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Review Article

Clinical Significance of IgG avidity testing and other considerations in the diagnosis of congenital cytomegalovirus infection

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ABSTRACT

Prompt and accurate laboratory testing of pregnant women during their antenatal clinic days is necessary for detecting the presence, immunological responses against cytomegalovirus (CMV) infection and to access the risk of transmitting the infection to their unborn fetuses. CMV is the most common viral pathogen with the greatest propensity for congenital transmission. Its clinical manifestations range from asymptomatic forms, sensorineural damages, severe fetal damage, and in rare cases, fetal death due to abortion. Most healthcare facilities in developing countries rely solely on anti-CMV IgM and IgG testing in diagnosing maternal CMV infections. However, the use of these parameters has some worrisome limitations especially cross-reaction with other viruses of the herpesviridae, elevated serum rheumatoid factor leading to false positive results and inability to categorically differentiate primary from non-primary CMV infections thus inadequate to assess the risk of congenital transmission. In view of this, we sought to present this review of relevant published articles using extensive literature search made through PubMed, Scopus, Google scholar and HINARI on the concepts of mother-to-fetus in-utero transmission of CMV and clinical significance of IgG avidity testing in diagnosis of congenital CMV (CCMV) infections. Findings from our review revealed that IgG avidity testing has frequently been utilized as to resolve dilemma associated with serodiagnosis of CMV infections mostly in developed societies. However there is paucity of information in regards to its use in developing countries. This could be a reason why most CCMV infections often go underdiagnosed in developing countries.

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1. Introduction

Human cytomegalovirus (CMV) is a member of the herpesviridae family. It is a double stranded, enveloped and ubiquitous DNA virus that rarely causes disease in healthy individuals yet can cause serious diseases in the fetus and in immunosuppressed individuals [1]. Most CMV infections are inapparent, but the virus can cause a wide range of diseases in susceptible individuals. Fetal CMV infection is of great public health concern because it is the most common cause of congenital infection worldwide, affecting 0.2% to 2.4% of all live births [2]. The overall birth prevalence of congenital CMV infection was reported to be 0.64% but varied considerably among different study location [3]. CMV is now the most common viral cause of mental retardation and hearing deficit of children in developed countries [4]. It causes deformation of preformed tissues rather than malformation of developing organs [4], so CMV can affect fetuses beyond the first trimester, although earlier primary infection is usually more severe [5].

Primary infection is defined as CMV infection in a previously seronegative person. Secondary infection is defined as intermittent excretion of the virus in the presence of host immunity and may be due to either reactivation of an endogenous virus [4, 5] or exposure to a new virus strain from an exogenous source [4]. Primary maternal infection is most likely to cause severe symptomatic congenital infection [4, 5] but recurrent infection may also rarely do so. Perinatal CMV infection is usually not associated with clinical illness in term babies, but may also cause serious problems in preterm infants. [4, 5].

Although the diagnosis of congenital CMV infection is very complex and challenging, important landmarks have been achieved in recent years, these included tests to determine the avidity index of anti-CMV IgG, allowing differential diagnosis of primary from non-primary CMV infections and innovative molecular techniques to detect the CMV in amniotic fluid. In this review, we sort to present the concepts of mother-to-fetus in-utero transmission of CMV and clinical significance of IgG avidity testing in diagnosis of congenital CMV infections.

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1.1 Epidemiology of maternal and fetal CMV infection

Transmission of CMV occurs from person to person through body fluids and requires close contact with contaminated secretions because the virus in not very contagious. CMV can be found in blood, urine, semen, cervical secretions, saliva, breast milk and transplanted organs, all these sites intermittently contain or excrete the virus [4]. Viral excretion is particularly prolonged after primary infection over years but also occurs with reactivation of infection [4]. Transmission of CMV to fetuses and newborn infants occurs in one of following modes (1) in-utero by transplacental passage from hematogenous spread to the fetus during maternal viremia; (2) at birth by intrapartum passage after exposure to infected cervical and vaginal secretions; (3) postnatally by ingestion of CMV-positive breast milk or infected blood transfusion. and that can persist for up to 18 months of age [6].

CMV infection is endemic and lacks seasonal variation. Congenital CMV infection can result from maternal primary or reactivated infection during pregnancy [7]. However, maternal reinfection of different strains of CMV can rarely lead to congenital symptomatic infection [8]. The prevalence of congenital CMV infection varies between 0.2 - 2.4% in different countries [9].

