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CONGENITAL CYTOMEGALOVIRUS INFECTION IN PREGNANCY - AN OVERVIEW OF THE FETAL ABNORMALITIES DETECTED BY ULTRASOUND

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Abstract: *Cytomegalovirus (CMV) is a DNA virus, which affects all ages individuals. During the intrauterine life, CMV can affect the foetus and can produce severe morphological abnormalities, especially in the brain structure, leading to various neurosensorial deficiencies after birth. This study aims to demonstrate the utility of ultrasonography in identifying and establishing the long-term prognosis of the foetuses with CMV congenital infection. After a systematic review of the last 10 years literature, fifteen articles were considered from the databases for this study. The most frequently detected abnormalities are represented by periventricular cerebral calcifications, ventricular dilatations, cerebellar hypoplasia, leukomalacia, microcephaly, foetal ascites, ventricular septal defects, intrauterine growth restriction, oligoamnios or anamnios. These pathological aspects could influence the evolution of the foetuses, their long-term development and could also produce intrauterine death of the foetus. Also, the addition of MRI increases the power of ultrasound for the diagnosis of cerebral damages. These techniques could be complementary, but they should not exclude each other in exposed foetuses.*

Keywords: *cytomegalovirus, congenital infection, ventriculomegaly, neurological deficiencies.*

1. Introduction

Cytomegalovirus (CMV) is defined as a common infectious agent, which has a great adaption to the host. On the evolutionary scale, CMV produced a series of immune evasion genes, which allowed the virus to persist into the organism in a latent state, and to infect other individuals with normal immune system, without producing any symptomatology [18]. Considering that CMV is an essential pathogenic agent widespread in the entire world that affects immunocompromised individuals, in the last decades, novel diagnostic tools for the detection of this

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pathogenic agent have been developed. CMV infection is considered when CMV or viral proteins are detected in different body fluid, such as blood, serum, plasma, urine, or even tissues [27].

This virus is the most representative beta herpesvirus and represents the leading cause of infectious congenital disabilities. The nucleocapsid consists of a 230 kb double-stranded DNA, enclosed by a lipid double layer. The symptoms appear following primary infection, reactivation, or reinfection [1]. Regarding the congenital infection, in almost 10% of cases, the infection is diagnosed after approximately six months from the maternal transmission via placental circulation or by breastfeeding [3]. In the USA, the prevalence of congenital infection varies between 0.5/1000 and 1.5/1000 live births [19]. Intrauterine infection is suspected in foetuses with intrauterine growth restriction, microcephaly, and intracerebral calcifications, detected by ultrasound. All these modifications may lead to cerebral palsy, mental retardation, visual defects, hearing loss, or seizures after birth [9]. In most of the cases, the sequelae occur when the primo infection happens in the first or the second trimester [35].

Congenital infections with CMV represent one common cause of hearing loss and neurological deficiencies. For this reason, intrauterine diagnosis and prognosis represent a significant challenge for the obstetricians, and the principal diagnostic tool is represented by ultrasonography. Moreover, some subtle findings could be discovered by ultrasound examination, but their value for the prognosis is still controversial [25].

The primary objective of the ultrasonography is to observe if high-risk foetuses developed any morphological anomalies of the central nervous system. Cytomegalovirus has a neurotrophic effect, which may generate a reduced proliferation and incomplete migration of the neurons and in some cases, abnormal neuronal distribution within the cortex. The inflammation induced by this virus at the level of astroglia can generate some neurotoxic factors, which can cause calcification or necrosis areas in the foetal brain [11]. The detection as soon as possible of these morphological brain anomalies related to the CMV intrauterine infection is crucial because it may permit the termination of pregnancy in countries where this action is possible before 24 weeks of gestation and may predict long-term outcomes of the pregnancy [14]. The majority of the brain abnormalities could be identified in the third trimester using ultrasonography and MRI. Few studies compared the efficiency of ultrasonography and MRI in the detection of cerebral abnormalities induced by CMV infection and concluded that these methods are complementary and MRI may provide a piece of additional information compared to those observed by ultrasonography [22].

