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SHORT COMMUNICATION

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Congenital cytomegalovirus infection with brainstem hemorrhage and polymicrogyria: Necropsic and histopathological findings

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Abstract

Congenital cytomegalovirus (CMV) infection can cause severe neurological sequelae or even fetal death. We present a 17-year-old pregnant woman with fetal CMV infection, leading to voluntary termination of pregnancy. Fetopsy demonstrated a brainstem hemorrhage and focal polymicrogyria. CMV inclusions were observed in the lung, liver, thyroid, pancreas, kidneys, adrenal, placenta, and central nervous system. Intracranial hemorrhage is a rare finding in the context of congenital CMV infection, with isolated brainstem hemorrhage being an exceptional form of presentation. Polymicrogyria appears to be a more frequent finding, although its actual incidence is unknown. Future studies are needed to determine the causal association.

KEYWORDS
congenital, cytomegalovirus, infection, intracranial hemorrhage, polymicrogyria

1 | INTRODUCTION

Cytomegalovirus (CMV) is a virus of the *Herpesviridae* family present in many mammalian species, including humans. Its name alludes to the large size of the cells infected by it, secondary to the weakening of their cytoskeleton. This genus includes 11 species, of which one, human betaherpesvirus 5 (HHV-5) causes disease in humans. Infection in humans usually occurs in immunocompromised patients and congenitally.

Congenital CMV incidence in the United States is estimated at 30 000 cases per year.[1] Characteristically, it affects low and middle-income countries.[2] Congenital CMV infection can occur in the context of maternal primoinfection or recurrence.[3] The rate of transmission to the fetus increases as pregnancy progresses, with the highest risk in the third trimester. However, fetal exposure in the first months of gestation carries a higher probability of sequelae.[4] Clinically it is characterized by the presence of chorioretinitis, ventriculomegaly, periventricular or intracerebral calcifications, sensorineural hearing loss, and developmental delay, although the pathologic spectrum includes many other manifestations.[5] Prenatal diagnosis combines maternal serology with amniocentesis.[3] Postnatal diagnosis is performed by PCR of the child's urine or saliva, with an estimated sensitivity of 95%.[6]

2 | MATERIALS AND METHODS

Clinical data, sociodemographic information, fetopsy photographs, and histological samples of a patient with confirmed diagnosis of congenital CMV infection diagnosed at our center in 2021 were collected.

Javier Arredondo Montero and Mónica Bronte Anaut contributed equally to this study.

