SONOGRAPHIC ASSESSMENT OF CONGENITAL CYTOMEGALOVIRUS

INTRODUCTION

Cytomegalovirus (CMV) is a double-stranded DNA virus of the herpes family. It is the most common in-utero infection, with an incidence of 0.6% of all live births. Approximately 8,000 newborns per year in the United States are born with CMV[1]. Adult seroprevalence is 50% in developed countries and as high as 90% in the developing world[2].

CMV is excreted in most bodily fluids, i.e. saliva, urine, semen, cervical secretions, and breast milk. Transmission is through contact with a person excreting the virus.

ETIOLOGY

The incubation period with CMV is 3-12 weeks. Maternal infection may be primary or secondary. Humoral immunity protects seropositive women against re-infection in 66-93% of cases[3]. Maternal re-infection rates are due to a different strain of CMV from the primary infection[4]. Hence, the delivery of a child with congenital CMV does not preclude a fetal infection in subsequent pregnancies.

Vertical transmission occurs in 30% of infected mothers after primary infection, but in 0.2-2% of secondary maternal infections[2,5]. The severity of congenital CMV may be the same for recurrent CMV as for a primary infection.

CLINICAL MANIFESTATIONS

10% of congenitally infected fetuses will be symptomatic at birth; 10% of asymptomatic infected newborns will have late neurologic sequelae, mainly sensorineural hearing loss[2,6]. Prognosis among symptomatic infants is poor; survivors generally have serious permanent sequelae.

Placental infection precedes fetal infection. The syncytiotrophoblast layer of the placenta acts as a reservoir for CMV. High placental viral loads increase the risk of in-utero transmission[7]. CMV replication in the placenta can result in placental insufficiency. 1st trimester miscarriage may occur due to placental infection without actual transmission to the fetus[8].

If the maternal immune system is competent, CMV becomes latent. When immunity is depressed, CMV can reactivate.

30-50% of symptomatic infants will have neurologic sequelae, including microcephaly, seizures, hypertonicity, motor disability and developmental delay. The severity of fetal disease and subsequent neonatal sequelae is determined by, not only the timing of infection, but also the affinity of a specific CMV strain for nervous tissue.

CMV infected children under the age of two may excrete virus for 24 months[8]. Hence, one of the risk factors for primary CMV in the United States is exposure to young children. A greater number of sexual partners is another risk factor for maternal infection. Native American and African American neonates are 2.34 and 1.89 times, respectively, more likely to die from congenital CMV then Caucasian neonates[9]. CMV DNA has been detected in 15% of singleton stillborn infants. While association is not necessarily

causation, it indicates that CMV should be part of the routine investigation of stillborn infants[10].

DIAGNOSIS

Maternal

Maternal CMV tends to be asymptomatic. Hence, the serologic documentation of a four-fold increase in CMV-specific IgG antibody titer over 4-6 weeks, along with the conversion from a negative to a positive IgM, rarely occurs. Anti-CMV IgM is, not only present during a primary infection, it may also be detected with a re-infection of CMV, or as a false positive due to other viral infections[2].

Another way to determine the timing of a CMV infection is to evaluate the strength or avidity of the antibody to the antigen. As the immunologic response matures, avidity increases. A low avidity anti-CMV IgG in early pregnancy suggests a recent infection. The presence of high avidity antibodies in the 1st trimester indicates an infection probably prior to conception[5,11].

Fetal

Once a recent maternal infection is suspected, an amniocentesis can be performed to confirm fetal exposure. Since the results of maternal IgG and IgM titers are not always clear-cut, amniocentesis should also be considered when there are multiple sonographic findings suggesting an in-utero infection.

An amniocentesis should be performed after 21 weeks' gestation and at least 5-6 weeks after the onset of maternal infection. The time lag between infection and amniocentesis is required to permit sufficient viral replication and subsequent renal excretion into the amniotic fluid. False negative results from an amniocentesis are common if the procedure is performed earlier[2,12].

The presence of CMV in amniotic fluid by polymerase chain reaction (PCR) has a sensitivity of 90-98% and a specificity of 92-98%, respectively. Viral isolation of CMV can also be performed. However, this test is less sensitive (70-80%)[2,12]. If both tests are properly performed and interpreted as negative, fetal infection is highly unlikely.

