

Congenital cytomegalovirus infection: Advocating for screening and education

Ching Yee Chan¹*FAMS*, Liying Yang²*FAMS*, Jiun Fong Thong³*FAMS*

Cytomegalovirus (CMV) infection is the leading non-genetic cause of congenital neurosensory hearing loss in children, accounting for 21% of cases of hearing loss at birth and 25% of deafness at age 4 years.¹ It can also give rise to other serious sequelae such as cerebral palsy, cognitive impairment, seizures and visual impairment.² CMV infection in children and adults is frequently either asymptomatic or gives rise to non-specific symptoms such as malaise and pharyngitis.² Infected pregnant patients are therefore often unaware of the infection, which leads to missed opportunities for diagnosis of congenital CMV (cCMV) and interventions for the fetus and infant.

Despite the potential harm, awareness of cCMV infection is low among women of reproductive age. A 2012 Singapore study by Lim et al. evaluating the awareness of pregnant women in Singapore about cCMV infection found that only 20% knew of the virus and that none of the participants had been informed about CMV by their obstetrician.³

The birth prevalence of cCMV infection is approximately 0.4–6%.⁴ This is higher than Down syndrome, for which screening has been offered as a standard part of antenatal care for decades, and also higher than inborn errors of metabolism, for which all neonates in Singapore are offered screening under the National Newborn Screening Programme. Despite this, cCMV screening is currently neither routinely offered in pregnancy nor in newborns, except in selected states in the US and Canada.

Screening for cCMV infection in pregnancy may be performed using CMV immunoglobulin (Ig) M and IgG antibodies as well as IgG avidity testing. This will identify 4 groups of women.

The first group consists of women who have never been infected (IgM and IgG negative), and who are at risk of primary infection. Primary CMV infection in pregnancy is associated with the highest risk (30–35%) of transplacental infection.⁵ These women would benefit from antenatal educational interventions aimed at primary prevention of CMV infection.

CMV is transmitted via bodily fluids such as saliva, urine and blood. As infected children may secrete the virus in their urine and saliva for 24 months,⁶ having a child in nursery is a major risk factor for primary maternal CMV infection during pregnancy. Hygiene counselling, which includes attention to hand-washing after contact with urine or saliva, avoiding sharing of food and drinks with young children, and not kissing them on or near the mouth, appears to be effective in preventing CMV infection in pregnancy.⁷ These recommendations are simple and 98% of mothers in Singapore who were surveyed felt it was easy to adopt them.³ They are also recommended by the Royal Australian and New Zealand College of Obstetricians and Gynaecologists, as well as the French National College of Obstetricians and Gynaecologists.

The second group would be those who are IgM negative and IgG positive, indicating a past infection. While these women have only a 0.51% chance of reactivation of CMV, or infection with a different strain of virus during pregnancy, non-primary infections make up the majority of maternal infections during pregnancy due to the relatively high seroprevalence rates in both developing and developed countries.⁵ Asymptomatic babies of these patients may be screened for cCMV within the first 21 days of life as positive tests beyond this window cannot differentiate between congenital and acquired infections. This has been traditionally done using urine culture, but salivary polymerase chain reaction (PCR) is an alternative technique that is highly sensitive, specific and more easily performed.⁸ Babies who test positive should undergo intensified follow-up screening as 10–12% of asymptomatic neonates may develop delayed, progressive hearing loss, and a smaller proportion may develop visual or neurodevelopmental disabilities.

The third group of women who test positive for both IgM and IgG may have avidity testing done to determine timing of infection, as IgM antibodies can persist for several months after infection. A high IgG avidity would indicate past infection, whereas a low IgG avidity is highly suggestive of a recent primary infection and a

¹ Department of Otolaryngology, KK Women's and Children's Hospital, Singapore

² Department of Obstetrics and Gynaecology, Singapore General Hospital, Singapore

³ Department of Otorhinolaryngology-Head & Neck Surgery, Singapore General Hospital, Singapore

Correspondence: Dr Ching Yee Chan, Department of Otolaryngology, KK Women's and Children's Hospital, 100 Bukit Timah Road, Singapore 229899.

Email: chan.ching.yee@singhealth.com.sg

fetus at risk of cCMV. The patients in the latter group should be offered amniocentesis for PCR amplification of CMV DNA to diagnose fetal CMV infection.⁶ This is recommended to be done 7–8 weeks after maternal infection, and after 21 weeks when fetal urine output accounts for the majority of amniotic fluid volume. Ville et al. have also recently demonstrated that chorionic villus sampling for viral DNA PCR at 13–14 weeks has good positive predictive values of 100% and negative predictive value of 91%, which may enable earlier diagnosis of fetal infection.⁵ Patients with positive amniocentesis results can be followed up with serial ultrasound scans with or without fetal therapy. Ultrasound scans will enable detection of signs such as ventriculomegaly, microcephaly, echogenic bowel, hydrops and intrauterine growth restriction, which can inform fetal prognosis.

