Evidence evaluation report — Cytomegalovirus

Consultation draft — October 2018

Contents

Key messages

Background

Congenital cytomegalovirus is the most frequent infectious cause of newborn disability in developed countries.

Mother-child transmission of cytomegalovirus is higher for maternal primary infection than re-activated (non-primary) infection (30–35% versus 1.4%). The risk for long-term outcomes appears to be highest in infants born to mothers with primary infection in the first half of pregnancy.

About 10% of babies infected with cytomegalovirus are born with symptoms and are at risk of developing sensorineural hearing loss (35%) or cognitive deficits (up to 60%) or of death (4%). Babies who are infected and who are born without symptoms may have normal hearing at birth but are also at risk of developing long-term neurological sequelae (10-15%), in particular hearing impairment (7-10%). In developed countries, congenital cytomegalovirus accounts for 21% and 24% of cases of hearing loss at birth and 4 years of age, respectively.

Prevalence and risk factors

Cytomegalovirus is a highly prevalent infectious agent in the general population; seropositivity rates in adult women range between 40 and 90%, with the highest rates occurring in individuals from lower socio-economic background.

Approximately 40% of Australian women of childbearing age are at risk of a primary cytomegalovirus infection during pregnancy. The rate of symptomatic disease resulting from congenital cytomegalovirus infection has been estimated at 3.7 per 100,000 live births (0.004%) but this may be an underestimate as it is based on voluntary reporting. Based on average global figures in all socioeconomic groups, it has been estimated that each year 437 children in Australia will be born with or develop cytomegalovirus-related disease resulting from primary or non-primary maternal infection.

Primary cytomegalovirus infection occurs following close personal contact and is transmitted via body fluids or objects that are likely to carry infection (eg utensils) between individuals, or vertically across the placenta resulting in congenital infection in the fetus. Children, when infected vertically or in the first few years of life, can shed virus in urine and saliva for many years either continuously or intermittently. Cytomegalovirus therefore spreads readily in settings where preschool children are concentrated. This places seronegative pregnant women who work in child care centres or who have a young child in the home or in day care at increased risk of seroconversion.

Testing for cytomegalovirus

Up to 50% of maternal cytomegalovirus infections have nonspecific clinical manifestations, and most remain undetected unless specific serological testing is undertaken. The combination of serology tests for cytomegalovirus-specific IgM, IgG and IgG avidity provide improved distinction between primary and secondary maternal infections.

However, difficulties in accurate diagnosis, absence of effective interventions in preventing transmission of cytomegalovirus from mothers with primary cytomegalovirus infection to their infant, possibility of reinfection or reactivation, and the challenges in providing definite prognosis to an individual mother means that universal testing of pregnant women is not currently recommended in most countries including the UK and North America. The International Congenital Cytomegalovirus Recommendations Group (Rawlinson et al 2017) noted that universal testing of pregnant women for primary cytomegalovirus infection is currently not recommended.

The consensus document recommends that cytomegalovirus serology tests (cytomegalovirus-specific IgG, IgM, and IgG avidity) should be offered when a pregnant woman develops an illness with influenza-like symptoms (typically fever, fatigue, and headache) not attributable to another specific infection, or when imaging findings (ultrasound or the less frequently used MRI) are suggestive of fetal cytomegalovirus infection.

Conclusions on the cost-effectiveness of testing for cytomegalovirus are limited by insufficient evidence on the effectiveness of treatments in preventing congenital cytomegalovirus.

Prevention and treatment

Prevention of maternal infection using hygiene and behavioural interventions reduces maternal seroconversion rates during pregnancy. Knowledge about cytomegalovirus among women who are pregnant or planning a pregnancy is limited to one in five women and only one in ten health professionals routinely discuss cytomegalovirus prevention with pregnant women.

Cytomegalovirus hyperimmune globulin treatment does not appear to reduce the risk of congenital infection and the evidence on adverse effects is inconsistent.

The evidence on cytomegalovirus antiviral therapy as prophylaxis or treatment is too limited for conclusions to be drawn.

1   Process of the review

1.1   Research questions

1.1.1   Prevalence and risk factors

Q1   What is the prevalence and incidence of cytomegalovirus in pregnancy, including population specific groups?

Q2   What are the risk factors for developing cytomegalovirus in pregnancy?

1.1.2   Testing for cytomegalovirus

Q3   What is the diagnostic accuracy of testing for cytomegalovirus?

Q4   What is the cost effectiveness of testing for cytomegalovirus?

Q5   What are the harms and benefits of testing for cytomegalovirus?

Q6   When should pregnant women be screened for cytomegalovirus?

1.1.3   Interventions

Q7   What interventions or treatment for cytomegalovirus are effective and safe in pregnancy?

1.1.4   Additional considerations

Q8   What are the additional considerations for Aboriginal and Torres Strait Islander women?

Q9   What are the additional considerations for migrant and refugee women

1.1.5   PICO criteria used to inform the literature search

Population	Intervention	Comparator	Outcomes
Pregnant women	Education	Usual care	Maternal cytomegalovirus infection
	Hyperimmune globulin	Placebo/no treatment	Transmission of cytomegalovirus
	Antivirals	Placebo/no treatment	Symptomatic congenital cytomegalovirus

1.2   Search strategy

To be included.

1.3   Exclusion criteria

Full texts of 74 papers were reviewed and the exclusion criteria outlined below applied.

• Background information (7 studies)

• Duplicate (4 studies)

• Not specific to target population (5 studies)

• Does not answer research question (15 studies)

• Narrative review (18 studies)

• Opinion paper (editorial, letter, comment) (7 studies).

The excluded studies are listed in Section 6.

Following application of the exclusion criteria, 18 studies were included in the analysis. These included a consensus document developed by the International Congenital Cytomegalovirus Recommendations Group (Rawlinson et al 2017) and a recent Australian narrative review (Naing et al 2016).

PRISMA diagram to be included.

1.4   Assigning level of evidence

Levels of evidence were assigned using the NHMRC levels and the study design definitions given in Section 1.5.

Level	Intervention
I	Systematic review of level II studies
II	A randomised controlled trial
III-1	Pseudo-randomised trial
III-2	A comparative study with concurrent controls: • Non-randomised experimental trial • Cohort study • Case-control study • Interrupted time series with control group
III-3	A comparative study without concurrent controls: ▪ Historical control study ▪ Two or more single arm study ▪ Interrupted time series without parallel control
IV	Case series with either post-test or pre-test/post-test outcomes

1.5   Study design definitions

- **Case series** — a single group of people exposed to the intervention (factor under study). **Post-test** – only outcomes after the intervention (factor under study) are recorded in the series of people, so no comparisons can be made. **Pre-test/post-test** – measures on an outcome are taken before and after the intervention is introduced to a series of people and are then compared (also known as a 'before- and-after study').

- **Case-control study** — people with the outcome or disease (cases) and an appropriate group of controls without the outcome or disease (controls) are selected and information obtained about their previous exposure/non-exposure to the intervention or factor under study.

- **Cross-sectional study** — a group of people are assessed at a particular point (or cross-section) in time and the data collected on outcomes relate to that point in time ie proportion of people with asthma in October 2004. This type of study is useful for hypothesis-generation, to identify whether a risk factor is associated with a certain type of outcome, but more often than not (except when the exposure and outcome are stable eg genetic mutation and certain clinical symptoms) the causal link cannot be proven unless a time dimension is included.

