

OBSTETRICS

Pregestational, periconceptional, and gestational primary maternal cytomegalovirus infection: prenatal diagnosis in 508 pregnancies

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OBJECTIVE: The objective of the study was to evaluate the vertical transmission rate and fetal risk following primary maternal cytomegalovirus infection before and around conception.

STUDY DESIGN: Data of patients referred to fetal medicine clinic in 1 tertiary center in Israel were evaluated. Each included subject had primary maternal cytomegalovirus infection determined by serology, precise gestational dating, and testing of fetal infection. Subjects were assigned to five subgroups: pregestational, periconception, and first, second, or third trimester of pregnancy.

RESULTS: Five hundred eight pregnancies were included. None of the 97 pregnancies in the preconception group and 6 of the 130

periconception subjects (4.6%) were congenitally infected. Transmission rates were 34.8%, 42.0%, and 58.6% for the first, second, and third trimesters, respectively ($P = .049$). Prenatal and postnatal follow-up indicated that third-trimester infection has no clinical effect on the fetus.

CONCLUSION: Pre- and periconception maternal infection carries small risk for fetal infection, whereas it is positively correlated to time of maternal infection during pregnancy.

Key words: cytomegalovirus, periconception, pregestation, prenatal diagnosis

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Cytomegalovirus (CMV) is the leading cause of fetal infection, and the consequential congenital disease is a major medical problem. Each year in the United States alone, hundreds of chil-

dren die and thousands develop permanent disabilities as a result of congenital CMV infection.^{1,2} More children may be affected by congenital CMV than by any other better known congenital conditions such as Down syndrome or neural tube defects. Therefore, prenatal CMV diagnosis and prevention of its associated fetal infection and disease is a major challenge in perinatology.

Although recurrent maternal CMV infection can occur, the risk of vertical transmission is much higher following primary maternal CMV infection. Many published studies have documented the epidemiology of congenital CMV following primary maternal infection. Nevertheless, most large studies are focused on maternal infection during the first half of pregnancy.³ Available data on fetal outcome following prepregnancy, periconception, and late pregnancy maternal infection is based on very small study groups.

We summarized the data and evaluated the risk of fetal infection and congenital disease of 508 pregnancies complicated by primary maternal CMV

infection before conception or during the different stages of pregnancy. The aim of the present study was to compare the vertical transmission rate and fetal outcome following pre- and periconception primary maternal CMV infection with those following infection at different gestational trimesters.

MATERIALS AND METHODS

Our study group included pregnant patients who were referred to a specialized fetal medicine clinic at the Sheba Medical Center in Israel for counseling and prenatal diagnostic workup for primary maternal CMV infection from January 2000 to December 2006.

Although there is no formal CMV screening program in Israel, it is a common practice of most obstetricians to advise patients to undergo CMV screening before planned pregnancy or during the first trimester of an ongoing pregnancy. CMV serological screening was performed with different commercially available kits for specific anti-CMV immunoglobulin G (IgG) and immunoglobulin M (IgM) as well as an IgG avid-

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ity test in IgG-positive patients.⁴ IgG seronegative women were reassessed during pregnancy. Patients considered screen positive by their primary care obstetricians were referred for further prenatal investigation and follow-up. Twelve patients had also minor, mostly unrelated, ultrasound findings or unspecific maternal symptoms described in the referral letter. However, each study subject had CMV infection documented by serologic assays.

All referred patients were primarily interviewed and counseled by fetal medicine specialist. Medical and obstetrical history as well as the detailed course of the ongoing pregnancy was documented. Precise gestational dating was determined by the first day of the last menstrual period (LMP) and ultrasonography at the first trimester.

Diagnosis of primary maternal CMV infection was exclusively determined by IgG seroconversion (the appearance of de novo-specific IgG antibodies in a previously seronegative patient) or positive specific anti-CMV IgG and IgM antibodies associated with low IgG avidity.

