OBSTETRICS

Ultrasound prediction of symptomatic congenital cytomegalovirus infection

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OBJECTIVE: The objective of the study was to assess the effectiveness of ultrasound in the antenatal prediction of symptomatic congenital cytomegalovirus (CMV) infection.

STUDY DESIGN: The sonograms of 650 fetuses from mothers with primary CMV infection were correlated to fetal or neonatal outcome. Infection status was disclosed by viral urine isolation at birth or CMV tissue inclusions at autopsy. Classification of symptomatic disease was based on postnatal clinical or laboratory findings or macroscopic evidence of tissue damage at autopsy.

RESULTS: Ultrasound abnormalities were found in 51 of 600 mothers with primary infection (8.5%) and 23 of 154 congenitally infected fetuses (14.9%). Symptomatic congenital infection resulted in 1 of 23 and 68 of 131 cases with or without abnormal sonographic findings, respectively. Positive predictive values of ultrasound vs symptomatic congenital infection was 35.3% relating to all fetuses or infants from mothers with primary infection and 78.3% relating to fetuses or infants with congenital infection.

CONCLUSION: When fetal infection status is unknown, ultrasound abnormalities predict symptomatic congenital infection in only a third of cases.

Key words: congenital symptomatic infection, cytomegalovirus, prenatal counseling, ultrasound

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Cytomegalovirus (CMV) is the most common cause of intrauterine infection, occurring in 0.3% to 2% of liveborn infants.[1] Although only 10-15% of infected fetuses show symptoms at birth, the clinical manifestations (mainly central nervous system and multiple organ involvement with petechiae, hepatomegaly, splenomegaly, jaundice, pneumonia and encephalitis, and delayed intrauterine growth with low birthweight) may be so severe as to lead to a high perinatal mortality rate and major neurologic sequelae in most of the surviving babies. In addition, 10-15% of asymptomatic neonates will develop long-term sequelae, namely progressive hearing loss and mental retardation.[2] CMV can be transmitted to the fetus in both primary and nonprimary maternal infection, but primary infection has a much greater clinical impact than does recurrent or exogenous reinfection.[3-5]

When a primary maternal infection is diagnosed, the identification of infected fetuses at risk of developing CMV disease or sequelae is crucially important for both parental counseling and infant management.

Ultrasound is currently offered to pregnant women with CMV infection because it will disclose any structural and/or growth abnormalities indicative of fetal infection such as intrauterine growth retardation (IUGR), ventriculomegaly, oligohydramnios, hyperechogenic bowel, polyhydramnios, hydrops, brain calcifications, pleural effusion, and placental enlargement.[6-8] Although an ultrasound abnormality detected in a pregnant woman with primary CMV infection strongly suggests fetal infection, ultrasonographic findings are not diagnostic because they share common features with other fetal diseases. In addition, ultrasound abnormalities are observed in only less than half of the infected fetuses.[8]

Some minor ultrasound signs have been suggested to identify fetuses at risk,[9] but new ultrasound parameters for the identification of infected fetuses at risk of symptoms after birth have yet to be devised.

The aim of this study was to assess the ability of ultrasound in the antenatal prediction of symptomatic congenital CMV infection in cases of serologically proven primary maternal infection.

MATERIALS AND METHODS

We undertook a retrospective cohort study reviewing the sonograms of fetuses from mothers with CMV primary infection diagnosed at our Maternal-Fetal

