Published in final edited form as:

Int J Gynaecol Obstet. 2024 October ; 167(1): 468–470. doi:10.1002/ijgo.15603.

Is valacyclovir being used for cytomegalovirus infection during pregnancy?

Oscar Rincón-Guevara[1], **Jessica Leung**[2], **David E. Sugerman**[2], **Tatiana M. Lanzieri**[2]

[1]Office of Public Health Data, Surveillance, and Technology, Division of Health Informatics and Surveillance, Centers for Disease Control and Prevention, Atlanta, Georgia, USA

[2]Division of Viral Diseases, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia, USA

Keywords

antiviral; CMV; cytomegalovirus; pregnancy; USA; valacyclovir

Congenital cytomegalovirus (cCMV) is a leading cause of sensorineural hearing loss and developmental disabilities in US children.[1] In the USA, neither prenatal screening nor antiviral treatment for cytomegalovirus (CMV) infection during pregnancy are currently recommended.[2] Several studies have found a lower rate of vertical transmission after primary CMV infection in the first trimester of pregnancy with high dose valacyclovir treatment (8 g daily), including a clinical trial conducted in Israel that was published in 2020.[3–5] Valacyclovir is administered in a lower dose regimen (1–2 g daily) to treat or prevent recurrency of herpes simplex virus (HSV) infections during pregnancy. Using electronic health record data, our main objective was to assess if high dose valacyclovir had been dispensed to pregnancies with a CMV diagnosis in the USA.

We used HealthVerity, Inc. 2022 Quarter 4, Maternal Outcomes Masterset data, which contained data on 3 712 592 pregnancies with a documented live birth during 2018–2022 (Data S1; Table S1). We limited the study to pregnancies with a live birth in order to be able to link the pregnancies to the infants. We identified pregnancies with a CMV infection based on a combination of CMV diagnostic codes (B25.xx) and laboratory test results (positive polymerase chain reaction, culture or IgM, IgG seroconversion or low IgG avidity) (Data S1; Table S1). We also used diagnostic codes from the medical claims to identify immunocompromising conditions, HSV, and varicella zoster virus infections that

Correspondence: Jessica Leung, Centers for Disease Control and Prevention, 1600 Clifton Rd NE, MS H24-5, Atlanta, GA 30333, USA. jleung@cdc.gov.

AUTHOR CONTRIBUTIONS

Oscar Rincón-Guevara was involved with conducting the data analysis. All authors (Oscar Rincón-Guevara, Jessica Leung, David E. Sugerman, and Tatiana M. Lanzieri) were involved with designing and planning the study as well as drafting and reviewing the manuscript.

CONFLICT OF INTEREST STATEMENT

The authors report no conflict of interest.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

could explain the use of antivirals. We identified valacyclovir, acyclovir, or famciclovir, using dispensed pharmacy claims (Data S1; Table S1). We also identified cCMV infection (P35.1) or CMV disease (B25.xx) within 45 days of birth to identify cCMV[1] among linked live births. The project was reviewed by the Institutional Review Board and was determined to be exempted.

We identified 1884 (0.05%) pregnancies with CMV infection of which 1023 (54%) had diagnostic codes only, 654 (35%) had positive laboratory tests only, and 207 (11%) had both. The first CMV diagnosis was at median 25 weeks gestational age. Immunocompromising conditions and other herpes virus infections (all had HSV) were more common in pregnant people with CMV infection (114 [6%] and 261[14%], respectively) than those without (22 311 [1%] and 207 009 [6%]) (Table 1).

Antiviral treatment, most commonly valacyclovir, was dispensed for 182 012 (5%) pregnancies without a CMV diagnosis and 185 (10%) pregnancies with a CMV diagnosis. In the latter group, 13 (7%) had a diagnosis of immunocompromising condition, and 114 (62%) had a diagnosis of other herpes virus infections (Table 1). Valacyclovir was first dispensed at a median of 34 weeks gestational age (146 [79%] in the third trimester), and at a median daily dose of 1000 mg for 30 days. There were 17 (9%) pregnancies with a daily dose of ≥8 g dispensed; all had CMV during pregnancy, seven (41%) in 2020 and 10 (59%) in 2021, though most received treatment during the second or third trimester and one (6%) was immunocompromised.

Among 558 (30%) pregnancies with a CMV diagnosis that were linked to live births, 71 (13%) of the infants had a diagnosis of cCMV. For the 71 infants, 10 (14%) of their mothers had documented antiviral treatment during pregnancy. Among 1 121 663 (30%) pregnancies without a CMV diagnosis that were linked to live births, 104 (0.01%) of the infants had a diagnosis of cCMV. For these 104 infants, 50 (48%) of their mothers had documented antiviral treatment during pregnancy. There was no difference in the median gestational age at initial treatment (both 34 weeks) or median daily dose (both 1000 mg) comparing pregnancies with and without CMV infection.

