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Cytomegalovirus Infection in Pregnancy: Prevention, Presentation, Management and Neonatal Outcomes

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Congenital cytomegalovirus (cCMV) is the most common congenital infection in the United States, with 1 of 200 live births affected. It is the leading viral cause of intrauterine fetal demise and miscarriage. It is a common cause of neonatal hearing loss, second only to genetic factors. Yet, health care provider awareness remains low. The purpose of this article is to provide a brief overview of the epidemiology, presentation, diagnosis, and treatment of antenatal cytomegalovirus (CMV) infection and cCMV in the neonate. Maternal CMV infection in pregnancy often presents with mild cold-like symptoms or is asymptomatic. The virus can be vertically transmitted to a growing fetus, the risk of transmission and severity of fetal impact varying by timing of exposure during pregnancy. Most neonates born with cCMV show no signs at birth, yet 15% to 25% will have long-term adverse neurodevelopmental conditions. Misconceptions that cCMV cannot be prevented or that neonates born without signs of the disease will be unaffected are common. Evidence supporting antenatal education around behavioral change to lower a woman's risk of acquiring CMV during pregnancy is mounting. CMV infection during pregnancy should be co-managed with a maternal-fetal medicine specialist. There is early evidence for the use of antiviral medication in reducing risk of vertical transmission. Identification of cCMV during pregnancy may help ensure the neonate receives timely treatment after birth. Midwives can play an important role in providing antenatal education about cCMV risk reduction and in initiating a diagnostic evaluation when there is clinical suspicion.
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Keywords: congenital cytomegalovirus, CMV, fetal infection, cytomegalovirus

CASE SUMMARY

A 32 year-old gravida 2, para 1patient who is approximately 10 weeks pregnant by last menstrual period presents to establish care at a midwifery practice. Her midwife provides standard antenatal education and care, recommending routine follow-up. Three weeks later, the patient calls to report a sore throat, fever, and fatigue, for which supportive care is recommended. She notes that she works in a daycare setting so "probably just picked something up from one of the kids." Echogenic bowel and symmetric intrauterine growth restriction (IUGR) are seen on her 20-week anatomy scan. After consulting with a maternal-fetal medicine specialist, the midwife orders blood work, including a fetal karyotype and a congenital infection panel. Results show elevated cytomegalovirus (CMV) immunoglobulin (Ig) IgG and IgM levels. IgG avidity testing is obtained, which comes back low. Suspecting a congenital CMV infection, the midwife collaborates with a maternal-fetal medicine colleague for the duration of the pregnancy. Amniocentesis to confirm the diagnosis is offered and declined by the patient. Serial ultrasounds show continued fetal IUGR and resolution of the echogenic bowel. A spontaneous vaginal birth occurs at 35 weeks, following premature rupture of membranes. Immediately after birth, the neonate is vigorous and is held skin-to-skin by her mother. On physical examination, the neonate measures at the second percentile for length, weight, and head circumference; is notably jaundiced; and has a faint diffuse petechial rash. The newborn's urine tests positive for CMV, confirming congenital CMV. Through an evaluation led by a pediatric infectious disease specialist, the neonate is found to have bilateral profound sensorineural hearing loss, as well as intracranial calcifications. The mother does well postpartum and is discharged home with her daughter on postpartum day 3. The neonate is further cared for on an outpatient basis by a team of subspecialists.

Note: This case is a composite of elements from different patients.

INTRODUCTION

Congenital CMV (cCMV) is the most common congenital infection in the United States, affecting 1 of 200 live births.[1,2] It is the leading viral cause of intrauterine fetal demise and miscarriage[3] and the leading cause of neonatal hearing loss, second only to genetic causes in the United States.[1] Neonates affected by the virus can experience a wide array of symptoms, from none to severe neurodevelopmental disability, and even death.[1] Furthermore, cCMV is more common than many other neonatal conditions, such as spina bifida and fetal alcohol syndrome. However, public and health care provider awareness remains low.[1,2,4,5]

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Table 1. Misconceptions and Facts about Congenital Cytomegalovirus