2. Objective

This study aims to evaluate the efficiency of ultrasonography in the diagnosis and prognosis of foetuses with congenital infection with CMV. We also aim to evaluate the outcome of the babies with and without abnormal ultrasound findings and to compare with abnormal magnetic resonance findings.

3. Material and Method

After a systematic review, we identified epidemiological studies, clinical cases, and meta-analysis regarding congenital infection with CMV and the

ultrasonographic features of the affected foetuses. Thirty-five articles initially selected were considered from databases (PubMed, Google Academic, and Cross Ref) for this study, but only 15 fitted the area of interest of this review, gathering recent statistics. Relevant articles were selected by using the Mesh keywords: cytomegalovirus, congenital infection, ventriculomegaly, and neurological deficiencies.

4. Results and Discussion

In the last decades, the transmission of CMV has been well documented in cases of blood transfusions, organ replacement, and last but not least in pregnancy infections [45]. In addition, the horizontal transmission of the virus is carried out by other infected body fluids such as saliva and urine. The vertical transmission of the virus could be produced transplacental during the pregnancy, intrapartum when the fetus takes contact with the cervical and vaginal infected secretions and postpartum, through breastfeeding. The most important route of transmission is considered the transplacental way, which frequently leads to foetal neurological abnormalities [3]. The infection may be initially asymptomatic when the neonates will develop long-term sequelae, or symptomatic, which evolves towards both short and long term psychomotor impairments [17], [21].

Considering the gestational age since contacting the virus, there is a directly proportional relationship between the rate of maternal transmission and the gestational age. In addition, the lower the gestational age is at the moment of infection, the higher is the risk for symptomatic infection [7], [16]. An interesting aspect of the primary infection with CMV in pregnancy is that the transmission rate to the foetus is yet undefined around the time of conception, both pre- and periconceptional. Also, periconceptional primo infection with this virus increases the risk of an unfavorable outcome, compared to pre-conceptional infection. For this reason, in these cases, adequate counselling should be adjusted accordingly [40].

The result of a study conducted by Kenneson and coworkers [21] showed that the prevalence of foetal infection in women with primary acquired infection during pregnancy is 14,2%, and in women with recurrent infection, the prevalence is ten times lower, of almost 1.4%. Several studies showed that the placenta is infected in almost all the cases with CMV primo infection in pregnancy, whether the foetus is affected or not. So, the placenta may be considered having a central role either in the foetal protection against infection or in the transmission of the virus, being a sizeable viral deposit.

Regarding the diagnosis tools, polymerase-chain-reaction (PCR) is considered the most sensitive method for virus detection. It is a quantitative method, which can detect the viral DNA into the amniotic fluid, and it reflects the viral load. The accuracy of the diagnosis usually depends on the gestational age. The sensitivity of PCR from the amniotic fluid is almost 30% before 21 weeks of gestation and jumps to 71% after 21st weeks [23]. Usually, the virus reaches the foetal kidneys after approximately seven weeks from the infection, so that the viral DNA will be present in the amniotic fluid only after 21 weeks of pregnancy and after the latent period. Due to the difficulties of the serological diagnosis and the lack of typical findings, serological investigations for CMV infection in pregnant or pre-conceptional women is not imposed by the medical protocols [34].

Foetal blood and amniotic fluid can be both used for the diagnosis of congenital infection with CMV. The foetal blood is collected from the umbilical cord, and specific IgM antibodies against CMV are being dosed. Furthermore, the viral load and the biochemical and haematological parameters should be correlated with the immunological status. High values of IgM, associated with the ultrasound appearance and biochemical status (high alanine aminotransferase (ALT/ALAT/ GPT) levels over 80 U/L, thrombocytopenia (less than 100,000 cells/mm3), and hyperbilirubinemia (up to 2 mg/dL) usually leads to a poor prognosis [8], [16].

