

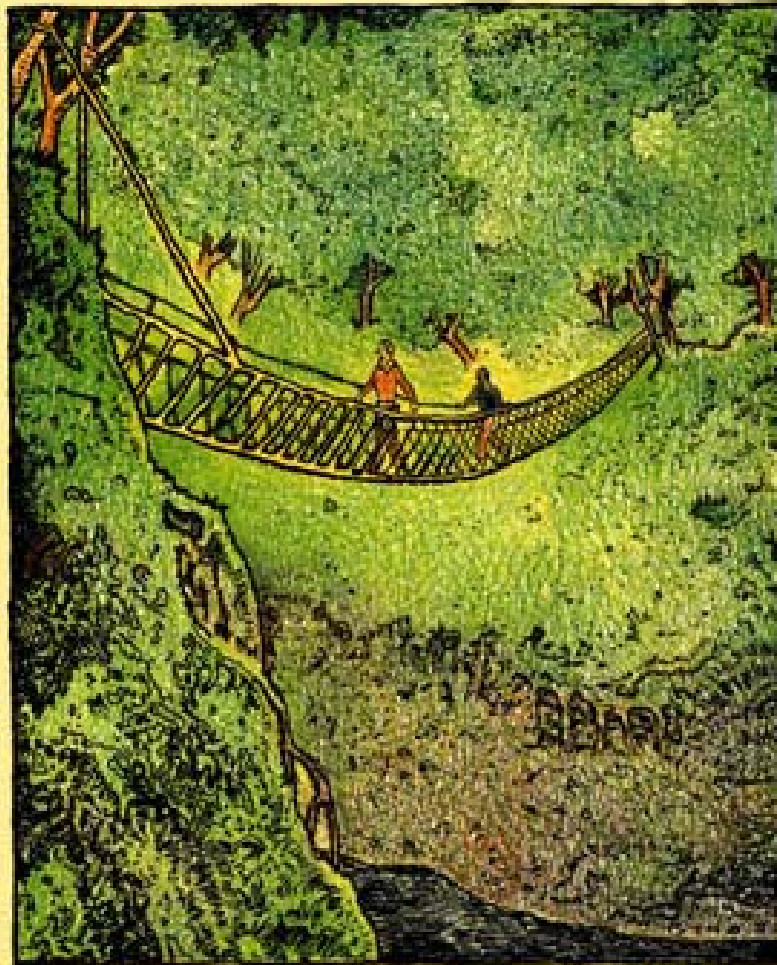
Cytomegalovirus infections of pregnancy and preventing complications

Is IVIG of use?

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LUCKILY WE HAD BEEN ABLE TO FIND A PARKING SPOT WITHIN EASY REACH OF THE CITY CENTRE.



Outline

- Cytomegalovirus
 - Clinical problems
 - Virology
 - Current therapies
- Congenital CMV
 - Outcomes
 - Therapy
- Current recommendations
- What to do



Outline

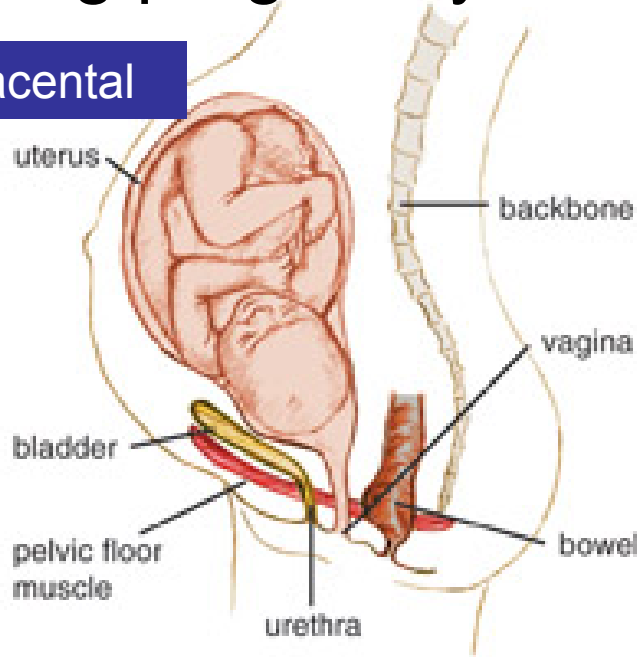
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Vertical transmission = passage of (virus) from mother to fetus

1. During pregnancy

Transplacental



Ascending

http://kidney.niddk.nih.gov/kudiseases/pubs/pregnancy_ez/

www.emorywomensprogram.org/images/QnA.jpg

2. During delivery

3. Postnally

Close contact with mother

Questions & Answers



Breast milk



Definitions

- Infections in the fetus/ newborn may be acquired
 - in utero (congenital)
 - at the time of birth (natal)
 - during the neonatal period (postnatal)



Maternal determinants of vertical transmission of viruses



- Anatomical changes in genital tract
 - Placenta usually is an effective immunological barrier
 - Changes in lower genital tract
- Hormonal changes
 - Direct effects on viral replication?