Timing of maternal infection was very carefully related to gestational age. Each patient was assigned to 1 of the 5 following subgroups: pregestational (12 months to 8 weeks before conception), periconception (between 8 weeks before and 6 weeks after conception), first trimester (up to full 13 weeks), second trimester (up to full 26 weeks), and third trimester (gestational age beyond 26 weeks).

Clear-cut differentiation between gestational and pregestational maternal infection is desired, however impossible in many around-conception cases. Therefore, we chose to define a group of periconception. Patients were assigned to first-trimester maternal infection when the serological data clearly supported it (IgG seroconversion during the first trimester or positive IgG and IgM associated with low IgG avidity beyond 8 weeks after conception). Patients were assigned to the periconception group when the serology was highly indicative of infection during the time period of 8 weeks before and 6 weeks after conception (IgG seroconversion) or when the data were not clearly indicative of first-trimester

infection (low IgG avidity before 8 weeks after conception).

Following the initial evaluation and counseling, all patients were offered to participate in our prenatal CMV diagnosis program, which includes amniocentesis and repeated detailed ultrasonographic evaluation. Amniocentesis was performed after 21 weeks from the LMP, allowing an interval of at least 7 weeks between the estimated date of maternal infection and the date of the invasive procedure. Transabdominal ultrasound-guided amniocentesis was performed using a 21-gauge needle to collect 30 mL of amniotic fluid for CMV assays and fetal karyotyping. Infectious virus was detected in amniotic fluid samples by rapid virus isolation in cell cultures (shell vial procedure), whereas the presence of viral genome was determined by polymerase chain reaction.⁴

Patients with proven fetal infection had a postamniocentesis counseling session. The risks of fetal CMV infection were discussed, and patients were offered to participate in a pre- and postnatal follow-up program. Serial detailed ultrasound examinations were performed every 3-4 weeks until delivery. Magnetic resonance imaging examination directed to identify fetal central nervous system pathology associated with CMV infection was also performed in these cases since August 2004.

Neonatal urine was tested after birth for CMV during the first 7 days of life to determine whether congenital CMV infection is present. All neonates with positive urine culture or prenatally documented CMV infection had a fundus examination, hearing evaluation, and brain ultrasound scan during the first few days of life. Results of these tests were obtained from hospital charts. The parents were referred for long term follow-up including a physical examination and hearing test in a pediatric infectious diseases unit at a near-home tertiary medical center. Information on the long-term follow-up was obtained from telephone interviews of the parents.

Data were prospectively collected and retrospectively evaluated for each case. Transmission rates were compared using

the χ^2 test. The study was approved by the institutional review board.

RESULTS

Five hundred eight women were diagnosed with primary maternal CMV infection, matched the inclusion criteria, and were included in the study group. All patients were referred to the fetal medicine clinic at the Sheba Medical Center between January 2000 and December 2006.

These 508 patients included 16 twin pregnancies, which summarize the number of cases included in the present study group to be 524 fetuses.

All 508 pregnancies were assigned to 1 of the 5 study groups based on gestational age at the time of maternal infection. Ninety-seven pregnancies were assigned to the pregestation group, 130 to the periconception group, 152 to the first-trimester group, 100 to the second-trimester group, and 29 to the third-trimester primary maternal CMV infection group.

Amniocentesis was performed in 485 of the 524 patients (92.6%), whereas diagnosis of congenital CMV infection was based on a postnatal CMV urine test alone in the remaining 39 neonates (7.4%). Amniocentesis and urine test results were both available in 379 of the 446 live-born neonates (85.0%).

The vertical transmission rate is presented in Table 1. Each twin pregnancy was considered as 1 data point for the calculation of transmission rates. Both fetuses of 14 sets of twins were negative (11 pairs) or positive (3 pairs) for CMV infection. Two twin pregnancies were considered as positive transmission, although 1 twin was positive and the other was negative for CMV.

The overall transmission rate in the present study group was 23.2% (118 of 508). The vertical CMV transmission rate of primary maternal infection during pregnancy was 39.9% (112 of 281). None of the 97 fetuses in the pregestation group was infected, whereas the virus was vertically transmitted in 6 of the 130 pregnancies included in the periconception study group (4.6%). The transmission rate was significantly correlated to

gestational age at the time of maternal infection (34.8%, 42.0%, and 58.6% for first second and third trimesters, respectively, $P = .049$ by χ^2).

