Treatment with valacyclovir during pregnancy for prevention of congenital cytomegalovirus infection: a real-life multicenter Italian observational study

Lorenzo Zammarchi, MD; Lina Rachele Tomasoni, MD; Giuseppina Liuzzi, MD; Giuliana Simonazzi, PhD; Camilla Dionisi, MD; Laura Letizia Mazzarelli, MD; Anna Seidenari, MD; Giuseppe Maria Maruotti, PhD; Sara Ornaghi, PhD; Francesco Castelli, MD; Isabella Abbate, PhD; Licia Bordi, PhD; Stefania Mazzotta, MD; Paolo Fusco, MD; Carlo Torti, MD; Francesca Ippolita Calò Carducci, PhD; Michela Baccini, PhD; Giulia Modi, MD; Luisa Galli, MD; Daniele Lilleri, MD; Milena Furione, MD; Maurizio Zavattoni, MD; Alessandra Ricciardi, MD; Alessia Arossa, MD; Antonella Vimercati, PhD; Sofia Lovatti, MD; Serena Salomè, MD; Francesco Raimondi, PhD; Laura Sarno, PhD; Anita Sforza, MD; Anna Fichera, MD; Leonardo Caforio, MD; Michele Trotta, MD; Tiziana Lazzarotto, PhD; On behalf of the MEGAL-ITALI Working Group

BACKGROUND: Valacyclovir is the only treatment demonstrated to be effective for the prevention of vertical transmission of cytomegalovirus within a clinical randomized, placebo-controlled trial and has been reimbursed by the Italian National Health System since December 2020.

OBJECTIVE: This study reported the results of a real-life Italian multicenter observational study on cytomegalovirus infection in pregnancy evaluating the effect of the introduction of valacyclovir in the clinical practice for the prevention of vertical transmission of cytomegalovirus.

STUDY DESIGN: The outcomes of women who received valacyclovir treatment and their fetuses or newborns were compared with those of a retrospective cohort observed between 2010 and 2020 who did not receive the antiviral treatment. The inclusion criterion was the diagnosis of cytomegalovirus primary infection occurring in the periconceptional period or up to 24 weeks of gestation. The primary outcome was the transmission by the time of amniocentesis. The secondary outcomes were termination of pregnancy, transmission at birth, symptomatic infection at birth, and a composite outcome (termination of pregnancy or transmission at birth).

RESULTS: A total of 447 pregnant women from 10 centers were enrolled, 205 women treated with valacyclovir (called the valacyclovir group, including 1 twin pregnancy) and 242 women not treated with valacyclovir (called the no-valacyclovir group, including 2 twin pregnancies). Valacyclovir treatment was significantly associated with a reduction of the diagnosis of congenital cytomegalovirus infection by the time of amniocentesis (weighted odds ratio, 0.39; 90% confidence interval, 0.22–0.68; *P*=.005; relative reduction of 61%), termination of pregnancy (weighted odds ratio, 0.36; 90% confidence interval, 0.17–0.75; *P*=.0021; relative reduction of 64%), symptomatic congenital cytomegalovirus infection at birth (weighted odds ratio, 0.17; 90% confidence interval, 0.06–0.49; *P*=.006; relative reduction of 83%). The treatment had no significant effect on the rate of diagnosis of congenital cytomegalovirus infection at birth (weighted odds ratio, 0.85; 90% confidence interval, 0.57–1.26; *P*=.500), but the composite outcome (termination of pregnancy or diagnosis of congenital cytomegalovirus infection at birth) occurred more frequently in the no-valacyclovir group (weighted odds ratio, 0.62; 90% confidence interval, 0.44–0.88; *P*=.024). Of note, the only symptomatic newborns with congenital cytomegalovirus infection in the valacyclovir group (n=3) were among those with positive amniocentesis. Moreover, 19 women (9.3%) reported an adverse reaction to valacyclovir treatment, classified as mild in 17 cases and moderate in 2 cases. Lastly, 4 women (1.9%) presented renal toxicity with a slight increase in creatinine level, which was reversible after treatment suspension.

CONCLUSION: Our real-life data confirm that valacyclovir significantly reduces the rate of congenital cytomegalovirus diagnosis at the time of amniocentesis with a good tolerability profile and show that the treatment is associated with a reduction of termination of pregnancy and symptomatic congenital cytomegalovirus infection at birth.

Key words: congenital, cytomegalovirus, fetal, immunoglobulin, pregnant, screening, valaciclovir, women

Introduction

The human cytomegalovirus (CMV) causes the most frequent congenital infection with a prevalence at birth of 0.5% to 2.0% and is a leading cause of permanent sequelae, responsible for 25% of cases of congenital sensorineural hearing loss, 10% of cases of cerebral palsy, and several neurologic abnormalities.[1] The seroprevalence in childbearing-aged women in high-income countries ranges between 50% and 85%, whereas the risk of acquiring a primary infection during pregnancy is 1% to 2% in this setting.[1] Primary infection in pregnancy is linked to a risk of transplacental transmission ranging from 21% in the periconceptional period to 66% in the third trimester of pregnancy,[2] whereas the risk of transplacental transmission is very low (<3.5%) in case of nonprimary maternal infection (reinfection or reactivation).[3] The probability of developing neurologic sequelae in the infant is strongly related to the timing of transplacental transmission. According to a recent systematic

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AJOG MFM at a Glance

Why was this study conducted?

