South Australian Perinatal Practice Guideline

Cytomegalovirus

Note:

This guideline provides advice of a general nature. This statewide guideline has been prepared to promote and facilitate standardisation and consistency of practice, using a multidisciplinary approach. The guideline is based on a review of published evidence and expert opinion.

Information in this statewide guideline is current at the time of publication.

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Health practitioners in the South Australian public health sector are expected to review specific details of each patient and professionally assess the applicability of the relevant guideline to that clinical situation.

If for good clinical reasons, a decision is made to depart from the guideline, the responsible clinician must document in the patient's medical record, the decision made, by whom, and detailed reasons for the departure from the guideline.

This statewide guideline does not address all the elements of clinical practice and assumes that the individual clinicians are responsible for discussing care with consumers in an environment that is culturally appropriate and which enables respectful confidential discussion. This includes:

- The use of interpreter services where necessary,
- Advising consumers of their choice and ensuring informed consent is obtained,
- Providing care within scope of practice, meeting all legislative requirements and maintaining standards of professional conduct, and
- Documenting all care in accordance with mandatory and local requirements

Note: The words woman/women/mother/she/her have been used throughout this guideline as most pregnant and birthing people identify with their birth sex. However, for the purpose of this guideline, these terms include people who do not identify as women or mothers, including those with a non-binary identity. All clinicians should ask the pregnant person what their preferred term is and ensure this is communicated to the healthcare team.

Explanation of the aboriginal artwork:
The Aboriginal artwork used symbolises the connection to country and the circle shape shows the strong relationships amongst families and the Aboriginal culture. The horse shoe shape design shown in front of the generic statement symbolises a woman and those enclosing a smaller horse shoe shape depicts a pregnant woman. The smaller horse shoe shape in this instance represents the unborn child. The artwork shown before the specific statements within the document symbolises a footprint and demonstrates the need to move forward together in unison.

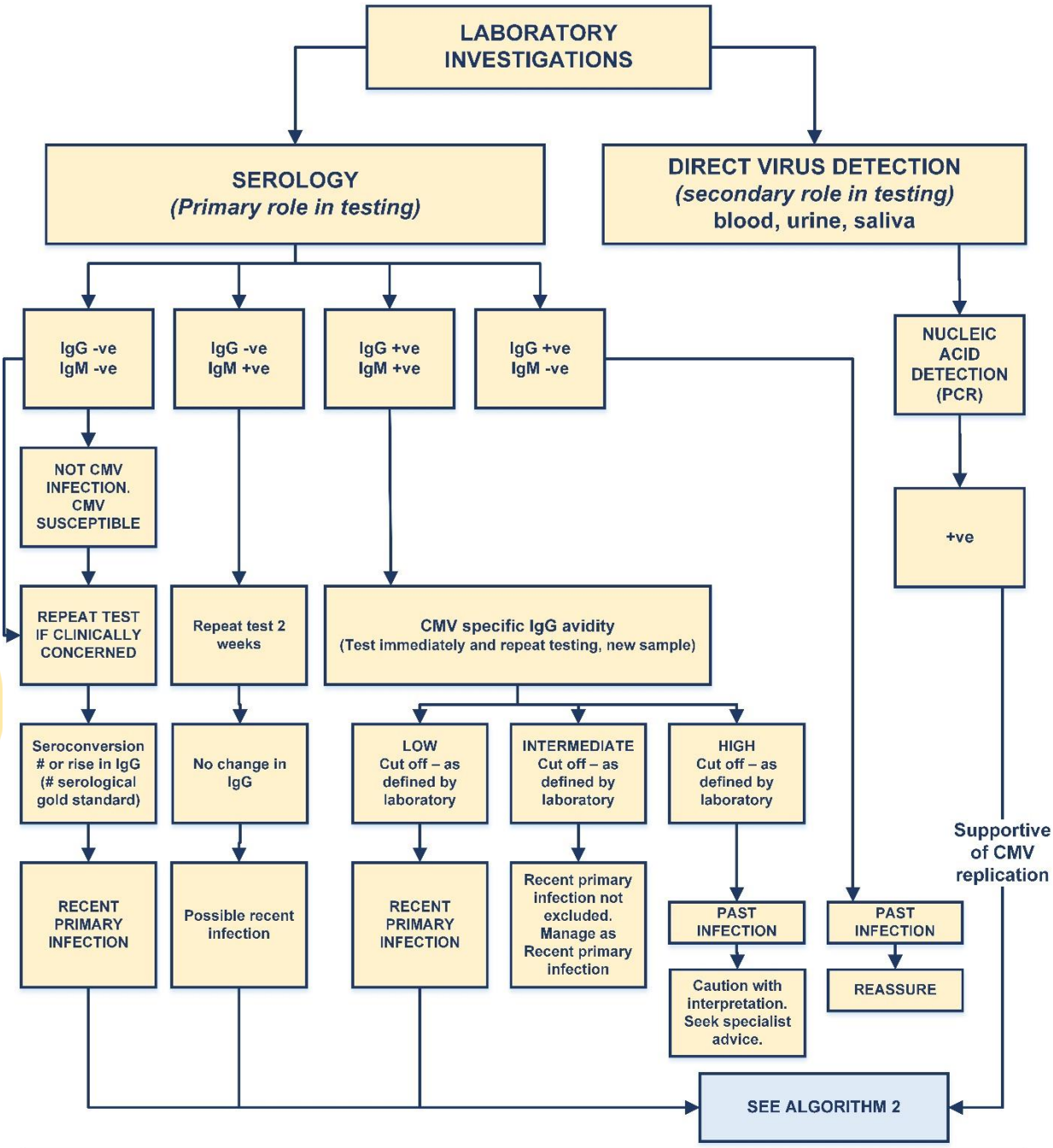
Australian Aboriginal Culture is the oldest living culture in the world yet Aboriginal people continue to experience the poorest health outcomes when compared to non-Aboriginal Australians. In South Australia, Aboriginal women are 2-5 times more likely to die in childbirth and their babies are 2-3 times more likely to be of low birth weight. The accumulative effects of stress, low socio economic status, exposure to violence, historical trauma, culturally unsafe and discriminatory health services and health systems are all major contributors to the disparities in Aboriginal maternal and birthing outcomes. Despite these unacceptable statistics, the birth of an Aboriginal baby is a celebration of life and an important cultural event bringing family together in celebration, obligation and responsibility. The diversity between Aboriginal cultures, language and practices differ greatly and so it is imperative that perinatal services prepare to respectfully manage Aboriginal protocol and provide a culturally positive health care experience for Aboriginal people to ensure the best maternal, neonatal and child health outcomes.

