Novel Insights from Clinical Practice

Fetal Diagnosis and Therapy

Fetal Diagn Ther
DOI: 10.1159/000479866

Received: April 10, 2017
Accepted after revision: July 25, 2017
Published online: September 13, 2017

New Insights into the Natural History of Congenital Zika Virus Syndrome

María Guadalupe Lovagnini Frutos[a, b] José Héctor Ochoa[a, b] María Gabriela Barbás[c] Héctor Dante Lucchini[a] Martín Moya[a] Gustavo Malinger[d, e]

[a]University Maternity Hospital (HUMN), Córdoba National University, [b]Diagnus SA. Prenatal Diagnosis Center, and [c]Central Laboratory Department, Ministry of Health, Córdoba, Argentina; [d]Division of Ultrasound in Obstetrics & Gynecology, Lis Maternity Hospital, Tel Aviv Sourasky Medical Center, [e]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

Established Facts

- Congenital Zika virus syndrome (CZVS) produces a wide range of brain insults and is frequently associated with microcephaly.
- Vertical transmission from the mother to the fetus is not always associated with CZVS.

Novel Insights

- Signs of CZVS may appear before 20 weeks; some of them are subtle and difficult to recognize.
- CZVS ultrasound signs are dynamic and show progressive worsening through pregnancy.

Keywords
Zika virus · Brain malformations · Congenital Zika virus syndrome · Prenatal diagnosis · Fetal ultrasound · Fetal MRI

Abstract
We describe the prenatal evolution of the brain findings in a patient with proved Zika virus infection at 8 weeks of gestation showing the very early appearance at 17 weeks of ventriculomegaly and signs of brain parenchymal involvement without microcephaly. The involvement of the brain becomes more evident at 22 and 27 weeks with the apparition of calcifications and microcephaly. Interestingly, the postnatal findings failed to show significant worsening when compared to these prenatal findings.

Case Report

A 27-year-old primigravida was referred at 17 weeks of gestation to our hospital for prenatal control. She was examined for the first time during the current pregnancy in Bolivia at 8 weeks of gestation because of arthromyalgia, conjunctivitis, maculopapular rash, and low-grade fever. The diagnosis of Zika virus (ZIKV) infection was reached by real-time reverse transcriptase polymerase chain reaction (RT-qPCR) in serum. She had a history of nonhemorrhagic dengue and of chikungunya fever. Five weeks after the onset of symptoms, the patient moved to Córdoba, Argentina; by this time she was asymptomatic. Fetal ultrasound (US) examination was performed at 17 weeks using transabdominal and transvaginal probes. The US findings were limited to the brain, showing mild ventriculomegaly and lack of visualization of the corpus callosum (Fig. 1a). A retrospective analysis of the acquired volumes showed a more severe insult, including hemispheric asymmetry and focal parenchymal thalamic, white matter, and cortical in-

E-Mail karger@karger.com
www.karger.com/fdt

Prof. Gustavo Malinger
Division of Ultrasound in Obstetrics & Gynecology
Lis Maternity Hospital, Tel Aviv Sourasky Medical Center
6 Weitzman Street, Tel Aviv 6423906 (Israel)
E-Mail gmalinger@gmail.com