Of 121 diagnosed positive fetal infection cases, 105 underwent amniocentesis, whereas the other 16 were diagnosed by postnatal urine culture alone. Two of the 105 amniocentesis subjects have shown negative results on amniotic fluid samples but had positive urine cultures for CMV infection immediately after birth. These 2 false-negative amniocenteses were performed strictly according to our protocol, at a gestational age beyond 21 weeks and also allowing at least 7 weeks from the time of the maternal infection.

We also found that rapid virus isolation in cell cultures (shell vial) and polymerase chain reaction for the detection of the viral genome share very high sensitivity and specificity because both were concurrently positive or negative in all studied cases.

Abnormal findings of detailed ultrasound imaging in 17 infected fetuses are described in Table 2. Our results indicate that severe disease may affect fetuses infected in the first as well as the second trimester, whereas no findings were identified in fetuses affected later in pregnancy.

Seventy-nine patients elected for termination of pregnancy during the follow-up period. Three terminations were indicated on the basis of CMV-unrelated chromosomal aberrations (aneuploidies detected by amniocenteses), whereas 13 terminations were performed following the identification of ultrasound findings suggestive of CMV-related fetal disease.

Forty-five congenitally infected fetuses were born alive, all asymptomatic at birth. One neonate in the periconception subgroup had normal ultrasound scans and is developing normally at the age of 12 months. Twelve infected neonates in the first-trimester group were born at term. In 1 of these 12 cases, a dilated loop of bowel was diagnosed during pregnancy follow-up, and hearing loss was diagnosed at the age of 8 months. In one other case, echogenic bowel was identified during pregnancy, whereas normal development was observed at the age of 15

TABLE 1
Vertical CMV transmission rate by gestational age at the time of maternal infection

Study group	Pregnancies, n ^a	CMV positive pregnancies, n	Transmission rate, %
Pregestation	97	0	0
Periconception	130	6	4.6
First trimester	152	53	34.8
Second trimester	100	42	42.0
Third trimester	29	17	58.6
All cases	508	118 ^b	23.2
Gestational cases ^c	281	112	39.9

CMV, cytomegalovirus.

^a Each of the 16 twin pregnancies is considered as 1 data point; ^b Each of the 2 twin pregnancies with 1 positive twin and 1 negative twin was calculated as 1 positive data point; ^c First-, second-, and third-trimester pregnancies only.

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months. All other 10 neonates had normal prenatal and postnatal follow-up.

Fifteen fetuses of the infected second-trimester group were born at term. One had echogenic bowel and another one had a relatively small head circumference and mild polyhydramnios. These 2 neonates are developing normally. In 1 other case of this group, the ultrasound evaluation was normal, whereas the newborn had an abnormal hearing test at the age of 3 months.

All of the third-trimester infected fetuses had no abnormal ultrasound scan findings during pregnancy, and all 17 of the term newborns of this subgroup had no apparent disease throughout the neonatal course, within a median follow-up period of 18 months.

The 400 live-born neonates with no evidence of vertical transmission and negative for CMV at amniocentesis and neonatal urine test were also followed up. Forty-six subjects were lost to postnatal follow-up, whereas all other parents were interviewed for possible CMV-related developmental abnormalities. No specific findings were reported in this group.

COMMENT

The prenatal CMV diagnosis program presented in this study takes advantage of the following important clinical factors: (1) diagnosis of primary maternal CMV infection is based on strict serological criteria: IgG seroconversion or positive IgM with

low IgG avidity; (2) gestational dating based on first-trimester ultrasound and serial CMV serological assays allow precise dating of maternal infection; (3) all subjects were evaluated and managed in 1 tertiary center according to a specified detailed clinical program; and (4) a relatively large number of subjects was included in each study subgroup, which allows significant evaluation.