Purpose and Scope of Perinatal Practice Guideline (PPG)

The *Cytomegalovirus Management PPG* has been developed to provide clinicians with information for the management of cytomegalovirus infection in pregnancy and thus reduce mother to child transmission of the virus. It includes details regarding the indications for testing, referral, diagnosis and counselling. Suggested newborn assessment and follow-up management is also described

Cytomegalovirus

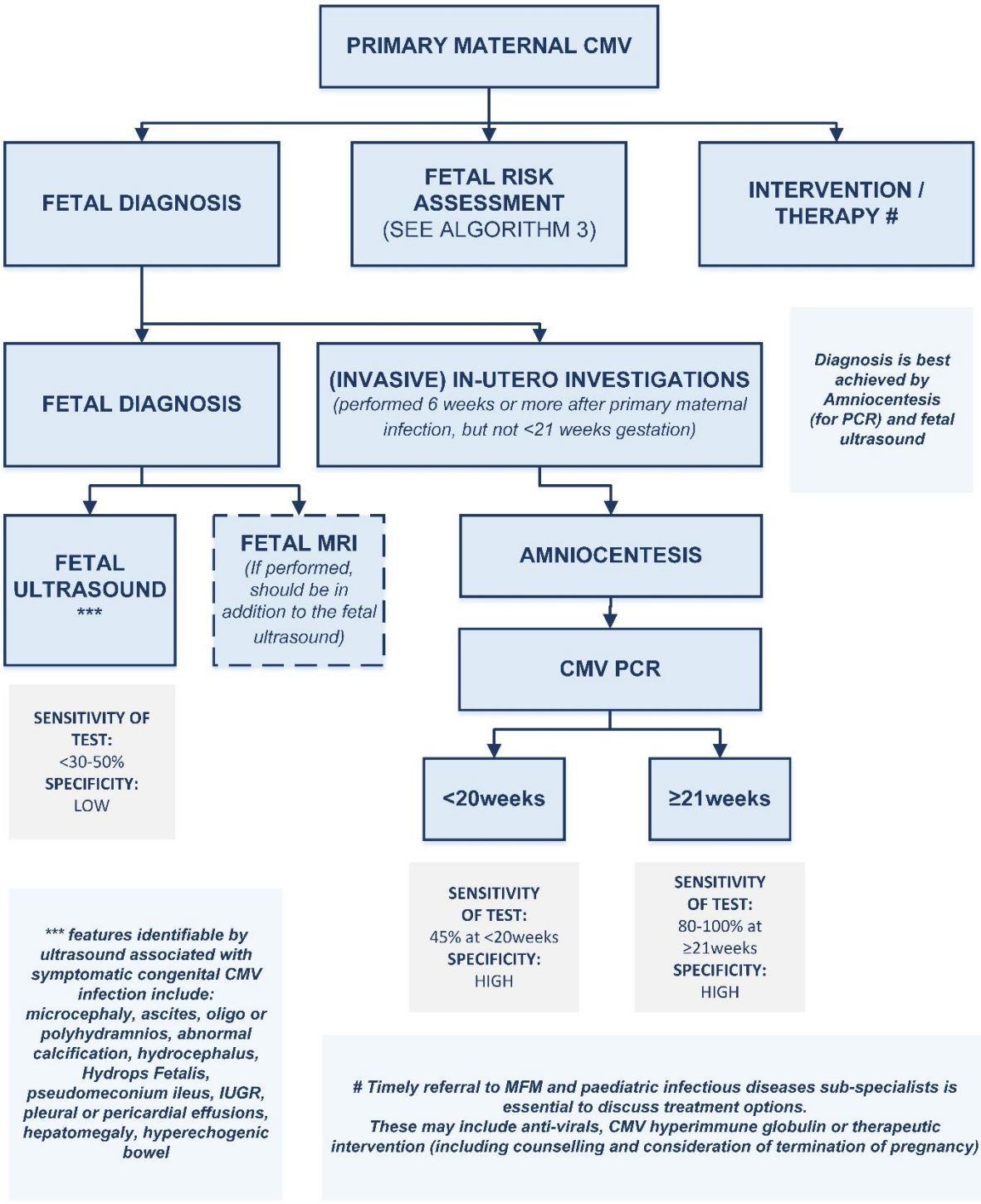
Flowchart 1 - Maternal Diagnosis