- **Historical control study** – outcomes for a prospectively collected group of people exposed to the intervention (factor under study) are compared with either (1) the outcomes of people treated at the same institution prior to the introduction of the intervention (ie. control group/usual care), or (2) the outcomes of a previously published series of people undergoing the alternate or control intervention.

- **Non-randomised, experimental trial** - the unit of experimentation (eg. people, a cluster of people) is allocated to either an intervention group or a control group, using a non-random method (such as patient or clinician preference/availability) and the outcomes from each group are compared. This can include:

  — **a controlled before-and-after study**, where outcome measurements are taken before and after the intervention is introduced, and compared at the same time point to outcome measures in the (control) group.

  — **an adjusted indirect comparison**, where two randomised controlled trials compare different interventions to the same comparator ie the placebo or control condition. The outcomes from the two interventions are then compared indirectly.

- **Prospective cohort study** — where groups of people (cohorts) are observed at a point in time to be *exposed or not exposed* to an intervention (or the factor under study) and then are followed prospectively with further outcomes recorded as they happen.

- **Pseudo-randomised controlled trial** - the unit of experimentation (eg. people, a cluster of people) is allocated to either an intervention (the factor under study) group or a control group, using a pseudo-random method (such as alternate allocation, allocation by days of the week or odd-even study numbers) and the outcomes from each group are compared.
- **Randomised controlled trial** — the unit of experimentation (eg. people, or a cluster of people4) is allocated to either an intervention (the factor under study) group or a control group, using a random mechanism (such as a coin toss, random number table, computer-generated random numbers) and the outcomes from each group are compared.
- **Retrospective cohort study** — where the cohorts (groups of people exposed and not exposed) are defined at a point of time in the past and information collected on subsequent outcomes, eg. the use of medical records to identify a group of women using oral contraceptives five years ago, and a group of women not using oral contraceptives, and then contacting these women or identifying in subsequent medical records the development of deep vein thrombosis.
- **Systematic literature review** — systematic location, appraisal and synthesis of evidence from scientific studies.
- **Two or more single arm study** – the outcomes of a single series of people receiving an intervention (case series) from two or more studies are compared.

Source: NHMRC (2009) *NHMRC levels of evidence and grades of recommendations for developers of guidelines.*

1.6   Selection of outcomes for GRADE analysis

Outcomes were selected on the basis of clinical impact.

Outcome	Importance	Inclusion
Maternal cytomegalovirus infection	9	☑
Transmission of cytomegalovirus	9	☑
Symptomatic congenital cytomegalovirus	9	☑

Key: 1 – 3 less important; 4 – 6 important but not critical for making a decision; 7 – 9 critical for making a decision

1.7   Quality assessment

Quality of included studies was assessed using adapted NHMRC criteria for quality assessment of systematic reviews and GRADE criteria for quality assessment of randomised controlled trials and observational studies.

Assessment of quality of systematic literature reviews

Considerations in assessing quality of systematic reviews
Questions and methods clearly stated
Search procedure sufficiently rigorous to identify all relevant studies
Review includes all the potential benefits and harms of the intervention
Review only includes randomised controlled trials
Methodological quality of primary studies assessed
Data summarised to give a point estimate of effect and confidence intervals
Differences in individual study results are adequately explained
Examination of which study population characteristics (disease subtypes, age/sex groups) determine the magnitude of effect of the intervention is included
Reviewers' conclusions are supported by data cited
Sources of heterogeneity are explored

Source: Adapted from (NHMRC 2000a; NHMRC 2000b; SIGN 2004).

Assessment of limitations of randomised controlled trials

Study limitation	Explanation
Lack of allocation concealment	Those enrolling patients are aware of the group (or period in a crossover trial) to which the next enrolled patient will be allocated (a major problem in "pseudo" or "quasi" randomised trials with allocation by day of week, birth date, chart number, etc.).
Lack of blinding	Patient, caregivers, those recording outcomes, those adjudicating outcomes, or data analysts are aware of the arm to which patients are allocated (or the medication currently being received in a crossover trial).
Incomplete accounting of patients and outcome events	Loss to follow-up and failure to adhere to the intention-to-treat principle in superiority trials; or in noninferiority trials, loss to follow-up, and failure to conduct both analyses considering only those who adhered to treatment, and all patients for whom outcome data are available. The significance of particular rates of loss to follow-up, however, varies widely and is dependent on the relation between loss to follow-up and number of events. The higher the proportion lost to follow-up in relation to intervention and control group event rates, and differences between intervention and control groups, the greater the threat of bias.
Selective outcome reporting	Incomplete or absent reporting of some outcomes and not others on the basis of the results.
Other limitations	Stopping trial early for benefit. Substantial overestimates are likely in trials with fewer than 500 events and large overestimates are likely in trials with fewer than 200 events. Empirical evidence suggests that formal stopping rules do not reduce this bias. Use of unvalidated outcome measures (e.g. patient-reported outcomes) Carryover effects in crossover trial Recruitment bias in cluster-randomised trials

Source: (Schünemann et al 2013).

Assessment of limitations of observational studies

Study limitation	Explanation
Failure to develop and apply appropriate eligibility criteria (inclusion of control population)	Under- or over-matching in case-control studies Selection of exposed and unexposed in cohort studies from different populations
Flawed measurement of both exposure and outcome	Differences in measurement of exposure (e.g. recall bias in case-control studies) Differential surveillance for outcome in exposed and unexposed in cohort studies
Failure to adequately control confounding	Failure of accurate measurement of all known prognostic factors Failure to match for prognostic factors and/or adjustment in statistical analysis
Incomplete or inadequately short follow-up	Especially within prospective cohort studies, both groups should be followed for the same amount of time.

Source: (Schünemann et al 2013).

Quality criteria of diagnostic accuracy studies derived from QUADAS-2

Domain	Patient Selection	Index Test	Reference Standard	Flow and Timing
Description	Describe methods of patient selection Describe included patients (previous testing, presentation, intended use of index test, and setting)	Describe the index test and how it was conducted and interpreted	Describe the reference standard and how it was conducted and interpreted	Describe any patients who did not receive the index tests or reference standard or who were excluded from the 2 X 2 table Describe the interval and any interventions between index tests and the reference standard

Domain	Patient Selection	Index Test	Reference Standard	Flow and Timing
Signalling questions	Was a consecutive or random sample of patients enrolled? Was a case-control design avoided? Did the study avoid inappropriate exclusions?	Were the index test results interpreted without knowledge of the results of the reference standard? If a threshold was used, was it pre-specified?	Is the reference standard likely to correctly classify the target condition? Were the reference standard results interpreted without knowledge of the results of the index test?	Was there an appropriate interval between index tests and reference standard? Did all patients receive a reference standard? Did all patients receive the same reference standard? Were all patients included in the analysis?
Risk of bias	Could the selection of patients have introduced bias?	Could the conduct or interpretation of the index test have introduced bias?	Could the reference standard, its conduct, or its interpretation have introduced bias?	Could the patient flow have introduced bias?

Source: (Schünemann et al 2013).