The screening for transplacental foetal infection, it is still controversial and widely discussed [32]. The screening may prevent congenital infections, and pregnant women must be informed to avoid all the sources of infection. The efficiency of CMV infection screening at the first prenatal visit was evaluated by Naessens and coworkers, and they showed that this procedure allows the detection of CMV infections in 82% of cases [31].

In affected women, the certification of foetal infection is usually possible by non-invasive (ultrasound examination) and invasive (amniocentesis) prenatal tests. Ultrasound is a non-invasive method of examination with high potential to detect any morphological abnormalities caused by this pathological agent. Its decreased sensitivity represents the main drawback of this technique, which allows the identification of no more than 5% of infected foetuses [44].

Ultrasound only allows the detection of severely affected babies with obvious ultrasonographic anomalies. Meanwhile, more subtle features is possible not to be observed. Furthermore, a regular ultrasound examination revealed by a foetus with a high risk of infection cannot predict a normal outcome.

CMV is a neurotropic virus, which spreads through the bloodstream, goes to the choroid plexus and replicates in the cerebrospinal fluid, capillary endothelium or into the germinal matrix. The damages produced at the level of the germinal matrix, usually result in neuronal migration defects, which lead to severe cerebral malformation. Also, the damage of the capillaries can produce thrombosis and secondary cerebral infarction [33]. The prognosis of the affected foetuses depends on the severity of the brain damages. The impairments in the neuro-psychiatric development cover a multitude of affections, from minor intellectual deficits to severe ones, such as mental retardation. Some of the most dangerous affections are the neurosensorial deafness (0.4-2.3% of live births), secondary to the cochlear damage, blindness, secondary to severe chorioretinitis or developmental verbal dyspraxia [12], [46, 47]. Among the infected neonates, from 90 to 95% do not present any clinical sign at birth, but almost 30% could develop late complications, during the first year [41].

Ultrasound could be a useful tool in the diagnosis of the infection because it reveals the modifications of the foetus and the placenta. The most typical ultrasound aspects, which indicate a possible foetal infection, are divided into two categories, cerebral and extracerebral changes. In many cases, congenital CMV infection remains undetected by routine ultrasound [26]. The most frequent morphological brain abnormalities consist of intracranial calcifications, ventriculomegaly (> 15 mm), periventricular hyperechogenicity, hydrocephaly, microcephaly (< 2DS), enlarged cisterna magna (> 8 mm), hypoplasia of the vermis, porencephaly,

lissencephaly, corpus callosum agenesis, and, sometimes, periventricular pseudocysts. Also, intrauterine growth restriction, ascites, hyperechogenic bowel, pleural effusion, oligohydramnios, microcephaly, or liver calcifications may be identified as ultrasonographic signs for foetal infection [8], [24], [28].

A study conducted by Drose et al. [15] that used the ultrasonographic approach on 19 foetuses with suspected congenital CMV infection reported that only 5 of them presented central nervous system ultrasonographic damages. The findings included periventricular calcifications, microcephaly, and abnormal cerebral structure. From all these foetuses, three died immediately after the birth, one died at 23 weeks of pregnancy, and only one survived, but its prognosis was unfavorable because he had hearing loss and presented developmental delay.

Porencephaly is a rare congenital disorder described as multiple cavities filled with CSF that results in cystic degeneration and encephalomalacia, and the formation of porencephalic cysts [6]. After birth, this affection might generate a poor prognosis, due to foetal hypotony, spastic contraction, spastic hemiplegia, cognitive impairments, lack of language development, growth retardation and developmental delay of the infected foetus. Moinuddin et al. [30] reported some ultrasound findings in a foetus with intracranial haemorrhage and porencephaly, presumed to be secondary to congenital CMV infection. The authors also correlated the ultrasonographic findings with magnetic resonance imaging findings. The investigators observed that the ultrasonographic image revealed multiple parenchymal cysts of the brain associated with porencephaly of the temporal and parietal region. They concluded that ultrasonography is an efficient diagnostic tool for the evaluation of the brain damages produced by CMV infection.