Fetal thrombocytopenia is an independent marker for a poor neonatal prognosis. Benoist et al13 have, therefore, suggested that cordocentesis should be considered in the prognostic evaluation of a fetus with congenital CMV. However, fetal blood sampling does not add additional diagnostic information to the results of amniocentesis. It should not, therefore, be utilized as a diagnostic test[1].

PRENATAL ULTRASOUND

Central Nervous System Sonographic Signs

The cerebral ultrasound findings associated with congenital CMV are numerous (Figs 1-5), but unfortunately, non-specific. Characteristically, an affected fetus will have more than one sonographic finding associated with a congenital CMV infection.

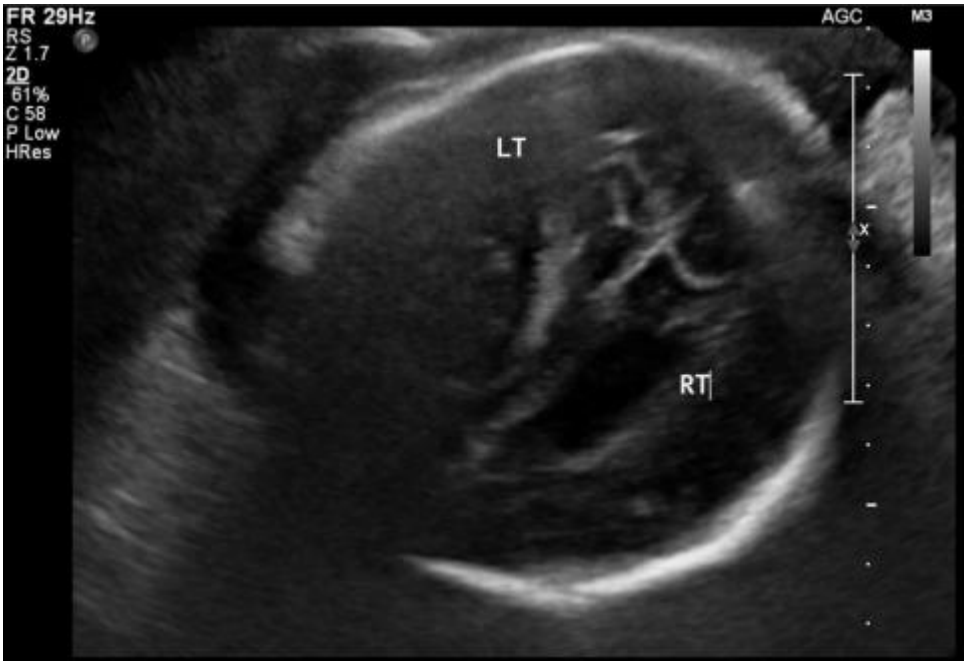

Fig 1. Unilateral (right) ventriculomegaly. Click for larger image.

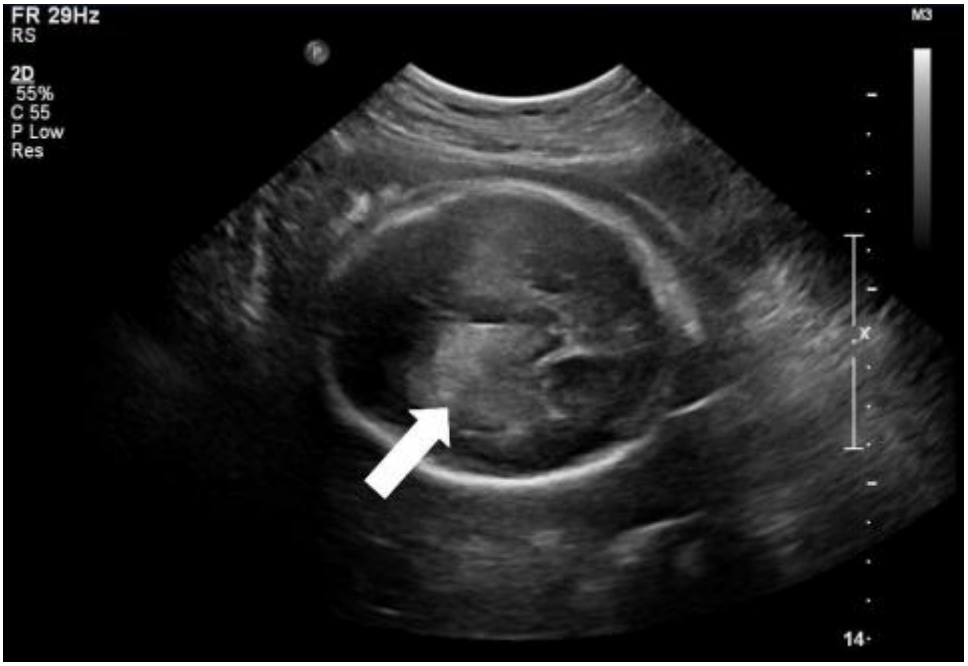

Fig 2. Intracerebral hemorrhage (arrow). Click for larger image.