1.8   Assessing clinical utility of tests

- *Risks*: what is the extent of the risks associated with the condition?
- *Diagnostic accuracy*: how does the test compare to a reference test?
- *Prevalence*: at what prevalence does testing make a difference?
- *Treatment*: is effective treatment available and does it improve maternal/fetal outcomes?
- *Cost-effectiveness*: is the test cost-effective for the target population in the Australian context?

1.9   Grading of the certainty of the body of evidence

Assessing the certainty of a body of evidence using GRADE involves consideration of the following five domains: risk of bias, inconsistency, indirectness, imprecision and publication bias.

For an evidence base drawn from RCTs, the grading of the certainty of the body of evidence starts at 'high'. An evidence base drawn from observational studies starts as 'low'. In both cases, the evidence can be downgraded for each of the five domains depending on whether the limitation is considered serious (downgrade one level) or very serious (downgrade two levels). Evidence can also be upgraded when the effect is large (upgrade one level) or very large (upgrade two levels), where confounders would reduce the effect or where there is a dose-response effect.

Diagnostic accuracy studies start as high quality evidence. However, these studies are vulnerable to limitations and often lead to low quality evidence, mostly owing to indirectness of evidence associated with diagnostic accuracy being only a surrogate for patient outcomes.

2 Prevalence and risk factors

2.1 Q1: What is the prevalence and incidence of cytomegalovirus in pregnancy, including population specific groups?

2.1.1 Background

Congenital cytomegalovirus is the most frequent, though under-recognised, infectious cause of newborn disability in developed countries (Rawlinson et al 2017).

The risk of mother-child transmission of cytomegalovirus is higher for maternal primary infection than re-activated (non-primary) infection (30 to 35% versus 1.4%) (Manicklal et al 2013). The risk for long-term outcomes appears to be highest in infants born to mothers with primary infection in the first half of pregnancy (Manicklal et al 2013).

About 10% of newborns with congenital cytomegalovirus are symptomatic at birth (Manicklal et al 2013). Physical signs including jaundice, petechiae (small spots caused by bleeding into the skin), enlarged spleen and liver and neurological abnormalities (eg microcephaly) are observed in most (~75%) symptomatic infants with congenital cytomegalovirus infection (Naing et al 2016). Among babies who are symptomatic at birth, sensorineural hearing loss occurs in about 35%, cognitive deficits in up to two-thirds and death in around 4% (Manicklal et al 2013).

Among asymptomatic infected newborns, 10-15% develop long-term neurological sequelae. While most asymptomatic babies have normal hearing at birth, hearing impairment has been reported in 7% to 10% of such infants (Manicklal et al 2013).

Overall (symptomatic and asymptomatic infections), permanent childhood hearing impairment is the commonest complication. In developed countries, congenital cytomegalovirus accounts for 21% and 24% of cases of hearing loss at birth and 4 years of age, respectively (Manicklal et al 2013).

2.1.2 Prevalence of cytomegalovirus in pregnancy

An Australian narrative review summarised recent evidence on the prevalence of cytomegalovirus in pregnancy and incidence of congenital cytomegalovirus (Naing et al 2016).

- Approximately 40% of Australian women of childbearing age are at risk of having a primary cytomegalovirus infection during pregnancy. The cytomegalovirus seroprevalence rate for pregnant women attending an antenatal clinic of a major teaching hospital in Sydney between 2002 and 2005 was 57%, which is comparable with an average seroprevalence of 58% for adults in the 14–44 age group (i.e childbearing age) examined in a nationwide survey. A single-centre study of 600 pregnant women in Sydney found a primary cytomegalovirus infection rate during pregnancy of approximately 1.2% and a rate of congenital cytomegalovirus infection of approximately 0.3% of live births, consistent with incidence in other populations of high socio-economic status.

- The rate of symptomatic disease resulting from congenital cytomegalovirus infection has been estimated at 3.7 per 100,000 live births (0.004%) by the Australian Paediatric Surveillance Unit. These infections are responsible for at least 9.4 per 100,000 hospital admissions of children between 0 and 4 years old in the Australian population. However, these figures rely on voluntary reporting or detection of clinical sequelae requiring hospitalisation and, because neonatal and maternal cytomegalovirus screening is currently not routinely undertaken and accurate diagnosis of cytomegalovirus usually requires directed blood testing, these are likely to be significant underestimates. It is estimated that 437 children in Australia will be born with or develop cytomegalovirus-related disease every year, based on the average global figures from a large and detailed meta-analysis for rates of congenital cytomegalovirus infection, symptomatic disease and later sequelae. These figures take into account congenital infections resulting from both primary and secondary maternal infections, in all socioeconomic groups within those populations.

2.1.3 Summary

Approximately 40% of Australian women of childbearing age are at risk of a primary cytomegalovirus infection during pregnancy. The rate of symptomatic disease resulting from congenital cytomegalovirus infection has been estimated at 3.7 per 100,000 live births (0.004%) but this may be an underestimate as it is based on voluntary reporting. Based on average global figures in all socioeconomic groups, it has been estimated that each year 437 children in Australia will be born with or develop cytomegalovirus-related disease resulting from primary or non-primary maternal infection.

2.2 Q2: What are the risk factors for developing cytomegalovirus in pregnancy?

2.2.1 Risk factors

The risk factors for cytomegalovirus are well-established and no studies were identified that specifically investigated risk factors. A recent narrative review summarised findings on the risk of developing cytomegalovirus in Australia (Naing et al 2016).

- Cytomegalovirus is a highly prevalent infectious agent in the general population; seropositivity rates in adult women range between 40 and 90%, with the highest rates occurring in individuals from lower socio-economic background.

- Primary cytomegalovirus infection occurs following close personal contact and is transmitted via body fluids or objects that are likely to carry infection (eg utensils) between individuals, or vertically across the placenta resulting in congenital infection in the fetus.

- Cytomegalovirus infections are common and usually asymptomatic in otherwise healthy children, with the seroprevalence in an Australian survey of children aged 1–2 years being 38%. This suggests that parents of young children are particularly at risk of being exposed to cytomegalovirus infection. This is consistent with the observed dramatic increase in overall seropositivity found in Australian women in the 35–39 age group (79%) compared to women in the 30–34 age group (56%), which was not consistent with the expected normal steady increase in seropositivity that occurs with age.

- A significant number (~23%) of women are therefore seroconverting to cytomegalovirus at a time of life associated with childbearing and childrearing, which is of relevance given that caring for young children is associated with increased risk of cytomegalovirus infection. If 30% of these women transmit virus during pregnancy, similar to current global estimates, and 11% of these transmissions result in a cytomegalovirus-affected child at birth, with an additional 13.5% of transmissions resulting in a child that develops later sequelae, it is clear that the burden of congenital cytomegalovirus disease in Australia has been significantly underestimated.

An additional narrative review (Manicklal et al 2013) noted that children, when infected vertically or in the first few years of life, can shed virus in urine and saliva for many years either continuously or intermittently. Cytomegalovirus therefore spreads readily in settings where preschool children are concentrated. This places seronegative pregnant women who work in child care centres or who have a young child in the home or in day care at increased risk of seroconversion.

