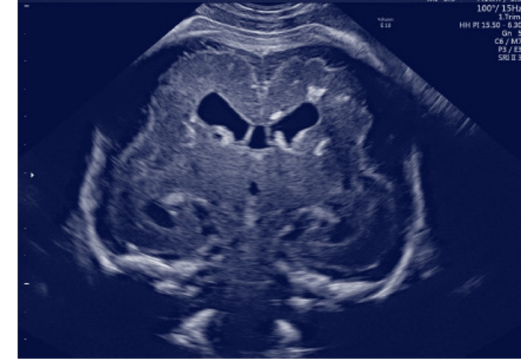




UNIVERSITÄTSKLINIK  
FÜR FRAUENHEILKUNDE  
MEDIZINISCHE UNIVERSITÄT WIEN  
Klinische Abteilung für Geburtshilfe  
und feto-maternale Medizin



FetoMed



# Therapie der CMV- Infektion in der Schwangerschaft

Ap. Prof. PD DDr. Julia Binder

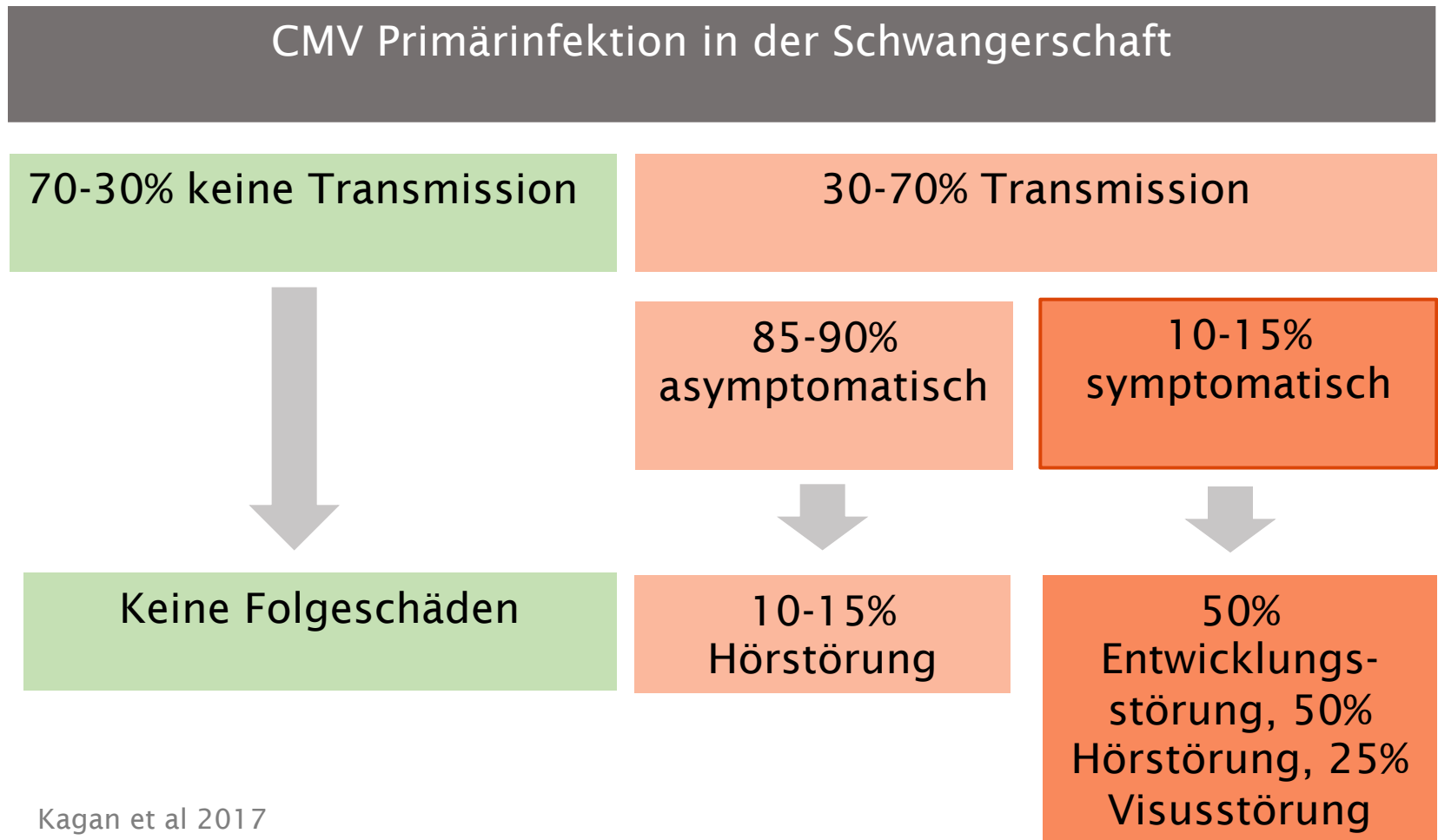
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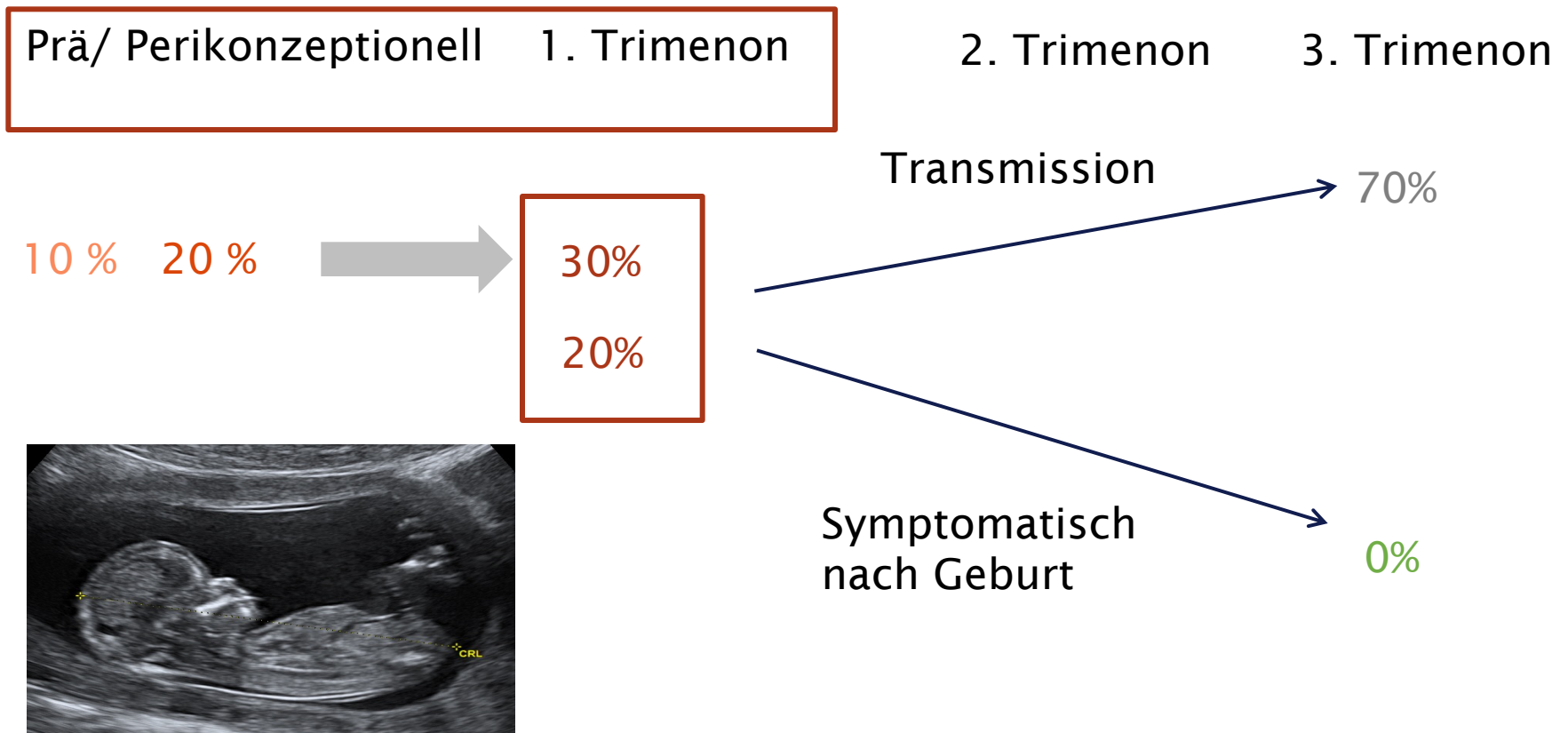