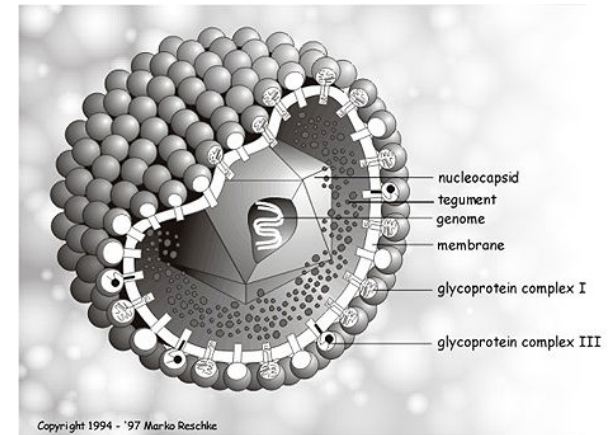


Determinants of fetal/newborn infection or disease



1. Maternal

2. Viral Factors



3. Fetal/newborn Factors

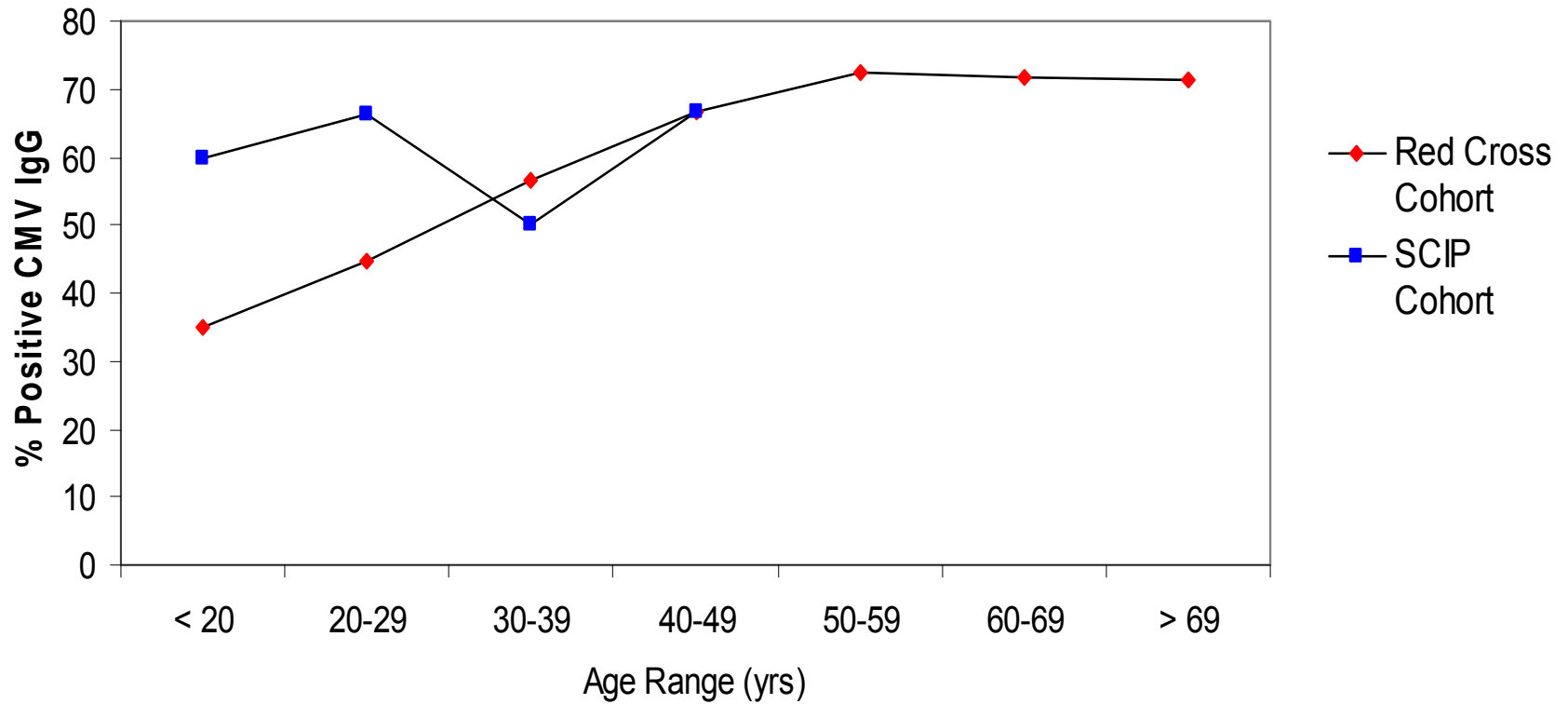


Fetal determinants of vertical transmission of viruses



- Clever ways of getting across the placenta
 - Transplacental trafficking of maternal lymphocytes: CMV, HIV, Hep C
 - Transplacental trafficking of free virus
 - Ascending infection
 - Specific receptors for transmission
- Effect of transplacental maternal antibody
 - May be Insufficient or ineffective
- Fetal immune response to the virus





[Munro, 2005]



Serology 600 pregnant women 2002-2004

CMV IgG	CMV IgM	CMV IgG Avidity	≤20 wks gestation	>20 wks gestation	Total