In developed countries, around 50-60% of pregnant, middle to high class women have antibodies to CMV, compared with around 7 0-85% of those from lower socioeconomic groups [9]. Recently, Adamu et al demonstrated that 2.2% and 79.1% of pregnant women had anti-CMV IgM and IgG antibodies respectively at Maiduguri, Nigeria [10]. Overall, 1-4% of susceptible women are affected with primary CMV infection during pregnancy, and around 30-40% of the fetus are transplacentally infected, and also about 10% infants manifest clinical signs and symptoms at birth [9]. Approximately 1-3% of infants born of women with preexisting antibody to CMV are infected in-utero, but they have rarely symptomatic ill nesses at birth (less than 1%) [8]. It has been known that the risk of symptomatic infections at birth or the baby who will develop sequelae is higher if maternal infection occurs during the first half of pregnancy and also most of severe congenital infection is caused by primary rather than recurrent infection of pregnant women [4].

1.1.1 Stages of CMV infections

a. Primary CMV Infection

"Primary CMV infection" is defined as the detection of CMV infection in an individual previously found to be CMV seronegative. The appearance of de novo specific antibodies in a seronegative patient may also be acceptable for the diagnosis of CMV, provided that passive transfer of antibodies via immunoglobulin or blood products can be excluded [11].

b. Recurrent Infection

"Recurrent infection" is defined as new detection of CMV infection in a patient who has had previously documented infection and who has not had virus detected for an interval of at least 4 weeks during active surveillance. Recurrent infection may result from reactivation of latent virus (endogenous) or reinfection (exogenous) [11].

c. Reinfection.

"Reinfection" is defined as detection of a CMV strain that is distinct from the strain that was the cause of the patient's original infection. For cases in which infection can be demonstrated on 2 different occasions, reinfection may be documented by sequencing specific regions of the viral genome or by using a variety of molecular techniques that examine genes known to be polymorphic. Reinfection is diagnosed if the 2 strains are distinct. Reinfection may also be inferred if the patient develops new immune responses to epitopes known to be polymorphic; however, interference from passive antibody must be excluded [11].

d. Reactivation.

Reactivation is assumed if the 2 strains are found to be indistinguishable either by sequencing specific regions of the viral genome or by using a variety of molecular techniques that examine genes known to be polymorphic [12].

1.2 Clinical Manifestations of Congenital CMV (CCMV) Infection

It has been estimated that about 10-20% of all children with CCMV infection, symptomatic or not in the neonatal period, will exhibit neurological damage when followed up [12]. Sensorineural hearing loss (SNHL), mental retardation, seizures, psychomotor and speech delays, learning disabilities, chorioretinitis, optic nerve atrophy, and defects in dentition are the most common long-term consequences [12]. SNHL is the most frequent long-term consequence and is not manifest invariably at birth or in the neonatal period but in many cases may fluctuate and be progressive in nature becoming clinically apparent in later childhood (during the first 6 years of life) [13].

The prevalence of SNHL caused by CCMV infection (symptomatic and asymptomatic) at birth is 5.2% and late-onset hearing loss at 6 years is 15.4% [14]. Generally, children with symptomatic neonatal infection have hearing loss at an earlier age and with greater severity than infants with asymptomatic infection [9]. An estimated 40-58% of infants with symptomatic CCMV infection suffer from severe neurologic sequelae and mortality rates range from 5% to 30% of them [15].

It is also now recognized that asymptomatic CCMV infection is associated with increased risk of SNHL [16]. In particular, different studies report that 6 to 25% of asymptomatic children will develop late-onset sequelae, overall neurological ones, the most important of them being SNHL, making CCMV infection as the probable leading non-genetic cause of SNHL in childhood [14].

Little attention has been focused on the influence of CCMV infection on children's physical growth and intellectual development. By following-up asymptomatically infected infants from 2003 to 2007, Shan et al investigated changes in audiology, nervous behavior, intellectual development, and behavioral development in order to find out the impact of asymptomatic CCMV infection [15]. Asymptomatic newborns were enrolled in the infection group. At one year of age, seven ears of 5 cases showed mild abnormal auditory thresholds in V waves with an abnormal rate of 14%, while no abnormalities were found in 21 cases in the control group, with a statistically significant difference between the 2 groups [15]. Five ears in 4 cases in the infection group showed prolonged intervals in I-V waves, whereas 3 ears in 2 cases in the control group showed this abnormality (no statistically significant difference). No significant differences in

mental development index (MDI) and psychomotive development index (PDI) were found. No abnormalities were found on cranial ultrasonographies and cranial computed tomography scans. This study indicated that asymptomatic CCMV infection had an impact on infant hearing [15].