MEDIZINISCHE  
UNIVERSITÄT WIEN

# CMV in der Schwangerschaft und postnatales Outcome



# Verlauf der CMV Infektion in der Schwangerschaft



Kagan et al 2017

# Timing of primary maternal cytomegalovirus infection and rates of vertical transmission and fetal consequences

Christos Chatzakis, MD, MSc; Yves Ville, MD, PhD; George Makrydimas, MD, PhD; Konstantinos Dinas, MD, PhD; Apostolos Zavlanos, MD, PhD; Alexandros Sotiriadis, MD, PhD

DECEMBER 2020 *American Journal of Obstetrics & Gynecology*

**TABLE 5**  
**Risk of CMV congenital infection (transmission) and SNHL or neurodevelopmental impairment, according to gestational age at maternal primary infection**

	Transmission rate	SNHL or neurodevelopmental impairment if fetus is infected	SNHL or neurodevelopmental impairment if transmission is unknown
First trimester	36.8% (95% CI, 31.9–41.6)	22.8% (95% CI, 15.4–30.2)	8.4%
Second trimester	40.3% (95% CI, 35.5–45.1)	0.1% (95% CI, 0–0.8)	0%
Third trimester	66.2% (95% CI, 58.2–74.1)	0% (95% CI, 0–2.1)	0%

CMV, cytomegalovirus; SNHL, sensorineural hearing loss.

Chatzakis. Timing of primary maternal cytomegalovirus infection and rates of vertical transmission and fetal consequences. *Am J Obstet Gynecol* 2020.

# Die Gefährliche CMV Infektion- Zeitachse



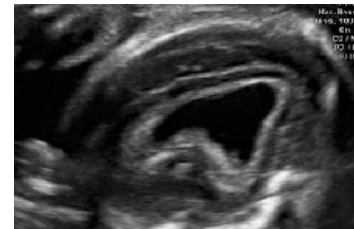
Infektion im I. Trimenon



Transmission bis SSW 20-23



Auffälliger US im III. Trimenon



Symptomatisches Neugeborenes

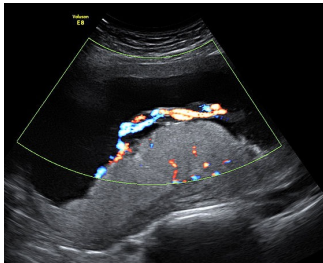


# Prävention- Therapiemöglichkeiten



Expositionsprophylaxe

Hygienemaßnahmen



Prävention der  
Transmission

Immunglobuline,  
Valaciclovir



Prävention der  
Symptomatik

Valaciclovir bei  
gesicherter  
Transmission

# Prävention- Expositionsprophylaxe

**CMV** is short for **cyto-megalo-virus**

# CMV is preventable



Pregnant women who already have young children, or who work with young children, are at highest risk of catching CMV

CMV is found in home and daycare settings



Avoid contact with saliva - Kiss kids under the age of 6 on the forehead instead of lips or cheek



**75%** of toddlers have CMV in their urine or saliva in studies at child-care settings



Wash your hands after contact with bodily fluids of kids under the age of 6



Don't share utensils, drinks, or toothbrushes with kids under the age of 6

NATIONAL  
**CMV**  
FOUNDATION

## HOW CAN I PREVENT CMV?

Contact with the saliva or urine of young children is a major cause of CMV infection among pregnant women, especially mothers, daycare workers, preschool teachers, therapists, and nurses.

