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REVIEW

Cytomegalovirus infection in pregnancy

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Abstract
Purpose Due to the severe risk of long-term sequelae, prenatal cytomegalovirus infection is of particular importance amongst intrauterine viral infections. This review summarizes the current knowledge about CMV infection in pregnancy.
Methods A search of the Medline and Embase database was done for articles about CMV infection in pregnany. We performed a detailed review of the literature in view of diagnosis, epidemiology and management of CMV infection in pregnancy.
Results The maternal course of the infection is predominantly asymptomatic; the infection often remains unrecognized until the actual fetal manifestation. Typical ultrasound signs that should arouse suspicion of intrauterine CMV infection can be distinguished into CNS signs such as ventriculomegaly or microcephaly and extracerebral infection signs such as hepatosplenomegaly or hyperechogenic bowel. Current treatment strategies focus on hygienic measures to prevent a maternal CMV infection during pregnancy, on maternal application of hyperimmunoglobulines to avoid materno-fetal transmission in case of a maternal seroconversion, and on an antiviral therapy in case the materno-fetal transmission have occurred.
Conclusion CMV infection in pregnancy may result in a severe developmental disorder of the newborn. This should be taken into account in the treatment of affected and non-affected pregnant women.

Keywords Cytomegalovirus · Congenital development disorders · Central nervous system · Immunoglobulins

Introduction

Prenatal cytomegalovirus infection (CMV) is of particular importance amongst intrauterine viral infections. It affects about 2–6 from every 1000 children being born. Depending on the gestational age at the time of infection, CMV carries a severe risk of long-term sequelae. Since the maternal infection is predominantly asymptomatic (ca. 80%), the infection often remains unrecognized until the actual fetal manifestation of the infection. The prognosis at this time is already significantly worse and only widespread screening could help with early recognition and treatment of asymptomatic infected mothers. However, at the moment, this cannot be recommended, since efficient therapeutic options like a vaccine are lacking.

This review summarizes the epidemiology of the infection, the natural course, and possible treatment approaches [1].

Basic virological data on human cytomegalovirus

Human cytomegaloviruses are enveloped, double-stranded DNA viruses within the family of β-herpesviruses (HHV-5: human herpesvirus 5) which consist of the capsid with DNA genome, a tegument layer, and the viral envelope with embedded viral glycoprotein products (gcI: gB; gCII:

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gM, gN; gcIII: gH, gL, gO), which are important for the viral entry into the host cell and the interaction with the cellular and humoral immune system. The linear genome is the largest of all herpes viruses at 235 kb and is divided into unique long (UL) and unique short (US) sections which encode a total of ca. 170–200 reading frames. Like other members of this group, after primary infection, they lead to a latent viral infection and persist lifelong in the host. One viral latency site is in CD34+ hemotopoetic cells in the bone marrow.

Cytomegaloviruses have strict species specificity. CMV infections and virus reactivation have particular clinical relevance in the transplant setting with solid organ (SOT) and stem cell transplantation (SCT), critical ill patients in intensive care units, severe burn patients as well as during vertical mother-to-infant virus transfer during pregnancy and lactation.

Epidemiology and symptoms of CMV infection in pregnancy

Some basic aspects have to be taken into account when assessing the risk for a congenitally infected child:

- First, a primary infection has to be distinguished from a non-primary infection. At least in our region, a primary infection carries a much higher risk for a symptomatic congenital infection.
- Second, materno-fetal transmission is obligatory before a developmental disorder may occur. Pregnancies with a transmission in the first and early second trimester carry the highest risk.
- Third, materno-fetal transmission results in a congenital infection, but it is not equivalent to a symptomatic congenital infection. The later the infection occurs in pregnancy, the higher the transmission rate is. In contrast, with increasing gestational age, the risk for a symptomatic congenital infection decreases.
- Fourth, most neonates with a congenital infection will be asymptomatic. However, these children carry a certain risk for long-term sequelae.
- Fifth, neonates with a symptomatic congenital infection are much more likely to suffer from short- and long-term physical and mental developmental disorders.

Primary infection

We focus on primary infection, since, depending on the gestational age, a materno-fetal transmission rate of 30–70% can occur [2].

The primary infection is asymptomatic in 80% of immunocompetent pregnant women. Only approximately 20% of patients have influenza or mononucleosis-like symptoms such as fever, rhinitis and pharyngitis, headache, arthralgia and myalgia, as well as physical exhaustion [3]. Viral DNAemia is observed in approximately 75% of cases during an acute primary infection. In about 0.5% of the cases, a prolonged presence of the viral DNA in blood can be observed [4]. The duration of the viral DNAemia differs individually and lasts for a period of 2–6 weeks. In an immunocompetent individual with a primary infection, the virus subsequently moves into a stage of lifelong latency, from which it can be reactivated during transient immunosuppression. CD34+ stem cells in the bone marrow are known to be a latency site.

The proportion of seronegative women who are able to experience a primary CMV infection greatly differs regionally between 10 and 60%. Using data from the congenital CMV study in Tuebingen, in which all mothers and children have been screened for CMV using serology and PCR at birth since 2008, it can be concluded that the maternal seroprevalence in our region is approximately 50% [5].

