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H．知的財産権の出願・登録状況

なし

表 1. 兵庫県 3 施設の新生児尿 CMV スクリーニングの結果

	陽性数/スクリーニング数	感染率
3 施設の総計	**32/6348 人**	**0.50%**
神戸大学病院	19/2476 人	0.76%
兵庫県立こども病院	7/1694 人	0.41%
なでしこレディースホスピタル	6/2178 人	0.27%

表 3. 一部の症例で抗ウイルス薬治療を行った英国からの報告（Townsend CL, et al. Arch Dis Child Fetal Neonatal Ed 2011）との後遺症発生率の比較

	神戸大学 2015	Townsend CL, et al. 2011	p 値
n	12	60	
治療施行症例	12 (100%)	16 (27%)	
後遺症			
重度	4 (33%)	36 (60%)	0.09
軽度	3 (25%)	13 (22%)	0.80
正常	5 (42%)	11 (18%)	0.08

表 2. 治療例 12 人の詳細

	在胎週	出生体重	治療前症状						治療時	神経学的予後評価			重症度評価
			SGA	血小板減少	肝炎/胆汁うっ滞	眼合併症	脳画像異常	ABR異常	副作用	重度精神運動発達障害	難聴	てんかん	
1	36 週 4 日	1860g	●	●	●	●	●	両側	好中球減少	●	両側□	●	重度
2	36 週 1 日	2184g	−	−	●	●	●	両側	好中球減少	●	両側□	●	重度
3	35 週 0 日	1255g	●	●	●	−	●	両側	性器出血	●	両側□	−	重度
4	32 週 2 日	940g	●	●	−	−	●	両側	−	●	−	−	重度
5	31 週 4 日	1378g	−	●	●	−	●	両側	好中球減少	−	片側	−	軽度
6	38 週 3 日	2956g	−	−	−	−	●	片側	好中球減少	−	片側	−	軽度
7	38 週 2 日	3312g	−	−	−	−	●	−	好中球減少	−	片側	−	軽度
8	36 週 1 日	2192g	−	●	●	−	●	両側	好中球減少	−	−	−	正常
9	32 週 6 日	1396g	●	−	−	−	−	両側	好中球減少	−	−	−	正常
10	38 週 4 日	3160g	−	−	−	−	●	片側	−	−	−	−	正常
11	36 週 4 日	2450g	−	−	−	●	●	−	−	−	−	−	正常
12	38 週 0 日	2868g	−	−	−	●	−	−	−	−	−	−	正常

●：症状や発症あり、−：症状や発症なし、SGA, Small-for-gestational age; ABR, Auditory brainstem response

研究成果の刊行に関する一覧表

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III. 研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

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IV. 研究成果の刊行物・別刷

Yasuhiko Ebina*, Toshio Minematsu, Ayako Sonoyama, Ichiro Morioka, Naoki Inoue, Shinya Tairaku, Satoshi Nagamata, Kenji Tanimura, Mayumi Morizane, Masashi Deguchi and Hideto Yamada

The IgG avidity value for the prediction of congenital cytomegalovirus infection in a prospective cohort study

Abstract

Background: Cytomegalovirus (CMV) causes congenital infection with high mortality and morbidity rates in affected neonates.
Objectives: To evaluate the maternal IgG avidity value for the prediction of congenital CMV infection.
Study design: The serum IgG avidity in all mothers was measured, and the urine of their neonates was assessed for CMV DNA in a prospective cohort study.
Results: Of 759 women with a positive test for CMV IgG, 14 had congenital CMV infection. CMV IgG avidity indices in the congenital infection group (median 35.1%) were significantly lower than those in the non-congenital infection group (70.4%). A cutoff value of <40% IgG avidity index with 96.1% specificity and 64.3% sensitivity for congenital infection was determined by receiver operating characteristic curve analyses. The highest sensitivity (88.9%), 96.2% specificity, 27.6% positive predictive value, 99.8% negative predictive value, and 96.1% accuracy were found when IgG avidity was measured in <28 weeks of gestation.
Conclusion: The IgG avidity measurement with a cutoff value of <40% IgG avidity index might be helpful in predicting congenital CMV infection, especially in <28 weeks of gestation.

