J Infect Chemother xxx (2018) 1–5

Contents lists available at ScienceDirect

Journal of Infection and Chemotherapy

journal homepage: http://www.elsevier.com/locate/jic

Original Article

Clinical factor associated with congenital cytomegalovirus infection in pregnant women with non-primary infection☆

Hideto Yamada [a, *], Kenji Tanimura [a], Shinya Tairaku [a], Ichiro Morioka [b], Masashi Deguchi [a], Mayumi Morizane [a], Satoshi Nagamata [a], Kana Ozaki [a], Yasuhiko Ebina [a], Toshio Minematsu [c]

[a] Department of Obstetrics and Gynecology, Kobe University Graduate School of Medicine, Kobe, Japan
[b] Department of Pediatrics, Kobe University Graduate School of Medicine, Kobe, Japan
[c] Reserch Center for Disease Control, Aisenkai Nichinan Hospital, Miyazaki, Japan

ARTICLE INFO

Article history:
Received 21 February 2018
Received in revised form
26 March 2018
Accepted 12 April 2018
Available online xxx

Keywords:
Congenital infection
Cytomegalovirus
Non-primary infection
Pregnancy
Screening

ABSTRACT

The aim of this nested case-control study was to evaluate clinical factors associated with the occurrence of congenital cytomegalovirus (CMV) infection in pregnant women with non-primary CMV infection. In a cohort study of CMV screening for 2193 pregnant women and their newborns, seven newborns with congenital CMV infection were identified among 1287 pregnant women with non-primary CMV infection that was defined as negative IgM and positive IgG with IgG avidity index >45%. In the 1287 women with non-primary CMV infection, clinical findings and complications were compared between pregnancies with and without congenital CMV infection. Clinical factors associated with the occurrence of congenital CMV infection were evaluated. The birth weight of newborns with congenital CMV infection was less than that of newborns without congenital infection ($p < 0.05$). Univariate logistic regression analyses demonstrated that threatened premature delivery (OR 10.6, 95%CI 2.0–55.0; $p < 0.01$) and multiple pregnancy (OR 7.1, 95%CI 1.4–37.4; $p < 0.05$) were associated with congenital infection. Multivariable logistic regression analyses demonstrated that threatened premature delivery (OR 8.4, 95%CI 1.5–48.1; $p < 0.05$) was a single risk factor for congenital CMV infection in pregnant women with non-primary CMV infection. This study revealed for the first time that threatened premature delivery was associated with the occurrence of congenital CMV infection in pregnant women with non-primary CMV infection, the pathophysiology of which may be closely associated with CMV reactivation during pregnancy.

1. Introduction

Cytomegalovirus (CMV) is the most common mother-to-child infection in humans. The prevalence of congenital CMV infection is 0.2–2.0% in newborns [1], and 10–15% of infected newborns have symptomatic CMV infection. The clinical manifestations include fetal growth restriction (FGR), low birth weight, central nervous system and multiple organ involvement with petechiae, hepatomegaly, splenomegaly, jaundice, pneumonia and encephalitis. It can be so severe that approximately 90% of the surviving infants have a high perinatal mortality rate and major neurological sequelae [2]. In addition, 10–15% of infants with asymptomatic congenital CMV infection develop long-term sequelae, such as progressive sensorineural hearing difficulty and mental retardation [2,3].

The risk of virus transmission to the fetus is highest in women with primary CMV infection during pregnancy [4,5]. Maternal serological screening is considered effective for detecting primary CMV infection in pregnant women; and maternal blood tests for CMV-specific immunoglobulin (Ig) G and IgM are widely used [6]. However, pregnant women can produce CMV IgM during viral reinfection and reactivation [7]; moreover, IgM may persist for

☆ All authors meet the ICMJE authorship criteria.

* Corresponding author. Department of Obstetrics and Gynecology, Kobe University Graduate School of Medicine, 7-5-1, Kusunoki-Cho, Chuo-ku, 650-0017, Kobe, Japan.
E-mail address: yhideto@med.kobe-u.ac.jp (H. Yamada).

https://doi.org/10.1016/j.jiac.2018.04.010
1341-321X/

more than several months after the primary infection [8]. Therefore, CMV IgG avidity test is employed for the detection of primary CMV infection in pregnant women with positive IgM [9], and low avidity index (AI) is considered a sign of primary infection during pregnancy [10,11].

Our prospective study of 2193 pregnant women and their newborns has evaluated the efficacy of maternal universal screening for the prediction of congenital CMV infection using CMV IgG, AI, and IgM. This cohort study has demonstrated that 30% (3/10) of newborns with congenital CMV infection are born to mothers with primary CMV infection, while 70% (7/10) are born to mothers with non-primary CMV infection, suggesting that the majority of congenital infection of newborns is caused by non-primary CMV infection during pregnancy [12]. Likewise, in the United States, 25% of newborns with congenital CMV infection are born to mothers with primary CMV infection, while 75% are caused by non-primary infection [13].

A case-control study nested in the cohort was conducted to determine clinical factors associated with the occurrence of congenital CMV infection in pregnant women with non-primary CMV infection.