Routine antenatal CMV screening not generally recommended in Australia, but is sometimes done.
Targeted screening recommended for women who:
- have a history suggestive of CMV illness
- have abnormalities on routine ultrasound (See Algorithm 2)
- exposure to known CMV infected individual
- frequent or prolonged contact with children in childcare (ie. Childcare worker, parent of a child in childcare)

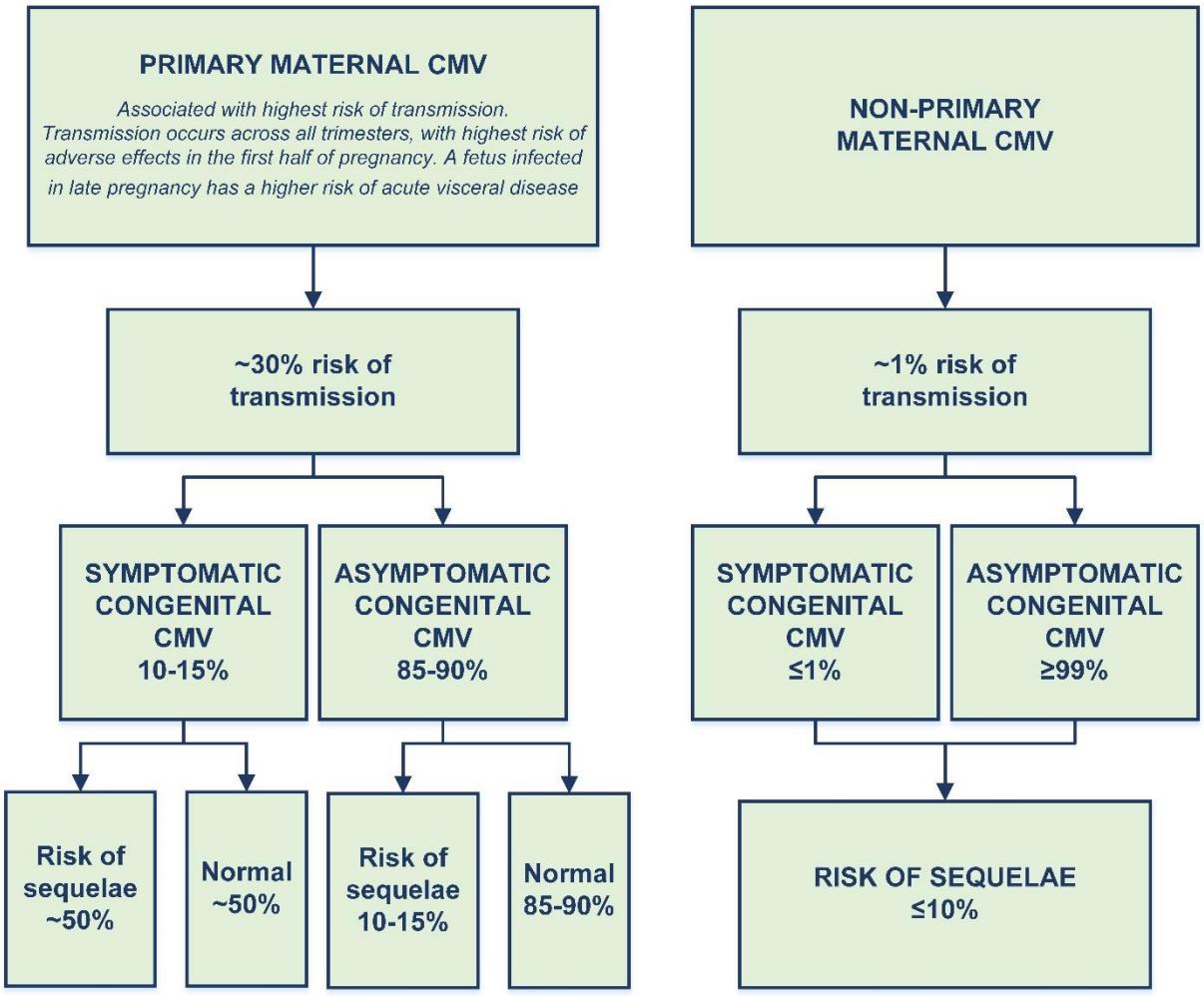
Adapted from Australasian Society for Infectious Diseases – Management of Perinatal Infections 'Cytomegalovirus' (2014)