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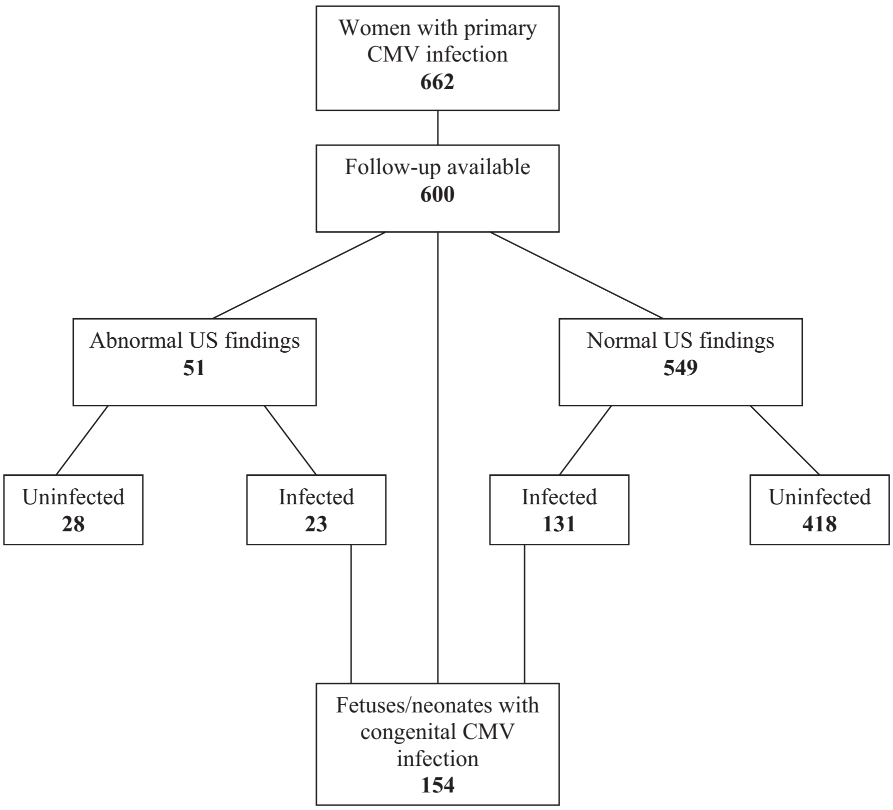
FIGURE 1

Ultrasound findings in pregnant women with CMV primary infection with respect to the presence or absence of CMV infection in fetus or neonate



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Medicine Division during the 10 year period ending in January 2006.

At our institution women with primary CMV infection (patients seroconverted to CMV IgG positivity or with anti-CMV IgG of low avidity combined with true IgM) are counseled about fetal risks, the advisability of ultrasound monitoring, and the possibility to diagnose fetal infection by amniocentesis at 20-21 weeks' gestation for cases of infection acquired early in gestation. If a high likelihood of fetal damage is recognized (ultrasound abnormalities and/or high viral load in the amniotic fluid), the couple may opt to terminate the pregnancy within the time frame currently provided by Italian legislation that does not allow late termination. Serial ultrasound scans are scheduled at 21, 28, and 33 weeks' gestation throughout continued pregnancy to evaluate the fetal anatomy.

The laboratory tests used to detect primary maternal CMV infection and diagnose CMV infection in utero, and a detailed description of prenatal counseling have been reported elsewhere.[10-12]

Ultrasound examinations were performed by doctors with extensive experience in ultrasound prenatal diagnosis. The ultrasonographic examinations included a survey of all fetal organs. Given the particular neurotropism of CMV, the intracranial anatomy was evaluated, when permitted by a low position of the fetal head, transvaginally using 5-10 MHz transducers.

Information concerning fetal and neonatal outcomes (uninfected or infected) was obtained directly when the mothers had terminated their pregnancies or given birth in our hospital. If the mothers had received care elsewhere, this information was elicited by means of either a questionnaire or a telephone interview or both.

Infection status of the neonates was classified on the basis of viral isolation from urine or saliva within the first 2 weeks after birth. The status of aborted fetuses was classified on the basis of macroscopic and histologic tissue examination (either CMV inclusions or antigen, or both, found in multiple organs). Infected fetuses were classified as having symptomatic infection when CMV inclusions were accompanied by macroscopic evidence of tissue damage in multiple organs with or without overt signs of malformation.

Newborns congenitally infected with CMV were assessed clinically for disease in the newborn period and were classified as having symptomatic or asymptomatic infection on the basis of physical, instrumental, and laboratory findings. Newborns were considered symptomatic when they presented with 1 of the following: signs and symptoms of systemic involvement such as intrauterine growth retardation, hepatosplenomegaly, skin petechiae/purpura, thrombocytopenia (platelet count: 100,000/mm^3), jaundice with direct bilirubin (3 mg/dL), alanine aminotransferase elevation (80 U/L), pneumonia, neurologic involvement (microcephaly, lethar-

TABLE 1

Screening efficiency of ultrasound examination in predicting congenital CMV infection

US finding	Uninfected	Infected	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Abnormal	28	23	14.93	93.72	45.09	76.13
Normal	418	131				
Total	446	154				

US, ultrasound; *PPV*, positive predictive value; *NPV*, negative predictive value.