Fowler et al through comparison with a control group which consisted of siblings or randomly selected children, reported that SNHL was only found in the asymptomatic infection group [17]. In a different study, Numazaki and Fujikawa found that among 17 cases of asymptomatic CCMV infection, 2 children developed late-onset SNHL, including 1 case of moderately binaural hearing loss and 1 case of unilateral hearing loss [18]. Whether infants with asymptomatic infection are at increased risk of mental retardation is controversial. According to a study, CCMV infection did not have a significant influence on total Intelligence Quotient of infants [19].

An analysis of the data of 180 children with CCMV infection showed that the presence of petechiae and intrauterine growth retardation were independently associated with the development of hearing loss [20], [21]. Microcephaly, after adjustment for weight deficit, had a 100% specificity for the prediction of mental retardation and/or major motor deficits but not with an increased risk for the development of SNHL [21].

Four studies have demonstrated that a high viral load in early infancy expressed by a high amount of virus in the urine (450,000 PFU/mL) is highly predictive of audiologic impairment [14, 21, 22, 23]. Greater than 70% of symptomatic (with or without CNS involvement) infants with viruria of > 5 · 104 PFU /mL will have poor neurodevelopmental outcome when compared with only 4% with viruria of < 3.5 · 103 PFU /mL [22, 24].

1.3 Laboratory investigations of CCMV infections

The diagnosis of CCMV infection in a neonate is based on demonstration of the virus by isolation from urine, by identification of CMV-DNA by polymerase chain reaction (PCR) in urine, blood, saliva and cerebrospinal fluid (CSF) sampled before 3 weeks of age or by detection of antigen or CMV-IgM in blood [25]. A rapid diagnosis may be obtained by detection of CMV antigen in blood but the sensitivity is low. IgG antibodies in neonates are mostly maternally transferred antibodies, while the demonstration of IgM antibodies in the newborn is indicative of congenital infection, because maternal IgM antibodies can't cross the placenta. However, only 70% of neonates with CCMV infection have IgM antibodies at birth [26]. With regards to the mother, seroconversion of CMV IgG between two serum samples obtained 2-3 weeks aparts provides the most reliable diagnosis of primary infection. The presence of CMV-IgM suggests a recent or ongoing infection, but they have a low specificity. However, further confirmation of a diagnosis of primary CMV in pregnancy is always required [26].

The CMV-IgG avidity test have also been successfully used to diagnose CCMV in neonates. Vilibic-Cavlek et al evaluated the value of IgG avidity in diagnosis of congenital cytomegalovirus (CMV) infection in newborns and infants [27]. They collected serum samples from 40 infants under 12 months of age with suspected congenital CMV infection. Findings from their study revealed that thirteen (32.5%) patients showed the presence of CMV IgM antibodies, 3 (7.5%) had equivocal IgM result, and 24 (60.0%) patients had IgG antibodies only. Using IgG avidity, CMV infection (low avidity index) was documented in 61.5% IgM positive and 54.2% IgM negative patients [27]. According to age, IgG avidity demonstrated acute/recent primary CMV infection in 58.8% patients younger than three months compared with 91.7% and 81.8% in 3–6 and 6–12 months old babies, respectively. They showed that IgG avidity is useful in diagnosis of CMV infection either in IgM positive or IgM negative children older than 3 months of age. In infants less than 3 months, transplacentally derived maternal IgG antibodies of high avidity influence on the IgG avidity result. However, they concluded that CMV infection should be confirmed by direct virologic methods such as virus isolation or PCR [27].

1.4 Clinical and Laboratory findings in Maternal CMV Infection

Most CMV infections encountered in pregnant women are asymptomatic even during the acute stage. Less than 5% of pregnant women with primary infection are reported to be symptomatic, and an even smaller percentage suffer from a mononucleosis syndrome [28]. Most frequent symptoms include malaise, persistent fever, myalgia, cervical lymphadenopathy, and, less commonly, pneumonia and hepatitis [29]. Laboratory tests may sometimes disclose atypical lymphocytosis and slightly raised transaminase levels. Virological and serological tests are the best means of establishing diagnosis [29].