2.2.2 Summary

Primary cytomegalovirus infection occurs following close personal contact and is transmitted via body fluids or objects that are likely to carry infection (eg utensils) between individuals, or vertically across the placenta resulting in congenital infection in the fetus. Children, when infected vertically or in the first few years of life, can shed virus in urine and saliva for many years either continuously or intermittently. Cytomegalovirus therefore spreads readily in settings where preschool children are concentrated. This places seronegative pregnant women who work in child care centres or who have a young child in the home or in day care at increased risk of seroconversion.

3 Testing for cytomegalovirus

3.1 Q3: What is the diagnostic accuracy of testing for cytomegalovirus?

3.1.1 Diagnostic accuracy of testing for cytomegalovirus

No studies that reported on the diagnostic accuracy of testing for cytomegalovirus were identified.

A consensus document developed by the International Congenital Cytomegalovirus Recommendations Group recommended that (Rawlinson et al 2017):

- For cytomegalovirus-seronegative pregnant women, the diagnostic assessment of primary cytomegalovirus infection should include the detection of cytomegalovirus-specific IgG in serum. When the immune status before pregnancy is unknown, the diagnosis of maternal primary cytomegalovirus infection should be on the basis of the detection of both cytomegalovirus IgM and cytomegalovirus IgG antibodies of low-to-moderate avidity.

- A confirmed diagnosis of fetal cytomegalovirus infection can be made after 20–21 weeks of gestation, and at least 6 weeks from the time of maternal infection, by testing amniotic fluid for cytomegalovirus using nucleic acid test assays such as real-time PCR.

An Australian narrative review stated that (Naing et al 2016):

- Up to 50% of maternal cytomegalovirus infections have nonspecific clinical manifestations, and most remain undetected unless specific serological testing is undertaken. The combination of serology tests for cytomegalovirus-specific IgM, IgG and IgG avidity provide improved distinction between primary and secondary maternal infections.

- In pregnancies with confirmed primary maternal cytomegalovirus infection, amniocentesis with cytomegalovirus-PCR performed on amniotic fluid, undertaken after 21-22 weeks gestation, may determine whether maternofetal virus transmission has occurred. Ultrasound and, to a lesser extent, magnetic resonance imaging are valuable tools to assess fetal structural and growth abnormalities. However, some features of cytomegalovirus infection are not detectable by antenatal imaging.

3.2 Q4: What is the cost effectiveness of testing for cytomegalovirus?

No studies on the cost-effectiveness of testing for cytomegalovirus were identified.

A study identified through the previous review found that conclusions on the cost-effectiveness of testing for cytomegalovirus are limited by insufficient evidence on the effectiveness of treatments in preventing congenital cytomegalovirus (Cahill et al 2009).

3.3 Q5: When should pregnant women be tested for cytomegalovirus?

The International Congenital Cytomegalovirus Recommendations Group consensus document recommends that cytomegalovirus serology tests (cytomegalovirus-specific IgG, IgM, and IgG avidity) should be offered when a pregnant woman develops an illness with influenza-like symptoms (typically fever, fatigue, and headache) not attributable to another specific infection, or when imaging findings (ultrasound or the less frequently used MRI) are suggestive of fetal cytomegalovirus infection (Rawlinson et al 2017).

3.4 Q6: What are the harms and benefits of testing for cytomegalovirus?

Maternal screening to identify primary CMV infection in pregnancy may allow for early identification of infected infants and such screening programmes have previously been carried out, or are being carried out in certain European countries (e.g. Italy, Belgium, France, Germany and Sweden) and in Israel (Lim & Lyall 2017). However, difficulties in accurate diagnosis, absence of effective interventions in preventing transmission of cytomegalovirus from mothers with primary cytomegalovirus infection to their infant, possibility of reinfection or reactivation, and the challenges in providing definite prognosis to an individual mother means that universal testing of pregnant women is not currently recommended in most countries including the UK and North America (Lim & Lyall 2017).

The International Congenital Cytomegalovirus Recommendations Group (Rawlinson et al 2017) noted that universal testing of pregnant women for primary cytomegalovirus infection is currently not recommended.

4 Interventions

4.1 Q7: What interventions or treatment for cytomegalovirus are effective and safe in pregnancy?

4.1.1 International consensus recommendations on prevention and treatment

A consensus document developed by the International Congenital Cytomegalovirus Recommendations Group recommended that (Rawlinson et al 2017):

- all pregnant women and health-care providers should be educated about congenital cytomegalovirus infection and preventive measures
- cytomegalovirus hyperimmunoglobulin should not be routinely administered to pregnant women with primary cytomegalovirus infection to prevent fetal cytomegalovirus infection
- cytomegalovirus hyperimmunoglobulin treatment should not be routinely administered for fetal cytomegalovirus infection
- routine antiviral therapy to prevent congenital cytomegalovirus infection during pregnancy is not recommended
- routine antiviral therapy to treat fetal cytomegalovirus infection during pregnancy is not recommended.

Hygiene precautions to prevent cytomegalovirus infection in pregnant women

- Do not share food, drinks, or utensils used by young children
- Do not put a child's dummy/soother/pacifier in your mouth
- Avoid contact with saliva when kissing a child
- Thoroughly wash hands with soap and water for 15-20 seconds, especially after changing nappies/diapers, feeding a young child, or wiping a young child's nose or saliva
- Other precautions that can be considered, but are likely to less frequently prevent infection, include clean toys, countertops, and other surfaces that come into contact with children's urine or saliva, and not sharing a toothbrush with a young child

Source: (Rawlinson et al 2017).

4.1.2 Education to prevent maternal infection

A systematic review found that prevention of maternal infection using hygiene and behavioural interventions reduced maternal seroconversion rates during pregnancy but that maternal adherence to education on preventative behaviours was a limiting factor (Hamilton et al 2014).

Observational studies found knowledge about cytomegalovirus to be limited to 12.5-20% of women who are pregnant or planning a pregnancy (Pereboom et al 2013; Price et al 2014; Thackeray et al 2017). An Australian survey of health professionals found that only 8.8% of respondents routinely discussed cytomegalovirus prevention with pregnant women (Shand et al 2018). The majority (69.3%) responded that professional societies should make practice recommendations and 88% thought more patient information was needed, preferably leaflets.

Studies into measures to increase women's knowledge and preventive activities found that:

- a brief behavioural intervention (video and motivational interview) was more effective than standard care (a brochure) (mean difference in change score 3.0; 95%CI 0.8 to 5.2; P=0.007; RCT) (Hughes et al 2017)
- identification and hygiene counselling of cytomegalovirus-seronegative pregnant women significantly reduced maternal infection compared to no intervention (1.2% vs 7.6%; delta=6.4%; 95%CI 3.2 to 9.6; P<0.001) (Revello et al 2015)
- both a video and a fact sheet increased women's knowledge significantly (from 3.7/10 to 9.1/10, p<0.001) (Price et al 2014).

Studies into communicating messages about cytomegalovirus suggest that:

- prevalence of congenital cytomegalovirus should be communicated as a ratio (eg 1 in 150) or compared to other well-known disabilities (Levis et al 2017)
- framing messages by what women stand to gain or lose interacts with perceived behavioural control and response efficacy to influence behavioural intention (Thackeray et al 2017)
- least positive attitudes were toward not kissing a child on the lips and not sharing foods (Thackeray & Magnusson 2016).