Doneda et al. [14] conducted another study in order to show the diagnostic and prognostic value of foetal cerebral ultrasound compared to MRI, in affected fetuses. Thirty-eight foetuses with certified infection were examined using serial ultrasonography and MRI. Their results showed that both ultrasound and MRI findings were normal in 47% of cases. In 47% of the affected pregnancies, MRI generated some additional information, being better in the detection of polar temporal lesions, microencephaly, and cortical anomalies, compared to ultrasound. Both ultrasound and MRI were sensitive but had a low positive predictive value of the lesions, which may substantially influence the prognosis of foetal infection.

In other two studies [5], [37], the authors compared the ultrasonographic and MRI findings in early pregnancies presumed to be infected with CMV. In the first study [5], MRI was performed at 31 weeks of pregnancy, and the authors did not describe polar temporal lesions. Also, they did not highlight any difference between ultrasound and MRI findings. In the second study [37] were included 38 foetuses with congenital CMV infection, from which only 23 cases performed an MRI before 25 weeks of gestation. Their results showed that MRI provided additional information regarding the damages of the cerebral substance.

Tassin and coworkers [42] also reported some ultrasonographic findings in three cases of congenital CMV infection, such as periventricular hyperechogenic areas, small cerebellum, ventriculomegaly, distortion of the morphology of the cerebral structures. Moderate to severe cerebral findings are moderate

ventriculomegaly (10-15 mm), interventricular synechiae, cerebral calcifications, subependymal and choroid cysts, basal ganglia calcification, especially in the arterial endothelium. Basal ganglia calcification can be physiologically found in elder individuals, as a sign of aging, but when it is found in newborns, it has a pathological meaning, suggesting congenital CMV infection [2]. The vessels that supply the basal ganglia are not usually conspicuous on the cranial ultrasonography of the foetuses. Analysing the ultrasonography of five babies with congenital CMV infection, Teele and colleagues [43] observed that they had abnormally echogenic or "bright" vessels on cranial sonograms. They concluded that ultrasound might be useful in the detection of non-calcific inflammation and mineralization in vasculitis, as a sign for CMV infection.

Corpus callosum agenesis consists in the absence of the part that connects the cerebral hemispheres and may be secondary to congenital CMV infection between 12 and 22 weeks of gestation. An epileptic episode in the first few weeks of life may draw attention to this condition if CMV infection is presumed. Mehta et al. [29] performed a case presentation of a baby with confirmed infection with the cytomegalic virus that also had corpus callosum agenesis, certified by ultrasound scanning and MRI. So, a proposed causative link between agenesis of the corpus callosum and congenital CMV infection may be discussed.

Lissencephaly represents a cerebral defect described as a thickened cerebral cortex with few and large gyri and is results from abnormal migration of the neurons in the cortex. When the infection with CMV occurs between the 9th and 12th week of gestation, lissencephaly may suggest the intrauterine infection with CMV [20]. Barkovich and coworkers [4] analyzed the cortical gyral patterns, myelination patterns, and focal brain lesions on 11 foetuses with confirmed congenital CMV infection. Lissencephaly was found in four patients, and the imagistic pattern consisted of small cerebellum and enlarged ventricles. In addition, five patients with variable small cerebellum and slightly enlarged ventricles presented foci of dysplastic cortex. The authors postulated that the association between a small cerebellum and myelination delay areas, associated with diffuse lissencephaly, could suggest the diagnosis of congenital CMV infection.

Achiron et al. [1] reported the case of a foetus diagnosed with congenital CMV infection at 30 weeks of pregnancy. The imagistic findings revealed ventriculomegaly, subependymal cysts, bilateral synechiae into the occipital horns, and some abnormal hyperechogenic foci. So, the use of ultrasound on foetuses with congenital CMV infection enables a good and detailed image of the brain structure, allows a detailed study of the brain structures, and can predict the outcomes of the babies.