2. Patients and methods

The institutional review board at Kobe University Hospital approved the prospective cohort study and nested case-control study, and written informed consent was obtained from all participants. All pregnant women who visited or were referred to Kobe University Hospital between February 2010 and April 2016 underwent maternal serological CMV screening. The screening method was described previously [12]. Briefly, pregnant women underwent initial blood screening for CMV IgG before 22 gestational weeks (GW) or when they were referred to the hospital. CMV IgG-negative women underwent IgG measurement again at 34–36 GW. All CMV IgG-positive women were tested for serum IgG avidity. Women who had a CMV IgG AI ≤45% underwent IgM measurement. Sera from women with an AI >45% were stored at −80 °C, and CMV IgM levels were later measured. All newborns received polymerase chain reaction (PCR) analyses of the urine, and congenital infection was diagnosed with the detection of CMV-DNA in the urine. Measurement methods for blood levels of CMV IgG, IgM, AI, and real-time PCR for CMV-DNA in the urine were described previously [12]. In this prospective study of CMV screening for 2193 pregnant women and their newborns, seven newborns with congenital CMV infections were identified among 1287 pregnant women with non-primary CMV infection that was defined as negative IgM and positive IgG with IgG avidity index >45% in their serum. Symptomatic congenital CMV infection was diagnosed when newborns with congenital CMV infections had microcephaly, hepatosplenomegaly/hepatitis, thrombocytopenia, abnormality of brain images, retinopathy, or abnormal auditory brain-stem response (ABR) [12].

In a nested case-control study for the 1287 pregnant women with non-primary CMV infection, clinical findings and pregnancy complications were compared between pregnancies with and without congenital CMV infection. Clinical findings including age, gravidity, parity, body mass index (BMI), percentage of referrals, history of recurrent pregnancy loss, presence of maternal fever or flu-like symptoms, GW at the initial CMV IgG measurement, GW at delivery and birth weight were compared between pregnancies with and without congenital CMV infection. Clinical factors associated with the occurrence of congenital CMV infection in pregnant women with non-primary CMV infection were evaluated. Pregnancy complications, including hypertensive disorders, thyroid diseases, diabetes mellitus/gestational diabetes mellitus, medical diseases requiring immunosuppressive therapy, threatened premature delivery, multiple pregnancy, FGR, preterm delivery and light-for-date, were assessed. Threatened premature delivery was diagnosed when pregnant women had opening of uterine os/shortening of uterine cervix with regular uterine contraction. Threatened premature delivery in this study was defined as the condition that required intravenous administration of tocolytic agents such as magnesium sulfate and β-stimulant during hospitalization for one or more weeks to suppress uterine contraction.

Differences between the two groups were analyzed using the Mann–Whitney *U* test, Fisher's exact test, and the chi-square test. Statistical significance was considered present at p values less than 0.05. A stepwise approach was used to evaluate risk factors for congenital CMV infection from women with non-primary infection. Variables with p-values less than 0.05 in univariate logistic regression analyses were subjected to multivariable logistic regression analyses, and variables with p-values less than 0.05 in multivariable logistic regression analyses were determined as independent factors. All statistical analyses were performed using SPSS software, version 19 (SPSS Inc., Chicago, IL, USA).

3. Results

In the prospective study of CMV screening for 2193 pregnant women and their newborns, three newborns with congenital CMV infection were born to mothers with primary CMV infection that was defined as IgG seroconversion, or positive/borderline IgM and positive IgG with AI <35% [12]. Seven (0.54%) newborns with congenital CMV infections were also identified in 1287 women with non-primary CMV infection that was defined as negative IgM and positive IgG with AI >45% (Table 1). Three (42.9%) of the seven newborns had symptomatic infection. Case 4 had bilateral abnormal ABR and ventriculomegaly; case 6 had low platelet counts and liver dysfunction; and case 7 had low platelet counts. Only case 4 received valganciclovir therapy (16 mg/kg/day, 6 weeks), after which the abnormal ABR was restored to normal. Case 5 was classified as asymptomatic congenital infection, because this case had only a symptom of small for gestational age.

Table 2 shows clinical characteristics of seven pregnancies with congenital CMV infection and 1280 pregnancies without congenital infection in women with non-primary CMV infection. The birth weight of newborns with congenital CMV infection was less than that of newborns without congenital infection ($p < 0.05$). The proportion of threatened premature delivery in pregnancies with congenital CMV infection of fetuses was higher than that in pregnancies without congenital infection ($p < 0.01$). Other clinical findings or pregnancy complications were not significantly different between the two groups.

Table 3 shows the results of univariate and multivariable logistic regression analyses of clinical factors associated with the occurrence of congenital CMV infection in pregnant women with non-primary infection. Univariate logistic regression analyses demonstrated that threatened premature delivery [odds ratio (OR) 10.6, 95% confidence interval (CI) 2.0–55.0; $p < 0.01$] and multiple pregnancy (OR 7.1, 95% CI 1.4–37.4; $p < 0.05$) were associated with the occurrence of congenital CMV infection. Multivariable logistic regression analyses of these two factors revealed that threatened premature pregnancy (OR 8.4, 95% CI 1.5–48.1; $p < 0.05$) was a significant risk factor for the occurrence of congenital CMV infection in pregnant women with non-primary CMV infection.

4. Discussion

The prospective study demonstrated that 7 (0.54%) of 1287 women with non-primary CMV infection during pregnancy delivered newborns with congenital CMV infection [12]. The

Please cite this article in press as: Yamada H, et al., Clinical factor associated with congenital cytomegalovirus infection in pregnant women with non-primary infection, J Infect Chemother (2018), https://doi.org/10.1016/j.jiac.2018.04.010