There is low awareness of congenital cytomegalovirus (CMV) in Australia. Routine pregnancy serological screening for CMV is not recommended, but all pregnant women should be given advice about CMV prevention. Obstetricians may be asked to see a pregnant woman when serology suggests CMV infection or when features of fetal infection are present on ultrasound. If maternal CMV infection is confirmed, the timing of infection (pre-pregnancy or gestation of pregnancy), must be determined to predict the fetal risks. In addition, it is important to establish whether maternal infection is primary or reactivation. If there is fetal infection, ultrasound can be used to attempt to establish whether the fetus may have been affected. Serial serology, CMV IgG avidity, maternal viraemia (using serum PCR), amniotic fluid CMV PCR, serial fetal ultrasounds, and possibly fetal MRI (magnetic resonance imaging) are investigations that may be useful to predict neonatal outcomes. Timely and accurate counselling is important to optimise maternal and neonatal management.

Primary maternal CMV infection in the first trimester of pregnancy has the greatest risk of adverse fetal and infant outcomes. These include hearing loss, adverse neurodevelopmental outcomes and in severe cases, fetal death. In first trimester CMV infection, approximately 35% of fetuses will develop CMV infection. Of these, only 25% will have an adverse outcome due to the infection. Thus, it is estimated 10% of women with a primary CMV infection in early pregnancy will have a fetus or infant with an adverse outcome. The rate of fetal infection increases with gestation, but the rate of fetal and infant adverse outcomes decreases with gestation. The rates of adverse outcomes with peri-conception CMV are lower still than in the first trimester. Furthermore, the risks of fetal infection and adverse outcomes are lower with CMV reactivation or re-infection, than with primary infection.

Routine serologic CMV screening in pregnancy is not recommended in Australia. The potential benefits of routine screening are outweighed by the harms. Screening women at high risk of acquiring CMV infection, ideally pre-pregnancy, may be considered. In addition, CMV serology testing may be indicated in women with signs or symptoms of infection. However, regardless of serological status, pregnant women should be given advice about how CMV is spread and how to reduce exposure to saliva and urine that might contain CMV: this includes advice about handwashing after contact with body fluids, and avoiding sharing food and eating utensils.

Most women with CMV infection are asymptomatic. In my practice, I see asymptomatic pregnant women who have had ad hoc screening and are CMV IgG positive and/or IgM positive. The differential diagnosis includes pre-pregnancy infection, primary infection (peri-conception or in pregnancy), reactivation/reinfection, or less commonly false positive serology. CMV IgM is a sensitive marker of primary infection, however only 50% of CMV positive individuals have primary infection, as CMV IgM may persist for long periods of time. Primary CMV infection can be diagnosed by IgG seroconversion. Antenatal booking serology is kept for 1 year. CMV IgG avidity may be useful to determine timing of CMV infection, especially if no other sample serology is available for comparison. High avidity during the first trimester excludes primary infection within the preceding 3–4 months. Low avidity suggests infection within the previous 3 months. Change in avidity may also be used to predict timing of infection. Maternal CMV viraemia using polymerase chain reaction (PCR) may be also useful to establish the time of infection.

Once the diagnosis of primary maternal CMV in pregnancy, or periconception is established, determining fetal infection will assist in predicting infant outcomes. Amniotic fluid CMV PCR is the most
accurate method of detection of fetal CMV infection\textsuperscript{15}. Ideally an amniocentesis should be performed after 20–22 weeks gestation, and a minimum of 6 weeks after the primary infection\textsuperscript{16}. A negative result before then may be falsely reassuring, and a repeat amniocentesis with a small risk of miscarriage (0.5%), may be required. If the amniotic fluid CMV PCR is negative, the risk of the fetus being infected at birth is small (8%), and the risk of an abnormal outcome is low (\textasciitilde0.5\%)\textsuperscript{3}.

Fetal ultrasound can be used to predict adverse fetal/neonatal outcomes of fetal CMV infection. The ultrasound features of congenital CMV are non-specific, but include microcephaly, echogenic bowel, intrauterine growth restriction, hydronephrosis, cerebral ventriculomegaly, brain calcifications and an enlarged placenta\textsuperscript{5,17,18}. The risk of adverse fetal/neonatal outcomes when there are ultrasound abnormalities and proven fetal infection is \textasciitilde46\%\textsuperscript{7}. This risk is significantly reduced to 13\%, when there are no ultrasound abnormalities\textsuperscript{3}. However, if there are no ultrasound abnormalities, ongoing ultrasound surveillance is recommended, as ultrasound evidence of CMV damage may develop later\textsuperscript{15}. MRI may give additional information in cases of confirmed fetal infection, especially if the fetal ultrasound shows no abnormality\textsuperscript{3}.