Along with the foetal cerebral damages, CMV infection may also induce extracerebral anomalies, which can be observed by ultrasonography, such as hyperechogenic bowel, hepatomegaly especially of the left hepatic lobe, which appears more than 40 mm, intrahepatic calcifications, IUGR, oligohydramnios, polyhydramnios, ascites, pleural effusion, subcutaneous oedema, hydrops or enlargement of the placenta [13].

Ayoubi et al. [38] conducted a study on 69 affected foetuses, and analysed the prenatal ultrasound findings. Ultrasound modifications were reported in 30 cases, as follows: 16 cases had both cerebral and

extracerebral abnormalities, 10 cases had only unusual brain features, and purely extracerebral features were described in only two cases. Nineteen cases had extracerebral features, and the most common were hyperechogenic bowel and intrauterine growth restriction.

Peters and coworkers [36] also presented the case of a primigravida with abnormal serologic results at 18 gestational weeks, and a positive result for CMV infection. The serial ultrasonographic scan of the foetus revealed intrauterine growth restriction, hydrops fetalis, and hyperechoic foetal bowel. The prognosis was deplorable and foetal death occurred at 32 gestational weeks.

Yamashita et al. [48] made the first report of a foetus of 20 gestational weeks with congenital CMV infection, and ultrasonography revealed ascites and intrahepatic calcifications. The foetus lungs were decompressed by aspiration, and after the birth, the newborn did not present hypoplasia of the lungs or any other respiratory complications. Therefore, the careful serial ultrasound monitoring of the foetuses with CMV infection is necessary for a good prognosis.

In order to predict the long-term prognosis of the infected foetuses, it is necessary to evaluate the clinical manifestation after birth and to find out the main cause for the cerebral injury. Inflammatory infiltration of the CNS or hypoxia due to placental damage are suitable for differential diagnosis in this condition. Only 10 to 15% of the foetuses from mothers with CMV primary infection in pregnancy are symptomatic.

A recent study revealed that 86% of the symptomatic neonates have at least two typical manifestations of CMV infection, the majority is determined by cerebral damages. 12% of the neonates die during the first six weeks of life if the cerebral abnormalities are severe and can be ultrasonographically detected. The mortality rate remains low in asymptomatic neonates, but they usually develop neurosensorial impairment or growth abnormalities [9].

Trans-fontanelar ultrasound, MRI or CT can reveal the neonatal diagnosis of the cerebral damage. Although ultrasonographic examination has multiple advantages, such as repeatability, low costs, and accuracy, there is some drawback linked to examiner's experience, image acquisition, and interpretation. For this reason, MRI is recommended as a complementary investigation in order to identify cerebellar or cortical anomalies [10] produced by CMV, and sometimes MRI may be more accurate compared to ultrasonography.

In conclusion, improving the knowledge of ultrasound findings linked to congenital infection with CMV, the sensitivity of this technique could be improved. Also, understanding why CMV leads to cerebral damages could be an adjunctive factor for the clarification of the pathophysiology of this congenital infection [38].

5. Conclusion

In conclusion, the presence of one or more of the described ultrasonographic foetal abnormalities, mainly when one or more are present in the same foetus, and when the maternal serology is positive for CMV, is an indication for congenital CMV infection. The long-term outcome of congenital infection with no associated abnormalities detected by ultrasound examination and by MRI is favourable. When one or more associated brain damages are discovered, the termination of pregnancy might be justified, but the prognostic value of subtle ultrasound and MRI findings is still controversial, and

further studies are necessary in order to justify the termination of the pregnancy.

Although ultrasonography is a readily available screening tool for congenital infection with significant cerebral involvement, further studies involving larger samples are necessary to determine the role of ultrasonography in the prognosis of isolated lesions of white matter.