Data from the latter study indicate that the prevalence of congenitally infected neonates is about 0.17% (evaluated for 2011). In comparison, the prevalence in Sweden was approximately 0.2%, whilst the prevalence in the USA, Brazil, and Cuba was observed to be over 1.0% [6]. In these countries, a higher rate of secondary infections need to be taken into account (see below). For a direct comparison of the rates, one should be aware of the fact that in several coutries such as Brazil, there is a ban on abortion, and that in European studies, the pregnancy termination rate for CMV has not been taken into account separately up to now; therefore, in Europe and Germany, there are inevitably lower rates of newborns with symptomatic congenital CMV in relation to all live births.

From the congenitally infected children, around 90% are asymptomatic after birth. About 8–15% of these asymptomatic infected children develop late complications in the form of a unilateral or bilateral hearing disorder.

Approximately 10% of neonates have symptomatic CMV infection. Clinical symptoms include petechiae (76%), jaundice (67%), hepatosplenomegaly (60%), microcephaly (53%), growth retardation (50%), chorioretinitis, and optic atrophy (20%). In severe congenital CMV infection, the blueberry muffin sign is known as a sign of cutaneous extramedullary hematopoiesis. It consists of petechiae, disseminated or dense red to reddish brown spots, papules and plaques, and blueberry coloured or reddish ecchymoses. Associated laboratory parameters may include: transaminase elevation (83%), conjugated hyperbilirubinaemia (81%), and thrombocytopenia (77%).

About 30–40% of the symptomatic children will develop a developmental disorder [7]. Consequences during early childhood include sensorineural hearing damage

(59%), mental retardation (IQ > 70: 47%, IQ > 50: 36%), psychomotor impairment (63%), and cerebral palsy (49%) [8–11].

Overall, around every fourth infected neonate will develop late episodes of congenital CMV infection after maternal CMV primary infection [7]. With approximately 40,000 infected children per year, congenital CMV infection is the most common cause of congenital, non-genetic sensorineural hearing loss in the USA [12].

Non-primary infection

In recent years, non-primary infection during pregnancy has gained epidemiological importance. In this context, IgG seroprevalence is of crucial importance. A distinction is made between "high" prevalence countries with a seroprevalence >70% and the "low" prevalence countries with 50–70% seroprevalence [13]. High prevalence continents are, for example, Africa, Asia, and South America. Depending on the ethnic background, the USA and Western Europe tend to be among the low-prevalence countries. There is a seroprevalence of about 50% in Germany [14]. If only primary infection was relevant, these pregnancies would actually be protected. However, data from high prevalence countries highlight the growing importance of secondary infection.

Recent epidemiological studies in the high prevalence country of Brazil have indicated a prevalence of congenital CMV infection of about 1.1% (87 from 7909 live births). Compared to Germany, this is significantly higher, although IgG seroprevalence is significantly higher in Brazil. The higher rate is attributable to a reinfection rate of up to 4.2% [15, 16]. The actual transmission rate of maternal non-primary infection is not yet known. In a meta-analysis, Kenneson and Cannon referred to a transmission rate of 1.4% [6]. However, this is controversially discussed, since the transmission rate of seropositive mothers in early pregnancy is also unknown [7, 13].

Populations with almost 100% CMV IgG seroprevalence are clearly not protected against reinfection with other viral strains or reactivation of their own virus. The rate of congenital CMV infections after maternal non-primary infection is thought to be about three-to-four times as high as the primary infection rate [17]. This would result in approximately 11 CMV infections per 1000 women with non-primary infection and approximately 3–6 CMV infections per 1000 women with primary infection [7].

Whether non-primary infection plays a major role in a CMV low-prevalence country—for example, in Germany—still has to be shown. With today's diagnostic methods, we can diagnose non-primary infections with reactivation and reinfection after initial screening with knowledge of the CMV serostatus before or at the beginning of pregnancy. Within the scope of the Tuebingen CMV congenital study, we were able to clearly identify various children after non-primary infection of the mother. This is because we documented the CMV serostatus from a previous pregnancy in sequential pregnancies in the same mother in a local registry. Therefore, we were able to clearly demonstrate that materno-fetal CMV transmission in two close pregnancies was based on a recurrent infection. However, these were random findings, which could only be obtained by systematic newborn screening at birth as part of combined mother-infant screening at birth. All neonates born after maternal non-primary infection in the Tuebingen cCMV study were asymptomatically infected. However, it is clear from international studies from high prevalence countries that in about 10% of these cases, a recurrent infection during pregnancy may also lead to long-term consequences in CMV-infected infants [7, 13].

Regardless of primary or non-primary infection, the urine or saliva of viral-shedding infants up to 3 years of age and the genital secretions of adolescents and adults are the main source of maternal infection. Data on CMV seroprevalence among children and adolescents in Germany (KiGGS, 2003–2006) show that CMV seroprevalence increases with age in children (21.5% at the age of 1–2 years, up to 32% at the age of 14–17 years) [18].

In view of the greater importance, the further focus is on primary infection.