4.1.3 Hyperimmune globulin to prevent maternal-fetal transmission

A systematic review found that treatment of maternal cytomegalovirus infection with hyperimmune globulin showed some evidence for efficacy in prevention of fetal infection and fetal/neonatal morbidity with a reasonable safety profile. However, more robust clinical evidence is required (Hamilton et al 2014).[1]

A randomised controlled trial (n=123) found no significant difference in rates of congenital infection between women with a primary cytomegalovirus infection in pregnancy who received cytomegalovirus hyperimmune globulin and those who received placebo (30% vs 44%; delta=14%; 95%CI -3 to 31; P=0.13) (Revello et al 2014). The number of obstetrical adverse events (preterm birth, pre-eclampsia, fetal growth restriction) was higher in the hyperimmune globulin group than in the placebo group (13% vs 2%; p=0.06).

Retrospective cohort studies suggest that

- hyperimmune globulin treatment is not associated with reduced birth weight (Nigro et al 2015; Chiaie et al 2018), head circumference (Chiaie et al 2018), or reduced duration of pregnancy (Nigro et al 2015; Chiaie et al 2018)

- prophylactic hyperimmune globulin treatment of pregnant women after cytomegalovirus primary infection does not seem to significantly reduce the rate of congenital infection (Blazquez-Gamero et al 2017).

4.1.4 Antiviral therapy

The evidence on the benefits and risks of antiviral treatment for maternal or fetal cytomegalovirus infection is limited.

- a systematic review of observational studies found some evidence for the safety and efficacy of established cytomegalovirus antivirals but a need for randomised trial data (Hamilton et al 2014)

- a systematic review of case reports found no short-term side effects associated with antiviral treatment of symptomatic maternal cytomegalovirus infection (Seidel et al 2017)

- compared with a historical cohort obtained by a meta-analysis of the literature, the use of valacyclovir (8 g daily) significantly increased the proportion of asymptomatic neonates from 43% without treatment to 82% with treatment (Leruez-Ville et al 2016).

4.1.5 Evidence summary

Prevention of maternal infection using hygiene and behavioural interventions reduces maternal seroconversion rates during pregnancy. Knowledge about cytomegalovirus among women who are pregnant or planning a pregnancy is limited to one in five women and only one in ten health professionals routinely discuss cytomegalovirus prevention with pregnant women.

Cytomegalovirus hyperimmune globulin treatment does not appear to reduce the risk of congenital infection and the evidence on adverse effects is inconsistent.

The evidence on cytomegalovirus antiviral therapy as prophylaxis or treatment is too limited for conclusions to be drawn.

4.1.6 Advice to the Expert Working Group

As there is no high-level evidence to support an evidence-based recommendation, suggest including consensus-based recommendations that:

- measures to prevent cytomegalovirus be discussed with women

- testing be offered to women who have frequent contact with large numbers of young children and when a pregnant woman develops an illness with influenza-like symptoms not attributable to another specific infection, or when imaging findings are suggestive of fetal cytomegalovirus infection.

This is consistent with the recommendations of the International Congenital Cytomegalovirus Recommendations Group.

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[1]   Note that this review included (Revello et al 2014) and (Nigro et al 2015), which are also summarised below.

4.1.7 Evidence table: Education to prevent maternal infection

Study ref	Design	LoE	N	Aim/population/methods	Results	Comments
(Rawlinson et al 2017)	Consensus	—	—	—	• All pregnant women and health-care providers should be educated about congenital cytomegalovirus infection and preventive measures.	Consensus recommendation
(Hamilton et al 2014)	SLR	IV	3 studies	**Aim**: To identify evidence-based interventions for prevention of congenital CMV at the primary level (prevention of maternal infection), secondary level (risk reduction of fetal infection and disease) and tertiary level (risk reduction of infected neonates being affected by CMV).	Prevention of maternal infection using hygiene and behavioural interventions reduced maternal seroconversion rates during pregnancy. However, evidence suggested maternal adherence to education on preventative behaviours was a limiting factor.	
(Hughes et al 2017)	RCT	II	187	**Aim**: to estimate the effects of a brief prenatal behavioural intervention on risk behaviours for maternal cytomegalovirus (CMV) infection. **Population**: Women screened for CMV before 20 weeks gestation, without serologic evidence of primary CMV infection. **Methods**: Participants were apprised of serostatus and then randomised 2:1 to either a brief behavioural intervention during their prenatal care visit or to standard care (a brochure). The 7 to 10-minute in-office intervention included a video and hygiene education using motivational interviewing. Participants were then given a reminder calendar to take home and weekly text message reminders. The primary outcome was change in behavioural compliance score on a scale of 0-100. Secondary outcomes included process evaluation and domains of behaviour change.	Baseline behavioural compliance scores increased modestly in the intervention group (mean: 7-point increase from 80.7 to 87.7, 95%CI 2.4 to 5.9) compared with the comparison group (mean: 4-point increase from 79.7 to 84.1, 95%CI 5.9 to 8.4; mean difference in change score: 3.0, 95% CI, 0.8-5.2; P=0.007). Women in the intervention group reported change in risk perception related to perceived severity and susceptibility, self-efficacy, and perceived norms (P<.05 for all).	

Study ref	Design	LoE	N	Aim/population/methods	Results	Comments
(Revello et al 2015)	Cohort	III-2	331	**Aim**: to investigate the effectiveness of hygiene information in reducing risk of CMV infection. **Population**: Pregnant women at risk of primary CMV infection for personal/occupational reasons. **Methods**: A mixed interventional and observational controlled study was conducted. In the intervention arm, CMV-seronegative women, identified at the time of maternal serum screening for fetal aneuploidy at 11-12 weeks of gestation, were given hygiene information and prospectively tested for CMV until birth. The comparison arm consisted of women enrolled at delivery who were neither tested for nor informed about CMV during pregnancy, and who had a serum sample stored at the screening for fetal aneuploidy. By design, groups were homogeneous for age, parity, education, and exposure to at least one risk factor. The primary outcome was CMV seroconversion. Acceptance of hygiene recommendations was a secondary objective and was measured by a self-report.	Four out of 331 (1.2%) women seroconverted in the intervention group compared to 24/315 (7.6%) in the comparison group (delta=6.4%; 95%CI 3.2 to 9.6; P<0.001). There were three newborns with congenital infection in the intervention group and 8 in the comparison group (1 with cerebral ultrasound abnormalities at birth). Ninety-three percent of women felt hygiene recommendations were worth suggesting to all pregnant women at risk for infection. This controlled study provides evidence that an intervention based on the identification and hygiene counselling of CMV-seronegative pregnant women significantly prevents maternal infection.	

Study ref	Design	LoE	N	Aim/population/methods	Results	Comments
(Levis et al 2017)	Cross-section	IV	102	**Aim**: We conducted formative research on fear appeals theory-based messages about CMV and prevention with U.S. women. Fear appeal theories suggest that message recipients will take action if they feel fear. **Population**: women who had young children who tested positive for cytomegalovirus (interviews); pregnant women and non-pregnant women who had young children (focus groups) **Methods**: In-depth interviews (N=32) and eight focus groups (N=70) were conducted. Participants reviewed and gave feedback on messages created around fear appeals theory-based communication concepts. The following concepts were tested in one or more of the three phases of research: CMV is severe, CMV is common, CMV is preventable, CMV preventive strategies are similar to other behaviour changes women make during pregnancy, CMV preventive strategies can be incorporated in moderation to reduce exposure, and CMV is severe but preventable.	Participants recommended communicating that CMV is common by using prevalence ratios (e.g., 1 in 150) or comparing CMV to other well-known disabilities. To convey the severity of CMV, participants preferred stories about CMV along with prevention strategies. Participants also welcomed prevention strategies when it included a message about risk reduction. In general, participants said messages were motivating, even if they felt that it could be difficult to make certain behaviour changes.	