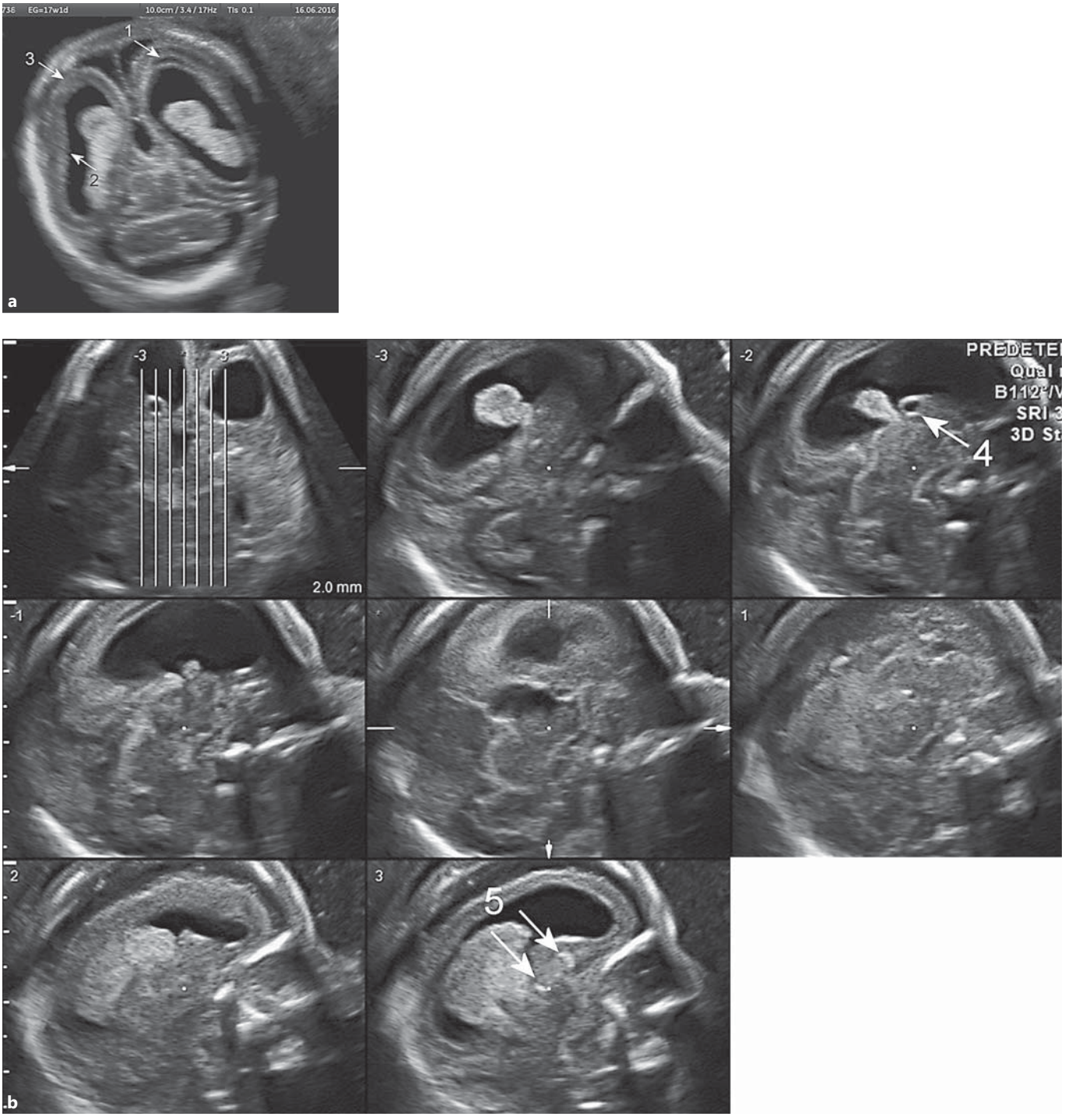
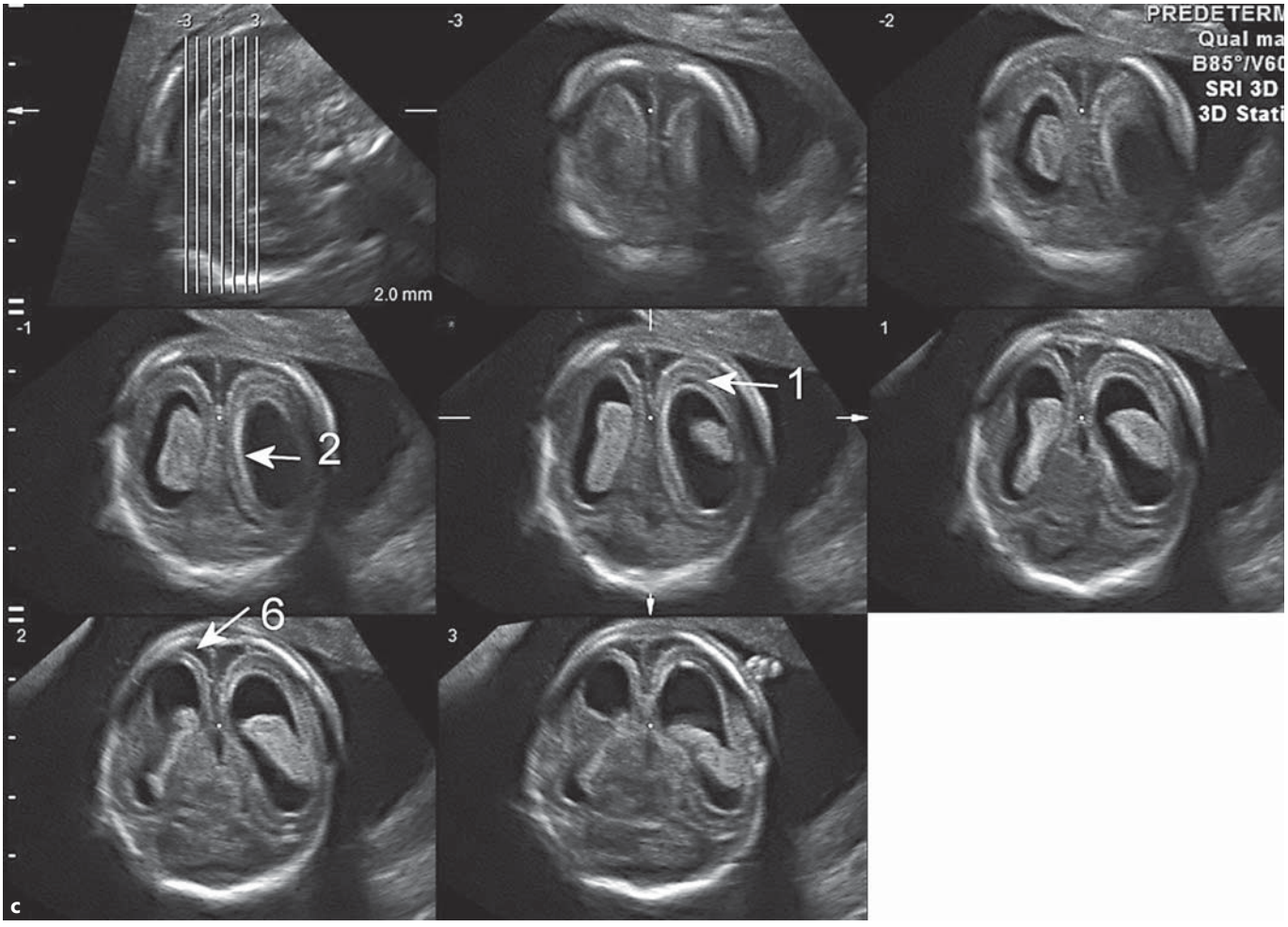


