Herpesvirusses in Pregnancy

Anne Naessens

Herpesvirussen able to interfere with normal pregnancy development

Herpes Simples Virus 1&2

Varicella zoster Virus

Cytomegalovirus

Genital herpes is very common

Prevalence HSV antibodies in adults

- **Type 1: high (> 90%) in adults**
- **Type 2: 15% (up to 30%)**

Genital herpes is caused by HSV 2 (70-85%) as wel as HSV 1 (15-30%)

- **HSV-1 rarely recurs after the first year of infection (except pregnancy)**
- **HSV-2 recurs frequently for many years**

Clinical characteristics of genital herpes in pregnancy

- 70 % of newly acquired genital herpes infections in pregnant women are asymptomatic or unrecognized
- Most reactivations of genital herpes are unrecognized
- Historically, women with a first episode genital herpes outbreak in pregnancy have a high rate of recurrence (18-37%) at delivery

Clinical manifestations of neonatal herpes simplex virus infections

At the onset, the disease is often difficult to distinguish from bacterial sepsis (delayed diagnosis)

- **Localized infections of skin, eye and mucous membranes (45-50%)**
- **Infections of the central nervous system (30-33%) (lethargy, seizures, irritability, tremor, poor feeding)**
- **Disseminated systemic infections (17-25%) (liver dysfunction, severe coagulopathy, pulmonary failure)**

The outcome of neonatal herpes remains poor

Characteristics of neonatal herpes simplex virus infections

Neonatal herpes is a rare disorder (3.2-7/100 000 live borns).

- **85-90% acquired at the time of delivery (virus present in genital secretions)**
- **5-10% are early postnatal acquisition**

Effect of serologic status and cesarean delivery on transmission rates of herpes simplex virus from mother to infant.

58362 pregnant women

- Viral shedding at birth
- Serological status
- Route of delivery

202 (0.3%) women with HSV shedding at the time of delivery

10 (0.02%)neonatal HSV

JAMA. 2003 8;289:203-9. Brown ZA et al.

Risk evaluation for neonatal herpes

- **Primary genital herpes at the time of delivery has a very high risk for neonatal herpes**

  30-50%

- **Recurrent genital herpes poses a low risk to the neonate:**

  0.02-0.05% in the absence of lesions at the time of delivery

  2-5% when lesions are present

Preventing Neonatal Herpes

1. Cesarean delivery
2. Antiviral therapy
3. Avoid unnecessary invasive procedures
   - Artificial rupture of membranes
   - Fetal scalp electrodes
   - Vacuum extraction, forceps delivery

Preventing Neonatal Herpes 1: cesarean delivery

- For women with genital lesions or prodromal symptoms
- Before membrane rupture or rupture of membranes <4 h
- (Primary genital herpes in third trimester of pregnancy?)

Preventing Neonatal Herpes 2: antiviral suppressive therapy during pregnancy

Cochrane Database:

- **There is insufficient evidence to determine if antiviral prophylaxis reduces the incidence of neonatal herpes.**
- **Antenatal antiviral prophylaxis (from 36 weeks) reduces viral shedding and recurrences at delivery and reduces the need for cesarean delivery for genital herpes.**

Preventing Neonatal Herpes 2: antiviral suppressive therapy

Results from the aciclovir-in-pregnancy registry do not show teratogenic effects of the drug. Comparable data have been reported for the oral administration of valaciclovir.

HSV during pregnancy Summary

- **Rare disorder: Women with recurrent genital herpes simplex virus should be informed that the risk of neonatal herpes is low.**
- **Preventive strategies are limited to**
  - **Cesarian delivery in the presence of genital lesions or prodromal symptoms**
  - **Antinatal therapy can be started from 36 weeks in women with recurrencies and in women with primary herpes around the delivery period**
  - **As aciclovir and valaciclovir are not officially approved for the treatment of pregnant women, patients should be informed about the limited information and give consent before the drug is used**

HSV during pregnancy Summary

Which strategies are Not recommended?