Since 2020, valacyclovir (VCV) has been reimbursed by the Italian National Health System for the secondary prevention of congenital cytomegalovirus (cCMV) infection and treatment of mild-to-moderate fetal cytomegalovirus (CMV) disease during pregnancy.

Key findings

This real-life study showed that the use of VCV in pregnant women with primary CMV infection significantly reduces the rate of positive amniocentesis, termination of pregnancy, and symptomatic cCMV infection at birth.

What does this add to what is known?

Our study shows that the use of VCV reduces not only the rate of cCMV infection diagnosed by the time of amniocentesis but also the rate of symptomatic cCMV infection at birth.

review and meta-analysis, if the infection is acquired during the periconceptional period or first trimester of pregnancy, the risk of permanent sequelae is 28.8% and 19.3%, respectively, although it drops below 1% during the second and third trimesters of pregnancy.[2] However, in previous reports, Bilavsky et al[4] found hearing loss at birth in 4.3% of children with late maternal-fetal transmission, and severely affected fetuses have also been described after second-trimester infection.[5,6]

Several years ago, there was no proven treatment option for preventing mother-to-child transmission.[7,8] Recently, the results of a randomized double-blind trial showed that the use of valacyclovir (VCV) in pregnant women with primary CMV infection acquired in the periconceptional period or during the first trimester of pregnancy at a dose of 8 g per day was associated with a 70% reduction in the vertical transmission rate diagnosed by amniocentesis.[9,10] Of note, 2 additional observational reports and 2 systematic reviews with meta-analysis confirmed the usefulness of VCV for secondary prevention of congenital CMV (cCMV) during pregnancy.[11–14]

In Italy, the management of CMV infection in pregnant women and their newborns is usually performed according to a national multisocietal consensus document released in 2012, which does not recommend any maternal treatment during pregnancy.[15] Following the most recent evidence,[9,10] in December 2020, VCV has been formally included in the list of reimbursed medicinal products by the Italian National Health System.[16,17] Since then, the use of VCV has become part of the standard of care for the secondary prevention of cCMV and treatment of mild-to-moderate fetal CMV disease during pregnancy.

This study aimed to evaluate and compare the outcome of pregnant women with primary CMV infection acquired in the periconceptional period or early pregnancy and of their fetuses or newborns before and after the introduction of maternal VCV treatment in Italy. Data were collected within the multicenter observational Italian study on CMV infection in pregnancy called MEGAL-ITALI, which was launched in 2020.[16]

Materials and Methods

Study design and setting

We performed an observational prospective study enrolling pregnant women with primary CMV infection accessing the participating centers from January 2010 to June 2022.

In Italy, serologic screening for CMV during pregnancy is not recommended by the national guidelines. However, it is commonly prescribed by obstetricians or general practitioners during early pregnancy, thus leading to variable detection of primary infections during pregnancy.[18]

Inclusion criteria and collected data

We included all pregnant women presenting for care at the participating centers, satisfying the Agenzia Italiana del Farmaco (AIFA) criteria for VCV treatment, namely a primary CMV infection acquired in the periconception period and up to 24 weeks of gestation.[17] The definition of CMV maternal primary infection was that provided by the AIFA in the technical document of VCV treatment[17]: (1) CMV immunoglobulin G (IgG) seroconversion defined as a negative IgG test during pregnancy followed by a positive IgG test later in the gestation; (2) CMV IgG and immunoglobulin M (IgM) positive with low IgG avidity index during pregnancy; and (3) CMV IgG and IgM positive, intermediate IgG avidity index, and detected CMV DNA in at least 1 body fluid (blood, saliva, or urine) during pregnancy.

The diagnosis of cCMV infection at birth was defined by the detection of CMV DNA in the newborn's urine within 2 weeks of life.

For each eligible women, we attempted to collect data on estimated timing of infection according to Revello et al,[19] presence of CMV-related maternal symptoms, results of maternal laboratory findings (CMV IgG, IgM, IgG avidity, and CMV DNA in maternal blood, urine, saliva, and amniotic fluid), timing of amniocentesis, miscarriage or termination of pregnancy (TOP), timing of delivery, occurrence of obstetrical complications, newborn laboratory findings (CMV DNA in urine, blood, and saliva within 2 weeks from birth), presence of newborn cCMV-related symptoms according to the European Society for Paediatric Infectious Diseases (ESPID) definition,[20] and use of valganciclovir treatment in newborns. Moreover, for women receiving VCV treatment, we recorded available data on the treatment scheme, length of treatment, occurrence of drug-related side effects, and the delay between the estimated date of infection and treatment. Clinical and laboratory data were retrieved from electronic or paper medical records according to the availability in the different participating centers.

Outcomes

The primary outcome was the transmission by the time of amniocentesis. The secondary outcomes were TOP, diagnosis of cCMV infection at birth (positive CMV DNA in the newborn's urine within 2 weeks of life), symptomatic cCMV infection at birth (according to the ESPID definition), and a composite outcome (TOP or diagnosis of cCMV infection at birth).

Valacyclovir treatment and follow-up protocol

According to the technical recommendation by the AIFA,[17] VCV can be used in pregnant women who acquire primary CMV infection (as defined above) in the periconception period and up to 24 weeks of gestation at a dose of 2 g every 6 hours (total 8 g per day).