Fig. 1. Transvaginal examination at 17 weeks. **a** Modified coronal image shows early development of ventriculomegaly (lateral ventricular width = 10–11 mm); the corpus callosum is not observed. **b** Multiplanar sagittal images. **c** Multiplanar modified coronal images; note the asymmetry of the hemispheres. (1) Periventricular cystic degeneration. (2) Irregular echogenic ventricular wall. (3) Parenchymal loss of lamination. (4) Caudate cyst. (5) Calcifications. (6) Parenchymal thinning.

(Figure continued on next page.)



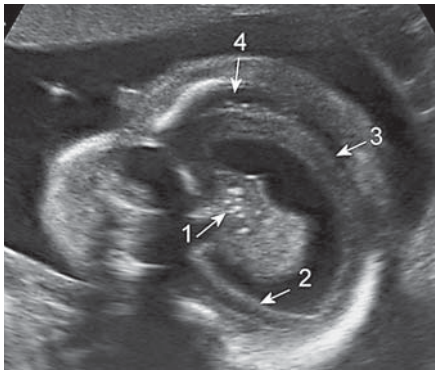


Fig. 2. Transabdominal examination at 21.6 weeks. Parasagittal plane. The ventricular dilatation and the calcifications are more prominent. (1) Calcifications. (2) Irregular echogenic ventricular wall. (3) Parenchymal thinning. (4) Large subarachnoid space.

volvement (Fig. 1b, c). Fetal biometry was normal for the gestational age. Maternal serology ruled out the possibility of other intrauterine infections.

A follow-up US examination performed at 22 weeks' gestation showed microcephaly, marked reduction in brain volume, ventriculomegaly, and broad-spread calcifications involving the white matter, the cortex, and the thalami; the corpus callosum appeared dysgenetic (Fig. 2).

Amniocentesis was performed and ZIKV infection was confirmed by RT-qPCR. The evolution of the disease was demonstrated by fetal magnetic resonance (MR) at 27 weeks showing further reduction in the thickness of the brain parenchyma with abnormal lamination, lack of development of normal sulcation, associated with increased severity of the ventriculomegaly, and a very small and thin corpus callosum (Fig. 3).