Women who have possible or proven CMV infection in pregnancy should be counselled by experienced clinicians\textsuperscript{10,19}. The role of maternal therapy to prevent adverse fetal and neonatal effects of CMV infection is uncertain\textsuperscript{20}. Ongoing research into the role of CMV hyperimmune globulin is in progress\textsuperscript{21}. Termination of pregnancy may be an option for some women, particularly if there is fetal infection and/or ultrasound evidence of fetal sequelae. The availability and timing of termination of pregnancy varies, as laws differ between states and territories in Australia\textsuperscript{22}. A previous study has found that 17\% of women with a CMV diagnosis in the first trimester will terminate the pregnancy, before undergoing an amniocentesis\textsuperscript{22}. If fetal or maternal CMV in pregnancy has been diagnosed and the pregnancy continues, neonatal investigation is recommended. Clinical examination and neonatal saliva PCR are the initial methods of choice\textsuperscript{23}, and placental examination may be useful. When neonatal CMV infection is detected, neonatal surveillance for hearing loss and long-term outcomes is recommended to reduce the risk of adverse sequelae\textsuperscript{24,25}. The role of antiviral therapies is less certain\textsuperscript{20}.

It is well recognised that CMV infection may persist\textsuperscript{25}. The optimal timing to avoid pregnancy after CMV infection is not known. However postponing pregnancy for a period of 6–12 months may be advisable after primary CMV infection, as periconception infection is also associated with fetal effects\textsuperscript{3,26}.26

References

Animal models of human cytomegalovirus congenital infection

Helen Farrell
School of Chemistry and Molecular Biology
University of Queensland
St Lucia, Qld 4067, Australia
Centre for Children’s Health Research
University of Queensland
South Brisbane, Qld 4101, Australia
Email: h.farrell1@uq.edu.au

Human cytomegalovirus (HCMV) infection is highly species-specific, which means that it is unable to productively infect laboratory animals. Despite this caveat, studies of animal CMV counterparts in their natural hosts have revealed significant correlations with observed neuropathological effects of congenital HCMV infection and have improved our understanding of host responses to vaccination. The biological relatedness between human and animal CMVs has been confirmed by phylogenetic analyses; the conservation of ‘core’ genes that are essential for virus replication as well as genes that contribute similar mechanisms for virus persistence in their respective host species. The common animal models of HCMV congenital infection include Rhesus CMV (RhCMV), guinea-pig CMV (GPCMV) and mouse CMV (MCMV). Whilst animal models of CMV do not fully recapitulate HCMV infection, they each offer specific advantages in understanding HCMV congenital/perinatal infection (summarised in Table 1).

Transplacental transmission and neonatal infections

The placentae of the guinea-pig and the rhesus macaque are structurally similar to the human placenta. Experimental infections with RhCMV and GPCMV result in foetal infection, with clinical manifestations that include CNS involvement and (for GPCMV) sensorineural hearing loss (SNHL). Systemic maternal infection causes syndromes deleterious for the developing foetus, (e.g. intrauterine growth restriction) with the incidence of foetal morbidity and mortality being highest when transmission occurs during early gestation. These key pathological features are similar to congenital HCMV infection.

Despite poor transplacental transmission of MCMV in the laboratory setting, direct injection into the foetus or the newborn pup has been shown to mimic HCMV-induced congenital disease. Similar to RhCMV, the susceptibility of neuronal stem cells to MCMV infection is maturation stage-dependent, with a rapid resistance to infection of the brain developing after birth. MCMV also infects the auditory nerve spiral ganglion and cochlea of newborn pups with measurable cytopathic effects and neuronal loss, and thus offers an amenable model for studying viral and host factors that contribute to SNHL.

Evaluation of antiviral therapies to ameliorate effects of congenital infection

Current antiviral therapies for HCMV target the viral replicative machinery (e.g. ganciclovir, valganciclovir, foscarnet and cidilovor). However, due to their toxicity, none are licenced for use during pregnancy and only ganciclovir/valganciclovir (that target the