Eligible pregnant women should start the treatment as soon as possible after the diagnosis of primary CMV infection. Treatment can be suspended if the pregnant woman undergoes amniocentesis and real-time polymerase chain reaction (PCR) on amniotic fluid for CMV DNA is negative. Amniocentesis has to be scheduled at least 8 weeks after the estimated time of primary infection and not before 20 1/7 weeks of gestation. If CMV DNA in amniotic fluid is positive, the treatment should be continued only in the presence of ultrasound or biohumoral signs suggestive of a mild-to-moderate fetal disease; otherwise, it should be discontinued. If the pregnant woman declines amniocentesis, the therapy is scheduled until 26 weeks of gestation. The exclusion criteria for VCV treatment during pregnancy are creatinine level of >1.1 mg/dL and glomerular filtration of <90 mL/min. Monitoring during VCV treatment is performed as follows: (1) blood tests in the pregnant woman (complete blood cell count with formula, transaminases, gamma-glutamyl transferase, total and fractionated bilirubin level, creatinine level, and CMV DNA in whole blood) at baseline, after 1 week, and every 14 days thereafter; (2) second-level obstetrical ultrasound examination every 2 to 4 weeks; (3) amniocentesis for CMV DNA via real-time PCR; (4) controls on the newborn: search for CMV DNA via real-time PCR in the urine of the newborn within 2 weeks of life and clinical assessment.

Untreated pregnant women observed before the AIFA authorization of VCV were managed according to the national multisocietal consensus document released in 2012, which recommends amniocentesis, obstetrical ultrasound examination, and neonatal virological testing at the same timing as above.[15]

Ethical approval

The protocol was approved by the local ethics committees for all study sites (code at the coordinating center 17802_bio).

Statistical analysis

Descriptive statistics were provided: proportions for categorical variables and means and standard deviations for quantitative variables. Crude odds ratios (ORs) and mean differences were calculated when appropriate.

We assessed the treatment effect on qualitative amniocentesis result, TOP, diagnosis of cCMV infection at birth, symptomatic cCMV infection at birth, and combined outcome (TOP or diagnosis of cCMV infection at birth). For this purpose, we adopted a marginal structural model approach[21] using inverse probability weighting to account for the confounding effect of the observed pretreatment variables, selection because of outcome missingness, and censoring by TOP (the newborn's outcomes were not observed in the case of TOP). First, the analysis required the specification of regression models for weights estimation. Next, these weights were used to calculate for each outcome the adjusted OR of the treatment condition vs the control condition. This analysis was performed on both the entire dataset and the subsets of women defined according to the enrollment criteria defined in the clinical trial by Shahar-Nissan et al.[9]

We investigated the effect modification of the treatment by time of infection onset and criteria for treatment eligibility (namely, seroconversion OR IgG-IgM positive with low IgG avidity OR IgG-IgM positive, intermediate IgG avidity, and positive CMV DNA in blood, urine, or saliva).

Details on the methods can be found in the Supplemental Materials. All the analyses were conducted using Stata (version 17; StataCorp, College Station, TX).

Results

Descriptive analysis

Overall, 460 pregnant women were evaluated for enrollment. We excluded from the analysis 13 women for whom none of the outcomes was available (missing data on all the following information: CMV DNA detection in amniotic fluid, CMV DNA detection in the urine of the newborn within 2 weeks from birth, and TOP).

Thus, the final study population included 447 pregnant women from 10 centers: 205 women were treated with VCV (VCV group, including 1 twin pregnancy), whereas 242 women did not receive any treatment (no-VCV group, including 2 twin pregnancies). Only 6 centers were able to provide data from both treated and untreated women, although the remaining were able to provide only data concerning the most recently observed patients because of problems in retrieving retrospective data.

The main baseline characteristics of included pregnant women are reported in Table 1. Mean age, timing of infection, and presence of any CMV-related maternal symptom were similar between women in the VCV group and untreated women. The distribution of the enrolment criteria was different, with untreated women presenting more often with CMV IgG and IgM positive and low IgG avidity than treated women (48.8% vs 38.3%; P=.0337). The enrollment criteria according to the center are reported in Supplemental Table 1.

Supplemental Figure 1 shows the flow and outcome of enrolled women and their fetuses and newborns.

The features related to VCV treatment in terms of infection to treatment delay, trimester of treatment initiation, duration of treatment, and treatment scheme are summarized in Table 2.

TABLE 1
Profile of pregnant women with CMV infection in pregnancy according to treatment received (women bearing a twin pregnancy were counted twice)

Variable	VCV		No VCV		All	
	n/N	%	n/N	%	n/N	%
Enrolment criteria						
CMV IgG seroconversion	81/206	39.3	77/244	31.6	158/450	35.1
CMV IgG+, IgM+, low IgG avidity	79/206	38.3	119/244	48.8	198/450	44.0
CMV IgG+, IgM+, intermediate IgG avidity, detected CMV DNA[a]	46/206	22.3	48/244	19.7	94/450	20.9
Periconceptional infection[b]	36/206	17.5	58/244	23.8	94/450	20.9
First-trimester infection	143/206	69.4	152/244	62.3	295/450	65.6
Second-trimester infection	27/206	13.1	34/244	13.9	61/450	13.6
Presence of maternal CMV-related symptoms	11/206	5.3	10/244	4.1	21/450	4.7
Age (y), mean (SD)	31.6 (5.3)		31.2 (5.5)		31.4 (5.4)	
Estimated week of pregnancy at infection,[c] mean (SD)	8.3 (6.1)		8.0 (6.4)		8.2 (6.3)	
Pregnancy week at amniocentesis, mean (SD)	20.7 (1.3)		20.9 (1.9)		20.8 (1.6)	

cCMV, congenital cytomegalovirus; *CMV*, cytomegalovirus; *IgG*, immunoglobulin G; *IgM*, immunoglobulin M; *SD*, standard deviation; *VCV*, valacyclovir.