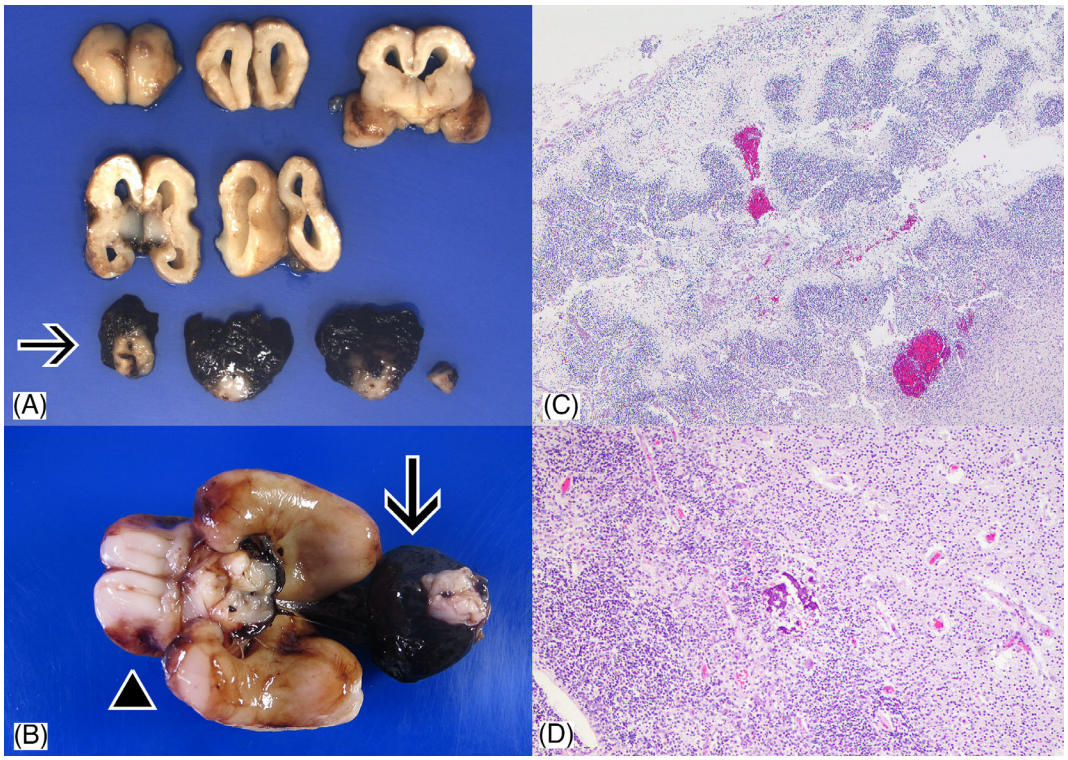

FIGURE 1 (A,B) Macroscopic view of the encephalus and the brainstem. Serial sections of the encephalus showed no intraventricular bleeding or macroscopic calcifications. The presence of meningeal ecchymosis (arrowhead) was observed. The presence of hemorrhagic debris in the cerebellum and brainstem was observed (arrows). (C) Microphotograph (H&E, ×40). Abrupt transition between normal cortex (right) and foci of abnormal arrangement and scalloped folding of cortical layers compatible with polymicrogyria (left). (D) Microphotograph (H&E, ×100). Isolated periventricular calcification.

All the information was anonymized in accordance with current legislation. Informed written and verbal consent for publication was obtained from the patient's parents.

3 | RESULTS

We present the case of a 17-year-old woman with no medical history of relevance, who came for evaluation for first gestation. Fetal ultrasound was performed in the 22nd week of gestation and showed intestinal echogenicity, as well as a fetus in marked dorsal flexion. Symmetrical encephalic structures and of normal configuration were identified (lateral ventricles of dimensions 7.7–7.4 mm; cerebellum of size 19.9 mm; third ventricle of 3 mm) and a periventricular echogenicity image surrounding both ventricles. A moderate increase in the peak systolic velocity of the middle cerebral artery was identified (47.16 cm/s). Both findings were considered suggestive of a potential congenital fetal infection.[7,8] Maternal serology was performed, showing an IgM for CMV of 1.51 and an IgG for CMV of 174 AU/ml, with an IgG avidity of 82.3%. PCR for CMV in maternal urine was performed, with a value of 14 280 IU/ml. Diagnostic amniocentesis was proposed. The procedure was uneventful. Fetal DNA study was performed, excluding the presence of common aneuploidies. The microbiological study of the amniotic fluid showed positivity for CMV by PCR technique, with 1 453 500 IU/ml. The available options were explained to the mother, and she opted for termination of pregnancy.

The termination of pregnancy was uneventful. The patient was administered 800 μg of misoprostol, and 20 h after administration she presented spontaneous rupture of membranes with meconium fluid leakage. Expulsion was vaginal and atraumatic. The fetus was born without a heartbeat, and the time at which the fetal heartbeat stopped was not reflected in the patient's history. Placental expulsion was immediate, and the placenta had a hydropic appearance suggestive of chorioamnionitis, with no other alterations. The uterus presented adequate posterior contraction. There was no bleeding during the procedure.

A clinical autopsy was performed. The fetus was female and was 22 + 6 weeks gestational development. Weight was 405 g; length was 27 cm; and head circumference was 20.5 cm. The external physical examination did not reveal any notable alterations. The internal physical examination showed bowel loops, heart, thymus, and lung with petechial stippling. The weight of abdominal and thoracic organs was as follows: lungs 8.6 g; thymus: 1.07 g; heart: 5.05 g; liver: 24.1 g; spleen: 1.7 g; kidneys (combined weight): 4.7 g; adrenal glands (combined weight): 1.06 g. At the opening of the cranial cavity there was abundant serohematic liquid and meningeal ecchymosis (Figure 1, arrowhead), predominantly in the right hemisphere. There was also an important hemorrhage around the brainstem (Figure 1A,B, arrows).