The risk of intrauterine transmission and the outcome of pregnancies complicated by primary CMV infection occurring before or around the time of conception are not known. The principal reasons are the absence of serologic screening programs carried out during pregnancy and the difficulty in dating the onset of primary CMV infection.

Revello et al⁵ reported on one case of congenital infection in 11 pregnancies with preconception infection, defined as occurring within 3 months before the LMP. This woman was assumed to be infected 8 weeks before her LMP, based on subjective symptoms. Her newborn was subclinically infected at birth and at the age of 6 months was asymptomatic and normally developed. The investigators also observed intrauterine transmission in 4 of 13 pregnancies (30.7%) complicated with periconception infection, defined as infection that occurred within 4 weeks after the LMP. One of these pregnancies was terminated, whereas the 3 others continued to term. One newborn

TABLE 2
Abnormal ultrasound findings in CMV-infected fetuses

Subject number	Ultrasound findings
Periconception	
1	Bilateral ventriculomegaly, IUGR, liver, and brain calcifications
2	Echogenic bowel
First trimester	
3	IUGR
4	IUGR
5	Echogenic bowel
6	Echogenic bowel
7	Ascites, echogenic bowel
8	Brain calcifications, echogenic bowel
9	Periventricular brain cysts, echogenic bowel
10	Dilated bowel loop
11	Echogenic bowel
Second trimester	
12	Unilateral ventriculomegaly
13	Hydrops
14	Microcephaly
15	IUGR, echogenic bowel
16	Echogenic bowel
17	Small head circumference, mild polyhydramnios

CMV, cytomegalovirus; IUGR, intrauterine growth restriction.

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was symptomatic at birth and developed mild neurological sequelae.

In a more recent report by these authors,⁶ the risk of vertical transmission was investigated in 14 women who had primary infection 2-18 weeks before their LMP. One of 12 newborns examined at birth (8.3%) was found to be subclinically infected. Daiminger et al⁷ defined preconception infection as occurring between 8 and 2 weeks before the LMP and periconception from 1 week before to 5 weeks after the onset of the LMP. Vertical transmission did not occur in any of the 3 pregnancies with preconception infection and in 45% (9 of 20) of the pregnancies with periconception infection.

These 3 studies⁵⁻⁷ are the only published so far on the risk of pre- and periconception primary CMV infection. However, the data these studies present are too limited to reach a significant conclusion. Our study, however, included

97 preconception and 130 periconception cases complicated with primary maternal CMV infection.

Our data show no evidence of congenital infection in pregnancies complicated by preconception maternal infection. Revello and colleagues^{8,9} recommended a waiting period of at least 6 months before conception. They based their recommendation on the detection of viral deoxyribonucleic acid (DNA) in blood samples of primarily infected immunocompetent adults, up to 6 months after the onset of infection.

Daiminger et al,⁷ however, could not detect viral DNA in any of the analyzed blood samples drawn from 15 patients beyond 7-14 weeks after primary infection. Considering these observations and the encouraging results of the present study, we conclude that the present recommendation of a 6 month waiting period is cautious enough to be followed.

Our definition of periconception might explain the relatively low transmission rate we have detected in this group (6 of 130, 4.6%) compared with 30.7% (4 of 13) and 45% (9 of 20) in previous studies.^{5,7} According to our criteria, cases were assigned to the periconception group when the serology was highly indicative of infection during the time period of 8 weeks before and 6 weeks after conception or when data were not clearly indicative of first-trimester infection. The wider definition that we chose seems more practical for clinical use because in most cases it is difficult, sometimes even impossible, to determine the exact week in which infection has occurred. Our low transmission rate probably reflects the fact that many of the periconception cases actually occurred before conception.

Our data show that the CMV transmission rate increases with advancing stage of pregnancy (34.8%, 42.0%, and 58.6% at first-, second-, and third-trimester infection, respectively). This is in accordance with the data presented by Bodeus et al¹⁰ on 123 cases of primary maternal infection (36.0%, 44.9%, and 77.6% transmission rates at first, second, and third trimesters, respectively).