[a] Detected CMV DNA in at least 1 maternal body fluid (blood, saliva, or urine); [b] Within 4 weeks before the last reported menstrual period and up to 3 weeks of gestation[9]; [c] According to Revello et al.[19]

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Supplemental Table 2 reports the diagnostic delay according to the participating centers.

The mean week of pregnancy at treatment start and treatment discontinuation were different in women undergoing amniocentesis and women not undergoing amniocentesis (14.8 [standard deviation (SD), 3.3] vs 19.0 [SD, 5.5] [*P*<.0001] and 22.7 [SD, 4.4] vs 27.1 [SD, 5.2] [*P*<.0001], respectively).

Weighted analysis

Table 3 reports for each outcome the observed distribution by treatment, crude OR, and adjusted OR from the weighted analysis, with their 90% confidence intervals (CIs). The *P* value of the statistical test for the null hypothesis of no causal effect of the treatment was reported as well.

Accounting for confounding and possible selection bias related to the fact that only part of the women performed amniocentesis, the odds of a positive amniocentesis was 61% lower under treatment than under the control

TABLE 2
Main characteristics of VCV treatment

Variable	Mead (SD) or n/N (%)
Mean infection to treatment delay in weeks, all VCV group	7.9 (4.6)
Mean infection to treatment delay in weeks, periconceptional infections	15.6 (5.5)
Mean infection to treatment delay in weeks, first-trimester infections	8.0 (3.9)
Mean infection to treatment delay in weeks, second-trimester infections	4.6 (3.1)
VCV initiation in the first trimester of pregnancy	51/205 (24.9)
VCV initiation in the second trimester of pregnancy	154/205 (75.1)
Mean duration of VCV treatment in days	57.8 (32)
VCV treatment regimen 2 g 4 times a day	203/205 (99.0)
VCV treatment regimen 4 g 2 times a day	2/205 (1.0)

SD, standard deviation; *VCV*, valacyclovir.

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TABLE 3
Observed distribution of the outcomes by treatment, crude ORs, and adjusted ORs from the weighted analysis, with 90% CIs, *P* value of the test for the null hypothesis of no casual effect (weighted OR=1)

		Crude comparison			Weighted analysis		
Outcome	VCV	No VCV	OR	90% CI	OR	90% CI	*P* value
	n/N (%)	n/N (%)					
All women (N=450)							
Positive CMV DNA in amniotic fluid	20/136 (14.7)	37/134 (27.6)	0.45	(0.27−0.75)	0.39	(0.22−0.68)	.005
TOP	7/206 (3.4)	24/244 (9.8)	0.32	(0.15−0.67)	0.36	(0.17−0.75)	.021
Positive CMV DNA in the newborn's urine within 2 wk of life	42/185 (22.7)	54/213 (25.3)	0.86	(0.59−1.27)	0.85	(0.57−1.26)	.500
Prevalence of symptomatic cCMV infection at birth	3/185 (1.6)	19/213 (8.9)	0.16	(0.06−−0.48)	0.17	(0.06−0.49)	.006
TOP or newborn's urine positivity within 2 wk of life	51/206 (24.7)	84/244 (34.4)	0.63	(0.44−0.89)	0.62	(0.44−0.88)	.024
Women satisfying the criteria of the RCT by Shahar-Nissan et al,[9] 2020 (n=333)[a]							
Positive CMV DNA in amniotic fluid	13/98 (13.3)	35/132 (26.5)	0.42	(0.23−0.76)	0.48	(0.26−0.88)	.047
TOP	6/123 (4.9)	26/210 (12.4)	0.36	(0.17−0.78)	0.35	(0.16−0.78)	.030
Positive CMV DNA in the newborn's urine within 2 wk of life	25/107 (23.4)	36/181 (19.9)	1.23	(0.76−1.99)	0.86	(0.48−1.54)	.669
Prevalence of symptomatic cCMV infection at birth	2/107 (1.9)	17/181 (9.4)	0.18	(0.05−0.64)	0.17	(0.03−0.96)	.093
TOP or newborn's urine positivity within 2 wk of life	31/123 (25.2)	62/210 (29.5)	0.80	(0.53−1.23)	0.81	(0.52−1.24)	.410
Women satisfying the criteria of the RCT by Shahar-Nissan et al,[9] 2020 (periconceptional infection only) (n=88)[b]							
Positive CMV DNA in amniotic fluid	3/25 (12.0)	10/32 (31.2)	0.30	(0.09−0.99)	0.33	(0.09−1.23)	.164
TOP	3/30 (10.0)	8/58 (13.8)	0.69	(0.21−2.26)	0.74	(0.22−2.51)	.688
Positive CMV DNA in the newborn's urine within 2 wk of life	3/22 (13.6)	9/49 (18.4)	0.70	(0.21−2.30)	1.06	(0.23−4.92)	.947
Prevalence of symptomatic cCMV infection at birth	0/22 (0)	4/49 (8.2)	—	—	—	—	—
TOP or newborn's urine positivity within 2 wk of life	6/30 (20.0)	17/58 (29.3)	0.60	(0.25−1.46)	0.77	(0.30−1.93)	.638
Women satisfying the criteria of the RCT by Shahar-Nissan et al,[9] 2020 (first-trimester infection only) (n=245)[c]							
Positive CMV DNA in amniotic fluid	10/73 (13.7)	25/100 (25.0)	0.48	(0.24−0.94)	0.57	(0.28−1.15)	.191
TOP	3/93 (3.2)	18/152 (11.8)	0.25	(0.10−0.81)	0.25	(0.08−0.75)	.039
Positive CMV DNA in the newborn's urine within 2 wk of life	22/85 (25.9)	27/132 (20.5)	1.35	(0.79−2.33)	0.96	(0.48−1.95)	.934
Prevalence of symptomatic cCMV infection at birth	2/85 (2.3)	13/132 (9.9)	0.22	(0.06−0.79)	0.23	(0.04−1.35)	.172
TOP or newborn's urine positivity within 2 wk of life	25/93 (26.9)	45/152 (29.6)	0.87	(0.54−1.42)	0.84	(0.51−1.39)	.570