## 5 SIMPLE STEPS TO PREVENT CMV



Avoid contact with saliva when kissing a child



Do not share food, utensils, drinks, or straws



Do not share a toothbrush



Wash your hands after changing a diaper



Do not put a pacifier in your mouth

## CMV?

CMV steht für  
Cytomegalovirus  
(= Zytomegalievirus)

Die Infektion mit **CMV** stellt  
in der Schwangerschaft eine  
der häufigsten Ursachen für  
schwere kindliche Entwick-  
lungsstörungen dar!

## CMV-Infektionen sind vermeidbar!

Infektionen entstehen am  
häufigsten durch Kontakt  
mit Speichel oder Urin  
kleiner Kinder (<6 Jahren)



Essen, Getränke oder  
Besteck nicht gemein-  
sam verwenden.



Den Schnuller des  
Kindes nicht in den  
Mund nehmen.



Speichelkontakt beim  
Küssen eines Kindes  
vermeiden – Kind nicht  
auf Mund oder Wan-  
gen, sondern auf den  
behaarten Kopf küssen.



Nach dem Windel-  
wechseln, Füttern oder  
Nase putzen von klei-  
nen Kindern die Hände  
für 15–20 Sekunden  
gründlich mit Seife und  
Wasser waschen.



# Prävention einer primären CMV Infektion



Contents lists available at ScienceDirect

EBioMedicine

journal homepage: [www.ebiomedicine.com](http://www.ebiomedicine.com)



Research Paper

## Prevention of Primary Cytomegalovirus Infection in Pregnancy<sup>☆</sup>



Maria Grazia Revello<sup>a</sup>, Cecilia Tibaldi<sup>e</sup>, Giulia Masuelli<sup>e</sup>, Valentina Frisina<sup>e</sup>, Alessandra Sacchi<sup>e</sup>, Milena Furione<sup>b</sup>, Alessia Arossa<sup>a</sup>, Arsenio Spinillo<sup>a</sup>, Catherine Klersy<sup>c</sup>, Manuela Ceccarelli<sup>f</sup>, Giuseppe Gerna<sup>d,\*</sup>, Tullia Todros<sup>e</sup>, for the CCPE Study Group<sup>1</sup>

alle Teilnehmer in SSW 11-12 IgM/IgG negativ

331 mit detaillierter Aufklärung

315 Kontrollgruppe

SSW 18 und p.p getestet

Bei Geburt getestet

Serokonversion 1.2% (4/331)

Serokonversion 7.6% (24/315)

Kong. Infektion 0.9% (3/331)

Kong. Infektion 2.5% (8/315)

Hygiene-  
Aufklärung:

- Hände-  
hygiene
- Küssen  
vermeiden
- kein  
gemein-  
sames  
Besteck  
ect.

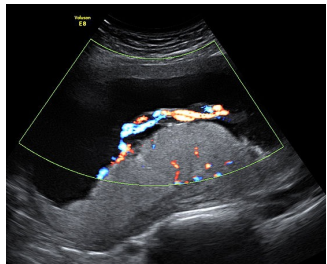
EBioMedicine 2015

# Prävention- Therapiemöglichkeiten



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Hygienemaßnahmen



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Transmission

Hyperimmunglobuline,  
Valaciclovir



Prävention der  
Symptomatik

Valaciclovir bei  
gesicherter  
Transmission

# Prävention der Transmission- HIG

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Passive Immunization during Pregnancy for Congenital Cytomegalovirus Infection

Giovanni Nigro, M.D., Stuart P. Adler, M.D., Renato La Torre, M.D., and Al M. Best, Ph.D., for the Congenital Cytomegalovirus Collaborating Group\*

N Engl J Med 2005;353:1350-62.

