# Neuroimaging Findings of Congenital Toxoplasmosis, Cytomegalovirus, and Zika Virus Infections: A Comparison of Three Cases

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## Abstract

**Objective:** Toxoplasmosis, cytomegalovirus (CMV), and Zika virus (ZIKV) are among the common infectious agents that may infect the fetuses vertically. Clinical presentations of these congenital infections overlap significantly, and it is usually impossible to determine the causative agent clinically. The objective was the comparison of neuroimaging findings in three fetuses who underwent intrauterine infection by toxoplasmosis, CMV, and ZIKV.

**Methods:** Three confirmed cases of congenital toxoplasmosis, CMV, and ZIKV infections were included in the study over 7 months prospectively. Prenatal ultrasound, fetal brain MRI, and postnatal neuroimaging (CT or MRI) were performed on all of the included cases and interpreted by an expert radiologist.

**Results:** The mean GA at the time of prenatal imaging was 34.5 ± 3.5 weeks. The main neuroimaging findings in congenital toxoplasmosis were randomly distributed brain calcifications and ventricular dilatation on ultrasounds (US), as well as white matter signal change on fetal brain MRI. The main neuroimaging findings of congenital CMV infection included microcephaly, ventriculomegaly, and periventricular calcifications on US, as well as pachygyria revealed by fetal MRI. The case of congenital ZIKV infection showed microcephaly, ventriculomegaly, and periventricular calcifications on ultrasound, as well as brain atrophy and brain surface smoothness on fetal MRI.

**Conclusion:** Although the neuroimaging findings in congenital infections are not pathognomonic, in combination with the patient history may be suggestive of one of the infectious agents, which will guide the management strategy.

**Key Words:** Toxoplasmosis, cytomegalovirus, Zika virus, ultrasound, magnetic resonance imaging

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Competing interests: None declared.

Received on March 22, 2017

Accepted on May 10, 2017

## Résumé

**Objectif :** *Toxoplasma gondii*, le cytomégalovirus (CMV) et le virus Zika (ZIKV) font partie des agents infectieux courants qui peuvent infecter les fœtus de façon verticale. Les signes cliniques de ces infections congénitales se chevauchent de façon importante, d'où l'impossibilité, la plupart du temps, de déterminer l'agent en cause par des méthodes cliniques. L'objectif était de comparer les résultats de neuroimagerie de trois fœtus ayant contracté la toxoplasmose, le CMV et le ZIKV en milieu intra-utérin.

**Méthodologie :** Trois cas confirmés d'infection congénitale de *Toxoplasma gondii*, de CMV et de ZIKV ont été étudiés dans le cadre de cette étude prospective de sept mois. Chacun des sujets a subi une échographie prénatale, une IRM du cerveau fœtal et une neuroimagerie postnatale (TDM ou IRM), et les résultats ont été interprétés par un radiologiste expert.

**Résultats :** L'AG moyen au moment de l'imagerie prénatale était de 34,5 semaines ± 3,5 semaines. Le cas de toxoplasmose congénitale présentait principalement des calcifications cérébrales aléatoirement distribuées et une dilatation ventriculaire à l'échographie, ainsi qu'une variation du signal de la substance blanche du cerveau fœtal à l'IRM. Le cas d'infection congénitale au CMV présentait notamment une microcéphalie, une ventriculomégalie et des calcifications périventriculaires à l'échographie, ainsi qu'une pachygyrie à l'IRM fœtale. Le cas d'infection congénitale au ZIKV, quant à lui, présentait une microcéphalie, une ventriculomégalie et des calcifications périventriculaires à l'échographie, ainsi qu'une atrophie cérébrale et un cerveau lisse à l'IRM fœtale.

**Conclusion :** Même si les résultats de neuroimagerie dans ces cas d'infections congénitales ne sont pas pathognomoniques, leur association aux antécédents du patient peut donner une idée de l'agent infectieux en cause, ce qui guidera la prise en charge.