- **Antenatal cultures.**
- **Serological screening for HSV 1 or 2**
- **Cesarean delivery in the absence of lesions or prodromal symptoms**

Varicella-Zoster infection during pregnancy

- **Varicella during pregnancy:**
  - **Pregnant women**
  - **Fetus**
  - **Neonate**
- **Zoster during pregnancy :**
  - **Zoster infections do not cause any harm to mother/ fetus or newborn**

Varicella in pregnancy: 1: effect on the pregnant women

- Rare disease during pregancy (> 90% antibodies) Calculated incidence: 0.7/1000
- High risk for varicella pneumonie (20%).
  - Smoking and > 100 chickenpox lesions are risk factors.
  - 40% may need mechanical ventilation
  - Medical emergency (mortality 10-14% despite adequate therapy)
  - Higher mortality in third trimester.

Varicella in pregnancy 2: effect on the fetus

- Congenital Varicella Syndrome
  - skin lesions in dermatomal distribution
  - limb hypoplasia
  - neurological deficits
  - eye disease

Varicella in pregnancy 2: effect on the fetus

- Congenital Varicella Syndrome
  - skin lesions in dermatomal distribution
  - limb hypoplasia
  - neurological deficits
  - eye disease
- Pathogenesis of CVS
  - Probably caused by intra-uterine zoster-like reactivations. Inabilty of the fetus to mount a VZV-specific cell mediated immune respons

Varicella in pregnancy: risk for CVS

Global risk: 9/1373 (0.7%) al before 20 weeks

Highest risk: 2% (7/351) between 13-20 weeks gestation

Before 13 weeks: 2/472 (0.4%)

Late sequel from maternal varicella: herpes zoster in infancy in 10

Lancet. 1994 18;343:1548-51. Consequences of varicella and herpes zoster in pregnancy: prospective study of 1739 cases. Enders G et al.

Varicella in pregnancy 3: effect on the neonate

Risk for neonatal varicella with high morbidity and mortality.

Severity in neonate is related to the time lapse between the onset of maternal rash and delivery.

Maternal rash

- **between 5 days before and 2 days after birth: possibility of fatal neonatal varicella**
- **Between 20 and 6 days before birth: non-fatal course**

Preventing and therapy of VZV in pregnant women:
1: post exposure profylaxis in non immune pregnancies

- **VZIG within 72h (96h) after exposure; 125U/10 kg max 625U**
  - **Prevent severe maternal varicella**
  - **No evidence that this prevents fetal infection**
  - **No effect when clinical illness is established**
  - **VZIG is NOT available in Belgium: alternative MULTIGAM (7.5U/ml) or VARIQUIN (Sanquin netherlands tel: 31/205123355; 100U/ml). Not reimboursed**
- **Vaccination: life attenuated. Not recommended during pregnancy. But on 629 accidental exposures: no increase in birth defects**

Preventing and therapy of VZV in Pregnant women
2: antiviral therapy

- All pregnant women with Varicella should recieve oral aciclovir 800mg x 5/d (valaciclovir 1g x 3)
- Start intravenous therapy on first sign of varicella pneumonitis

Preventing and therapy of VZV:
3: neonate

- **Neonate**
  - **VZIG or comparable formulas**
  - **Aciclovir**
- **Isolation**

VZV during pregnancy Summary

- Problems only with varicella infections not with Zoster
- Maternal risk: high risk for Varicella pneumonia. Treatment during pregnancy highly recommended.
- Fetal risk: CVS when infection before 20 weeks (0.9%). Risk 2% when infection between 13-20 weeks
- Neonatal risk: high risk for fatal varicella infections when maternal rash between 5 days before and 2 days after birth. VZIG for neonate is indicated

Considerations on CMV and pregnancy

- Congenital infection occurs after primary as well as recurrent maternal infection
- No screening test available to detect recurrent maternal infection
- No treatment available during pregnancy