The fourth group of women are those who test positive for IgM but negative for IgG. While this may suggest a recent active primary infection, it may also be a false positive, hence IgG will need to be repeated in 10–14 days. If this turns positive, IgG avidity testing can be done to confirm recent primary infection.

When should maternal screening be done? The timing is important. Recent evidence suggests that all long-term sequelae (hearing loss and neurodevelopmental delay) develop in fetuses infected in the first trimester.⁹ Screening should therefore be done by 14 weeks of gestation to detect these women who have the highest risk of having an affected neonate.⁵

From a purely practical standpoint, an opportune time for CMV screening would be at the time of the routine antenatal bloods at around 11–14 weeks. Earlier screening at the time of the booking visit has also been advocated,⁵ as this not only enables earlier detection of infection occurring in the peri-conceptional period and start of the first trimester, but also early hygiene counselling of susceptible women. However, this will mean that patients will need to be re-screened at the end of the first trimester so as not to miss late first trimester infections. Further studies to compare the feasibility, acceptability and cost-effectiveness of the various screening protocols will be beneficial.

Resistance to CMV screening may be partly due to historical reasons, as fetal CMV infection used to be challenging to diagnose because of poor serological assays and difficulty in differentiating between recent and old infections. This is however no longer the case. Maternal infection can be sensitively and reliably diagnosed with CMV serology and avidity testing.^{10,11} A positive IgM and IgG with a low IgG avidity indicates

infection in the preceding 3 months with a sensitivity and specificity of over 90%,¹² while amniocentesis for fetal infection has a 100% specificity and 85–95% sensitivity to detect fetal infection.

Some have proposed routine ultrasound scans be used to screen for CMV infection. These have however been reported to be able to identify only 26% of infected fetus that developed long-term sequelae, in contrast to targeted ultrasound performed after known fetal infection, which has a high sensitivity (91%) and negative predictive value (96%) for predicting long-term complications.¹³ This approach also precludes primary prevention with hygiene education, and early initiation of treatment for secondary prevention of CMV infection.

Is there effective treatment for secondary prevention of cCMV infection or tertiary prevention of cCMV sequelae? A recent randomised trial looking at the efficacy of high-dose oral valaciclovir (8g/day) showed a 71% reduction in congenital infection in women with primary infection between -3 and 12 weeks gestation.¹⁴ In addition, a phase II trial of oral valaciclovir reported a significantly higher chance of delivering an asymptomatic neonate versus the untreated group.¹⁵ Hyperimmunoglobulin (HIG) may also be effective if started early after maternal infection; a non-randomised study by Kagan et al. where HIG was started at an average of 10 days after maternal infection reported a 7.5% risk of fetal transmission with high-dose HIG (200UI/kg) versus 35% in untreated women.¹⁶ Even so, the safety and efficacy of HIG needs further evaluation as 2 other randomised studies where treatment was initiated later did not show any benefit and 1 reported an increase in prematurity in the treated group.^{17,18}

Another concern raised about screening is related to the unpredictability of the postnatal course. While it is true that this can result in parental anxiety and may lead to the termination of pregnancies in which the fetuses might not have developed long-term sequelae, this uncertainty is a common feature of many prenatally diagnosed conditions and is not unique to cCMV infection. We are of the opinion that patients and their partners would benefit from the autonomy and knowledge to make informed decisions about their pregnancies. Indeed, the 2012 study by Lim et al. showed that the majority of mothers would like to be given the option of receiving prenatal CMV serologic screening, and most would choose it if it was offered by their obstetrician.³

The cost-effectiveness of universal screening has been explored in a previous study, which suggested that universal screening would be cost-effective if prevention of fetal transmission was 30% effective and the primary

CMV incidence was $\geq 0.82\%$.¹⁹ The incidence of primary CMV infection in Singapore is currently not known and would be an important area for further study. However, with valganciclovir appearing to reduce the risk of transmission by $>70\%$, universal screening is likely to be cost-effective even at a lower incidence of primary CMV infection. Screening of asymptomatic infants with cCMV also allows for early diagnosis of affected children; this can lower the costs currently incurred working up infants and children with delayed onset disabilities, reduce the stress and anxiety caused by an unknown diagnosis, and indirectly affect future reproductive decision-making by excluding genetic causes.

Finally, vaccine development has been proposed as a more effective way for CMV prevention. There are currently several vaccine candidates, including a messenger RNA vaccine that is undergoing phase II trials.²⁰ CMV screening, however, remains an important step to reduce fetal morbidity from cCMV infection while a safe and efficient vaccine is being developed.