J Obstet Gynaecol Can 2017;■(■):1–6

https://doi.org/10.1016/j.jogc.2017.05.013

## INTRODUCTION

Congenital toxoplasmosis results from prenatal infection with the protozoan *Toxoplasma gondii*, and confirmation of the fetal infection is performed by polymerase chain reaction testing of amniotic fluid. The main fetal ultrasound findings of congenital toxoplasmosis include parenchymal echogenic nodules representing foci of calcification, as well as ventriculomegaly. Fetal MRI may provide complementary diagnostic information, demonstrating abnormal cortical development in a few cases.[1]

Cytomegalovirus is a DNA virus considered as the most prevalent congenital viral infection occurring in 0.5—2.5% of live births. Up to 90% of newborns affected by congenital CMV infection are asymptomatic at birth.[2] The most common prenatal ultrasound findings of congenital CMV infection include microcephaly, ventriculomegaly, periventricular echogenic foci (representing calcifications), and periventricular cysts.[3] MRI may be of additional help revealing cortical abnormalities and temporal pole cysts.[4]

Zika virus belongs to the family Flaviviridae; the family is also responsible for dengue virus and chikungunya virus infections. ZIKV is usually transmitted by *Aedes aegypti* and *Aedes albopictus* mosquitoes as the main vectors in the current outbreaks. Beginning in 2015, ZIKV outbreak in Brazil has been associated with a significant increase in the number of congenital microcephaly cases in the endemic areas (particularly in the northeastern Brazil).[5] The most important prenatal US findings in congenital ZIKV infection include severe microcephaly, periventricular and/or parenchymal calcifications, symmetrical or asymmetrical ventriculomegaly, cerebellar abnormalities, and brain parenchymal atrophy.[6] Fetal brain MRI may better delineate malformations of cortical development and myelination abnormalities.[7]

Neuroimaging findings of congenital toxoplasmosis, CMV, and ZIKV infections are very similar in several aspects. On the other hand, screening by maternal serologic or molecular testing and definitive diagnosis by amniotic fluid PCR are not feasible in the majority of endemic areas regarding the cost and availability. In this article, we aim to describe and illustrate the neuroimaging findings of congenital toxoplasmosis, CMV, and ZIKV infections in three confirmed cases. A detailed knowledge of prenatal imaging findings in each congenital infection is helpful to suspect one of them more than others based on the neuroimaging studies, which in part will guide the patient management.

### ABBREVIATIONS

| | |
|---|---|
| CMV | cytomegalovirus |
| ZIKV | Zika virus |
| CTX | congenital toxoplasmosis |
| CCID | congenital cytomegalic inclusion disease |
| CZS | congenital Zika syndrome |
| US | ultrasound |

## MATERIALS AND METHODS

In a prospective study between January 2016 and July 2016, three confirmed cases of congenital toxoplasmosis, CMV, and ZIKV infections were included. All of the included pregnant women filled the informed consent. The pregnant women were presented to the public health services of Rio de Janeiro, Brazil, and the congenital infections were confirmed by PCR testing on the amniotic fluid. All of the US and MRI examinations were performed and interpreted by an expert radiologist. Prenatal US follow-up examinations were performed in all of the cases, but only the initial US examinations in each patient were used for describing and comparing the findings. All US examinations were done utilizing both transvaginal (RIC 5-9W) and transabdominal (RAB 4-8L) probes (Voluson E8; GE Healthcare, Milwaukee, WI).

MRI studies were performed on a 1.5-Tesla magnet (Magnetom Aera; Siemens Healthcare, Erlangen, Germany). With the patients in supine or left lateral decubitus position (whichever was better tolerated by the patient), the following standard protocols were performed: (1) T2-weighted HASTE (Half-Fourier Acquisition Single-shot Turbo spin Echo) sequence in the axial, coronal, and sagittal planes of the fetus, (2) T1-weighted in-phase/out-of-phase gradient echo sequences in the axial, coronal, and sagittal planes of the fetus, and (3) 3-D TrueFISP (true fast imaging with steady-state free precession) sequence, preferably in the sagittal plane of the fetus. Each MRI study was performed in less than 40 minutes. A body phased-array surface coil was positioned over the abdomen during the image acquisition. No intravenous contrast media was used for these studies.

Other possible concomitant TORCH infections (including syphilis, parvovirus-B19, rubella, and herpes viruses) were excluded by maternal serologic testing. All of the included pregnant women were followed until delivery. Postnatal MRI or CT was performed for all infants, and the 3-D physical model was printed on thermoplastic acrylonitrile butadiene styrene (ABS) (Stratasys uPrint; Stratasys, Ltd.,

**Table 1. General characteristics of the included cases and the perinatal outcomes**

| Case | Maternal age (yrs) | Parity | GA at the time of US (wks) | GA at the time of MRI (wks) | Birth weight (g) | Apgar scores at the 1st and 5th min | Infectious agent | GA at delivery (wks) | Route of delivery |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 42 | 2 | 32 | 32 | 2321 | 7 and 8 | Cytomegalovirus | 37 | CS |
| 2 | 32 | 1 | 33 | 33 | 3010 | 8 and 9 | Toxoplasmosis | 38 | CS |
| 3 | 27 | 1 | 37 | 37 | 2210 | 8 and 9 | Zika virus | 38 | CS |

Eden Prairie, MN) in the congenital ZIKV infection case utilizing data of the head CT scan.