Influence of gestational age on the course of CMV primary infection

Materno-fetal transmission occurs in approximately 30–70% of cases [2, 3, 19]. The frequency is strongly dependent on the gestational age of primary infection. Enders et al. summarised the transmission rates of 248 primary infections [2]. In the first trimester, the transmission rate was 30%. In the second and third trimesters, the transmission rate increased to 38 and 72%, respectively. In a pre- (−8 to −2 weeks before start of the last menstruation) and peri- (−1 to +5 weeks after the start of the last menstruation, up to the 5th week of pregnancy) conceptional primary infection (±3 weeks around the time of conception), a transmission rate of 17 and 35%, respectively, was observed. Similarly, Picone et al. investigated 238 pregnancies with CMV primary infection. The transmission rate increased between the first and third trimesters from 30 to 40% and was approximately 9 and 20% for pre- or peri-conceptional infection [3].

As discussed before, transmission is equivalent to a fetal infection or the materno-fetal transfer of the virus to the child, but not with a symptomatic congenital CMV infection at birth. Unlike transmission, the frequency of symptomatic infections decreases steadily during the course of

pregnancy. In a study by Picone et al., symptomatic intrauterine and postnatal courses were only observed after first trimester or pre- and peri-conceptional infections [3]. Lipitz et al. observed the course of 145 pregnancies with a primary CMV infection. After infection in the first trimester, a symptomatic postnatal course was observed in 20% of the pregnancies and in about 6% after infection in the second trimester [20]. Bilavsky et al. examined 138 children with a congenital CMV infection. In the majority of these pregnancies, the infection occurred in the first and second trimesters or periconceptual. In all pregnancies, an amniocentesis was performed, predominantly at about 20–23 weeks. In the cohort of infants with a normal amniocetensis ($n = 46$), none of the children had long-term complications. There was one child (2.2%) in this study group with hearing impairment at birth but normal hearing at 5.5 years after prolonged antiviral treatment. In contrast, in the cohort with a positive amniocentesis, 14% suffered from long-term sequelae [21].

Signs of CMV primary infection

Since the infection is asymptomatic for most pregnant woman, obstetricians encounter the CMV infection either after checking the antibody status or as a result of a conspicuous ultrasound examination.

Antibody kinetics

The new German AWMF guideline for the diagnosis of viral infections during pregnancy has suggested determining the CMV serostatus at the beginning of pregnancy for occupationally or intra-familiar CMV-exposed pregnant women to infants of less than 3 years of age. The implementation of this S2 k guideline will make it possible to identify pregnant seronegative patients and to provide specific information on hygiene measures for the prevention of viral transmission during pregnancy, as well as to document seroconversion by means of a test in the second trimester, since this guideline stipulates that a retained serum sample should be taken at the start of pregnancy and cryopreserved for 2 years [14].

The natural course of the primary infection is associated with an increase in IgG antibodies and a fall in IgM antibody indices with initially low CMV IgG avidity. Using immunoblotting, there is the possibility of displaying different CMV-specific antibodies over time. For example, antibodies against viral surface glycoprotein B cannot be detected in the first 3 months of primary infection [22, 23]. The same applies to CMV IgG avidity maturation. High-avidity polyclonal antibodies which bind to the antigen develop over the course of the primary infection. It has to be taken into account that the transition between the low, intermediate, and high IgG avidity stages is highly test dependent [24]. Furthermore, the detection of CMV-IgM is variable due to IgM persistence, non-specific reactivity, or, for example, by induction of broad anti-herpes virus IgM reactivity, e.g., with simultaneous detection of CMV IgM and EBV IgM. The most diagnostically safe parameter is currently determination of quantitative CMV IgG levels even in the absence of a WHO standard for IgG since test-dependent deviations are not in the same category as with IgM assay systems. Positive IgG and IgM levels (indices) should always be supplemented by CMV IgG avidity determination and quantitative real time PCR from whole EDTA blood and urine should be performed to complete the diagnosis of an early maternal CMV primary infection in pregnancy.

Maternal CMV primary infection in the first trimester has different diagnostically relevant virological characteristics compared to non-primary infection. However, we cannot adequately diagnose recurrent infection with the equipment available in routine diagnostics today [25, 26]. Therefore, the retained serum sample required in the AWMF Guidelines 2014, which is taken at the time of the initial proof of pregnancy and cryopreserved for 2 years, has exceedingly important relevance for the differentiation of primary and non-primary infections. We are currently only at the beginning of this development and new methods for the quick and uncomplicated diagnosis of recurrence are required.

Ultrasound signs

Severe manifestations of CMV infection are almost invariably caused by an infection in the first trimester. However, since about 6 weeks usually elapse between the time of maternal infection and transmission, it is clear that the symptoms of an early CMV infection during pregnancy can to some extent only be detected later in the course of the pregnancy.

Typical ultrasound signs, which should arouse suspicion of intrauterine CMV infection, can be distinguished into CNS signs and extracerebral infection signs. Table 1 summarizes the classic symptoms [27].

