Cytomegalievirusinfektion in der Schwangerschaft

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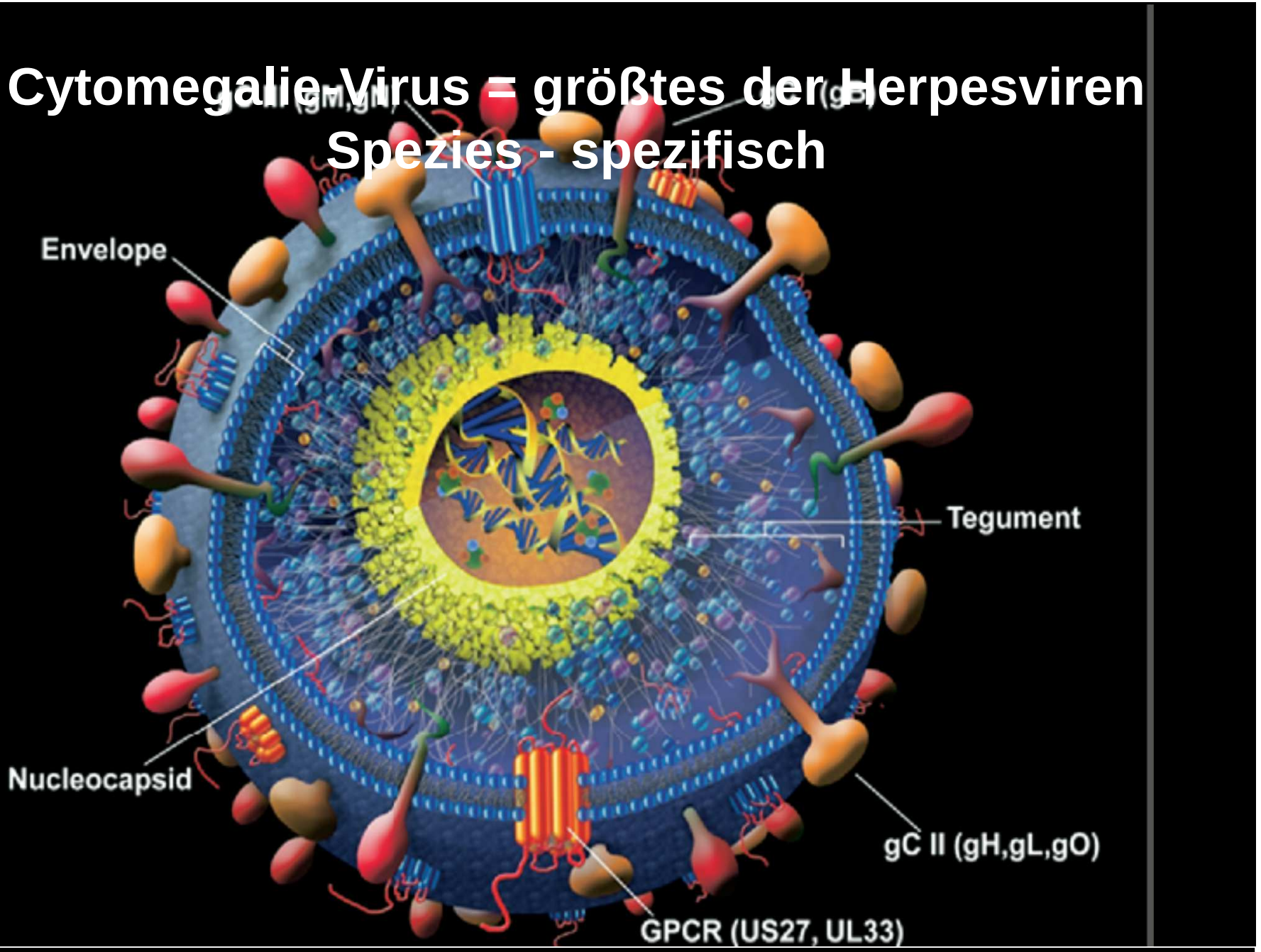
11. 4. 2013

Cytomegalie-Virus = größtes der Herpesviren
Spezies - spezifisch



Schematic representation of the CMV virion with a depiction of potential vaccine targets.
A. Townsend-Extreme Images. In: Schleiss, J Pediatr 2007;151:564-70

Klinik der CMV-Primärinfektion in der Schwangerschaft

Maternal

blande, unspezifisch

Fieber 60%
Lymphknotenschwellung, Müdigkeit 50%
Kopfschmerzen 27%

- 75% der Schwangeren mit CMV-Primärinfektion haben keinerlei klinische Symptomatik!

- Ultraschalldiagnostik erkennt nur 20% aller Primärinfektionen

- Virologische Pränataldiagnose ist unentbehrlich

Pränatales CMV - Screening ?

- Krankheit „wichtig“
  (Schwerwiegend, häufig?)
- Pränatal behandelbar ?
- Test: hohe Sensitivität und Spezifität
- Kosten / Nutzen

- Prävention

Konnatale CMV-Infektion

- Nicht ganz geklärt ist der Zusammenhang:
- Zeitpunkt der mat. Infektion in der SS
  vs.
  Schweregrad der fet. Erkrankung

Gindes et al. BJOG 2008;115:830-5

CMV-Transmission
< 20. SSWoche

- Die meisten Kinder mit kongenitaler Infektion wurden im 1. Trimester infiziert.

Stagno S et al. JAMA 1986;256:1904-8
Daiminger A et al. BJOG 2005;112:166-172

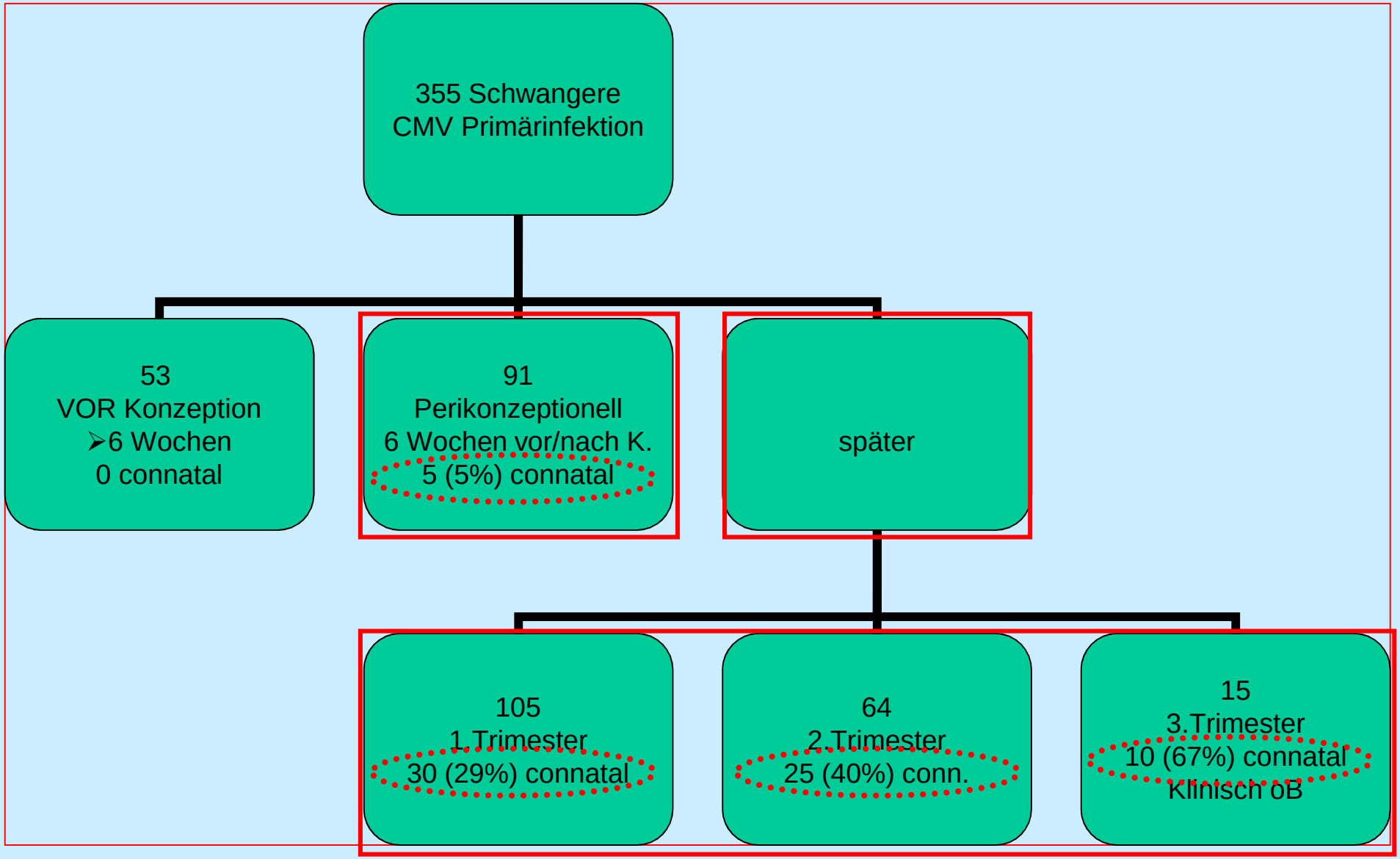
CMV-Transmission
im 3. Trimester

- Maternale Erstinfektion > 25. SSWoche
- 75% (21/28) Transmissionsrate.

- ... follow up 3 Jahre
- n=28, 1 IR, 27 Kinder gesund

Gindes et al. BJOG 2008;115:830-5.

Konnatale CMV-Transmission / Gestationszeit



Feldmann B, et al. AJOG 2006, S52 (SMFM abstract)

CMV-**Transmission** - nach Gestationszeit

Mat. Infektion im 3. Trimester 79%

Erhöhte plaz. Durchblutung !

Mat. Infektion im 2. Trimester 46%

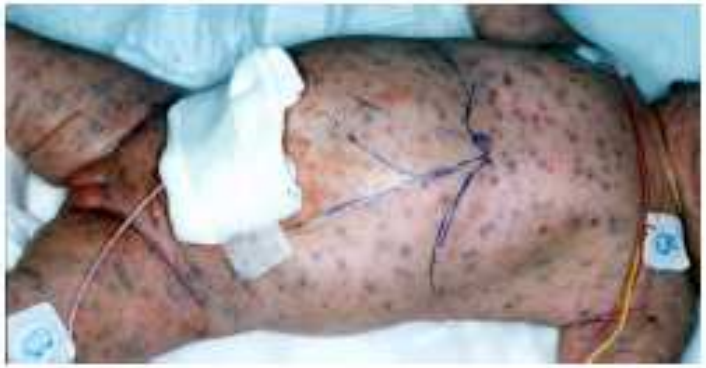
Mat. Infektion im 1. Trimester 46%

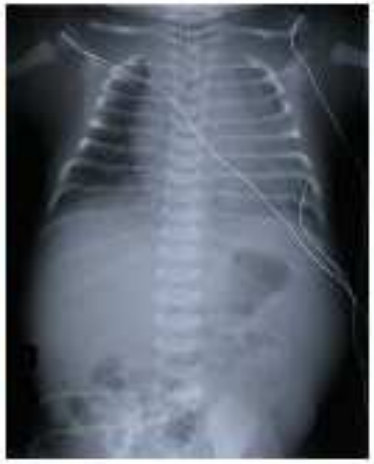
Bei mat. Reinfektion 1-2% (keine Virämie!)