Misconception	Fact
cCMV is rare	cCMV is the most common TORCH infection, affecting 1 in 200 live births.[1]
cCMV cannot be prevented	Individuals may lower their risk of contracting CMV when pregnant by practicing hand hygiene and avoiding the saliva of young children.[26]
If a woman has had CMV in the past, she is immune	Individuals can become reinfected with a new strain of CMV when pregnant or have a reactivation of a latent infection even if they have preexisting IgG antibodies.[8]
If neonate does not have signs of cCMV at birth, they will not have later sequelae	Neonates with cCMV but without visible signs at birth (also known as having asymptomatic cCMV) may still have hearing loss at birth and are at risk for later onset hearing loss.[10]
There is no treatment for neonates with asymptomatic cCMV	Although antiviral medication is not yet proven to be safe and effective for asymptomatic neonates, treatment may also include early intervention services and close monitoring of hearing, vision, and development.[21]
Most ineonates with cCMV are diagnosed by pediatricians at birth	More than 90% of cases of cCMV go undiagnosed at birth. The majority of cases of cCMV present with subtle signs or no signs at all, which make the diagnosis challenging.[21,26]

Abbreviations: CMV, cytomegalovirus; cCMV, congenital cytomegalovirus infection; Ig, immunoglobulin; TORCH, Toxoplosmasis, Other, Rubella, Cytomegalovirus, Herpes Simplex Virus.

Some have called cCMV the *silent virus*. This is not only because of its association with hearing loss but also because it is underemphasized in health care education across disciplines and thus is underdiagnosed and undertreated.[2] Evidence supporting the effectiveness of antenatal counseling about behavior changes to reduce the risk of cCMV in pregnancy is mounting.[6] Yet, at present, antenatal education about cCMV risks is not common practice for most United States obstetrician-gynecologists or midwives.[7] This may be because of the ambiguity of evidence surrounding antenatal screening and treatment. Several misconceptions about cCMV continue to be widespread (Table 1), which may perpetuate the tendency to overlook the risks of this virus. Health care providers who care for pregnant people should educate themselves about cCMV.[8] The purpose of this article is to provide a brief overview of the epidemiology, presentation, diagnosis, treatment, and long-term neurodevelopmental outcomes of cCMV, highlighting the role of the midwife in perinatal care, and awareness.

EPIDEMIOLOGY

CMV infection is common; by adulthood, approximately 50% to 80% of Americans are seropositive, meaning they have previously been exposed to CMV. The prevalence of a *primary infection* in pregnancy, defined as an individual's first infection with CMV, is 1% to 2% in the United States, whereas *nonprimary infections* (defined as a reinfection with a different strain or reactivation of a latent virus) may occur in up to 10% of pregnancies.[8,9] The risk of vertical transmission is greatest in primary infections, as is the risk of poorer fetal outcomes. Transmission can also occur from a CMV infection in the weeks prior to conception.[8] Risk of transmission in a primary infection increases steadily from the weeks just prior to conception (14%) to the third trimester (68%), whereas risk of transmission in a nonprimary infection is significantly lower (~1%).[8,9] Individuals who have already given birth to a neonatei with cCMV continue to have a risk of nonprimary infections in subsequent pregnancies.

Roughly 20,000 to 30,000 neonates with cCMV are born in the United States each year, although the exact incidence is unknown because of lack of universal screening.[1] Of those, 10% to 15% will be born with visible signs at birth (eg, small for gestational age, microcephaly, hepatosplenomegaly). The other 85% to 90% are born without visible signs.[1] However, even neonates born without visible signs have an increased risk of hearing loss (10% to 15%), which may be progressive with onset later in childhood.[10] Approximately 50% of neonates born with visible signs will have long-term sequelae.[11] African American and Hispanic individuals, as well as those who live in poverty, have a 5-fold increase of having a neonate with cCMV.[12] These disparities are hypothesized to be linked to social determinants of health (evidence of increased housing density, poorer access to prenatal care and prenatal education), which are, in turn, influenced by structural racism and inequities.

TRANSMISSION

CMV is transmitted through bodily fluids, such as saliva, semen, vaginal or cervical secretions, urine, and tears.[8,9] After a CMV infection, an individual can shed the virus in their bodily fluids for months after their symptoms have resolved. Children in daycare settings are known to be at increased risk of shedding the virus, with one study finding that on average, 54% of children in daycare are actively shedding CMV in their saliva at any time.[13] If an individual who is about to become pregnant, or is pregnant, comes in contact with another person's infected bodily fluids, they may contract the virus. Transmission most often occurs through the oral route. Although all people are at risk of contracting CMV just prior to conception or during pregnancy, those who have regular contact

Table 2. Behavioral Modifications that may Lower Risk of Contracting Cytomegalovirus
Behavioral Risk Reduction
Avoid kissing young children on the lips
Avoid sharing cups, straws, and utensils
Avoid sharing food with young children
Wash hands well after changing a diaper
Avoid contact with bodily fluids of young children

Source: Rawlinson, 2017.[4]

with young children (eg, preschool teachers, child-care workers, mothers of children who attend daycare) are at increased risk.[8]

Pathophysiology

While circulating in the maternal serum, CMV infects and crosses the placenta, with a propensity toward several types of cells in the fetal brain (eg, astrocytes, neural stem cells).[14] Once infected, these cells can support further viral replication in the brain, causing end organ central nervous system damage. CMV-induced hearing loss is thought to be caused by a viral labyrinthitis.[14] CMV's affinity for cells in the central nervous system and inner ear accounts for much of the clinical presentation of cCMV, which includes brain abnormalities, hearing loss, seizures, microcephaly, and intrauterine growth restriction.[14]

ANTENATAL COUNSELING

Avoidance of Higher Risk Behaviors

As CMV is transmitted through bodily fluids, antenatal behavior changes may reduce risk of contracting the virus.[7] Such behavior changes may include avoiding oral contact with the bodily fluids of young children, who are frequent vectors of transmission (Table 2). Like most infectious diseases for which there are not yet vaccines, behavioral modifications do not completely eliminate the risk of cCMV. However, there is increasing evidence that antenatal education about cCMV and risk reduction strategies may significantly lower rates of antepartum seroconversion.[6]

Routine Antenatal Counseling

Routine preconception and prenatal counseling on CMV risk reduction strategies is encouraged by some,[15] but not all, professional organizations.[16] In the 2015 American College of Obstetricians and Gynecologists Practice Bulletin on CMV infection during pregnancy, antenatal CMV patient education was described as "unproven as a method to reduce the risk of congenital CMV infection," and behavioral modifications may be "considered impractical or burdensome" to implement.[16] However, since 2015, evidence to support prenatal prevention education has increased. A recent expert review published in the American Journal of Obstetrics and Gynecology highlighted cCMV prevention behaviors, specifically that "both parents avoid contact with body fluids from infected individuals, especially toddlers, from before conception until 14 weeks (gestation)."[8] Prenatal cCMV education has been found to be viewed favorably by women[17,18] and has been associated with increased engagement in recommended hygiene practices.[19] Observational controlled studies have found that hygiene counseling of CMV-seronegative pregnant women significantly decreased risk of both seroconversion and congenital infection.[6,17] Some practitioners may not want to worry their patients by discussing the risks of cCMV, but these risks deserve consideration by expectant individuals. Empowerment with knowledge about CMV risk reduction strategies is the only way (short of a vaccine) to mitigate risk. A recent qualitative study of parents of children with cCMV found frequent "frustration about not knowing about CMV infection during their pregnancies and therefore not having the opportunity to take measures to reduce their risk of acquiring CMV while pregnant."[20] Leading experts in infectious diseases in obstetrics have lent their support to prenatal CMV prevention education,[8,15,21] although further research about the ideal format of such interventions is needed.[6]

ANTENATAL PRESENTATION

Symptoms of an acute CMV infection may include a mononucleosis-like presentation, such as fever, malaise, and adenopathy; however, most individuals are asymptomatic.[8,22] Routine antepartum serologic screening for CMV is not endorsed by guidelines, because of ambiguity in interpreting the results.[16,22,23] There are no hallmark signs of a CMV infection, which makes its diagnosis challenging. However, a health care provider may consider testing symptomatic individuals who present with cold-like symptoms, and/or those who have contact with young children, either at home or at work.[22] Ultrasound findings suggestive of a cCMV infection that warrant further investigation include, but are not limited to, echogenic fetal bowel, cerebral calcifications, ventriculomegaly, microcephaly, hydrops, and fetal growth restriction.[22,23] Serologic testing may be offered to individuals with such ultrasound findings. However these findings are not specific to CMV; thus, providers may keep a broad differential diagnosis, including chromosomal abnormalities or other congenital infections (eg, toxoplasmosis, syphilis, rubella).