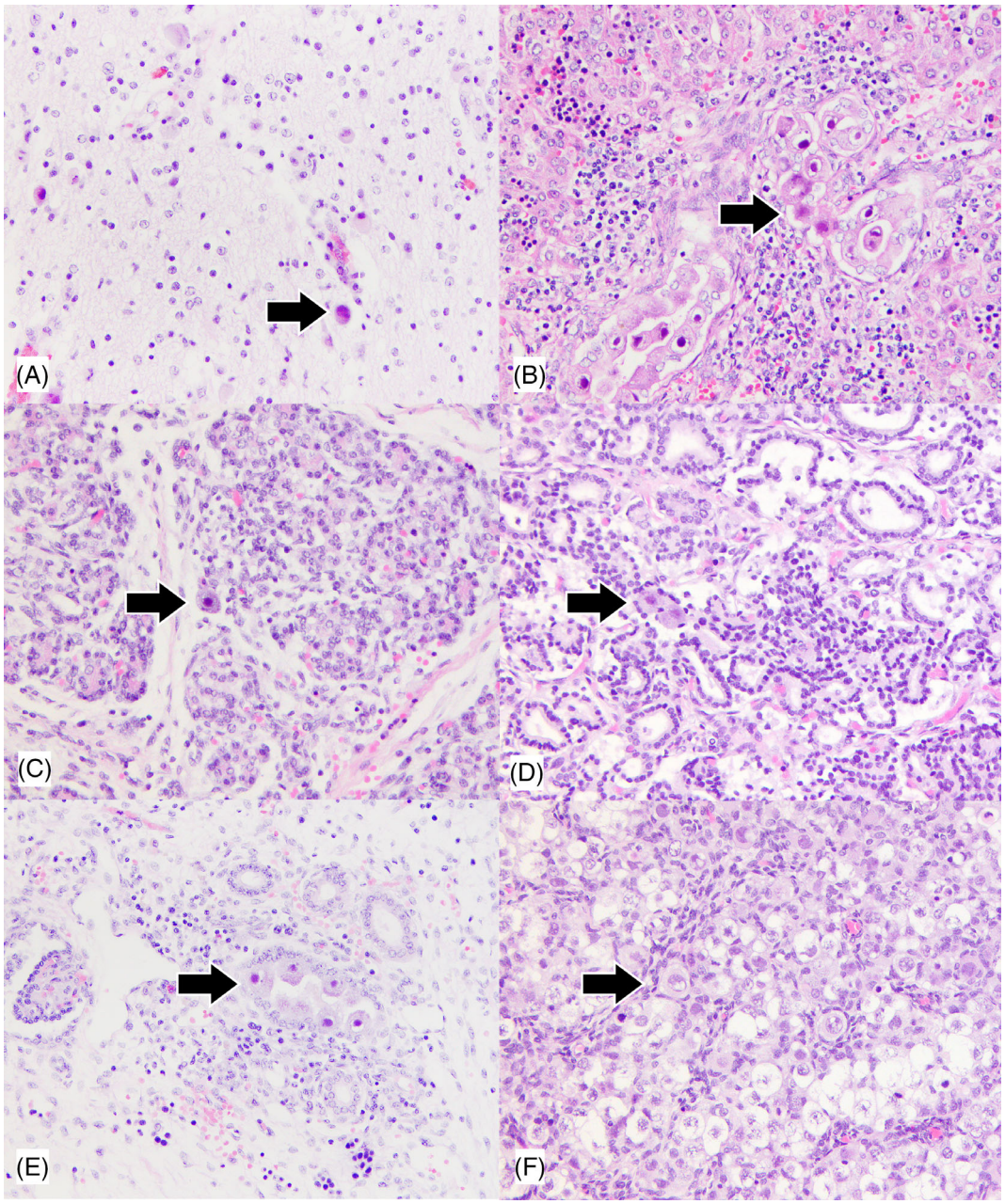

FIGURE 2 Photomicrographs (H&E, ×200). Histological study of the involved organs. Cells with ample and eosinophilic cytoplasm, large nucleus in ground glass, and intranuclear CMV inclusions are observed (arrows), with an accompanying inflammatory infiltrate. (A) Midbrain. (B) Liver (infiltration of the hepatic epithelium). (C) Pancreas. (D) Lung (canalicular phase of development. Intra-alveolar CMV inclusions). (E) Kidney (CMV inclusions in tubular epithelium). (F) Adrenal gland.