CMV infection during pregnancy

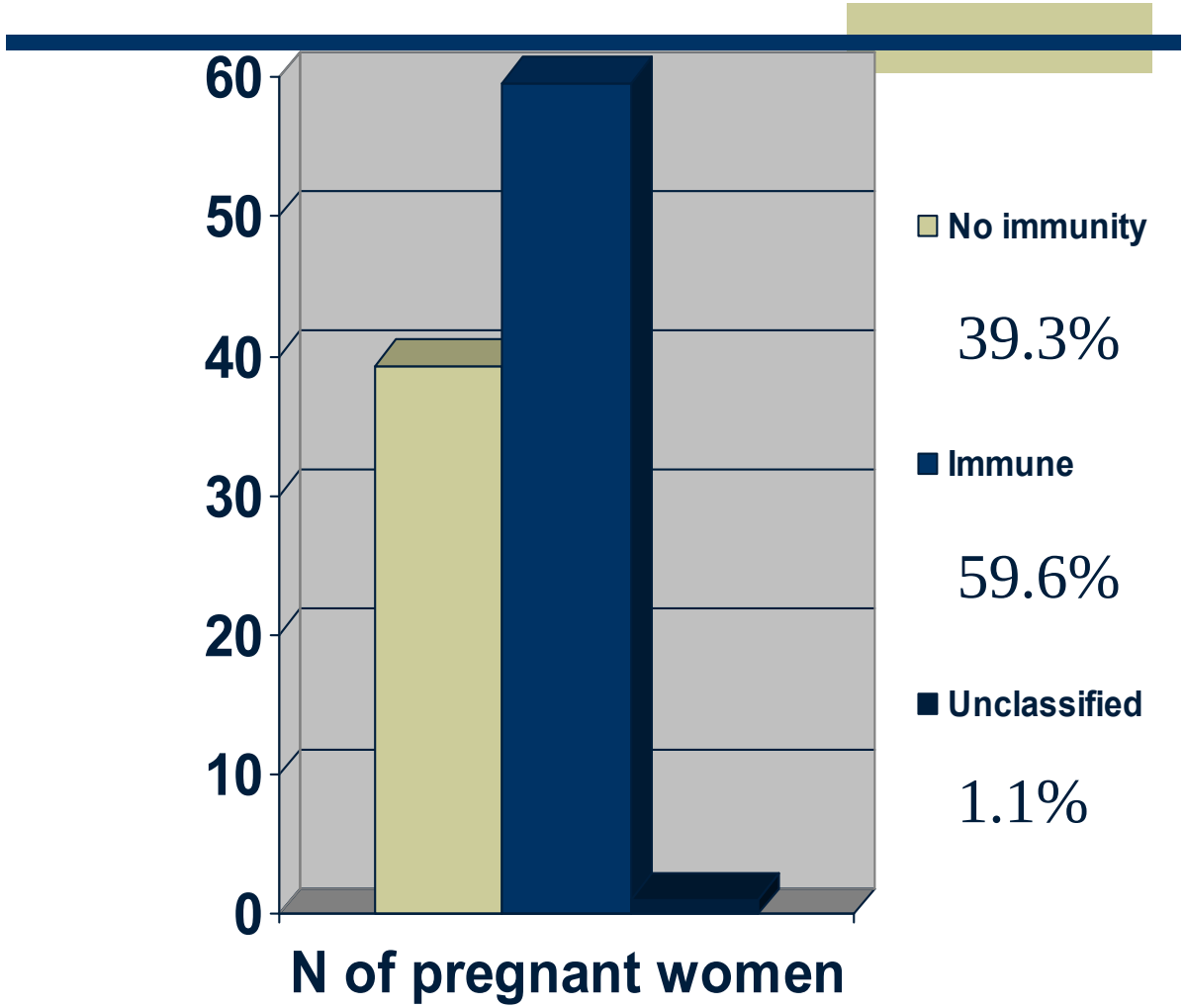
1. Epidemiological survey UZ Brussels
    1. Incidence
    2. Risk for a cCMV
    3. Outcome
2. Prenatal diagnosis: prediction of sequels
3. Treatment