Nicht randomisierte klinische Studie, n=157 mit gesicherter prim. CMV Infektion

31/157 gesicherte CMV Infektion und pos. AC  
- 200 U/kg HIG

1/31 (3%)  
symptomatisches NG vs  
7/14 (50%) ohne HIG

37/157 gesicherte CMV Infektion ohne AC  
- 100 U/kg alle 4 Wo HIG

6/37 (16%)  
symptomatisches NG vs  
19/47 (40%) ohne HIG

# Prävention der Transmission- HIG

The NEW ENGLAND JOURNAL of MEDICINE

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\*

*N Engl J Med* 2014;370:1316-26.

Randomisierte doppel-blind kontrollierte Phase II Studie; n=123

61/123 HIG, Transmission  
18/61 (30%)

62/123 Placebo, Transmission  
27/62 (44%)

Kein signifikanter Unterschied- under powered?  
Einschluss SSW 5- 26- in 25% >18-20 SSW  
5 Wochen zwischen Diagnosestellung und Behandlung  
Endpunkt: Transmission bei Geburt/pos AC, nur 15-20% AC  
HIG alle 4 Wochen, Dosis 100U/kg KG- mehr Adverse events

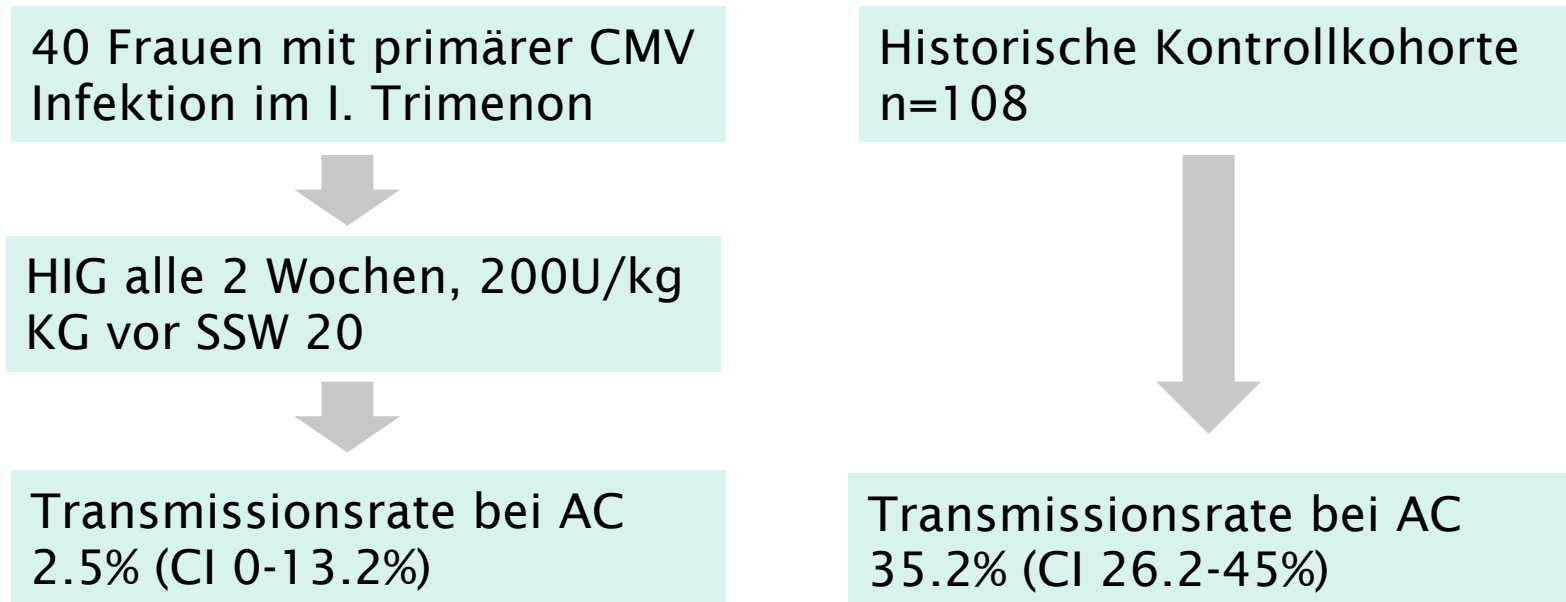
# Prävention der Transmission- HIG

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



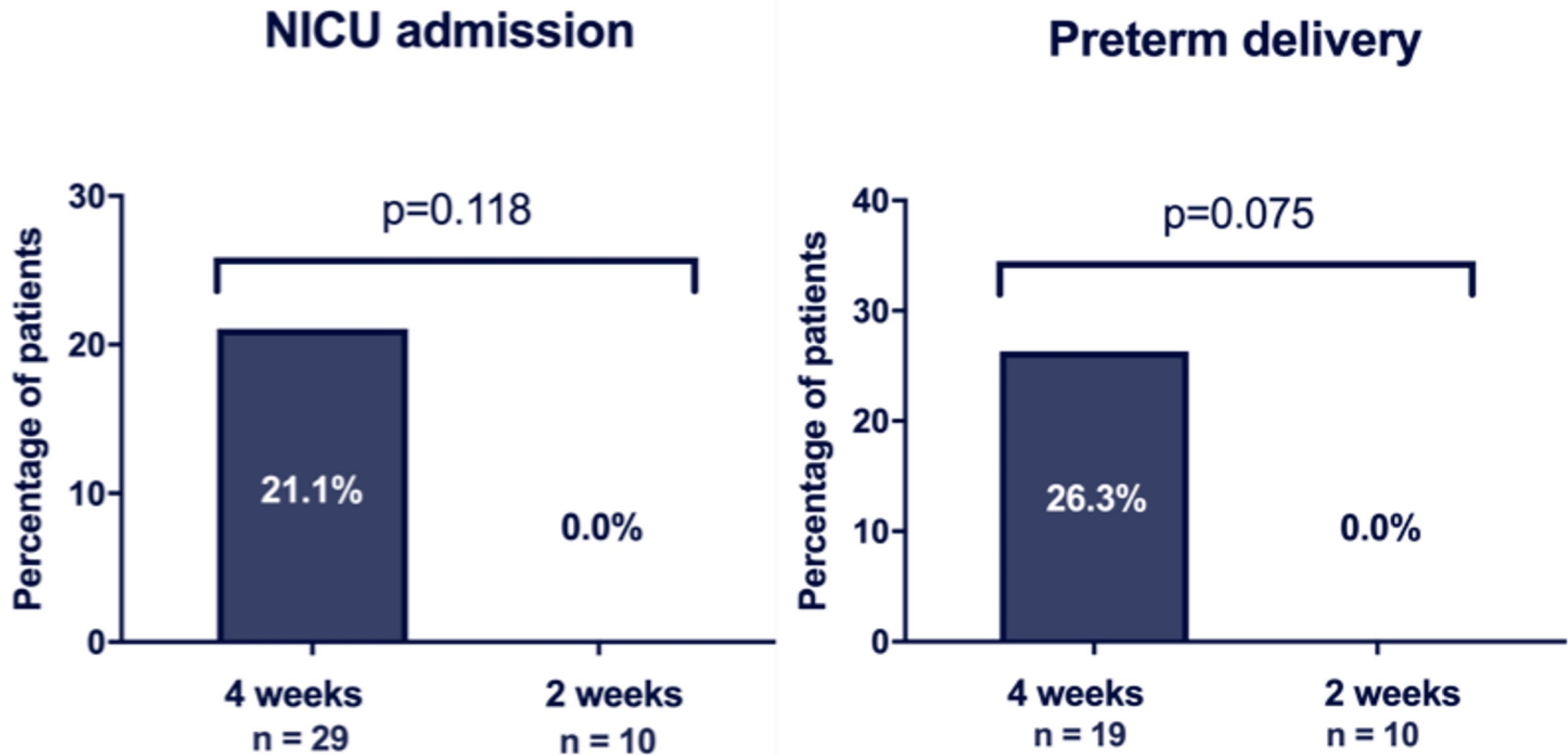
# Prävention der Transmission- HIG

Article

## Biweekly Versus Monthly Hyperimmune Globulin Therapy for Primary Cytomegalovirus Infection in Pregnancy

Nawa Schirwani-Hartl <sup>1</sup>, Pilar Palmrich <sup>1</sup>, Christina Haberl <sup>1</sup>, Nicole Perkmann-Nagele <sup>2</sup>, Herbert Kiss <sup>1</sup>, Angelika Berger <sup>3</sup>, Judith Rittenschöber-Böhm <sup>3</sup>, Gregor Kasprian <sup>4</sup>, Patric Kienast <sup>4</sup>, Asma Khalil <sup>5</sup> and Julia Binder <sup>1,\*</sup>

