovirus (arthropod-borne virus), is transmitted by domestic mosquitos such as *Aedes aegypti* and, to a lesser extent, by *A. albopictus*. It was isolated for the first time in 1947, from a febrile *Rhesus* monkey, in the Zika Forest (Uganda) and recognized in men in Nigeria in 1953 (1).

The last epidemiological update of the World Health Organization, dated September 8, 2016 (2), reports that, since 2015, 46 American countries and territories confirmed native cases by vector transmission, and 5 countries reported sexually transmitted Zika cases. At present, vertical transmission (mother to fetus) is also recognized.

The virus, as opposed to other arboviruses, such as dengue and chikungunya, presents a strong neurotropism (3). On April 13, 2016, the Centers for Disease Control and Prevention (CDC) of the United States recognized the causal relationship between ZIKV infection during pregnancy and fetal microcephaly and other serious cerebral anomalies (4). However, at present, the incidence of fetal anomalies related to ZIKV infection during pregnancy is unknown.

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Providing counseling is challenging because currently available data are limited. To determine the gestational consequences of ZIKV infection could be useful for preconception and postconception counseling.

CASE REPORT

A French couple, married for 2 years, with no known medical or family history, attended a consultation in November 2015, because of a 2-year primary infertility. The woman was 36 years old, nulliparous, and her husband was 34 years old at the time. The couple had lived in Caracas, Venezuela, for 4 years.

A fertility study showed the infertility to be caused by endocrine factors, positive antithyroglobulin antibodies, and insulin resistance. Hence, we suggested an IUI; but given the lengthy period of infertility, they decided on IVF.

In February 2016, the couple returned to undergo the procedure. Controlled ovarian hyperstimulation (COH) was performed with 225 IU of recombinant FSH (Gonal-F, Merck Serono) for 12 days and fixed antagonist protocol: 0.25 mg cetrotide (Merck Serono), 81 mg baby aspirin, 5 mg folic acid. Comorbid pathologies were treated with 50 μg/d levothyroxine, 1,500 mg/d metformin, and prophylactic antibiotic therapy with 1 g of azithromycin at the beginning of the stimulation cycle. The trigger injection with 250 μg of recombinant hCG (Ovidrel, Merck Serono) was performed when the follicular measurements of at least one or two follicles had ranged $\geq$18 mm in diameter. Thirty-five hours after hCG, follicular aspiration was performed under IV sedation. Eight oocytes were obtained and, afterward, four blastocysts. Only one blastocyst was transferred to the uterus. Support of the luteal phase was started 2 days after follicular aspiration, with micronized P soft gelatin capsules (Utrogestan, Laboratorios Seid), 200 mg every 8 hours administered intravaginally until the ninth week of gestation.

Real-time polymerase chain reaction (PCR) for ZIKV in plasma was performed at 10 weeks gestation at Instituto de Higiene Rafael Rangel, Universidad Central de Venezuela, Caracas, Venezuela. The PCR of amniotic fluid and umbilical cord blood were performed at 19 and 24 weeks of gestation, respectively, at the Hôpital Necker in France. Institutional Review Board approval was obtained.

RESULTS

Pregnancy was confirmed by quantitative β-hCG in plasma (549.8 mU/mL) 10 days after blastocyst transfer. Cardiac activity was confirmed at 6 weeks with the first transvaginal ultrasound. Obstetric examinations were conducted on appropriate dates, and prenatal tests were performed, including the TORCH profile (toxoplasmosis, rubella, cytomegalovirus, and herpes simplex), all of which were negative.

At 10 weeks of gestation, the patient presented with fever and erythematous and pruriginous cutaneous exanthema. The IgG and IgM antibodies for dengue and chikungunya were tested, and real-time PCR for ZIKV in plasma was performed. Only ZIKV returned a positive result. Ultrasound findings after the clinical expression of infection, performed at 12 weeks gestation, showed a cranial-caudal longitude of 51.8 mm and nuchal translucency of 0.4 mm. The couple was informed of the probability that the fetus would be affected given that infection manifested in the period of morphogenesis. Echography at a gestational age of 14 weeks + 3 days revealed a biparietal diameter of 27.1 mm and femur length of 11.5 mm, without detection of any anatomic abnormality.

Given the patient's age and the ZIKV infection during the early gestational period, we suggested genetic amniocentesis and virus detection in amniotic fluid at 15 weeks (according to CDC Guidelines: Amniocentesis performed at $\geq$15 weeks of gestation is associated with lower rates of complications than when performed at earlier gestational ages). Nonetheless, the couple refused to undergo such procedures.

Toward the end of June 2016, the patient traveled to France, where she underwent ultrasonic examination at 19 weeks of gestation; biometrically, less than three SDs below the average was evidenced for all parameters, with no anatomic abnormality. Given these findings, the couple accepted amniocentesis for ZIKV detection in the amniotic

TABLE 1

Evolution of laboratory and ultrasound findings.

Gestational age (wk+d)	10	12	14+3	19	21+4	24
Weeks after infection	1			9		14
Symptoms	Fever exanthema					
Ultrasound		Normal	Normal	<3 SD below average for all parameters; No anatomic abnormalities	Cerebellar hypoplasia and ventricular dysmorphia	
ZIKV RT-PCR maternal blood	Positive					
TORCH	Negative					
CMV PCR toxoplasma PCR				Negative		
ZIKV PCR urine and amniotic fluid				Positive		
ZIKV PCR cord blood						Positive
Pregnancy interruption						X

Note: CMV = Cytomegalovirus; PCR = polymerase chain reaction; RT = real-time; ZIKV = Zika virus.

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