## RESULTS

### General characteristics of the included cases

The mean maternal age at the time of presentation was 34.5 ± 10.6 years, and the mean GA at the time of US and MRI examinations was 34.5±3.5 weeks. All of the babies were delivered via CS. The mean GA and the mean birth weight at the time of delivery were 37.5±0.7 weeks and 2265.5 ± 78.4 grams, respectively. The mean Apgar scores at the 1st and the 5th minutes following delivery were 8 ± 1.4 and 8.5 ± 0.7, respectively. Table 1 shows the general characteristics and perinatal outcomes of the included cases.

### Neuroimaging findings of congenital toxoplasmosis

The included fetus with congenital toxoplasmosis showed large cystic dilatation of the posterior horns of the lateral ventricles and randomly distributed echogenic nodules

**Figure 1. Neuroimaging findings of a 33-week fetus with congenital toxoplasmosis. (A) Transabdominal ultrasound in the axial view showing cystic dilatation of the posterior horns of the lateral ventricles (*), and the cortical nodular foci (*arrow*). (B) MRI T2-weighted in sagittal views demonstrating multiple annular lesions of varying size with heterogeneous signal intensity, predominantly hyperintense (*arrows*). Note diffusely distributed edema throughout the parenchyma. Note hepatomegaly (*black arrow*). (C) MRI T2-weighted (left) and T1-weighted with fat saturation (right) in axial view showing the supratentorial ventricular dilatation (*). (D). Postnatal MRI showing the ventriculomegaly and diffuse hyperintensity throughout the parenchyma, representing myelination disorder or diffuse white matter edema.**