cCMV, congenital cytomegalovirus; *CI*, confidence interval; *CMV*, cytomegalovirus; *OR*, odds ratio; *RCT*, randomized controlled trial; *TOP*, termination of pregnancy; *VCV*, valacyclovir.

[a] Infection acquired periconceptionally or during the first trimester of pregnancy and treatment start within 16 weeks of gestation; [b] Infection acquired periconceptionally and treatment start within 16 weeks of gestation; [c] Infection acquired during the first trimester of pregnancy and treatment start within 16 weeks of gestation.[20]

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condition (causal OR, 0.39; 90% CI, 0.22−0.68; *P*=.005), suggesting that the treatment had a clear protective effect.

The rate of TOP was lower in the VCV group than in the no-VCV group with a crude OR equal to 0.32. After adjustment, the OR was slightly higher (causal OR, 0.36; 90% CI, 0.17−0.75; *P*=.021). Of note, most TOP cases were decided after a positive result of CMV DNA in amniotic fluid (5/7 [71.4%] in the VCV group and 18/24 [75.0%] in the no-VCV group), whereas the TOP cases among women with a CMV-negative amniocentesis were decided because of fetal abnormalities detected with ultrasound not related to CMV.

The rate of diagnosis of cCMV infection at birth (positive CMV DNA in urine within 2 weeks of life) was similar in the VCV and no-VCV groups. Interestingly, the rate of diagnosis of cCMV infection at birth after a negative

amniocentesis was higher in the VCV group than in the no-VCV group (16/103 [15.5%] and 6/89 [6.7%], respectively), explaining the increased rate of diagnosis of cCMV infection at birth compared with the diagnosis of cCMV infection by the time of amniocentesis.

We estimated an 83% reduction in the odds of newborn symptoms under maternal treatment (causal OR, 0.17; 90% CI, 0.06−0.49; *P*=.006). Only 3 of 42 newborns (7.1%) with cCMV in the VCV group were symptomatic at birth compared with 19 of 54 newborns (35.2%) with cCMV in the no-VCV group. The 3 symptomatic newborns with cCMV in the VCV group were among those with positive amniocentesis. Supplemental Table 3 reports details on the 22 symptomatic newborns with congenital infection. The treatment with valganciclovir was used in 23 of 54 newborns (42.6%) with cCMV infection in the no-VCV group and in 9 of 42 newborns (21.4%) with cCMV infection in the VCV group (OR, 2.72).

Overall, we found a protective effect of treatment on the occurrence of the composite event TOP or newborn's urine positivity within 2 weeks of life, with a causal OR equal to 0.62 (90% CI, 0.44−0.88; *P*=.024).

Restricting the analysis to pregnant women satisfying the inclusion criteria used in the randomized controlled trial by Shahar-Nissan et al[9] (namely, women with primary CMV infection acquired in the periconceptional period or up to 14 weeks of gestation and VCV treatment started within 16 weeks of gestation), the protective effect of VCV on transmission by the time of amniocentesis, TOP, and symptomatic cCMV infection at birth was confirmed (Table 3). Considering the periconceptional infection and first-trimester infection groups separately, the null hypothesis of no causal effect was not rejected, likely because of the small number of patients in the 2 subgroups (Table 3).

Additional analysis

Supplementary Table 4 reports the results of the subgroup analyses performed on the main transmission outcomes, positive CMV DNA in amniotic fluid and positive CMV DNA in urine within 2 weeks of life, by enrolment criterion and timing of maternal infection. No effect modification of the treatment was found by enrolment criterion. A stronger protective effect of the VCV on urine positivity was estimated among women who developed an infection during the second trimester of pregnancy (causal OR, 0.23; 90% CI, 0.09−0.62; effect modification test, *P*=.005).

Supplemental Tables 5 to 8 report the crude rate of transmission according to the enrolling center and maternal characteristics associated with the diagnosis of cCMV infection at amniocentesis or birth among women treated with VCV. The only difference observed was that women giving birth to newborns with cCMV infection were more likely to have had a diagnosis of primary CMV infection by seroconversion (57.1% vs 35.4%; OR, 2.43; 95% CI, 1.21−4.90; *P*=.0189). In addition, these women were more likely to be viremic by the time of the diagnosis of the primary CMV infection (76.2% vs 39.8%; OR, 4.85; 95% CI, 1.63−14.43; *P*=.0033). There was no difference in the rate of transmission as diagnosed by amniocentesis among women with an estimated delay higher or lower than 4 or 6 weeks between infection and the start of treatment.