Revello MG et al. J Clin Virol 2004;29:71-83

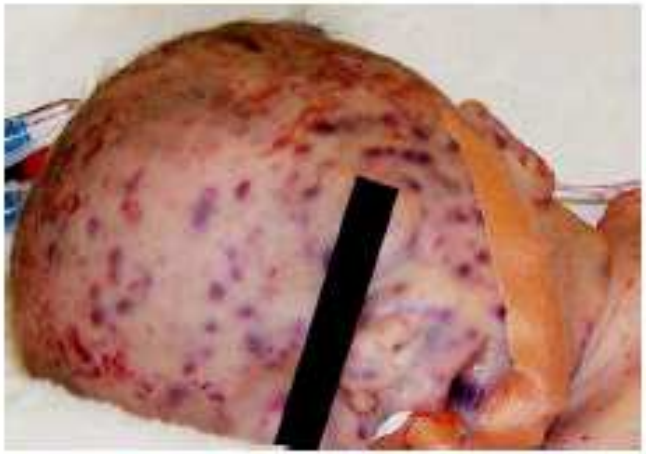
Transmission und Schädigung des Kindes

Die CMV-Infektion des Neugeborenen ist die weltweit häufigste kongenitale Infektion mit bis zu 10% schwerer ZNS-Schädigung





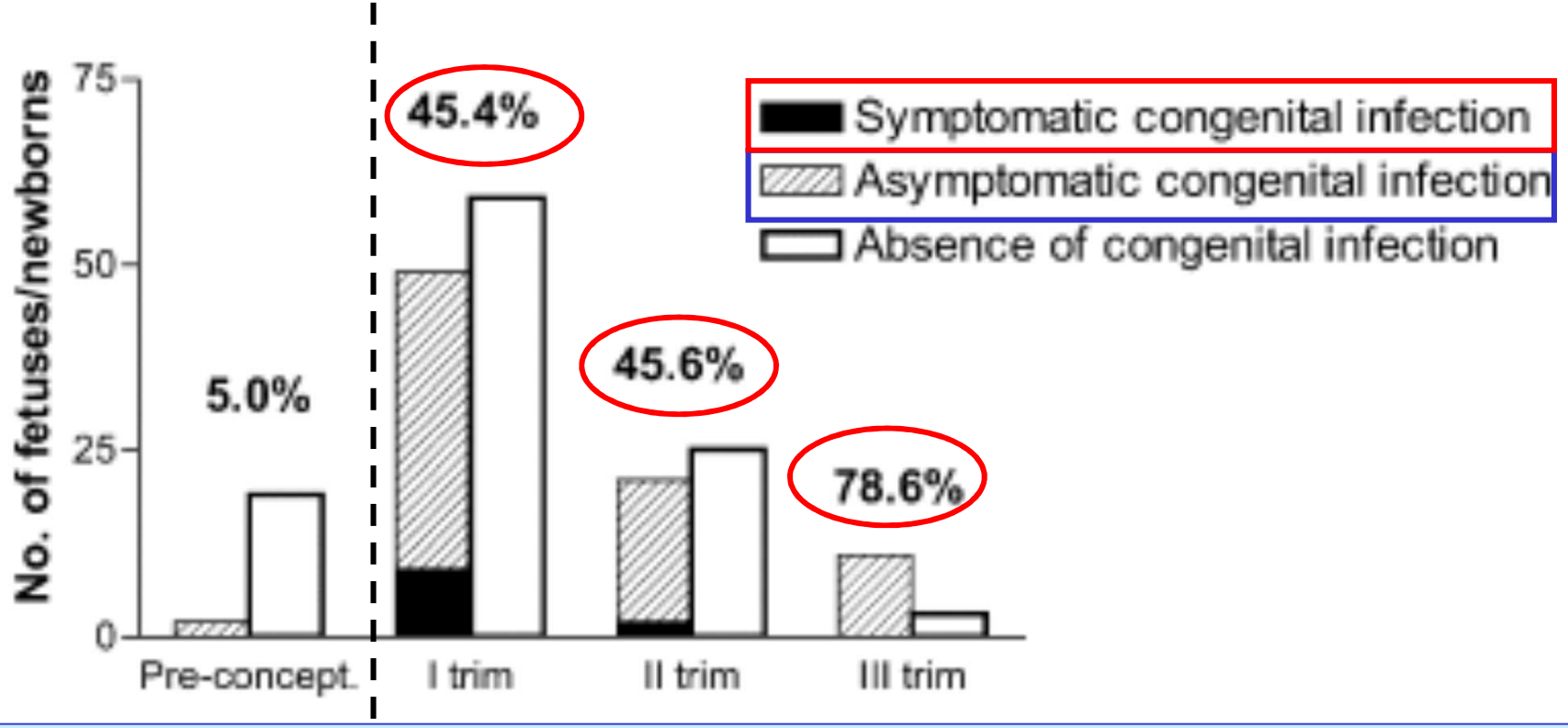
Schwere CID, Langzeit-GCV-Therapie, UL97 Mutation C607Y
Haas, Dep Neonatology, Greifswald, Germany



INfauste kongenitale CMV Infektion
M El-Amin Abdel Latif, E Sugo
NEJM, 362, 2010

K. Hamprecht/Tübingen

CMV Transmissionsrate Mutter > Kind nach Gestationszeit



Revello MariaGrazia et al. J Clin Virol 2004;29:71-83

CMV Erstinfektion / Gestationszeit

• **1. Trimenon** *n = 34*	• **2. + 3. Trimenon** *n = 40*
• Gehörschaden 24 %	• 2,5 %
• ZNS – Folgen (Gehör, geistige Entwicklung, Lähmungen, Krampfleiden, Chorioretinitis) 32 %	• 15 %
• Mehrf. Folgen 12%	• 0

Pass RF, et al. J Clin Virol 2006;35:216-20

OBSTETRICS

Pregestational, periconceptional, and gestational primary maternal cytomegalovirus infection: prenatal diagnosis in 508 pregnancies

Baruch Feldman, MD, PhD; Yoav Yinon, MD; Michal Tepperberg Oikawa, MSC; Rakefet Yoeli, MD; Eyal Schiff, MD; Shlomo Lipitz, MD

OBJECTIVE: The objective of the study was to evaluate the vertical transmission rate and fetal risk following primary maternal cytomegalovirus infection before and around conception.

STUDY DESIGN: Data of patients referred to fetal medicine clinic in 1 tertiary center in Israel were evaluated. Each included subject had primary maternal cytomegalovirus infection determined by serology, precise gestational dating, and testing of fetal infection. Subjects were assigned to five subgroups: pregestational, periconception, and first, second, or third trimester of pregnancy.

RESULTS: Five hundred eight pregnancies were included. None of the 97 pregnancies in the preconception group and 6 of the 130 periconception subjects (4.6%) were congenitally infected. Transmission rates were 34.8%, 42.0%, and 58.6% for the first, second, and third trimesters, respectively ($P = .049$). Prenatal and postnatal follow-up indicated that third-trimester infection has no clinical effect on the fetus.

CONCLUSION: Pre- and periconception maternal infection carries small risk for fetal infection, whereas it is positively correlated to time of maternal infection during pregnancy.

Key words: cytomegalovirus, periconception, pregestation, prenatal diagnosis

Cite this article as: Feldman B, Yinon Y, Tepperberg Oikawa M, et al. Pregestational, periconceptional, and gestational primary maternal cytomegalovirus infection: prenatal diagnosis in 508 pregnancies. Am J Obstet Gynecol 2011;205:342.e1-6.

TABLE 1

Vertical CMV transmission rate by gestational age at the time of maternal infection

Study group	Pregnancies, n[a]	CMV positive pregnancies, n	Transmission rate, %
Pregestation	97	0	0
Periconception	130	6	4.6
First trimester	152	53	34.8
Second trimester	100	42	42.0
Third trimester	29	17	58.6
All cases	508	118[b]	23.2
Gestational cases[c]	281	112	39.9

CMV, cytomegalovirus.

[a] Each of the 16 twin pregnancies is considered as 1 data point; [b] Each of the 2 twin pregnancies with 1 positive twin and 1 negative twin was calculated as 1 positive data point; [c] First-, second-, and third-trimester pregnancies only.

Feldman. Prenatal diagnosis of primary maternal CMV. Am J Obstet Gynecol 2011.

S. Lipitz, AJOG 1011

TABLE 1

Vertical CMV transmission rate by gestational age at the time of maternal infection

LB/Gehör

Study group	Pregnancies, n[a]	CMV positive pregnancies, n	Transmission rate, %	
Pregestation	97	0	0	
Periconception	130	6	4.6	1 / 0
First trimester	152	53	34.8	12 / 1
Second trimester	100	42	42.0	15 / 1
Third trimester	29	17	58.6	17 / 0
All cases	508	118[b]	23.2	
Gestational cases[c]	281	112	39.9	

CMV, cytomegalovirus.

[a] Each of the 16 twin pregnancies is considered as 1 data point; [b] Each of the 2 twin pregnancies with 1 positive twin and 1 negative twin was calculated as 1 positive data point; [c] First-, second-, and third-trimester pregnancies only.

Feldman. Prenatal diagnosis of primary maternal CMV. Am J Obstet Gynecol 2011.