References

1. Achiron, R., Pinhas-Hamiel, O., Lipitz, S., Heiman, Z., Reichman, B., Mashiach, S.: *Prenatal ultrasonographic diagnosis of fetal cerebral ventriculitis associated with asymptomatic maternal cytomegalovirus infection.* In: Prenat Diagnosis (1994**),** Vol**.** 14(7), p. 523-526.
2. Adams, A.E.: *Basal ganglia calcification. Characteristics of CT scans and clinical findings.* In: Neurosurg Rev. (1980) Vol. 3(3), p. 201-203.
3. Azam, A.Z., Vial, Y., Fawer, C.L., Zufferey, J., Hohlfeld, P.: *Prenatal diagnosis of congenital cytomegalovirus infection.* In: Obstet Gynecol. (2001) Vol**.** 97(3), p. 443-448.
4. Barkovich, A.J., Lindan, C.E.: *Congenital cytomegalovirus infection of the brain: imaging analysis and embryologic considerations.* In: Am J Neuroradiol. (1994), Vol. 15 (4), p. 703-715.
5. Benoist, G., Salomon, L.J., Mohlo, M., Suarez, B., Jacquemard, F., Ville, Y.: *Cytomegalovirus related fetal brain lesions: comparison between targeted ultrasound examination and magnetic resonance imaging*. Int: Ultrasound Obstet Gynecol. (2008) Vol. 32 (7), p. 900 – 905.
6. Bianchi, D.W., Crombleholme, T.M., D'Alton, M.E.: *Fetology, diagnosis & management of the fetal patient.* McGraw-Hill Professional, 2000. Available online on https://radiopaedia.org/articles/porencephaly
7. Bodéus, M., Kabamba-Mukadi, B., Zech, F., Hubinont, C., Bernard, P., Goubau, P.: *Human cytomegalovirus in utero transmission: follow-up of 524 maternal seroconversions.* In: J Clin Virol. (2010) Vol**.** 47(2), p. 201-202.
8. Bonalumi, S., Trapanese, A., Santamaria, A., D'Emidio, L., Mobili, L.: *Cytomegalovirus infection in pregnancy: review of the literature.* In: J Prenat Med. (2011) Vol. 5(1), p. 1-8.
9. Boppana S.B., Pass, R., Britt, W., Stagno, S., Alford, C.: *Symptomatic congenital cytomegalovirus infection: neonatal mortality and morbidity.* In: Pediatr Inf Dis J. (1992), Vol. 11(2), p. 93-99.
10. Carpretti, M.G., Lanari, M., Tani, G. et al.: *Role of cerebral ultrasound and magnetic resonance imaging in newborns with congenital cytomegalovirus infection.* In: Brain Dev. (2014) Vol. 36 (3), p. 203-211.
11. Cheeran, M.C., Lokensgard, J.R., Schleiss, M.R.: *Neuropathogenesis of congenital cytomegalovirus infection: disease mechanisms and prospects for intervention.* In: Clin Microbiol Rev. (2009**)** Vol. 22 (1), p. 99–126.
12. Damago, E.G., Winnen, C.W.: *Cytomegalovirus infection: perinatal implications*. In: J Obstet Gynecol Neonatal Nurs. (2002**)** Vol**.** 31(1), p. 86-92.
13. Degani, S.: *Sonographic Findings in Fetal Viral Infections: A Systematic Review*. In: Obstet Gynecol Survey. (2006) Vol**.** 61(5), p. 329-336.
14. Doneda, C., Parazzini, C., Righini, A., Rustico, M., Tassis, B., Fabbri, E. et al.: *Early cerebral lesions in Cytomegalovirus infection: prenatal MR imaging.* In: Radiology (2010**),** Vol. 255 (2), p. 613-621.