Microscopically, foci of polymicrogyria, well demarcated, with scalloped folding of the cerebral cortex, were observed. These findings affected bilaterally the frontal, temporal, and parietal lobes (Figure 1C). Foci of laminar necrosis were also identified in the cerebral cortex in the areas of polymicrogyria. Immunohistochemical staining for CD3 (T lymphocytes), CD20 (B lymphocytes), and CD68 (macrophages) was performed, all of them being present in brain parenchyma and meninges. The patient had periventricular microcalcifications (Figure 1D). No vascular pathology was observed in the central nervous system.

CMV inclusions were observed in the lung, liver, thyroid, pancreas, kidneys, adrenal glands, and central nervous system (encephalon and brainstem) (Figure 2). Immunohistochemical stainings for CMV antigen were also performed, corroborating these findings (Figure 3). No viral inclusions were observed in the rest of the organs.

The placenta weighed 250 grams (P90). Its study showed marked villous fibrosis and increased Hofbahuer cells, with abundant CMV intranuclear inclusions (Figure 4). No villitis or chorioamnionitis was observed.

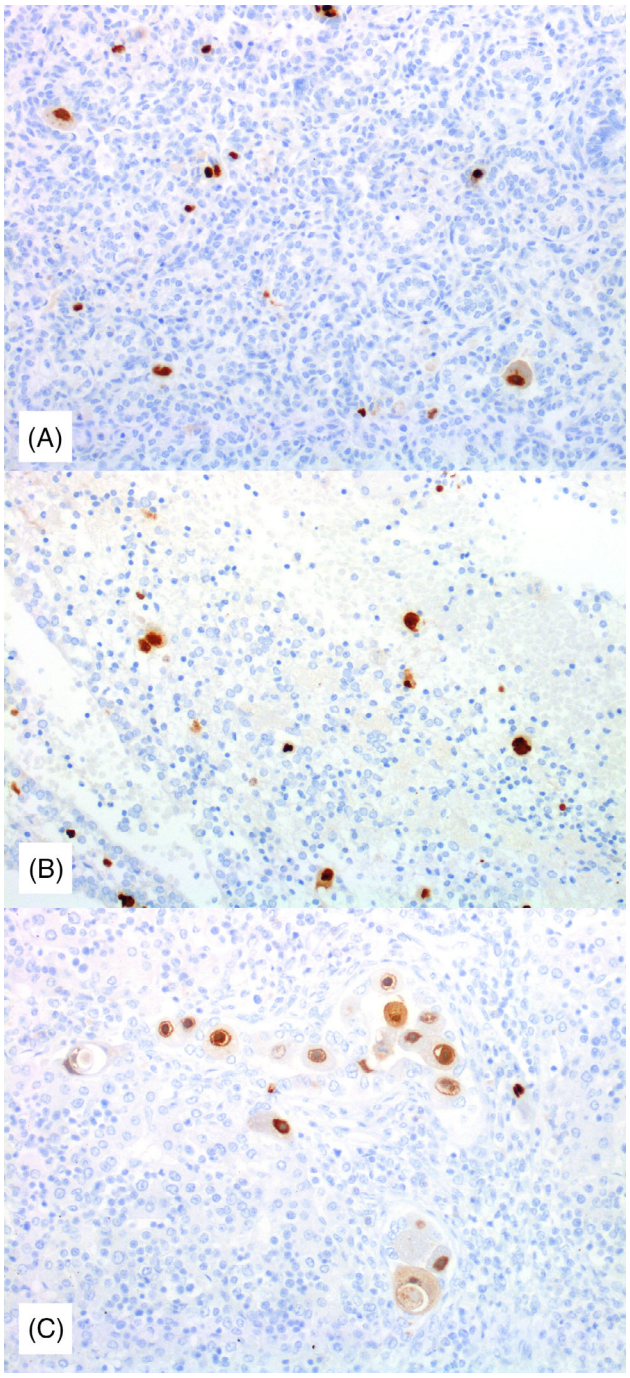

FIGURE 3 Photomicrographs (Immunohistochemical stainings for CMV antigen, ×200). (A) Lung; (B) central nervous system; (C) liver.

