

Experience in the Use of CMV Hyperimmunoglobulin in Pregnant Women at Risk for Congenital CMV Infection in Brazil

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Abstract

Cytomegalovirus (CMV) infection is widely distributed globally and usually asymptomatic in healthy children and adults and it is a relevant cause of congenital infection, especially in cases of primary maternal infection, often leading to severe cognitive impairment (intellectual disability) and developmental disorders (1-3).

Objective: to review and describe the management of primary maternal CMV infections using CMV hyper immunoglobulin (CMVIG) and the outcome of the newborns and update the international experience.

Methods: Open, non-comparative, retrospective observational and descriptive study based on medical records and neonatal outcomes observed in newborns according to the management of primary CMV infection during pregnancy, at Santa Joana Maternity Hospital from 2014 to 2020. CMV hyper immunoglobulin (CMVIG) was used as prophylaxis in pregnant women diagnosed with primary CMV in early pregnancy, before amniocentesis. A “no intervention” group was used as a control for comparison.

Results: In total 19 pregnant women were diagnosed with primary CMV infection during pregnancy and were followed up until delivery. All pregnant women had a positive IgG test and 17/19 (89.5%) had a IgM positive test. Documented serum conversion, characterizing primary infection of the remaining cases. CMVIG was used in 6/19 pregnant women and 13 patients had no specific intervention (control). In CMVIG group, there were no cases of symptomatic congenital infection, 6/13 (46.1%) from the no intervention group had congenital CMV disease. The tolerability of the CMVIG infusion was good, without adverse effects.

Conclusion: The group with prophylactic use of CMVIG benefited compared to the group that did not receive prophylaxis, since none of the six women who received CMVIG resulted in symptomatic congenital disease. The tolerability of IGCMV was good. This series of case motivate us to continue studying the CMVIG use in CMV primary infection.

Keywords: Congenital Cytomegalovirus; Hyperimmunoglobulin; Pregnant Women

Abbreviations: CMV: cytomegalovirus; CMVIG: CMV hyperimmunoglobulin; GA: gestational age; IV: intravenous; NB: Newborn; PCR: polymerase chain reaction

Background

Cytomegalovirus (CMV) infection is widely distributed globally and usually asymptomatic in healthy children and adults. However, CMV is a relevant cause of congenital infection, especially in cases of primary maternal infection, often leading to severe cognitive impairment (intellectual disability) and developmental disorders [1-3].

In Europe and United States about 80.000 pregnant women annually acquire primary CMV infection and transmit the virus to the fetus increasing the risk of transmission from 30% to 73% as gestation progresses [4].

Primary maternal CMV infection occurs at variable rates, depending on regional factors, but it is estimated that it occurs in about 0.5% to 5.0% of pregnancies of susceptible mothers (CMV seronegative) [5]. Primary maternal CMV infections during the first trimester of pregnancy lead to about 25% of infections in newborns (NB); in the second trimester, approximately 50%; and in the third, about 75% will be infected [1-5]. Cytomegalovirus is one of the most common causes of congenital infection with a global prevalence of approximately 0.64% of all births.

A review that pooled data from 10 studies (2942 fetuses) of maternal-fetal CMV transmission in women who seroconverted just before or during pregnancy reported the following rates of transmission (6):

- Preconception period (up to 12 weeks before the last menstrual period) – 5.5 percent
- Periconceptional period (4 weeks before to 6 weeks after the last menstrual period) – 21 percent
- First trimester – 36.8 percent
- Second trimester – 40.3 percent
- Third trimester – 66.2 percent

Although the risk of maternal-fetal viral transmission is lower in early pregnancy compared with late pregnancy, the risk of symptomatic disease at birth and long-term sequelae is higher when infection occurs in early pregnancy.

Furthermore, although there is still no consensus, evidence from recent years has shown that neonatal infections may have their course modified through passive immunization with high avidity neutralizing antibodies directed against CMV [7-11].

Data on CMV during pregnancy are scarce in our country and, in particular, there are no Brazilian data on the management of pregnant women diagnosed with primary infection with neutralizing antibodies for CMV.

Objective

This study aims to review and describe the management of primary maternal CMV infections using CMV hyperimmunoglobulin (CMVIG) and the outcome of the newborns and update the international experience.

Materials and methods

Open, non-comparative, retrospective observational and descriptive study based on medical records and neonatal outcomes observed in newborns according to the management of primary CMV infection during pregnancy.

Retrospective multicenter study based on a review of medical records of patients from the Santa Joana Hospital Group, in São Paulo, between 2014 and 2020.

Primary CMV infection during pregnancy was established under the following criteria:

1. IgG/IgM seroconversion documented during pregnancy and detection of low-avidity IgG (< 40%).

The use of CMVIG was considered as prophylaxis in patients diagnosed with primary CMV BEFORE amniocentesis. CMVIG (Cytotect® CP Biotest, Biotest) was administered monthly as an intravenous (IV) infusion of 70 IU/kg of body weight. The diagnosis of primary CMV infection of the fetus was done using polymerase chain reaction (PCR) technique in amniotic fluid on opportune time.

In cases of CMV PCR positivity in the amniotic fluid, therapeutic intervention with valacyclovir 8 g/day orally, was suggested until near the end of pregnancy as early therapy.

A group of patients did not receive any type of intervention by choice of the patient and/or depending on the period of gestation that the patient come to the consultation (too close to delivery, no Intervention group).