Keywords: Congenital infection; cytomegalovirus; IgG avidity.

***Corresponding author: Yasuhiko Ebina,** MD, PhD, Associate Professor, Department of Obstetrics and Gynecology, Kobe University Graduate School of Medicine, 7-5-1 Kusunoki-cho, Chuo-ku, Kobe 650-0017, Japan, E-mail: ebiyas@med.kobe-u.ac.jp
Toshio Minematsu: Research Center for Disease Control, Aisenkai Nichinan Hospital, Miyazaki, Japan
Ayako Sonoyama, Shinya Tairaku, Satoshi Nagamata, Kenji Tanimura, Mayumi Morizane, Masashi Deguchi and Hideto Yamada: Department of Obstetrics and Gynecology, Kobe University Graduate School of Medicine, Kobe, Japan
Ichiro Morioka: Department of Pediatrics, Kobe University Graduate School of Medicine, Kobe, Japan
Naoki Inoue: National Institute of Infectious Diseases, Department of Virology I, Tokyo, Japan

Introduction

Human cytomegalovirus (CMV) is the most common virus responsible for severe diseases in the fetus and newborn. The epidemiology of CMV infection is related to ethnicity and socioeconomic status. Children in developing countries usually acquire CMV perinatally during vaginal delivery, or postnatally through breastfeeding or from the virus shedding from other children's saliva or urine. Therefore, most women in the reproductive age have CMV antibody before becoming pregnant. The CMV IgG-positive rate among Japanese pregnant women has decreased from 85% in 1988 to 68% in 2000 [9]. Recently, a multicenter study of neonatal urine screening has revealed that congenital CMV infection develops in 0.31% of newborns in Japan [5].

Ten percent to 15% of affected fetuses show symptomatic congenital CMV infection at birth with clinical manifestations including fetal growth restriction, low birth weight, and central nervous system and multiple organ involvement. These may be so severe as to lead to a high perinatal mortality rate and major neurological sequelae in approximately 90% of the surviving infants with symptomatic congenital infection. In addition, 10–15% of infants with asymptomatic congenital infection develop long-term sequelae, namely progressive sensorineural hearing difficulty and mental retardation [11]. Symptomatic congenital infection develops commonly from primary/acute infection rather than reinfection or reactivation in mothers [12].

A positive test for CMV IgM antibody is assumed to be a good indicator of acute or recent infection but does not always correlate with primary infection. Pregnant women may produce CMV IgM during reactivation or reinfection, and IgM may persist for 6–9 months after the end of the acute phase of primary infection [6]. It has been demonstrated that

measurement of CMV-specific IgG avidity helps in diagnosing recent primary CMV infection [1, 4, 7]. IgG avidity indicates the strength with which multivalent antibodies binds to multivalent antigens. IgG antibodies show a low avidity for the antigen during early weeks after the primary infection; however, they progressively mature, initially acquiring moderate and then high avidity. This process reflects the maturation of the immune response, and the high-avidity IgGs are maintained for many years.

To evaluate maternal IgG avidity value for the prediction of congenital CMV infection, we conducted a prospective cohort study in which serum IgG avidity in all mothers was measured and the urine of their neonates was assessed for CMV DNA.

Patients and methods

This study was conducted with informed consent from all of the subjects. The institutional ethical boards of Kobe University Hospital approved this prospective cohort study, which was conducted according to the Declaration of Helsinki. During the period between April 2009 and January 2013, pregnant women who underwent maternity checkups and women who were referred to the university hospital because of obstetrical complications were enrolled. Serum CMV IgG were measured generally at 16–18 weeks of gestation (GW) or when they were referred. When they had a positive test for CMV IgG, the IgG avidity was measured subsequently.

To assess the presence or absence of congenital infection, all neonates underwent PCR analyses for CMV DNA in the urine collected during the first week of the life [5]. When the neonatal urine tested positive for CMV DNA, workup for CMV infection, including ophthalmofundoscopy, cerebral ultrasound, and physical and neurological examinations, was performed. Head magnetic resonance imaging and computed tomography were performed if necessary. Auditory brain-stem response was periodically tested to find sensorineural hearing difficulty as one of major sequelae of congenital infection.