*J. Clin. Med.* **2023**, *12*, 6776. <https://doi.org/10.3390/jcm12216776>

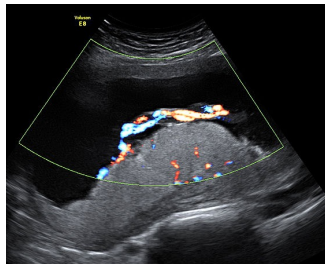


# Prävention- Therapiemöglichkeiten



Expositionsprophylaxe

Hygienemaßnahmen



Prävention der  
Transmission

Hyperimmunglobuline,  
Valaciclovir



Prävention der  
Symptomatik

Valaciclovir bei  
gesicherter  
Transmission

# Prävention der Transmission- Valaciclovir

**Valaciclovir to prevent vertical transmission of cytomegalovirus after maternal primary infection during pregnancy: a randomised, double-blind, placebo-controlled trial**

*Keren Shahar-Nissan\*, Joseph Pardo\*, Orit Peled, Irit Krause, Efraim Bilavsky, Arnon Wiznitzer, Eran Hadart, Jacob Amirt*

*Lancet 2020; 396: 779-85*

Prospektive,  
randomisierte  
placebo-  
kontrollierte  
Studie  
Nov 2015-Okt  
2018

100 Teilnehmerinnen mit primärer CMV Infektion- perikonzeptionell oder im 1. Trim.- randomisiert zu 8g Valaciclovir/d oder Placebo

50 Teilnehmerinnen- 8g  
Valaciclovir/d

50 Teilnehmerinnen- Plazebo

AC SSW 21-22

45 Teilnehmerinnen-11% pos AC

45 Teilnehmerinnen-30% pos AC

$p=0.29$ , OR 0.29, CI 95% 0.09-0.90



# Prävention der Transmission- Valaciclovir

## Effectiveness and safety of prenatal valacyclovir for congenital cytomegalovirus infection: systematic review and meta-analysis

Table 4 Pooled odds ratios (OR) of risk of congenital cytomegalovirus infection in pregnancies treated compared to those not treated with prenatal valacyclovir (VCV) therapy, according to timing of maternal infection

<i>Timing of infection</i>	<i>Studies (n)<sup>ref</sup></i>	<i>Fetuses affected: VCV vs no VCV (n/N)</i>	<i>Pooled OR (95% CI)</i>	<i>I<sup>2</sup> (%)</i>	<i>P</i>
<b>All studies</b>					
All maternal infections	3 <sup>7,8,11</sup>	23/164 vs 49/161	0.37 (0.21–0.64)	0	< 0.001
Periconceptional infection	3 <sup>7,8,11</sup>	5/67 vs 5/54	0.77 (0.21–2.80)	0	0.688
First-trimester infection	3 <sup>7,8,11</sup>	17/91 vs 38/93	0.34 (0.15–0.74)	20.9	0.001
Second-trimester infection	1 <sup>8</sup>	1/6 vs 6/13	0.020 (0.002–0.190)	—	0.001
Third-trimester infection	1 <sup>8</sup>	0/0 vs 0/1	—	—	—
<b>RCT</b>					
All maternal infections	1 <sup>11</sup>	5/45 vs 14/47	0.29 (0.10–0.90)	—	0.033
Periconceptional infection	1 <sup>11</sup>	3/26 vs 3/24	0.91 (0.17–5.03)	—	0.917
First-trimester infection	1 <sup>11</sup>	2/19 vs 11/23	0.13 (0.02–0.69)	—	0.002
Second-trimester infection	0	—	—	—	—
Third-trimester infection	0	—	—	—	—
<b>Observational studies</b>					
All maternal infections	2 <sup>7,8</sup>	18/119 vs 35/114	0.40 (0.21–0.76)	0	0.001
Periconceptional infection	2 <sup>7,8</sup>	2/41 vs 2/30	0.60 (0.08–4.42)	0	0.914
First-trimester infection	2 <sup>7,8</sup>	15/72 vs 27/70	0.43 (0.20–0.90)	0	0.026
Second-trimester infection	1 <sup>8</sup>	1/6 vs 6/13	0.020 (0.002–0.190)	—	0.001
Third-trimester infection	1 <sup>8</sup>	0/0 vs 0/1	—	—	—