Flowchart 2 - Antenatal Management of Primary Maternal CMV infection



Adapted from Australasian Society for Infectious Diseases – Management of Perinatal Infections 'Cytomegalovirus' (2014)

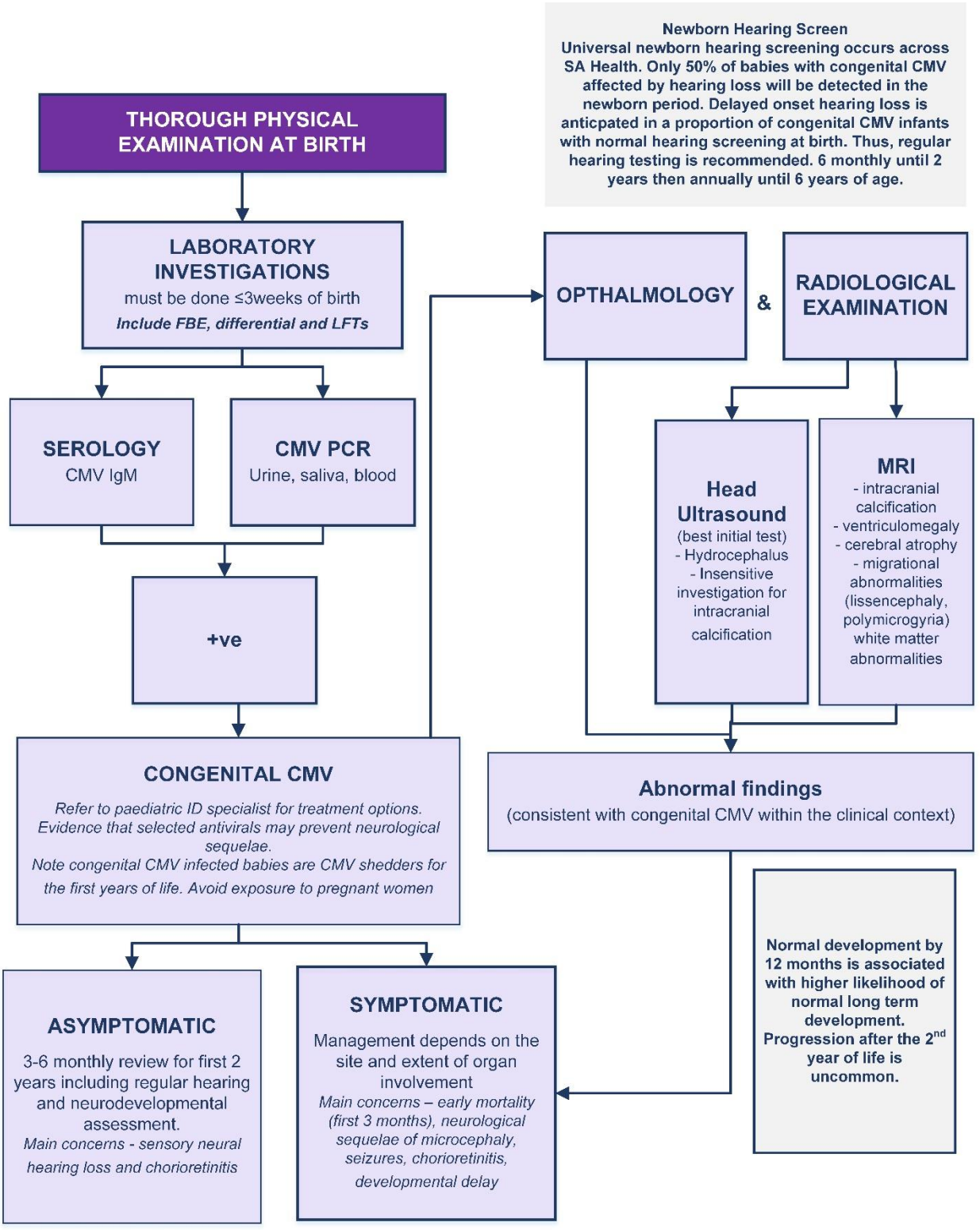
Flowchart 3 – Risk Estimates of Fetal Transmission



Overall risk of long term sequelae in a congenitally infected child is ~10-20%
See FLOWCHART 4

Adapted from Australasian Society for Infectious Diseases – Management of Perinatal Infections 'Cytomegalovirus' (2014)

Flowchart 4 – Neonatal Diagnosis and Management



Adapted from Australasian Society for Infectious Diseases – Management of Perinatal Infections 'Cytomegalovirus' (2014)

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Summary of Practice Recommendations