Adverse events possibly related to valacyclovir treatment

Of 205 treated women, 19 (9.3%) reported an adverse reaction possibly related to VCV treatment (headache in 5 cases, gastrointestinal problems in 5 cases, renal toxicities in 4 cases, fatigue in 3 cases, and dizziness in 2 cases), classified as mild in 17 cases and moderate in 2 cases (renal toxicity in both cases). The 4 women (1.9%) with renal toxicity (3 women treated with 2 g 4 times a day and 1 treated with the 4 g 2 times a day) presented a slight increase of creatinine level (maximum creatinine level of 1.5 mg/dL in 1 patient), which was reversible after treatment suspension. In 2 women with an increase in creatinine level, the treatment was discontinued before the planned.

Discussion

Principal findings

We found that VCV treatment in pregnant women with primary CMV infection significantly reduces the rate of positive amniocentesis, TOP, and symptomatic cCMV infection at birth; however, VCV treatment did not lead to a reduction of cCMV prevalence at birth (Figure).

Results in the context of what is known

The reduction of cCMV transmission diagnosed by amniocentesis is lower than the results observed in the clinical trial by Shahar-Nissan et al[9] (61% vs 70%). The reasons for these results are not clear but could be related to several factors, such as that this study collected data from the clinical practice in a different regional setting where the CMV testing and referral system of women with primary infection are not well established. The median delay between infection and the start of treatment was high (7.9 weeks); moreover, a previous study has highlighted that the efficacy of treatment may be time related.[9] Here, the delay between the estimated date of infection and treatment initiation was quite variable among centers. It has been hypothesized that the sequence of events leading to fetal infection takes approximately 7 to 8 weeks.[9]

However, here, we did not observe a significantly different efficacy of VCV, considering the timing of maternal infection, the enrolment criteria, and the estimated treatment delay. Only women with infection acquired in the second trimester of pregnancy showed a significantly lower rate of newborns diagnosed with cCMV infection at birth than untreated controls. In our opinion, this result could be explained by some degree of inaccuracy in estimating the timing of maternal infection because of different laboratory tests performed in different centers and different timing of testing in the cohort of pregnant women because of the nonexistence of a national screening program ensuring a

standardized testing protocol during pregnancy.[22] Recently Amir et al[23] published the data of a revised protocol for the secondary prevention of cCMV infection with valaciclovir after an infection in early pregnancy. By limiting the initiation of treatment up to 9 weeks from the presumed time of infection, the protective effect of VCV was also seen in periconceptional infections in addition to infections acquired in the first trimester of pregnancy.[23]

In addition, our study highlights that VCV treatment is linked to a significant reduction of TOP (relative reduction of 64%) mainly for the reduction of the number of CMV DNA−positive amniocentesis. Moreover, even though the prevalence of cCMV infection at birth was similar in newborns born from treated and untreated women, we report a reduction in the prevalence of symptomatic cCMV infection at birth. Some asymptomatic newborns with cCMV infection received valganciclovir, even though neither the Italian nor the international guidelines recommend it. In these cases, newborn treatment was probably due to a mild disease with isolated or transient features at birth not fulfilling the ESPID criteria for cCMV symptomatic disease at birth. The lack of difference in the cCMV prevalence at birth was mainly due to the high number of infections diagnosed at birth after a negative amniocentesis in the VCV group. However, it should be noted that all the 16 newborns diagnosed with cCMV at birth after a negative amniocentesis were asymptomatic. In addition, the higher number of TOP after a CMV DNA−positive amniocentesis in the no-VCV group reduced the frequency of newborns with cCMV infection in this group. Moreover, it should be considered that the composite outcome (TOP or diagnosis of cCMV infection at birth) occurred significantly more frequently in the no-VCV group (34.4%) than in the VCV group (24.7%).

Among the 103 women with a negative amniocentesis for whom newborn data were available, the rate of diagnosis of cCMV infection at birth was 15.5% compared with 6.7% observed in untreated women of our cohort. In the clinical trial by Shahar-Nissan et al,[9] the authors reported a rate of diagnosis of cCMV infection at birth of 20%, and a rate of diagnosis of cCMV infection at birth in women with negative amniocentesis of 10%. In the observational study by De Santis et al,[22] the authors reported a rate of diagnosis of cCMV infection at birth of 42% after VCV treatment until amniocentesis and a rate of diagnosis of cCMV infection at birth in women with a negative amniocentesis of 30%. A previous study conducted in the absence of treatment with VCV showed that the risk of a diagnosis of cCMV infection after a negative amniocentesis was approximately 8%,[24] similar to the value observed in our study among untreated women. Egloff et al[12] in their series of pregnant women treated with VCV reported a somehow different result, as they described only 1 case of diagnosis of cCMV infection at birth after a negative amniocentesis in 44 women (2%). However, in that study, the duration of VCV treatment was unclear, and in some cases, the treatment could have been prolonged until delivery.