In conclusion, there is a dire need to improve awareness of CMV in the medical community and couples of reproductive age, and to consider introducing screening for cCMV in pregnancy and newborns. Similar to Down syndrome screening, parents should have the opportunity to make an informed choice on whether they wish to proceed with testing. Mothers should not find out retrospectively about cCMV, nor should they feel guilty knowing it could have been prevented.

REFERENCES

1. Morton CC, Nance WE. Newborn hearing screening – A silent revolution. *N Eng J Med* 2006;354:2151-64.
2. Akpan US, Pillarisetty LS. Congenital cytomegalovirus infection. Treasure Island (FL): StatPearls Publishing, 2022. Available at: <https://www.ncbi.nlm.nih.gov/books/NBK541003/>. Accessed on 18 June 2022.
3. Lim SL, Tan WC, Tan LK. Awareness of and attitudes towards congenital cytomegalovirus infection among pregnant women in Singapore. *Int J Gynaecol Obstet* 2012;117:268-72.
4. Coppola T, Mangold JF, Cantrell S, et al. Impact of maternal immunity on congenital cytomegalovirus birth prevalence and infant outcomes: a systematic review. *Vaccines* 2019;7:129.
5. Leruez-Ville M, Ville Y. Is it time for routine prenatal serological screening for congenital cytomegalovirus? *Prenat Diagn* 2020; 40:1671-80.
6. Adler SP, Nigro G, Pereira L. Recent advances in the prevention and treatment of congenital cytomegalovirus infections. *Semin Perinatol* 2007;31:10-8.
7. Adler SP, Finney JW, Manganello AM, et al. Prevention of child-to-mother transmission of cytomegalovirus among pregnant women. *J Pediatr* 2004;145:485-91.
8. Boppana SB, Ross SA, Shimamura M, et al. Saliva polymerase-chain-reaction assay for cytomegalovirus screening in newborns. *N Eng J Med* 2011;364:2111-8.
9. Faure-Bardon V, Magny JF, Parodi M, et al. Sequelae of congenital cytomegalovirus following maternal primary infections are limited to those acquired in the first trimester of pregnancy. *Clin Infect Dis* 2019;69:1526-32.
10. Revello MG, Vauloup-Fellous C, Grangeot-Keros L, et al. Clinical evaluation of new automated cytomegalovirus IgM and IgG assays for the Elecsys® analyser platform. *Eur J Clin Microbiol Infect Dis* 2012;31:3331-9.
11. Berth M, Grangeot-Keros L, Heskia F, et al. Analytical issues possibly affecting the performance of commercial human cytomegalovirus IgG avidity assays. *Eur J Clin Microbiol Infect Dis* 2014;33:1579-84.
12. Ville Y. Advocating for cytomegalovirus maternal serologic screening in the first trimester of pregnancy: if you do not know where you are going, you will wind up somewhere else. *Am J Obstet Gynecol MFM* 2021;3:100356.
13. Leruez-Ville M, Ren S, Magny JF, et al. Accuracy of prenatal ultrasound screening to identify fetuses infected by cytomegalovirus which will develop severe long-term sequelae. *Ultrasound Obstet Gynecol* 2021;57:97-104.
14. Shahar-Nissan K, Pardo J, Peled O, et al. Valganciclovir to prevent vertical transmission of cytomegalovirus after maternal primary infection during pregnancy: a randomised, double-blind, placebo-controlled trial. *Lancet* 2020;396:779-85. Erratum in: *Lancet* 2020;396:1070.
15. Leruez-Ville M, Ghout I, Bussi eres L, et al. In utero treatment of congenital cytomegalovirus infection with valganciclovir in a multicenter, open-label, phase II study. *Am J Obstet Gynecol* 2016;215:462.e1-462.e10.
16. 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 Gynaecol* 2019;53:383-9.
17. Revello MG, Lazzarotto T, Guerra B, et al. A randomized trial of hyperimmune globulin to prevent congenital cytomegalovirus. *N Eng J Med* 2014;370:1316-26.
18. Hughes B. LB17. Randomized Trial to Prevent Congenital Cytomegalovirus (CMV). *Open Forum Infect Dis* 2019; 6(Suppl 2):S1000-S1001.
19. Albright CM, Werner EF, Hughes BL. Cytomegalovirus Screening in Pregnancy: A Cost-Effectiveness and Threshold Analysis. *Am J Perinatol* 2019;36:678-87.
20. John S, Yuzhakov O, Woods A, et al. Multi-antigenic human cytomegalovirus mRNA vaccines that elicit potent humoral and cell-mediated immunity. *Vaccine* 2018;36:1689-99.