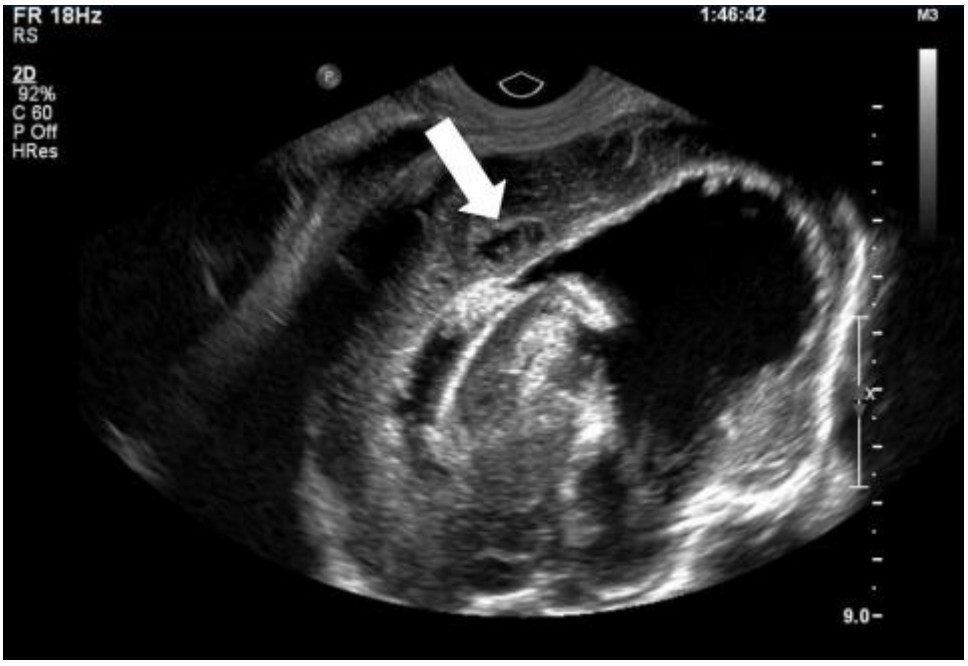

Fig 3. Periventricular leukomalacia (arrow). Click for larger image.

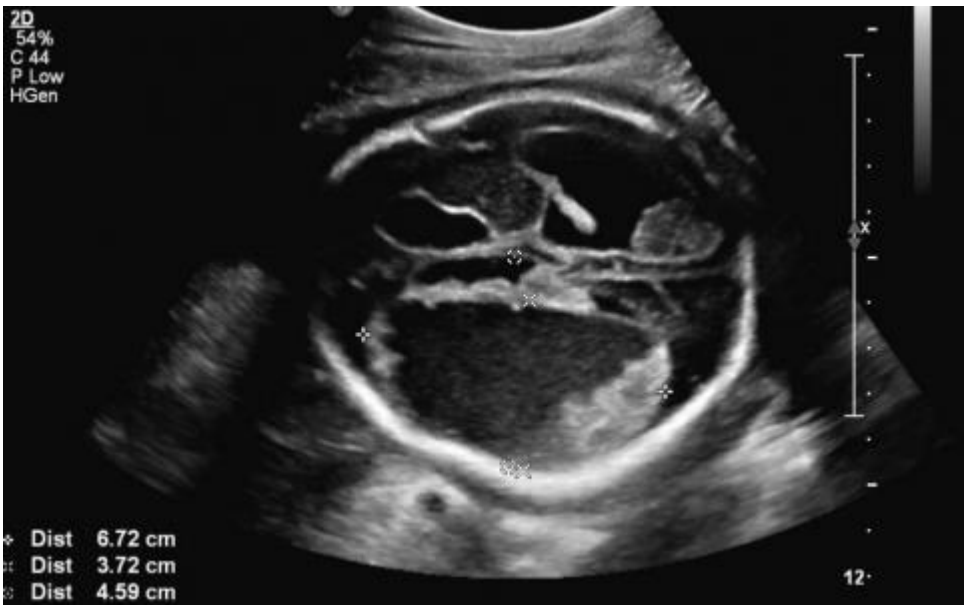

Fig 4. Porencephaly (6.72 cm by 3.72 cm). Click for larger image.