From the cerebral side, ventriculomegaly and increased periventricular echogenicity (Fig. 1) are frequently present in periventriculitis. Microcephaly and intraventricular calcification are late manifestations and signs of past encephalitis. The calcification can be plaque-like or isolated in all areas of the brain (Figs. 2, 3). The plaque-like distribution pattern mainly affects the periventricular area. Periventricular pseudocysts and intraventricular synechiae are the consequences of destructive processes in the brain (Fig. 1). Very early brain involvement during pregnancy may lead to cortical developmental disorders such as

Table 1 Ultrasound abnormalities that can be associated with CMV (from Leruez-Ville et al. [27])

Serious cerebral signs	Mild cerebral signs	Extracerebral signs
Ventriculomegaly >15 mm	Mild ventriculomegaly 10–15 mm	Echogenic fetal bowel
Increase periventricular echogenicity	Intraventricular synechiae	Hepatomegaly (left hepatic lobe >40 mm)
Hydrocephalus	Intracerebral calcifications	Intrauterine growth retardation
Microcephaly ≤2 SD	Subependymal cysts	Oligohydramnios
Enlarged cisterna magna >8 mm	Choroid plexus cysts	Polyhydramnios
Vermian hypoplasia	Calcifications of the anterolateral central arteries in the basal ganglia	Ascites, pleural effusion, subcutaneous oedema, hydrops fetalis
Porencephaly		Placentomegaly
Lissencephaly		Intrahepatic calcification
Periventricular cystic lesions		
Corpus callosum agenesis		

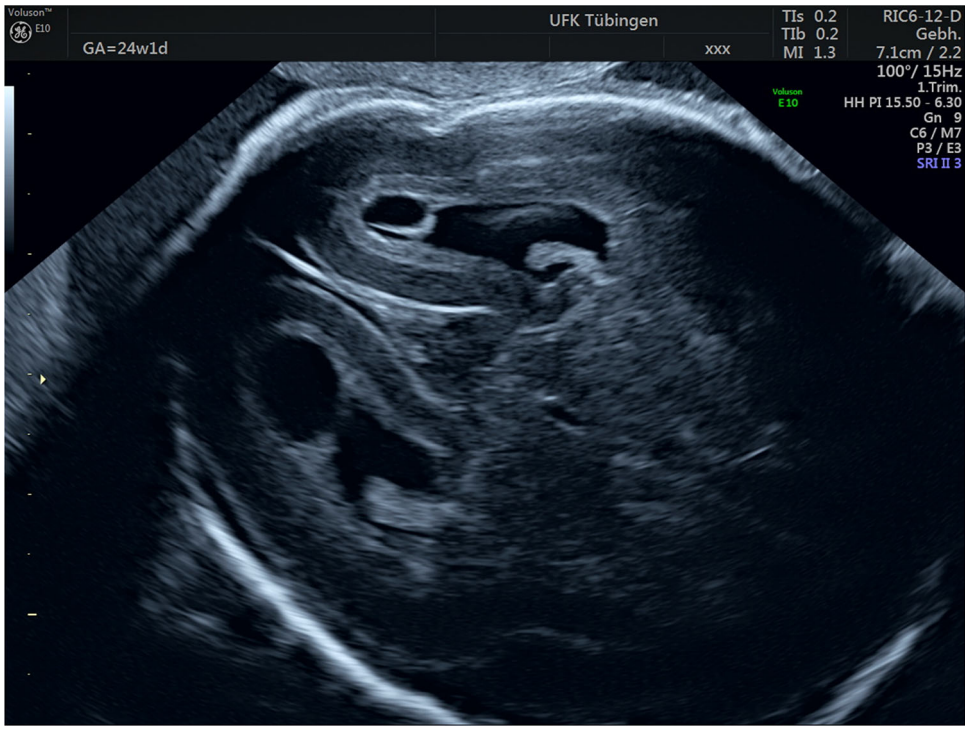

Fig. 1 Increased periventricular echogenicity as a result of periventriculitis with destructive lesions in the posterior horn

lissencephaly or pachygyria [28]. Teissier et al. showed that the extent of cerebral injury correlates with the incidence of CMV-infected CNS cells [29].

The extracerebral manifestation is unspecific and shows that the entire fetal body can be affected as a result of the affinity of the virus to endothelial and epithelial cells. The most common manifestations are intrauterine growth retardation, hepatosplenomegaly, and echogenic fetal bowel (Figs. 4, 5). In addition, oligohydramnios and placentomegaly are common [27].

If severe intrauterine CNS symptoms such as microcephaly or destructive lesions are present, a postnatal developmental disorder is almost certain. This is not the case with non-specific extracerebral symptoms. We have already seen several CMV-affected fetuses, where symptoms such as a pericardial effusion disappeared during the course of the pregnancy, without symptomatic congenital CMV being present after birth. One could speculate that in some cases, fetuses may recover from an intrauterine CMV infection as long as the brain is not affected.