15. Drose, J.A., Dennis, M.A., Thickman, D.: *Infection in utero: US findings in 19 cases*. In: Radiol. (1991) Vol. 178, p. 369–374.
16. Enders, G., Daiminger, A., Bader, U., Exler, S., Enders, M.: *Intrauterine transmission and clinical outcome of 248 pregnancies with primary cytomegalovirus infection in relation to gestational age.* In: J Clin Virol. (2011)**,** Vol**.** 52(3), p. 244-246.
17. Gaytant, M.A., Steegers, E.A., Semmekrot, B.A., Merkus, H.M., Galama, J.M.: *Congenital cytomegalovirus infection: review of the epidemiology and outcome.* In: Obstet Gynecol Surv (2002**)** Vol**.** 57(4), p. 245-256.
18. Griffiths, P.D., Whitley, R.J.: *Cytomegalovirus*. In: Pract Guidelines Antiviral Ther (2002), p**.** 151-171.
19. Hanshaw, J.B. *Congenital cytomegalovirus infection: a 15 year perspective.* In: J Infect Dis. (1971), Vol. 123, p. 555-561.
20. Hayward, J.C., Titelbaum, D.S., Clancy, R.R., Zimmerman, R.A.: *Lissencephaly-pachygyria associated with congenital cytomegalovirus infection*. In: J Child Neurol. (1991), Vol. 6, p.109-114.
21. Kenneson, A., Cannon, M.J.: *Review and meta-analysis of the epidemiology of congenital cytomegalovirus (CMV) infection.* In Rev Med Virol *(*2007) Vol**.** 17(4), p. 253-276.
22. Levine, D.: *Fetal magnetic resonance imaging*. In: J Matern Fetal Neonatal Med. **(**2004) Vol. 15 (2), p. 85–94.
23. Liesnard, C., Donner, C., Brancart, F., Gosselin, F., Delforge, M.L., Rodesch, F.: *Prenatal diagnosis of congenital cyto-megalovirus infection: prospective study of 237 pregnancies at risk.* In: Obstet Gynecol. (2000) Vol. 95 (6), p. 881-888.
24. Lipitz, S., Achiron, R., Zalel, Y., Mendelson, E., Tepperberg, M., Gamzu, R.: *Outcome of pregnancies with vertical transmission of primary cyto-megalovirus infection.* In: Obstet Gynecol. (2002) Vol. 100 (3), p. 428–33.
25. Lipitz, S., Hoffmann, C., Feldman, B., Tepperberg-Dikawa, M., Schiff, E., Weisz, B.: *Value of prenatal ultrasound and magnetic resonance imaging in assessment of congenital primary cytomegalovirus infection.* In Ultrasound Obstet Gynecol (2010**),** Vol. 36 (6), p. 709-717.
26. Lipitz, S., Yagel, S., Shalev, E., Achiron, R., Mashiach, S., Schiff, E.: *Prenatal diagnosis of fetal primary cytomegalovirus infection*. In: Obstet Gynecol. (1997) Vol. 89 (5), p. 763–767.
27. Ljungman, P., Griffiths, P., Paya, C.: *Definitions of Cytomegalovirus Infection and Disease in Transplant Recipients.* In: Clin Infectious Diseases (2002) Vol. 34(8), p.1094-1097.
28. Malinger, G., Lev, D., Zahalka, N., et al.: *Fetal cytomegalovirus infection of the brain: the spectrum of sonographic findings*. In: Am J Neuroradiol. (2003) Vol. 24 (1), p. 28–32.
29. Mehta, N.M., Hartnoll, G.: *Congenital CMV with callosal lipoma and agenesis.* In: Pediatr Neurol. (2001**)** Vol. 24, p. 222-224.
30. Moinuddin, A., McKinstry, R.C., Martin, K.A., Neil, J.J.: *Intracranial hemorrhage progressing to porencephaly as a result of congenitally acquired cyto-megalovirus infection—an illustrative report*. In: Prenat Diagnosis. (2003**)** Vol**.** 23, p. 797-800.
31. Naessens, A., Casteels, A., Decatte, L., Foulon, W.: A serologic strategy for detecting neonates at risk for congenital cytomegalovirus infection. *J Pediatr.* **2005,** 146(2), 194-197.
32. Nelson, C.T., Demmler, G.J.: *Cytomegalovirus infection in the pregnant mother, fetus, and newborn*