- Most primary maternal CMV infections are asymptomatic[1].
- Advise all pregnant women about hygiene measures to reduce the risk of CMV infection including:
  - Good handwashing after handling articles contaminated with saliva, urine, secretions – particularly after changing nappies,
  - Not sharing drinks, food, cups, water, toothbrushes and utensils with young children (< 3 years of age),
  - Avoiding contact with the saliva of young children (<3 years of age),
  - Avoiding saliva when kissing a child (<3 years of age),
  - Not sharing a dummy/soother with a child,
  - Regular cleaning of toys and counter tops and other surfaces with simple detergent[6].
- Risk of vertical transmission to the fetus after maternal primary CMV infection increases with increasing gestation. However, risk of severe fetal impairment is rare when infection occurs after the first trimester[1].
- Adherence to standard precautions is sufficient when caring for a woman and baby suspected or confirmed CMV infection. Standard precautions are used when there is the potential for contact with blood or body fluids from any patient regardless of infectious status. Personal protective equipment such as gloves, gowns/aprons, masks and face shields are used to protect the healthcare worker from unprotected exposure to blood or body fluids, and to prevent the transmission of infection to other patients.
- Offer CMV testing for all women who have frequent or prolonged contact with large numbers of young children (ie. Childcare workers and mothers of children in childcare) using serology (CMV IgG)[21]
- The pregnant woman should be tested for CMV infection if they have a history suggestive of CMV illness, exposure to known CMV infected individual, are immunocompromised or have suggestive abnormalities on routine antenatal ultrasound[6].
- Specific clinical, laboratory and radiological assessment of the baby of a woman who has CMV infection during pregnancy is required. CMV screening in the pregnant woman should include IgG and IgM antibodies. Further CMV avidity testing may be required.
- The pregnant woman with CMV requires specialist counselling. Treatment measures for the prevention or treatment of congenital CMV are under investigation, and are still of uncertain effectiveness. Timely referral is paramount[4].
- Fetal diagnosis of CMV is best achieved by a combination of fetal ultrasound and amniocentesis[5]
- Current information indicates that the risk of congenital CMV infection after primary maternal CMV infection remains elevated for up to 12 months post pregnancy[3].This may have implications for family planning.
- The CMV infected, asymptomatic baby of a woman who has CMV infection during pregnancy also requires paediatric follow-up for 2 years[3].

Abbreviations

AABR	Automated Auditory Brainstem Response
AF	Amniotic Fluid
AFI	Amniotic Fluid Index
ASID	Australasian Society for Infectious Diseases
CMV	Cytomegalovirus
CT	Computed Tomography scan
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IUGR	Intra-Uterine Growth Restriction
MRI	Magnetic resonance imaging
mL	Millilitre/s
PCR	Polymerase chain reaction
PPV	Positive Predictive Value

Definitions

Amniocentesis	A process in which amniotic fluid is sampled using a hollow needle inserted into the uterus, to screen for abnormalities in the developing fetus
Chorioretinitis	Inflammation of the choroid, which is a lining of the retina deep in the eye
Counselling	Voluntary discussions aimed at assisting the individual to recognise and better manage or reconcile problems affecting their life
Hepatomegaly	Abnormal enlargement of the liver
Hydrocephalus	A condition in which fluid accumulates in the ventricles of the brain, which may cause damage to the brain
Hydrops	A condition that develops if a fetus become severely anaemic, is fluid overloaded, or goes into heart failure. Large amounts of fluid build-up in the baby's tissues and organs. It is diagnosed when there are at least 3 of the following on ultrasound examination - 1) fluid around the heart, 2) fluid around the lungs, 3) fluid around the gut, 4) swelling of tissue under the skin.
Intrauterine growth restriction	Otherwise called “small-for-gestational age’ whereby the estimated fetal weight measures < 10th percentile on ultrasound. This diagnosis does not necessarily imply pathologic growth abnormalities, and may simply describe a fetus at the lower end of the normal range
Microcephaly	An abnormal smallness of the fetus’ head; a congenital condition associated with incomplete brain development
Oligohydramnios	Refers to a low level of amniotic fluid during pregnancy. It is defined by an amniotic fluid index that is below the 5th centile for the gestational age.
Polyhydramnios	Excessive amniotic fluid present during pregnancy. Is diagnosed if the deepest vertical pool is more than 8 cm or amniotic fluid index (AFI) is more than 95th percentile for the corresponding gestational age

Cytomegalovirus

Introduction

- Most primary CMV infections are asymptomatic
- The incidence of primary cytomegalovirus (CMV) infection in pregnancy in Australia is estimated to be 6 per 1,000 pregnancies, with 0.2 – 2.2% of live births affected[2].
- Most pregnant women with primary CMV infections are asymptomatic[3].
- CMV is the commonest congenital infection with medical significance[3].
- Risk of vertical transmission to the fetus after maternal primary CMV increases with increasing gestation. Severe fetal impairments are rare when infection occurs after the first trimester[4].
- In Australia CMV causes abnormalities (evident in 200 – 600 babies each year), such as:
  - Deafness
  - Intellectual impairment
  - Hepatitis
  - Pneumonitis
  - Blindness[6].

Background

- Cytomegalovirus (CMV) is a beta herpes virus with worldwide distribution.
- After primary infection, the virus remains present in the resting or latent phase (indicated by CMV specific IgG seropositive result).
- The virus can reactivate spontaneously or in conditions where immunity is suppressed, such as in pregnancy.
- Primary infection is limited to women who are CMV IgG negative and seroconvert during pregnancy, or periconceptually. CMV infection leads to the production of CMV-specific IgM production which can persist for up to 2-3 years.
- Reactivation occurs when CMV is isolated in a woman known to have CMV IgG[7].

Transmission

- Mother to fetus: vertical transmission after maternal primary CMV infection increases with advancing gestation, from approximately 21% in the preconception period, to 66% in the 3rd trimester[1].
- Importantly, risk of fetal injury after primary infection decreases significantly after the first trimester:
  - Periconception 29%
  - First trimester 19%
  - 2nd trimester 1%
  - 3rd trimester <1%[1]
- Therefore, the highest risk of fetal injury follows primary infection in the periconception period or first trimester, being in the order of approximately 6-7% (risk of transmission x risk of fetal insult)[1].
- If infected in the first trimester, the newborn will be symptomatic in approximately 9% of cases, with much lower injury rates of ≤1% following periconception or 2nd/3rd trimester infection[1].
- In pregnancy CMV is transmitted by:
  - handling articles contaminated with saliva, urine, secretions – particularly after changing nappies,
  - sharing drinks, food, cups, water, toothbrushes and utensils with young children (< 3 years of age) during pregnancy,
  - contact with the saliva of young children (<3 years of age),
  - saliva when kissing a child (<3 years of age),
  - sharing a dummy/soother with a child,

- toys, counter tops and other surfaces that have not been regularly cleaned with simple detergent [6].

> Infection with CMV can also occur via:
  - Breast milk,
  - Sexual contact,
  - Blood transfusions (Negligible risk associated – less than 1 in 1million)[22]

Prevention

> All pregnant women should be advised to adopt simple hygiene precautions, including:
  - Good handwashing after handling articles contaminated with saliva, urine, secretions – particularly after changing nappies,
  - Not sharing drinks, food, cups, water, toothbrushes and utensils with young children (< 3 years of age) during pregnancy,
  - Avoiding contact with the saliva of young children (<3 years of age),
  - Avoiding saliva when kissing a child (<3 years of age),
  - Not sharing a dummy/soother with a child,
  - Regular cleaning of toys, counter tops and other surfaces with simple detergent[6].

See SA Health *Prevent CMV during pregnancy* brochure

Diagnosis

Testing criteria

Clinical presentation

> Women with CMV may present with a mononucleosis-like syndrome; flu-like symptoms, infection of the gastrointestinal tract, abnormal liver function, or rashes[10].

High risk groups for primary CMV

> Child care workers (incidence of 12% per annum)[3].

> Parents with a child in child care (incidence of 20 – 30 % per annum) [3].

Universal routine serological screening for CMV in pregnancy is currently not recommended [5]
Targeted screening based on clinical presentation suggestive of CMV, or risk groups above (frequent, prolonged exposure to children in child care) is recommended[6].

Aboriginal women should be referred to an Aboriginal Healthcare Work to support their care when discussing testing criteria and testing

Testing

> Obtain maternal serology for the detection of CMV antibodies,

> IgG positive, IgM negative indicates past exposure,

> IgG negative or positive with IgM positive requires further testing in 2-4 weeks, (Interpretation of CMV IgM results in pregnancy requires specialist virological interpretation – see ASID guideline for more detail: https://www.asid.net.au/documents/item/368

> Maternal Fetal Medicine and paediatric infectious disease subspecialist consultation should be sought (both with 24 hour referral availability at the WCH)

> Seroconversion (IgG negative to positive) or a significant rise in IgG indicates a recent primary CMV infection,

> The pregnant woman with suspected CMV infection should have CMV serology testing for IgG and IgM, and IgG avidity if CMV IgG and IgM are positive[4]. Consider CMV serology testing on previous antenatal serology samples often obtained in the first or second trimester of pregnancy (these antenatal blood samples are usually kept for 12 months).

- Avidity testing for CMV IgG can indicate the timing of primary infection with respect to the pregnancy.[15] Low CMV IgG avidity is an accurate indicator of primary infection within the preceding 3 to 4 months, whereas high avidity excludes primary infection within the preceding 3 months.

- Serologic testing for cytomegalovirus is recommended for the following women in pregnancy:
  - history suggestive of CMV illness
  - exposure to known CMV infected individual or blood product
  - immunocompromised women
  - abnormalities on routine antenatal ultrasound (usually at 18 - 20 weeks)[3].
- Recent cost effectiveness analysis taking into account new treatment options for CMV have triggered debate on the possible future of routine CMV screening[16]

Management of CMV Infection

- Whilst there is currently no approved treatment for maternal primary CMV, evidence is emerging regarding the use of high dose Valaciclovir to reduce secondary (vertical) infection[4 (3, 4)]. Valaciclovir may be offered if amniocentesis for CMV PCR after 21 weeks gestation is positive, after MFM and paediatric infectious disease subspecialist consultation. The effectiveness of this treatment option is still under investigation
- Some pregnant women with CMV may present with acute visceral disease (hepatitis, pneumonia, purpura and severe thrombocytopenia)[10]. Supportive management should be considered for these women, including increased oral hydration with intravenous support if required.