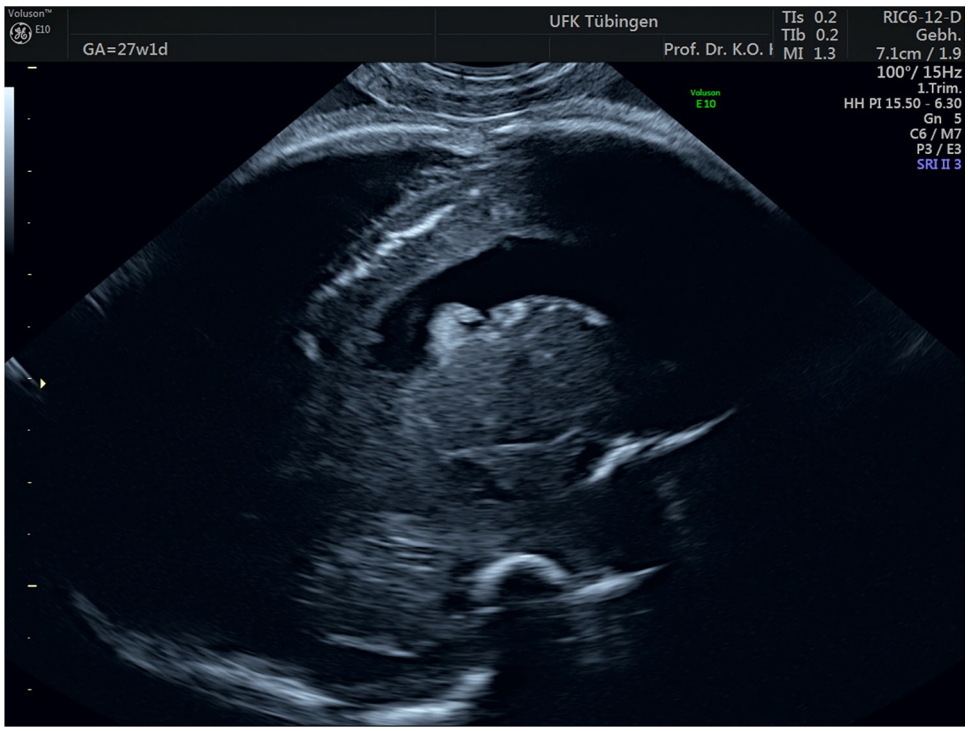

Fig. 2 CNS calcifications

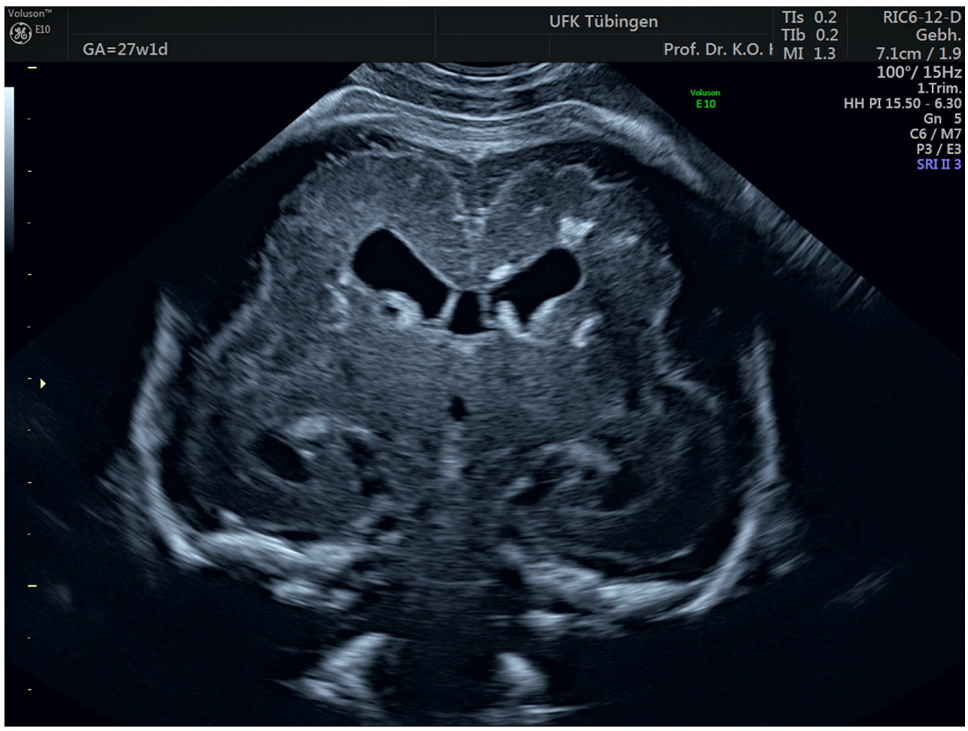

Fig. 3 CNS calcifications

The signs described are most likely to be those of a direct infection ("CMV inclusion disease") rather than an isolated severe placental function disorder. Gabrielli et al. pointed out that the pattern of damage is more pronounced with increasing frequency of infected cells in an organ [30]. Inevitably, the placenta plays a central role in the context of CMV infection. It is a viral reservoir, the first infected "gestational" organ and responsible for growth retardation and the reduced amniotic fluid volume.