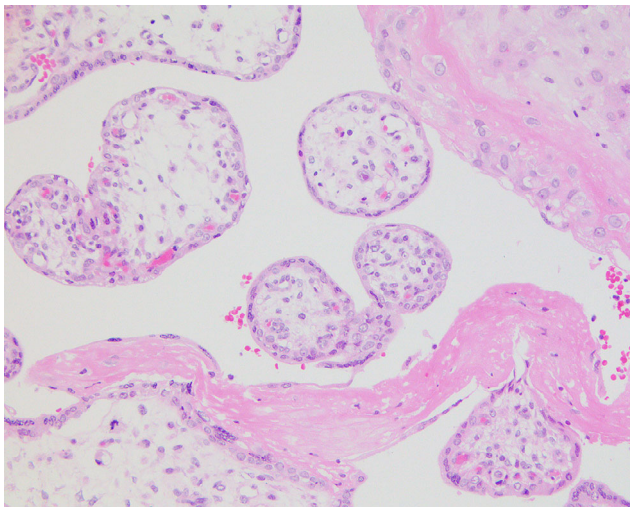

FIGURE 4 Photomicrograph (H&E, ×200). Histological study of the placenta. The villi show a morphology and size in accordance with the gestational stage. There is an increased stromal cellularity at the expense of Hofbahuer cells. CMV intranuclear inclusions are observed.

4 | DISCUSSION

In this case we present a prenatal diagnosis of maternal CMV primary infection with fetal involvement that culminated in a voluntary termination of pregnancy. The autopsy showed the classic owl's eye-shaped viral inclusion in almost all fetal organs. Viral placental inclusions were also observed, without signs of intervillositis.

Similar to other *Herpesvirus*, CMV enters a latent state after first acute infection and can suffer a reactivation at any time of life. When a pregnant woman without antibodies is exposed to CMV, the chances of acquiring primary infection are 40%, with a risk of fetal transmission of approximately 10%. On the other hand, the risk of fetal transmission following a reactivation is <0.05%. Although the mechanism of vertical transmission is not clearly defined, it seems to be related to the active replication of the virus at the level of the maternally derived decidua, which generates a reservoir of viral load that predisposes to its passage through the fetoplacental barrier.[9] Other authors propose virus replication in cytotrophoblasts as one of the causes of altered development of new villi and the appearance of placental fibrosis.[10] In our case, the placenta showed marked fibrosis, which we attributed to this mechanism.

Regarding intracranial findings, our patient presented a brainstem hemorrhage. There are publications in which similar findings have been documented.[11,12]

The occurrence of fetal intracranial hemorrhage during pregnancy can have multiple etiologies, including trauma, seizures, hypoxia, autoimmune thrombocytopenia, coagulation disorders, drugs, maternal vitamin K deficiency, preeclampsia, placental disorders, maternal–fetal or fetal–fetal transfusion, umbilical cord thrombosis or twisting, and congenital infections, including toxoplasmosis and CMV.[13] In our case, the anamnesis, detailed physical examination and maternal serology and laboratory tests reasonably excluded all the previously mentioned causes.

Although in our case intracranial hemorrhage could not be reliably demonstrated in the ultrasound scans performed during pregnancy, we believe that this was due to the fact that the hemorrhage was of limited thickness and that it is a difficult finding to diagnose. We believe that there are several facts that allow us to attribute the etiology of the hemorrhage to congenital CMV infection and not to the delivery itself: first, the abortion was

atraumatic and not instrumented. Second, the brainstem is an infrequent location for birth-associated traumatic injuries in the newborn. Third, no traumatic lesions were found in any other organ of the patient, including the rest of the central nervous system. Fourth, this finding has previously been attributed to congenital CMV infection.

The main hypothesized pathophysiological mechanisms that may be involved in the development of the intracranial hemorrhage are direct neuronal damage and central nervous system vasculitis without coagulopathy, with associated thrombotic and hemorrhagic processes.

