SITA

11° CONGRESSO NAZIONALE

FIRENZE | 3 dicembre 2021

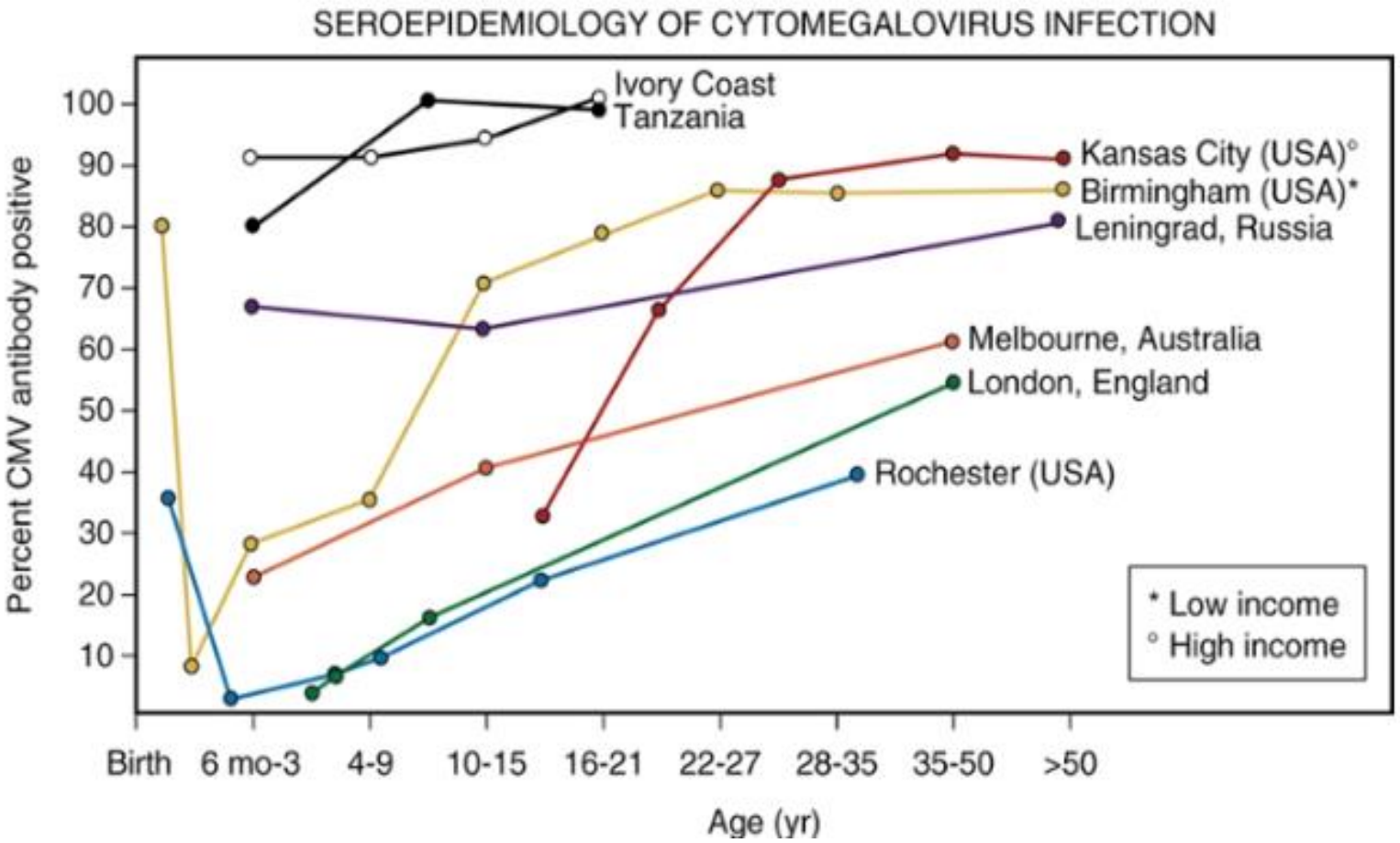
Problematiche di terapia delle infezioni in gravidanza

Michele Trotta

Cytomegalovirus

Per essere trattato deve essere diagnosticato

Epidemiologia



Italy 2019

Reviews in Medical Virology

REVIEW

Estimation of the worldwide seroprevalence of cytomegalovirus: A systematic review and meta-analysis

Mohamed Zuhair, G. Suzanne A. Smit, Gabriel Wallis, Faiz Jabbar, Colette Smith, Brecht Devleesschauwer, Paul Griffiths

First published: 31 January 2019 | https://doi.org/10.1002/rmv.2034 | Citations: 158

The copyright line for this article was changed on 01 March 2019 after original online publication.

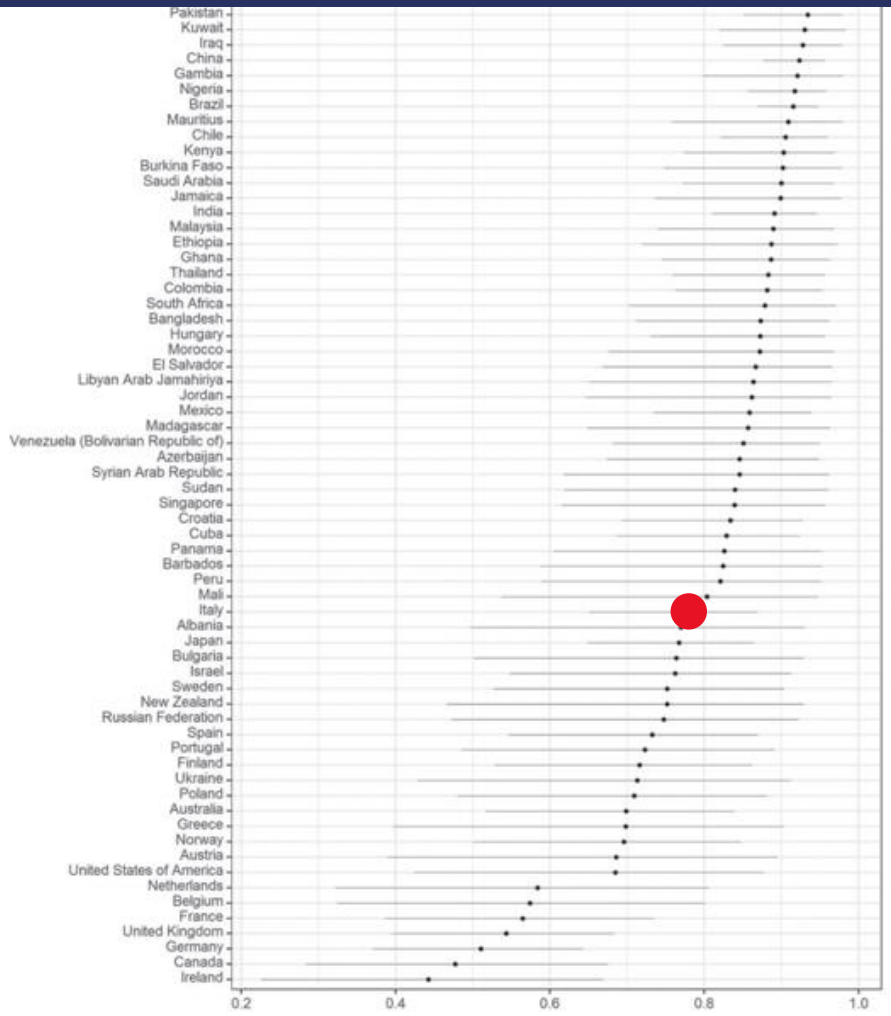


FIGURE 2 Meta-regression–based estimates of country specific mean seroprevalence and 95% uncertainty interval in women of reproductive age

Original Investigation | Infectious Diseases

August 23, 2021

Congenital Cytomegalovirus Infection Burden and Epidemiologic Risk Factors in Countries With Universal Screening

A Systematic Review and Meta-analysis

Paddy Ssentongo, MD, PhD, MPH[1,2,3]; Christine Hehnly, BS[4]; Patricia Birungi[5]; et al

» Author Affiliations | Article Information

JAMA Netw Open. 2021;4(8):e2120736. doi:10.1001/jamanetworkopen.2021.20736

Metanalisi

77 ARTICOLI comprendenti 515 646 bambini

La prevalenza complessiva stimata di cCMV è stata dello 0,67% (IC 95%, 0,54%-0,83%).

La prevalenza alla nascita di cCMV era 3 volte maggiore nei LMIC (1,42%; 95% CI, 0,97%-2,08%; n = 23 studi) rispetto agli HIC (0,48%; 95% CI, 0,40%-0,59%, n = 54 studi).

Rischio acquisizione infezione primaria CMV in gravidanza

1 – 2 % in donne senza contatti con figli

4- 5% in donne con figli o maestre d’asilo, etc

CMV epidemiologia (CDC)

- 70% delle gravide sono protette
- 30% delle gestanti sono suscettibili
- 1 neonato ogni 150 è infettato
- 1 neonato ogni 750/800 sviluppa o svilupperà malattia (1/5) degli infettati

22.883 gravidanze in Toscana

153 neonati infettati (30 malattia)

404.104 gravidanze in Italia

2707 neonati infettati (541 malattia)

Casi di cCMV regionali e nazionali calcolati

2020

Epidemiologia fenilchetonuria

CMV

30 toscana
541 italia

Toscana nati 22.883

Italia 404.104

PKU Italia 1/12.000 nati

Toscana 2 PKU/anno

Italia 33 PKU/anno

Epidemiologia fibrosi cistica

CMV

30 toscana
541 italia

Toscana nati 22.883

Italia 404.104

Fibrosi cistica 1/2600 neonati

Toscana 10 FC /anno

Italia 155 FC /anno

Perché non vi è lo screening?