Daiminger et al⁷ reported on similar results based on 120 cases (transmission rates of 30% and 58% at 6-20 weeks and 20-38 weeks of gestation, respectively). Revello and Gerna⁹ reported transmission rates of 45.4%, 45.6%, and 78.6% following primary maternal infection in the first, second, and third trimesters, respectively, demonstrating, similarly to us, the increased transmission rate in more advanced stages of pregnancy.

One weakness of the present study group is the relatively high number of patients elected termination of pregnancy following evidence of vertical transmission, mostly at the first trimester. Even with deep discussion of these points with the patients, one cannot ignore the fact that the risk of congenital disease is generally known, whereas the sensitivity of the diagnostic tools is not well established, and the treatment options are yet very limited.

Published data regarding the outcome of CMV infection occurring at the third

trimester of pregnancy are very limited. The series by Daiminger et al⁷ included only 18 cases of CMV infection, occurring after 20 weeks of gestation, in which none of them had evidence of congenital disease. Liesnard et al¹¹ described 16 cases infected after 20 weeks of gestation, and only 1 had minor sequelae of retinitis. Pass et al¹² found hearing loss in 24% (8 of 34) of children following first trimester infection compared with 2.5% (1 of 40) of those infected later in pregnancy. Another recently published report¹³ included 20 live-born fetuses following vertical CMV transmission after 25 weeks of gestation. None of them had evidence of CMV-related congenital disease.

In the present study, the timing of infection was more accurately defined, and we subdivided the cases according to trimesters. Our study included 29 pregnancies of third-trimester infection in which 17 of them including 1 pair of twins had evidence of vertical transmission. One patient elected termination of pregnancy following third-trimester infection, despite a normal ultrasound scan and very encouraging counseling. All 17 third-trimester-infected infants had no abnormal ultrasound scan findings during pregnancy, and all had no apparent disease throughout the neonatal course. Our results together with previous published data confirm the favorable outcome of primary CMV infections, which occur at the late stages of pregnancy.

In conclusion, the results of our study can be useful in facilitating informed decisions by pregnant women. From a practical point of view, pregnant women with documented primary infection acquired before conception can be reassured and counseled to continue their pregnancy without performing antenatal testing. On the other hand, prenatal diagnosis should be offered to women with periconception infection in view of its higher incidence of vertical transmission. Finally, primary CMV infection acquired during the third trimester is associated with a high risk of intrauterine transmission but a favorable outcome for the infant.

Deep discussion on the different aspects of the ongoing debate on the im-

plementation of a routine prenatal CMV screening program¹⁴⁻¹⁹ is beyond the scope of this paper. Some points, however, can be made. The tools for effective prenatal diagnosis of primary maternal and fetal CMV infection are readily available.²⁰ Adding IgG avidity assays makes the diagnosis of primary maternal infection accurate, specific, and sensitive.^{21,22} The very high predictive values of prenatal diagnosis of fetal infection by amniocentesis are also very encouraging.

Some arguments used against routine screening are based on the concerns that a patient might choose to terminate an unaffected pregnancy based on positive serology alone. We believe that like any other medical screening program, one should provide expert prenatal counseling as well as confirmatory and diagnostic tests to deal with the screen-positive cases. Guerra et al²³ have recently shown that such measures will significantly reduce the number of patients who choose termination based on positive serology screen alone.

The main argument against routine screening is the limited options available for management of infected fetuses. Intrauterine or postnatal medical treatment is available but not yet proved to be highly effective.^{24,25} Serial ultrasound scans during pregnancy and perhaps other imaging utilities such as magnetic resonance imaging can be used to identify the most severely affected fetuses. However, the sensitivity and specificity of such measures are not yet fully evaluated.

Griffiths¹⁹ in his very stimulating editorial described the question of prenatal CMV screening debate as a classical catch-22 problem. We have the tools to diagnose primary CMV infection during pregnancy, but we choose not to use them routinely because we do not have enough validated measures to treat fetal infection or diagnose affected fetuses. On the other hand, we cannot develop and evaluate improved diagnostic and treatment options unless patients are routinely and accurately diagnosed and recruited into controlled clinical trials. ■

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