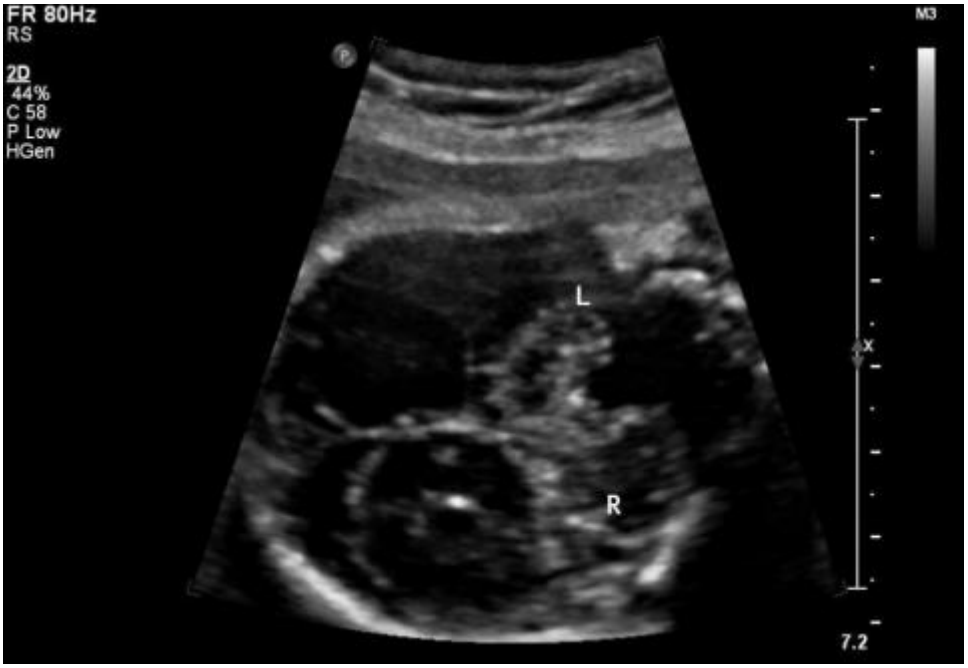

Fig 5. Left cerebellar hypoplasia; punctate echogenicities throughout cerebellar hemispheres due to CMV. Click for larger image.

Neurologic abnormalities are particularly common. Enders and co-workers[14] reported that 9 of 39 (23.1%) fetuses with proven congenital CMV had ventriculomegaly. Microcephaly is another central nervous system manifestation of congenital CMV and is the best predictor of subsequent mental and motor disabilities[15]. However, it may not be apparent until the neonatal period.

Calcifications within the brain are a hallmark of an intrauterine infection. They may either have a punctuate appearance or coalesce into a larger plaque. The latter is usually periventricular in location[16].

Lenticulostriate vasculitis results in the deposit of amorphous echogenic material in the walls of vessels within the basal glanglia and thalamus. Congenital infections, prematurity and chromosomal abnormalities have all been associated with this sonographic finding[17].

Increased periventricular echogenicity surrounding the lateral ventricles is due to ventriculitis. Congenital CMV prior to 16 weeks' gestation may result in lissencephaly[18] or cerebellar vermian hypoplasia[19].

Polymicrogyria is due to an injury at 18-24 weeks' gestation[18]. Table I provides additional central nervous sonographic findings that may occur with congenital CMV.

Table I. Sonographic findings with congenital cytomegalovirus.

- Central nervous system
  - Ventriculomegaly
  - Microcephaly
  - Punctuate calcifications
  - Periventricular calcifications
  - Increased periventricular echogenicity
  - Ventricular cysts
  - Ventricular adhesions
  - Perivenetricular leukomalacia
  - Micropthalmia
  - Porencephaly
  - Lissencephaly
  - Polymicrogyria
  - Cerebellar hemorrhage
  - Cerebellar/vermian hypoplasia
  - Cerebellar calcifications
  - Callosal dysgenesis
  - Linear lenticulostriated echogenicities
- Echogenic bowel
- Echogenic liver foci
- Hepatomegaly
- Splenomegaly
- Echogenic nephromegaly
- Non-immune hydrops
- Ascites
- Pleural effusions
- Cardiomegaly
- Intrauterine growth restriction
- Abnormalities of amniotic fluid volume

Although there are a plethora of sonographic stigmata associated with congenital CMV, the emphasis on fetal neuroanatomy is due to the close association between central nervous system abnormalities and subsequent long-term outcome[20]. In series of 34 fetuses with sonographic findings associated with congenital CMV, 27 (79%) involved the central nervous system[13]. Since the central nervous system sonographic signs associated with congenital CMV may be subtle, transvaginal sonography should always be attempted when the vertex is in a suitable position. 3rd trimester MRI has, therefore, become a complimentary imaging modality in the evaluation of congenital CMV.

While abnormal central nervous system abnormalities are highly suggestive of poor neurodevelopmental outcome[13], the potential outcome for each individual sonographic marker has not been quantitated. For example, it is not known if isolated mild ventriculomegaly or isolated calcifications in the context of congenital CMV is consistently associated with poor neurologic outcome[6,21]. In contrast, microcephaly, which is generally a late 3rd trimester or neonatal diagnosis is an accepted risk factor for a developmental delay[21].

OTHER SONOGRAPHIC SIGNS OF CONGENITAL CMV

In the 2nd and 3rd trimesters women with primary CMV have significantly thicker placentas then controls[22]. The syncytiotrophoblast layer of the placenta functions as a viral reservoir. Hence, during an active infection, there is a lack of correlation between the viral load in maternal blood[23] and intrauterine transmission.

Multiple hepatic calcifications (Fig 6) are secondary to hepatitis[24]. Similarly, viral enterocolitis may result in echogenic fetal small bowel (Fig 7)[25].

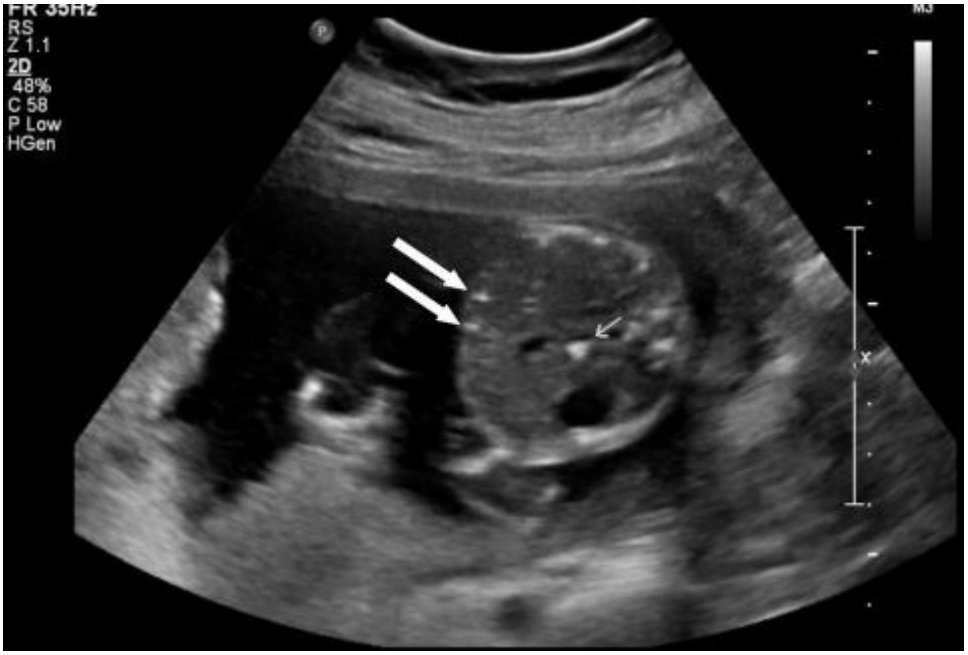

Fig 6. Hepatic echogenicities (arrows). Click for larger image.

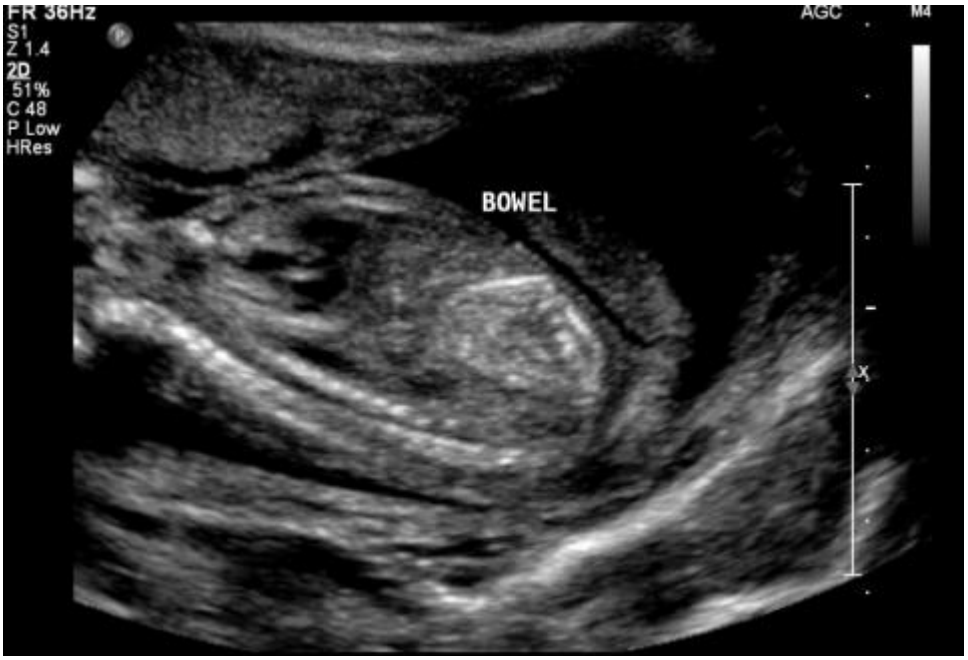

Fig 7. Echogenic bowel. Click for larger image.

Isolated fetal ascites (Fig 8) or non-immune hydrops (Figs 9-11) are due to hepatic dysfunction[26].

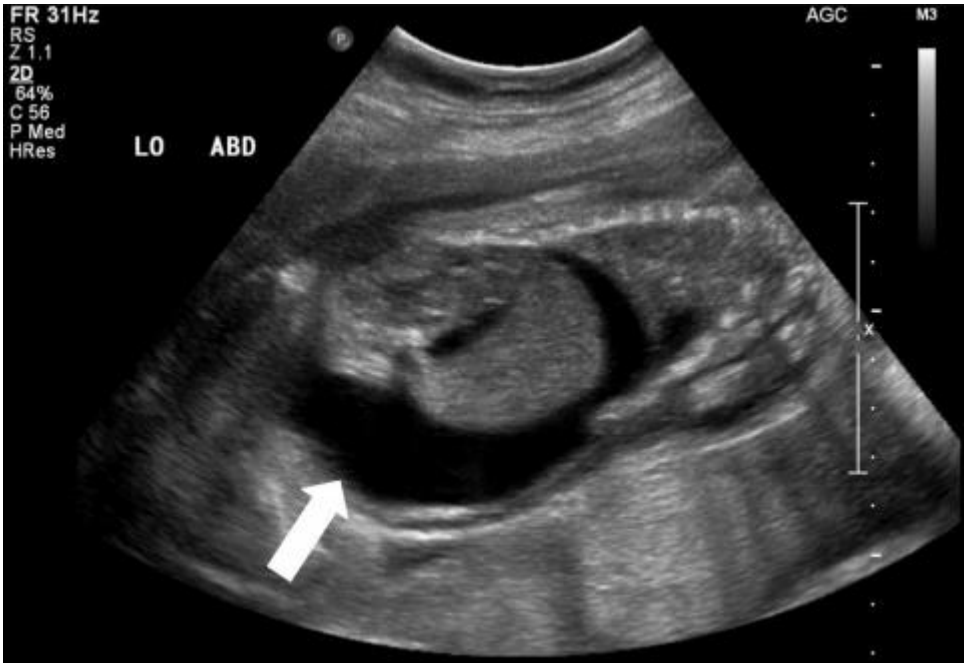

Fig 8. Ascites (arrow). Click for larger image.

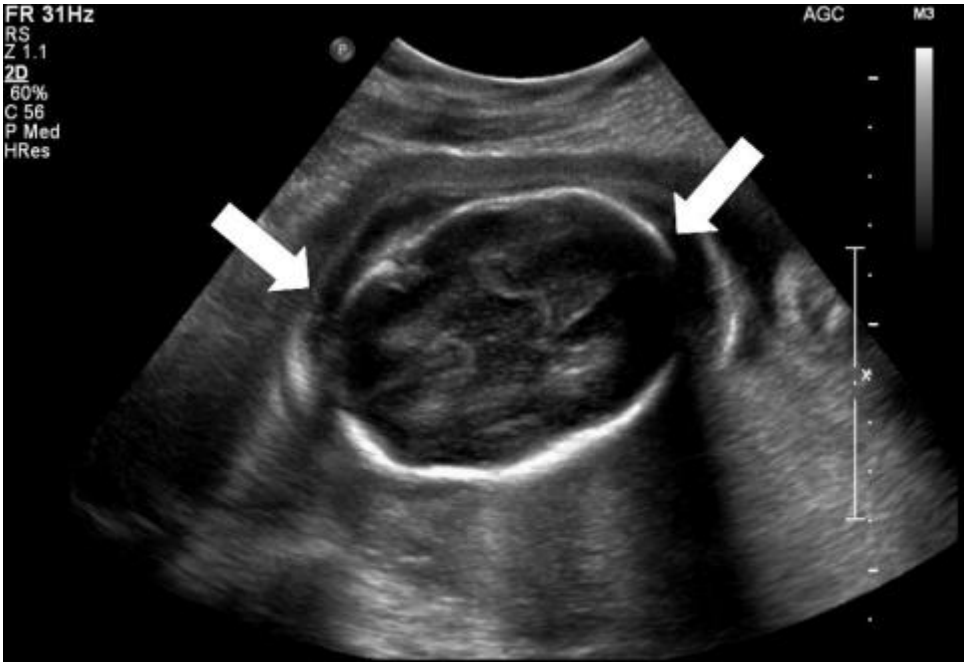

Fig 9. Scalp edema (arrows) due to congenital CMV non-immune hydrops. Click for larger image.

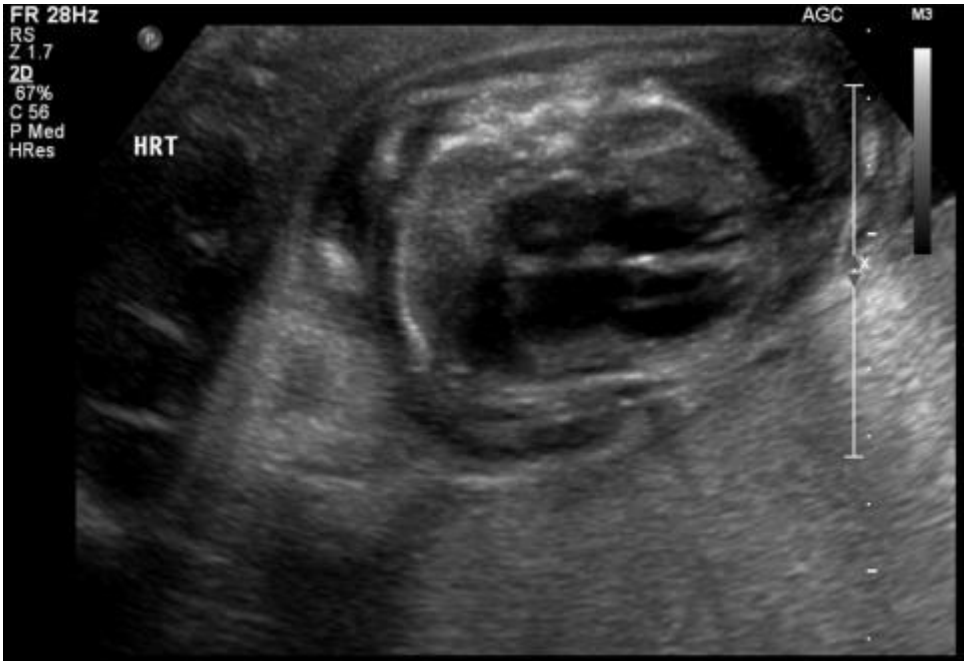

Fig 10. Cardiomegaly. Click for larger image.