Motivazioni per cui non è previsto il test

- No terapia (come per la Rosolia)
- Diagnosi Prenatale: limiti predittivi
- Aborti inutili
- Sierologia materna con parecchio grigio

Prevenzione

Does hygiene counseling have an impact on the rate of CMV primary infection during pregnancy? Results of a 3-year prospective study in a French hospital

Christelle Vauloup-Fellous[a,b,*,1], Olivier Picone[c,d,1], Anne-Gaëlle Cordier[c], Isabelle Parent-du-Châtelet[e], Marie-Victoire Senat[c,f], René Frydman[c,d], Liliane Grangeot-Keros[a,b]

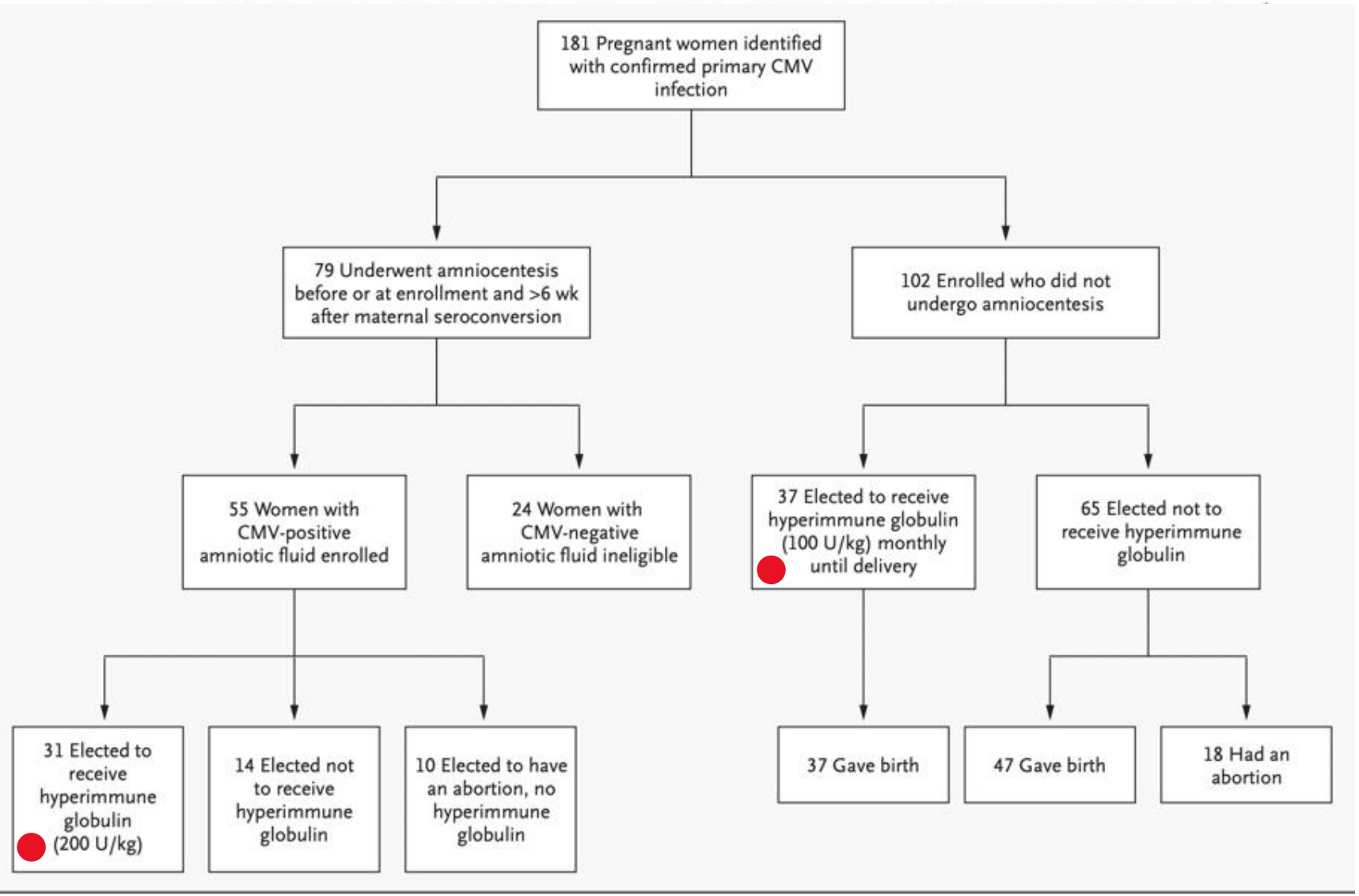
[a] INSERM U764, Université Paris-Sud, Clamart, F-92140, France
[b] AP-HP, Service de Microbiologie-Immunologie Biologique, Hôpital Antoine Béclère, Clamart, F-92140, France
[c] AP-HP, Service de Gynécologie-Obstétrique, Hôpital Antoine Béclère, Clamart, F-92140, France
[d] Université Paris-Sud, UMR-S0782, Clamart, F-92140, France
[e] Institut National de Veille Sanitaire, St. Maurice, F-94415, France
[f] Service d'Epidémiologie, Démographie et Sciences Sociales, INSERM U822, Le Kremlin-Bicêtre, F-94276, France

The rate of seroconversion following counseling was very low (0.19%) compared with the rate in previously published series (0.9–1.4%) in which CMV seroprevalence was similar to ours (51.5–53.9%) between 12 and 36 WG

terapia

ORIGINAL ARTICLE

Passive Immunization during Pregnancy for Congenital Cytomegalovirus Infection



Gruppo terapia

31 donne HIG

1 neonato (3%) sintomatico

4 donne no HIG

7 neonati (50%) sintomatici

Prevenzione

37 donne HIG

6 neonati infettati(16%)

47 donne no HIG

19 neonati infettati (40%)

The NEW ENGLAND JOURNAL of MEDICINE

Current Issue: April 3, 2014

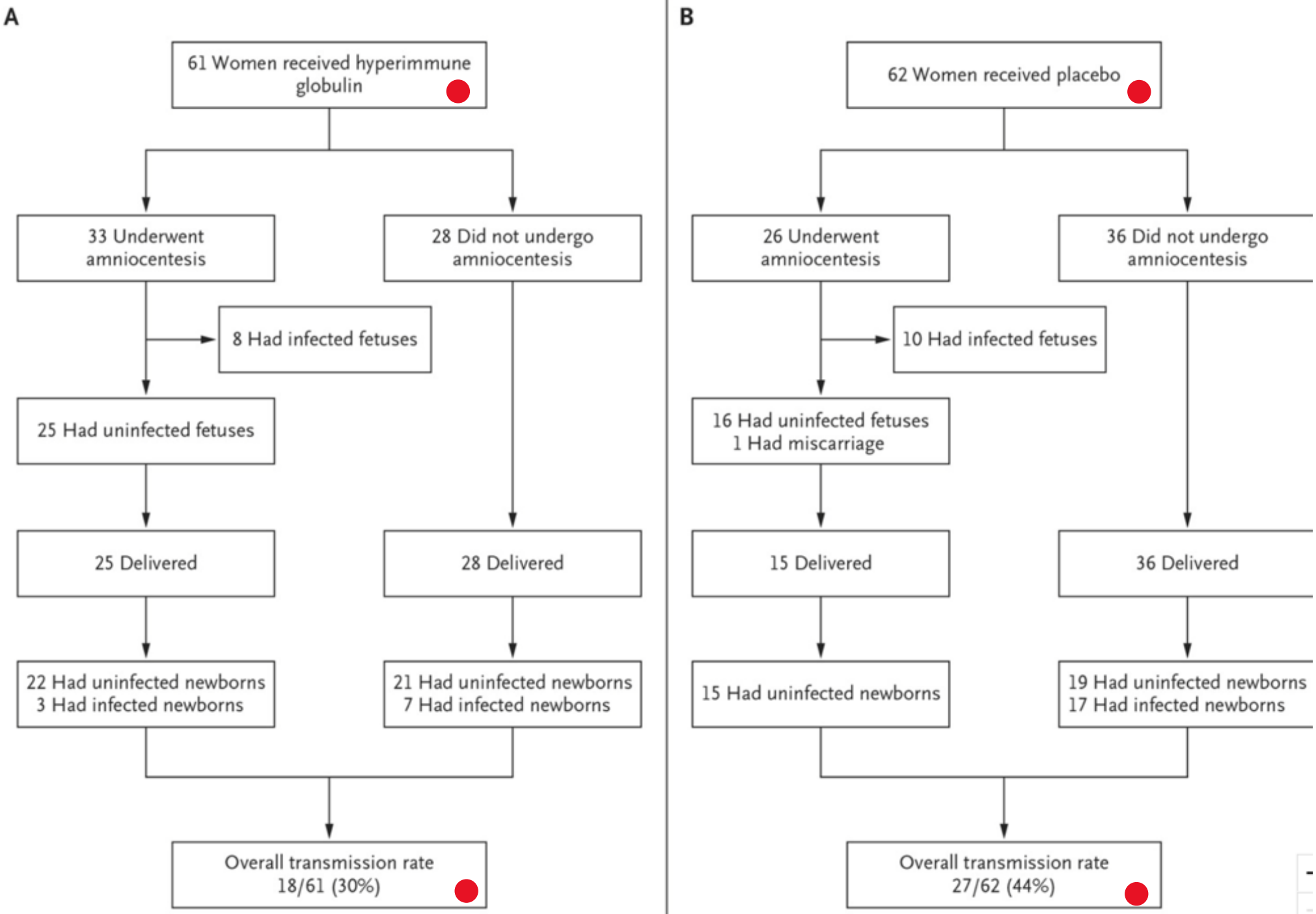
ORIGINAL ARTICLE

A Randomized Trial of Hyperimmune Globulin to Prevent Congenital Cytomegalovirus

Maria Grazia Revello, M.D., Tiziana Lazzarotto, Ph.D., Brunella Guerra, M.D., Arsenio Spinillo, M.D., Enrico Ferrazzi, M.D., Alessandra Kustermann, M.D., Secondo Guaschino, M.D., Patrizia Vergani, M.D., Tullia Todros, M.D., Tiziana Frusca, M.D., Alessia Arossa, M.D., Milena Furione, M.D., Vanina Rognoni, M.D., Nicola Rizzo, M.D., Liliana Gabrielli, M.D., Catherine Klersy, M.D., and Giuseppe Gerna, M.D., for the CHIP Study Group*

CONCLUSIONS

In this study involving 123 women who could be evaluated, treatment with hyperimmune globulin did not significantly modify the course of primary CMV infection during pregnancy. (Funded by Agenzia Italiana del Farmaco; CHIP ClinicalTrials.gov number, NCT00881517; EudraCT no. 2008-006560-11.)