Serological tests for CMV IgG were performed using the EIA kit produced by Siemens Healthcare Diagnostics (Tokyo, Japan). CMV IgG avidity was measured in Aisenkai Nichinan Hospital as described previously [10, 13]. For each serum, the optical density (OD) of the reference well was compared with the OD obtained by the urea denaturation procedure. The avidity index was calculated and expressed as a percentage: avidity index (%)=(OD urea/OD reference)×100. Serial CMV IgG avidity measurements in some women who were suspected of having primary infection were performed with informed consent. Real-time PCR analysis was performed at a commercial laboratory (SRL, Tokyo, Japan).

The CMV IgG avidity indices were compared between a congenital CMV infection group and a non-congenital infection group. A receiver operating characteristics (ROC) curve was constructed to determine the cutoff value for the prediction of congenital CMV infection. Statistical analyses were carried out using Statistica (StatSoft, Tulsa, OK, USA) software. Mann-Whitney *U*-test was used to analyze differences between the two groups. A P-value of <0.05 was considered to indicate statistical significance; all tests were two-tailed.

Results

Nine hundred and thirteen pregnant women, including 331 women who were referred after 18 GW, underwent serum CMV IgG measurement, and 759 pregnant women (83.1%) had positive IgG results. Of the 759 women with positive CMV IgG, 14 (1.8%) had congenital CMV infection and the other 745 (98.2%) had negative tests for CMV DNA in the urine of their neonates. The CMV IgG avidity indices in the congenital CMV infection group (median 35.1%, range 2.3–77.8%) were significantly lower than those in the non-congenital CMV infection group (70.4%, 7.6–97.3%) (P<0.0001). Of 14 neonates with congenital CMV infection, five were asymptomatic and the remaining nine had symptomatic congenital infection involving hepatosplenomegaly (n=4), intracranial calcification (n=3), ventriculomegaly (n=3), fetal growth restriction (n=3), thrombocytopenia (n=2), retinitis (n=2) and microcephaly (n=1), and fetal ascites (n=1).

Figure 1 shows the CMV IgG avidity indices in the 759 pregnant women according to GW. Without consideration of when IgG avidity was measured, 6 of 12 (50.0%) women who yielded results of <20% IgG avidity index had congenital CMV infection. Similarly, 6 of 20 (30.0%) women with <30% IgG avidity index and 9 of 38 (23.7%) women with <40% IgG avidity had congenital CMV infection. In contrast, 5 of 721 (0.7%) women with >40% IgG avidity index and 3 of 389 (0.8%) women with >70% IgG avidity had congenital CMV infection.

In the ROC curve, a high area under the curve (0.802) was obtained when IgG avidity indices were used to discriminate between women with congenital CMV infection and those with non-congenital CMV infection (Figure 2). Using a cutoff value of 40% IgG avidity index, the best result with 96.1% specificity and 64.3% sensitivity for the prediction of congenital CMV infection was obtained by ROC analyses. When the analyses were restricted to subjects of <26 (n=527), 28 (n=565), 30 (n=607), or 32 (n=663) GW, the sensitivities to detect congenital CMV infection were found to be 83.3%, 88.9%, 80.0%, or 72.7%, respectively. The highest sensitivity value (88.9%), together with 96.2% specificity, 27.6% positive predictive value, 99.8% negative predictive value, and 96.1% accuracy was found when a cutoff value of 40% IgG avidity index was used for subjects of <28 GW.

Six women who had congenital CMV infection experienced flu-like symptom, fever, and/or lymphadenitis. The changes of CMV IgG avidity indices according to weeks after the appearance of the initial symptom are shown in Figure 3. Within 12–13 weeks after the appearance of maternal symptom of CMV infection, their IgG avidity indices were <40%.