In relation to neuronal damage, this hypothesis is supported by the neurotropism of the virus itself, especially in the first months of gestation, and by the fact that the finding of cortical, hippocampal, and cerebellar dysplasia in cases of congenital CMV infection is well documented.

Regarding the possible associated infectious vasculitis, it has been documented more clearly in extreme premature infants. This in turn leads to diagnostic difficulty, since these patients present hemorrhagic diathesis in relation to thrombocytopenia, prothrombotic alterations, and metabolic alterations due to their physiological immaturity.[11] The authors note the importance of considering congenital CMV infection in the diagnosis of fetal intracranial hemorrhage during pregnancy. Although other authors have recently reported vascular pathology in the context of intracranial hemorrhage in the fetus with CMV infection,[12] in our case we did not observe vascular pathology in the central nervous system. The pathophysiological mechanisms that can potentially cause this damage are not known, nor have specific patterns of vascular damage been described to date, except from retinal vascular changes similar to retinopathy of prematurity.[14]

We believe that there may be other etiopathogenic mechanisms that may have contributed to the development of hemorrhage that are not known to date.

In relation to polymicrogyria, although there is no mechanism described, there are several publications in which this finding has been documented in patients with congenital CMV infection.[15,16] This finding appears to be concomitant with signs of cortical dysplasia, radial glial lesions, cortical plate atrophy and neuronal heterotopia.[17] Although due to the infrequency of this pathology it is not possible to establish a real estimated incidence, in several of the series described, polymicrogyria has been found to be a frequent finding in the context of congenital CMV infection.[17]

At present, serological CMV infection screening prior to or during pregnancy is not currently routinely indicated. The request for the study should be individualized according to the risk factors and clinical situation of each patient.[18]

There is currently no vaccine for CMV. However, primary, secondary, and tertiary prevention is possible. To give an example, a study has recently been published in which a reduction of up to 71% in the vertical transmission of CMV in pregnant patients with primary infection after taking oral valacyclovir was observed.[19] Similarly, a recent study has shown that bimonthly administration of hyperimmunoglobulin in maternal CMV primary infections decreases maternal–fetal transmission of the virus.[20] In patients who do not wish to have a voluntary termination of pregnancy, treatment with Ganciclovir for at least 6 months is the treatment of choice in children with moderate to severe symptomatic CMV infection at birth. It has been shown to reduce the risk of sensorineural hearing loss and improve Denver II test scores during the first 12 months of life.[1]

In conclusion, the finding of neuropathological alterations secondary to congenital CMV infection is extensive and the precise mechanisms of injury are not known. The detailed description of clinical presentations not previously described, such as the present one—in which polymicrogyria and an isolated hemorrhage in the brainstem without associated vascular pathology and without intraparenchymal hemorrhage were found—can contribute to expand the knowledge about this entity and its potential lesional mechanisms.

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Permission was obtained from the patient's parents for presentation.

CONFLICT OF INTEREST

There is no conflict of interest or external funding to declare. None of the authors have anything to disclose.

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REFERENCES

1. Patel P. Congenital infections of the nervous system. *Continuum*. 2021;27(4):1105-1126. doi:10.1212/CON.0000000000000991
2. Ssentongo P, Hehnly C, Birungi P, et al. Congenital cytomegalovirus infection burden and epidemiologic risk factors in countries with universal screening: a systematic review and meta-analysis. *JAMA Netw Open*. 2021;4:e2120736. doi:10.1001/jamanetworkopen.2021.20736
3. Dinsmoor MJ, Fette LM, Hughes BL, et al. Amniocentesis to diagnose congenital cytomegalovirus infection following maternal primary infection. *Am J Obstet Gynecol MFM*. 2022;5:100641. doi:10.1016/j.ajogmf.2022.100641
4. Périllaud-Dubois C, Belhadi D, Laouénan C, Mandelbrot L, Picone O, Vauloup-Fellous C. Current practices of management of maternal and congenital cytomegalovirus infection during pregnancy after a maternal primary infection occurring in first trimester of pregnancy: systematic review. *PLoS One*. 2021;16(12):e0261011. doi:10.1371/journal.pone.0261011
5. Kasuga M, Yoshimura H, Shinagawa J, Nishio SY, Takumi Y, Usami SI. Frequency and natural course of congenital cytomegalovirus-associated hearing loss in children. *Acta Otolaryngol*. 2021;141(12):1038-1043. doi:10.1080/00016489.2021.2000638
6. Kadambari S, Williams EJ, Luck S, Griffiths PD, Sharland M. Evidence based management guidelines for the detection and treatment of congenital CMV. *Early Hum Dev*. 2011;87(11):723-728. doi:10.1016/j.earlhumdev.2011.08.021
7. Navti OB, Al-Belushi M, Konje JC. FRCOG. Cytomegalovirus infection in pregnancy: an update. *Eur J Obstet Gynecol Reprod Biol*. 2021;258:216-222. doi:10.1016/j.ejogrb.2020.12.006
8. Duncan JR, Schenone MH, Argoti PS, Mari G. Middle cerebral artery peak systolic velocity in perinatal cytomegalovirus infection. *J Clin Ultrasound*. 2019;47(6):372-375. doi:10.1002/jcu.22715
9. Megli CJ, Coyne CB. Infections at the maternal–fetal interface: an overview of pathogenesis and defence. *Nat Rev Microbiol*. 2021;20:67-82. doi:10.1038/s41579-021-00610-y