In conclusion, these observations suggest that the use of VCV could modify the disease course and delay transplacental infection after amniocentesis when VCV is discontinued. The increase in the rate of diagnosis of cCMV infection at birth after a negative amniocentesis could be related to a restart of viral replication after drug discontinuation by the time of amniocentesis as observed in other types of patients with CMV.[25,26] A recent case report raises the question about a possible delay of adaptive maternal immune response induced by VCV treatment during primary CMV infection,[27] which could further contribute to explain the unexpectedly high rate of diagnosis of cCMV infection at birth after a negative amniocentesis. The clinical relevance of the diagnosis of cCMV infection after a negative amniocentesis is probably minimal or null as argued in the conclusions of a recent systematic review and meta-analysis.[28] However, these data came from studies conducted in women not treated with VCV; thus, in our opinion, a long-term follow-up in these newborns is in any case warranted.

Our rate of symptomatic cCMV at birth in newborns born from untreated women (35.2%) seems higher than what is generally reported (<15%).[1,29,30] However, the classification of symptomatic cCMV is notoriously challenging,[31] and different findings are available in the literature. Other studies have reported that symptomatic cCMV infection at birth was encountered in 29% to 37% of newborns with cCMV infection.[32−34]

Concerning the occurrence of VCV adverse events, they were observed in 9.3% of cases and were mild in most cases. Mild reversible renal toxicity was observed in 1.9% of patients (with both the 4 times a day and 2 times a day regimens). Overall, the risk of renal toxicity was similar to those found in a recent systematic review (1.7%).[13]

Clinical implications

Our study confirms that VCV is an effective treatment option for primary CMV infection acquired in early pregnancy being able to reduce the rate of vertical transmission by the time of amniocentesis, TOP, and symptomatic cCMV infection at birth with minimal side effects.

Research implications

It is probably time to reevaluate the opportunity for introducing a universal serologic screening for CMV during pregnancy in Italy given the availability of VCV at country level. In addition, there is a need to update the Italian multisociety consensus document for the management of CMV in pregnancy with the introduction of VCV as a treatment option in the prevention of cCMV infection.

The institution of a formal screening program will probably enhance the efficacy of VCV, leading to earlier detection of primary infection in pregnancy than the current situation.

Several models are now illustrating the possible cost-effectiveness of VCV treatment during pregnancy, leading to different results according to the

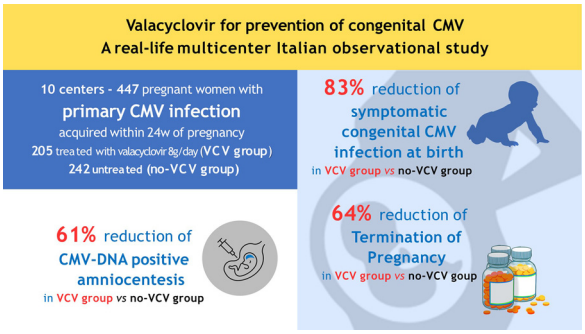
assumptions made and the context where they are applied.[35–39] An economic evaluation of cCMV burden vs screening and prevention costs will help the policymakers and political decision-makers about the introduction of a universal serologic screening at country level.

Finally, it should be remembered that interesting data are emerging in favor of CMV hyperimmune immunoglobulins at a high dose (200 UI/kg biweekly) as a treatment strategy for the secondary prevention of cCMV infection during pregnancy; however, this strategy is far more costly than VCV, and there are no data from randomized clinical trials for this intervention.[40,41] In the next years, we will probably have the opportunity to see additional data on other pharmacologic treatment for the treatment of CMV infection in pregnancy. Currently, an RCT on the use of letermovir, a CVM-specific antiviral drug, for prenatal treatment of confirmed fetal infection is ongoing.[42]

Strengths and limitations

The main strengths of the study are the multicenter design and the large sample size of pregnant women with primary CMV infection treated with VCV in the context of the national introduction of publicly funded therapy for the secondary prevention of cCMV. The study has several limitations mainly linked to its retrospective design, which leads to the lack of complete data concerning details about laboratory tests and obstetrical ultrasound findings. Moreover, the cases and controls were not matched, and the laboratory procedures were not centralized or standardized, leading, probably, to some degree of inaccuracy in the dating of the primary CMV infection, especially with the historical control group. Different laboratory tests are used in different centers, and different timing of testing in the whole cohort of pregnant women occurred because of the nonexistence of a national screening program ensuring a standardized testing protocol during pregnancy.

FIGURE
Graphical abstract



The use of valacyclovir in pregnant women with primary CMV infection significantly reduces the rate of positive amniocentesis, termination of pregnancy, and symptomatic cCMV infection at birth.

cCMV, congenital cytomegalovirus; *CMV*, cytomegalovirus; *VCV*, valacyclovir.

Zammarchi. Valacyclovir for cytomegalovirus in pregnancy. Am J Obstet Gynecol MFM 2023.

Conclusions

Our study corroborates available data concerning the efficacy of VCV in reducing the diagnosis of cCMV infection by the time of amniocentesis even though the observed reduction in our study is lower than that of some previous studies. Moreover, our study indicates that treatment with VCV may reduce the frequency of TOP and symptomatic cCMV at birth (Figure). Lastly, our results have been obtained through a collaborative multicenter national study involving different realities from the geographic areas of all countries (North Italy, Central Italy, and South Italy). ■

Supplemental materials

Supplemental material associated with this article can be found in the online version at doi:10.1016/j.ajogmf.2023.101101.