Study ref	Design	LoE	N	Aim/population/methods	Results	Comments
(Thackeray et al 2017)	Cross-section	IV	840	**Aim**: to evaluate the effect of message framing on women's intention to perform cytomegalovirus (CMV) prevention behaviours. **Population**: An online panel of women 18-40 years, who were pregnant or planning a pregnancy. **Methods**: Women were randomised in a 2 x 2 factorial design to receive one of four CMV fact sheets. The fact sheets were framed as either what could be gained or be lost by following (or not) the recommendations and the likelihood of being affected by CMV (i.e., small chance or one of the most common infections in infants). The questionnaire measured CMV knowledge, participation in CMV risk or prevention behaviours, perceived severity of and susceptibly to CMV, and the perceived control over and the efficacy of recommended prevention behaviours. The dependent variable, intention to modify behaviour, was an index score that ranged from 0 to 16 with higher values indicating greater intention. Linear regression was used to evaluate the association between all independent variables and overall behavioural intention.	Among participants, 15.5% were familiar with CMV. Behavioural intention was high (M=10.43; SD=5.13) but did not differ across the message frames (p=0.23). Overall, behavioural intention was predicted by CMV knowledge, message credibility, perceived severity of CMV, perceived behavioural control and response efficacy. Significant interactions with gain vs loss frame were observed for perceived behavioural control (p=0.03) and response efficacy (p=0.003). Framing CMV messages by what women stand to gain or lose interacts with perceived behavioural control and response efficacy to influence behavioural intention. Perceived behavioural control and response efficacy were most predictive of behavioural intention overall regardless of frame. Messaging that focuses on these two variables, particularly for avoiding kissing a child on the lips and sharing food, cups and utensils, may result in greater gains in intention to participate in CMV prevention behaviours.	

Study ref	Design	LoE	N	Aim/population/methods	Results	Comments
(Thackeray & Magnusson 2016)	Cross-section	IV	840	**Aim**: To examine women's attitudes toward CMV prevention behaviours. **Population**: women 18-40 years of age, who had a child < 5 years of age, and were pregnant or planning a pregnancy in the next 12 months **Methods**: Data were collected from an online panel of women. Questions assessed CMV awareness, frequency of past behaviours that transmit CMV, and attitudes toward eight CMV prevention behaviours.	Only 15.5% of women were somewhat or very familiar with CMV. Very few women (6.1%) reported hearing from their provider about CMV. Women held positive attitudes toward the CMV prevention behaviours and perceived them as feasible. Least positive attitudes were toward not kissing a child on the lips and not sharing foods. Predictors of positive attitudes were CMV awareness, past behaviour, talking to a healthcare provider, and perceived risk reduction.	
(Price et al 2014)	Case series	IV	809	**Aim**: To pilot test two health education materials to gauge their appeal and to determine if they increase knowledge about CMV and motivate audiences to seek additional information on CMV and adopt CMV prevention behaviours. **Population**: African-American (n=404) and Caucasian women (n=405), who had a young child and were either pregnant or planning a pregnancy **Methods**: Participants were randomly assigned to view one of two CMV health education materials, either a factsheet or video. Pre- and post-survey measures were used to assess changes in knowledge of CMV and motivation to adopt prevention behaviours. Audience preferences regarding materials and motivation were also examined.	CMV knowledge score increased significantly after presentation of either the video or factsheet (from 3.7 out of 10 to 9.1 out of 10, $p<0.001$). The average materials appeal score was high, with a mean of 3.6 on a four-point scale, indicating women responded very positively to both materials. Regression analyses indicated that appeal, message involvement (e.g., information seeking, discussing with others), post materials knowledge score, and viewing the video (vs. factsheet) were significantly positively associated with increased support for CMV prevention behaviours.	

Study ref	Design	LoE	N	Aim/population/methods	Results	Comments
(Pereboom et al 2013)	Cross-section	IV	1,097	**Aim**: to assess knowledge and risk behaviour related to toxoplasmosis, listeriosis and CMV infection prevention in pregnant women. **Population**: Pregnant women. **Methods**: Women from twenty midwifery practices across the Netherlands participated in the DELIVER study, between October 2010 and December 2010. The questionnaire items covered respondents' knowledge of preventive practices in general, risk behaviour, and sources of received information.	Among respondents (response 66.0%), 12.5% had heard, read or seen information about CMV. The majority reported having heard about these infections from their care providers or read about these in printed media or on the Internet. Respondents showed limited knowledge about preventive practices for CMV infection. Regarding CMV infections, risk behaviour was less prevalent among respondents who were in their third trimester of pregnancy.	
(Shand et al 2018)	Cross-section	IV	774	**Aim**: To assess the knowledge, practice and attitudes of maternity clinicians regarding congenital cytomegalovirus (CMV). It is the most common congenital infection, and well-recognised cause of neurodevelopmental disability and hearing loss. New consensus recommendations state all pregnant women and health-care providers should be educated about congenital CMV infection and preventive measures. **Methods**: An email questionnaire was distributed in October 2015 to specialists (37.3%), general practitioners (17.3%), and trainees of the Royal Australian New Zealand College of Obstetricians and Gynaecologists (16.8%), and Victorian and New South Wales midwives (28.6%).	Overall, 30.2% felt confident about discussing CMV in pregnancy: less than 10% of midwives (7.4%) and less than half of specialists (47.1%, $p < .0001$). Only 8.8% of respondents routinely discussed CMV prevention with pregnant women. The majority (69.3%) responded that professional societies should make practice recommendations, and 88% thought more patient information was needed, preferably leaflets.	

4.1.8   Evidence table: Hyperimmunoglobulin

Study ref	Design	LoE	N	Aim/population/methods	Results	Comments
(Rawlinson et al 2017)	Consensus	—	—	—	• Cytomegalovirus hyperimmunoglobulin should not be routinely administered to pregnant women with primary cytomegalovirus infection to prevent fetal cytomegalovirus infection. • Cytomegalovirus hyperimmunoglobulin treatment should not be routinely administered for fetal cytomegalovirus infection.	Consensus recommendation
(Hamilton et al 2014)	SLR	IV	4 prophylaxis 6 treatment	**Aim:** To identify evidence-based interventions for prevention of congenital CMV at the primary level (prevention of maternal infection), secondary level (risk reduction of fetal infection and disease) and tertiary level (risk reduction of infected neonates being affected by CMV).	Treatment of maternal CMV infection with hyperimmune globulin (HIG) showed some evidence for efficacy in prevention of fetal infection and fetal/neonatal morbidity with a reasonable safety profile. However, more robust clinical evidence is required before HIG therapy can be routinely recommended.	Included (Revello et al 2014) and (Nigro et al 2015)
(Revello et al 2014)	RCT	II	123	**Aim:** To evaluate the efficacy of CMV-specific hyperimmune globulin in reducing intrauterine transmission. **Population**: Pregnant women with primary CMV infection at 5 to 26 weeks of gestation. **Methods**: Women were randomly assigned within 6 weeks after the presumed onset of infection to receive hyperimmune globulin or placebo every 4 weeks until 36 weeks of gestation or until detection of CMV in amniotic fluid. The primary endpoint was congenital infection diagnosed at birth or by means of amniocentesis.	The rate of congenital infection was 30% in the hyperimmune globulin group and 44% in the placebo group (a difference of 14 percentage points; 95%CI -3 to 31; P=0.13). The clinical outcome of congenital infection at birth was similar in the two groups. The number of obstetrical adverse events was higher in the hyperimmune globulin group than in the placebo group (13% vs. 2%).	