Epidemiological study 1: study design

From june 1996-december 2007: 13370 mother/infants pairs

- **Pregnant women**
  - Serological screening at the first prenatal visit / at birth
  - Investigation of late trimester abortion or mors in utero for cCMV
- **Neonates**
  - Urine CMV culture within 7 days after birth
- **Exclusion**
  - Referal patients

Epidemiological study
2: results of the initial serological screening

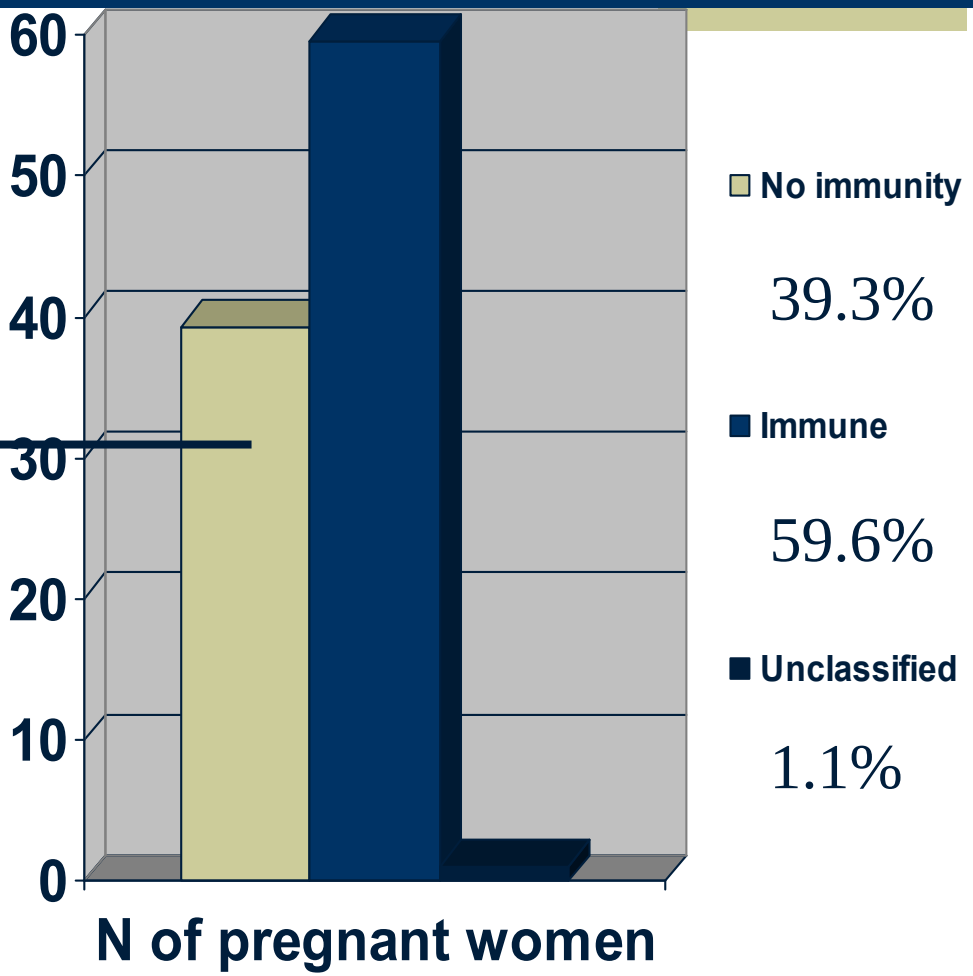


Epidemiological study: 3: Primary CMV infections during pregnancy

78 (0.58%) primary maternal CMV infections

⇓

Transmission?
Related to the gestational age at maternal infection?