S. Lipitz, AJOG 1011

Symptomatische, kongenitale CMV

Kind

Kongenital CMV - infiziert

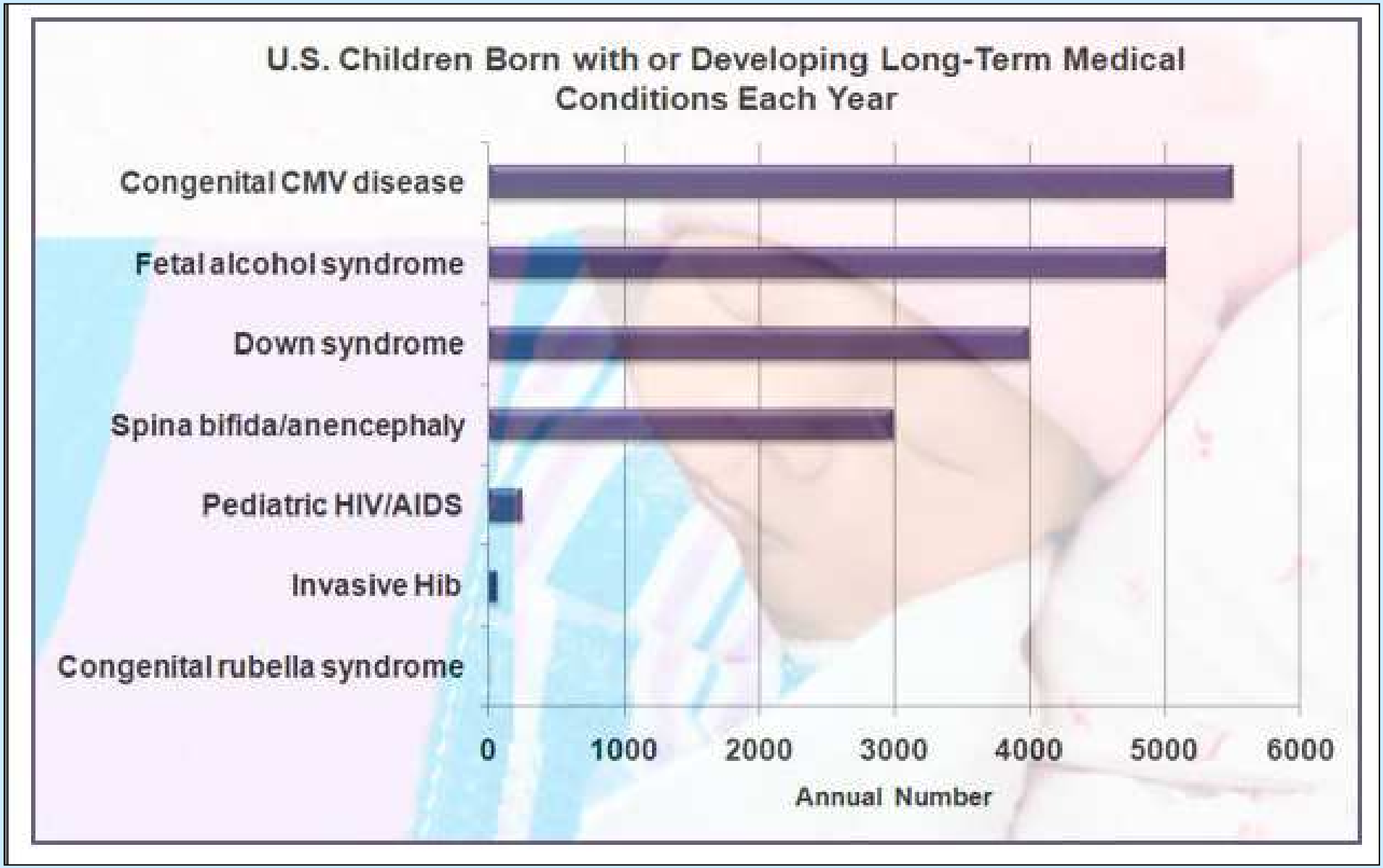
85-90% klinisch oB.

5-15% auffällig

Innerhalb 2 Jahren

5-15% Gehörverlust, Optikusatrophie,
psychomotor. Entw.-Verzögerung
(geistige Retardierung).

Stagno S et al. NEJM 1985;313:1270-1273 Demmler et al. Rev Infect Dis 1991;13:315-29



http://www.**cdc**.gov/cmv/trends-stats.html#affected

Prävalenz der CMV-Infektion in der Schwangerschaft

Cytomegalovirus (CMV)

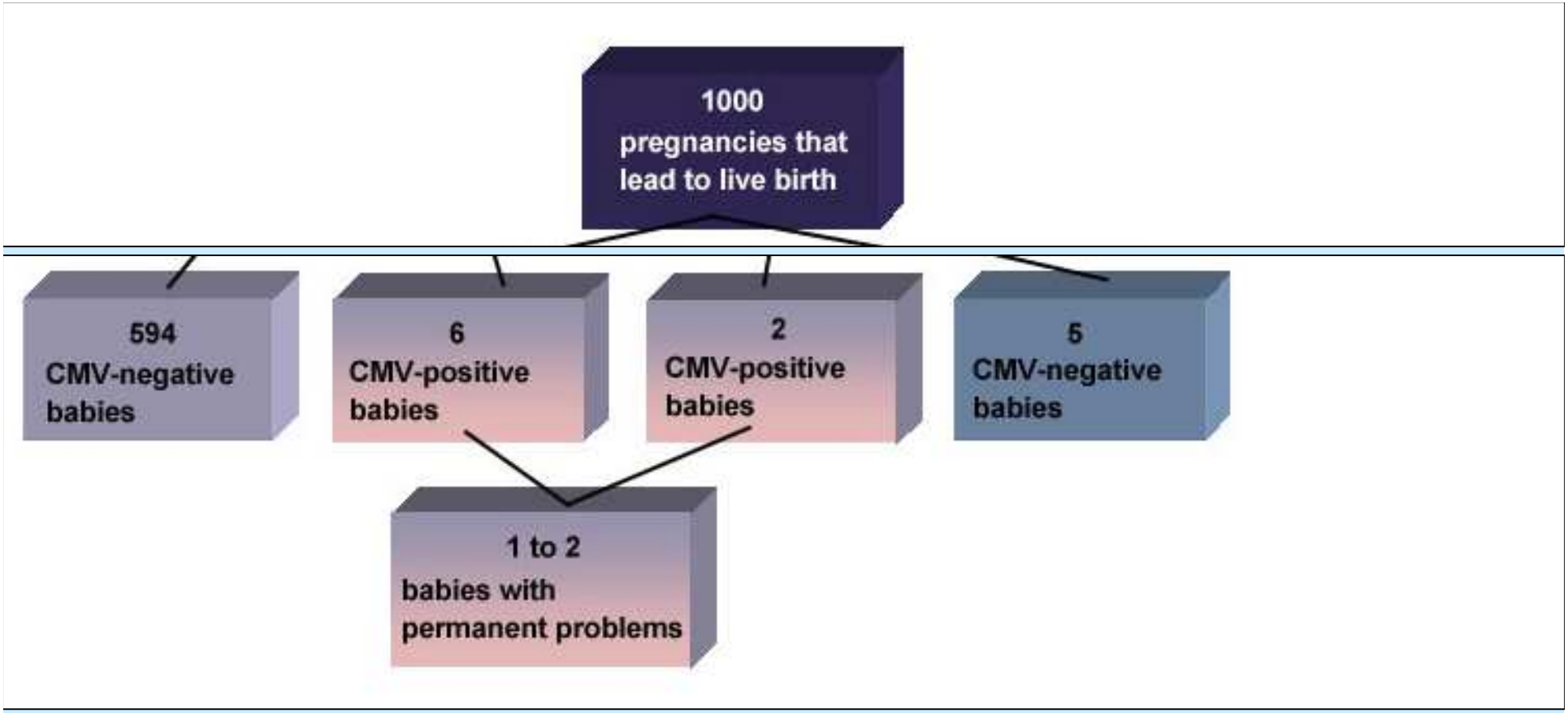
Pregnancy

Each year in the United States, about 1 in 750 children are born with or develop disabilities as a result of CMV infection.

Most babies with congenital (meaning from birth) CMV never have health problems. But, in some babies, congenital CMV causes health problems when the baby is born or later in the baby's life. These health problems may include

- Hearing loss
- Vision loss
- Mental disability
- Lung problems
- Bleeding problems
- Liver problems
- Spleen problems
- Growth problems

Sometimes health problems such as hearing or vision loss do not occur until months or years after



OVERALL, OUT OF 1,000 LIVE BIRTHS,
ABOUT 8/1000 INFANTS (LESS THAN 1%) WILL HAVE CONGENITAL CMV INFECTION, OF WHICH
1-2/1000 (0.1%) WILL HAVE PERMANENT PROBLEMS.

CANNON MJ. CONGENITAL CMV EPIDEMIOLOGY AND AWARENESS
J CLIN VIROL. 2009;46 [SUPPL 4]:S6-10.

Prävalenz der CMV-Infektion in der Schwangerschaft Grazer Studie

Grazer Studie (1999-2000)

- 947 **Schwangere** (Serumscreening)
  486 CMV-Ig**G** positiv = 51%
  Bereits < 20 J ca. 51%
  …also altersunabhängig

  461 CMV-Ig**G** negativ = 49%

- (< 30 J ... 56% CMV-Ig**G** positiv
  Munro SC et al. J Clin Microbiol 2005;43(9):4713-18)

Halwachs-B. G, Genser B. Die konnatale CMV-Infektion. Springer 2003, S. 43

Grazer Studie (1999-2000)

- 947 **Schwangere** (Serumscreening)

- 18 CMV-Ig**M** positiv
  36 CMV-Ig**M** Grenzbereich, unklar

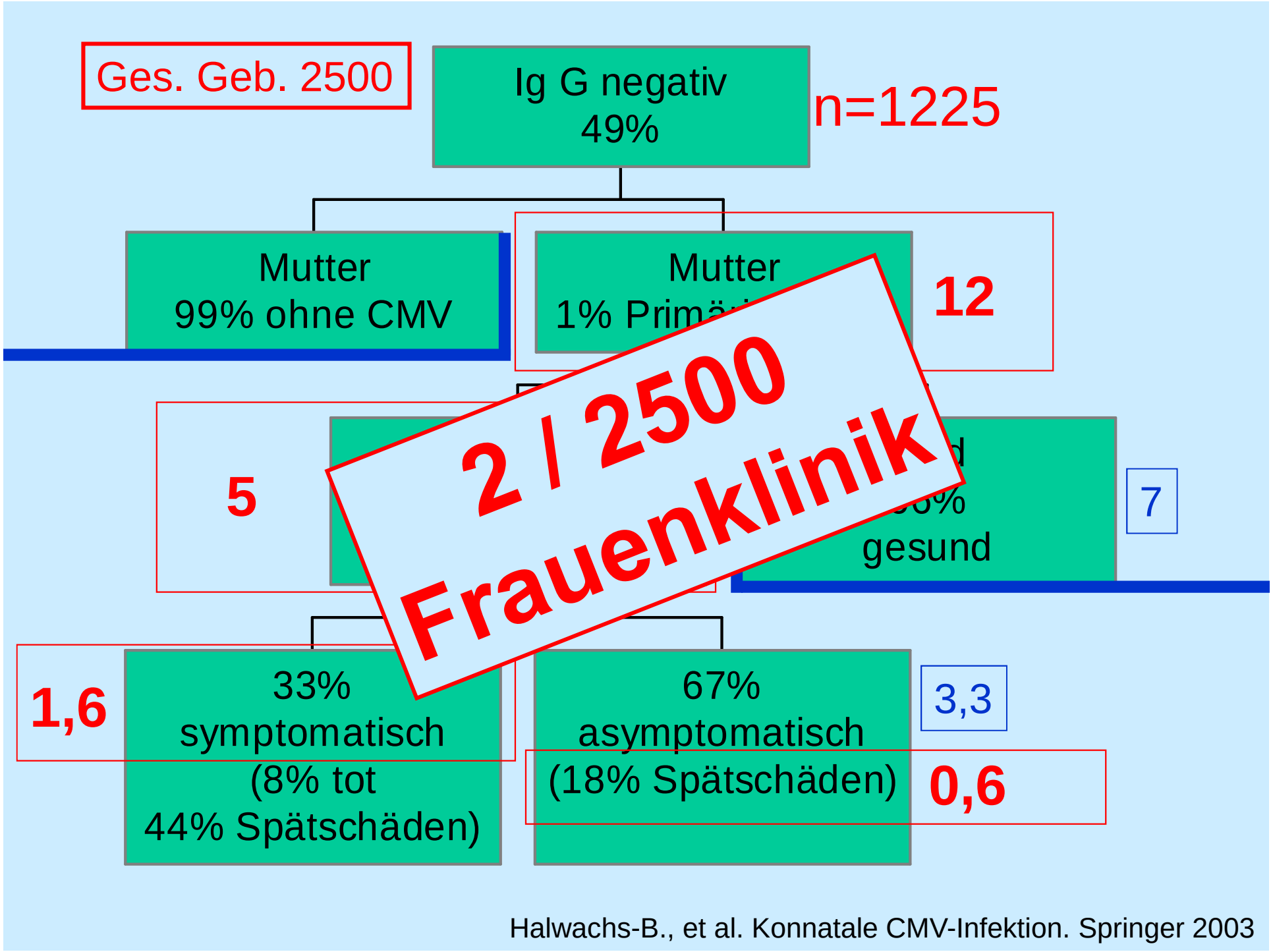
Halwachs-B. G, Genser B. Die konnatale CMV-Infektion. Springer 2003, S. 43