Pregnancy continued without significant changes in the US examinations. Delivery occurred at term resulting in a 3,390-g male newborn. The Apgar score was 7/8 at 1 and 5 min, respectively. Postnatal head circumference was 31 cm (2.1 SD below expected value). He did not require specialized support; on day 1, blood tests were normal. All samples from the newborn (blood, cerebrospinal fluid, urine, placenta, membranes, and umbilical cord blood) were

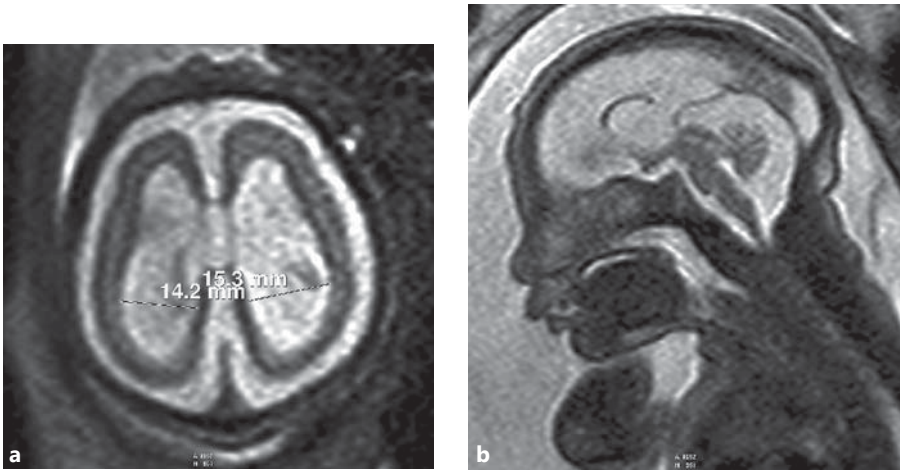


Fig. 3. Fetal T2-weighted MR images at 27 weeks. **a** Axial plane shows severe ventriculomegaly; the brain parenchyma is extremely thin without sulcation. **b** Midline plane shows a very small corpus callosum. The infratentorial structures are relatively spared.

negative for ZIKV by RT-qPCR, but anti-ZIKV IgM antibodies were positive in the cerebrospinal fluid and serum by capture enzyme-linked immunosorbent assay (MAC-ELISA). Computed tomography (CT) scan confirmed the prenatal findings (Fig. 4).

The neonatal evolution was uneventful and the child was discharged from the neonatal unit. He had small head circumference below 2 SD and a normal auditory and ophthalmologic examination at 2 months of age, and the first neurologic examination was consistent with mild hypertonicity and irritability.

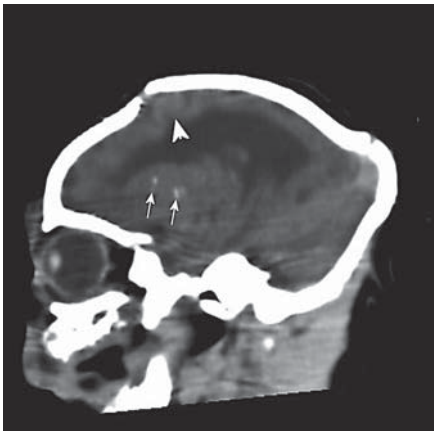


Fig. 4. Postnatal CT at day 2. The size of the lateral ventricles remains unchanged. Calcifications are clearly observed (arrows). Note the characteristic skull shape found in patients with congenital Zika virus syndrome as well as in other conditions associated with microcephaly due to severe brain insults (arrowhead).

Discussion

Due to the severe involvement in fetuses and newborns and its catastrophic consequences, the recent outbreak of ZIKV infection in Latin America rapidly reached world attention and scientific community interest. Although more than 1,500 studies have been published during the last year on this issue, relatively few information is available on the natural history of the fetal disease during its early stages and on the dynamics of brain involvement during pregnancy [1–3].

Since most of the cases reported during the ZIKV epidemics were diagnosed late in pregnancy or after birth in zones with relatively few resources, the amount and quality of the US fetal descriptions of the diagnosed cases was not optimal [4]. Particularly intriguing was the almost complete lack of cases diagnosed before 19–20 weeks [5]. More importantly, knowing the natural history of other intrauterine viral infections and particularly cytomegalovirus, it was clear that fetal ZIKV will result in a broad spectrum of anomalies being diagnosed in some cases during pregnancy and in other cases only after delivery and childhood; nonetheless, it was expected that some infected fetus will remain unaffected [6].