infant. In: Clin Perinatol. (1997) Vol. 24, p.151-160.
33. Neuberger, I., Garcia, J., Meyers, M.L., Feygin, T., Bulas, D.I., Mirsky, D.M.: *Imaging of congenital central system infections.* In: Pediatr Radiol. (2018) Vol**.** 48 (4), p. 513-523.
34. Ornoy, A.: *The effects of Cytomegalic virus (CMV) infection during pregnancy on the developing human fetus*. In: Harefuah (2002**)** Vol**.** 141(6), p. 565-568.
35. Pass, R.F., Fowler, K.B., Boppana, S.B., Britt, W.J., Stagno, S.: *Congenital cytomegalovirus infection following first trimester maternal infection: symptoms at birth and outcome*. In: J Clin Virol. (2006**)**, Vol. 35 (2), p. 216–220.
36. Peters, M.T., Thomas, W.M., Carpenter, A., Kole, S.: *Prenatal diagnosis of congenital cytomegalovirus infection with abnormal triple-screen results and hyperechoic fetal bowel.* In: Am J Obstet Gynecol. (1995**)** Vol**.** 173(3), p. 953-954.
37. Picone, O., Simon, I., Benachi, A., Brunelle, F., Sonigo, P.: *Comparison between ultrasound and magnetic resonance imaging in assessment of fetal cytomegalovirus infection*. In: Prenat Diagn. (2008) Vol. 28 (8), p. 753 – 758.
38. Picone, O., Teissier, N., Cordier, A.G., Vauloup-Fellous, C., Adle-Biassette, H., Matinovic, J. et al.: *Detailed in utero ultrasound description of 30 cases of congenital cytomegalovirus infection.* In: Prenat Diagn. (2014**)** Vol**.** 34, p. 518-524.
39. Revello, M.G., Gerna, G.: *Pathogenesis and prenatal diagnosis of human cytomegalovirus infection.* In: J Clin Virol. (2004) Vol. 29, p.71-83.
40. Revello, M.G., Zavattoni, M., Furione, M., Lilleri, D., Gorini, G., Gerna, G.: *Diagnosis and outcome of preconceptional and periconceptional primary human cytomegalovirus infections.* In: J Infect Dis. (2002) Vol. 186, p. 553-557.
41. Stagno, S., Pass, R.F., Cloud, G. et al.: *Primary cytomegalovirus infection in pregnancy: incidence, transmission to fetus, and clinical outcome*. In: JAMA (1986) Vol. 256 (14), p.1904–1908.
42. Tassin, G.B., Maklad, N.F., Stewart, R.R., Bell, M.E.: *Cytomegalic inclusion disease: intrauterine sonographic diagnosis using findings involving the brain*. In: Am J Neuroradiol. (1991) Vol. 12, p. 117–122.
43. Teele, R.L., Hernanz-Schulman, M., Sotrel, A.: *Echogenic vasculature in the basal ganglia of neonates: a sonographic sign of vasculopathy.* In: Radiol. (1988**)** Vol**.** 169 (2), p. 423-427.
44. Ville, Y. *The megalovirus*. In: Ultrasound Obstet Gynecol. (1998) Vol. 12, p. 151-153.
45. Wilhelm, J.A., Matter, L., Schopfer, K.: *The risk of transmitting Cytomegalovirus to patients receiving blood transfusions.* In: J Infectious Diseases (1986) Vol.154, p.169-171.
46. Williamson, W.D., Desmond, M.M., LAFevers, N., Taber, L.H., Catlin, F.I., Weaver, T.G.: *Symptomatic congenital cytomegalovirus. Disorders of language, learning, and hearing.* In: Am J Dis Child. (1982) Vol. 136, p. 902-905.
47. Witters, I., Van Ranst, M., Fryns, J.P.: *Cytomegalovirus reactivation in pregnancy and subsequent isolated bilateral hearing loss in the infant*. In: Genet Couns. (2000) Vol. 11, p. 375-378.
48. Yamashita, Y., Iwanaga, R., Goto, A., Kaneko, S., Yamashita, F., Waseda, N., et al.: *Congenital Cytomegalovirus Infection Associated with Fetal Ascites and Intrahepatic Calcifications*. In: Acta Paediatr. (1989**)** Vol**.** 78(6), p. 965-967.