Hochrechnung
für die Grazer Frauenklinik,
2500 Geburten / Jahr

49% IgG negativ

51% IgG positiv

Halwachs-B., Genser. Die konnatale CMV-Infektion. Springer 2003, S. 46



Halwachs-B., et al. Konnatale CMV-Infektion. Springer 2003

Intrauterine Therapie der CMV-Infektion ?

Symptomatische, kongenitale CMV

- Erster Bericht / Nachweis im Fruchtwasser:

  Davis LE, et al.

  1971

  Intrauterine diagnosis of CMV infection: viral recovery from amniocentesis fluid.

  Am J Obstet Gynecol 1971;109:1217-19

Therapie – (erster Bericht)

Gynäko-Infektiologie

Zytomegalie-Infektion bei Zwillingsschwangerschaft – Reversibilität eines Hydrops fetalis nach Behandlung mit Humanimmunglobulin (Cytotect®)

A. Breinl und R. Laßmann

Bei der 23jährigen Zweitgravida handelte es sich um eine Zytomegalie-Infektion der biamnialen Zwillingsschwangerschaft. Die Infektion war durch Anamnese, Symptomatologie und Serologie gesichert. Der Hydrops fetalis mit isoliertem Aszites, Hautödem und Kardiomegalie des einen Zwillingskindes war in der 26. Schwangerschaftswoche sonographisch diagnostiziert worden. In der Folge wurde eine Therapie mit dem humanen Hyperimmunglobulin Cytotect® und Digitalisierung versucht. Die

„Grippaler Infekt", geringe Gewichtszunahme

Menstruationsanamnese und dokumentierte Ultraschallbefunde (ab dem ersten Trimenon) sprachen bei der 23jährigen Zweitgravida für ein gesichertes Gestationsalter der biamnialen Zwillingsschwangerschaft. Wegen schlechten Allgemeinbefindens wurde die Patientin in der 26. Schwangerschaftswoche stationär aufgenommen. Die Anamnese ergab einen „grippalen Infekt" mit subfebrilen T… schmerzhafter Ansch… …len zwischen … …er-schaftswoche.

1989

Die Gewichtszunah… …nger-schaft betrug bis zu diesem … …ledig-lich 6 Kilogramm. Laborchemis… …fanden sich eine ausgeprägte Anämie (Hb 9,0 g/100 ml, Hämatokrit 25 %), eine mäßige Leukozytose mit 13 200 Leukozyten/mm³ Blut, eine Hyperbilirubinämie und pathologische Leberfunktionsproben (Bilirubin direkt 1,77 mg/100 ml, Bilirubin indirekt 0,85 mg/100 ml, SGOT 51 U/l, SGPT 107 U/l, Cholinesterase 2,4 mg/100 ml) sowie eine für die Schwangerschaft bedingt erhöhte alkalische Phosphatase (350 U/l). CRP und ASL: positiv, Gamma-GT: normal, Urikult: negativ, Hepatitisserologie: negativ, Blutgruppe: 0, Rhesusfaktor: positiv. Antikörpersuchtest: negativ.

Das Infektionsscreening bei der Mutter erbrachte den hochgradigen Verdacht auf Zytomegalie-Infektion: CMV-KBR: 1:40, CMV-IgM: positiv, CMV-IgG: positiv (5, 11, 12).

- Breinl A, Laßmann R
  CMV-Infektion bei Zwillingsschwangerschaft – Reversibilität eines Hydrops fetalis nach Behandlung mit CMV-IgG (Cytotect):

- 26.SSW Hydrops + Cardiomegalie
  ... „Therapievorschlag Dr. Popov, Hygieneinstitut Wien“…
  28. SSW Cytotect 2ml/kgKG
  31.,34. und 37.SSWoche 1ml/kgKG
  Follow up 11. Lebensmonat: gesund

  gyne 1989;12:xxx

Therapie-Berichte

1995

- Bratcher DF, et al.

  Effect of passive antibody on congenital cytomegalovirus infection in guinea pigs.

  J Infect Dis 1995;172:944-950

Therapie-Berichte

1999

- Zwillinge, mat. CMV Infektion ein Zwilling IUGR, dicke Plazenta und NS-Ödem.
- ... CMV IgG
- Post partum: 1 Kind infiziert, aber gesund

Nigro G, et al. Am J Obstet Gynecol **1999**;180:1222-1226

Therapie-Berichte

2000

- Cosmi E, Nigro G, et al.

  Therapy or prevention of fetal infection by CMV with immunoglobulin infusion in pregnant women with primary infection

  Acta Biomed Aten Parm **2000**;71suppl1:547-551

The NEW ENGLAND JOURNAL of MEDICINE

2005

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*

ABSTRACT

BACKGROUND

Currently, there is no effective intervention for a primary cytomegalovirus (CMV) infection during pregnancy.

METHODS

We studied pregnant women with a primary CMV infection. The therapy group comprised women whose amniotic fluid contained either CMV or CMV DNA and who were offered intravenous CMV hyperimmune globulin at a dose of 200 U per kilogram of maternal weight. A prevention group, consisting of women with a recent primary infection before 21 weeks' gestation or who declined amniocentesis, was offered monthly hyperimmune globulin (100 U per kilogram intravenously).

From the Departments of Pediatrics (G.N.) and Gynecological Sciences, Perinatology, and Child Health (G.N., R.L.), La Sapienza University, Rome; and the Department of Pediatrics and Biostatistics, Medical College of Virginia Campus, Virginia Commonwealth University, Richmond (S.P.A., A.M.B.). Address reprint requests to Dr. Nigro at Via dei Villini 35, 00161 Rome, Italy, or at nigrogio@libero.it.

*Members of the Congenital Cytomegalovirus Collaborating Group are listed in the Appendix.

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

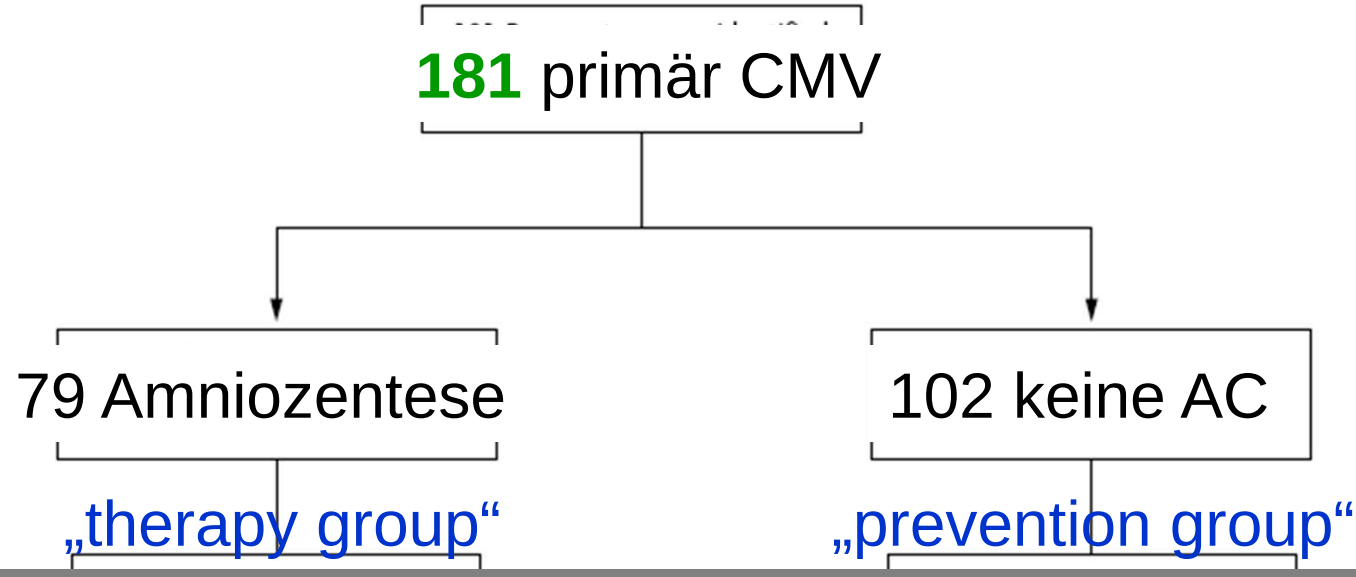
Prospektive Studie 1995-2003

Nigro G, et al. NEJM **2005**;353:1350-62

„Primäre CMV-Infektion“ =

181 Serokonversionen

26 IgM AK pos. gegen CMV,
und CMV IgG steigend,
und Avidität < 25%



Einschluss:

Primäre CMV-Infektion

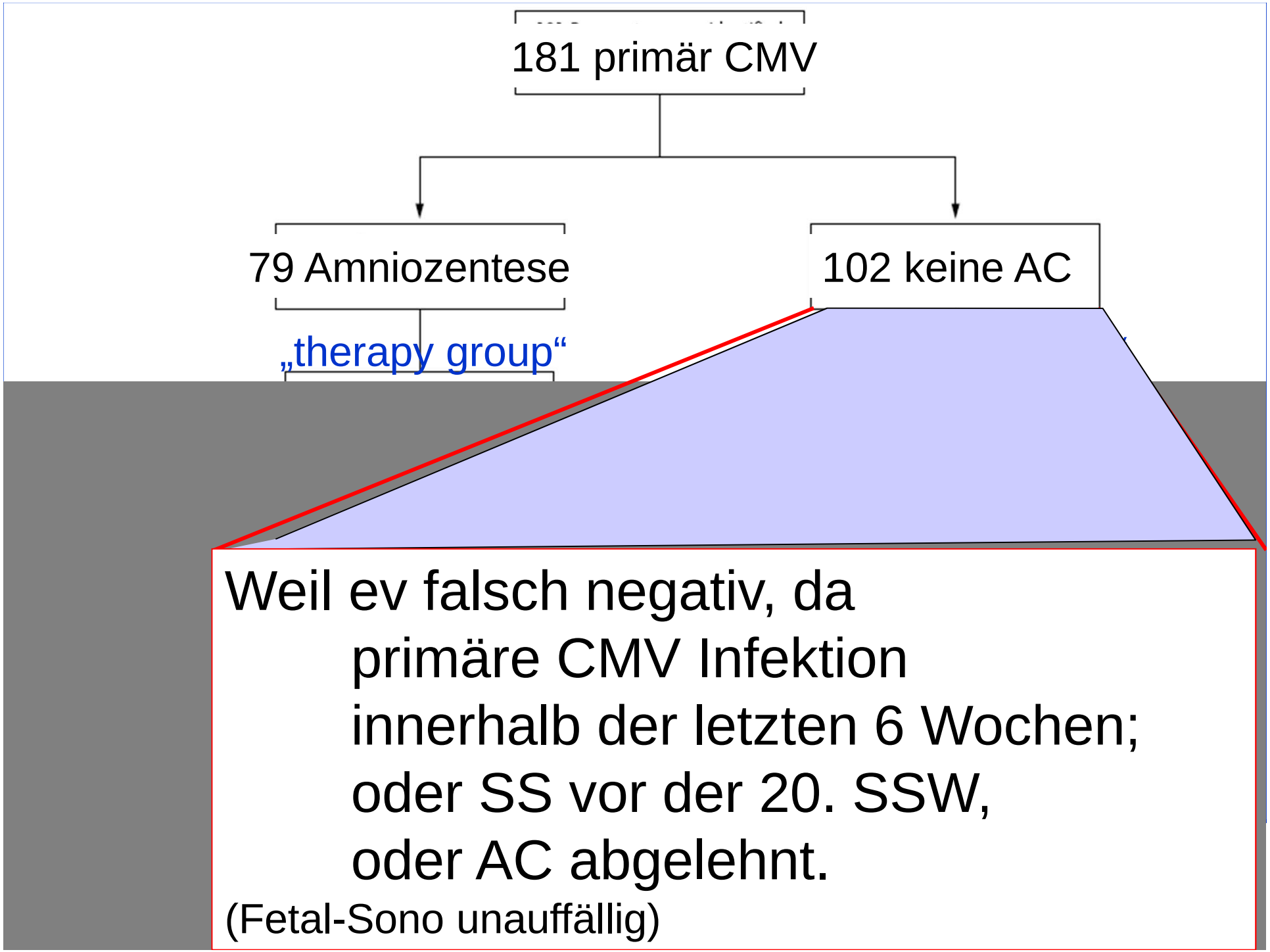
einige Monate vor SS

während der SS

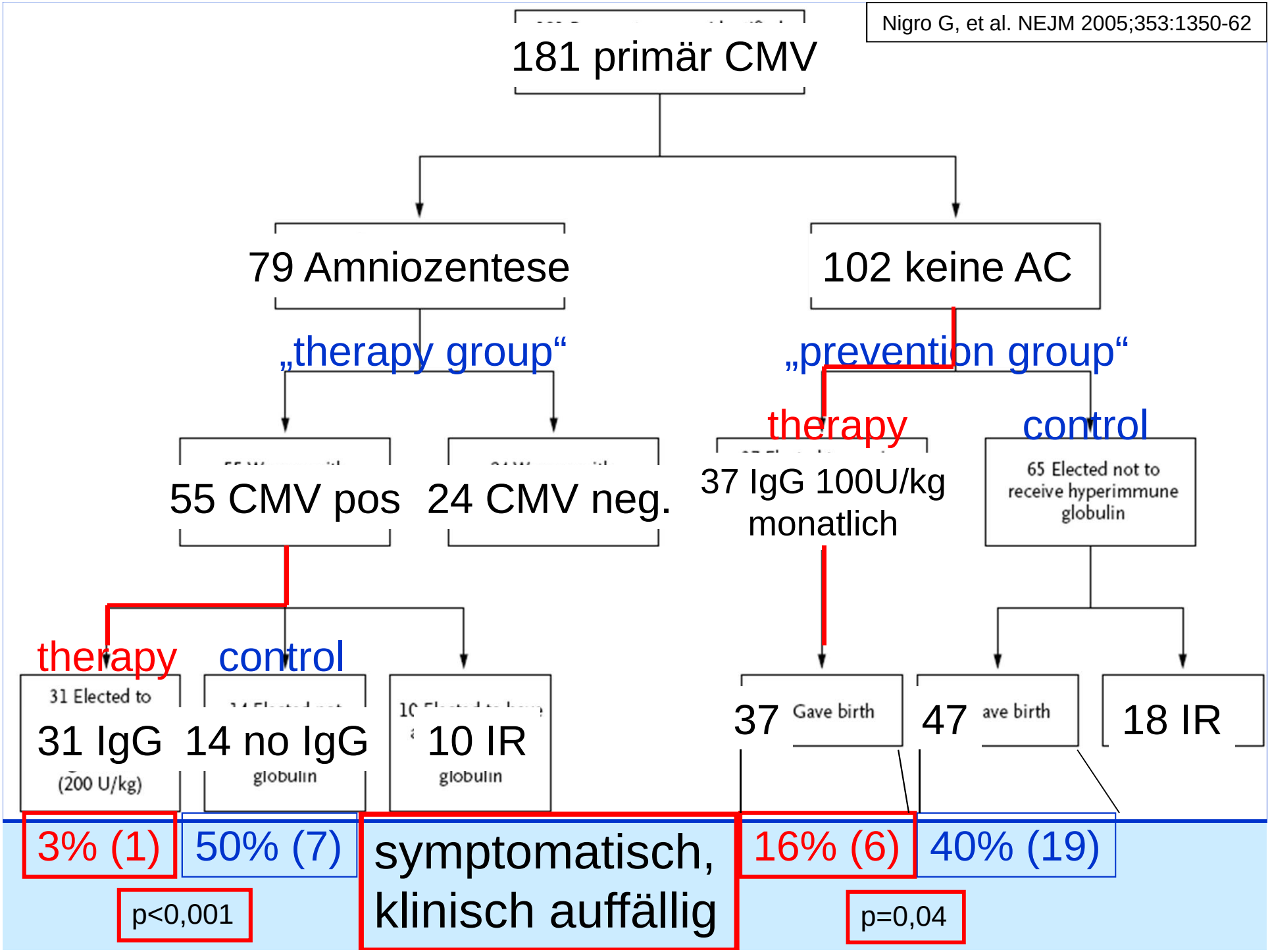
Amniozentese CMV pos.

(PCR...DNA, oder Kultur).

Nigro G, et al. NEJM 2005;353:1350-62


181 primär CMV
79 Amniozentese
102 keine AC
„therapy group“
Weil ev falsch negativ, da
primäre CMV Infektion
innerhalb der letzten 6 Wochen;
oder SS vor der 20. SSW,
oder AC abgelehnt.
(Fetal-Sono unauffällig)

Nigro G, et al. NEJM 2005;353:1350-62



Pränatal „symptomatische“ CMV

- Wurde bei 14 Feten unter mat. CMV-IgG-Behandlung unauffällig.

  (Plazenta und Kind therapiert).

Nigro G, et al. NEJM 2005;353:1350-62

Nigro-Studie weitere Ergebnisse

- Cytotect Biotest im 3. Trimester ist eher nicht hilfreich. (Obwohl besserer anti-CMV IgG – Transfer Mussi et al. J Med Virol 2003;69:232-9)
- Infusion ins Fruchtwasser sinnlos.
- Intra-umbilical (NS) ist fraglich.
- Cytotect weniger effektiv in Verhütung fetaler Infektion, als in deren Therapie.

Nigro G, et al. NEJM 2005;Sept.29:1350-62

Nigro, 2008

PRENATAL DIAGNOSIS
Prenat Diagn 2008; **28**: 512–517.
Published online in Wiley InterScience
(www.interscience.wiley.com) **DOI:** 10.1002/pd.2013

Regression of fetal cerebral abnormalities by primary cytomegalovirus infection following hyperimmunoglobulin therapy

Giovanni Nigro[1]*, Renato La Torre[2], Henny Pentimalli[3], Paola Taverna[4], Mario Lituania[5], Begoña Martinez de Tejada[6] and Stuart P. Adler[7]

Table 1—Outcome among children born to women with CMV-infected amniotic fluid and ultrasonographic evidence of fetal CMV disease after HIG therapy (cases 1–3) or nontherapy (cases 4–5)

Mother–infant pair	Maternal time of seroconversion (weeks gestation)	HIG administered (weeks' gestation)	Ultrasonographic evidence of fetal CMV disease (weeks gestation)	Signs and symptoms at birth
1	10–21	29 IV 33 IV + IA	Ventriculomegaly, periventricular echodensities (29)	None
2	7–12	24 IV 26 IV 30 IV + IA	Ventriculomegaly, ascites, hepatosplenomegaly (24)	None
3	8–19	22 IV 25 IV + IA	Ventriculomegaly, intestinal echodensities (22)	None
4	10	None	Ventriculomegaly (29)	Microcephaly, Ventriculomegaly, endoventricular cyst, subcortical atrophy bilateral chorioretinitis and deafness
5	<12	None	Ventriculomegaly (35)	Periventricular calcifications, cortical and cerebellar atrophy, leukomalacia

CMV, cytomegalovirus; HIG, hyperimmunoglobulin; IV, intravenous HIG administered; IA, intra-amniotic HIG administered.