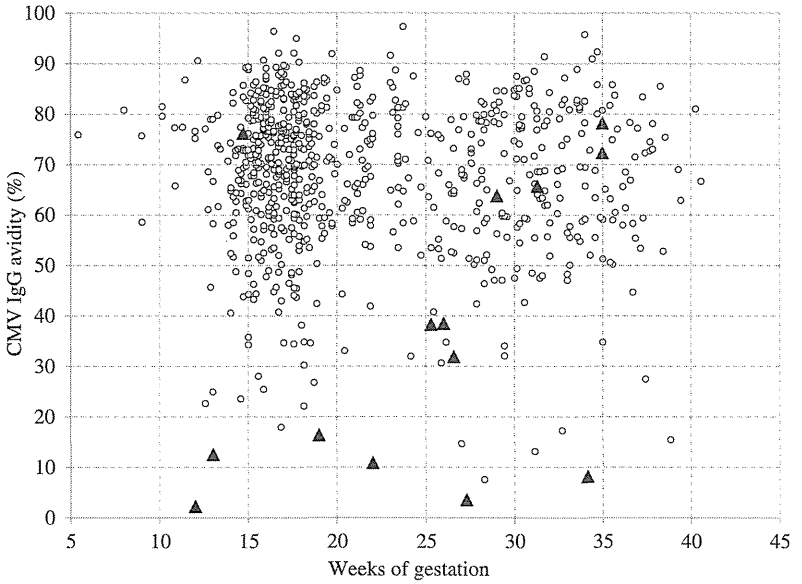

Figure 1 The value of maternal CMV IgG avidity according to GW.
▲, Congenital CMV infection (n=14). ○, Non-congenital CMV infection (n=745).

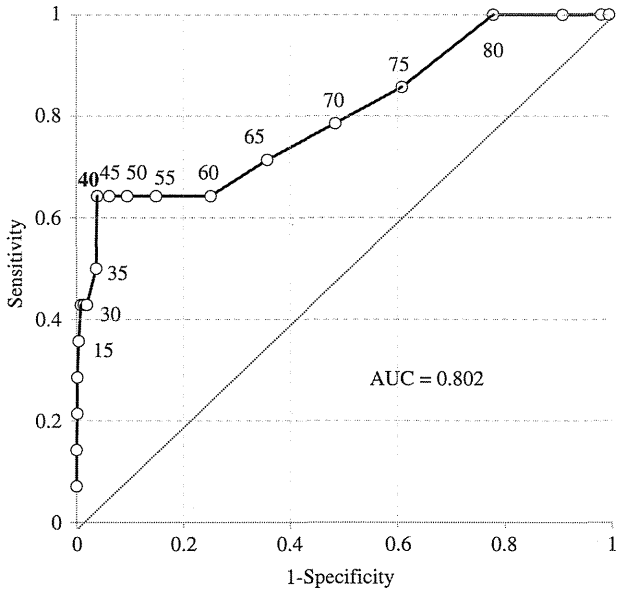

Figure 2 Receiver operating characteristic curve for CMV IgG avidity index for the prediction of congenital CMV infection.
AUC, area under curve.

Discussion

In the present cohort study, 14 of 759 (1.8%) women with positive tests for CMV IgG were found to have congenital CMV infection. This percentage was higher than the epidemiologically known frequency because this study involved pregnant women who were suspected of having CMV infection and referred to the university hospital. The serum CMV IgG avidity index (median 35.1%) in women who had congenital CMV infection was significantly lower than that (70.4%) in women without congenital infection. Thus, it was confirmed that pregnant women with low IgG avidity had a higher risk for the development of congenital CMV infection. In pregnant women who had <20%, <30%, and <40% serum IgG avidity index, the incidences of congenital infection were found to be 50.0%, 30.0%, and 23.7%, respectively. The ROC analysis determined a cutoff value of 40% IgG avidity index with 96.1% specificity and 64.3% sensitivity for the prediction of congenital CMV infection. Among women of <28 GW, the highest values, including 88.9% sensitivity, 96.2% specificity, 27.6% positive predictive value, 99.8% negative predictive value, and 96.1% accuracy, were obtained. If pregnant women show a low CMV IgG avidity index (<40%) during the first and second trimesters, the development of congenital CMV infection might be suspected.