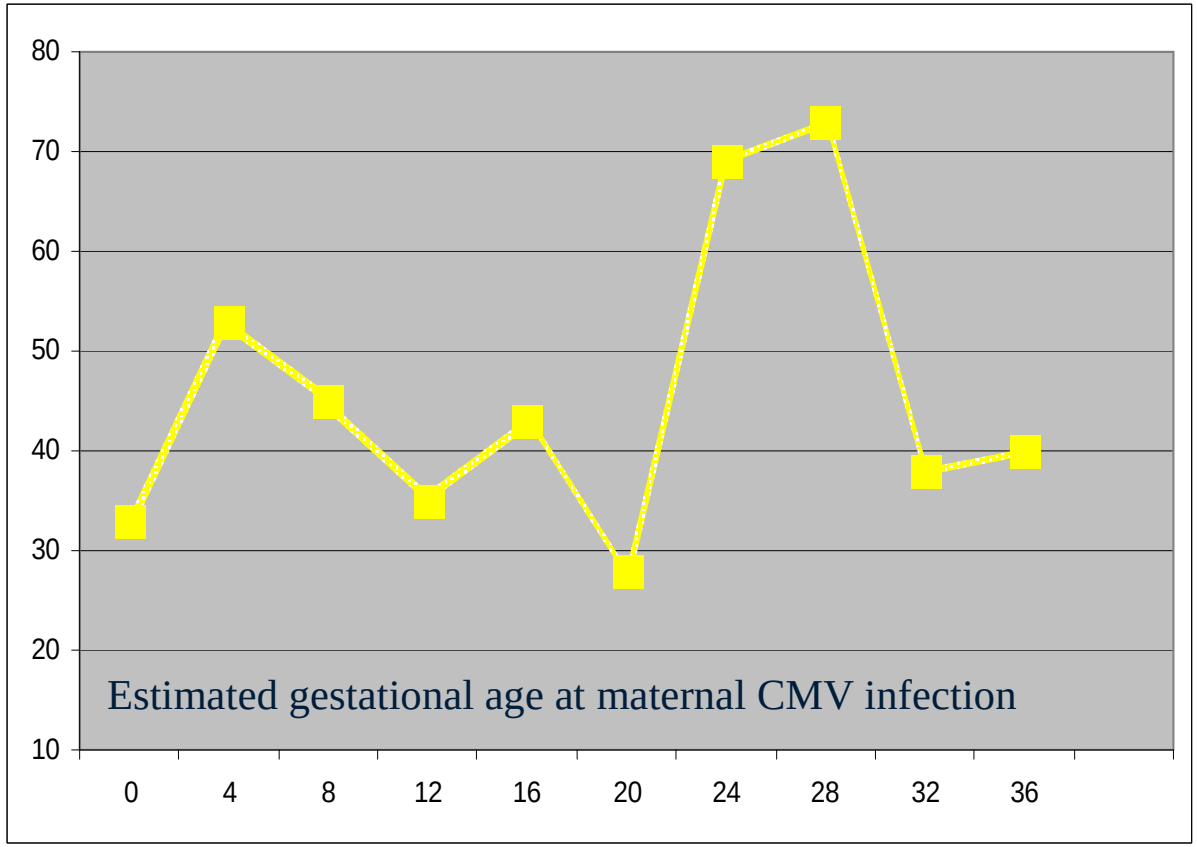


Percentage transmission

- **78 primary infections**
  - **global risk of 0.6% for primary maternal CMV infection**
- **72 complete follow up**
  - **33 congenitale CMV (46%)**

Transmission risk according to the gestational age at maternal primary infection

% transmission



Epidemiological study: 4: Incidence of congenital infection accorrding to the maternal serological status