A
61 Women received hyperimmune globulin
33 Underwent amniocentesis
28 Did not undergo amniocentesis
8 Had infected fetuses
25 Had uninfected fetuses
25 Delivered
28 Delivered
22 Had uninfected newborns
3 Had infected newborns
21 Had uninfected newborns
7 Had infected newborns
Overall transmission rate
18/61 (30%)
B
62 Women received placebo
26 Underwent amniocentesis
36 Did not undergo amniocentesis
10 Had infected fetuses
16 Had uninfected fetuses
1 Had miscarriage
15 Delivered
36 Delivered
15 Had uninfected newborns
19 Had uninfected newborns
17 Had infected newborns
Overall transmission rate
27/62 (44%)

THE LANCET
Infectious Diseases
Volume 17, Issue 6, June 2017, Pages e177-e188

Review

Congenital cytomegalovirus infection in pregnancy and the neonate: consensus recommendations for prevention, diagnosis, and therapy

2017

Therapy

- Cytomegalovirus hyperimmunoglobulin treatment should not be routinely administered for fetal cytomegalovirus infection.
- Routine antiviral therapy to treat fetal cytomegalovirus infection during pregnancy is not recommended.
- Valganciclovir treatment for 6 months is only recommended for congenitally infected neonates with moderately to severely symptomatic disease.
- Antiviral therapy should not be administered to neonates with asymptomatic congenital cytomegalovirus infections.
- Antiviral therapy is not routinely recommended for asymptomatic congenital cytomegalovirus infection with isolated sensorineural hearing loss, or for neonates with mildly symptomatic congenital cytomegalovirus infection.

40 DONNE

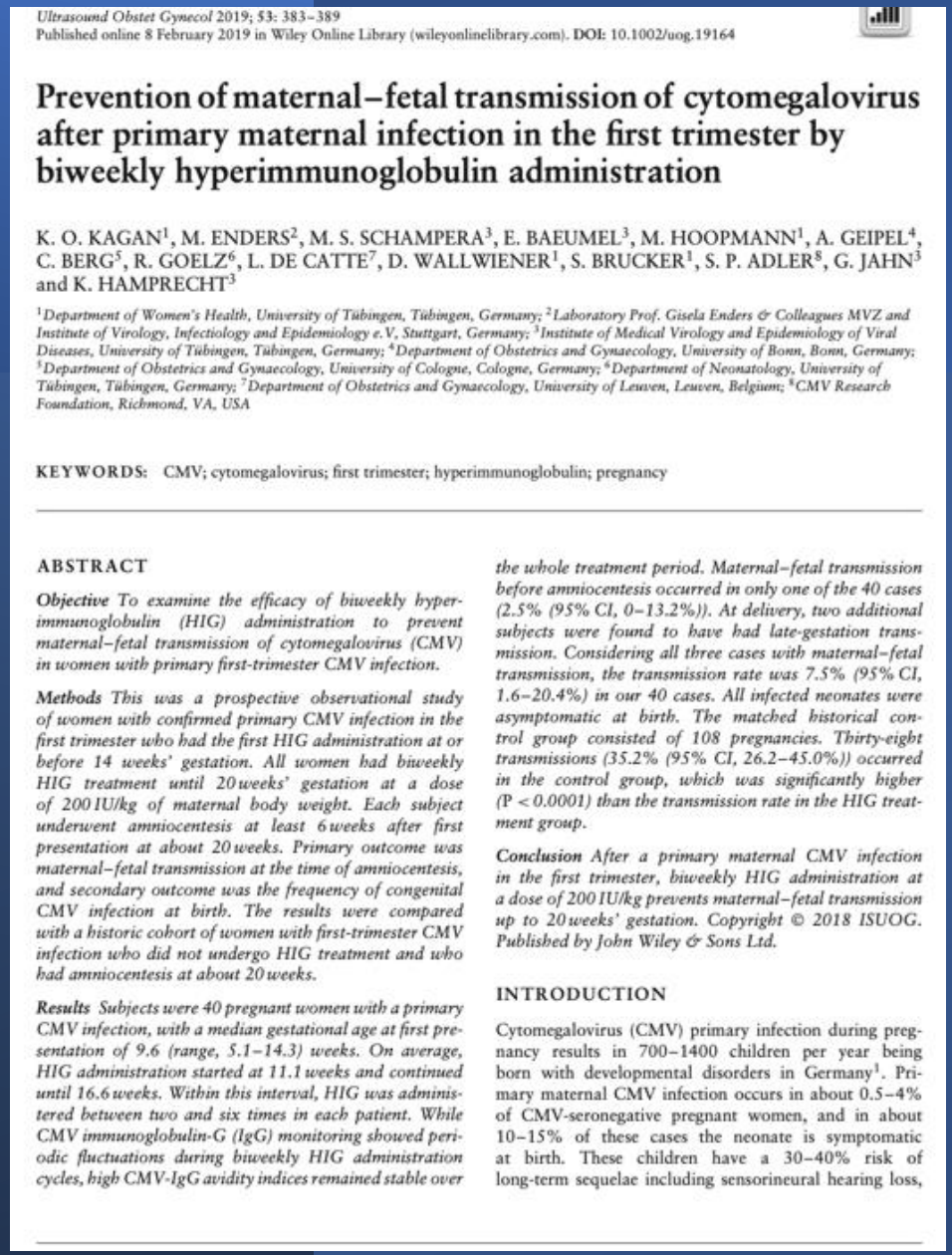
INFEZIONE CONTRATTA NEL I TRIMESTRE

200 UI/KG OGNI 2 WK FINO A 20 WK

MEDIA PRESENTAZIONE 9,6 WK

TRATTAMENTO A PARTIRE DA 11 FINO 16 WK (DA 2 --> 6 SOMMINISTRAZIONI)

AMNIOCENTESI ATTORNO A 20 WK



Ultrasound Obstet Gynecol 2019; 53: 383–389
Published online 8 February 2019 in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.19164

Prevention of maternal–fetal transmission of cytomegalovirus after primary maternal infection in the first trimester by biweekly hyperimmunoglobulin administration

K. O. KAGAN[1], M. ENDERS[2], M. S. SCHAMPERA[3], E. BAEUMEL[3], M. HOOPMANN[1], A. GEIPEL[4], C. BERG[5], R. GOELZ[6], L. DE CATTE[7], D. WALLWIENER[1], S. BRUCKER[1], S. P. ADLER[8], G. JAHN[3] and K. HAMPRECHT[3]

[1]*Department of Women's Health, University of Tübingen, Tübingen, Germany;* [2]*Laboratory Prof. Gisela Enders & Colleagues MVZ and Institute of Virology, Infectiology and Epidemiology e.V, Stuttgart, Germany;* [3]*Institute of Medical Virology and Epidemiology of Viral Diseases, University of Tübingen, Tübingen, Germany;* [4]*Department of Obstetrics and Gynaecology, University of Bonn, Bonn, Germany;* [5]*Department of Obstetrics and Gynaecology, University of Cologne, Cologne, Germany;* [6]*Department of Neonatology, University of Tübingen, Tübingen, Germany;* [7]*Department of Obstetrics and Gynaecology, University of Leuven, Leuven, Belgium;* [8]*CMV Research Foundation, Richmond, VA, USA*

KEYWORDS: CMV; cytomegalovirus; first trimester; hyperimmunoglobulin; pregnancy

ABSTRACT

Objective *To examine the efficacy of biweekly hyperimmunoglobulin (HIG) administration to prevent maternal–fetal transmission of cytomegalovirus (CMV) in women with primary first-trimester CMV infection.*

Methods *This was a prospective observational study of women with confirmed primary CMV infection in the first trimester who had the first HIG administration at or before 14 weeks' gestation. All women had biweekly HIG treatment until 20 weeks' gestation at a dose of 200 IU/kg of maternal body weight. Each subject underwent amniocentesis at least 6 weeks after first presentation at about 20 weeks. Primary outcome was maternal–fetal transmission at the time of amniocentesis, and secondary outcome was the frequency of congenital CMV infection at birth. The results were compared with a historic cohort of women with first-trimester CMV infection who did not undergo HIG treatment and who had amniocentesis at about 20 weeks.*

Results *Subjects were 40 pregnant women with a primary CMV infection, with a median gestational age at first presentation of 9.6 (range, 5.1–14.3) weeks. On average, HIG administration started at 11.1 weeks and continued until 16.6 weeks. Within this interval, HIG was administered between two and six times in each patient. While CMV immunoglobulin-G (IgG) monitoring showed periodic fluctuations during biweekly HIG administration cycles, high CMV-IgG avidity indices remained stable over the whole treatment period. Maternal–fetal transmission before amniocentesis occurred in only one of the 40 cases (2.5% (95% CI, 0–13.2%)). At delivery, two additional subjects were found to have had late-gestation transmission. Considering all three cases with maternal–fetal transmission, the transmission rate was 7.5% (95% CI, 1.6–20.4%) in our 40 cases. All infected neonates were asymptomatic at birth. The matched historical control group consisted of 108 pregnancies. Thirty-eight transmissions (35.2% (95% CI, 26.2–45.0%)) occurred in the control group, which was significantly higher ($P < 0.0001$) than the transmission rate in the HIG treatment group.*