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gy/hypotonia, poor sucking, and seizures) and sensorineural defects (chorioretinitis and deafness), and CMV-associated patterns at neuroimaging (abnormal periventricular hyperechogenicity, intracranial calcifications, ventriculomegaly, hyperechogenicity of lenticolostriatal vessels, etc).[13]

Long-term sequelae were defined during postnatal follow-up. Follow-up visits, including clinical evaluation, neurodevelopmental and psychointellectual assessment, cranial ultrasound, cerebral computed tomography (in case of doubts at sonographic examination) and magnetic resonance imaging (in case of neurologic symptoms or pathologic ultrasound), funduscopic examination, and audiological assessment, were scheduled at 1, 3, 6, 12, and 18 months of life and then annually up to school age. Infected neonates enrolled in this study were followed up for a median of 42 months (range, 6-72 months).

The virologic, clinical, and histologic examinations were carried out by the virology, pediatric, and pathology departments of the hospital in which a given delivery or termination occurred.

Statistical analysis

Cross-tabs were used to calculate univariate sensitivities, specificities, and positive and negative predictive values of ultrasound vs symptomatic congenital infection. Statistical analysis was performed using the Windows Statistical Package for Social Science (version 11, SPSS, Chicago, IL).

Ethics

The study was carried out following the ethical rules of St. Orsola-Malpighi General Hospital, Bologna, Italy.

RESULTS

During the 10 year period ending in January 2006, 662 pregnant patients with primary CMV infection were seen at our center. All women received counseling. Except for 8 pregnancies resulting in spontaneous abortion and 4 terminated electively in the first trimester, the remaining 650 pregnant women were offered ultrasound monitoring. Of these, 339 also underwent amniocentesis. Among the 600 fetuses/neonates with available follow-up information (postnatal urine test; autopsy in the case of the fetus terminated in the second trimester), 154 had CMV infection.

Abnormal sonographic findings were found in 51 of 600 pregnant women with primary infection (8.5%) and 23 of 154 fetuses with documented congenital infection (14.9%). Fetal abnormalities could not be attributed to intrauterine CMV infection in 28 of 51 cases (54.9%) (Figure 1). Sensitivity, specificity, and positive and negative predictive value of ultrasound vs congenital infection are reported in Table 1.

The abnormal sonographic findings identified in uninfected cases are listed in Table 2.

TABLE 2
Abnormal ultrasonographic findings in uninfected newborns from mothers with primary CMV infection

Ultrasonographic findings	Number
Choroid plexus cysts	7 cases
Mild monolateral pyelectasis	7 cases
IUGR	6 cases
Hyperechogenic bowel	5 cases (of which 3 normalized at subsequent ultrasound follow-up at 28 wks)
Mild monolateral ventriculomegaly	1 case
Cerebral ventriculomegaly and corpus callosum agenesis	1 case
Mild enlargement of the quadrigeminal cistern and dilation of the posterior fossa with slight rotation of the vermis with respect to the brain stem axis	1 case

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Abnormal sonographic findings identified in infected cases included hyperechogenic bowel (n = 7), cerebral ventriculomegaly (n = 7), IUGR (n = 3), hydronephrosis (n = 1), hydrops (n = 1), cerebral periventricular echogenicity (n = 1), and the association of 2 (hyperechogenic bowel and cerebral ventriculomegaly, n = 2) or more fetal abnormalities (cerebral ventriculomegaly, cerebral atrophy, cerebellar hypoplasia, hepatomegaly, hyperechogenic bowel, and IUGR, n = 1).

Eighteen of the 23 fetuses/neonates with CMV congenital infection (78.3%) were symptomatic at birth (6 cases) or later (2 cases) or were classified as symptomatic at autopsy (10 cases). Among the remaining 131 cases without abnormal sonographic findings, 68 fetuses/neonates (51.9%) were classified as symptomatic, whereas 63 were asymptomatic (48.1%).

The sonographic findings in the 7 fetuses resulting asymptomatic at birth were hyperechogenic bowel (2 cases), IUGR (3 cases), mild cerebral ventriculomegaly (1 cases), and severe hydronephrosis (1 case). Two of the newborns asymptomatic at birth presented problems at follow-up: 1 neonate with fetal evidence of hyperechogenic bowel showed psychomotor retardation and monolateral hearing impairment 1 year later; 1 newborn with fetal intrauterine growth restriction late during gestation showed bilateral hearing loss within a year.