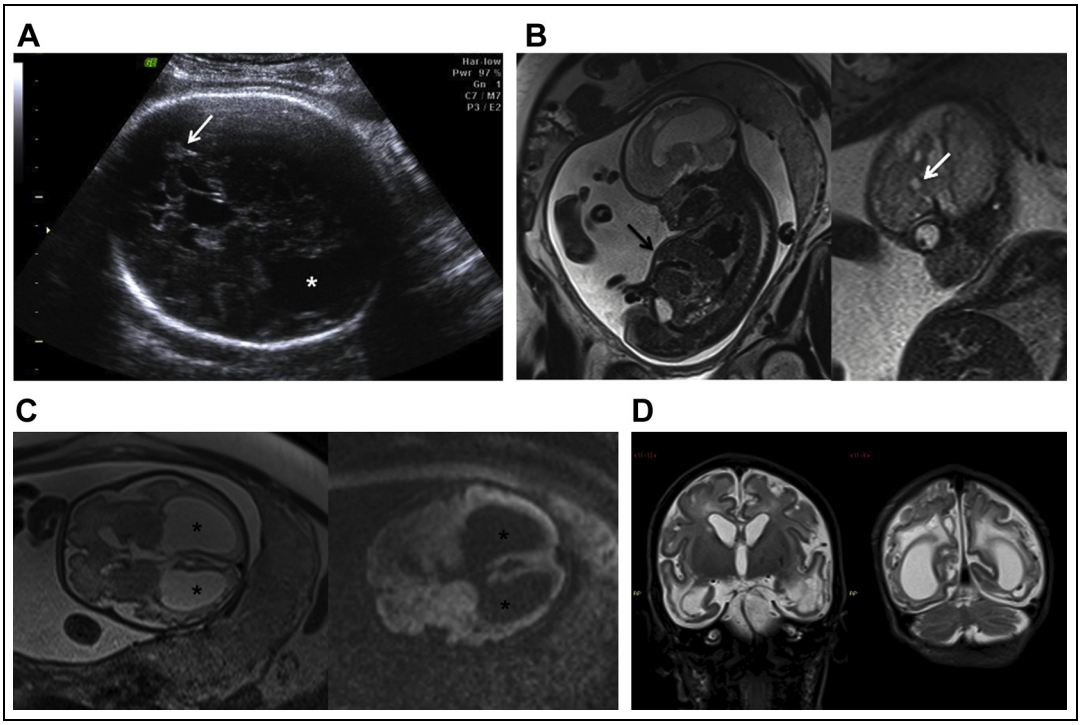
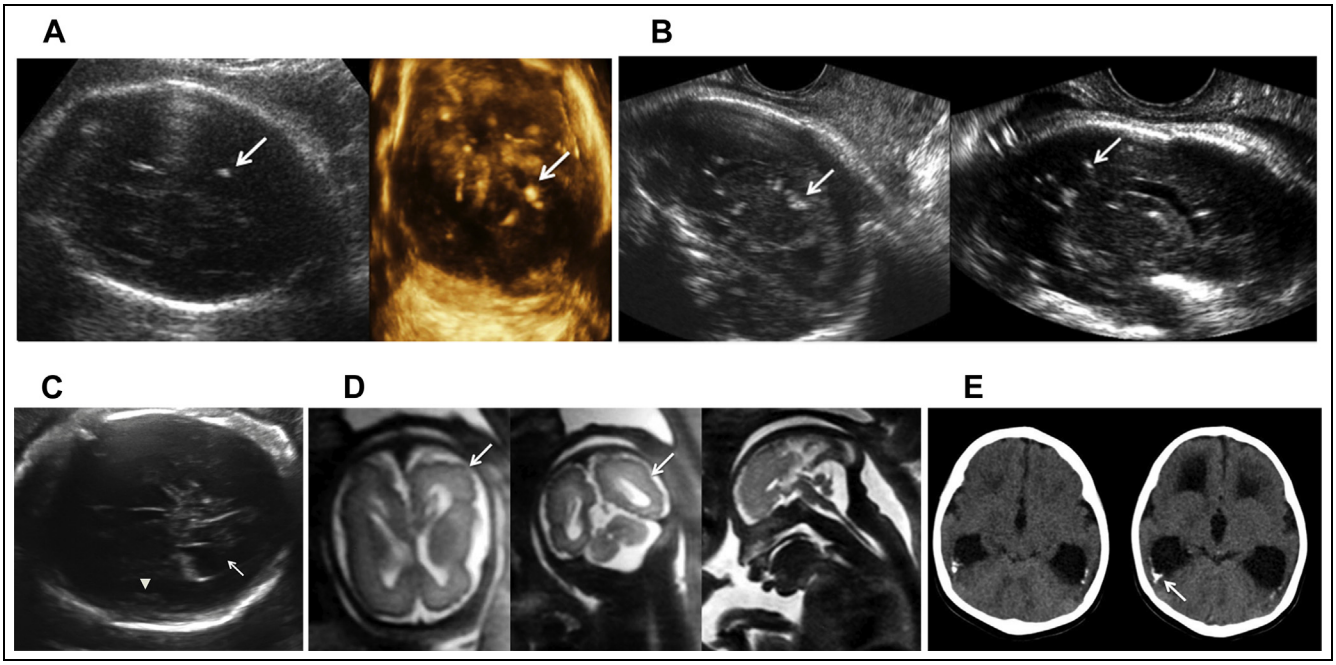


**Figure 2. Neuroimaging findings of a 32-week fetus with congenital cytomegalovirus infection. (A) Transabdominal fetal head ultrasound (lest) with 3-D reconstruction in the rendering mode (right) showing microcephaly, and periventricular calcifications (*arrows*). (B) Transvaginal fetal US clearly demonstrating the periventricular calcifications (*arrows*). (C) Transabdominal US in the axial plane showing mild ventriculomegaly. An intraventricular septation is present, but it is difficult to be visualized (*arrow*). Note the abnormal development of the Sylvian fissure (*arrowhead*). (D) T2-weighted MRI in axial, coronal, and sagittal planes showing ventriculomegaly, abnormal development of the Sylvian fissure, and pachygyria (*arrows*). (E) Postnatal CT demonstrating ventricular dilatation and periventricular calcifications (*arrow*).**




representing foci of calcification on the prenatal US at 33 weeks of gestation (Figure 1A). In addition, fetal MRI depicted diffuse hyperintensity throughout the brain parenchyma in the fluid sensitive sequences, which is suggestive of diffuse edema (Figure 1B and C).