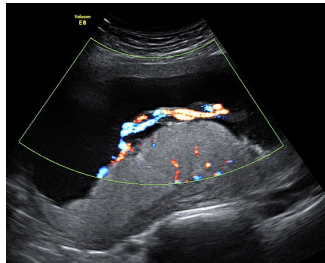
RCT, randomized controlled trial; ref, reference.

# Prävention- Therapiemöglichkeiten



Expositionsprophylaxe

Hygienemaßnahmen



Prävention der  
Transmission

Immunglobuline bis  
SSW 20-23, Valciclovir?



Prävention der  
Symptomatik

Valaciclovir bei  
gesicherter  
Transmission

# Prävention der Symptomatik

## In utero treatment of congenital cytomegalovirus infection with valacyclovir in a multicenter, open-label, phase II study

Marianne Leruez-Ville, MD, PhD; Idir Ghout, MSc; Laurence Bussi eres, PhD;  
Julien Stirnemann, MD, PhD; Jean-Fran ois Magny, MD; Sophie Couderc, MD;  
Laurent J. Salomon, MD, PhD; Tiffany Guilleminot, BA; Philippe Aegerter, MD, PhD;  
Guillaume Benoist, MD, PhD; Norbert Winer, MD; Olivier Picone, MD, PhD;  
Fran ois Jacquemard, MD; Yves Ville, MD, FRCOG

American Journal of Obstetrics & Gynecology OCTOBER 2016

41 Schwangere- 43 symptomatische Feten (US Zeichen)



8g/d Valaciclovir bis zur Geburt, mindestens 24 Wochen



34/41 asymptomatische NG (82%), 9 symptomatisch oder TOP (17%)

Historische Kohorte:  
Asymptomatische NG in nur 43%

# 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 Mazzei, 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

October 2023 **AJOG MFM**

**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)**

Outcome	Crude comparison				Weighted analysis		
	VCV n/N (%)	No VCV n/N (%)	OR	90% CI	OR	90% CI	<i>P</i> value
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

# Take Home Message



Expositionsprophylaxe- Hygienemaßnahmen



Immunglobuline (200 U/kg KG alle 2 Wochen)  
bis SSW 20 bzw Valaciclovir 8g/d zur  
Prävention einer Transmission bei primärer  
CMV Infektion

cave: Kontrolle der Nieren und  
Leberfunktionsparameter!  
- adverse outcome rate 2-3%



Valaciclovir (8g/d) zur Prävention einer  
Symptomatik bei pos AC

# Valacyclovir for prevention of congenital CMV

## A real-life multicenter Italian observational study

10 centers - 447 pregnant women with  
**primary CMV infection**  
acquired within 24w of pregnancy  
205 treated with valacyclovir 8g/day (VCV group)  
242 untreated (no-VCV group)

**61%** reduction of  
**CMV-DNA positive  
amniocentesis**  
in **VCV group** vs no-VCV group



**83%** reduction of  
**symptomatic  
congenital CMV  
infection at birth**  
in **VCV group** vs no-VCV group



**64%** reduction of  
**Termination of  
Pregnancy**  
in **VCV group** vs no-VCV group



Zammarchi et al AJOG 2023





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