Conclusion *After a primary maternal CMV infection in the first trimester, biweekly HIG administration at a dose of 200 IU/kg prevents maternal–fetal transmission up to 20 weeks' gestation.* *Copyright © 2018 ISUOG. Published by John Wiley & Sons Ltd.*

INTRODUCTION

Cytomegalovirus (CMV) primary infection during pregnancy results in 700–1400 children per year being born with developmental disorders in Germany[1]. Primary maternal CMV infection occurs in about 0.5–4% of CMV-seronegative pregnant women, and in about 10–15% of these cases the neonate is symptomatic at birth. These children have a 30–40% risk of long-term sequelae including sensorineural hearing loss,

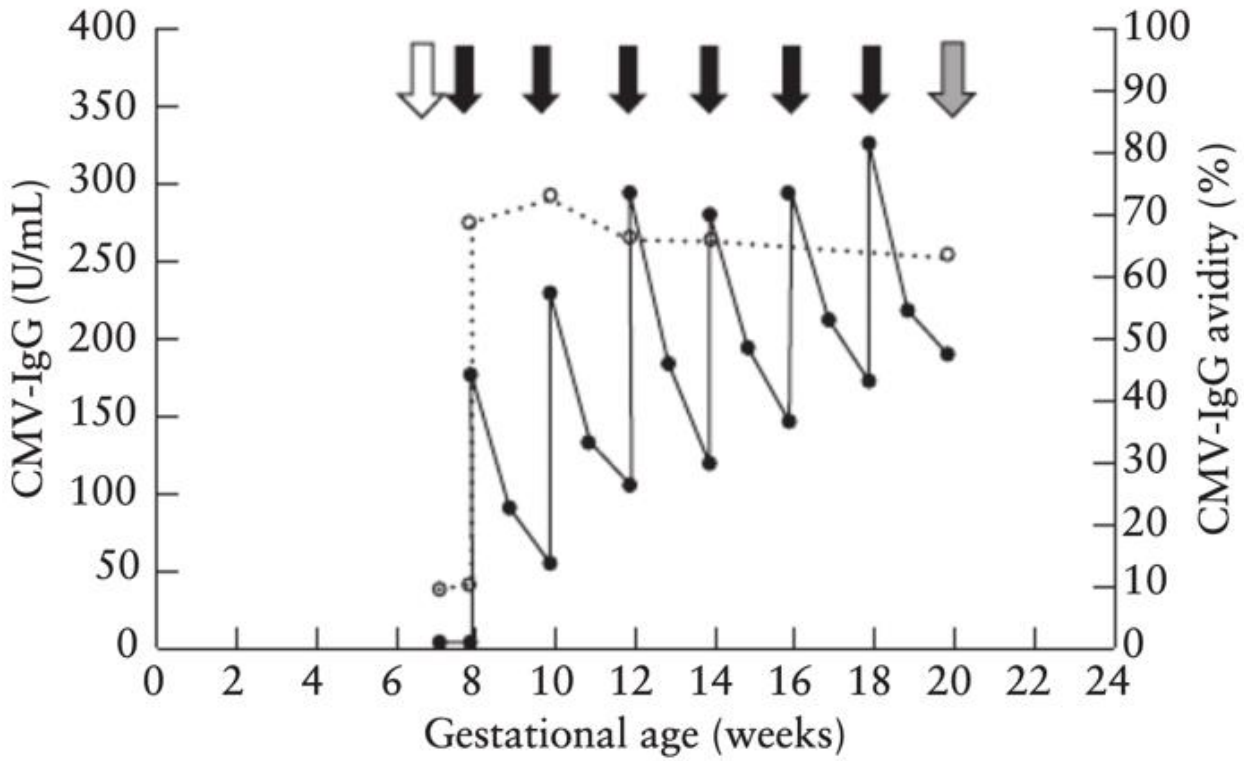


Figure 3 Cytomegalovirus immunoglobulin-G (CMV-IgG) levels (solid line) and respective IgG avidity (dotted line) in woman with first-trimester primary CMV infection, at first presentation (white arrow), during hyperimmunoglobulin treatment (six courses, black arrows) and at amniocentesis (gray arrow).

TRASMISSIONE

7,5%

vs

35%(108)

RISULTATI

1 CASO DI AMNIOCENTESI POSITIVA

3 NEONATI CON DIAGNOSI DI INFEZIONE CONNATALE

304 DONNE 2010 – 2017
281 PARTI
173 UNINFECTED
108 INFECTED

High-Dose Cytomegalovirus (CMV) Hyperimmune Globulin and Maternal CMV DNAemia Independently Predict Infant Outcome in Pregnant Women With a Primary CMV Infection

Giovanni Nigro[1,2] and Stuart P. Adler[3]; for the Congenital Cytomegalic Disease Collaborating Group[a]

[1]Association of Mother-Infant Cytomegalovirus Infection, Rome, Italy, [2]Pediatric Unit, University of L'Aquila, Italy, and [3]Cytomegalovirus Research Foundation, Richmond, Virginia, USA

(See the Editorial Commentary by Schleiss on pages 1499–501.)

Background. After primary maternal cytomegalovirus (CMV) infection during pregnancy, infants are at risk for disease.

Methods. Factors predictive of infant outcome were analyzed in a database of 304 pregnant women with primary infection. These women were enrolled between 2010 and 2017 and delivered 281 infants, of whom 108 were CMV infected. Long term follow-up occurred for 173 uninfected and 106 infected infants at age 4 years (range, 1–8 years). One hundred fifty-seven women were treated with an average of 2 doses (range, 1–6 doses) of high-dose hyperimmune globulin (HIG: 200 mg/kg/infusion). We used a regression model to define predictors of fetal infection, symptoms at birth, and long-term sequelae; 31 covariates were tested.

Results. Four factors predicted fetal infection: a 1.8-fold increase (30% vs 56%) in the rate of congenital infection without HIG (adjusted odds ratio [AOR], 5.2; $P < .0001$), a 1.8-fold increase (32% vs 56%) associated with maternal viral DNAemia prior to HIG administration (AOR, 3.0; $P = .002$), abnormal ultrasounds (AOR, 59; $P = .0002$), and diagnosis of maternal infection by seroconversion rather than avidity (AOR, 3.3; $P = .007$). Lack of HIG and abnormal ultrasounds also predicted symptoms ($P = .001$). Long-term sequelae were predicted by not receiving HIG (AOR, 13.2; $P = .001$), maternal infection in early gestation (odds ratio [OR], 0.9; $P = .017$), and abnormal ultrasounds (OR, 7.6; $P < .003$). Prevalence and copy/number of DNAemia declined after HIG.

Conclusions. Maternal viremia predicts fetal infection and neonatal outcome. This may help patient counseling. High-dose HIG may prevent fetal infection and disease and is associated with the resolution of DNAemia.

Keywords. cytomegalovirus; pregnancy; hyperimmune globulin; DNAemia.

HIG infusions (200 UI/KG) were repeated every three weeks or until amniocentesis or delivery. If amniocentesis was negative, HIG infusions were stopped. If amniocentesis was positive, another infusion was administered and repeated every two to three weeks if US or MRI abnormalities were also observed.

L'HIG ad alte dosi può prevenire l'infezione e la malattia fetale ed è associata alla risoluzione della DNAemia

	Feti infettati	Feti non infettati			
All women #	131	173			
Mean maternal age (years) at enrollment	32±5 (n=131)	33±5 (n=173)	0.18	ND	
Maternal infection – Mean weeks gestation	13.6±7.9 (n=131)	11.7±7.3 (n=173)	P=0.02	0.84	
Time of primary infection. No. women ≤14 weeks gestation >14 weeks gestation	70 61	112 61	P=0.06	P= 0.14	
No. of primary infections (<14 weeks gestation) identified by: Seroconversion[&] Low avidity	48 25	53 55	P=0.03	P=0.007	3.3 (1.75-7.2)
HIG therapy No. mothers: HIG yes HIG no	47 84	110 63	P<0.0001	P<0.0001	5.2 [2.4-11.5]
Mean number of HIG doses/woman who	2.2±1.3	2.0±1.4 (n=110)	P=0.25	ND	

Primary and Secondary Outcomes				
	HIG (N=206)	Placebo (N=193)	Relative Risk (95% CI)	P Value
	no. (%)			
Primary outcome	46 (22.7)	37 (19.4)	1.17 (0.80 - 1.72)	0.424
Neonatal CMV infection	37	32		
Neonatal death without evidence of CMV	0	0		
Fetal death with evidence of CMV infection	6	3		
Fetal death without evidence of CMV	3	2		
Fetal/neonatal outcomes				
Fetal death	9 (4.4)	5 (2.6)	1.69 (0.58 - 4.97)	0.330
Neonatal death	1	0	-	-
Fetal growth restriction < 5th percentile	21 (10.7)	10 (5.3)	2.01 (0.97 - 4.16)	0.052
Head circumference < 3rd percentile	6 (3.1)	6 (3.2)	0.97 (0.32 - 2.95)	0.956
Maternal outcomes				
Any side effects	81 (39.3)	62 (32.1)	1.22 (0.94 - 1.60)	0.134
Preterm birth < 37 weeks	25 (12.2)	16 (8.3)	1.47 (0.81 - 2.67)	0.200

Sono state somministrate infusioni mensili di HIG (100 unità/chilogrammo) o placebo fino al parto.

Lo studio è stato interrotto per inutilità, su raccomandazione del Comitato di monitoraggio dei dati a causa di un'analisi ad interim che ha rivelato che era improbabile che l'arruolamento completo dimostrasse un risultato significativo.

CMV HIG was not effective at decreasing risk of congenital CMV infection or fetal death among women with primary CMV infection in early pregnancy.