PRENATAL SEROLOGY TESTING

Serologic evaluation for a recent CMV infection includes CMV IgG, IgM, and IgG avidity testing.[23] However, interpretation of results in the absence of symptoms can be challenging, which is why routine prenatal screening is controversial. A positive IgG alone indicates prior life exposure to CMV; however, it does not differentiate recent from years past infections. Although a positive IgM suggests an acute CMV infection, it cannot determine how recently the parent was infected (eg, 1 month ago vs several months ago). Even in the situation of a true acute infection, IgM levels may take weeks to be detectable and can be present in nonprimary infections.[14] As such, interpretation of a positive or negative IgM level in the presence of a positive IgG may be ambiguous.[8] This may, in turn, lead to unnecessary and invasive testing, as well as parental distress, which some find difficult to warrant in the

absence of symptoms. In contrast, knowing an individual's prenatal IgG status may be helpful if symptoms arise during the pregnancy. For instance, seroconversion from a negative to a positive IgG status is suggestive of a primary CMV infection, for which risk of vertical transmission and poorer fetal outcomes are higher. Or, if an individual is seropositive for IgG prenatally and develops an elevated IgM midpregnancy, a nonprimary infection would be suspected. In the absence of prenatal serologies, it is impossible to distinguish a primary from a nonprimary infection.[8] Knowing one's serological status early in pregnancy may also encourage adherence to primary prevention measures.

IgG avidity, which measures the binding strength of CMV to IgG antibodies, is a proxy for antibody maturity and can be helpful in assessing the recentness of an infection.[8] Lower IgG avidity indicates less mature antibodies and is suggestive of a more acute infection. The Society of Maternal-Fetal Medicine recommends a person with suspected primary CMV infection in pregnancy be tested and diagnosed either by IgG seroconversion or by a positive CMV IgM, positive IgG, and low IgG avidity.[14]

Figure 1. Neonate with a Blueberry Muffin Appearance Associated with Congenital Cytomegalovirus Infection
Classically described "blueberry muffin" appearance of a neonate with congenital CMV consisting of a diffuse petechial or purpuric rash and jaundice (conjugated).
Source: Johan, 2007.[30]

DIAGNOSIS AND MANAGEMENT

Diagnosis

A patient with serologic or ultrasound findings concerning for cCMV should be referred to a maternal-fetal medicine specialist for further testing and management recommendations.[4] Neither serology nor imaging alone should be used to confirm a diagnosis of cCMV, but imaging may be helpful in assessing the severity of fetal involvement. Diagnosis of fetal cCMV is made by CMV isolation in the amniotic fluid via amniocentesis at greater than 21 weeks' gestation and greater than 6 weeks from maternal infection.[14] Alternatively, a congenital infection can be confirmed by testing the neonate shortly after birth.[4]

Management

After confirmation of maternal and/or fetal CMV infection, it is important to use an interprofessional approach to provide the best care for the patient and fetus. The maternal-fetal medicine specialist, obstetrician-gynecologist or midwife, and pediatrician should create a collaborative care plan. Guidelines for monitoring and management of cCMV during pregnancy are lacking; therefore, the plan of care is left to the discretion of the maternal-fetal medicine specialist.[4]

Antenatal cCMV treatment with antiviral medication is not recommended,[8,22] because of inconclusive evidence and risk of side effects. Valaciclovir has shown recent promise in small studies at reducing rates of vertical transmission by 60% but has not been studied in a large randomized controlled trial.[24] CMV hyperimmunoglobulin is also not recommended, as studies have shown that it neither lowers risk of vertical transmission or improves fetal outcomes.[4] There is no evidence to support increased risk of premature rupture of membranes in CMV affected pregnancies, although some studies have found increased prevalence of cCMV in preterm neonates.[4]

Mode of Birth and Breastfeeding

Congenital CMV alone is not a contraindication for a vaginal birth; however, a cesarean may be advised in the case of a nonreassuring fetal status. It is important to note that even if cCMV is suspected prior to the birth, a stable neonate may remain with the parent after birth, doing skin-to-skin, latching, and spending those first hours of life bonding. The decision whether or not to recommend birth at a tertiary care facility may be made in discussion with the maternal-fetal medicine specialist. Most neonates with cCMV do not require an urgent evaluation by a pediatrician in the hours after birth. In fact, much of the evaluation can happen in the outpatient setting.[21] As long as a newborn is stable, they may remain in the well-baby nursery or rooming with their parent. Breastfeeding can be encouraged for all except for very-low-birthweight neonates, who may be vulnerable to a severe sepsis-like syndrome from CMV shed in breastmilk.[8]