Study ref	Design	LoE	N	Aim/population/methods	Results	Comments
(Blazquez-Gamero et al 2017)	Retrospective cohort	III-2	36	**Aim**: to investigate the effectiveness of cytomegalovirus hyperimmune globulin (CMV-HIG) for the prevention and treatment of congenital CMV (cCMV) infection. **Population**: Pregnant women with primary CMV infection and/or detection of CMV-DNA in amniotic fluid **Methods**: A retrospective observational study was conducted in three tertiary hospitals in Madrid. In the period 2009-2015, CMV-HIG treatment was offered to all pregnant women with primary CMV infection and/or detection of CMV-DNA in amniotic fluid in participating centres. Women were divided into prevention and treatment groups (PG [n=17] and TG [n=19], respectively). Those with primary CMV infection who had not undergone amniocentesis comprised the PG and received monthly CMV-HIG (100 UI/kg). If CMV-DNA was subsequently detected in amniotic fluid, one extra dose of CMV-HIG (200 UI/kg) was given 4 weeks after the last dose. Those women were considered to be part of the PG group despite detection of CMV-DNA in amniotic fluid. In the case of a negative result in CMV-DNA detection in amniotic fluid or if amniocentesis was not performed, monthly HIG was given up to the end of the pregnancy.	Amniocentesis was performed in 83.4% of pregnancies and CMV PCR was positive in 21 of them (70%). One fetus with a positive PCR in amniotic fluid who received one dose of HIG after amniocentesis presented a negative CMV-PCR in urine at birth, and was asymptomatic at 12 months of age. Twenty-four children were infected at birth, and 16/21 (76.2%) presented no sequelae at 12 months, while two (9.5%) had a mild unilateral hearing loss and three (14.3%) severe hearing loss or neurological sequelae. In the PG 41% of fetuses were infected, one pregnancy was terminated due to abnormalities in cordocentesis and one showed a mild hearing loss at 12 months of age. The generally reported rate of congenital infection is 40%. In the TG, 18/19 children (95%) were diagnosed with cCMV, while the remaining neonate had negative urine CMV at birth. Eight out of the 19 fetuses (42.1%) showed CMV related abnormalities in the fetal US before HIG treatment. Complete clinical assessment in the neonatal period and at 12 months of age was available in 16 and 15 children, respectively. At birth 50% were symptomatic and at 12 months of age, 4/15 (26.7%) showed a hearing loss and 3/15 (20%) neurologic impairment. Fetuses with abnormalities on ultrasonography before HIG presented a high risk of sequelae (OR 60; 95%CI 3 to 1185; p=0.007).	

Study ref	Design	LoE	N	Aim/population/methods	Results	Comments
(Nigro et al 2015)	Retrospective cohort	III-2	358	**Aim**: To monitor hyperimmune globulin for a possible effect on duration of gestation and birth weight. **Population**: women with a primary CMV infection in pregnancy. **Methods**: We used clinical data on 358 women with a primary CMV infection during pregnancy, 164 of whom received one or more infusions of HIG.	The receipt of HIG was not associated with either a diminished birth weight or a reduced duration of pregnancy. The receipt of multiple doses of HIG (range 1-8) was significantly correlated with an increase in birth weight (p=0.006) and gestational age at delivery (p=0.014). This correlation was also significant for all asymptomatic infants and for infants whose mothers received multiple doses of HIG to prevent fetal infection.	
(Chiaie et al 2018)	Retrospective cohort	III-2	50	**Aim**: To determine the frequency of obstetrical adverse events and clinical outcome in infants following antenatal hyperimmune globulin (HIG) treatment for primary cytomegalovirus (CMV) infection in pregnancy. **Population**: Pregnant women, including three twin pregnancies. **Methods**: Primary infection was defined by seroconversion or the presence of CMV-specific IgM and low IgG avidity. All women received two or more infusions of HIG (200 U/kg). Congenital CMV (cCMV) infection was diagnosed by detection of CMV in amniotic fluid and/or neonatal urine. We compared gestational age (GA) at birth, head circumference (HC) and birth weight (BW) of infants in our study cohort with those of live-born infants delivered in our clinic between 2015 and 2016.	Median gestational age at time of maternal CMV diagnosis was 13 weeks. One-hundred-forty-one maternal HIG doses were given. No HIG-related severe adverse reactions occurred. Preterm birth rate was 4.2% (2/47) in singleton pregnancies. None of the neonates had birth weight or head circumference <3rd percentile for gestational age. There was no statistically significant difference regarding GA, BW and HC between our study cohort and the total population of live-born infants. The frequency of CMV-related sequelae in infants with cCMV infection was 10.5% (2/19) (one with bilateral hearing loss and one with mild motoric delay), both cases following first trimester maternal infection.	

4.1.9   Evidence table: Antiviral therapy

Study ref	Design	LoE	N	Aim/population/methods	Results	Comments
(Rawlinson et al 2017)	Consensus	—	—	—	• Routine antiviral therapy to prevent congenital cytomegalovirus infection during pregnancy is not recommended. • Routine antiviral therapy to treat fetal cytomegalovirus infection during pregnancy is not recommended.	Consensus recommendation
(Hamilton et al 2014)	SLR	IV	10 studies	**Aim**: To identify evidence-based interventions for prevention of congenital CMV at the primary level (prevention of maternal infection), secondary level (risk reduction of fetal infection and disease) and tertiary level (risk reduction of infected neonates being affected by CMV).	Limited evidence existed for the safety and efficacy of established CMV antivirals (valaciclovir, ganciclovir and valganciclovir) to treat neonatal consequences of CMV infection, but toxicity and lack of randomised clinical trial data remain major issues.	Included (Revello et al 2014)
(Seidel et al 2017)	SR	IV	7 case reports	**Aim**: to review the evidence on the use of ganciclovir (GCV) or valganciclovir (VGCV) during pregnancy, including safety of its use for mother and fetus. **Methods**: A PubMed database search was done up to November 16, 2016 without any restrictions of publication date or journal. Citations were searched and expert references were obtained. Reported cases were considered if therapy was in humans and initiation of treatment of the CMV infection was during pregnancy. In addition, two cases of VGCV treatment in pregnancy from the authors' tertiary care centre are reported.	Four cases reported on side effects in the fetus with antiviral treatment for symptomatic CMV infections in pregnant women. These varied in exposure and underlying comorbidity of the mother (two women also received antiretroviral therapy for HIV coinfection and two received immunosuppressive therapy following an organ transplant). There were no malformations of the fetus but long-term outcomes were not reported Three cases reported on antiviral treatment of proven fetal infection. Intrauterine GCV administration via cordocentesis was associated with preterm stillbirth. Following GCV treatment from 22 to 36 weeks gestation, the child was asymptomatic at 3 years. Following VGCV therapy from 30 to 38 weeks, the baby was asymptomatic at 2 weeks except for a unilateral hearing deficiency. Maternal side effects were not reported.	Review of case reports