Hughes B. LB17. Randomized Trial to Prevent Congenital Cytomegalovirus (CMV). *Open Forum Infect Dis*. 2019;6(Suppl 2):S1000-S1001. Published 2019 Oct 23. doi:10.1093/ofid/ofz415.2500

Clinical Infectious Diseases

EDITORIAL COMMENTARY

The Value of Hyperimmune Globulin in Pregnancies Complicated by Cytomegalovirus Infection: A Continuing Saga

Mark R. Schleiss

Center for Infectious Diseases and Microbiology Translational Research and Division of Pediatric Infectious Diseases and Immunology, Department of Pediatrics, University of Minnesota Medical School, Minneapolis, Minnesota, USA

(See the Major Article by Nigro et al on pages 1491–8.)

Jacquemard F. • **Yamamoto M.** • **Costa J.M.** • **Romand S.** • **Jaqz-Aigrain E.** • **Dejean A.** • **et al.**
Maternal administration of valaciclovir in symptomatic intrauterine cytomegalovirus infection.
BJOG. 2007; : 1113-1121

Shahar-Nissan K. • **Pardo J.** • **Peled O.** • **Krause I.** • **Bilavsky E.** • **Bilavsky E.** • **et al.**
Valacyclovir to prevent vertical transmission of cytomegalovirus after maternal primary infection during pregnancy.
Open Forum Infect Dis. 2019; **6**: S1002

Crossref • Google Scholar

Leruez-Ville M. • **Ghout I.** • **Bussieres L.** • **Stirnemann J.** • **Magny J.F.** • **Couderc S.** • **et al.**
In Utero treatment of congenital cytomegalovirus infection with valacyclovir in a multicenter, open-label, phase II study.
Am J Obstet Gynecol. 2016; **215**: 462 e1-462 e10

Codaccioni C. • **Vauloup-Fellous C.** • **Letamendia E.** • **Saada J.** • **Benachi A.** • **Vivanti A.J.**
Case report on early treatment with valaciclovir after maternal primary cytomegalovirus infection.
J Gynecol Obstet Hum Reprod. 2019; **48**: 287-289

Somministrazione materna di valaciclovir(8 gr) nell'infezione sintomatica intrauterina da citomegalovirus.

BJOG 2007

F Jacquemard et al

- 20 gravidanze (21 feti) sono state trattate a 28 settimane (mediana, range: 22-34) per 7 settimane .

- Le concentrazioni terapeutiche di valaciclovir sono state raggiunte nel sangue materno e fetale. La carica virale nel sangue fetale (VLFB) è diminuita significativamente dopo 1-12 settimane di trattamento

TABLE 1
Main inclusion criteria

At least 1 extracerebral abnormality compatible with fetal CMV infection	
	Fetal growth restriction[42]
	Abnormal amniotic fluid volume
	Ascites and/or pleural effusion
	Skin edema
	Hydrops
	Placentomegaly >40 mm[43]
	Hyperechogenic bowel[a]
	Hepatomegaly >40 mm[44]
	Splenomegaly >30 mm[45]
	Liver calcifications
And/or 1 isolated cerebral abnormality	
	Moderate isolated ventriculomegaly (<15 mm)
	Isolated cerebral calcification
	Isolated intraventricular adhesion
	Vasculopathy of lenticulostriate vessels
And/or laboratory findings of generalized CMV infection in fetal blood	
	Fetal viremia >3000 copies/mL
	Fetal platelet count <100,000/mm^3

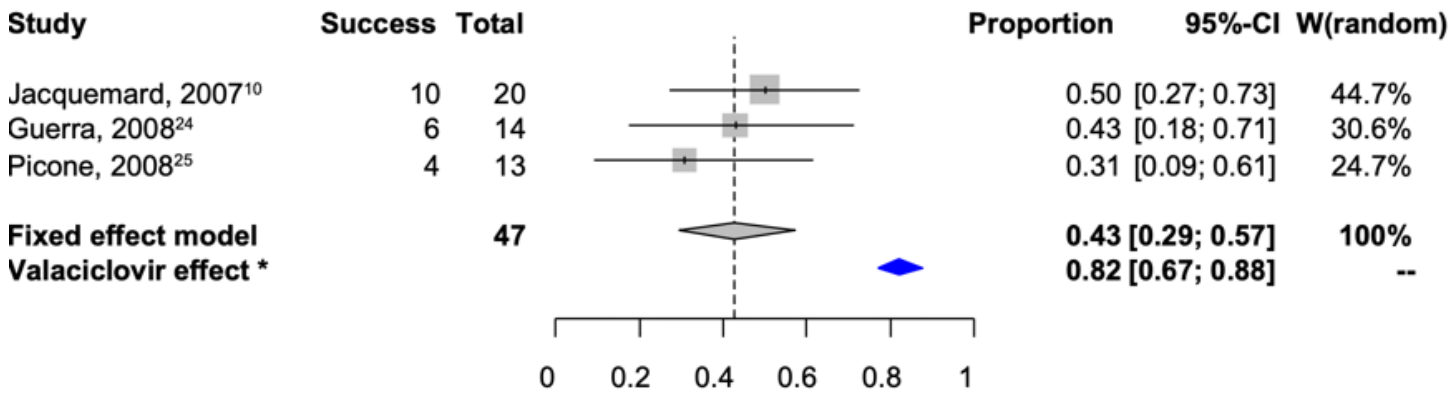
All ultrasound examinations leading to inclusion in study were reviewed by principal investigator at each center. Measurements of spleen, liver, and placenta were standardized according to literature.[43-45]

CMV, cytomegalovirus.

[a] Since diagnosis of hyperechogenic bowel can be subjective and associated with high interoberver and intraobserver variability, diagnosis of hyperechogenic bowel was only considered for grade-2 or grade-3 hyperechogenic bowel[46]; this semiquantitative analysis was chosen to limit subjectivity sometimes associated with ultrasound findings.

Leruez-Ville et al. In utero treatment of congenital cytomegalovirus infection. Am J Obstet Gynecol 2016.

FIGURE 2
Valacyclovir effect compared to historical control group



Proportion of asymptomatic neonates and 95% confidence interval (CI) were calculated with unbiased estimator.[26] In historical control group, we used random effects model to calculate overall proportion of asymptomatic neonates and 95% CI for 43 cases reported in 3 suitable published studies. *Unbiased estimation of binomial probability in multistage design.

Leruez-Ville et al. In utero treatment of congenital cytomegalovirus infection. Am J Obstet Gynecol 2016.

Studio randomizzato, in doppio cieco, di fase 2/3 controllato con placebo (NCT02351102)

Nello studio, 90 donne in gravidanza (92 feti, due gravidanze gemellari) sono state randomizzate 1:1 a ricevere valaciclovir ad alte dosi (8 g al giorno) o placebo dopo l'infezione primaria da CMV durante il periodo periconcezionale o il primo trimestre. Il trattamento è stato iniziato al momento della diagnosi sierologica di infezione primaria ed è proseguito fino all'amniocentesi. Nel gruppo valaciclovir, 5/45 (11,1%) erano positive per CMV, rispetto a 14 su 47 (29,8%) nel gruppo placebo (P GLMM = 0,03), corrispondente a un odds ratio di 0,29 (intervallo di confidenza 95% : 0,09-0,90) per la trasmissione verticale di CMV (tasso di riduzione del 71% nella trasmissione fetale).

Shahar-Nissan K. • Pardo J. • Peled O. • Krause I. • Bilavsky E. • Bilavsky E. • et al.

Valacyclovir to prevent vertical transmission of cytomegalovirus after maternal primary infection during pregnancy.

Open Forum Infect Dis. 2019; **6**: S1002

Crossref • Google Scholar

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Narrative review

Management of cytomegalovirus infection in pregnancy: is it time for valacyclovir?

L. Zammarchi [1, 2, 3, *], T. Lazzarotto [4], M. Andreoni [5], I. Campolmi [1], L. Pasquini [6], M. Di Tommaso [7], G. Simonazzi [8], L.R. Tomasoni [9], F. Castelli [9, 10], L. Galli [11], B. Borchi [2, 3], P. Clerici [12], A. Bartoloni [1, 2], M. Tavio [13], M. Trotta [2, 3]

AIFA LEGGE 648/96

- Infine, del tutto recentemente, a seguito di richiesta elaborata con la collaborazione del Centro di Riferimento della Regione Toscana per le Malattie Infettive in Gravidanza e inviata formalmente AIFA dalla SIMIT, AMCLI e Società di Medicina Perinatale (SIMP) è stato decretato l'inserimento del medicinale valaciclovir nell'elenco dei medicinali erogabili a totale carico del Servizio Sanitario Nazionale, per la prevenzione dell'infezione fetale e il trattamento della malattia fetale da citomegalovirus ai sensi della legge 648/96

Spediz. abb. post. - art. 1, comma 1
Legge 27-02-2004, n. 46 - Filiale di Roma

Anno 161° - Numero 322

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DECRETO DEL PRESIDENTE DEL CONSIGLIO DEI MINISTRI 23 dicembre 2020, n. 180.

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DECRETI PRESIDENZIALI

DELIBERA DEL CONSIGLIO DEI MINISTRI 10 dicembre 2020.

Proroga dello stato di emergenza nel territorio del Comune di Formazza, in Provincia di Verbano-Cusio-Ossola, interessato dagli eventi meteorologici verificatisi nei giorni 11 giugno e 12 agosto 2019. (20A07130) ..... *Pag.* 18

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DECRETO 18 dicembre 2020.

Adeguamento delle modalità di calcolo dei diritti di usufrutto e delle rendite o pensioni in ragione della nuova misura del saggio di interessi. (20A07188) *Pag.* 19

Prevenzione dell'infezione fetale in caso di infezione primaria acquisita in epoca periconcezionale → 24ª wk

Terapia fino ad esito amniocentesi altrimenti fino 26 settimane

Trattamento della malattia «mild» e dimostrazione dell'infezione fetale

Terapia fino al parto eventualmente aggiuntiva alla precedente.