The diagnosis of primary CMV infection is straight forward if seroconversion to CMV is detected. However, since documentation of CMV seroconversion is rare, as women are not routinely screened for CMV antibodies prior to gestation, the detection of CMV IgM has been used as a marker of active or recent CMV infection. Different kits can be used; agreement varies from 56% to 75% with a sensitivity between 30% and 88% [30]. When anti-CMV IgM antibodies are detected in a pregnant woman, the diagnosis remains open, because they cannot always be correlated to primary infection. Infact, pregnant women can produce IgM during reactivations or reinfections [30]. In addition, anti-CMV IgM antibodies have been detected in some pregnant women from six to nine months after the end of the acute phase of primary infection and false positive results are common and may arise in subjects with other viral infections (B19 Virus, Epstein Barr Virus, etc.) [31].

The anti-CMV IgG avidity test is currently the most reliable procedure to identify primary infection in pregnant women [32, 33]. The IgG avidity test is highly specific (100%) and sensitive (94.3%). The degree of antibody avidity increases progressively and slowly reflecting the maturation of the immune response. Low avidity indices indicate low avidity IgG antibodies in serum caused by acute or recent primary CMV infection [30, 33]. Low avidity indices are encountered 18-20 weeks after the onset of symptoms inimmunocompetent subjects [33].

The determination of anti-CMV IgG avidity performed before the 16th-18th week of pregnancy identifies all women who will have an infected fetus/newborn (sensitivity 100%), after 20th weeks' gestation, sensitivity is drastically reduced (62.5%) [34]. A high avidity index during the first 12-16weeks of gestation could be considered as a good indicator of past infection. The presence of true IgM combined with low/moderate avidity index has the same diagnostic value as seroconversion [35].

Virological tests play a secondary role in the diagnosis of primary CMV infection in pregnant women. Virus isolation in urine and/or cervical secretions is a poor indicator of the risk of intrauterine transmission and the severity of fetal/neonatal

damage [36]. CMV can be detected in blood by virus isolation and/or the search for viral components by the antigenaemia tests and polymerase chain reaction (PCR). Nevertheless, the results of these diagnostic tests also fail to correlate with either the clinical course of infection and/or the risk of intrauterine transmission and the severity of fetal/neonatal injury [37]. Both antigenaemia and PCR tests had a low sensitivity (14.3% and 47.6%, respectively) for detecting vertical CMV transmission in a group of pregnant women who acquired primary CMV infection between four and 30-week-gestation.Specificity and positive and negative prediction rates were also poor [31]. These findings suggest that CMV may or may not be detected in maternal blood in pregnant women undergoing primary infection at the time of diagnosis. Positive viral detection is not associated with a greater risk of infection and/or fetal/neonatal injury [31].

Screening for CMV by serology has been and still is a debated issue. Routine serologic screening for pregnant women has never been recommended by any public health authority [37, 38]. The screening, if done, should be performed at the beginning of pregnancy or even prior to a planned pregnancy. If a woman is seronegative, repeated examinations during pregnancy should be done when there is clinical suspicion. However, screening is usually done before pregnancy for diseases such as rubella and varicella against which immunization can be provided, whereas there is currently no effective and safe immunization against CMV [38]. Moreover, because effective prenatal treatment options are not yet available, the choices when a women is carrying a baby with CMV infection or disease are limited to elective termination of the pregnancy or expectant observation until delivery. Prenatal testing, however, offers an opportunity to educate women about behaviours, and precautionary measures can be suggested to seronegative women [39]. Routine antibody testing, especially if done before pregnancy, may help to differentiate between primary and secondary infection in cases of suspected CMV infection during pregnancy [40]. Naessens et al evaluated a screening program for CMV in which serological testing was performed at the first prenatal visit; they showed that such screening allows the detection of 82% of all congenital CMV infections [41].

1.5 IgG avidity testing

The functional binding affinity or avidity of IgG antibodies increases progressively over time after immunization, also known as maturation of the humoral immune response [42]. High percentage of low avidity IgG antibodies may indicate a primary infection whereas high percentage of high avidity IgG antibodies may indicate a recurrent infection. In several studies, an avidity index (AI) above 65 % during the first trimester of pregnancy could reasonably be considered a good indicator of past CMV infection, whereas in all women with a low AI (≤50%), there was a risk of congenital CMV infection [40, 43, 44, 45]. Maternal CMV infections, which have been considered as significant factors in the causation of poor pregnancy outcome; to the best of knowledge, there have not been extensively studied so far in Nigeria that made used of CMV IgG avidity indices in establishing primary maternal CMV infection.