The sonographic anomaly was diagnosed for the first time at 20-22 weeks in 15 cases (65.2%) and between 27 and 33 weeks' gestation in 34.8% of the fetuses (8 of 23) (Table 3).

Among 23 fetuses showing abnormal sonographic findings, 9 were terminated (39.1%), 1 died in utero at 22 weeks' gestation (4.3%), and 13 newborns were delivered (56.5%). Abnormal sonographic findings and outcome of infected cases are listed in Table 3.

TABLE 3
Sonographic abnormalities and pregnancy outcomes of CMV infected infants/fetuses

	Abnormal sonographic findings	20-22 wks	30-33 wks	Outcome
1	Cerebral ventriculomegaly	X	NP	TOP: disseminated CMV infection, pneumonitis, corpus callosum agenesis, hepatomegaly
2	Mild cerebral ventriculomegaly	X	NF	CMV-infected neonate with mild hepatitis; fetal ventriculomegaly resolved in utero
3	Cerebral ventriculomegaly; hyperechogenic bowel	X	X	CMV-infected neonate severe cerebral ventriculomegaly, diffuse microcalcified areas, hepatosplenomegaly; chorioretinitis and mental retardation after first year
4	Mild cerebral ventriculomegaly hyperechogenic bowel	X	NP	TOP: mild cerebral ventriculomegaly and CMV disseminated infection with severe involvement of liver and lung
5	IUGR	NF	X	Symptom-free CMV-infected neonate at birth; bilateral hearing loss within 1y
6	Cerebral ventriculomegaly	NF	X	CMV-infected neonate with mild cerebral ventriculomegaly and monolateral hearing impairment at 1 y
7	Hyperechogenic bowel	X	X	Symptom-free CMV-infected neonate at birth; hearing loss and poor psychomotor development after 1 y
8	Hyperechogenic bowel	X	NP	TOP: disseminated CMV infection with hepatomegaly and cerebral ventriculomegaly
9	IUGR	NF	X	Symptom-free CMV-infected neonate
10	Hyperechogenic bowel	X	NP	TOP: CMV infection with massive involvement of lung, heart and kidney; hepatomegaly and ileal atresia
11	Hyperechogenic bowel	X	NP	TOP: disseminated CMV infection with hepatomegaly and liver and brain calcifications
12	Cerebral ventriculomegaly	X	NP	TOP: disseminated CMV infection with massive involvement of lung, liver, pancreas, kidney, brain, and bilateral cerebral ventriculomegaly
13	Hydronephrosis	X	X	Symptom-free CMV-infected neonate
14	Cerebral ventriculomegaly	NF	X	Symptom-free CMV-infected neonate
15	Cerebral ventriculomegaly	NF	X	CMV-infected neonate with severe cerebral ventriculomegaly and diffuse brain calcifications at birth; lissencephaly within 1y with poor psychomotor development and bilateral hearing loss
16	Cerebral ventriculomegaly, cerebral atrophy, cerebellar hypoplasia, hepatomegaly, hyperechogenic bowel, IUGR	X	NP	TOP: disseminated CMV infection with massive involvement of lung, liver, pancreas, kidney and brain; bilateral cerebral ventriculomegaly and cerebellar hypoplasia
17	Hyperechogenic bowel	NF	X	CMV-infected neonate with cerebral calcifications, hearing loss, and chorioretinitis
18	Hyperechogenic bowel	X	NP	TOP: cerebral periventricular monolateral calcifications
19	Cerebral periventricular echogenicity	NF	X	CMV-infected neonate with cerebral calcifications, cerebral palsy and mental retardation after first year
20	IUGR	NF	X	Symptom-free CMV-infected neonate
21	Hyperechogenic bowel	X	X	Symptom-free CMV-infected neonate
22	Hydrops	X	NP	IUD at 22 wks gestation: CMV-infected fetus with severe involvement of lung, liver, and brain
23	Cerebral ventriculomegaly	X	NP	TOP: cerebral ventriculomegaly and brain calcifications

Amniotic fluid samplings were obtained at 21 weeks of gestation in cases 1-4, 8-10, and 12-22. Negative results of amniocentesis were obtained in cases 13, 20, and 21.
IUD, intrauterine death; *NF*, normal finding; *NP*, ultrasound not performed; *TOP*, termination of pregnancy; *X*, presence of fetal anomalies.