-	-	ND	169	90	259
+	-	ND	202	106	308
+	+	Low	5	2	7
+	+	High	20	6	26

Low avidity <35%



Congenital Diagnosis

- Clinical suspicion
 - IgM seropositive
 - IgG seropositive
 - IgG avidity
 - Maternal urine culture
 - Maternal blood NAT
 - Affected child
- Amniocentesis
 - NAT
 - Q-NAT
 - Culture
- Affected child
 - Usually after 4 wks age
 - Dried blood spot

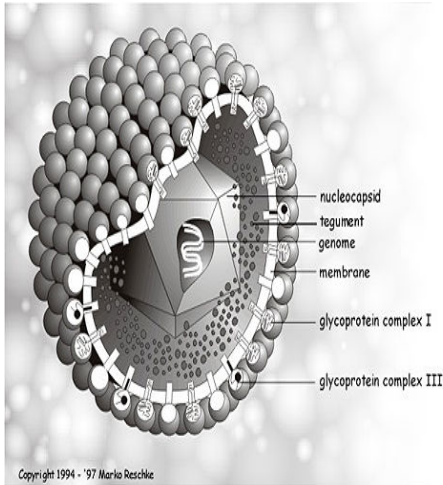


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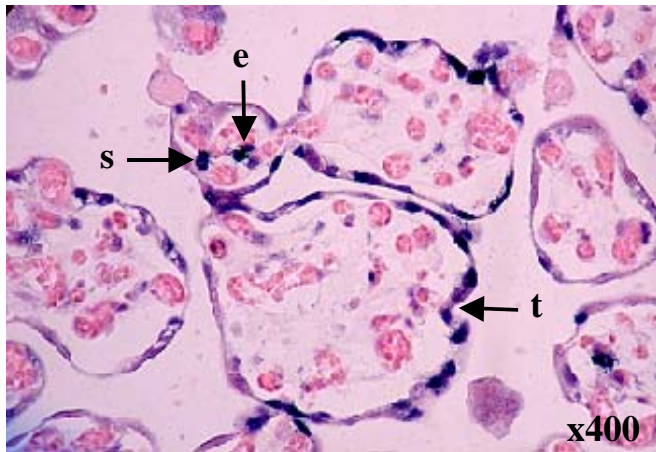
Viral determinants of vertical transmission



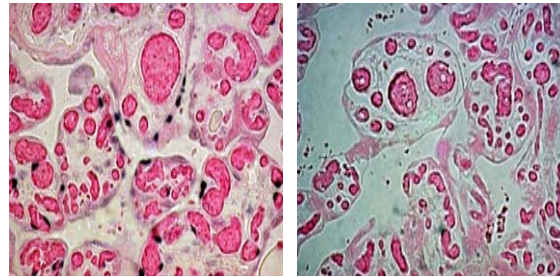
- ▶ Dose of virus
 - Increased risk of transmission primary CMV, HSV,
 - high viral loads, HIV, Hep C
- ▶ Increased risk of transmission:
 - HepBeAg positive
- