GinPolMedProject ©
3 (41) 2016: 013-019 • REVIEW ARTICLE

Prophylaxis of congenital cytomegalovirus infections

Dorota Bulsiewicz (ABDEF), Justyna Czech-Kowalska (DE), Julita Latka-Grot (BF), Anna Dobrzańska (E)

Klinika Neonatologii, Patologii i Intensywnej Terapii Noworodka, Instytut Pomnik – Centrum Zdrowia Dziecka w Warszawie
Kierownik Kliniki: prof. dr n. med. Anna Dobrzańska

AUTHORS' CONTRIBUTION: **(A)** Study Design · **(B)** Data Collection · **(C)** Statistical Analysis · **(D)** Data Interpretation · **(E)** Manuscript Preparation · **(F)** Literature Search · **(G)** Funds Collection

SUMMARY

Cytomegalovirus infection is one of the most common congenital infections (about 1% of all newborns). Only 10–15% of infected newborns have specific symptoms at birth, 90% are asymptomatic. Irrespective of the clinical picture at birth, congenital cytomegalovirus infection could lead to sensorineural hearing loss, neurodevelopment deficits and ocular abnormalities (10–50%). In Poland, routine screening programs of newborns and pregnant women do not include human cytomegalovirus (HCMV) assays. The efficacy of passive immunization and antiviral treatment in pregnant women has not been well-established. An effective HCMV vaccine remains unavailable. Education about possible ways of HCMV transition and prevention effectively reduces the risk of HCMV infection in pregnant women. Spreading information about the most common sources of HCMV infection and ways to prevent it are of particular importance. Good hand-washing technique should be suggested to pregnant women having contact with children in day care and other persons with high HCMV infection risk. Gynecologists and obstetricians play a crucial role in prevention of congenital cytomegalovirus infection among women of childbearing age and pregnant women.

Key words: congenital cytomegalovirus infection; human cytomegalovirus; HCMV; prophylaxis

Address for correspondence: Dorota Bulsiewicz
Klinika Patologii i Intensywnej Terapii Noworodka
Instytut Pomnik – Centrum Zdrowia Dziecka
Aleja Dzieci Polskich 20; 04-736 Warszawa
Tel./fax: +48 22 815-77-66, +48 22 815-17-85
e-mail: d.bulsiewicz@ipczd.pl

Word count: 2991 **Tables:** 3 **Figures:** 0 **References:** 33

Received: 11.01.2016
Accepted: 14.03.2016
Published: 19.09.2016

INTRODUCTION

Human cytomegalovirus, also called Human Herpesvirus-5, belongs to the Herpes family. It is the most common virus transmitted from the mother to the fetus *in utero* [1]. In developed countries, the rate of newborns infected with cytomegalovirus amounts to 1% [1], which constitutes approximately 3,695 newborns in Poland according to the data provided by the Polish Central Statistical Office from 2013 [2].

The virus crosses the placenta after primary infection in a pregnant woman. The prevalence of primary infections in the USA ranges from 1–4% annually. The risk of fetal infection reaches 30–70% and increases as pregnancy progresses [1,3–5]. Since after a cured infection the virus remains in the organism in the latent form, it can be reactivated when the immune system is weakened and due to other infections or as a result of hormonal changes during pregnancy [6]. Latent virus reactivation is also reported to have occurred in immunocompetent, otherwise healthy pregnant women. In these cases, however, fetal infection is rare; the risk of transplacental transition is 1–3%. Superinfection with another virus in persons with the history of HCMV infection is also possible. In this situation, the risk of fetal infection is lower than in primary infection by 69%. It must be remembered that 30–75% of all congenital HCMV infections in the USA are found in women who were seropositive prior to conception [7,8]. In these cases, however, infection in a newborn is much more frequently asymptomatic and late complications are much rarer [9].

Cytomegalovirus infection in pregnant women is usually asymptomatic. Sometimes, it presents with a mild mononucleosis-like infection (fever, sore throat, myalgia, fatigue, enlarged lymph nodes, hepatosplenomegaly, liver function disorders, lymphocytosis with increased percentage of atypical lymphocytes) [1]. In

congenital infections, the disease is asymptomatic in most patients (85–90%), with no symptoms either in the prenatal period or after birth. The remaining 10% of newborns present with signs and symptoms specific for congenital HCMV infection, including: petechiae, thrombocytopenia, neutropenia, hypertransaminasemia, cholestasis and prolonged jaundice, hypotrophy, neurological signs (muscle tone disorders, convulsions, microcephaly), hypoacusis or chorioretinitis. Abnormalities indicating fetal HCMV infection can be noticed even during pregnancy in an ultrasound scan (Tab. 1) [1,6]. It must be remembered, however, that the sensitivity of prenatal ultrasound as a method to diagnose congenital cytomegalovirus infection is relatively low (8–14%) [1]. Moreover, HCMV infection in a pregnant woman can lead to miscarriage or pre-term birth.

Inflammation and fibrosis of the placenta play a significant role in the pathogenesis of congenital cytomegalovirus infection. This results in relative hypoxia, disorders in fetal nutrition and is responsible for clinical signs, such as: intrauterine growth retardation, hepatosplenomegaly, thrombocytopenia, petechiae and compensatory placental overgrowth [1,10]. Irrespective of whether or not infected newborns present with signs and symptoms at birth, they are at risk of late complications, including: progressive sensorineural hypoacusis or hearing loss, amblyopia, psychomotor or mental retardation and epilepsy. The risk reaches 25% in asymptomatic children. As for symptomatic congenital HCMV infection, and when causal treatment is not implemented, these complications develop in 90% of cases [1,11]. Due to significant adverse effects of antiviral medications, neonates and newborns deemed eligible for treatment present with symptomatic congenital infection with central nervous system involvement, hypoacusis, chorioretinitis or a septic course of the disease. It has been demonstrated that therapy significantly reduces the risk of hypoacusis or hearing loss and (according to certain authors) neurodevelopment deficits (to a certain degree) [12,13].

HCMV INFECTION PREVENTION IN WOMEN OF CHILD-BEARING AGE

American (Jeon et al.) and French studies (Cordier et al.) have shown that knowledge about cytomegalovirus infection in the population of women of child-bearing age is insufficient [14,15]. Only 22% of American and 60% of French respondents stated that they had heard of congenital cytomegalovirus infection before. For comparison, 98% knew about the risk carried by human immunodeficiency virus (HIV) even though it is much rarer in newborns [14,15] (Tab. 2). A higher rate of awareness in French women probably resulted from certain preventive measures undertaken (74% of women who were informed about cytomegalovirus infection during a medical appointment vs 34% of French women in whom such actions were not conducted) [15].

Women are not aware of dangers associated with congenital cytomegalovirus infection. Most of them possess no knowledge about the risks connected with such an infection, routes of infection or preventive measures [7,14]. Education is essential, particularly among seronegative women. According to the guidelines of the American College of Obstetricians and Gynecologists, information provided by gynecologists

Tab. 1. Symptoms of congenital cytomegalovirus infection in the prenatal period

Organ	Symptom
Skin, pleural cavity	Generalized edema
Liver	Hepatomegaly, calcifications
Spleen	Splenomegaly, calcifications
Digestive system	Intestinal inflammatory edema, hyperechogenicity of intestinal wall, calcifications
CNS	Periventricular calcifications, callosal agenesis, schizencephaly, cerebellar hypoplasia, microcephaly, ventriculomegaly
Cardiovascular system	Congenital cardiac defects
Placenta	Inflammatory edema, placental overgrowth
Other	Intrauterine hypotrophy, prematurity, polyhydramnios

to women of child-bearing age and pregnant ones plays a major role. French studies have shown that instructing patients about the necessity to observe hygiene occurred effective in a reduction of HCMV infection in a group of pregnant women [16,17]. It is therefore justified to increase awareness of cytomegalovirus infection among doctors attending patients of child-bearing age (internists, gynecologists), which might facilitate prophylaxis in this group of patients [7].

SOURCES OF INFECTION AND PRIMARY PREVENTION

Humans are the only carriers of cytomegalovirus. Infection takes place via exposure to blood, body fluids (saliva, tears, milk) and excreta (urine) [1]. The main sources of infection for pregnant women are children aged 1–4 years. It has been proven that children at day care catch primary infections much more frequently than those remaining at home [11]. Due to contact with peers, sharing toys and the lack of or limited hygiene, the risk of a horizontal infection is the highest in this age group. At this age, the duration and quantity of copies of the virus excreted in urine and saliva can be considerably higher than in infancy or in older children [6,11]. Viruria can last even 42 months post-infection [1]. Pregnant women should observe hygiene principles, including hand washing after changing diapers or wiping the child's nose, avoiding kissing children on the mouth, licking their pacifiers, sharing food, drinks or towels and sanitary articles (such as a toothbrush) (Tab. 3).

A child infected with HCMV constitutes a much greater risk to his or her mother than to medical staff. This is apparently associated with sanitary regime observed by health care workers (hand disinfection, avoiding contact with body fluids and excreta). Annually, at least 50% of primarily seronegative mothers of children attending day care undergo seroconversion [1]. Moreover, the possibility of transmitting infection between adults must also be taken into account. In this case, saliva, vaginal secretions and sperm constitute the greatest threat. Women get infected during intercourse, kiss or oral sex. Therefore, limiting sexual interaction with new partners during pregnancy and using condoms seem indicated. Intercourse with one's permanent partner is not a significant risk factor since the partner's serological status is probably identical to that of the pregnant woman. Only 20% of seronegative women have been observed to have seropositive partners [6]. An increased risk of congenital HCMV infection more frequently concerns children of young women (<25 years of age), multiparous women, women with multiple sexual partners, of low socioeconomic status and belonging to national minorities [19,20]

Tab. 2. Knowledge of some childhood illnesses among women of childbearing age (following *Knowledge and awareness of congenital cytomegalovirus among women"* (Jiyeon J. Infect. Dis. Obstet. Gynecol. 2006, Volume 2006, 1–7) in the author's own modification

Disease entity	(%)
Congenital cytomegalovirus infection	22
Parvovirus B19 infection	32
Congenital toxoplasmosis	37
Congenital rubella syndrome	53
Beta-hemolytic streptococcus (GBS) infection	59
Spina bifida	76
Fetal alcohol syndrome (FAS)	83
Sudden infant death syndrome	94
Down syndrome	97
HIV/AIDS	98

Tab. 3. Recommendations of Centers for Disease Control and Prevention for reducing the risk of HCMV infection in pregnant women [18] (author's own modification)

Recommendations for reducing the risk of CMV infection
1. Wash hands frequently with soap for 10–20 seconds, especially after: • changing diapers; • feeding; • wiping oral cavity of drooling children; • wiping children's nose; • handling children's toys.
2. Avoid sharing everyday articles (towels, toothbrushes, dishes, eating utensils) with young children.
3. Avoid sharing food and drinks with young children.
4. Do not put children's pacifier to the mouth.
5. Avoid kissing children on the mouth and other contact with saliva.
6. Clean toys and furniture that come into contact with children's urine or saliva.

In a Polish study, it was confirmed that young women (<20 years of age), uneducated ones and multiparous women are at an increased risk of cytomegalovirus infection during pregnancy. Neither profession (contact with children) nor income status were found to affect HCMV infection, which could result from a non-representative group of respondents [21].

DIAGNOSIS IN PREGNANT WOMEN

At present, routine screening programs of pregnant women for cytomegalovirus are not recommended in most countries in the world, including Poland [1,4,5,22]. The prevalence of the virus in the population (62% of seropositive women of child-bearing age in Poland) is associated with a relatively low risk of primary infection during pregnancy (1–4% of pregnant patients annually in the USA) [6,21]. However, ruling out primary active infection in a pregnant patient does not exclude fetal infection (possible reinfection, reactivation of infection). Moreover, asymptomatic or oligosymptomatic disease in immunocompetent adults is also a challenge. It must be underlined, however, that only a diagnostic process conducted in a pregnant patient makes it possible to make an early diagnosis in a newborn and conduct subsequent monitoring, even if he or she presents no symptoms at birth.

In everyday practice, a question arises: when to implement diagnostic measures in a pregnant patient? It seems that symptomatic HCMV infection in a pregnant woman and abnormalities seen on fetal ultrasound have the most significant predictive value of congenital cytomegalovirus infection [5,22]. Interpretation of serological tests is usually difficult. Maternal HCMV infection is certain if seroconversion is detected during pregnancy or if IgM antibodies are present with a low IgG avidity index [5,22, 23]. According to Lazzarotto et al., IgG avidity assays prior to week 18–20 of gestation are characterized by 100% of sensitivity for HCMV infection. After this period, sensitivity declines to 62% [23]. It is therefore concluded that low avidity does not always mean a recent infection and a high index does not always rule it out [1,6]. Moreover, significant increases in IgG concentrations (3- or 4-fold) can indicate activation of the maternal immune system in response to the virus. It must be remembered, however, that maternal infection does not necessarily entail fetal infection. Other data, such as: IgG antibody titer or the presence of only IgM antibodies, do not allow unequivocal conclusions to be drawn. IgM antibodies can persist in the serum for several months post-infection (up to 6–9 months), but their presence can also result from reactivation of a latent infection [1,5,6]. The plateau of IgG antibody levels is an individual matter. There are considerable discrepancies in results depending on the applied method or laboratory in which tests are carried out. A condition essential for proper interpretation of multiple assays is their performance in a single laboratory.

Fetal infection can be suspected if, apart from the above mentioned serological assays, a pregnant woman presents abnormalities on ultrasound (Tab. 1). In cases of doubts, diagnostic amniocentesis, conducted to collect amniotic fluid for molecular tests, can be considered. This examination should be performed at least 6 weeks after the diagnosis of maternal infection but not earlier than in the 21st week of gestation. Only then, fetal diuresis is sufficiently effective to enable excretion of the virus to the amniotic sac [1]. According to Lazzarotto et al., the presence of viral DNA in sufficient quantity (i.e. >10ł copies/ml) is an evidence for fetal infection whereas a negative result does not preclude infection [22]. However, an increased risk of miscarriage carried by this examination makes its role debatable. This is mainly due to the impossibility to implement adequate causal treatment in women with primary HCMV infection during pregnancy. The application of hyperimmunoglobulin therapy and administration of valganciclovir in pregnant women with primary HCMV infection are still being investigated.

SECONDARY PREVENTION

Vaccination

The attempts of developing an effective and safe vaccine against HCMV have been conducted since the 1960s. Initially, vaccines based on live attenuated viruses were studied. However, despite their safety and good tolerance, their immunogenicity was not sufficient to enable effective infection prevention [1,24]. A recombinant vaccine with gB glycopeptide and MF59 adjuvant also occurred to be well-tolerated and safe. Its efficacy was 50%, but the effects were short-term and lasted for approximately 18 months [1,18,24,25]. Studies on peptide, DNA (plasmid immunization) and vector vaccines are underway. Even though the outcomes of these

studies are promising, none of the aforementioned vaccines has shown preventive action against congenital HCMV infection. The studies are still in phase I or II. Currently, it is not possible to prevent cytomegalovirus infection by active immunization.

Immunoprophylaxis

There are reports on effective administration of a specific hyperimmunoglobulin of high antibody avidity in order to both prevent and treat fetal infection. Unfortunately, these studies were mostly observational and conducted on small groups of patients. Nigro et al. report that immunoglobulin administration significantly reduced the risk of transplacental transition (16% in treated patients vs 56% in untreated ones). Additionally, it was shown that children born of mothers treated with immunoglobulin significantly more rarely presented with symptomatic cytomegalovirus infection than those born of women who did not receive this medication (3 and 50%, respectively). Moreover, the therapy caused no adverse effects [26]. Following passive immunization of mothers (200 IU of immunoglobulin/kg i.v.; in some cases additional 500 IU/kg administered to the amniotic sac; the intravenous dose was repeated in certain cases), sonographic signs of fetal infection (ventriculomegaly, enlarged placenta, hepatomegaly and ascites) regressed [27].

A retrospective study by Buxmann et al. also proves that immunoglobulin is effective in prevention and treatment of congenital cytomegalovirus infection. The frequency of transplacental transition was 23%. All 9 infected children presented no signs and symptoms of congenital cytomegalovirus infection either at birth or later (follow-up up to 12–36 months of life). Considerable heterogeneity of the investigated patients, e.g. in terms of time of infection (at the time of conception, in the first and second trimester of pregnancy), drug dosage (100–270 IU/kg), number of reinjections (1–6 times) and the lack of control group, were significant limitations of the study [28]. Moreover, Visentin et al., based on 31 pregnant patients, demonstrated the efficacy of 1 dose of immunoglobulin (200 IU/kg in the 20–24th week of gestation) in the case of primary HCMV infection documented prior to gestational week 17. Administration of Cytotect® significantly reduced the percentage of children with late complications of congenital HCMV infection (13% vs 43% among untreated women). It must be emphasized that the follow-up in these children lasted up to the first year of life and, for instance, hearing impairment resulting from vertical HCMV infection can be progressive and diagnosed after several years [29]. The only multicenter randomized trial available in the literature was a study conducted in Italy by Ravello. Pregnant women with primary HCMV infection diagnosed in gestational week 5–26 were administered 100 IU/kg of Cytotect® i.v. (n=61) or placebo (n=63) within the first 6 weeks of the diagnosis and subsequently in 4 week intervals (on average 5 infusions during pregnancy). The diagnosis was based on serology (seroconversion within IgG antibodies or the presence of IgM antibodies with low IgG avidity). Transplacental transition took place in 30% of cases in the treated group and in 44% of patients in the placebo group. The difference was not statistically significant. There were no statistically significant differences in terms of the frequency of clinical symptoms between children with prenatal HCMV infection born by treated (n=10) and untreated women (n=17), who were diagnosed on the basis of molecular tests after birth (30% for the treated group vs 24% for the placebo group). Longer observation of further development of these children was not conducted [30]. To sum up, the outcomes of the trial did not confirm the efficacy of hyperimmunoglobulin therapy at a dose of 100 IU/kg in prevention of congenital cytomegalovirus infection in children. Currently, two phase III large randomized trials evaluating the use of immunoglobulin in the prevention of congenital HCMV infection are underway (*A Randomized Trial to Prevent Congenital Cytomegalovirus*, NCT01376778, www.clinicaltrials.gov and *Interim analysis of the Cytotect® Phase III trial in congenital cytomegalovirus (CMV) infection shows clear indication of efficacy* of a German company Biotest). These results will have great impact on a decision concerning routine use of IgG hyperimmunoglobulin in the prevention of congenital HCMV infection.

Treatment

Antiviral medications (valacyclovir and ganciclovir) for prevention of congenital infection and treatment of congenital HCMV infection during pregnancy have been investigated for many years. Valacyclovir (Valtrex®, Vaciclor®) is the L-valyl ester of acyclovir for oral administration. Roxby et al., in their randomized study conducted among 148 pregnant women with primary

HCMV infection and concomitant human immunodeficiency virus (HIV) infection, did not demonstrate a statistically significant difference between children born of women treated with valacyclovir and those who did not receive the drug in terms of the incidence of congenital and acquired CMV infection in newborns. These conclusions probably result from a too low dose of the drug (1 g daily) [31]. In a study by Jacquemark et al., it was shown that oral administration of valacyclovir to pregnant women (8 g daily) results in therapeutic drug concentrations in maternal and fetal blood and reduces fetal viremia. No adverse effects were noted [32]. Two large randomized trials on prevention and treatment of *in utero* congenital HCMV infection with valacyclovir are underway (*Valacyclovir to Prevent Vertical Transmission of Cytomegalovirus After Maternal Primary Infection During Pregnancy* NCT02351102 and *In UTERO Treatment of Cytomegalovirus Congenital Infection With Valacyclovir* NCT01037712, www.clinicaltrials.gov).

Ganciclovir, a synthetic analogue of deoxyguanosine, is more effective than acyclovir in HCMV infection, but also more toxic and potentially teratogenic. The literature mentions one case of ganciclovir treatment in a pregnant patient with renal transplant with the history of symptomatic cytomegalovirus infection 3 months prior to infection. Due to the presence of viral DNA in the amniotic fluid, the mother was administered ganciclovir from gestational week 22. The child was born healthy, with no symptoms of infection. There were no signs of viremia in body fluids. A diagnosis of congenital cytomegalovirus infection was made on the basis of a molecular test of amniotic fluid where the virus was found in the quantity of 80 copies/500 ng of DNA (positive result >10). There was no other evidence for infection reactivation during pregnancy. It is significant and noteworthy that long-term administration of ganciclovir caused no fetal injury despite detection of drug concentrations in the amniotic fluid that exceeded minimum therapeutic doses (14 vs 3 μM). Moreover, the number of virus copies in the amniotic fluid reduced (8 vs 30) [33].

CONCLUSION

Congenital cytomegalovirus infection is a common problem. Its late complications are severe (abnormal psychomotor development, hypoacusis/hearing loss, ocular dysfunction) and have an impact on the whole life of infected children. Routine screening programs of pregnant women are not conducted in Poland. Studies on the use of immunoprophylaxis and antiviral drugs in prevention of congenital HCMV infection are underway, but currently the outcomes concerning their efficacy are insufficient. Moreover, an effective vaccine against cytomegalovirus remains unavailable. It is therefore essential to undertake effective actions to raise awareness concerning pro-health behaviors among women of child-bearing age.

REFERENCES

1. **Dunal M, Trzcińska A, Siennicka J**. Wirus cytomegalii – problem zakażeń wrodzonych. *Post Mikrobiol* 2013; 52(1):17–28.
2. Komitet redakcyjny Głównego Urzędu Statystycznego: Zakład Wydawnictw Statystycznych, *Rocznik Demograficzny* 2014; Warszawa 2014.
3. **Enders G, Daiminger A, Bäder U, et al**. Intrauterine transmission and clinical outcome of 248 pregnancies with primary cytomegalovirus infection in relation to gestational age. *Journal of Clinical Virology* 2011;52:244–246.
4. **Evans C, Brooks A, Anumba D, et al.** Dilemmas regarding the use of CMV-specific immunoglobulin in pregnancy. *Journal of Clinical Virology* 2013;57:95– 97.
5. **Manicklal S, Emery VC, Lazzarotto T, et al.** The "Silent" Global Burden of Congenital Cytomegalovirus. *Clinical Microbiology Reviews* 2013;26(1):86–102.
6. **Cannon MJ, Hyde TB, Schmid DS.** Review of cytomegalovirus shedding in bodily fluids and relevance to congenital cytomegalovirus infection. *Rev Med Virol* 2011; 21(4):240–255.
7. **Cannon MJ**. Congenital cytomegalovirus (CMV) epidemiology and awareness. *Journal of Clinical Virology* 2009; 46:6–10.
8. **Ross SA, Arora N, Novak Z, et al.** Cytomegalovirus reinfections in healthy seroimmune women. *The Journal of Infectious Diseases* 2010;201:386–389.
9. **Fowler KB, Stagno S, Pass RF, et al.** The outcome of congenital cytomegalovirus infection in relation to maternal antibody status. *N Engl J Med* 1992;326:663–667.
10. **Maidji E, Nigro G, Tabata T, et al.** Antibody treatment promotes compensation for human cytomegalovirus-induced pathogenesis and a hypoxia-like condition in placentas with congenital infection. *Am J Pathol* 2010; 177:1298–1310.
11. **Nassetta L, Kimberlin D, Whitley R**. Treatment of congenital cytomegalovirus infection: implications for future therapeutic strategies. *Journal of Antimicrobial Chemotherapy* 2009;63:862–867.
12. **Kimberlin DW, Lin CY, Sanchez PJ i wsp.:** Pharmacokinetic and pharmacodynamic assessment of oral valganciclovir in the treatment of symptomatic congenital cytomegalovirus diseases. *The Journal of Infectious Diseases* 2008;197(15):836-845.
13. **Kimberlin DW, Lin CY, Sanchez PJ.** Effect of ganciclovir therapy on hearing in symptomatic congenital cytomegalovirus disease involving the central nervous system: a randomized, controlled trial. *J Pediatr* 2003;143(1):16-25.
14. **Jiyeon J.** Knowledge and awareness of congenital cytomegalovirus among women. Infect. *Dis. Obstet. Gynecol* 2006;2006:1–7.
15. **Cordier AG, Guitton S, Vauloup-Fellous C, et al.** Awareness of cytomegalovirus infection among pregnant women in France. *Journal of Clinical Virology* 2012;53: 332–337.