Our case being well documented since the beginning of the disease and with an early complete neurosonographic examination helps answer some of these still unresolved aspects of congenital Zika virus syndrome. The first examination performed 9 weeks after the appearance of clinical signs and confirmed by serum RT-qPCR showed that although the head circumference was normal, the brain presented signs of being affected. Some of the findings are obvious, as ventriculomegaly, but others are more subtle and they easily may escape recognition

(Fig. 1). These early findings apparently demonstrate a more aggressive neurotropism of ZIKV, particularly when compared with cytomegalovirus, a condition that may present with very similar imaging findings but is rarely detected before 20 weeks.

In a relative short period of 5 weeks, between this examination and the second one at 22 weeks (Fig. 2), the findings became much more severe; it is important to note the overwhelming increased amount and extension of the calcifications and increase in the severity of the ventriculomegaly. Although we can suspect the presence of abnormal Sylvian fissure, this finding and the thinning of the brain parenchyma are more evident at the 27-week MR (Fig. 3). Interestingly, from this time and until the postnatal CT, the findings remained mainly unchanged (Fig. 4).

It is to note that although the US findings appeared severe, the immediate neonatal neurological examination was apparently normal, besides the small head circumference. This fact is to be taken into consideration when assessing the risks of congenital Zika virus syndrome, since the diagnosis of children not evaluated during pregnancy may be initially not so obvious.

Acknowledgement

We gratefully acknowledge the staff of the Health Ministry of the Province of Córdoba, Argentina for the support in the management of this patient.

Statement of Ethics

Informed consent and protocol approval were not needed since the case is reported retrospectively. The patient was evaluated and treated according to current clinical standards.

Disclosure Statement

There is no conflict of interest.

References

1 Oliveira Melo AS, Malinger G, Ximenes R, Szejnfeld PO, Alves Sampaio S, Bispo de Filippis AM: Zika virus intrauterine infection causes fetal brain abnormality and microcephaly: tip of the iceberg? Ultrasound Obstet Gynecol 2016;47:6–7.

2 Melo AS, Aguiar RS, Amorim MM, Arruda MB, Melo FO, Ribeiro ST, Batista AG, Ferreira T, Dos Santos MP, Sampaio VV, Moura SR, Rabello LP, Gonzaga CE, Malinger G, Ximenes R, de Oliveira-Szejnfeld PS, Tovar-Moll F, Chimelli L, Silveira PP, Delvechio R, Higa L, Campanati L, Nogueira RM, Filippis AM, Szejnfeld J, Voloch CM, Ferreira OC Jr, Brindeiro RM, Tanuri A: Congenital Zika virus infection: beyond neonatal microcephaly. JAMA Neurol 2016;73:1407–1416.

3 Soares de Oliveira-Szejnfeld P, Levine D, Melo AS, Amorim MM, Batista AG, Chimelli L, Tanuri A, Aguiar RS, Malinger G, Ximenes R, Robertson R, Szejnfeld J, Tovar-Moll F: Congenital brain abnormalities and Zika virus: what the radiologist can expect to see prenatally and postnatally. Radiology 2016;281:203–218.

4 Brasil P, Pereira JP Jr, Moreira ME, Ribeiro Nogueira RM, Damasceno L, Wakimoto M, Rabello RS, Valderramos SG, Halai UA, Salles TS, Zin AA, Horovitz D, Daltro P, Boechat M, Raja Gabaglia C, Carvalho de Sequeira P, Pilotto JH, Medialdea-Carrera R, Cotrim da Cunha D, Abreu de Carvalho LM, Pone M, Machado Siqueira A, Calvet GA, Rodrigues Baiao AE, Neves ES, Nassar de Carvalho PR, Hasue RH, Marschik PB, Einspieler C, Janzen C, Cherry JD, Bispo de Filippis AM, Nielsen-Saines K: Zika virus infection in pregnant women in Rio de Janeiro. N Engl J Med 2016;375:2321–2334.

5 Driggers RW, Ho CY, Korhonen EM, Kuivanen S, Jaaskelainen AJ, Smura T, Rosenberg A, Hill DA, DeBiasi RL, Vezina G, Timofeev J, Rodriguez FJ, Levanov L, Razak J, Iyengar P, Hennenfent A, Kennedy R, Lanciotti R, du Plessis A, Vapalahti O: Zika virus infection with prolonged maternal viremia and fetal brain abnormalities. N Engl J Med 2016;374:2142–2151.

6 Pomar L, Malinger G, Benoist G, Carles G, Ville Y, Rousset D, Hcini N, Pomar C, Jolivet A, Lambert V: Association between Zika virus and fetopathy: a prospective cohort study in French Guiana. Ultrasound Obstet Gynecol 2017;49:729–736.