Infection precautions

- Staff precautions: - To help prevent CMV infections, employers and workers should treat all body fluids as if they are potentially infectious with CMV, using Standard Infection Control Precautions (including the use of gloves and regular hand washing)[9].
- After a risk assessment, maternity and/or neonatal units may initiate transmission based precautions if there are poor infection control practices in that unit.
  - This may include sub-optimal hand hygiene and adherence to standard precautions.
  - It may also be considered not to allocate pregnant staff to care for the suspected or confirmed CMV positive patient

Maternal counselling

- Women with suspected CMV infection should be considered for referral to a Maternal Fetal Medicine and Infectious Diseases service for counselling at the earliest opportunity[9].
- Aboriginal women should be referred to their nominated Aboriginal Health Professional or an Aboriginal healthcare worker at the earliest opportunity to support a culturally safe, appropriate and responsive care plan
- All Aboriginal women and/or an appropriate family member should be consulted regarding any decisions in relation to their care, in the first instance.
- Women with amniotic fluid (AF) positive samples by PCR or culture for CMV should be counselled of their options for non-treatment, treatment with uncertain effectiveness or they may consider termination of the pregnancy (depending on gestational age) [10].
- Caution should be advised when interpreting findings as features associated with symptomatic congenital infection are not always predictive of the degree of fetal damage[9].
- The risk of severe adverse neonatal neurological outcome is highest after primary infection in the first half of pregnancy[11].
- Features of fetal infection in early pregnancy include:
  - Severe early onset fetal growth restriction
  - Microcephaly
  - Intracranial calcifications[10].

- Features of fetal infection in late pregnancy include:
  - acute visceral disease (hepatitis, pneumonia, purpura and severe thrombocytopenia)[11].
- Mother to fetus: vertical transmission after maternal primary CMV increases with advancing gestation[3].
  - Periconception period 21%
  - 1st trimester 37%
  - 2nd trimester 40%
  - 3rd trimester 66% [4].
- Importantly, risk of fetal insult after primary infection decreases significantly after the first trimester[1]
  - Periconception 29%
  - First trimester 19%
  - 2nd trimester 1%
  - 3rd trimester <1%[4].
- Therefore, the highest risk of fetal insult follows primary infection in the periconception period or first trimester, being in the order of approximately 6-7% (risk of transmission x risk of fetal insult)[4].
- If infected in the first trimester, the newborn will be symptomatic in approximately 9% of cases, with much lower rates of ≤1% following periconception or 2nd/3rd trimester infection[4].

Fetal risk assessment

- Fetal diagnosis is best achieved by a combination of fetal ultrasound, amniocentesis and + / - fetal serology.
  - Positive results do not predict any degree of fetal damage, a referral to a maternal fetal medicine specialist, and a specialist with expertise in perinatal infections is recommended[9].

Ultrasound

- Consider serial fetal ultrasound to detect features associated with symptomatic congenital CMV infection (sensitivity around 30 – 50 %)[12].
- Features associated with symptomatic congenital infection:
  - Microcephaly
  - Fetal Ascites
  - Hydrops
  - Oligo or polyhydramnios
  - Hepatomegaly
  - Pseudomeconium ileus
  - Hydrocephalus (ventricular dilation)
  - Intrauterine growth restriction (IUGR)
  - Pleural or pericardial effusions
  - Intracranial calcification
  - Abdominal calcification[4].

Amniocentesis

- Consider amniocentesis for polymerase chain reaction (PCR) and culture
  - Sensitivity is increased by waiting ≥ 6-8 weeks after infection at not less than 21 weeks gestation; with sensitivity 45% at < 20 weeks gestation, and 80-100% if performed ≥ 21 weeks gestation[2].
  - Specificity approaches 100%
  - Positive results identify CMV-infected fetuses (PPV=100%) but cannot predict the degree

of fetal damage[2].

Low viral loads (<10^3 copies/mL) are often associated with asymptomatic congenital infection, although a correlation between high viral loads and fetal/neonatal outcomes has not been demonstrated[2].

Congenital CMV management

> The prevention of congenital CMV is based on interrupting the maternal-fetal transmission or preventing maternal infection during pregnancy[6]. The role of hyper-immune globulin (HIG) in acute infection is controversial[20]

Maternal primary CMV infection

> The newborn will be symptomatic in 10% of cases, and carry a 90 % risk of sequelae including:
  - Mortality (rate 5-10%)[3],
  - Neurological abnormalities (microcephaly (rate 35-50%), seizures (rate 10%), chorioretinitis (rate 10-20%), mental retardation (rate ≤70%)[3],
  - Hearing loss (rate 20-50%)[3].