64 (0.48%) cCMV

20 cCMV infections

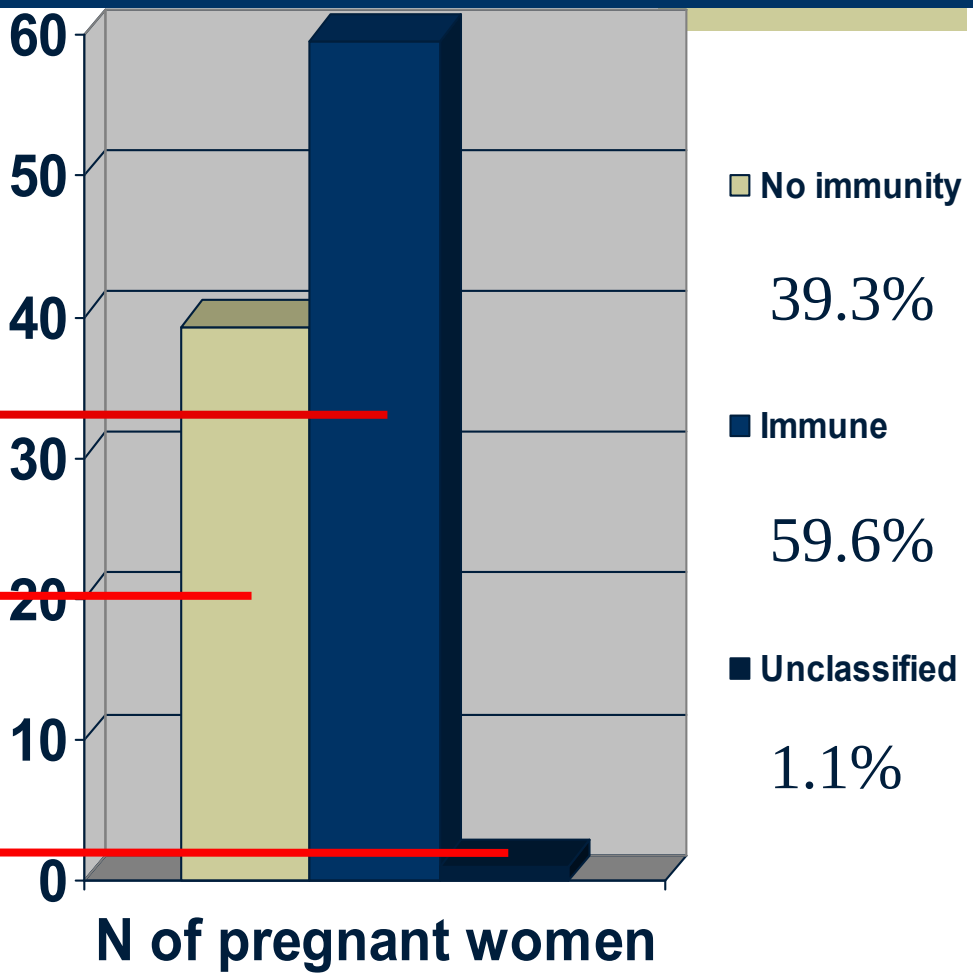
Recurrent maternal

33 cCMV infections

Primary maternal

11 cCMV infections

Primary and recurrent



Risk for cCMV according to immune status of the pregnant women

Immuun status of pregnant women	N	Risk for cCMV	N (%) congenital infections
Previous immunity	7977	0.3%	20
No immunity (78 primary infections)	5254	46%	33
Non classified	143	7.7%	11
Total	13370	0.48	64

Outcome of the cCMV

Type of maternal infection	Primary N= 33	Recurrent N=20	Unclassified N = 11
Induced abortion	3/4 CMV inclusions	1/1 hydrocephalus + inclusions	1/1 hydrocephalus + calcifications
Intra Uterine death		1/1 CMV inclusions + Intracranial calcifications	
Live born symptomatic	2	1	1
Severely affected	15%	15%	18%

Auditory sequelae in relation with maternal infection type

Detection of auditory sequelae in 13/60 (22%) live born children

Primary infections: 15%

Recurrent maternal infections: 7%

Unclassified: 40%

I. Foulon et al. A 10-Year Prospective Study of Sensorineural Hearing Loss in Children with Congenital Cytomegalovirus Infection, *J Pediatr 2008;153:84-8*

Hearing loss in children with CCMV in Relation to the Maternal Trimester in Which the Maternal Primary Infection Occurred.