10. Auriti C, De Rose DU, Santisi A, et al. Pregnancy and viral infections: mechanisms of fetal damage, diagnosis and prevention of neonatal adverse outcomes from cytomegalovirus to SARS-CoV-2 and Zika virus. *Biochim Biophys Acta Mol Basis Dis*. 2021;1867(10):166198. doi:10.1016/j.bbadis.2021.166198
11. Capasso L, Coppola C, Vendemmia M, et al. Severe fetal intracranial hemorrhage: congenital cytomegalovirus infection may play a role? A case report and review of literature. *IDCases*. 2021;25:e01188. doi:10.1016/j.idcr.2021.e01188
12. de Vrijer B, Crowley D, Cosma D, Muscedere G, Hammond R. Congenital CMV infection presenting with massive intracerebral hemorrhage. *Clin Neuropathol*. 2021;40:341-346. doi:10.5414/NP301341
13. Society for Maternal-Fetal Medicine (SMFM), Monteagudo A. Intracranial hemorrhage. *Am J Obstet Gynecol*. 2020;223(6):B34-B37. doi:10.1016/j.ajog.2020.08.183
14. Ozen Tunay Z, Derme T, Erginturk Acar D, Beser E. Retinal findings similar to retinopathy of prematurity in a term-infant with congenital cytomegalovirus infection. *Eur J Ophthalmol*. 2021;12. doi:10.1177/11206721211039344
15. Hranilovich JA, Park AH, Knackstedt ED, et al. Brain magnetic resonance imaging in congenital cytomegalovirus with failed newborn hearing screen. *Pediatr Neurol*. 2020;110:55-58. doi:10.1016/j.pediatrneurol.2020.05.006
16. Vande Walle C, Keymeulen A, Schiettecatte E, et al. Brain MRI findings in newborns with congenital cytomegalovirus infection: results from a large cohort study. *Eur Radiol*. 2021;31:8001-8010. doi:10.1007/s00330-021-07776-2
17. Teissier N, Fallet-Bianco C, Delezoide AL, et al. Cytomegalovirus-induced brain malformations in fetuses. *J Neuropathol Exp Neurol*. 2014;73(2):143-158. doi:10.1097/NEN.0000000000000038
18. Gerna G, Fornara C, Furione M, Lilleri D. Congenital human cytomegalovirus infection: a narrative review of maternal immune response and diagnosis in view of the development of a vaccine and prevention of primary and non-primary infections in pregnancy. *Microorganisms*. 2021;9(8):1749. doi:10.3390/microorganisms9081749
19. Tol I, Heath PT, Khalil A. Prevention strategies for congenital cytomegalovirus infection. *Curr Opin Infect Dis*. 2021;34(5):546-551. doi:10.1097/qco.0000000000000777
20. Kagan KO, Enders M, Schampera MS, et al. Prevention of maternal-fetal transmission of cytomegalovirus after primary maternal infection in the first trimester by biweekly hyperimmunoglobulin administration. *Ultrasound Obstet Gynecol*. 2019;53:383-389. doi:10.1002/uog.19164

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