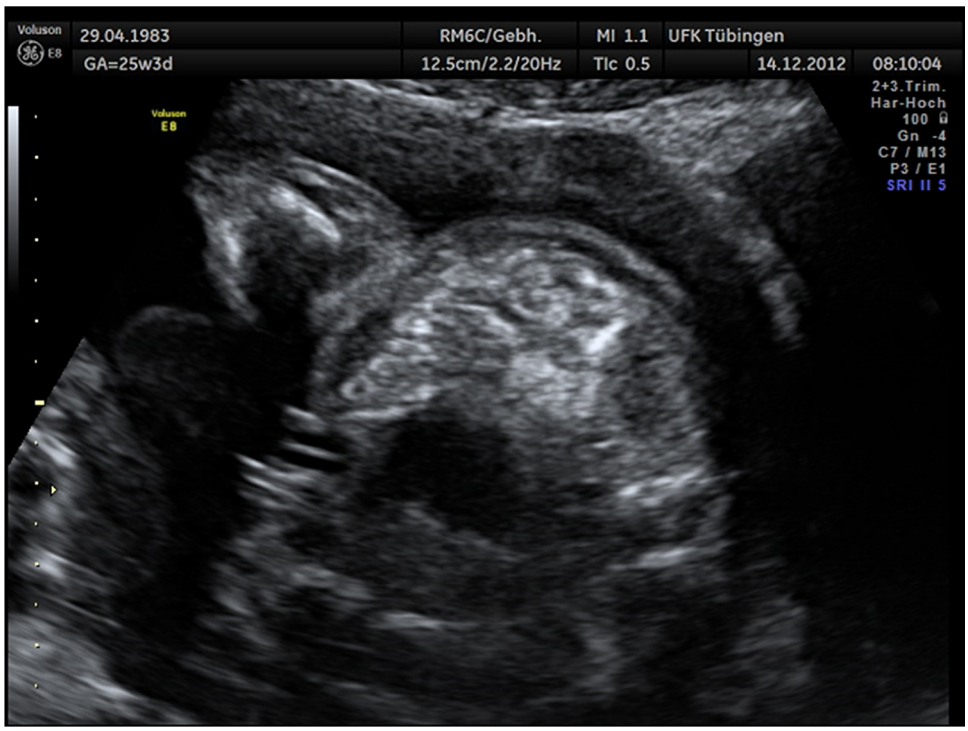

Fig. 4 Hyperechogenic bowel

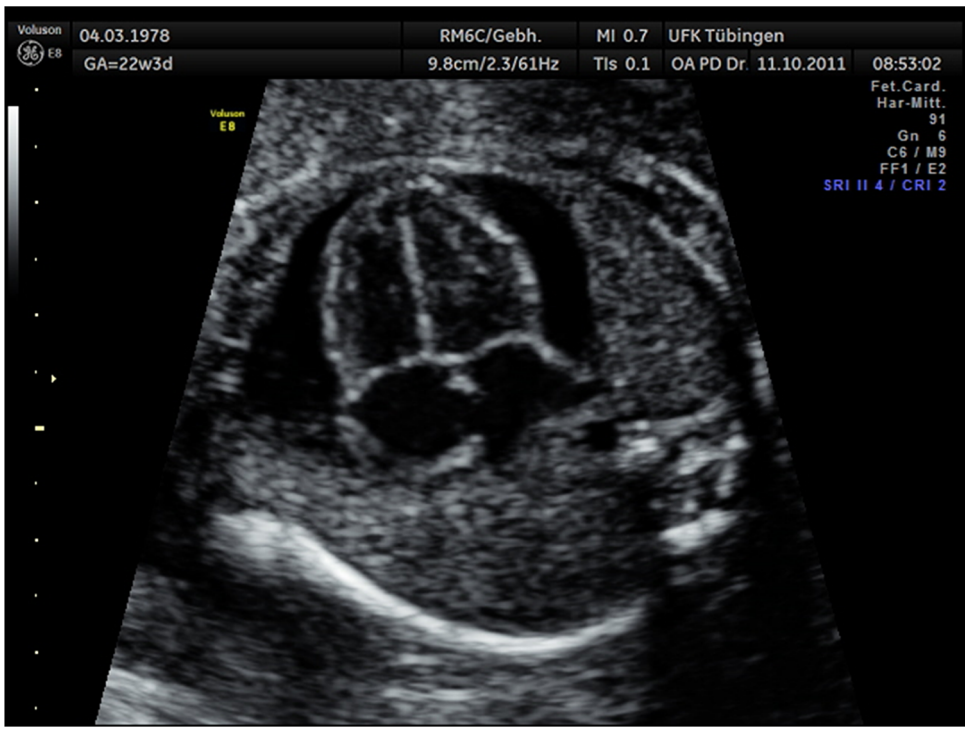

Fig. 5 Pericardial effusion

Prediction of the outcome

Numerous studies have dealt with the prediction of an adverse pregnancy outcome in terms of congenital CMV infection.

In a meta-analysis of Hui and Wood, the authors tried to estimate the risk of congenital CMV infection at different times during pregnancy, based on several previous studies [31]. The authors concluded that the risk for a symptomatic congenital CMV infection is about 1 in 10 after maternal

seroconversion in the first trimester. The risk changes to 1 in 4 or 1 in 200 depending on whether materno-fetal transmission occurs or not. In cases with materno-fetal transmission and ultrasound signs, the risk exceeds 1 in 2. The risk is 1 in 8 if there are no ultrasound signs.

In more detail, Guerra et al. observed 600 pregnant women with primary CMV infection [32]. In 549 pregnancies, no signs of CMV were found, and still, a fourth of these fetuses were infected. On the other hand, infection was suspected in 51 fetuses, but more than half of these cases were unaffected. In summary, the detection rate for a congenital CMV infection was only about 15% for a false-positive rate of about 6%. Benoist et al. investigated the possible predictors of an adverse outcome using a multiple regression analysis. They found that fetal thrombocytopenia as well as fetal abnormalities could best define the high-risk group. CNS abnormalities increased the risk ten times more than non-cerebral markers [33].