The CMV IgG Avidity assay is a qualitative method for the determination of the avidity of IgG antibodies to cytomegalovirus in human serum and plasma. It is used as an aid in the differentiation between primary and non-primary infection. If primary infection needs to be excluded, CMV IgG reactive samples should be tested for CMV IgM and CMV IgG Avidity. A positive CMV IgM result in combination with a low avidity result is a strong indicator of a primary CMV infection within the last 4 months [9].

Table 1. Interpretation of CMV serological test results

CMV IgG	CMV IgM	CMV IgG Avidity	Indication for
Nonreactive	Nonreactive	N/A	No infection
Reactive	Nonreactive	High avidity	Past infection; low risk for in-utero ransmssion
Reactive	Reactive	Low avidity	Primary infection; high risk for in-utero transmission
Reactive	Reactive	High avidity	non-primary infection; low risk for in-utero transmission

Source: Guideline for serological diagnosis of congenital CMV infections, Centers for Diseases Control and Prevention, 2010 [25].

1.5.1 Quality control measures in IgG avidity testing

The recommended control requirement for the CMV IgG Avidity assay is that a single sample of each control be tested once every 24 hours each day of use. Controls are ordered as multiconstituent controls for "CMV Avidity".

1.5.2 Interpretation of Results

Avidity index to anti-CMV IgG test result are mainly interpreted as follows, even though slight adjustment of cut-offs has been adopted by some researchers.

(a) Greater than 50.0 % Avidity: Low avidity

(b) 50.0 – 59.9 % Avidity: Gray zone

© Greater or equal to 60.0 % Avidity: High avidity.

1.6 Findings of CMV IgG avidity testing from previous studies

This was done using extensive internet search of relevant published articles through PubMed, Scopus, Google scholar and HINARI on the concepts of mother-to-fetus in-utero transmission of CMV and clinical significance of IgG avidity testing in diagnosis of CCMV infections.

In 2011, Dollard et al [46] conducted a study on CMV IgG and IgM antibody levels and IgG avidity in sera from a population sample of 6,067 U.S. women aged 12 to 49 years from National Health and Nutrition Examination Survey. The CMV IgM prevalence was 3.0% overall and remained relatively flat across age groups. The prevalence of low IgG avidity was 2.0% overall, decreased sharply with age, and was seen mainly among IgM-positive sera. 14 to 18% of the CMV IgM-positive sera were low IgG avidity, presumably representing primary CMV infection. High CMV IgM antibody titer was a strong predictor of low IgG avidity. They asserted that the ability to reliably identify primary CMV infection during pregnancy is important for management of the pregnancy, including possible treatment options for the fetus and concluded that both IgM and IgG avidity measurements provide useful clinical information for evaluating primary CMV infection [46].

Vauloup-Fellous et al [5] showed that determination of CMV IgG avidity helps to establish the timing of infection as IgG avidity matures during the course of infection. They made use of the Elecsys® assay discriminate early (low avidity) and late (high

avidity) phases of infection in sequential serum samples. Overall, 98.8 % of low-avidity samples corresponded to infection onset <180 days before sampling and 77.8 % of all high-avidity results corresponded to infection onset >90 days before sampling. They found that the assay's sensitivity was 90–97 %, with specificity ranging from 89 to 100 % [5].

In a case-control study conducted on 43 women with recurrent pregnancy loss (RPL) referred to a clinical immunology out-patient clinic in Isfahan (Iran), and 43 age-matched multiparous women without history of abortion as control subjects [47]. One case (2.3%) of positive anti-CMV IgM was detected in each group. Anti-CMV IgG positivity was more frequent in patients than in controls (90.6% vs. 69.8%, P= 0.014), but there was no difference between the two groups in anti-CMV IgG Avidity Index (79.4 ± 11.4 vs. 80.1 ± 10.2, P= 0.781). IgG titer was significantly higher in seropositive cases with RPL than seropositive controls (5.18 ± 1.99 vs. 2.00 ± 0.81, P< 0.001). [47] They concluded that previous exposure to CMV was significantly higher in patients with RPL than the control group. However, no association was found between IgG Avidity Index and RPL.