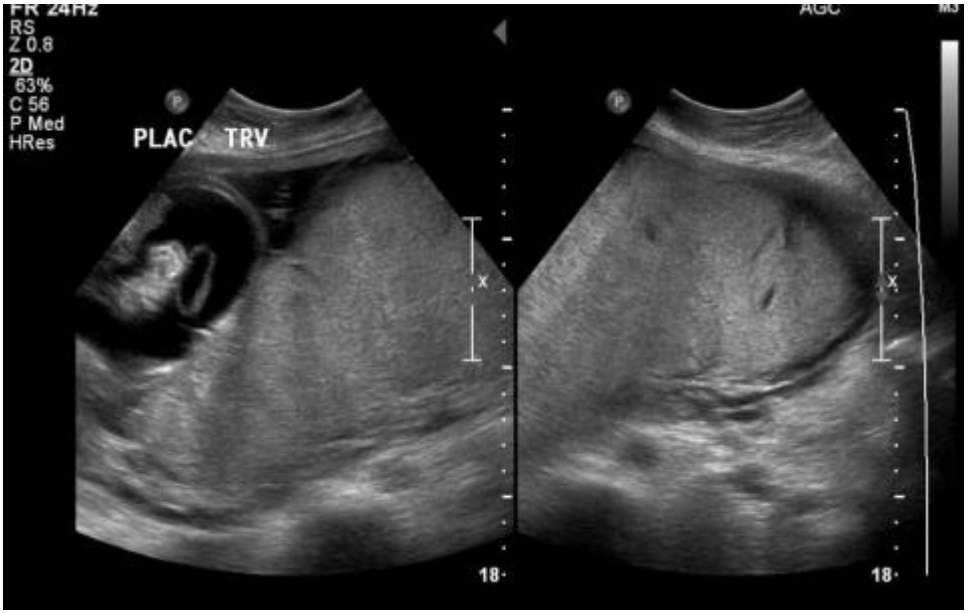

Fig 11. Placentomegaly. Click for larger image

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Intrauterine growth restriction occurs in 50% of symptomatic infants with CMV; the prematurity rate is as high as 34%[27].

Renal manifestations of congenital CMV include not only echogenic nephromegaly, but also alterations in renal function that may result in oligohydramnios or polyhydramnios.

SONOGRAPHIC DETECTION RATE OF CONGENITAL CMV

The sonographic detection rate of congenital CMV is difficult to determine because of small sample size, variable time of onset of CMV, different strains of CMV; gestational age at the time of the ultrasound examination; and the utilization of a single or serial ultrasound examinations in the detection of the sonographic signs outlined above. In two series of 62 infected fetuses with sonographic finding, half were detected prior to 22 weeks' gestation and half were identified later in gestation. While a normal 2nd trimester ultrasound examination is reassuring, it does not exclude the birth of an infant with significant CMV sequelae[28]. Farkas et al[29] and Lipitz and co-workers[30] studied a combined 37 fetuses with congenital CMV and reported that serial normal ultrasound examinations through the 3rd trimester, in association

with a normal 3rd trimester MRI, predicted a normal early neurodevelopmental outcome. Since the number of cases evaluated are limited, one cannot accurately derive any statistical conclusions about outcome in an individual case.

TREATMENT

Prenatal

When CMV is diagnosed early in pregnancy, treatment of the mother and, hence the fetus, should be considered investigational. In a study of 21 fetuses with confirmed CMV, oral valacyclovir was found to decrease the CMV viral load, but did not show a significant improvement in prenatal outcome[31].

CMV human immunoglobulin (HIG) is enriched CMV specific immunoglobulins. In contrast to oral valacyclovir, there are numerous studies that have shown treatment with CMV-HIG is efficacious[32,33]. CMV-HIG may be given intravenously to the mother, intra-amniotically, intraperitoneally into the fetus or via the umbilical vein[5]. The infusion of CMV-HIG has been shown to result in the regression of fetal ventriculomegaly in 3 cases[32].

The Cochran Collaboration[34] has concluded that there is insufficient data to assess whether any intervention can significantly reduce congenital CMV and its sequelae after a primary maternal CMV infection. Because of the large number (> 100,000) of pregnant women who would have to be tested to obtain a few hundred fetal infections, a randomized controlled trial of HIG will likely not be initiated in the United States[3].

Postnatal

The use of gancyclovir in neonates with symptomatic CMV is well documented. A 6 week intravenous course significantly reduces the likelihood of sensori-neural hearing loss[35].

A number of CMV vaccines have been evaluated in clinical trials. In a phase II trial a vaccine to a purified glycoprotein B (a viral glycoprotein necessary for viral infectivity) was found to have an overall efficacy of 50%. This level of effectiveness may be sufficient to prevent CMV within a community[36]. Until a CMV vaccine completes testing and is licensed, hygienic intervention as been shown to significantly decrease seroconversion when compared to a control group. As a result, the American College of Obstetricians and Gynecologists recommends that all pregnant women be educated about how a CMV infection can be acquired[37].

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