Perinatal Grief and Loss - Aboriginal people experience very high levels of Grief and Loss in their communities. Perinatal loss demands ceremonial acknowledgement. Please discuss with their nominated Aboriginal Health Professional or Aboriginal Liaison Officer

Maternal non-primary CMV infection (reactivation or reinfection)

> There is a ≤ 1 % risk of transmission of CMV to the newborn[3],
> Most newborns will have asymptomatic congenital CMV (≥ 99 %)[3],
> Of these, approximately 5 % will suffer sensory neural hearing loss and 2 % will suffer chorioretinitis[3],
> If hearing is preserved at one year of age, intellectual development is unlikely to be affected[3].

Management of the Newborn

> Medical review at birth[6],
> Detailed physical examination[3].
> Aboriginal woman should be consulted on the care of the newborn baby in the first instance. Consult with the preferred aboriginal health professional if requested
> Decisions regarding the care of a newborn may vary among Aboriginal cultural groups. The involvement of an Aboriginal health professional should be sought to ensure cultural sensitivity and practices are acknowledged in the care and management of the newborn

Laboratory investigations

> Should be done as soon as possible after birth and before 3 weeks of age to confirm congenital CMV:
  - CMV PCR of urine is the gold standard for congenital infection,
  - PCR testing of saliva should be confirmed with a PCR urine test[3],
  - Blood for quantitative CMV should be collected if anti-viral therapy in indicated,
  - After 3 weeks of age, confirmation of fetal infection also requires evidence of CMV via a PCR on the Newborn Screening Test or immunofluorescence studies of placental tissue[2].

Investigations

> Where laboratory investigations confirm CMV, the following investigations are recommended:
  - Ophthalmology examination[3],

- Cranial ultrasound (hydrocephaly)[3],
- CT of brain is not indicated due to the risks associated with radiation exposure, balanced against the low likelihood of sequelae (signs of intracranial calcification, ventriculomegaly, cerebral atrophy)[2],
- For symptomatic infants, magnetic resonance imaging is the preferred imaging modality for CMV infection of the brain[3].

Follow up

> Infectious Diseases consultation in regard to possible treatment with Ganciclovir / valganciclovir[13].
> Paediatric review of asymptomatic infants with congenital CMV, minimum of 1 visit at 12 months, up to every 3–6 months for the first 2 years (include neurodevelopmental assessment)
  - The frequency of paediatric review of symptomatic infants with congenital CMV will depend on the extent of organ involvement[5].
  - Routine AABR screening, with the addition of referral to paediatric audiology for long term review of possible late onset hearing loss[5].

All follow up plans should be referred to an Aboriginal health professional and/or Aboriginal Community Controlled health service where the family will receive follow up care.

For further information, refer to Flowchart 4 – Neonatal Diagnosis and Management

Future Pregnancies

> There are no consistent guidelines available in relation to the timing of a subsequent pregnancy, however most sources advise 6-12 months[12].
> Awaiting a decline in CMV IgM to an undetectable level with a concurrent increase in CMV IgG avidity to a high level is likely to represent a low risk of vertical CMV transmission in future pregnancies[14,15].

Supporting Documents

This PPG must be used in conjunction with:

> Standards for Maternity and Neonatal Services in SA 2021 Clinical Directive. Available at www.sahealth.sa.gov.au/perinatal and web-based App named Practice Guidelines available at https://extapps.health.sa.gov.au/PracticeGuidelines
> SA Health Perinatal Practice Guidelines. www.sahealth.sa.gov.au/perinatal and web-based App named Practice Guidelines available at https://extapps.health.sa.gov.au/PracticeGuidelines

Additional Resources

“Prevent CMV during pregnancy”
Prevent CMV during pregnancy brochure (SA Health)

“Reducing the risk of CMV during pregnancy” Pamphlet,
an initiative of The Cerebral Palsy Alliance, CMV Australia and The Australian College of Midwives
Reducing the risk of CMV in pregnancy (Cerebral Palsy Alliance)

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Does this policy amend or update and existing policy? **Y**
If so, which version? **V4.1**
Does this policy replace another policy with a different title? **N**

Approval Date	Version	Who approved New/Revised Version	Reason for Change
10 March 2022	V5	Domain Custodian Executive Director Commissioning and Performance Department for Health and Wellbeing, SA	Reviewed to align with revised national guidelines
5 July 2018	V4.1	SA Health Safety and Quality Strategic Governance Committee	Review date extended to 5 years following risk assessment. New template.
19 Dec 2014	V4	SA Health Safety and Quality Strategic Governance Committee	Reviewed
08 Jan 2013	V3	SA Health Safety and Quality Strategic Governance Committee	Reviewed in line with scheduled review date
05 May 2009	V2	Maternal and Neonatal Clinical Network	Reviewed in line with scheduled review date
08 Apr 2004	V1	Maternal and Neonatal Clinical Network	Original approved version.