Grangeot-Keros et al. [4] demonstrated that among pregnant women with well-documented seroconversion, the CMV IgG avidity index in their blood obtained <14 weeks after the latest seronegative status was a mean of 30% (range, 8–58%) and mostly <50%. Another study showed that pregnant women with primary CMV infection within the past 3 months usually had a <50% IgG avidity index [2]. A recent study also confirmed that <20% and <40% IgG avidity index indicated primary infection

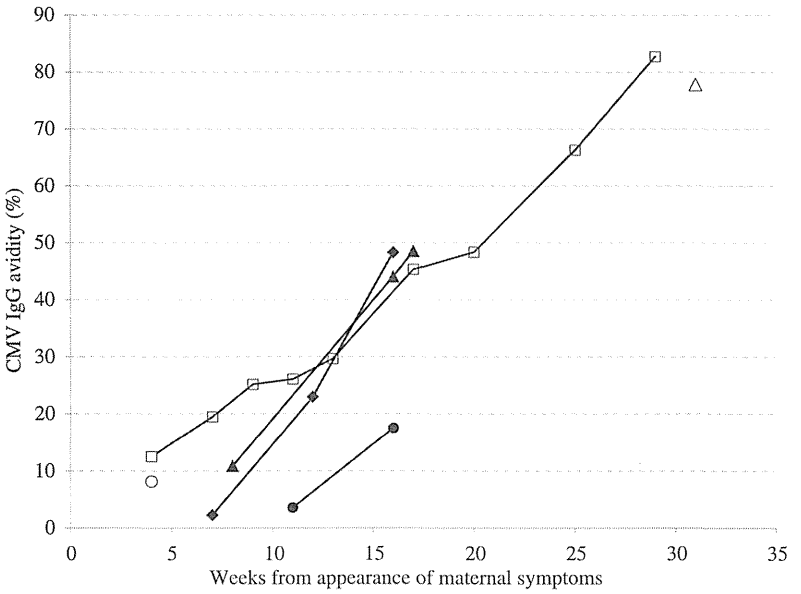

Figure 3 The value of CMV IgG avidity according to weeks from the appearance of maternal symptoms.

within the last 12 and 20 weeks, respectively [3]. However, no prospective clinical study has evaluated IgG avidity value to be predictive of congenital CMV infection thus far. In the present cohort study, we, for the first time, determined a cutoff value of 40% IgG avidity index for the prediction of congenital CMV infection, but not for the detection of primary infection in pregnancy. Six women with congenital CMV infection had symptoms associated with primary/acute infection. Their IgG avidity indices were <40% within 12–13 weeks after the appearance of the symptoms (Figure 3), suggesting that a <40% IgG avidity value might correspond to the value for the detection of primary/acute CMV infection during pregnancy.

CMV IgG avidity measurements at <28 GW might be clinically useful in assessing the risk for the presence of primary infection or the development of congenital CMV infection. However, IgG avidity measurements are not able to predict congenital infection owing to CMV reactivation or reinfection in general. Four of five women with congenital infection had high IgG avidity indices obtained after 28 GW in the present study. If the IgG avidity index was measured later in pregnancy, the sensitivity for the congenital CMV infection or primary infection was extremely reduced [8].

The findings in the present study will provide helpful information for clinical practice. However, interpreting avidity results is crucial because serological tests vary from one laboratory to another, and therefore the method used and its reference values must be carefully assessed. The results of the present study included several uncertainties. The scale of the study, comprising 14 cases of congenital infection, was not large enough. The time of IgG avidity measurements ranged broadly. Further studies are necessary to confirm the conclusions of this study.

Conflict of interest statement

Grant sponsor: This work was supported in part by Grants-in-Aid from the Ministry of Health, Labor and Welfare of Japan (grant no. H23-Jisedai-Ippan-001) and the Japan Association of Obstetricians and Gynecologists (grant no. H22-Ogyah-Kenkin).

Conflicts of interest: None.

Ethical approval: This study was conducted with informed consent from all of the subjects. The study was approved by the institutional ethical boards of the Kobe University Hospital.