	Maternal trimester			
	1 st (n=5)	**2 nd (n=12)**	**3th (n=11)**	T (n=28)
SNHL	**4 (80%)**	**1 (8%)**	**0 (0%)**	**5 (18%)**
Moderate	1(20%)	1(8%)	0	2(7%)
Severe	3 (60%)	0	0	3(11%)

I. Foulon et al. ***Pediatrics 2008 122:e1123-7.***

Prenatal diagnosis of cCMV : sensitivity and specificity

Global sensitivity of the prenatal diagnosis was 80%.

Best sensitivity and 100% specificity were achieved by PCR done on AF sampled after 21 weeks' gestation, respecting a mean interval of 7 weeks between diagnosis of maternal infection and prenatal diagnosis

Prenatal diagnosis of congenital cytomegalovirus infection: prospective study of 237 pregnancies at risk. Liesnard C, Donner C, Brancart F, Gosselin F, Delforge ML, Rodesch F. Obstet Gynecol 2000 Jun;95:881-8

Prenatal diagnosis of CMV Quantitative PCR as a prediction of sequellae?

Prenatal diagnosis of symptomatic congenital cytomegalovirus infection. Guerra B, Lazzarotto T, Quarta S, Lanari M, Bovicelli L, Nicolosi A, Landini MP. Am J Obstet Gynecol. 2000 Aug;183(2):476-82.

Quantitative PCR with >/=10^3 genome equivalents predicts fetal infection with 100%

>/=10^5 genome equivalents predicts symptomatic infection

Congenital human cytomegalovirus infection: value of human cytomegalovirus DNA quantification in amniotic fluid. Nedelec O, Bellagra N, Devisme L, Hober D, Wattre P, Dewilde A. Ann Biol Clin (Paris) 2002 Mar-Apr;60(2):201-7

High viral load in all fetuses (1.10^5 to > 10^7 cop/mL). No difference between symptomatic and asymptomatic .

