



Short communication

Intrauterine transmission and clinical outcome of 248 pregnancies with primary cytomegalovirus infection in relation to gestational age

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ABSTRACT

Background: The risk of intrauterine cytomegalovirus (CMV) infection and disease in the fetus or newborn largely depends on time of primary maternal infection during pregnancy.

Objectives: Prospective cohort study of pregnancy outcome in relation to gestational age at primary maternal CMV infection.

Study design: In a total of 248 pregnancies with primary infection the onset of infection was determined by IgG seroconversion, IgG avidity and/or onset of clinical symptoms. Congenital infection was diagnosed by CMV detection in amniotic fluid, fetal tissue or urine of the neonate in the first 2 weeks of life. Clinical symptoms were retrieved from ultrasound and medical records.

Results: The intrauterine transmission rates following primary CMV infection in the pre- and periconceptional period were 16.7% (4/24) and 34.5% (10/29), respectively. For the first, second and third trimester of pregnancy transmission rates were 30.1% (25/83), 38.2% (29/76) and 72.2% (26/36), respectively. The rate of symptomatically infected fetuses or newborns at birth was 22.8% for any symptoms and 10.3% for severe manifestations. No symptoms were observed in infected newborns of mothers with primary infection in the preconceptional period and in the third trimester.

Conclusions: The risk of intrauterine transmission following primary maternal infection in the third trimester is high, but the risk of neonatal disease is low. The highest risk of severe symptoms in the fetus and newborn exists around conception and in the first trimester of pregnancy.

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1. Background

Age of pregnancy at time of maternal primary cytomegalovirus (CMV) infection is regarded to have a significant effect on intrauterine CMV transmission and symptoms at birth. This is in contrast to Stagno's earlier report, showing similar rates of fetal infection following maternal infection in early or late gestation.¹ Recent studies by Bodeus et al. in Belgium^{2,3} and Revello et al. in Italy⁴ investigated the vertical transmission rate in over 500 pregnancies each in relation to onset of primary infection in the first to third trimester of pregnancy. Both studies showed an increased risk of virus transmission of 73.3%³ or 64.1%⁴ after maternal third trimester infection. Transmission rates in the first trimester were 34.5%³ or 42.2%⁴ and in the second trimester 44.1%³ or 43.5%⁴. The risk of symptomatic congenital infection was mainly connected with maternal first and second trimester infection.^{5–9}

2. Objectives

We present our findings on the risk of intrauterine transmission according to gestational age at which primary maternal infection occurred. In addition to the cited studies,^{2–4} we report on the clinical outcome of congenitally infected fetuses and newborns.

3. Study design

We have extended our first study on CMV primary infection in 166 pregnancies (from 1990 to 2003)⁹ with 82 pregnancies (from 2004 to 2010) to a total of 248 pregnancies. All women had experienced a serologically proven primary CMV infection, with timing of infection to gestational age and known outcome of pregnancy. Women were identified in our laboratory in daily routine diagnosis and then prospectively followed up. We assigned cases to one of the following categories according to time of maternal infection (see Table 1): preconceptional period (1) from 1 to 10 weeks before last menstrual period (LMP), periconceptional period (2) from 1 week before LMP to gestational week (gw) 4 + 6 and the first (3), second (4) and third (5) trimester of pregnancy. None of the pregnant women had received CMV hyperimmune globuline (HIG) or antivirals. For safe serological diagnosis of maternal primary CMV

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Table 1Intrauterine CMV transmission and outcome of pregnancies in relation to onset of maternal primary infection ($n = 248$).

Time of maternal infection	Gestational age	Intrauterine transmission			Outcome of pregnancies with intrauterine infection ($n = 94$)				
		Congenital infections/total	Rate%	95% CI	TOP (gw < 15)	TOP Abnormal US (gw ≥ 15)	Symptoms in newborns		
							Severe	Mild/transient	None
(1) Pre- conceptional	1–10 weeks before LMP	4/24	16.7	4.7–37.4	1	0	0	0	3
(2) Peri- conceptional	1 week before LMP to gw 4+6	10/29	34.5	17.9–54.3	3	4	1	0	2
(3) First trimester	gw 5+0 to 13+6	25/83	30.1	20.5–41.2	3	2	1	6	13
(4) Second trimester	gw 14+0 to 25+6	29/76	38.2	27.3–50.0	0	1	0	4	24
(5) Third trimester	gw 26+0 to delivery	26/36	72.2	54.8–85.8	0	0	0	0	26
Total		94/248	37.9	31.8–44.3	7	7	2	10	68

LMP, last menstrual period; gw, gestational week (in completed weeks + days); TOP, termination of pregnancy.

infection the following criteria are used: (a) IgG seroconversion with or without IgM (b) a significant, at least four-fold, IgG-rise in the presence of high level IgM (c) high level IgM and IgG with low IgG avidity concordant with clinical symptoms.

Sera were tested at our laboratory for CMV-specific IgG by an indirect enzyme-linked immunosorbent assay (ELISA) (Enzygnost, Siemens, Marburg, Germany), for CMV-specific IgM by an enzyme-linked antigen assay (ELA) (Medac PKS, Hamburg, Germany) and IgG avidity by the Vidas CMV IgG avidity assay (bioMérieux, Nürtingen, Germany) using an in-house evaluation.⁹ In 102 of the 248 pregnancies CMV prenatal diagnosis was performed by investigation of amniotic fluid and/or fetal blood samples. From all 248 pregnancies we received samples either after termination of pregnancy (TOP) or delivery. Intrauterine infection was diagnosed by CMV detection in fetal tissues of various organs in 18 cases with TOP or in urine samples of all 230 live-born newborns within the first 2 weeks of life. Infectious virus was detected in cell culture using the rapid shell vial assay as previously described.¹⁰ CMV DNA was detected by an in-house real time LC-PCR.¹¹ The absence of infection was assessed by negative culture results and absence of viral DNA. Information on fetal abnormalities at ultrasound (DEGUM level 2/3) indicative of congenital CMV infection¹² and/or on symptoms at birth were reported to us by prenatal medical centres, neonatal care units and office-based physicians. In about one third of all congenitally infected newborns hearing was investigated by otoacoustic emission testing (OAE) or brainstem evoked response audiometry (BERA). In Germany newborn hearing screening was increasingly used since 2004; since 2009 it is obligatory.

4. Results

The results of this study are summarized in Table 1. The mean rate of intrauterine transmission was 37.9%. The rate was significantly higher following maternal infection in the third trimester compared to the first trimester (72.2% versus 30.1%; $p < 0.0001$, χ^2 -test). From the 248 pregnancies with serological proven maternal infection ten pregnancies were terminated before gw 15 shortly after diagnosis of CMV primary infection, of which seven fetuses had a proven congenital infection and three were uninfected. Furthermore TOP was performed in eight women due to fetal ultrasound abnormalities and seven of the eight fetuses proved to be infected. Of the 230 live-born neonates congenital CMV infection was confirmed in 80 and excluded in 150.

In total 22.8% of the intrauterine infected fetuses or newborns (19/87; 95% CI: 13.7–32.0%) showed various symptoms from mild/transient (e.g. petechia, thrombopenia, anemia) to severe (with affection of the central nervous system (CNS) causing permanent damage). Severe damage was detected in seven fetuses following TOP by abnormal prenatal ultrasound findings (e.g. microcephaly, ventriculomegaly or fetal growth retardation), which all had disseminated CMV infection, and in two newborns

with CNS manifestations, resulting in an overall rate of 10.3% (9/87; 95% CI: 4.8–18.7).

5. Discussion

Our findings confirm an increased risk for in-utero transmission of CMV in the third trimester as already demonstrated by Bodeus et al.^{2,3} and Revello et al.⁴ Moreover our study adds data to the observation that the risk of symptomatic disease in the fetus or newborn after primary maternal infection in the third trimester of pregnancy is low, since all 26 infected newborns were healthy at birth. From 14 of them (54%) we have obtained follow-up information at age 5 months to 4 years. All infants showed normal hearing and development (data not shown).

This is in concordance with previous studies: Gindes et al.⁵ found a high transmission rate of 75% in 28 pregnancies after gw 25 and all 20 live-born congenitally infected infants were healthy. Lipitz et al.⁶ reported that all 8 children infected during the third trimester of pregnancy were asymptomatic at birth and later. In the third study Foulon et al.⁷ investigated sensorineural hearing loss (SNHL) in 28 congenitally infected infants in relation to onset of primary maternal infection. SNHL was detected in four, one and none of the infants of mothers with primary infection in the first ($n = 5$), second ($n = 12$) and third ($n = 11$) trimester, respectively.

Preconceptional CMV infection is known to be associated with a lower risk of fetal infection,^{4,5,13} this could be confirmed with our study. However, the definitions for pre- and periconceptional periods vary between studies. Compared to our study Hadar et al.¹⁴ reported a lower transmission rate of 25.5% following periconceptional maternal primary infection in 43 pregnancies. But in this study the periconceptional period is large, ranging from 4 weeks prior to LMP up to 3 weeks following the expected date of the missed menstrual period (about gw 6), and may include cases with preconceptional according to the definitions in our study and in that of Revello et al.¹³

If primary maternal infection occurred around conception and in the first trimester prenatal invasive diagnosis should be offered. Amniocentesis should be performed beyond gw 21 and at least 6–8 weeks after the assumed onset of primary maternal infection.^{4,12} In case of a negative result in prenatal diagnosis, which can be expected in 70% of pregnancies with maternal primary infection in early gestation, the prognosis for birth of a healthy and uninfected baby is very good (negative predictive value 97.9%; $n = 189$; Enders et al.)¹²

In concordance with the cited studies our data emphasize, that the major risk factor for severe CNS sequelae in the congenitally infected fetus is maternal primary infection around conception up to the second trimester.

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Competing interest

None declared.

Ethical approval

Not required.

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