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Prophylactic Intravenous Immunoglobulin Injections to Mothers with Primary Cytomegalovirus Infection

KENJI TANIMURA[1], SHINYA TAIRAKU[1], MASASHI DEGUCHI[1], AYAKO SONOYAMA[1], MAYUMI MORIZANE[1], YASUHIKO EBINA[1], ICHIRO MORIOKA[2], and HIDETO YAMADA[1]*

[1]*Department of Obstetrics and Gynecology, Kobe University Graduate School of Medicine*

[2]*Department of Pediatrics, Kobe University Graduate School of Medicine*

*7-5-1 Kusunoki-cho, Chuo-ku, Kobe 650-0017, Japan *Corresponding author*

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ABSTRACT

The aim of this trial study was to assess the preventive efficacy of immunoglobulin with a high titer of anti-CMV antibody for mother-to-fetus cytomegalovirus (CMV) transmission among pregnant women with primary/acute CMV infection. The primary CMV infection in mothers was diagnosed by a positive test for CMV IgM and/or low IgG avidity. Intact type immunoglobulin with a high titer of anti-CMV antibody was injected intravenously at a dosage of 2.5-5.0 g/day for consecutive 3 days to mothers with primary CMV infection. Four pregnant women were enrolled. One pregnancy ended in no congenital infection, while two pregnancies ended in congenital CMV infection. The other one pregnancy was terminated. The mother-to-fetus CMV transmission rate was found to be high as 66.7% (2/3). This preliminary result suggests that intravenous immunoglobulin injections are not effective for the prevention of mother-to-fetus CMV transmission in the present protocol.

INTRODUCTION

Cytomegalovirus (CMV) is the most common cause of intrauterine infection, occurring in 0.2-2.0% of live born infants [1]. When pregnant women have primary/acute CMV infection during the first trimester, approximately 25% of their fetuses will be infected [2]. Although 10-15% of infected fetuses show symptomatic congenital CMV infection at birth, the clinical manifestations including fetal growth restriction, low birth weight, central nervous system and multiple organ involvement may be so severe as to lead to a high perinatal mortality rate and major neurological sequelae in approximately 90% of the surviving infants [2-4]. In addition, 10-15% of infants with asymptomatic congenital infection will develop long-term sequelae, namely progressive sensorineural hearing difficulty and mental retardation [3, 4]. No guidelines concerning medical intervention for prenatally diagnosed congenital CMV infection is currently available. Therefore, aiming improvement of fetal/infantile prognosis many clinicians have tried a variety of fetal therapies for symptomatic congenital CMV infection including ganciclovir injection into fetal umbilical cord blood [5], hyper-immunoglobulin injection into peritoneal cavity of a fetus [6-8], hyper-immunoglobulin injection into maternal blood, amniotic fluid and umbilical cord blood [9, 10] and valaciclovir injection into maternal blood [11]. On the other hand, studies to prevent mother-to-fetus CMV transmission have reported a modality of intravenous injections of hyper-immunoglobulin [10, 12] to pregnant women with primary CMV infection. In these reports, immunoglobulin enriched for antibodies against CMV, such as Cytogam (CSL Behring) and Cyotect (Biotest AG), was used, whereas they are not available in many countries, including Japan. Therefore, we used conventional polyclonal-immunoglobulin with a high titer of anti-CMV antibody as substitutes for hyper-immunoglobulin. The aim of the present trial study was to assess the preventive efficacy of immunoglobulin with a high titer of anti-CMV antibody for mother-to-fetus CMV transmission among pregnant women with primary CMV infection.

PATIENTS AND METHODS

This trial study was performed prospectively with informed consent from all of the patients. The institutional ethical boards of the Kobe University Hospital study approved this study. During the period between August 2009 and April 2013, pregnant women who had primary CMV infection were enrolled. The

Phone: +81-78-382-6000 Fax: +81-78-382-5756 E-mail: yhideto@med.kobe-u.ac.jp

primary CMV infection in mothers was diagnosed by a positive test for CMV IgM and/or low IgG avidity. Women with fetal abnormalities detected by ultrasound were excluded from the study.

After confirmation of CMV primary infection, intact type immunoglobulin with a highest titer of anti-CMV antibody which was available at the time of treatment, Kenketsu venilon-I (Teijin Pharma, Tokyo), was injected intravenously at a dosage of 2.5-5.0 g/day for consecutive 3 days to mothers with informed consent. A couple was counseled about a possible risk of indefinite infection and other adverse effects of immunoglobulin, and they selected daily dose of 2.5 g or 5.0 g. The amniocentesis followed by PCR analysis for CMV DNA was performed with informed consent, if a couple desired it.