MEGAL ITALI

Studio osservazionale sull'infezione da citomegalovirus in gravidanza in Italia

Studio retro-prospettico nazionale

Obiettivi: Valutazione degli approcci diagnostico-terapeutici utilizzati nei vari centri, (compreso eventuale utilizzo di terapie off-label) ed eventuali differenze negli outcome riportati ai punti materno-fetali in base all'utilizzo dei diversi trattamenti.

MEGAL-ITALI working group include:

- **AOU Careggi – Università di Firenze**: Lorenzo Zammarchi, Alessandro Bartoloni, Beatrice Borchi, Irene Campolmi, Michele Trotta, Mariarosaria Di Tommaso, Lucia Pasquini, Giulia Modi
- **IRCCS Policlinico San'Orsola Malpighi- Università di Bologna**: Tiziana Lazzarotto, Giuliana Simonazzi
- **Spedali Civili di Brescia – Università di Brescia**: Lina Rachele Tomasoni, Francesco Castelli
- **Università Federico II**: Laura Letizia Mazzarelli, Giuseppe Maria Maruotti
- **IRCCS INMI Lazzaro Spallanzani, Roma**: Giuseppina Liuzzi, Alessandra Oliva
- **Fondazione MBBM, Monza**: Sara Ornaghi, Vergani Patrizia,
- **Università di Catanzaro**: Carlo Torti
- **Azienda Ospedaliero Universitaria Meyer, Firenze**: Luisa Galli, Carlotta Montagnani, Leila Bianchi, Elisabetta Venturini
- **Università Tor Vergata, Roma**: Massimo Andreoni (**SIMIT**)
- **AOU Ospedali Riuniti di Ancona, Ancona:** Marcello Tavio (**SIMIT**)
- **Istituto Giannina Gaslini, Genova**: Luca Antonio Ramenghi (**SIMP**)
- **Ospedale Civile Legnano**: Pierangelo Clerici (**AMCLI**)

Distribuzione geografica dei centri e numero pazienti trattate con valaciclovir per prevenzione di cCMV

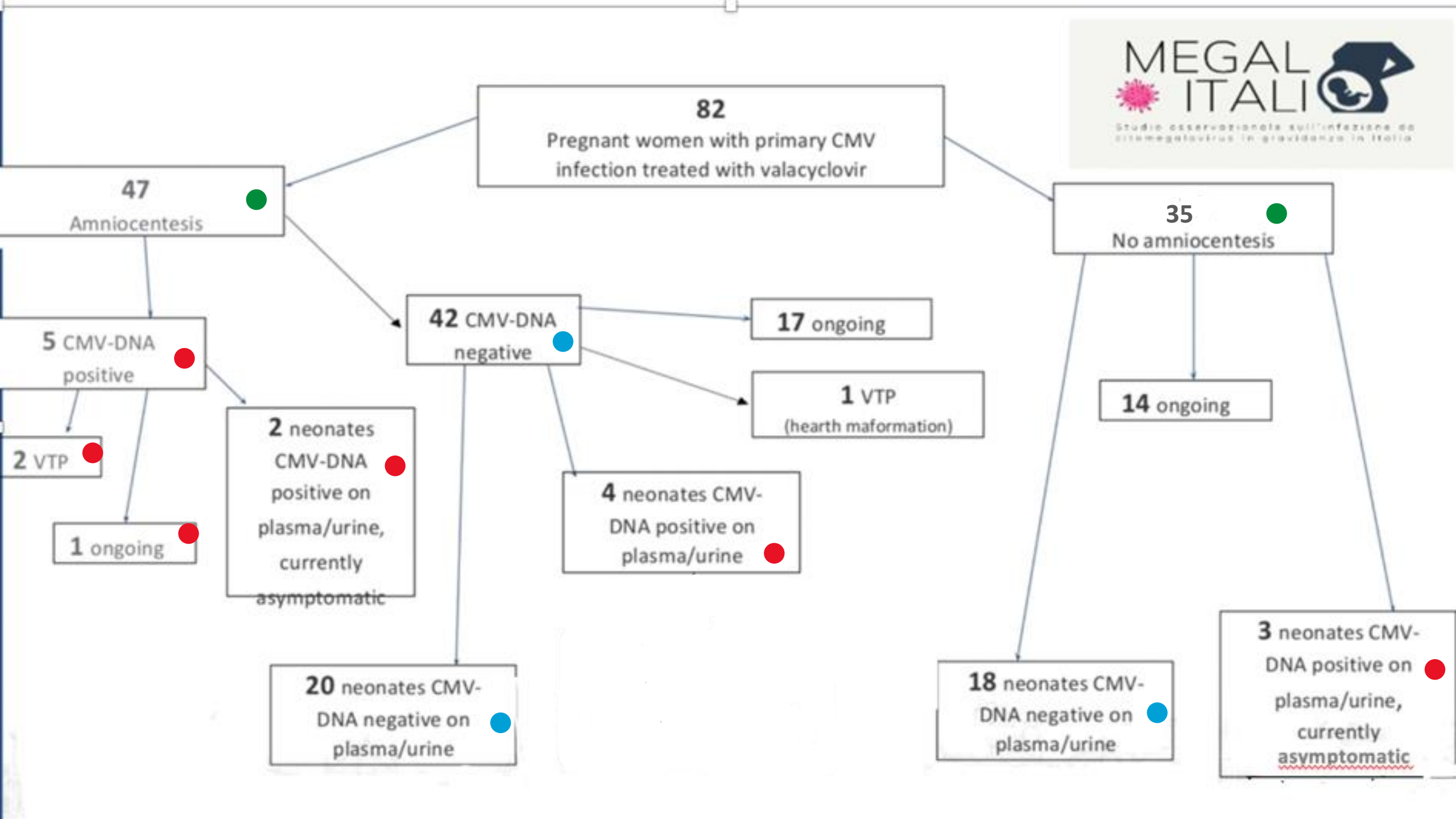
Totale 7 centri n=82

Criteri per il trattamento

- Infezione primaria da CMV contratta entro 24 settimane di gestazione

Criterio	
Sieroconversione in gravidanza	20 (24%)
IgG pos + IgM pos + IgG avidity bassa	34 (41%)
IgG pos + IgM pos + IgG avidity intermedia + CMV-DNA pos (su sangue e/o urine e/o saliva)	19 (23%)
(non specificato)	9 (11%)

- Trattamento iniziato non appena possibile a seguito della diagnosi di infezione primaria
- Dosaggio 2g ogni 6 ore
- Interrotto dopo l'amniocentesi o max a 26° settimana di gestazione se amniocentesi non eseguita


MEGAL ITALI
Studio osservazionale sull'infezione da citomegalovirus in gravidanza in Italia
82
Pregnant women with primary CMV infection treated with valacyclovir
47
Amniocentesis
35
No amniocentesis
5 CMV-DNA positive
42 CMV-DNA negative
17 ongoing
1 VTP
(hearth maformation)
14 ongoing
2 VTP
1 ongoing
2 neonates CMV-DNA positive on plasma/urine, currently asymptomatic
4 neonates CMV-DNA positive on plasma/urine
20 neonates CMV-DNA negative on plasma/urine
18 neonates CMV-DNA negative on plasma/urine
3 neonates CMV-DNA positive on plasma/urine, currently asymptomatic

risultati

Tasso di trasmissione di cCMV (pazienti sottoposte a amniocentesi, n=47)

- CMV-DNA positivo su liq. amniotico: **5/47 (11%)**
  - 2 IVG (ecografia fetale normale)
  - 2 neonati asintomatici con cCMV
  - 1 gravidanza in corso (feto con ecografia normale)

- CMV-DNA negativo su liq. amniotico: 42/47 (89%)
  - 17 gravidanza in corso
  - 1 IVG per malformazioni cardiache
  - 24 nati a termine
    - 20/24 (83%) neonati negativi
    - **4/24 (17%)** neonati con cCMV
      - 1 neonato con alterazioni segni «minori»
      - 3 neonati asintomatici

Tasso di trasmissione di cCMV (pazienti non sottoposte a amniocentesi, n=35)

- 14 gravidanze in corso
- 21 neonati
    - **3/21 (14%)** neonati con cCMV
    - 18/21 (86%) neonati negativi

Tasso di trasmissione di cCMV (tutte le gravidanza completate, n=50)