### Neuroimaging findings of congenital CMV infection

The included fetus with congenital CMV infection demonstrated microcephaly, ventriculomegaly, and periventricular calcifications on the prenatal US examination at 32 weeks of gestation (Figure 2A–C). T2-weighted MRI of the fetal brain revealed abnormal development of the Sylvian fissure and the associated malformation of cortical development (pachygyria) (Figure 2D).

### Neuroimaging findings of congenital ZIKV infection

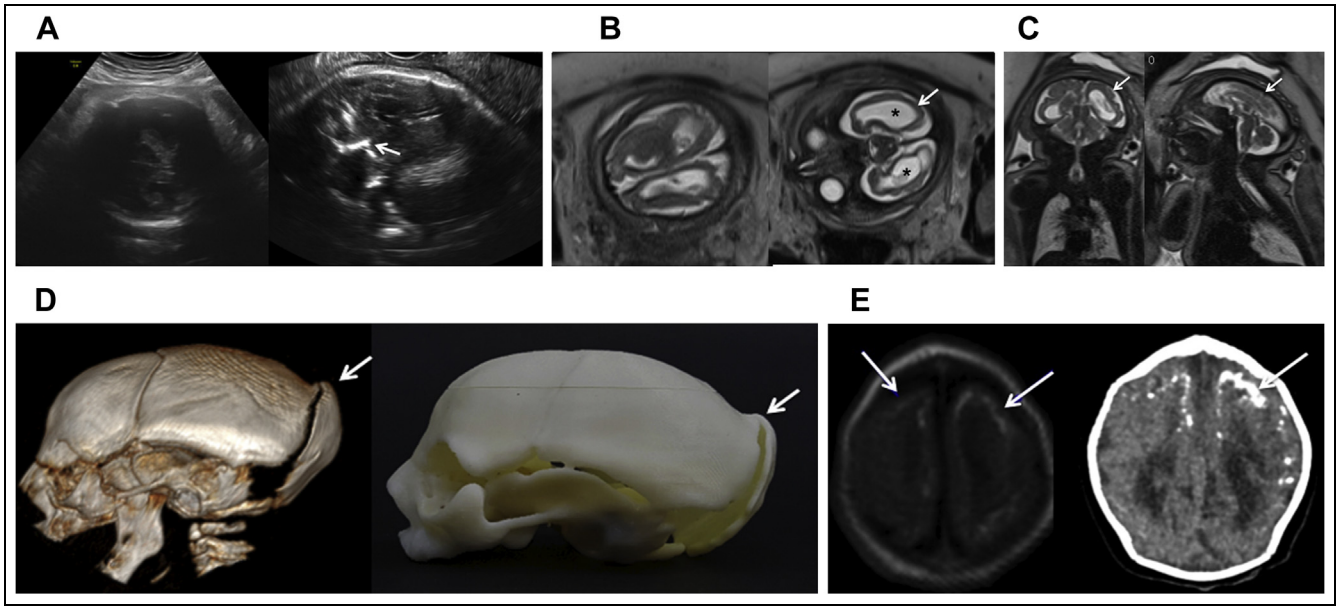
The included fetus with congenital ZIKV infection showed microcephaly and parenchymal calcifications (mainly periventricular in distribution) on the prenatal US performed at 37 weeks of gestation (Figure 3A). Fetal brain MRI showed cortical atrophy, relative smoothness of the brain surface, and asymmetric dilatation of occipital horns (Figure 3B and C). 3-D physical model of the skull demonstrated its collapsed appearance and the redundant occipital fold (Figure 3D).

## DISCUSSION

In utero fetal infection by toxoplasmosis, CMV, and ZIKV can cause multiple abnormalities. The constellation of abnormalities in these conditions are called as congenital toxoplasmosis,[1] congenital cytomegalic inclusion disease,[2] and congenital Zika syndrome,[8] respectively. Most associated abnormalities occur in the fetal brain; therefore, neuroimaging plays an important role in the diagnosis and management of these conditions.