The diagnosis of congenital CMV infection was determined by the presence of CMV DNA in the urine or blood of neonates. Live-birth neonates received the workup for congenital CMV infection. Ophthalmofundoscopy, cerebral ultrasound, physical and neurological examinations were performed. Head MRI and CT were used if necessary. Auditory brain-stem response was periodically tested to find sensorineural hearing difficulty as one of major sequelae. Neurological development of the infants was followed up.

Serological tests for CMV IgG (negative 0-230.99, borderline 231-239.99, positive ≥240) and IgM (negative 0-0.89, borderline 0.90-1.99, positive ≥ 2.0) were performed using EIA kits produced by Siemens Healthcare Diagnostics (Tokyo, Japan). CMV IgG avidity was measured in the Aisenkai Nichinan Hospital, and the index of 35% or less is defined as low IgG avidity as described previously [13]. A real-time PCR analysis was performed at a commercial laboratory (SRL, Tokyo, Japan). C7-HRP (CMV antigen test "TEIJIN" TFB, Tokyo, Japan) was used as CMV antigenemia test.

RESULTS

Clinical findings of 4 women who received prophylactic immunoglobulin injections and the outcome are summarized in Table I.

Case 1 woman had antibody screening test and was found to have low CMV IgG avidity (22.7%) in the university hospital. CMV DNA in maternal blood was detected by PCR analysis. Intravenous immunoglobulin (IVIg) injections at a dosage of 2.5 g/day for 3 days were performed at 21 weeks of gestation (GW). Ultrasound examinations demonstrated no abnormalities of the fetus. CMV DNA in the amniotic fluid was not detected at 31 GW. A female baby weighing 2,650 g was delivered at 37 GW by elective cesarean section due to breech presentation. The baby had no congenital CMV infection and developed normally until 2 years 5 months old.

Case 2 woman was referred to the university hospital as she had antibody screening test and a positive test for CMV IgM in the former hospital. CMV IgG avidity (2.3%) in her blood was found to be extremely low. IVIg injections (2.5 g/day for 3 days) were performed at 17 GW. Ultrasound examinations demonstrated no abnormalities of the fetus. The pregnancy ended in preterm premature rupture of the membranes due to subchorionic hematoma and vaginal delivery of a stillbirth at 23 GW. The stillbirth had congenital CMV infection with the presence of CMV DNA in the cord blood serum. The consent to postmortem examinations was not obtained.

Case 3 woman was referred to the university hospital as she had liver dysfunction and a positive test for CMV IgM in the former hospital. CMV IgG avidity was found to be low as 12.6 %. IVIg injections (5.0 g/day for 3 days) were performed at 13 GW. The amniocentesis and subsequent PCR analysis revealed the presence of CMV DNA in the amniotic fluid at 16 GW. A couple desired the continuation of the pregnancy and IVIg injections, so that IVIg injections with informed consent were performed additionally at 18, 22 and 26 GW. Thereafter, the couple declined further injections because of private reasons. Ultrasound examinations demonstrated no abnormalities of the fetus. A female baby weighing 2,758 g was delivered vaginally at 37 GW. The baby had congenital CMV infection with the presence of CMV DNA in the blood and the urine. She is 1 year and 5 months old and develops normally without any sequela.

Case 4 woman was referred to the university hospital as she had flu-like symptoms with fever and a positive test for CMV IgM in the former hospital. CMV IgG avidity was found to be low as 8.9%. Her blood was tested positive for CMV antigenemia at 18 GW. IVIg injections (5.0 g/day for 3 days) were performed at 18 GW. Ultrasound examinations demonstrated no abnormalities of the fetus. The pregnancy was terminated at 21 GW, and the consent to postmortem examinations was not obtained.

Table I. Clinical findings of 4 women with prophylactic immunoglobulin injections and the outcome

