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INFECÇÃO PELO CITOMELOGÁVIRUS NA GESTAÇÃO

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ABSTRACT

Congenital cytomegalovirus (CMV) infection is the leading cause of infectious congenital defects and disabilities. Its transmission can occur in primary and non-primary infections; however, the transmission rate is considerably higher in primary infections. The diagnosis of congenital infection is complex, and there is a discussion concerning serological evaluation during pregnancy. This article aims to review the literature concerning CMV infection, its diagnosis and epidemiology.

Key words: pregnancy; cytomegalovirus; cytomegalovirus infections.

INTRODUCTION

Cytomegalovirus (CMV) is widely distributed among humans. As other viruses of the Herpesviridae family, it causes a primary infection and then remains latent in the body. Despite causing a usually harmless primary infection, CMV can be life-threatening for immunocompromised patients and can cause serious fetal damages. Hence, infection in pregnant women assumes high importance.

Congenital CMV infection is the main cause of infectious congenital defects and disabilities, being the most frequent congenital infection in the United States. The infection can be asymptomatic or cause severe hearing loss, microcephaly, hydrocephaly and neurological impairments. Pregnant women can transmit the virus to the fetus in case of either a primary infection, a reactivation of a latent infection or a secondary infection. Vertical transmission can either occur after a primary or a secondary infection. In both situations, the fetal infection is important to guide the correct treatment and to enable the early detection of any sequelae.

PATHOGENESIS

CMV, also known as human herpesvirus 5 (HHV-5), belongs to the Herpesviridae family and is a double-stranded deoxyribonucleic acid (DNA) enveloped virus. It is capable of infecting most of the body cells and acting in the cytoplasm and the nucleus of the infected cells, forming inclusions.

CMV presents the capacity to evade the immune system and, through that mechanism, it remains latent in the body. When the host faces a situation of immunosuppression (such as pregnancy, chemotherapy, acquired immunodeficiency syndrome [Aids], amongst others), the virus can reactivate from latency and infected cells shed infectious virus.

The primary infection is often silent or subclinical, and during the period of an infection (primary or secondary), the host excretes viral particles in urine, blood, semen and saliva. Therefore, people can be easily infected (including pregnant women) by person-to-person contact, sexual contact or taking care of young infected children.

Vertical transmission can either occur after a primary or a secondary infection. In both situations, the fetal infection...
may occur after infected leucocytes reach the fetus through the placenta. Moreover, CMV can infect the placenta itself creating a contamination in the amniotic fluid, which is then swallowed by the fetus (20).

SCREENING AND DIAGNOSIS OF CONGENITAL INFECTION

Although the detection of maternal anti-CMV antibodies is easy to perform, there is still no consensus about serological screening during pregnancy (21). While some European and Asian countries recommend it, in other countries, such as Brazil, the screening of CMV is not mandatory (22).

As the primary infection is commonly subclinical, it is hard to determine its outset. Normally, positive immunoglobulin class M (IgM) antibodies indicate an acute and recent infection, whereas positive immunoglobulin class G (IgG) antibodies indicate a past infection.

Furthermore, IgM can remain positive for several months making it difficult to establish the time of infection (23). IgM can also reappear in case of a secondary infection, a reactivation of a past infection, or in consequence of cross-reactivity to other viroses (24).

In cases with a dubious diagnosis, it is recommended to perform an IgG avidity assay. This test shows the strength with which the antibody binds to the antigen (25). At the beginning of infection, the produced IgG shows a low avidity for the virus that increases within weeks after exposure to the antigen. Thus, acute and recently produced IgG molecules show low avidity (below 35%), whereas in past infections IgG presents high avidity (above 60%) (26, 27). Unfortunately there is still an area of uncertainty, when avidity falls into a gray zone (between 35% and 60%). Follow-up samples should be requested in order to better define the level of avidity, as it is a dynamic process and avidity values can change in three to four weeks. Therefore, the IgG avidity assay is very useful to determine the time of infection and may help to avoid unnecessary worries.

Serological evaluation is also important to identify seronegative pregnant women in order to prevent seroconversion. Although there is no vaccine available to prevent CMV infection, simple measures (such as hand washing after contact with saliva or urine, and avoiding to share glasses and cutlery amongst others) (25, 26) are proven to be effective in order to minimize virus transmission.

Fetal infection is usually diagnosed after ultrasound abnormalities are seen or after maternal infection is confirmed. The gold standard method for fetal infection diagnosis is the detection of viral DNA by polymerase chain reaction (PCR) of the amniotic fluid. However, amniocentesis is an invasive procedure and can only be performed after 18 weeks of gestation and 6-8 weeks after seroconversion, time it takes the fetus to excrete the virus through the urine (24, 29).

It is important to note that virus detection alone in the amniotic fluid does not determine whether the fetus is going to show signs of infection. Following up with ultrasounds is important to observe if there are any central nervous system abnormalities. After delivery, otologic evaluation is necessary to investigate hearing impairment, which is the most common sequela of CMV.

TREATMENT

The treatment of congenital infections is complex and controversial. Available antiviral drugs, such as ganciclovir, cidofovir and foscarnet, are commonly used in immunocompromised patients, but their toxicity (especially renal and hematological) and teratogenic effects restrict their use during pregnancy (24).

Recently, a pilot study performed in France assessed the pharmacological efficacy of oral valacyclovir in cases of congenital infection. The drug was able to reach therapeutic levels in both maternal and fetal blood and also had effect on the viral load in fetal blood (30). Although the study aim was not to evaluate therapeutic effects, its results are encouraging.

An Italian study analyzed the efficacy of a treatment with CMV hyperimmune globulin for maternal primary CMV infection showing promising results for prevention and treatment of congenital infection with no signs of side effects (31, 32). The study has also shown that hyperimmune globulin has immunomodulatory effects that can decrease the pathogenic effects of CMV (31).

In spite of those evidences, more controlled trials with larger number of patients are needed to properly evaluate treatment in this scenery.

EPIDEMIOLOGY

Although CMV is widely distributed, CMV epidemiology is diverse. As its transmission is deeply related to low sanitarian conditions and high population density, higher seroprevalence is expected to be found in developing countries (32).
A German study carried out in 1996-2010 showed a 42.3% seroprevalence among pregnant women. In the United States, a seroprevalence of 50% has been reported in the general population. Following the same trend, a study with pregnant women in France reported an overall seroprevalence of 51.5%. Concerning the low-income countries, overall seroprevalence is higher than that found in developed countries. A cross-sectional study conducted in Iran found 97.7% seropositivity. A similar rate was found in Turkey, where a retrospective observational study showed 94.9% seropositivity.

When women's origin was taken into consideration, seroprevalence among pregnant women of low socioeconomic level was 95%; among pregnant students, 69.9%, according to a cross-sectional study undertaken in Chile. Those findings are similar to what is found in Brazil, where a study conducted with low- and medium-income pregnant women showed seroprevalence of 92.9%. Controversially, a study among high-income pregnant women in Brazil showed a seroprevalence of 84%. Two other studies performed in Brazil in different demographic regions demonstrated seroprevalences of 75.1% and 76.6% among pregnant women, highlighting the variety of seroprevalence that may be found in the country.

It is also important to emphasize that in a same country one may find great differences in seroprevalence depending on socioeconomic status, ethnicity, and geographical region. For instance, two studies performed in Japan reported CMV seroprevalences of 66% and 87.3%. Such disparity shows how complex CMV epidemiology can be. Accordingly, an Italian study also correlated socioeconomic status and seroprevalence, showing that seroprevalance was 62.5% in non-immigrant women, while in immigrant women it was 91.4%.

**FINAL CONSIDERATIONS**

Since CMV is present everywhere, people are normally exposed to the virus, what increases the risk of primary infections in pregnancy when women are seronegative. In countries where seroprevalence is high, secondary infection and reactivation can still occur.

Despite being controversial, the screening of CMV during pregnancy can be effective in order to implement preventive measures or diagnosis of fetal infection. In those cases, diagnosis is important to perform the correct treatment and follow-up of the infected child. Moreover, recent researches have shown promising results concerning treatment and prevention, what enhances the importance of diagnosis.

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**REFERENCES**

1. Stagno S, Paass RF, Dworsky ME, et al. Congenital cytomegalovirus infection: the relative importance of primary and recurrent maternal infection. N Engl J Med. 1982; 306(16): 945-9. PubMed PMID: 6278309.
2. Ornoy A, Diav-Citrin O. Fetal effects of primary and secondary cytomegalovirus infection in pregnancy. Reprod Toxicol. 2006; 21(4): 399-409. PubMed PMID: 16580941.
3. Kenneson A, Cannon MJ. Review and meta-analysis of the epidemiology of congenital cytomegalovirus (CMV) infection. Rev Med Virol. 2007; 17(4): 253-76. PubMed PMID: 17579921.
4. Nankervis GA, Kumar ML, Cox FE, Gold E. A prospective study of maternal cytomegalovirus infection and its effect on the fetus. Am J Obstet Gynecol. 1984; 149(4): 435-40. PubMed PMID: 6328998.
5. Collinet P, Subtil D, Houfflin-Debarge V, Kacet N, Deswilde A, Puech F. Routine CMV screening during pregnancy. Eur J Obstet Gynecol Reprod Biol. 2004; 114(1): 3-11. PubMed PMID: 15099862.
6. Boppana SB, Pass RF, Britt WK, Stagno S, Alford CA. Symptomatic congenital cytomegalovirus infection: neonatal morbidity and mortality. Pediatr Infect Dis J. 1992; 11: 93-9. PubMed PMID: 1311066.

7. Wang C, Zhang X, Bialek S, Cannon MJ. Attribution of congenital cytomegalovirus infection to primary versus non-primary maternal infection. Clin Infect Dis. 2011; 52(2): e11-3. PubMed PMID: 21288834.

8. Fowler KB, Stagno S, Pass RF. Maternal immunity and prevention of congenital cytomegalovirus infection. JAMA. 2003; 289(8): 1008-11. PubMed PMID: 12597753.

9. Stagno S, Pass RF, Cloud G, et al. Primary cytomegalovirus infection in pregnancy. Incidence, transmission to fetus, and clinical outcome. JAMA. 1986; 256(14): 1904-8. PubMed PMID: 3020264.

10. Yamamoto M, Castellucci AC, Aragon DC, Mussi-Pinhata MM. Early high CMV seroprevalence in pregnant women from a population with a high rate of congenital infection. Epidemiol Infect. 2013; 141(10): 2187-91. PubMed PMID: 23200458.

11. Gaytant MA, Steegers EA, Sennmekot BA, Merkus HM, Galama JM. Congenital cytomegalovirus infection: review of the epidemiology and outcome. Obstet Gynecol Surv. 2002; 57: 245-56. PubMed PMID: 11961482.

12. Staras SAS, Dollard SC, Radford KW, Flanders WD, Pass RF, Cannon MJ. Seroprevalence of cytomegalovirus infection in the United States, 1988-94. Clin Infect Dis. 2006; 43: 1143-51. PubMed PMID: 17029132.

13. Vide Tavares M, Domingues AP, Tavares M, Malheiro E, Tavares F, Moura P. Cytomegalovirus: existe lugar para o rastreio durante a gravidez? Acta Med Port. 2011; 24(Suppl 4): 1003-8.

14. Puccio G, Cajozzo C, Canduscio LA, et al. Epidemiology of toxoplasma and CMV serology and of GBS colonization in pregnancy and neonatal outcome in a Sicilian population. Ital J Pediatr. 2014; 40: 23. PubMed PMID: 24559197.

15. Sygellou A, Iacovidou N, KLOUDAS S, Christoni Z, Papaevangelou V. Congenital cytomegalovirus infection: review of the epidemiology and outcome. Obstet Gynecol Surv. 2002; 57: 245-56. PubMed PMID: 11961482.

16. Schleiss MR. Congenital cytomegalovirus infection: molecular mechanisms mediating viral pathogenesis. Infect Disord Drug Targets. 2011; 11(5): 449-65. PubMed PMID: 21827434.

17. Landollo S, Gariglio M, Gribaudo G, Lembo D. The human cytomegalovirus. Pharmacol Ther. 2003, 98: 269-97. PubMed PMID: 12782241.

18. Gandhi MK, Khanna R. Human cytomegalovirus: clinical aspects, immune regulation, and emerging treatments. Lancet Infect Dis. 2004; 4(12): 725-38. PubMed PMID: 15567122.

19. Boeck M, Gehalle AP. Cytomegalovirus: pathogen, paradigm, and puzzle. J Clin Invest. 2011; 121(5): 1673-80. PubMed PMID: 21659716.

20. Gaytant MA, Rours GI, Steeger EA, Galama JM, Sennmekot BA. Congenital cytomegalovirus infection after recurrent infection: case reports and review of the literature. Eur J Pediatr. 2003; 162(4): 248-53. PubMed PMID: 12667198.

21. Johnson JM, Anderson BL. Cytomegalovirus should we screen pregnant women for primary infection? Am J Perinatol. 2013; 30(2): 121-4. PubMed PMID: 23292913.

22. Ministério da Saúde. Pré-natal e puerpério: atenção qualificada e humanizada – manual técnico. Brasília: Ministério da Saúde; 2005. p. 40-8.

23. Duff P. A thoughtful algorithm for the accurate diagnosis of primary CMV infection in pregnancy. Am J Obstet Gynecol. 2007; 196(3): 196-7. PubMed PMID: 17346521.

24. Benoist G, Leruez-Ville M, Magny JE, Jacquelard F, Salomon L, Ville Y. Management of pregnancies with confirmed cytomegalovirus fetal infection. Fetal Diagn Ther. 2013; 33(4): 203-14. PubMed PMID: 23571413.

25. Lazzarotto T, Guerra B, Gabrielli L, Lanari M, Landini MP. Update on the prevention, diagnosis and management of cytomegalovirus infection during pregnancy. Clin Microbiol Infect. 2011; 17(9): 1285-93. PubMed PMID: 21634672.

26. Macé M, Sissoeff L, Rudent A, Grangeot-Keros L. A serological testing algorithm for the diagnosis of primary CMV infection in pregnant women. Prenat Diagn. 2004; 24(11): 861-3. PubMed PMID: 15565653.

27. Lazzarotto T, Varani S, Spezzacatena P, et al. Maternal IgG avidity and IgM detected by blot as diagnostic tools to identify pregnant women at risk of transmitting cytomegalovirus. Viral Immunol. 2000; 13(1): 137-41. PubMed PMID: 10733175.

28. Walker SP, Palma-Dias R, Wood EM, Shekleton P, Giles ML. Cytomegalovirus in pregnancy: to screen or not to screen. BMC Pregnancy Childbirth. 2013; 13: 96. PubMed PMID: 23594714.

29. Revello MG, Gerna G. Diagnosis and management of human cytomegalovirus infection in the mother, fetus, and newborn infant. Clin Microbiol Rev. 2002; 15(4): 680-715. PubMed PMID: 12366675.

30. Cannon MJ, Britt WK, Schmid SD, Stagno S, Alford CA. Symptomatic congenital cytomegalovirus infection in the mother, fetus, and newborn infant. Clin Microbiol Rev. 2002; 15(4): 680-715. PubMed PMID: 12366675.

31. Sygellou A, Iacovidou N, Kloudas S, Christoni Z, Papaevangelou V. Cytomegalovirus (CMV) seroprevalence and demographic characteristics associated with infection. Rev Med Virol. 2007; 114(9): 1113-21. PubMed PMID: 17617198.

32. Nigro G, Adler SP, La Torre R, Best AM. Congenital Cytomegalovirus Collaborating Group. Passive immunization during pregnancy for congenital cytomegalovirus infection. N Engl J Med. 2005; 353(13): 1350-62. PubMed PMID: 16192480.

33. Schleiss MR. Congenital cytomegalovirus infection: molecular mechanisms mediating viral pathogenesis. Infect Disord Drug Targets. 2011; 11(5): 449-65. PubMed PMID: 21827434.

34. Gratacap-Cavallier B, Bosson JI, Morand P, et al. Cytomegalovirus (CMV) seroprevalence in pregnant women, bone marrow donors and adolescents in Germany, 1996-2010. Med Microbiol Immunol. 2012; 201: 303-9. PubMed PMID: 22398714.

35. Gaynant MA, Rours GI, Steeger EA, Galama JM, Sennmekot BA. Congenital cytomegalovirus infection after recurrent infection: case reports and review of the literature. Eur J Pediatr. 2003; 162(4): 248-53. PubMed PMID: 12667198.

36. Oacak S, Zeteroglu S, Ozer C, Dolapcioglu K, Gunogone A. Seroprevalence of Toxoplasma gondii, rubella and cytomegalovirus among pregnant women in southern Turkey. Scand J Infect Dis. 2007; 39(3): 231-4. PubMed PMID: 17366053.
37. Suárez GM, Briones MH, Luchsinger FV, et al. [Primary cytomegalovirus infection in pregnant women of different socioeconomic status]. Rev Med Chil. 1994; 122: 1153-7. PubMed PMID: 7659881.

38. Serra FC, Machado J, Nicola MH, et al. Soroprevalência de citomegalovírus em gestantes brasileiras de classe socioeconômica favorecida. J Bras Doenças Sex Transm. 2009; 21(1): 12-5.

39. Figueiró-Filho EA, Senefonte FRA, Lopes AHA, et al. [Frequency of HIV-1, rubella, syphilis, toxoplasmosis, cytomegalovirus, simple herpes virus, hepatitis B, hepatitis C, Chagas disease and HTLV I/II infection in pregnant women of State of Mato Grosso do Sul]. Rev Soc Bras Med Trop. 2007; 40(2): 181-7. PubMed PMID: 17568885.

40. Inagaki ADM, Oliveira LAR, Oliveira MFB, et al. [Seroprevalence of antibodies for toxoplasmosis, rubella, cytomegalovirus, syphilis and HIV among pregnant women in Sergipe]. Rev Soc Bras Med Trop. 2009; 42(5): 532-6. PubMed PMID: 19967235.

41. Taniguchi K, Watanabe N, Sato A, et al. Changes in cytomegalovirus seroprevalence in pregnant Japanese women — A 10-year single center study. J Clin Virol. 2014; 59(3): 192-4. PubMed PMID: 24468011.

42. Tagawa M, Minematsu T, Masuzaki H, Ishimaru T, Moriuchi H. Seroprevalence study of cytomegalovirus infection among pregnant women in Nagasaki, Japan. Pediatr Int. 2010; 52(3): 459-62. PubMed PMID: 19919637.

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