Nigro, 2010, Am J Pathol

The American Journal of Pathology, Vol. 177, No. 3, September 2010
Copyright © American Society for Investigative Pathology
DOI: 10.2353/ajpath.2010.091210

Immunopathology and Infectious Diseases

Ekaterina Maidji,* Giovanni Nigro,† Takako Tabata,* Susan McDonagh,* Naoki Nozawa,* Stephen Shiboski,‡ Stefania Muci,† Maurizio M. Anceschi,§ Natali Aziz,¶ Stuart P. Adler,‖ and Lenore Pereira*

Antibody Treatment Promotes Compensation for Human Cytomegalovirus-Induced Pathogenesis and a Hypoxia-Like Condition in Placentas with Congenital Infection

factor. With hyperimmune globulin treatment, placentas appeared uninfected, vascular endothelial growth factor and Flt1 expression was reduced, and sFlt1 levels in amniotic fluid were lower. An increase in the number of chorionic villi and blood vessels over that in controls suggested compensatory development for a hypoxia-like condition. Taken together the results indicate that antibody treatment can suppress HCMV replication and prevent placental dysfunction, thus improving fetal outcome. *(Am J Pathol 2010, 177:1298–1310; DOI: 10.2353/ajpath.2010.091210)*

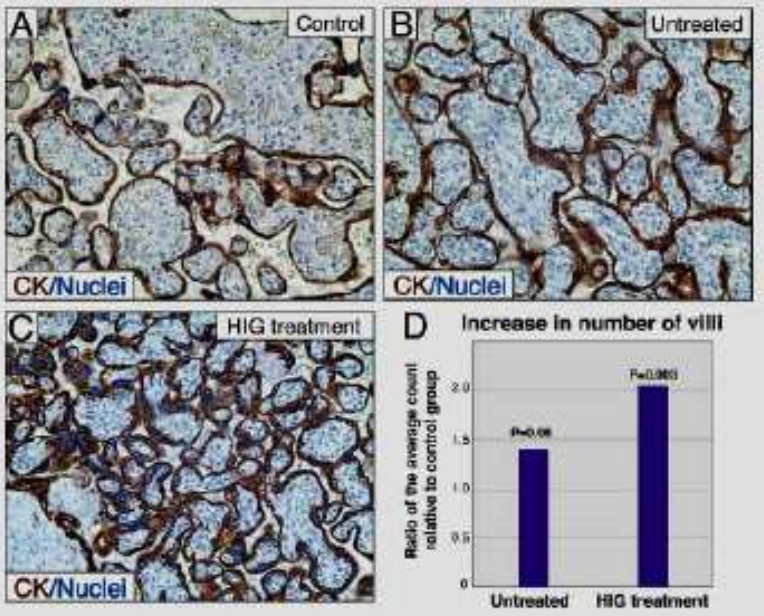


Figure 3. Significant increase in the number of chorionic villi in placentas in

Antenatal interventions for preventing the transmission of cytomegalovirus (CMV) from the mother to fetus during pregnancy and adverse outcomes in the congenitally infected infant (Review)

McCarthy FP, Giles ML, Rowlands S, Purcell KJ, Jones CA

THE COCHRANE COLLABORATION®

Ausschlußkriterien für 6 klinische Studien (McCarthy rt al., 2011)

Study	Reason for exclusion
Adler 1996	A RCT in which seronegative non-pregnant mothers with a child less than 36 months of age and shedding cytomegalovirus were assigned to 1 of 3 groups. An education group, an adherence and education group or a control group. A fourth group of pregnant women were included in the trial. However, these pregnant women all were assigned to the education group without randomisation. This trial was excluded as it addressed the prevention of child to mother transmission of CMV.
Adler 2004	A prospective RCT which investigated interventions for the prevention of child to mother transmission of CMV among pregnant women. Seronegative women, pregnant or attempting pregnancy were randomised to behavioural recommendations and education regarding CMV infection. We excluded this trial as it addressed the prevention of child to mother transmission of CMV.
Jiang 2006	Prospective non-blinded non-placebo controlled randomised trial examining the effects of Jinye Baidu Granule (JYBDG) on fetal growth and development in women with maternal active human CMV infection. We excluded this trial because of methodological issues. There were insufficient diagnostic criteria for determining both primary maternal CMV infection and congenital CMV infection. Pregnant women with a history of an abnormal pregnancy were included. Of 118 controls and 122 interventions fetal outcomes were available on only 38 control pregnancies and 46 treatment pregnancies. The corresponding author was contacted to clarify diagnostic criteria, the exact nature of the "filial" samples used, the exact histories of women with abnormal pregnancies, allocation concealment and missing data. We received no response.
Nigro 2005	Pregnant women with a confirmed primary CMV infection were assigned to a therapy group who were offered intravenous CMV hyperimmune globulin or a prevention group who were offered monthly hyperimmune globulin. We excluded this trial as it was a non-RCT.
Pass 2009	Double blinded RCT which investigated the use of a vaccine to prevent maternal CMV infection. We excluded this trial because the vaccine was administered exclusively to non-pregnant postpartum women to investigate the prevention of primary maternal CMV infection.
Picone 2009	A prospective trial in which women were screened for CMV by serological testing at 12 weeks gestation. If women screened negative, both parents were provided with detailed hygiene information on the prevention of transmission of CMV. Serological testing was then repeated at 36 weeks' gestation. We excluded this study because it was not a RCT but a prospective cohort study, and it used a historical control.

Objectives

The aim of this review was to assess the benefits and harms of interventions used during pregnancy to prevent mother to fetus transmission of CMV infection.

Search strategy

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (31 December 2010).

Selection criteria

All randomised controlled trials (RCTs) and quasi RCTs investigating antenatal interventions for preventing the transmission of CMV from the mother to fetus during pregnancy and adverse outcomes in the congenitally infected infant.

Data collection and analysis

Two review authors independently assessed studies for inclusion.

Main results

We identified six studies from the search. None of these studies met the pre-defined criteria for inclusion in this review.

Catch-22 Problem

Wir können primäre CMV Infektionen in der SS diagnostizieren, aber wir tun es nicht routinemäßig, weil wir keine klare Behandlungsmöglichkeit haben. Aber wir können eine solche Therapie nicht entwickeln, solange Schwangere nicht routinemäßig gescreent und in Studien eingeschlossen werden.

Griffiths PD. RevMedVirol 2006;16:1-4

Aktuell laufende HIG-Studien zur Prävention der connatalen CMV Infektion

M G Revello, Pavia, Italien

Efficacy Study of Human Cytomegalovirus (HCMV) Hyperimmune Globulin to Prevent Congenital HCMV Infection (**CHIP**)
Double blinded RCT, presumed diagnosis, no screening
HIG: **100 U/kg** (Cytotect) **iv** every 4 weeks

K Friese, München, Germany

Biotest Study 963: CMV Study
Prevention of congenital CMV infection in infants of mothers with primary CMV infection during pregnancy
Study inclusion: seronegative women, CMV screening
In case of seroconversion : **200 U/kg** HIG (Cytotect) **iv**

K. Hamprecht/Tübingen

Biotest Studie 963

>Prävention kongenitaler

CMV Infektion

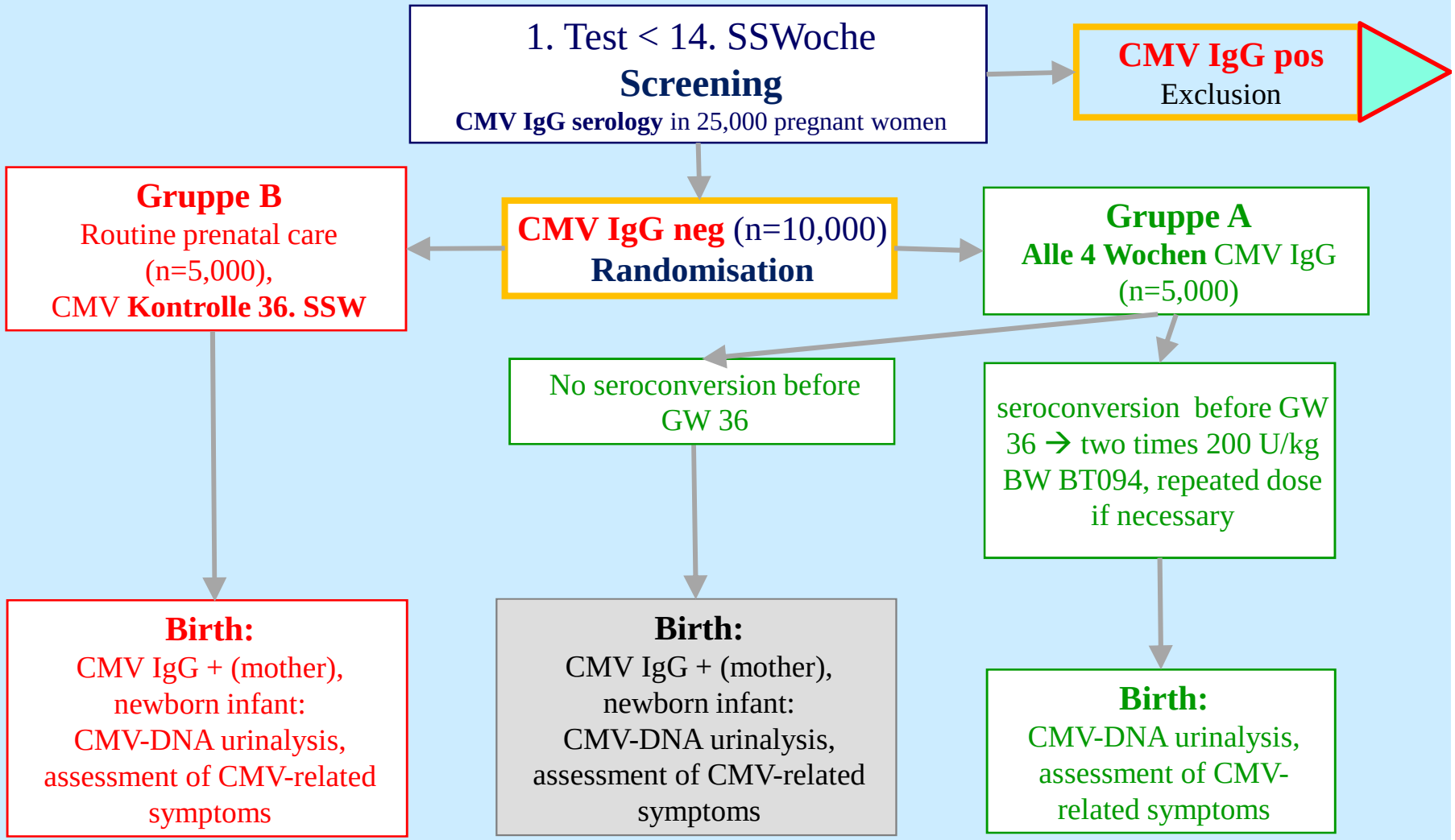
bei primärer Infektion in der Schwangerschaft<

Cytomegalievirus Infektion in der Schwangerschaft
Biotest Phase III Study 963 / Design

- **Studientitel**
  Prävention kongenitaler CMV Infektion bei primärer Infektion in der Schwangerschaft
- **Study Design**
  A randomised, open, controlled, prospective, multicentre and multinational study investigating efficacy and safety of Cytotect FH, nanometer filtered (BT094)
- **Study Drug**
  BT094 (Cytotect FH, nanometer filtered)
  Human CMV immunoglobulin with
  >70 U/ml of high avidity anti-CMV IgG

Cytomegalievirus Infektion in der Schwangerschaft

Biotest Phase III Study 963 Design



April 2013

Biotest AG, Corporate Clinical Research, Dr. G. Niemann

Studie "*CMV - Infektion in der Schwangerschaft*"

➢ Dosierung

- 200 U/kg Körpergewicht = 4ml/kgKG
- *1. Gabe:* Within 7 days after detection of primary CMV infection
- *2. Gabe:* 2 Wochen später
- *ev. 3. Gabe, 4 Wochen nach der 2. Gabe:* abhängig von Laborwerten (Avidität).