Case no. Gravida/Para Age (years old)	Maternal IgM/ IgG avidity (GW)	Maternal symptoms (GW)	GW of diagnosis*	Doses of maternal IVIg (GW)	Viral loads before / after injection** (GW)	Clinical findings at birth	IgM of neonatal blood	Viral loads in neonate** (days old)	Outcome
1 3/0 30	0 – (18) / 22.7 % (12)	Flu-like symptom (11)	18	7.5g (21)	MB 1.4×10^2 (18) / < 20 (22) AF ND/ < 100 (31)	37 GW CS, 2,650g	0.1 –	Blood < 20 (0) Antigenemia – (3) Urine – (0)	No congenital infection
2 3/3 35	5.5 + (12) / 2.3 % (12)	Fever (5)	12	7.5g (17)	MB < 20 (12) / < 20 (18)	23 GW VD, pPROM, still birth, 760g	1.0 ±	Serum 3.0×10^5	Congenital infection, stillbirth
3 0/0 29	9.3 + (13) / 12.6 % (13)	Fever, liver dysfunction (9)	13	15g (13) 15g (18) 15g (22) 15g (26)	MB < 20 (13) / < 20 (34) AF ND/ 1.1×10^4 (16) 1.8×10^5 (24) 2.1×10^5 (39)	39 GW VD, 2,758g	4.4 +	Blood 1.7×10^2 (0) / – (1year old) Antigenemia – (0) Urine 5.3×10^7 (0) / 4.5×10^5 (1year old)	Congenital infection, normal development at 1 year and 6 months old
4 2/1 24	4.6 + (12) / 8.9 % (18)	Fever, flu-like symptom (12)	18	15 g (18)	MB < 20 (18) / ND	21 GW TOP, 328g	ND	ND	Stillbirth

GW, weeks of gestation; IVIg, intravenous administration of cytomegalovirus hyper immunoglobulin; MB, maternal blood, AF, amniotic fluid; ND, not determined; CS, cesarean section; VD, vaginal delivery; pPROM, preterm premature rupture of the membranes; TOP, termination of pregnancy

*Weeks of gestation when the maternal primary infection was diagnosed with laboratory data.

** Numbers shown are the results of real time PCR analyses. Units of amniotic fluid/urine /serum and blood samples are gene copy number/ ml and gene copy number/ 10^6 white blood cells, respectively.

DISCUSSION

This trial study of prophylactic IVIg injections enrolled 4 pregnant women with primary/acute CMV infection. Three of the four women had low IgG avidity and high IgM levels. The diagnosis of primary CMV infection in pregnant women based on CMV IgM is difficult, because the presence of CMV IgM may represent either recent primary infection or reactivation. CMV IgG avidity tests have been used to distinguish recent from distant infection. In addition, Ebina et al. suggested that a cut-off value of <40% IgG avidity index had a specificity of 96.1% and a sensitivity of 64.3% sensitivity for prediction of congenital infection[14]. For these reasons, a positive test for CMV IgM and/or low IgG avidity were used as diagnostic tools for detecting primary CMV infection in this study. The other woman, case 1 had low IgG avidity level and CMV DNA but not a positive test for IgM in her blood. Only one pregnancy (case 1) ended in no congenital infection, while two pregnancies (case 2 and case 3) ended in congenital CMV infection. Examinations of CMV infection for the stillbirth could not be performed in case 4. Therefore, excluding one pregnancy, mother-to-fetus CMV transmission rate was found to be high as 66.7% (2/3) among pregnant women who received prophylactic IVIg injections in the present study. This preliminary result suggests that IVIg injections are not effective for the prevention of mother-to-fetus CMV transmission. The plausible reasons for the ineffectiveness might involve delay of injections and insufficient doses of IVIg. Interval periods between appearance of maternal symptoms and IVIg injections ranged from 4 to 12 weeks in the present study. Case 3 experienced general symptoms of CMV infection at 9 GW and IVIg injections were able to start at 13 GW. However, CMV already existed in the amniotic fluid at 16 GW. The case 3 received relatively a high dose (a total of 60g) of IVIg within 26 weeks. Her baby had asymptomatic congenital CMV infection but normally developed without any sequela. It is suggested that the prevention of mother-to-fetus CMV transmission with use of IVIg is not easy, but the high amount of IVIg with repeated injections may reduce the severity of congenital CMV infection symptoms and the sequelae.

Nigro et al. reported that 37 pregnant women with primary CMV infection received prophylactic IVIg and 6 (16%) pregnancies ended in asymptomatic congenital CMV infection [10]. Buxmann et al. also reported that 39 pregnant women with primary CMV infection received prophylactic IVIg and 9 (23%) pregnancies ended in congenital CMV infection consisting of 8 asymptomatic infection and 1 termination of pregnancy [12]. In