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Author and article information

From the Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy (Dr Zammarchi and Dr Modi); Infectious and Tropical Disease Unit, Careggi University Hospital, Florence, Italy (Dr Zammarchi and Dr Trotta); Tuscany Regional Referral Center for Infectious Diseases in Pregnancy, Florence, Italy (Dr Zammarchi and Dr Trotta); Department of Infectious and Tropical Diseases, Azienda Socio-Sanitaria Territoriale (ASST) Spedali Civili, University of Brescia, Brescia, Italy (Dr Tomasoni, Dr Lovatti, and Dr Sforza); National Institute for Infectious Diseases Lazzaro Spallanzani, IRCCS, Rome, Italy (Dr Liuzzi, Dr Abbate, Dr Bordi, and Dr Mazzotta); Obstetric Unit, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy (Dr Simonazzi, Dr Dionisi, and Dr Seidenari); Department of Medical and Surgical Sciences, Alma Mater Studiorum - University of Bologna, Bologna,

Italy (Dr Simonazzi, Dr Dionisi, Dr Seidenari, and Dr Lazzarotto); Department of Public Health, University of Naples Federico II, Naples, Italy (Dr Mazzarelli and Dr Maruotti); Department of Obstetrics, Fondazione IRCCS San Gerardo dei Tintori, Monza, Italy (Dr Ornaghi); University of Milano-Bicocca School of Medicine and Surgery, Monza, Italy (Dr Ornaghi); Infectious and Tropical Diseases Unit, Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy (Dr Castelli); Infectious and Tropical Diseases Unit, Department of Medical and Surgical Sciences, Magna Graecia University, Catanzaro, Italy (Dr Fusco and Dr Torti); Infectious Disease Unit, Bambino Gesù Children's Hospital, Rome, Italy (Dr Calò Carducci); Department of Statistics, Computer Science, Applications "G. Parenti," University of Florence, Florence, Italy (Dr Baccini); Infectious Diseases Unit, Meyer Children's Hospital IRCCS, Florence, Italy (Dr Galli); Department of Health Sciences, University of Florence, Florence, Italy (Dr Galli); Microbiology and Virology Unit, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy (Dr Lilleri, Dr Furione, and Dr Zavattoni); Infectious Diseases Unit, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy (Dr Ricciardi); Department of Obstetrics and Gynecology, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy (Dr Arossa); Department of Precision and Regenerative Medicine and Ionian Area, University of Bari Aldo Moro, Bari, Italy (Dr Vimercati); Division of Neonatology, Department of Translational Medical Sciences, University of Naples Federico II, Naples, Italy (Dr Salomè and Dr Raimondi, and Dr Sarno); Division of Obstetrics and Gynecology, Department of Clinical and Experimental Sciences, ASST Spedali Civili, University of Brescia, Brescia, Italy (Dr Fichera); Fetal and Perinatal Medicine and Surgery Unit, Bambino Gesù Children's Hospital, Rome, Italy (Dr Caforio); Microbiology Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy (Dr Lazzarotto).

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M.T. and T.L. contributed equally to this work. Michela Baccini performed the statistical analysis.

The members of the MEGAL-ITALI (Studio osservazionale sull'infezione da citomegalovirus in Italia - MEGAL-ITALI) Working Group are as follows: L.Z. (Florence, Italy), L.R.T. (Brescia, Italy), G.L. (Rome, Italy), G.S. (Bologna, Italy), L.L. M. (Naples, Italy), A.S. (Bologna, Italy), G.M.M. (Naples, Italy), S.O. (Monza, Italy), F.C. (Brescia, Italy), C.T. (Catanzaro, Italy), P.F. (Catanzaro, Italy), Helen Linda Morrone (Catanzaro, Italy), Maria Teresa Tassone (Catanzaro, Italy), Chiara Costa (Catanzaro, Italy), F.I.C.C. (Rome, Italy), Stefania Bernardi (Rome, Italy), M.B. (Florence, Italy), G.M. (Florence, Italy), L.G. (Florence, Italy), Carlotta Montagnani (Florence, Italy), Elisabetta Venturini (Florence, Italy), Leila Bianchi (Florence, Italy), Martina Di Nunzio (Pavia, Italy), Gabriela Cassinelli (Pavia, Italy), D.L. (Pavia, Italy), Adriana Valcamonico (Brescia, Italy), A.F. (Brescia, Italy), Vania Spinoni (Brescia, Italy), M.T. (Florence, Italy), A.V. (Bari, Italy), T.L. (Bologna, Italy), Beatrice Borchi (Florence, Italy), Irene Campolmi (Florence, Italy), Alessandro Bartoloni (Florence, Italy), Lucia Pasquini (Florence, Italy), Mariarosaria Di Tommaso (Florence, Italy), Federica Fernicola (Monza, Italy), Francesca Arienti (Monza, Italy), Anna Locatelli (Monza, Italy), Maria Teresa Sinelli (Monza, Italy), L.C. (Rome, Italy), S.S. (Naples, Italy), L.S. (Naples, Italy), F.R. (Naples, Italy), Caterina Fulgione (Naples, Italy), Luigi Carbone (Naples, Italy), Giuliana Orlandi (Naples, Italy), Nunzia Carlea (Naples, Italy), Gabriele Saccone (Naples, Italy), Marcello Tavio (Ancona, Italy), Massimo Andreoni (Rome, Italy), Pierangelo Clerici (Legnano, Italy) and Luca Antonio Ramenghi (Genova, Italy).

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Corresponding author: Lorenzo Zammarchi, MD. lorenzo.zammarchi@unifi.it