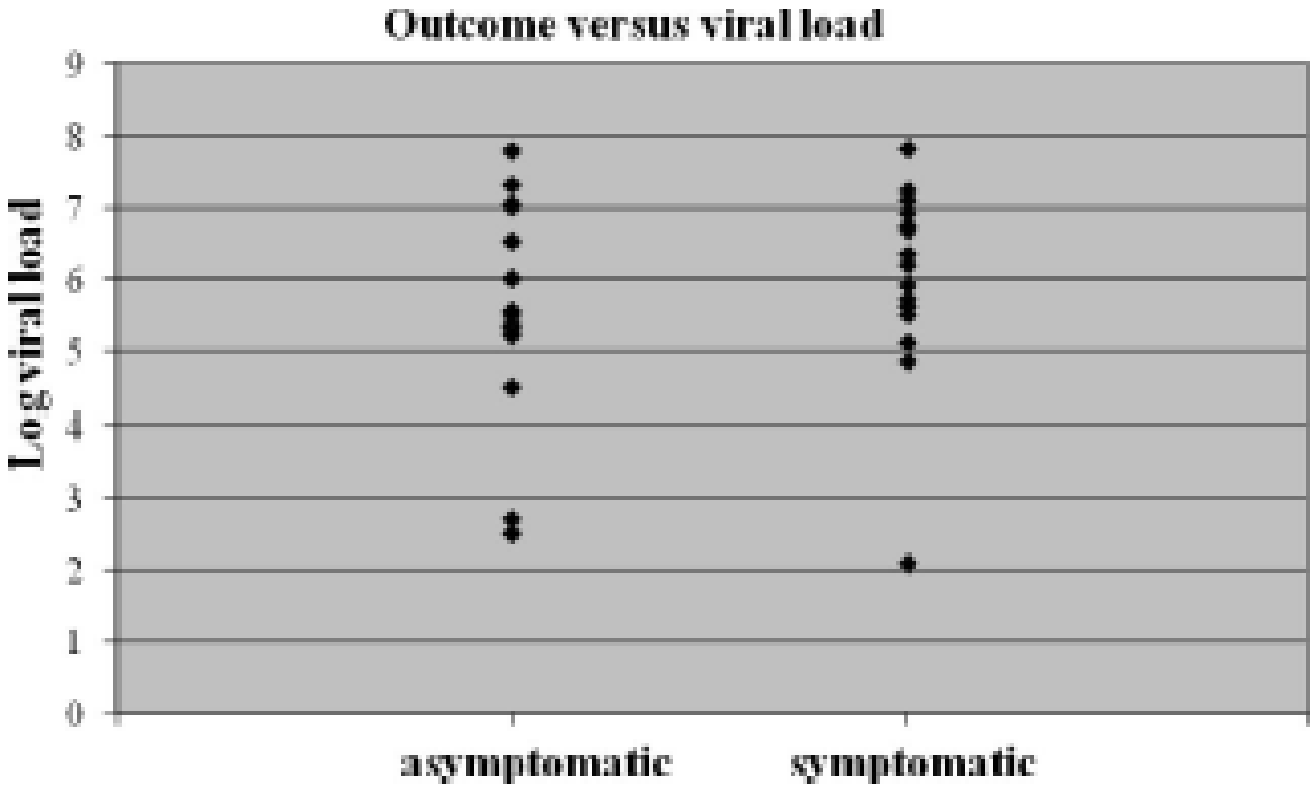
More data necessary

Prenatal diagnosis of CMV

Real-time PCR quantification of human cytomegalovirus DNA in amniotic fluid samples from mothers with primary infection. J Clin Microbiol 2002 May;40(5):1767-72 Gouarin S, Gault E, Vabret A, Cointe D, Rozenberg F, Grangeot-Keros L, Barjot P, Garbarg-Chenon A, Lebon P, Freymuth F.

- **Our findings suggest that HCMV load level in AF samples correlates with fetal clinical outcome but might also be dependent on other factors, such as the gestational age at the time of AF sampling and the time elapsed since maternal infection.**

Clinical predictive value of real-time PCR quantification of human cytomegalovirus DNA in amniotic fluid samples.



T. Goegebuer et al. Journal of Clinical Microbiology, 2009, 47, 660-665

Treatment options in pregnant women

Treatment of pregnant women with CMV-specific hyperimmune globulin is safe, and the findings of this nonrandomized study suggest that it may be effective in the treatment and prevention of congenital CMV infection.

Passive immunization during pregnancy for congenital cytomegalovirus infection Nigro et al. N Engl J Med. 2005: 29;353:2818-20

Treatment options in pregnant women

- **Drawbacks from the study**
  - **Non randomized study**
  - **High incidence of sequelae seen on Ultrasound**
  - **No specifications on neonatal follow-up**
  - **Cost: 200u/kg= 38 Euro/kg =2320 euro/60kg**

- **More carefully designed randomized studies needed!**

CMV and pregnancy Summary

- Congenital CMV infection was found in 0.48% of our population
- Immune patients have a low risk (0.3%) for delivering a congenitally infected infant
- Patients with primary infection have a high risk for delivering a congenital infected infant (46%)
- Severe sequels may be found even in patients with prior immunity
- Auditive sequelae are more frequent after primary infection.
- Primary infections in the first trimester are frequently associated with auditive sequelae
- Prenatal diagnosis can predict fetal infection
- Quantitative PCR results are not indicative for symptomatic disease
- NO proven effective therapy can be given during pregnancy