Study ref	Design	LoE	N	Aim/population/methods	Results	Comments
(Leruez-Ville et al 2016)	Cohort	III-2	43	**Aim**: To evaluate the efficacy of oral valacyclovir, 8 g daily to treat cytomegalovirus in the fetus. **Population**: Pregnant women carrying a symptomatic cytomegalovirus-infected fetus, targeting a high-risk group for developing both neurosensory and neurological impairment. **Methods**: We designed a multicentre, open-label, phase II study with 1 arm, using one of Simon's optimal 2-stage designs. Symptomatic fetuses were defined by the presence of measurable extracerebral or mild cerebral ultrasound symptoms. They were treated in utero from prenatal diagnosis at a median of 25.9 weeks' gestation until delivery or termination of pregnancy (mean treatment 89 days). Fetuses with severe brain anomalies on ultrasound were not included as were cases completely asymptomatic at presentation, because treatment was unlikely to modify either outcome. The primary endpoint was the proportion of asymptomatic neonates born to treated mothers.	There were 34 asymptomatic neonates, more than the 31 required to indicate efficacy according to the Simon 2-stage design. They remained asymptomatic at 12 months. Fetal blood viral loads decreased and platelet counts increased, both significantly ($P=0.01$ and $P<0.001$, respectively), between treatment initiation and birth, regardless of duration of fetal infection. Compared with a historical cohort obtained by a meta-analysis of the literature, the use of valacyclovir (8 g daily) significantly increased the proportion of asymptomatic neonates from 43% without treatment to 82% with treatment. Although the pill burden was high (16 pills a day) adherence to treatment was >90%. Finally, valacyclovir at this high dosage was extremely well tolerated.	

4.1.10   Evaluation of quality of systematic reviews

(Hamilton et al 2014)	Comment
Questions and methods clearly stated	The review question is implicit in the title and objective of the review. Methods used are clearly stated.
Search procedure sufficiently rigorous to identify all relevant studies	Electronic databases, including PubMed, MEDLINE, Embase and ClinicalTrials.gov, were searched from January 1968 to June 2014 for relevant studies using the terms ' congenital cytomegalovirus' and ' treatment' , ' prophylaxis' , ' therapeutic' , ' prevention' , ' intervention' , ' antiviral' or ' hyperimmune globulin' .
Review includes all the potential benefits and harms of the intervention	Fetal/neonatal outcomes reported.
Review only includes randomised controlled trials	Review included observational studies.
Methodological quality of primary studies assessed	Assessment of risk of bias was performed using the most updated Oxford Centre for Evidence-based Medicine (OCEBM) 2011 Levels of Evidence (Treatment Benefits) quality scale. Two reviewers independently assessed the quality of the study according to the OCEBM guidelines, and the level of evidence attributed was decided by consensus.
Data summarised to give a point estimate of effect and confidence intervals	Data were limited and no point estimate of effects are given.
Differences in individual study results are adequately explained	Studies not meta-analysed.
Examination of which study population characteristics (disease subtypes, age/sex groups) determine the magnitude of effect of the intervention is included	Not applicable
Reviewers' conclusions are supported by data cited	Review states that more clinical evidence is required before conclusions can be drawn.
Sources of heterogeneity are explored	No meta-analysis was conducted, heterogeneity is not explored.

(Seidel et al 2017)	Comment
Questions and methods clearly stated	The review question is implicit in the title and objective of the review. Methods used are clearly stated.
Search procedure sufficiently rigorous to identify all relevant studies	Pubmed was searched without date or language restrictions and cited references followed up. Search terms are described.
Review includes all the potential benefits and harms of the intervention	Fetal/neonatal outcome and side effects of the mother reported.
Review only includes randomised controlled trials	Review included case studies.
Methodological quality of primary studies assessed	Review states that studies are case studies. No assessment of quality is reported.
Data summarised to give a point estimate of effect and confidence intervals	Data were limited and no point estimate of effects are given.
Differences in individual study results are adequately explained	Review notes the heterogeneity in intention of treatment and underlying conditions of the mother.
Examination of which study population characteristics (disease subtypes, age/sex groups) determine the magnitude of effect of the intervention is included	Not applicable
Reviewers' conclusions are supported by data cited	Review states that the number of cases reported is too small to support general conclusions.
Sources of heterogeneity are explored	Review states that studies were heterogeneous in terms of intention of treatment and underlying conditions of the mother. No meta-analysis was conducted.

4.1.11 Evaluation of quality of randomised controlled trials

Study limitation	Judgement	Support for judgement
(Hughes et al 2017)		
Random sequence generation	Low risk	The website Sealed Envelope (https://www.sealedenvelope. com/; retrieved February 6, 2013) was used to generate randomization assignments by permuted block randomization with varying block sizes and an allocation ratio of 2:1 for the intervention to comparison groups. Randomization assignments were printed on cards and stored in opaque envelopes labeled with the sequence number. Randomly varying block sizes were used to reduce the ability to guess future allocations. After eligibility was confirmed, the study coordinator opened the next envelope in sequential order. The group assignment was recorded in a password-protected database.
Allocation concealment	Low risk	Patients allocated to the intervention were contacted by phone by the study coordinator and informed that a face-to-face educational intervention would be delivered during her next routine prenatal visit. The study was singlemasked.
Blinding	Low risk	Baseline and follow-up assessments were conducted by research assistants blinded to group assignments.
Incomplete outcome data	Low risk	Loss to follow-up reported.
Selective reporting	Low risk	Pre-specified outcomes reported.
Other limitations	Low risk	No significant differences between baseline characteristics of groups

Study limitation	Judgement	Support for judgement
(Revello et al 2014)		
Random sequence generation	Low risk	Randomisation was performed with the use of a computer-based randomisation list that was generated by the study statistician and provided to the study pharmacists by the contract research organization. Randomisation, which was performed with the use of Stata software, was balanced in blocks of various sizes, with stratification according to centre.
Allocation concealment	Low risk	Participants, personnel administering the study drugs, physicians, technicians, and the study statistician were unaware of the study group assignments until completion of the study and retrospective analysis of the samples.
Blinding	Low risk	Infusion bags containing the required volume of drug or placebo were prepared at each centre by the study pharmacist and sealed with aluminium foil. Only the randomisation number was written on the label.
Incomplete outcome data	Low risk	One women was lost to follow-up in the placebo group. Analysis does not include woman lost to follow-up.
Selective reporting	Low risk	Pre-specified outcomes reported.
Other limitations	Low risk	No significant differences between baseline characteristics of groups

5 Additional considerations

5.1 Q8: What are the additional needs of Aboriginal and Torres Strait Islander women?

No studies were identified to answer this question.

5.2 Q9: What are the additional considerations for migrant and refugee women?

No studies were identified to answer this question.

6 Excluded studies

6.1 Background information

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6.2 Duplicate

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6.3 Not specific to target population

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6.4 Does not answer research question

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6.5 Narrative review

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