> 50 U/ml anti-CMV-IgG

Apothekenpreis	
Euro	260,-
	495,-
	1158,-

Packungsgrößen:

10ml Ampulle
20ml Ampulle
50ml Durchstichflasche

560 ml = 12.760 Euro
280 ml = 6.555 Euro … monatlich

Dosierung

nach Münchner Studienprotokoll

- **CMV-Hyperimmunglobulin (Cytotect^{R})** innerhalb 7 Tagen ab Diagnose, < 36+0
- 200 E = 4ml / kg KG (bei 70kg / 280ml / 7.200 €)
- Wiederholung nach 2 Wochen
- WH nach weiteren 4 Wochen, je nach CMV-IgG recombinant blot mit Avidität und anti-hCMV gB IgG ELISA Ergebnissen

Biotest

From Nature for Life

www.biotest.at

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  + Intraglobin
  + Pentaglobin
  + Varitect
  + Cytotect
  + Hepatect CP
  + Haemoctin SDH
  + Biseko
  + Humanalbumin
  + Intratect
+ Diagnostik
+ Qualität und Sicherheit
- Kontakt

Immunglobulin vom Menschen

Varitect®

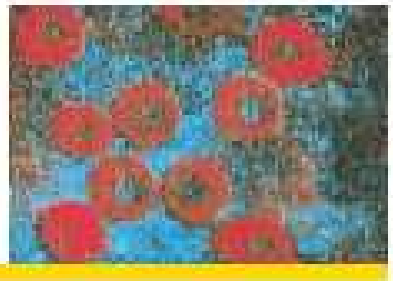
Varicella-Zoster-Immunglobulin vom Menschen

Cytotect®

Human Immunoglobulin gegen Cytomegalovirus

Hepatect® CP

Hepatitis B-Immunglobulin vom Menschen



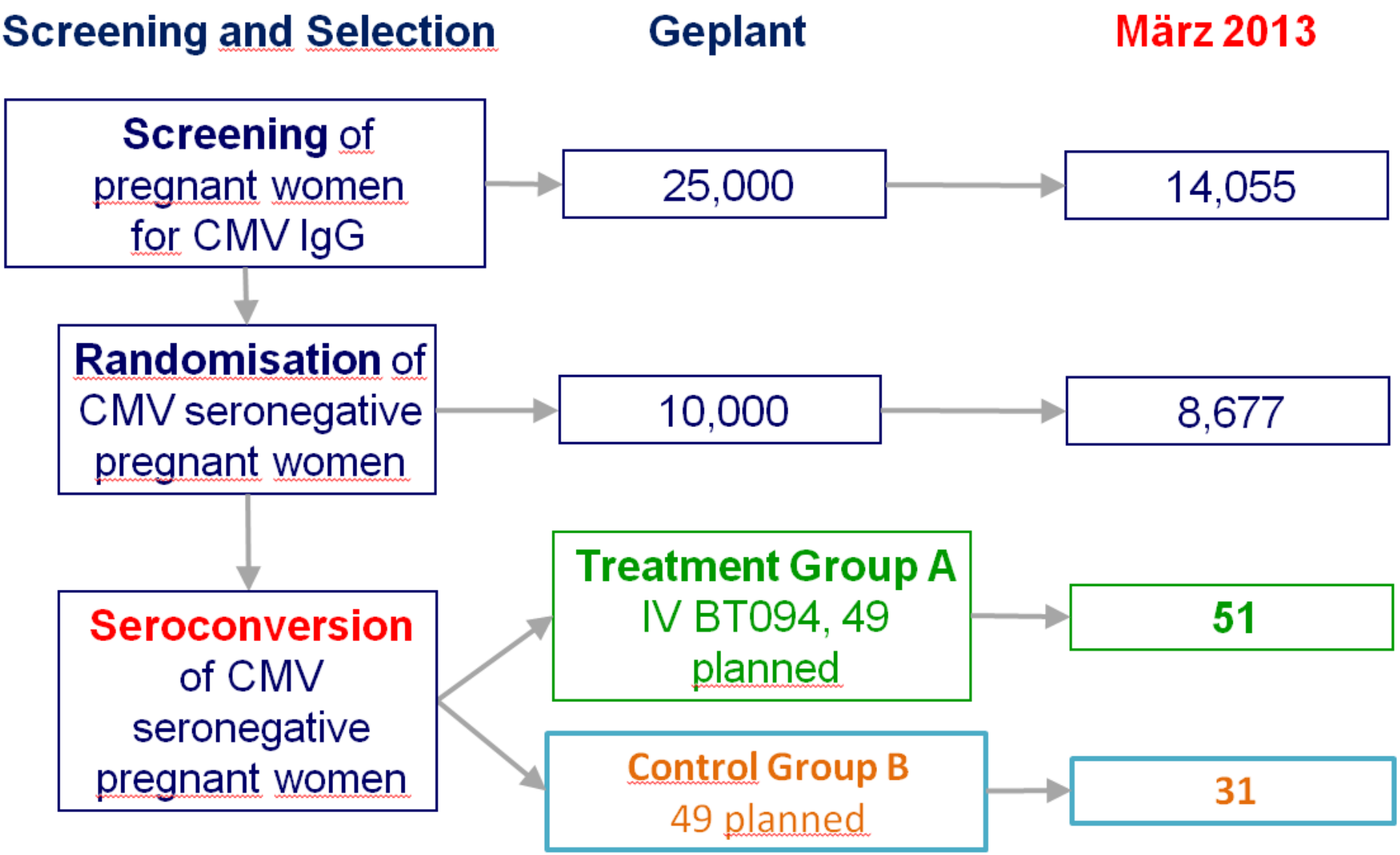
Studie "*CMV - Infektion in der Schwangeschaft*"
Biotest Phase III Study 963 Design
Bei Primärinfektion in der SS + Therapie:

- **Primary Efficacy Parameter**
  - 1. Lebenswoche: Urine CMV-PCR
  - Comparison of the number of congenital CMV-infected newborns/foetuses from mothers treated with BT094 (Group A) to untreated mothers (Group B).
- **Secondary Efficacy Parameters**
  - Folgeuntersuchungen:
    at birth, with 6 months, 1 year and 2 years
    - Physical Examination
    - Ultrasound examination
    - Otoacustic emmission
    - Fundoscopy
    - Bayley II

  →Clinical manifestation of CMV disease

Aktueller Stand der CMV-Studie

Aktueller Stand der CMV-Studie



Studie *CMV - Infektion in der Schwangerschaft*
Biotest Phase III Study 963 – Current Status

Recruitment Status March 2013

	Austria	Belgium	Germany	Hungary	Italy	Total
Number of Centres	4	8	26	9	2	49
Screened	2.220	3.703	7.132	972	28	14.055
Randomised	797	3.333	4.157	368	22	8.677
Seroconversions	3	61	16	2	0	82
% Seronegativity	36%	90%	58%	38%	79%	62%
% Seroconversion	0.38%	1.83%	0.38%	0.54%	0.00%	0.95%
Fälle / Zentrum:	555	463	274	108	14	

Monthly Status of Subject Recruitment: **March 2013**

Status: Screenings per study site in March 2013

Site No	Country	Region	Investigator	TC	Screenings March
1301	Austria	Wien	Husslein	TC	42
1402	Austria	Graz	Breinl		20
1401	Austria	Graz	Lang	TC	12
0112	Germany	München	Schulze		7
2001	Italy	L´Aquila	Nigro	TC	6
0504	Germany	Berlin	Maaser		5
0613	Germany	Frankfurt a. M.	Arnolds		5
0120	Germany	München	Gassner		5
0609	Germany	Frankfurt a. M.	König		4
0616	Germany	Frankfurt a. M.	Zink		4
0105	Germany	München	Frank		4
0123	Germany	München	Kusch		4
0502	Germany	Berlin	Geisler		3
0803	Hungary	Budapest	Boros		3
0808	Hungary	Budapest	Radnai		3
0801	Hungary	Budapest	Siklos	TC	3
0115	Germany	München	Liegsalz		3

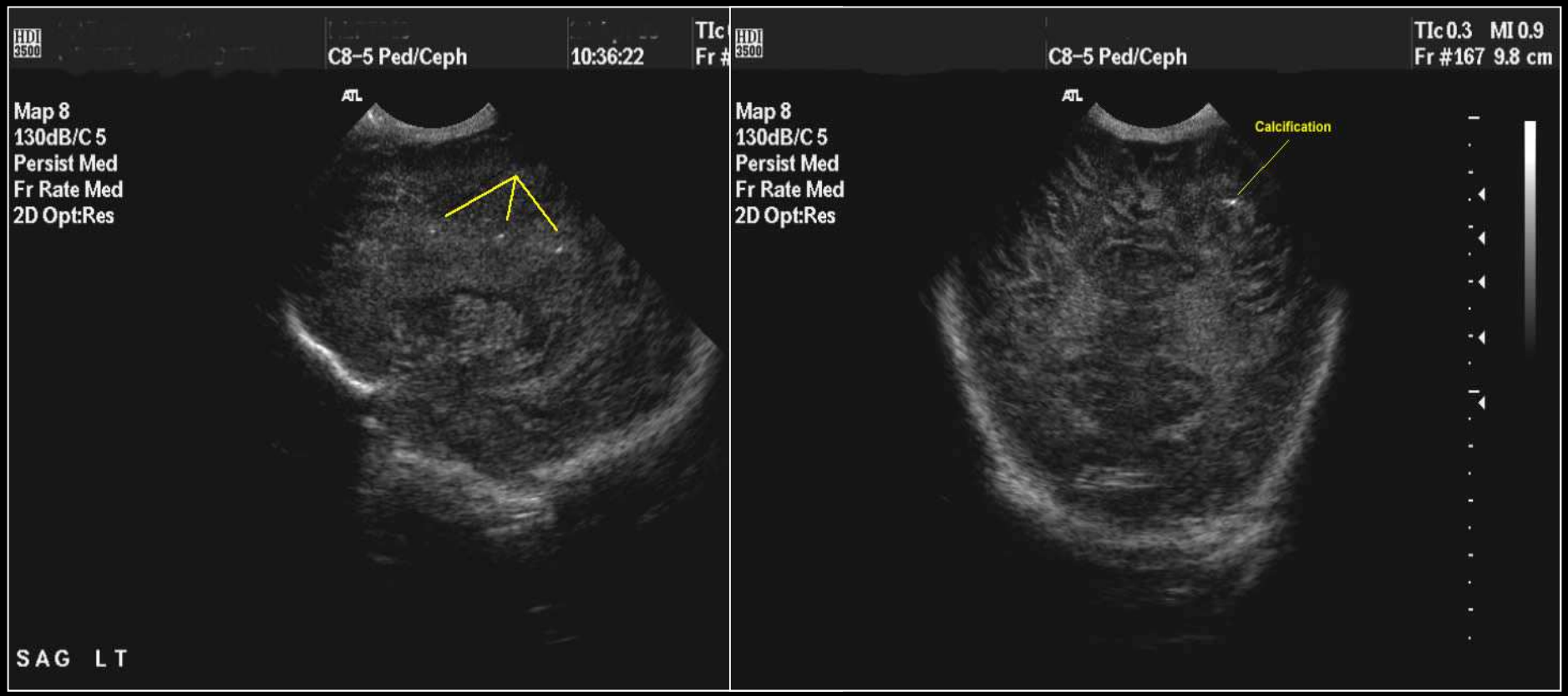
Ultraschall bei CMV

- Gezielter US nötig durch Experten, manche Auffälligkeiten minimal
  Ev. durch andere Ursache
- Diagnose führt ev. zu SSAbbruch
- Berichte über gutes Outcome trotz auffälligen Ultraschalls
- Beratungsdilemma

Benoist G et al. BJOG 2008;115:823-9
Lisnard C et al. Obstet Gynecol 2000;95:881-8
Lipitz S et al. Obstet Gynecol 2002;100:428-33.