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The screening efficiency of ultrasound in predicting congenital symptomatic CMV infection is reported in Tables 4 and 5. An abnormal sonographic finding relating to all fetuses/infants from mothers with primary CMV infection yielded a positive predictive value (PPV) of 35.3% (Table 4), whereas an abnormal sonographic finding relating to fetuses/infants with congenital CMV infection was associated with a PPV of 78.3%. Furthermore, there was a 48.1% probability that a normal ultrasound finding excluded the development of symptomatic infection (Table 5).

TABLE 4
Screening efficiency of ultrasound examination in predicting symptomatic CMV infection in all fetuses exposed in utero

US finding	Uninfected/infected asymptomatic	Infected symptomatic	Total	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Abnormal	33	18	51	20.93	93.57	35.29	87.61
Normal	481	68	549				
Total	514	86	600				

PPV, positive predictive value; *NPV*, negative predictive value; *US*, ultrasound.

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COMMENT

In our experience, a fetus with congenital CMV infection and abnormal sonographic findings has a high probability of postnatal disease. When the status of infection is not known in fetuses exposed to maternal CMV infection, ultrasound abnormalities predict symptomatic congenital infection in only a third of cases. By contrast, a normal fetal anatomic survey may reassure patients at risk for fetal symptomatic infection but is associated with a normal outcome in less than half the cases.

Ultrasound monitoring is crucial for pregnant women with proven primary CMV infection because it is the only means of disclosing fetal abnormalities caused by congenital infection. Although ultrasound is not the best means to establish fetal CMV infection, it is a useful adjunct in predicting the likelihood of postnatal CMV disease. Parental counseling can be tailored to the status of fetal infection after invasive prenatal diagnosis, supporting findings that ultrasonographic abnormalities associated with in utero fetal infection might increase the risk of adverse neonatal outcomes.[6] In fact, the PPV of ultrasound increases 2-fold when results indicate fetal infection.

Among the abnormalities encountered in our infected fetuses, it is difficult to pinpoint ultrasound features pathognomonic for CMV infection. Hyperechogenic bowel and ventriculomegaly are the most common abnormal findings, but they are also seen in uninfected fetuses. However, ventriculomegaly is the least common sign in uninfected fetuses, compared with its frequency among infected fetuses.

Around 5% of all ventriculomegaly diagnosed in utero are of infectious origin.[14] Our study documented isolated ventriculomegaly in 7 infected cases with different postnatal implications. The postnatal outcome of the 4 pregnancies carried to term varied from no symptoms to mild hepatitis without neurological sequelae either at birth or 5 years later; mild ventriculomegaly at birth monolateral hearing loss at 1 year; and severe ventriculomegaly and diffuse calcifications at birth with lissencephaly, poor psychomotor development, and sensorineural hearing loss within the first year. Only 1 case of mild ventriculomegaly was encountered in an uninfected newborn.

The significance of hyperechogenic bowel in maternal CMV infection remains unsettled.[15] Viral enterocolitis often shows the transient appearance of hyperechogenic bowel, but echogenic bowel may occur as a normal variant in the second trimester or in association with pathologic conditions like cystic fibrosis and chromosomal abnormalities. To avoid overdiagnosis of this condition, our center considers only grade 2 hyperechogenicity (Figure 2).[16] Our study disclosed isolated hyperechogenic bowel in 7 cases of congenital CMV infection (5 symptomatic, 1 asymptomatic at birth but presenting neurosensory sequelae at postnatal follow-up, and 1 asymptomatic) but also in 5 uninfected newborns. By contrast, no cases of congenital cytomegalovirus infection were reported in a recent prospective analysis of 60 fetuses with isolated hyperechogenic bowel.[17]

Although abnormal prenatal sonographic findings are important predictive markers for an adverse outcome, ultrasound identifies only 15% of the fetuses at risk of symptomatic congenital CMV infection, even in this selected population. Enders et al[18] detected ultrasound abnormalities in only 2 of 17 infected fetuses (11.8%) from mothers with proven or suspected primary infection, whereas Liesnard et al[19] found major ultrasound abnormalities in 5 of 55

TABLE 5
Screening efficiency of ultrasound examination in predicting symptomatic CMV infection in congenitally infected fetuses/newborns

US finding	Symptomatic congenital infection: Yes	No	Total	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Abnormal	18	5	23	20.93	92.64	78.26%	48.09
Normal	68	63	131				
Total	86	68	154				

PPV, positive predictive value; *NPV*, negative predictive value; *US*, ultrasound.