Leruez-Ville et al. investigated the prognostic value of ultrasound and clinical laboratory parameters in the second and third trimesters after transmission in 82 infected fetuses. Severe CNS abnormalities were found in 19 pregnancies, which were all terminated except for one. In 22 fetuses, abnormalities were observed that were classified as "non-severe" (Table 1). Three pregnancies were terminated. At birth, ten (45%) of the remaining 19 fetuses were symptomatic. After 24 months, there were nine (47.4%) symptomatically infected children in this group. These had uni- or bilateral hearing impairment. Only one child had a neurological development disorder. In the group of 41 pregnancies without ultrasound signs, three pregnancies were terminated and 38 were continued. None of these 38 neonates were symptomatic after birth and only two (5.3%) of the children had abnormalities in the form of hearing impairment after 24 months [27].

Interestingly, the authors also investigated the predictive value of the platelet concentration in combination with the viral load in fetal blood. At a platelet concentration of less than 114,000/mm^3, 62.5% of the neonates were symptomatic or the pregnancies were terminated. In the case of a higher thrombocyte concentration, the authors recommended measurement of the viral load in fetal blood. At a viral load above 4.93 log10 IU/ml, 57.1% of the pregnancies ended with a symptomatic neonate or with termination. With a lower viral load, it was only 3.1%. In the context of a fetal infection, the detection of elevated IgM indices in the fetal blood may contribute to diagnosis.

In individual cases, MRI may be used to increase the test quality in addition to ultrasound examination. If there are clear sonographic abnormalities, the use of an additional MRI examination is limited. In the case of an inconspicuous ultrasound scan, MRI can be a useful, complementary examination. Lipitz et al. pointed out that the risk of congenital CMV infection is reduced by approximately 60% with normal ultrasound and MRI examinations [20].

It is clear from the data that none of the imaging techniques can exclude congenital CMV infection after maternal seroconversion. In this respect, amniocentesis to diagnose or exclude transmission is of central importance. This should be performed if there in case of ultrasound signs or at least 6 weeks after maternal seroconversion. In general, amniocentesis is recommended after 20 weeks' gestation [12].

Diagnostic reliability of amniocentesis

PCR analysis is considered gold standard in the diagnosis of CMV in amniotic fluid. Specificity ranges between 97 and 100% [34–36]. In terms of sensitivity, Enders et al. highlighted that the sensitivity is about 90% irrespective from whether the amniocentesis is performed after 17 or 20 weeks as long as the time interval between the seroconversion and the amniocentesis is 8 weeks or more [37].

Based on unpublished own data, we could demonstrate that the combination of two different PCR types with short- and long-term microculture was able to detect CMV DNA and infectious virus in 30 of 30 cases in amnion fluid. We used therefore a nested PCR with IE1Ex4 target gene with a quantitative real-time PCR with either gB or pp65 target gene. Prior to inoculation to human fibroblast monolayers, we concentrated the virus by a 50,000g centrifugation step resulting in a fivefold virus enrichmant in the pellet. Microcultures were inoculated even 18h or 10 days. In all cases of CMV-infected amnion fluid samples, the virus infection was already detectable in fibroblast nuclei by CMV IE1 immunostaining after 18h. Plaque formation could be observed already in some cases after overnight incubation. In all cases we performed amniocentesis at a gestational age of about 20 weeks.

However, viral transmission in the third trimester may occur in cases with a late infection after 20-week gestation. Obviously, these cases cannot be detected by amniocentesis in the second trimester. Theoretically, transmission after the 20 weeks' gestation can also be caused by reinfection with a new viral strain. This could be revealed by modern, highly sensitive NGS sequencing methods. It is already clear today that we must abandon the image of a single viral variant which is disseminated and transmitted during the viraemic phase of the primary infection. In CMV, we also see the formation of viral quasi-species and viral families that co-circulate [38].

Preventive and treatment approaches

Symptomatic congenital CMV infection could be avoided on three different stages of the disease: first, by hygienic

measures to prevent a maternal CMV infection during pregnancy, second, by avoiding materno-fetal transmission in case of a maternal seroconversion, and third, by treating the fetus in case of a materno-fetal transmission.

Hygienic measures and vaccination for the prevention of CMV infection during pregnancy

In a phase 2 study with recombinant viral glycoprotein B (gB), Pass et al. showed that vaccination against CMV is possible in principle and that this could reduce the infection rate by 50% [39]. This vaccine-limited efficacy led to the fact that the vaccination was not approved by the FDA, since simple hygienic measures can at least equally prevent CMV infection.

However, awareness of CMV infection and its routes of transmission must be increased amongst the general population. Priority must be given to informing pregnant women that the main infection pathway is via small children in the family. They are infected by droplet infection from contact with other children, for example, in playgroups [22]. About a quarter of all infants are viral shedders [40]. Since the infection usually occurs asymptomatically in the child and the mother, the infection remains unrecognized.

Adler et al. and Vauloup-Fellous et al. highlighted that the infection rate of pregnant women could be significantly reduced by a detailed explanation of the infection and the necessary hygiene measures [40, 41]. Revello et al. also demonstrated this in a prospective, controlled intervention study. As part of first trimester screening, the serostatus was assessed in the intervention group. In the case of negative IgG and IgM, the pregnant women received a detailed explanation of the routes of transmission and instructions on how to avoid infection. This also meant that kissing children with potential mucosal contact (mouth) should be avoided. In the intervention group, the seroconversion rate was 1.2%, whereas in the control group without consultation at the beginning of pregnancy, seroconversion was observed in 7.6% of cases [42].