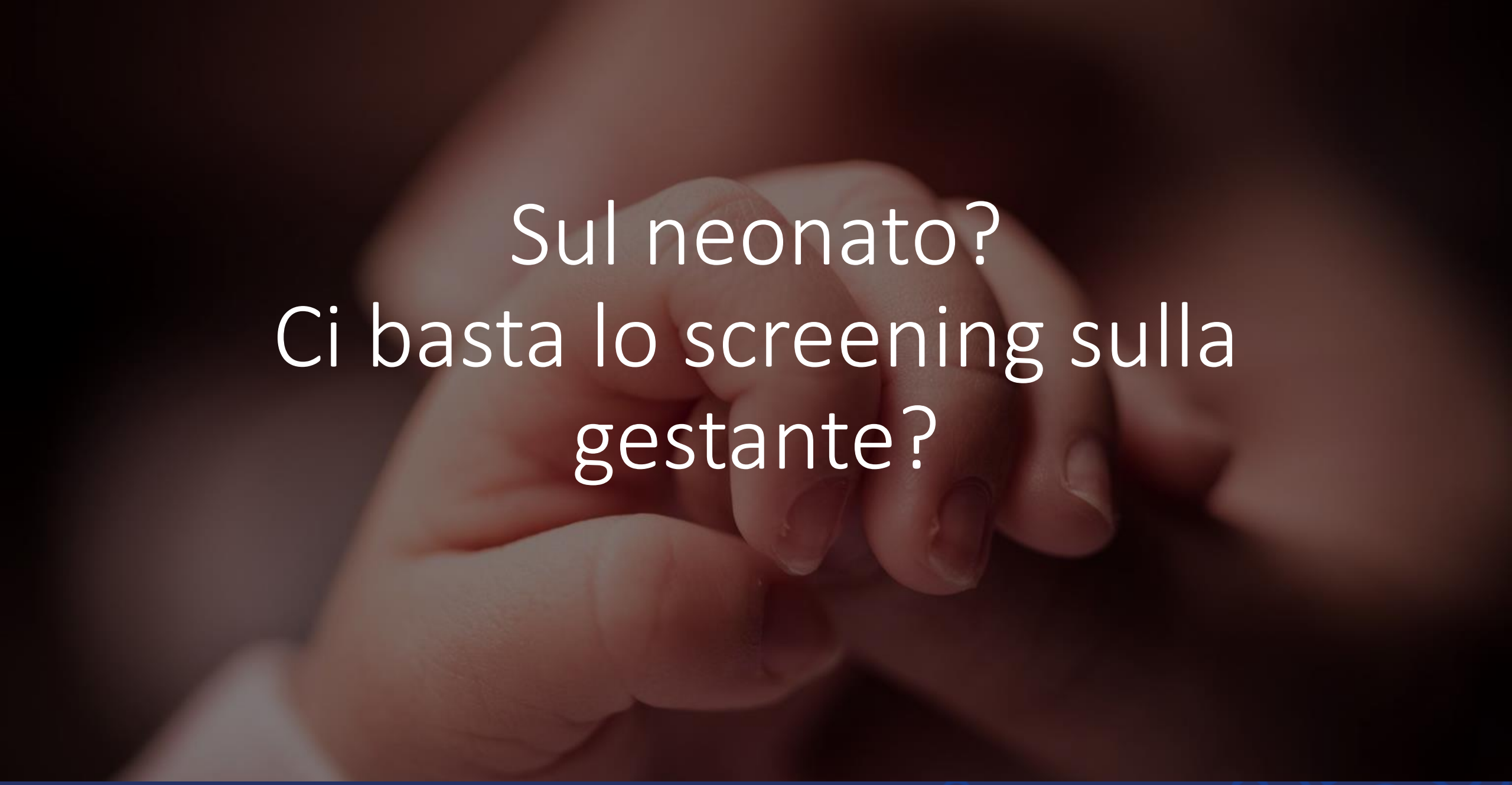
- CMV-DNA positivo su liq. amniotico e/o su urine/sangue del neonato: 12/50 (24%)
- cCMV esclusa (CMV-DNA negativo su urine del neonato): 38/50 (76%)

Risultati

coorte storica AOUC 2012-2019 (87 gestanti= 41 sottoposte a amniocentesi + 46 no amniocentesi)

	Coorte MEGAL-ITALI (valacyclovir)	Coorte storica AOUC (no valaciclovir)	Confronto
Diagnosi all'amniocentesi	5/47 (11%)	14/41 (34%)	p=0.009 ; OR 0.22 (CI95% 0.07-0.71) *
Diagnosi a fine gravidanza	12/50 (24%)	29/87 (33%)	p=0.9114 ; OR 0.63 (CI95% 0.28-1.38)

* Riduzione significativa di prevalenza di cCMV all'amniocentesi



Sul neonato?
Ci basta lo screening sulla gestante?

Clinical Rounds

Continuing Education

Cytomegalovirus Infection in Pregnancy: Prevention, Presentation, Management and Neonatal Outcomes

Megan H. Pesch[1,2], MD, MS, Natalie A. Saunders[3], MD, Samia Abdelnabi[4], MSN, FNP, CNM

Congenital cytomegalovirus (cCMV) is the most common congenital infection in the United States, with 1 of 200 live births affected. It is the leading viral cause of intrauterine fetal demise and miscarriage. It is a common cause of neonatal hearing loss, second only to genetic factors. Yet, health care provider awareness remains low. The purpose of this article is to provide a brief overview of the epidemiology, presentation, diagnosis, and treatment of antenatal cytomegalovirus (CMV) infection and cCMV in the neonate. Maternal CMV infection in pregnancy often presents with mild cold-like symptoms or is asymptomatic. The virus can be vertically transmitted to a growing fetus, the risk of transmission and severity of fetal impact varying by timing of exposure during pregnancy. Most neonates born with cCMV show no signs at birth, yet 15% to 25% will have long-term adverse neurodevelopmental conditions. Misconceptions that cCMV cannot be prevented or that neonates born without signs of the disease will be unaffected are common. Evidence supporting antenatal education around behavioral change to lower a woman's risk of acquiring CMV during pregnancy is mounting. CMV infection during pregnancy should be co-managed with a maternal-fetal medicine specialist. There is early evidence for the use of antiviral medication in reducing risk of vertical transmission. Identification of cCMV during pregnancy may help ensure the neonate receives timely treatment after birth. Midwives can play an important role in providing antenatal education about cCMV risk reduction and in initiating a diagnostic evaluation when there is clinical suspicion.

J Midwifery Womens Health 2021;0:1–6

Table 1. Misconceptions and Facts about Congenital Cytomegalovirus

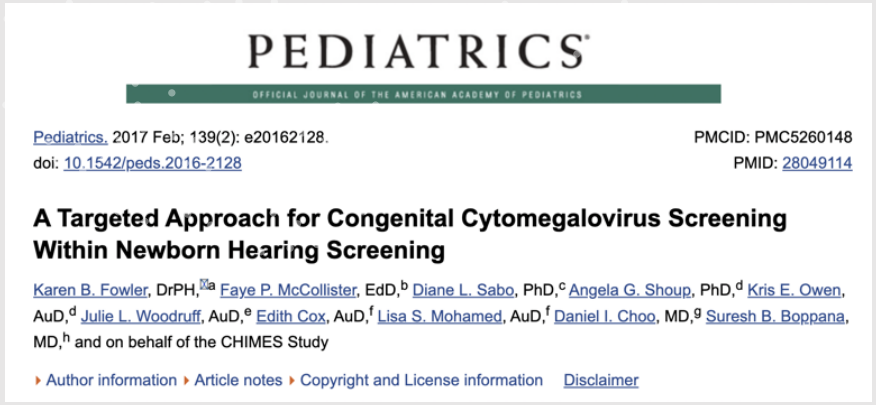
Misconception	Fact
cCMV is rare	cCMV is the most common TORCH infection, affecting 1 in 200 live births.[1]
cCMV cannot be prevented	Individuals may lower their risk of contracting CMV when pregnant by practicing hand hygiene and avoiding the saliva of young children.[26]
If a woman has had CMV in the past, she is immune	Individuals can become reinfected with a new strain of CMV when pregnant or have a reactivation of a latent infection even if they have preexisting IgG antibodies.[8]
If neonate does not have signs of cCMV at birth, they will not have later sequelae	Neonates with cCMV but without visible signs at birth (also known as having asymptomatic cCMV) may still have hearing loss at birth and are at risk for later onset hearing loss.[10]
There is no treatment for neonates with asymptomatic cCMV	Although antiviral medication is not yet proven to be safe and effective for asymptomatic neonates, treatment may also include early intervention services and close monitoring of hearing, vision, and development.[21]
Most ineonates with cCMV are diagnosed by pediatricians at birth	More than 90% of cases of cCMV go undiagnosed at birth. The majority of cases of cCMV present with subtle signs or no signs at all, which make the diagnosis challenging.[21,26]

Fowler e Boppana (2018)

90% dei cCMV sono asintomatici alla nascita → 10% - 15% late sequelae

10% sintomatici →40%–60 % → late sequelae

Screening neonatale universale: come mai?



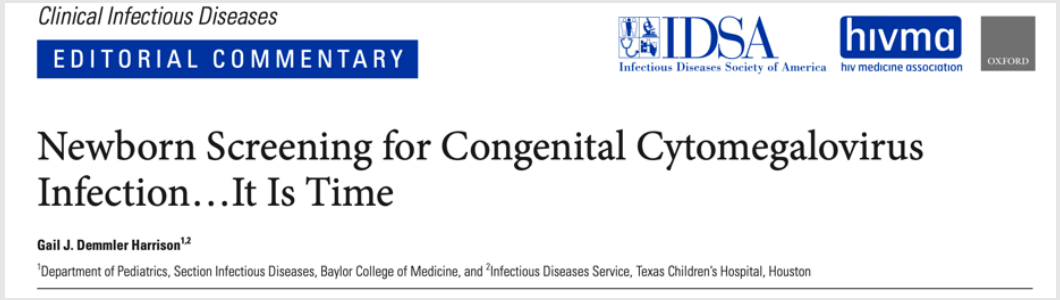
PEDIATRICS

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Pediatrics. 2017 Feb; 139(2): e20162128.
doi: 10.1542/peds.2016-2128
PMCID: PMC5260148
PMID: 28049114

A Targeted Approach for Congenital Cytomegalovirus Screening Within Newborn Hearing Screening

Karen B. Fowler, DrPH,[a] Faye P. McCollister, EdD,[b] Diane L. Sabo, PhD,[c] Angela G. Shoup, PhD,[d] Kris E. Owen, AuD,[d] Julie L. Woodruff, AuD,[e] Edith Cox, AuD,[f] Lisa S. Mohamed, AuD,[f] Daniel I. Choo, MD,[g] Suresh B. Boppana, MD,[h] and on behalf of the CHIMES Study



Clinical Infectious Diseases

EDITORIAL COMMENTARY

IDSA Infectious Diseases Society of America · hivma hiv medicine association · OXFORD

Newborn Screening for Congenital Cytomegalovirus Infection…It Is Time

Gail J. Demmler Harrison[1,2]