NEONATAL SEQUELAE

Presentation in the Neonate

Contrary to common belief, 85% to 90% of neonates born with cCMV have no signs or symptoms at birth,[2,4] making the diagnosis challenging for pediatricians, and is likely why most cases of cCMV go undiagnosed. Classically, neonates with cCMV have been classified as either symptomatic or asymptomatic, based on their physical examination findings at birth. This categorization may lead to confusion, as neonates who are asymptomatic may still have invisible symptoms, such as hearing loss.[1,4] Those born with visible signs (10%—15%) may present with one or a combination of often subtle signs (Table 3). The classic *blueberry muffin baby* presentation (small for gestational age, petechial rash, microcephaly, conjugated hyperbilirubinemia),[25] occurs in less than 5% of cases (Figure 1).[26]

Table 3. Possible Signs, Symptoms at Birth and Long-Term Health Conditions Associated with Congenital Cytomegalovirus Infection

Possible signs and symptoms of congenital cytomegalovirus at birth
Microcephaly
Small for gestational age
Direct hyperbilirubinemia
Petechial rash
Seizures
Chorioretinitis
Hepatomegaly
Splenomegaly
Feeding difficulties
Hearing loss
Preterm birth
Intracranial abnormalities
Thrombocytopenia
Possible long-term health conditions associated with congenital Cctomegalovirus
Developmental delays
Hearing loss (progressive childhood onset)
Intellectual disability
Cerebral palsy
Epilepsy
Vision loss
Impaired activities of daily living
Vestibular dysfunction
Tooth enamel defects
Behavioral disorders
Autism spectrum disorder
Learning disabilities
Reliance on tube feeding

Source: Kylat et al, 2006;[28] Sakamoto et al, 2015.[29]

Testing and Management in the Neonate

Testing for cCMV in the neonate is performed by CMV extraction from saliva or urine.[21] Serum cCMV testing has not been validated in newborns. Testing for IgG or IgM is also not helpful, as maternal antibodies remain in infant circulation for up to a year after birth. A neonate must be tested for cCMV in the first 21 days of life, after which it becomes difficult to distinguish a congenital infection from a postnatal exposure (which is generally not harmful).[4,21] In cases in which cCMV is suspected in older infants, banked cord blood or the remaining dried blood spot from the newborn metabolic screening may be tested for the virus.

The evaluation of a neonate with cCMV focuses on evaluating the extent to which the neonate has been affected by the virus. This process is generally overseen by a pediatric infectious disease specialist and includes cranial imaging (ultrasound is acceptable), laboratory studies, and referrals to audiology and ophthalmology.[27] Some neonates may be eligible for oral antiviral treatment, which has been shown to improve long-term developmental and hearing outcomes.[28] For all neonates with cCMV, routine long-term surveillance of their hearing and development into late childhood is important.[4,21]

Neurodevelopmental Outcomes

There is a wide spectrum of possible neurodevelopmental outcomes in affected neonates. Most neonates will have no long-term adverse outcomes, which is important to emphasize to families.[10] Those with intracranial pathology or microcephaly are at increased risk of global developmental delay, cerebral palsy, and intellectual disability, among other conditions (Table 3).[29,30] Learning and developmental delays and vestibular dysfunction are also common, even in the absence of hearing loss.

CONCLUSION

Congenital CMV is common and can lead to permanent disability. As in the case presented, people who are around young children are at increased risk. Midwives play an important role in providing antenatal risk reduction education and can initiate evaluation for a CMV infection when clinical suspicions arise (eg, ultrasound findings or cold-like symptoms, as in the case). Management of known cCMV infection should be in collaboration with a maternal-fetal medicine specialist, with additional fetal imaging to estimate the degree of involvement. Vaginal birth is appropriate in most cases; most neonates may breastfeed and stay with their parent(s) after birth. There is infrequent need for urgent evaluation. Neonates can be tested for cCMV using saliva or urine and referred to an infectious disease specialist for additional evaluation, often as an outpatient. Most neonates born with cCMV do very well; however, 20% will have long-term sequelae such as hearing loss or cerebral palsy.

Midwives play a crucial and trusted role in the holistic care of expectant individuals. As such, midwives are uniquely positioned to counsel about potential CMV health risks and prevention strategies and to empower people to make informed decisions about their health and well-being. Future research should evaluate the impact of midwife delivered antenatal counseling on cCMV prevention.

CONFLICT OF INTEREST

Dr. Pesch serves on the Board of Directors of the National CMV Foundation, which is an unpaid position. The National CMV Foundation did not contribute to the conceptualization or creation of this manuscript. The other authors have no conflicts of interest to disclose.

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