16. **Picone O, Vauloup-Fellous C, Cordier AG et al.** A 2-year study on cytomegalovirus infection during pregnancy in a French hospital. *BJOG* 2009;116 (6):818–823.
17. **Vauloup-Fellou C, Picone O, Cordier A-G, et al.** Does hygiene counseling have an impact on the rate of CMV primary infection during pregnancy? A 3-year experience in a French hospital. *J Clin Virol* 2009;46(4):49–53.
18. **Johnson J, Anderson B, Pass RF.** Prevention of maternal and congenital cytomegalovirus infection. *Clin Obstet Gynecol* 2012;55(2):521–530.
19. **Fowler KB, Stagno S, Pass RF**. Maternal age and congenital cytomegalovirus infection: screening of two diverse newborn populations, 1980-1990. *J Infect Dis* 1993; 168(3):552-556.
20. **Basha J, Iwasenko JM, Robertson P, et al.** Congenital cytomegalovirus infection is associated with high maternal socio-economic status and corresponding low maternal cytomegalovirus seropositivity. *J Paediatr Child Health* 2014;50(5):368-372.
21. **Wujcicka W, Gaj Z, Wilczyński J, et al.** Impact of socioeconomic risk factors on the seroprevalence of cytomegalovirus infections in a cohort of pregnant Polish women between 2010 and 2011. *Eur J Clin Microbiol Infect Dis* 2014;33(11):1951-1958.
22. **Lazzarotto T, Varani S, Guerra B, et al.** Prenatal indicators of congenital cytomegalovirus infection. *J Pediat* 2000;137(1):90–95.
23. **Lazzarotto T, Guerra B, Lanari M, et al.** New advances in the diagnosis of congenital cytomegalovirus infection. *Journal of Clinical Virology* 2008;41:192–197.
24. **Fu T-M, An Z, Wang D.** Progress on pursuit of human cytomegalovirus vaccines for prevention of congenital infection and disease. *Vaccine* 2014;32:2525–2533.
25. **Pass RF, Zhang C, Evans A, et al.** Vaccine prevention of maternal cytomegalovirus infection. *N Engl J Med* 2009; 360:1191–1199.
26. **Nigro G, Adler SP, La Torre R, et al.** Passive Immunization during pregnancy for congenital cytomegalovirus infection. *N Engl J Med* 2005;353(13):1350-1362.
27. **Nigro G, La Torre R, Pentimalli H, et al.** Regression of fetal cerebral abnormalities by primary cytomegalovirus infection following hyperimmunoglobulin therapy. *Prenat Diagn* 2008;28:512–517.
28. **Buxmann H, Stackelberg OM, Schlößer RL, et al.** Use of cytomegalovirus hyperimmunoglobulin for prevention of congenital cytomegalovirus disease: a retrospective analysis. *J Perinat Med* 2012;40(4):439-446.
29. **Visentin S, Manara R, Milanese L, et al.** Early primary cytomegalovirus infection in pregnancy: maternal hyperimmunoglobulin therapy improves outcomes among infants at 1 year of age. *Clin Infect Dis* 2012;55(4):497-503.
30. **Revello MG, Lazzarotto T, Guerra B, et al.** A randomized trial of hyperimmune globulin to prevent congenital cytomegalovirus. *N Engl J Med* 2014;370(14):1316-1326.
31. **Roxby AC.** Maternal valacyclovir and infant cytomegalovirus acquisition: a randomized controlled trial among HIV infected Women. *PLoS One* 2014;9(2):1-7.
32. **Jacquemard F, Yamamoto M, Costa J-M, et al.** Maternal administration of valaciclovir in symptomatic intrauterine cytomegalovirus infection. *BJOG An International Journal of Obstetrics and Gynaecology* 2007;114:1113–1121.
33. **Puliyanda DP, Silverman NS, Lehman D, et al.** Successful use of oral ganciclovir for the treatment of intrauterine cytomegalovirus infection in a renal allograft recipient. *Transpl Infect Dis* 2009;46(S4):49–53.