[1]Department of Pediatrics, Section Infectious Diseases, Baylor College of Medicine, and [2]Infectious Diseases Service, Texas Children's Hospital, Houston

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Closer to Universal Newborn Screening for Congenital Cytomegalovirus Infection but Far Away from Antiviral Therapy in All Infected Infants

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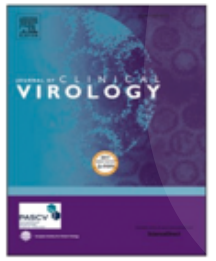
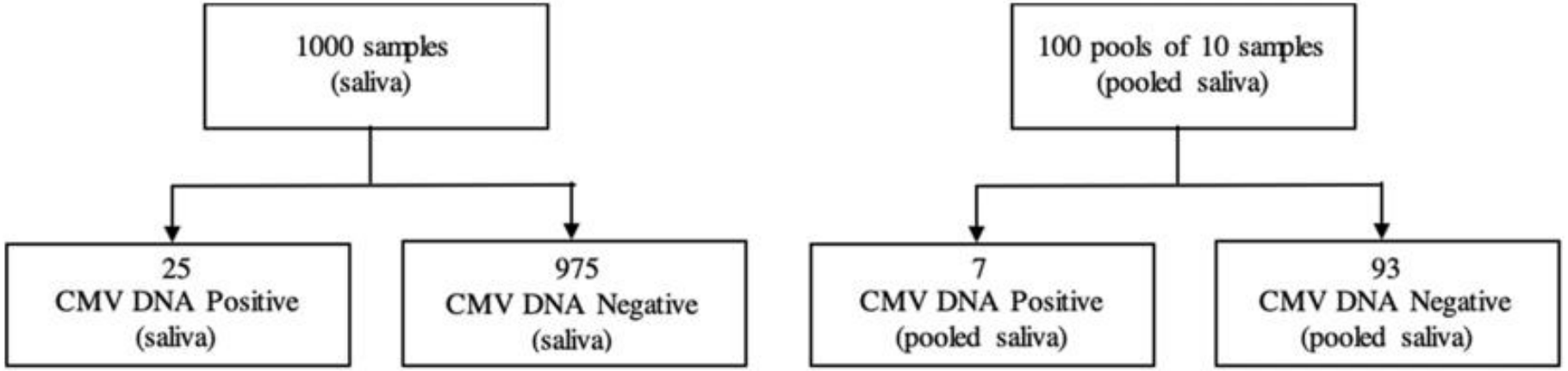


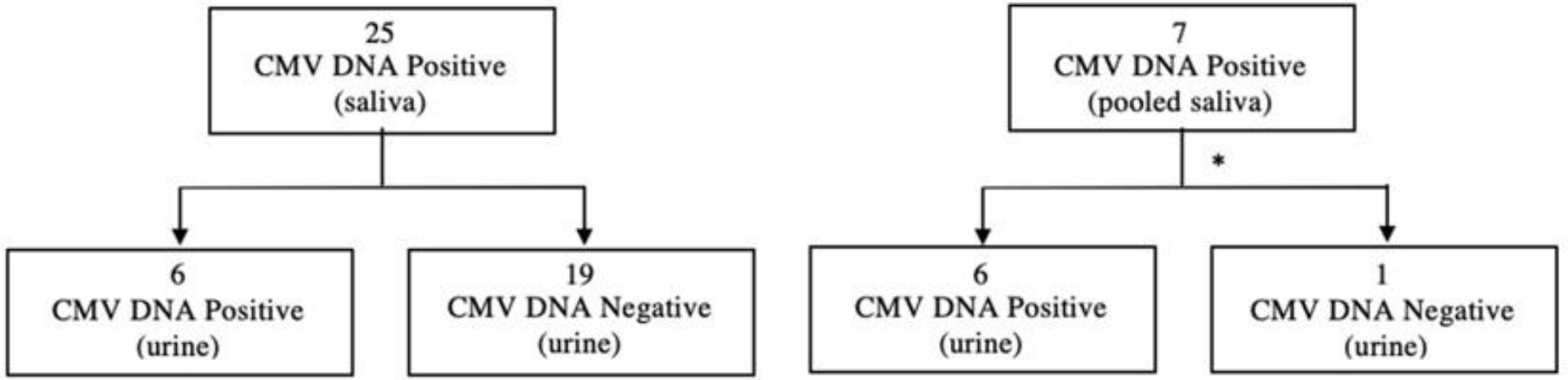
Pooled saliva CMV DNA detection: A viable laboratory technique for universal CMV screening of healthy newborns

Yulia Shlonsky [a,1], Narmin Shehade Smair [a,1], Raeda Mubariki [a], Ellen Bamberger [a,*], Miri Hemo [a], Sarah Cohen [b], Arieh Riskin [a], Isaac Srugo [a], David Bader [a], Orit Golan-Shany [a]

[a] *Bnai Zion Medical Center, Haifa, Israel*
[b] *Harvard Medical School, Boston, USA*


1000 samples
(saliva)
25
CMV DNA Positive
(saliva)
975
CMV DNA Negative
(saliva)
100 pools of 10 samples
(pooled saliva)
7
CMV DNA Positive
(pooled saliva)
93
CMV DNA Negative
(pooled saliva)

a


25
CMV DNA Positive
(saliva)
6
CMV DNA Positive
(urine)
19
CMV DNA Negative
(urine)
7
CMV DNA Positive
(pooled saliva)
*
6
CMV DNA Positive
(urine)
1
CMV DNA Negative
(urine)

b

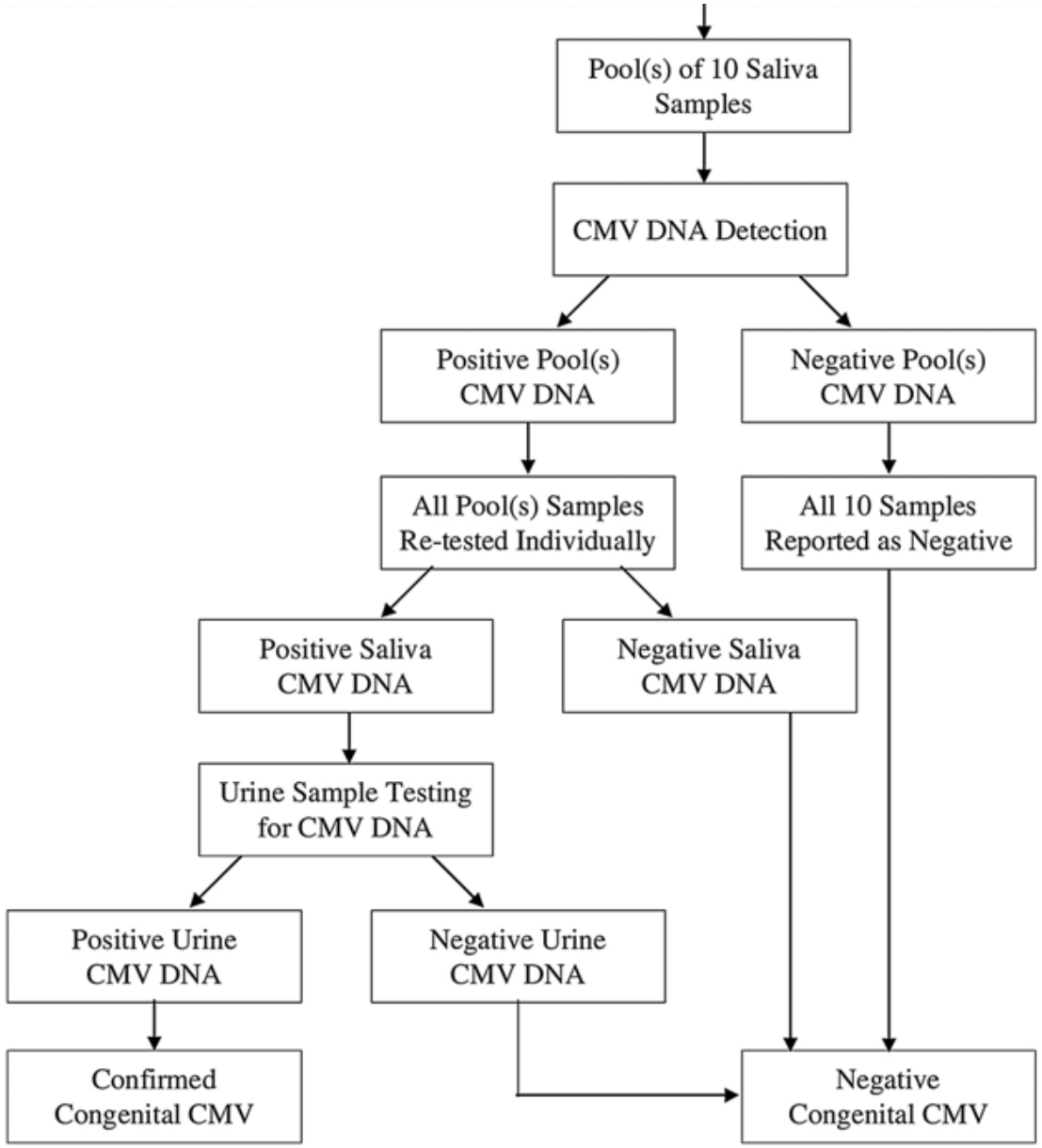
Proposta

- In Toscana
- 22.000 nascite
- 14.000 da donne CMV+ve

- 1400 – 1500 test /anno

- In Italia
- 404.000 nascite
- 120.000 da donne CMV+ve

- 12.000 test/anno



E’ tempo di agire

- Screening in gravidanza : auspicabile
- Trattamento antivirale / HIG in gravidanza : opportuno
- Screening neonatale : imperativo
- Trattamento antivirale sul neonato: troppi casi non riconosciuti

GRAZIE

GRAZIE