In this study, we found the characteristics of dispensed valacyclovir treatment (i.e., dosage, duration, and timing) and high proportion with HSV diagnosis suggested use for treatment or suppression of recurrent genital herpes in most cases with or without a CMV diagnosis recorded during pregnancy. Most pregnant people did not receive high dose valacyclovir. Although a few pregnant people had recorded high dose valacyclovir being dispensed during 2020–2021, most were after the first trimester of pregnancy. We only assessed pregnancies with live birth outcomes and diagnostic codes or treatment may have been missed or incorrect. We were also unable to examine potential side effects of treatment. These data are potentially useful in the future for monitoring trends in laboratory testing, diagnoses, and treatment for CMV infection during pregnancy. Reviewing the evidence on efficacy and safety of high dose valacyclovir treatment given early in pregnancy to prevent vertical transmission of CMV will be helpful to inform future guidance on prenatal CMV screening and treatment in the USA.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

We would like to acknowledge CDC Epidemiologist Lara Bull, PhD, for her valuable guidance and detailed technical review.

FUNDING INFORMATION

No financial support was received for this work.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study were obtained from a third party vendor. Restrictions apply to the availability of these data, which were used under license for this study that do not allow sharing of this data.

REFERENCES

1. Leung J, Grosse SD, Hong K, Pesch MH, Lanzieri TM. Changes in valganciclovir use among infants with congenital CMV diagnosis in the United States, 2009–2015 and 2016–2019. J Pediatr. 2022;246:274–278. [PubMed: 35358586]
2. American College of Obstetricians and Gynecologists. Practice bulletin no. 151: cytomegalovirus, parvovirus B19, varicella zoster, and toxoplasmosis in pregnancy. Obstet Gynecol. 2015;125:1510–1525. [PubMed: 26000539]
3. Chatzakis C, Shahar-Nissan K, Faure-Bardon V, et al. The effect of valacyclovir on secondary prevention of congenital cytomegalovirus infection, following primary maternal infection acquired periconceptionally or in the first trimester of pregnancy. An individual patient data meta-analysis. Am J Obstet Gynecol. 2024;230(2):109–117.e2. [PubMed: 37473793]
4. Shahar-Nissan K, Pardo J, Peled O, et al. Valaciclovir to prevent vertical transmission of cytomegalovirus after maternal primary infection during pregnancy: a randomised, double-blind, placebo-controlled trial. Lancet. 2020;396(10253):779–785. [PubMed: 32919517]
5. Zammarchi L, Lazzarotto T, Di Tommaso M, et al. Valacyclovir for prevention and treatment of fetal CMV infection: inclusion in the law 648/96 list and launch of the Italian multicentre observational prospective study “MEGAL-ITALI”. Infez Med. 2021;29(2):299–303. [PubMed: 34061801]

TABLE 1

Selected characteristics of pregnancies with a live birth by CMV diagnosis.

	No. (%) of pregnancies		
		With CMV diagnosis[a]	
	Without CMV diagnosis[a]	All	With dispensed antiviral prescription
Characteristics	***n* (%)**	***n* (%)**	***n* (%)**
Overall[b]	3 710 708 (99.95)	1884 (0.05)	185 (9.82)
Period[c]			
2018–2020	2 782 495 (75)	1219 (77)	112 (9)
2021–2022	928 213 (25)	665 (23)	73 (11)
Medical history			
Immunocompromising condition[d]	22 311 (1)	114 (6)	13 (7)
Other herpes virus infection			
HSV	207 009 (6)	261 (14)	113 (61)
VZV	2240 (0)	4 (0)	0 (0)
HSV and VZV	403 (0)	8 (0)	1 (1)
None documented	3 503 296 (94)	1615 (86)	71 (38)
Antiviral treatment	182 012 (5)	–	185 (10)
Valacyclovir[e]	130 291 (72)	–	126 (68)
Acyclovir	42 758 (23)	–	32 (17)
Acyclovir and valacyclovir	8454 (5)	–	15 (8)
Other	509 (0)		12 (6)
Gestational age when treatment first dispensed			
Median (q1, q3)	34 (20, 36)	–	34 (29, 36)
First trimester (0–13 weeks)	28 650 (16)	–	4 (2)
Second trimester (14–27 weeks)	33 341 (18)	–	35 (19)
Third trimester (28–end)	120 021 (66)	–	146 (79)
Pregnancies linked to live births	1 121 663	558	–
Infants with a diagnosis of congenital CMV	104[f] (0.01)	71 (13)	10 (14)

Abbreviations: CMV, cytomegalovirus; HSV, herpes simplex virus; VZV, varicella zoster virus.

[a] Among 1884 pregnancies identified with CMV infection, 1023 (54%) had a diagnostic code for CMV disease (B25.xx) and 861 (46%) had a positive CMV test (197 by polymerase chain reaction, 3 culture, 668 IgM, and 24 IgG seroconversion).

[b] Percentages for the row with overall data reflect ROW percentages. The percentages calculated for pregnancies without and with a CMV diagnosis were among all 3 712 592 pregnancies. The percentage among those with a CMV diagnosis with dispensed antiviral prescription were calculated among the 1884 with a CMV diagnosis.

[c] We examined the data before and after 2020, the year when the clinical trial that examined valaciclovir for prevention of vertical transmission of CMV after maternal primary infection during pregnancy was published.

[d] Before or during pregnancy episode.

[e] Valacyclovir was administered at median daily dose of 1000 mg for 30 days; 17 pregnancies with daily dose ≥8 g.

[f] Among whom 50 (48%) had prenatal antiviral treatment.