In 2005, Munro et al performed a diagnostic algorithm utilizing immunoglobulin G (IgG), IgM, and IgG avidity to prospectively screen serum from 600 pregnant women enrolled from two groups:<20 weeks gestation (n = 396) or >20 weeks gestation (n = 204). PCR testing of urine and/or blood was performed on all seropositive women (n =341). The majority (56.8%) of women were CMV IgG seropositive, with 5.5% being also CMV IgM positive. In the IgM-positive women, 1.2% had a low-avidity IgG, indicating a primary CMV infection and a high risk of intrauterine transmission. Two infants with asymptomatic CMV infection were born of mothers who had seroconverted in the second trimester of pregnancy [35].

More so, Paschale et al [48] assessed the incidence and risk of CMV infection pregnancy in 2817 women who underwent anti-CMV IgG and IgM antibody screening during the period 2005–2007. The prevalence of anti-CMV IgG antibodies was 68.3% (95% CI: 66.6–70.0); the seroconversion rate in the 892 seronegative women was 0.32%; the results of IgG avidity testing revealed an cumulative incidence of 1.4% (95% CI: 0.97–1.83), density incidence of 0.8% (as cases/pregnant woman-trimester) (95% CI: 0.47–1.13), and a risk of infection of 0.5% (95% CI: 0.24–0.76) [48]. The screening identified 13 cases of primary infection (84.6% of which occurred in the first trimester of pregnancy). They concluded that the possibility to identify these cases will consequently help to plan appropriate interventions. Thus supports the use of IgG avidity screening during pregnancy, especially in the first trimester when the risk of infection is greater [48].

Data from other studies indicated that the results from CMV IgG avidity assays vary greatly. Differences have been observed in the ability of assays to correctly detect or exclude recent infection [49, 50] and in the results reported by different assays for the same samples. A comprehensive study by Revello et al using eight commercial CMV IgG avidity assays to test 198 samples found that none of the results were the same for all assays [37]. Furthermore, the same qualitative result obtained with at least five assays was only reported for 59.6 % of the samples, highlighting the lack of standardization between the assays and the need to test sequential follow-up samples with the same assay. In addition, delayed IgG avidity maturation has been observed in pregnant women with CMV [32, 50, 51] thus potentially leading to misclassification of the actual phase of infection. Finally, changing the cutoff level may be necessary in order to improve performance, as recently reported for the VIDAS assay [5].

1.7 Conclusions

Congenital CMV infection is a leading infectious etiology of mental retardation and sensorineural deafness in children. It has been recognized that primary CMV infections are transmitted more frequently to the fetus and are more likely to cause fetal damage than recurrent infections. Positive anti-CMV IgM and low IgG avidity indices less than 50% is diagnostic of primary maternal CMV infection. Quantitative PCR determination of amniotic fluid viral load predict both the infectious and the clinical outcomes of maternal CMV infection on fetuses and neonates. There is paucity of information in regards the use of anti-CMV IgG avidity test in developing countries, consequently, limiting the serodiagnostic power of maternal CMV infections and inadequate for assessing risk for CCMV transmission. Once primary maternal CMV infection with high viral load has been established, congenital fetal infection is most likely to occur. These findings might help clinicians to counsel pregnant women infected by CMV about the likely outcome for their offspring and enable couples themselves decide the future of the pregnancy.

1.8 Recommendations

The quality of evidence reported in this review can lead to the following recommendations:

1. Use of serologic testing should be used only in pregnant women who develop mononucleosis-like illness or following detection of sonographic findings suggestive of CMV infection.

2. Diagnosis of primary maternal cytomegalovirus (CMV) infection in pregnancy should be based on detection of specific IgM antibody associated with low IgG avidity.

3. In case of primary maternal infection, parents should be informed about a 30% to 40% risk for intrauterine transmission and fetal infection, and a risk of 20% to 25% for development of sequelae postnatally if the fetus is infected

4. The prenatal diagnosis of fetal CMV infection should be based on amniocentesis, which should be done at least 7 weeks after presumed time of maternal infection and after 21 weeks of gestation. This interval is important because it takes 5 to 7 weeks following fetal infection and subsequent replication of the virus in the kidney for a detectable quantity of the virus to be secreted to the amniotic fluid.

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