Administration of hyperimmunoglobulins after primary infection in the first trimester for the prevention of transmission

After seroconversion, there is a temporary lack of maternal antibodies with high IgG avidity and high neutralization capacity that could prevent materno-fetal transmission. Therefore, this time interval, which is usually characterized by the presence of low-avidity IgG antibodies, could be bridged by the administration of high-avidity immunoglobulin preparations to prevent materno-fetal CMV transmission and subsequently to reduce the rate of postnatal symptomatic CMV infections [43].

Nigro et al. followed this approach in a non-randomized study and gave 37 women hyperimmunoglobulins (HIG) after seroconversion; 47 remained untreated. A congenital CMV infection was detected in six (16%) fetuses in the treatment arm and 19 (40%) fetuses without treatment [44]. In the first randomized, placebo-controlled double-blind study by Revello et al., the authors examined the transmission rate in 61 and 62 mother–child pairs after infection, predominantly in the first trimester [45]. In the treatment group, the transmission rate was 30%, and in the control group, it was 44%. Despite the clinically relevant differences, these were not statistically significant. Buxmann et al. reported on 38 pregnant women who received HIG during pregnancy. The transmission rate in this study was 23% [46].

Still, in the very recent consensus recommendations from Rawlington et al., the authors did not recommend administration of HIG to pregnant women with primary CMV infection [47]. This aspect remains controversy and more studies are needed for clarification. As the main aim of HIG is to prevent transmission up to 20 weeks, there is no rationale for administration of HIG after that timepoint. However, in cases with primary infection in the first and early second trimesters, HIG may still be beneficial. Additional trials are currently on their way, including a study in our unit.

Interestingly, all studies administered HIG at intervals of 4 weeks. The basis for this time interval is the half-life of 22.1 days, published by Thürmann et al. who analysed the kinetics of anti-HBs following passive immunization against HBV [48]. Our own experience suggests that the half-life time of the transfused CMV IgG antibody preparation Cytotect® (HIG) is much shorter and that a 2-week rhythm would be more appropriate [49]. The corresponding studies are still awaited.

Therapy approaches after transmission

After transmission, administration of HIG can also be considered to either prevent a symptomatic infection at birth or lessen the symptoms. Visentin et al. treated 31 women with HIG after positive amniotic fluid detection. The control group consisted of 37 women. In the treatment group, four (13%) neonates were symptomatic compared to 16 in the control group (43%) [50]. Nigro et al. treated 31 women and found one (3%) symptomatic child, whereas in the control group, half of the children were symptomatically ill at birth [44].

It is speculated that in these cases, it is the placentitis, that is treated as an adequate transplacental transfer of the immunoglobulins to the baby is only expected after 26

weeks' gestation [51] In view of CMV as a direct organ-damaging disease (CMV inclusion disease), sufficient immunoglobulin concentrations cannot be achieved in the fetal circulation via maternal administration. Therefore, in these cases, direct fetal administration of the HIG could be considered via chordocentesis. This must be considered as an experimental approach, since studies on this procedure are not available. Any of these interventions cannot be recommended on an evidence-based background.

Recent studies have focused on valaciclovir for the intrauterine treatment of CMV. This drug has a high bioavailability, so that there is a sufficient concentration of the medication in the amniotic cavity when taken orally. Leruez-Ville treated 43 mothers with a CMV infection and transmission with valaciclovir [52]. Fetuses without ultrasound signs or with severe CNS signs were not treated. At birth, 34 (79%) neonates were asymptomatic. These showed no symptoms, even after 12 months. However, the potential toxicity of antiviral therapy should also be taken into account.

Postpartum treatment approaches

There is an ongoing debate on whether targeted or universal CMV screening should be offered after birth. In contrast to a *universal CMV screening* test, where each neonate is tested, a targeted screening approach only focuses on children with an abnormal newborn hearing screening test. Cost-effectiveness studies have demonstrates that—under well-defined circumstances—universal screening may result in larger net savings [53–55].

It has been shown that by a 6-week intravenous administration of ganciclovir, the deterioration of hearing after birth can be halted and the psychomotor development can be improved [56, 57].

Kimberlin et al. also examined the oral use of valganciclovir [58]. They showed that with 6 months of treatment, the hearing ability as well as the cognitive development after 12 and 24 months was significantly improved. The possibility of oral treatment was the decisive breakthrough for such a long treatment. CMV excretion in the child was significantly reduced during therapy, but increased immediately after discontinuation of the drug. The infectiousness also remained during and after therapy.

Irrespective of drug treatment, the hearing, cognitive, and motor development must be regularly monitored during the first 6 years of life. From a certain level of hearing loss, hearing aids have to be adjusted to enable adequate language acquisition. Early intervention and physiotherapy are further therapeutic principles for psychomotor development. In addition to close supervision from their paediatrician, a link to a social paediatrics centre is highly recommended for these affected children, which, in addition to developmental diagnostics, also coordinates all further therapeutic and diagnostic steps.

Author contributions KOK and KH: both authors have contributed equally in terms of project development, manuscript writing, and editing.

Compliance with ethical standards

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Conflict of interest K Hamprecht is a member of the Scientific Advisory Board of the Initiative for the Prevention of Congenital Cytomegaly Disorders (ICON). All related honoraria are paid into a UKT Institute for Medical Virology grant account to support the Tuebingen Congenital CMV Study.

Ethical approval This is a review of the actual literature.

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