The same clinician throughout the pregnancy followed up pregnant women and prenatal care was performed according to the obstetrics routine All pregnant women were instructed in relation to the risks and benefits of each intervention.

Data analysis: Univariate analysis was used for group comparisons with Chi-squared (χ^2) test or Fisher exact test, as applicable. Two-tailed t-tests were used to compare means and standard deviations. One-way ANOVA was used to contain continuous data for gestational week and weight at birth. Results are shown with χ^2 or z or Fisher exact two-tailed values and respective P value. P values < 0.05 were considered significant. The study was approved by the research ethics committee of HOSPITAL E MATERNIDADE SANTA JOANA (opinion number 4,221,672).

Results

In total 19 pregnant women were diagnosed with primary CMV infection during pregnancy and were followed up until delivery. The median age of pregnant women was 33 years (17 – 39y; min-max.) (Table 1). Among the pregnant women, 5/19 (26.3%) were nulliparous. The median gestational age (GA) at diagnosis of primary CMV infection was 17.3 weeks, ranging from 6 to 38 weeks.

Regarding serological tests, all patients had positive IgG, 17/19 (89.5%) had positive IgM, but documented serum conversion, characterizing primary infection. The IgG avidity test was available in 14/19 patients. Of those 8 (57.1%) had low avidity ($\leq 40\%$).

Characteristic	Mean	Standard deviation
Age – year	33	±4.24
Weeks of pregnancy at screening	17.3	±9.01
Gestational Age at delivery (w)	39	±1.94

Table 1: Maternal characteristics at screening

CMV serology at pregnancy screening		
	No	%
IgM+, IgG+	17	89.5
IgM-, seroconversion	2	10.5

The distribution of pregnant women in relation to the type of intervention submitted is detailed in table 2.

Intervention	N
P (CMVIG)	6
NI (no intervention)	13
Total	19

P: prophylaxis (IGCMV), NI: no intervention

Table 2: Pregnant women with primary CMV and Intervention submitted

Concerning amniocentesis performance, 8/19 patients (42.1%) underwent to amniocentesis, no patient had a positive CMV test by PCR in amniotic fluid, 4 from CMVIG group and 4 from no intervention group.

Table 3 shows the outcome found in the newborns of the 19 pregnant women with primary CMV infection.

	CMVIG		No intervention	
	N	%	N	%
NB with PCR+ (urine)	2	33.3%	7	53.8%
NB with symptomatic congenital CMV	0	-	6	46.1%
Valganciclovir post natal as treatment	0	-	6*	46.1%
*1 symptomatic death				

NB: New born; PCR: Polymerase Chain Reaction

Regarding the outcome of CMV-related neonatal disease, we have the following results:

Symptom	CMVIG	NI
Hearing loss or deficiency	0	2
Hepatitis and/or liver / spleen enlargement	0	1
CNS alterations (calcifications, elevated CSF protein, and/or ventriculitis)	0	1
Anaemia and/or thrombocytopenia	0	2
Retinal Disease	0	2
Other manifestations (petechiae and pericardial effusion)	0	1

NI: no intervention,

Regarding the safety data of the interventions performed, in the prophylactic groups, there was no moderate or severe adverse event, nor the need to discontinue the drug.

Discussion

In this descriptive study on the clinical management of pregnant women with primary CMV infection, the use of CMVIG was based on according to the institutional protocol. CMVIG was indicated prophylactically for those women diagnosed with CMV in early pregnancy and before amniocentesis. Results were compared with no intervention cases (choice of the patient and/or depending on the period of gestation that the patient come to the consultation, that means too close to delivery).

Although the small sample size, it is noteworthy that the group with prophylactic use of CMVIG benefited compared to the group that did not receive prophylaxis, since none of the six women who received CMVIG resulted in amniotic fluid infection or congenital neonatal disease. The tolerability of CMVIG was very good.

The use of CMVIG to prevent neonatal CMV infection upon primary infection is controversial.

When we analyzed data from published studies that used CMVIG in this setting some reported favorable outcomes, while others showed less favorable results.

Nigro G et al. study found four factors predictive of infant outcome congenital CMV infection: maternal viremia DNAemia prior CMVIG administration, congenital infection without CMVIG, abnormal ultrasounds and diagnosis of maternal infection via seroconversion rather than avidity [4]. His group used a high dose of CMVIG (200mg/Kg/infusion). They concluded that maternal viremia predicts fetal infection and neonatal outcome. High dose CMVIG may prevent fetal infection and disease, and is associated with the resolution of DNAemia.

On the other side Hughes BL et al. study showed no advantage in terms of prevention of neonatal outcome in pregnant women who used IGCMV up to 24 weeks of pregnancy [8]. Other studies prior to this demonstrated encouraging results with the use of CMVIG, despite the different methodologies [2,3].

An important aspect in cases of primary CMV infection in pregnant women is that we have a significant risk of poor neonatal outcome and sequelae, and there is an absence of specific effective and safe therapies. CMVIG maternal infusion seems to be safe in many studies analyzed as well as in our study [4,7].

This observational study is limited by potential selection bias and lack of an appropriate placebo control.

It is important to develop further clinical trials in order to clarify the usefulness of passive immunotherapy for CMV early-infected pregnant woman once there is not current available antiviral treatment indicated for this obstetrical situation.

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