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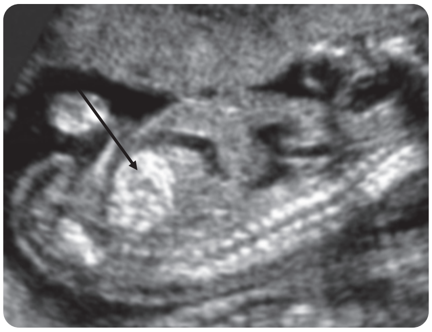
FIGURE 2

Longitudinal view of the fetal abdomen at 22 weeks' gestation showing hyperechoic bowel



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infected fetuses of mothers with primary infection (9.1%). Minor ultrasound findings (IUGR and/or hyperechogenicity of the fetal bowel) were diagnosed in 9 of 55 infected fetuses (16.4%), but the majority of infected newborns were asymptomatic. Azam et al[20] observed abnormal sonographic findings in 5 of 26 infected fetuses (19.2%), whereas Lipitz et al[6] reported ultrasonographic abnormalities associated with in utero fetal infection in 11 of 51 fetuses (21.5%).

The limitations of ultrasonography in identifying predictive markers for adverse fetal outcome are well known, and its detection rate of fetal infection is influenced by many variables. First, the performance of fetal ultrasound examination varies greatly according to degree of infection[9]: only fetuses with severe CMV infection will show obvious ultrasound abnormalities, whereas more subtle or nonspecific ultrasound features are likely to escape detection. Second, ultrasound examinations are more targeted, and more effort is made to recognize any fetal damage in the serological risk groups, especially after CMV detection in amniotic fluid. Finally, the ultrasound detection rate of fetal disease will depend on the ultrasound screening policy in different countries and whether patients with maternal primary infection are offered repeated and level 2 and 3 ultrasound follow-up.[21]

In our experience, abnormal sonographic findings were detected for the first time in the third trimester in more than a third of the cases, after a normal ultrasound examination in midgestation. Because of the pathophysiology of fetal CMV infection, several weeks can elapse before any features of fetal infection show up on ultrasound.[9] In addition, a normal second-trimester ultrasound scan does not rule out significant intracranial anomalies or microcephaly, a feature highly suggestive for fetal CMV infection.[22] Malinger et al[23] retrospectively reviewed the images of 203 abnormal central nervous system ultrasound examinations performed between 13 and 37 weeks of gestation, finding that at least 1 previous second-trimester ultrasound examination had been performed and considered normal in 16.7%. A repeat third-trimester scan may lead to a more accurate diagnosis and counseling, but it is too late to allow pregnancy termination.

The present study classified 55% of congenitally infected fetuses/newborns as symptomatic. This proportion is higher than expected and probably is due to the fact that our institution is a tertiary reference center for CMV infection in pregnancy. Similar high rates (57.6% and 43%) were found in the studies of Enders et al[18] and Liesnard et al.[19] In addition, we defined infected fetuses as having symptomatic infection when CMV inclusions were accompanied by macroscopic evidence of tissue damage in multiple organs, even without overt signs of malformation. Although a negative outcome would be expected in these cases, this approach may have overestimated the number of symptomatic fetuses.

Despite ongoing research, no vaccine is currently available for use prior to conception to prevent congenital CMV infection.[24] Prevention must thus be based on correct hygiene and behavior.[25] Preventive administration of immunoglobulins to pregnant women with primary infection may reduce the rate of vertical transmission and improve neonatal outcome,[26] but these findings await confirmation in randomized studies on large patient cohorts.

The lack of prenatal treatment for CMV infection will often lead to termination of pregnancy. In this setting ultrasound investigation plays a primary role. Our findings may help clinicians to counsel pregnant women infected with CMV. Although it is not surprising that an ultrasound abnormality may significantly predict postnatal disease in fetuses with congenital CMV infection, parents and physicians should be informed about the limitations of second-trimester sonography as far as brain diagnosis is concerned. ■

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