Konnatale CMV – Klinik

- Intrauterine Wachstumsretardierung
- Mikrozephalie, Ventrikulomegalie, intrakranielle Verkalkungen – meist periventrikulär lokalisiert

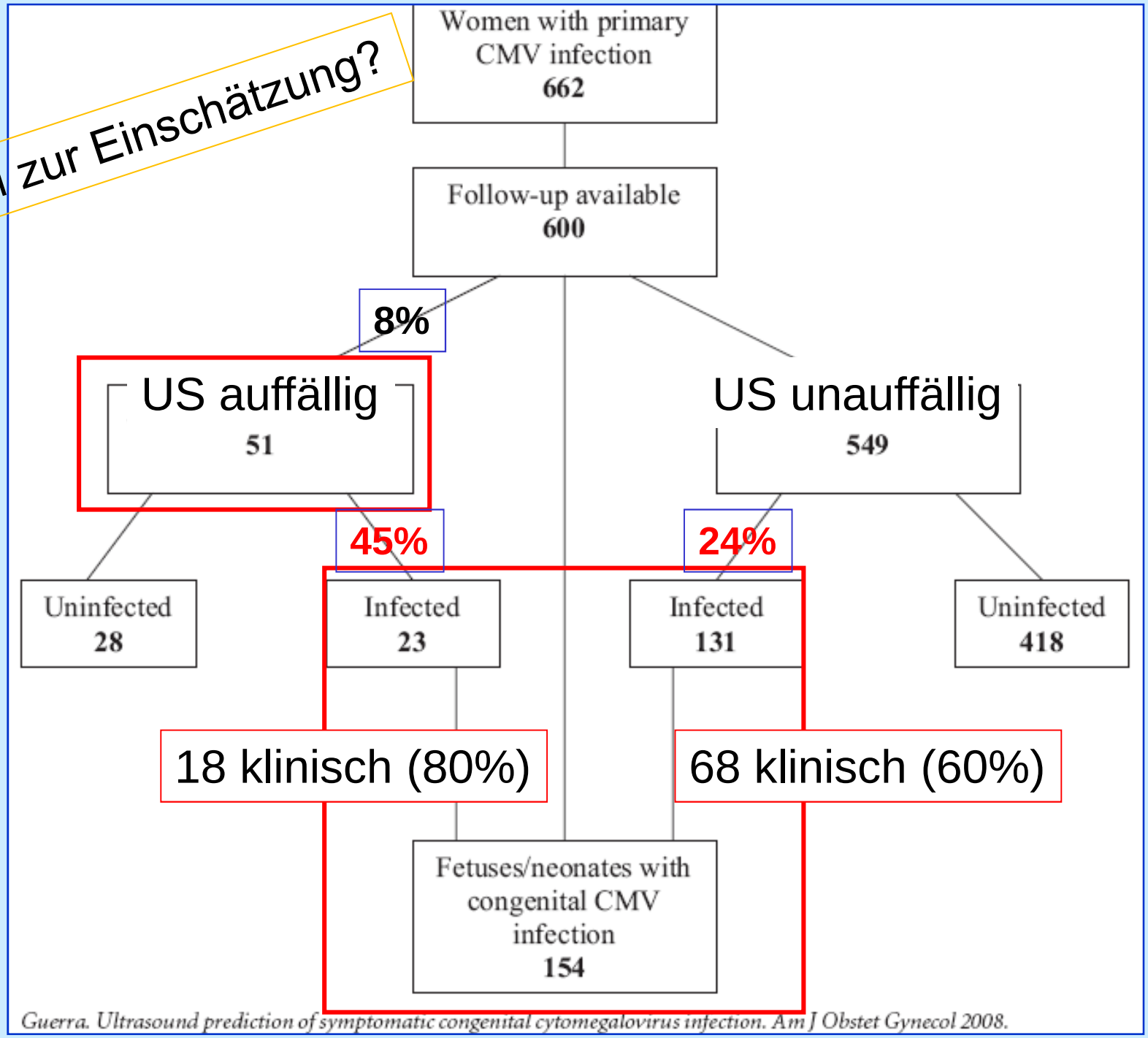


Ultraschall bei CMV

- Geringe Sensitivität
- **Auffälligkeiten** oft erst Wochen nach der fetalen Infektion ... erst im 3. Trimester; Änderung, Besserung möglich.
- US unauffällig: nicht beruhigend dennoch krank: 1/5 bis 1/7
- US auffällig: beunruhigend.
  Sensitivität 21-86%, Spez. 79% !

Watt.Morse ML et al. Prenat Diagn 1995;15:567-70
Guerra B et al. AJOG 2007;196:221
Benoist G et al. BJOG 2008;115:823-9

Ultraschall zur Einschätzung?



Guerra et al. AJOG März 2008;1.e1-1.e7

Pränatale Prognosefaktoren bei CMV für „poor outcome“

	• Odds ratio
• Thrombopenie	1,2
• Sono auffällig nonzerebral	7,2
• Sono auffällig	22,5
• Sono auffällig zerebral	25,5

γGT, Viruslast (FW, Blut), CMV-IgM (?)

Benoist G et al. BJOG 2008;115:823-829

Pränatale Prognosefaktoren bei CMV für „poor outcome“ (10/33 Neurologie post partum)

- Odds ratio

- Ascites, Hepatosplenomegalie oder
- Ventriculomegalie
  Kalzifikationen
  Mikrocephalie **39**

Keines von beiden NPV 100%

Maruyama Y et al. J Obstet Gynaecol Res 2007;33(5):619-623

Pränatale Prognosefaktoren bei CMV für „poor outcome“ (6/33 gestorben post partum)

- Odds ratio für **Tod**
- Ascites, Hepatosplenomegalie **40**
- Kein Ascites, Hepatosplenomeg. NPV 100%

... Leberbeteiligung, -versagen = schlimmste Form

Maruyama Y et al. J Obstet Gynaecol Res 2007;33(5):619-623

„one step closer to a CMV vaccine“ (Dekker und Arvin, N Engl J Med 360, 2009)

Vaccine Prevention of Maternal Cytomegalovirus Infection

Robert F. Pass, M.D., Changpin Zhang, M.D., Ashley Evans, M.D., Tina Simpson, M.D., William Andrews, M.D., Meei-Li Huang, Ph.D., Lawrence Corey, M.D., Janie Hill, R.N., Elizabeth Davis, R.N., M.P.H., Cynthia Flanigan, B.S., and Gretchen Cloud, M.S.

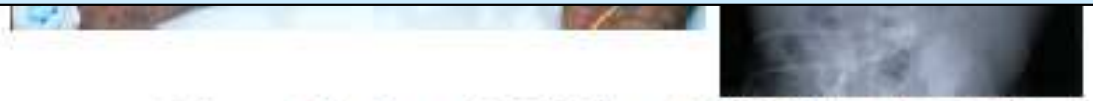
ABSTRACT

BACKGROUND

Congenital infection with cytomegalovirus (CMV) is an important cause of hearing, cognitive, and motor impairments in newborns.

METHODS

In this phase 2, placebo-controlled, randomized, double-blind trial, we evaluated a vaccine consisting of recombinant CMV envelope glycoprotein B with MF59 adjuvant, as compared with placebo. Three doses of the CMV vaccine or placebo were given at 0, 1, and 6 months to CMV-seronegative women within 1 year after they had given birth. We tested for CMV infection in the women in quarterly tests during a 42-month period, using an assay for IgG antibodies against CMV proteins other than glycoprotein B. Infection was confirmed by virus culture or immunoblotting. The primary end point was the time until the detection of CMV infection.



Schwere CID, Langzeit-GCV-Therapie, UL97 Mutation C607Y
Haas, Dep Neonatology, Greifswald, Germany

INfauste kongenitale CMV Infektion
M El-Amin Abdel Latif, E Sugo
NEJM, 362, 2010

Wie können wir die Krankheitslast kongenitaler CMV-Infektion reduzieren?

„A logical first step for public health action towards awareness, prevention and treatment is to
screen all newborns for congenital CMV infection at birth.

A second logical step for public health action towards awareness, prevention and treatment is to
mandate routine prenatal screening of all pregnant woman for the presence of CMV IgG antibody.“

Gail Demmler-Harrison, J Clin Virol, 46S, S1-S5, 2009

K. Hamprecht/Tübingen

Hygienemaßnahmen zur Reduktion des Risikos seronegativer Schwangerer, eine HCMV-Infektion durch Kleinkinderbetreuung zu erwerben

(Adler et al., 2004; Adler, 2005; Cannon und Davis, 2005).

- Annahme, daß das zu betreuende Kleinkind (< 3 Jahre) HCMV im Urin und Speichel ausscheidet.

- Händehygiene mit Seife und warmem Wasser nach Windelwechsel, Füttern, Baden, Nase schnäuzen, Spielzeug anfassen.

- Vermeidung der gemeinsamen Benutzung von Tassen, Tellern, Zahnbürsten und gemeinsamer Nahrungsaufnahme. Kein Küssen auf den Mund, kein gemeinsamer Gebrauch von Handtüchern und Waschlappen.
- Reinigung von Spielzeug und anderen Oberflächen, die mit Urin oder Speichel des Kindes in Kontakt kamen.

Cytomegalovirus (CMV)

Pregnancy

Contact Information

Via E-mail:

Preventing Congenital CMV Infection

Pregnant women may want to take steps to reduce their risk of exposure to CMV and so reduce the risk of CMV infection of their fetus. (See Transmission to learn about possible spread of CMV infection during pregnancy.)

Here are a few simple steps you can take to avoid exposure to saliva and urine that might contain CMV:

- Wash your hands often with soap and water for 15-20 seconds, especially after
  - changing diapers
  - feeding a young child
  - wiping a young child's nose or drool
  - handling children's toys
- Do not share food, drinks, or eating utensils used by young children
- Do not put a child's pacifier in your mouth
- Do not share a toothbrush with a young child
- Avoid contact with saliva when kissing a child
- Clean toys, countertops, and other surfaces that come into contact with children's urine or saliva