Prenatal US is an easy-to-access and safe tool, and is currently the first-line modality of choice for screening for various fetal anomalies. Neurosonography can easily detect microcephaly, ventriculomegaly, parenchymal calcifications, intraventricular adhesions, brain parenchymal atrophy, and overt malformations of cortical development from early second trimester (16 weeks of gestation) on.[9] When these findings are present on fetal US examination, further evaluation is recommended for ruling out congenital infections as well as aneuploidies or genetic disorders. For this purpose, maternal serologic or molecular and/or amniotic fluid molecular testing can be performed. In addition, neurosonographic findings may suggest one of

**Figure 3. Neuroimaging findings of a 37-week fetus with congenital Zika syndrome. (A) Transabdominal axial (left) and transvaginal sagittal (right) ultrasound showing microcephaly and parenchymal calcifications (*arrow*). (B) T2-weighted MRI in axial view showing microcephaly, cortical atrophy, relative smoothness of the brain surface (*arrow*), and asymmetric colpocephaly (*). (C) T2-weighted MRI in coronal and sagittal views showing the smoothness of the brain surface (*arrows*). (D) 3-D sagittal reconstruction from head CT (left), and the corresponding 3-D printed model on thermoplastic acrylonitrile butadiene styrene (ABS) (right). Note collapsed appearance of the skull, and the redundant occipital fold (*arrows*). (E) T1-weighted MRI in axial view (left) showing multiple hyperintense foci (*arrows*) at the corticomedullary junction in correspondence to the calcifications (*arrow*) seeing on the CT axial image (right).**




the infectious agents as the most probable etiopathogenesis.[10] Microcephaly is more common in CZS,[7,8] and CCID[2–4] patients, but may also be seen in CTX patients occasionally.[1,11,12] Ventriculomegaly is a feature that may occur in all of these congenital infections,[1,2,7] as it was present in all of the fetuses included in our study. Although presence of ventriculomegaly should prompt further evaluation and close US follow-up, this finding cannot differentiate between these infections. Parenchymal calcifications however usually occur with a distinct pattern in each individual infection. In CTX,[1,10,11] punctuate calcifications are usually scattered randomly throughout the brain parenchyma; while in CCID[2–4] and CZS,[6–9] calcifications tend to be linear in shape and periventricular in location on prenatal US. Malformations of cortical development (mostly polymicrogyria and lissencephaly-pachygyria spectrum) are more common in CZS and CCID compared to CTX patients.[1,2,7] Fetal US however can only detect overt malformations and may miss more subtle ones, therefore fetal brain MRI utilizing ultrafast techniques is offered for better delineation of such subtle malformations. It should be emphasized that although MRI can show mild malformations of cortical development, as well as white matter changes and parenchymal atrophy, it is usually unable to reveal foci of calcification precisely.[9]

Neonatal head CT can detect intracranial calcifications and show changes of bony cranium very well. Similar to prenatal US, calcifications have characteristically random and periventricular distributions in CTX[1,11,12] and CCID[2–4] patients, respectively. In CZS,[7,9,13] however, the majority of calcifications are interestingly seen at the corticomedullary junction on neonatal head CT scan in contrast to their periventricular location on prenatal US, the finding that was detected in the CZS patient of the current study as well. Postnatal CT scan, particularly utilizing 3-D reconstruction, is capable of depicting the bony skull changes associated with these congenital infections with the most common being a pointed appearance of the frontal and occipital regions, which is secondary to the parenchymal atrophy and the bony skull collapse.[9,13] Neonatal brain MRI is helpful for precise evaluation of the malformations of cortical development, parenchymal atrophy, and white matter changes. All of these infections can cause abnormalities of myelination (most commonly delayed myelination and/or dysmyelination), which are seen as areas of high signal intensity on fluid sensitive sequences (i.e., T2-weighted and T2-FLAIR MR images). In addition, MRI is very helpful for assessing associated abnormalities within the posterior cranial fossa such as cerebellar atrophy or an associated Dandy-Walker malformation/variant.[9,13]

In addition to the capabilities of neuroimaging to make the diagnosis, it has been confirmed that severity and extent of infantile neuroimaging findings in congenital infections is well correlated with the neurodevelopmental outcome, which is not always true about the severity of clinical findings at birth.[14] Moreover, neuroimaging can be used for following the disease course, since these conditions can be associated with some late complications on occasions.[14,15] Therefore, a detailed knowledge of possible neuroimaging findings in each congenital infection is of paramount importance to suspect them, make an early correct diagnosis, determine the prognosis, follow the disease course, and counsel the parents.

## CONCLUSION

Congenital toxoplasmosis, CMV, and ZIKV infections can cause severe abnormalities in the infected fetuses. Upon a detailed knowledge of the possible prenatal neuroimaging findings, particularly on US, the perinatologist, obstetrician, or radiologist may suspect the possibility of these congenital infections, and even may suggest one of the infectious agents as the causative etiology based on some characteristic imaging features. Neuroimaging is also helpful for prognostication, and following the disease course.

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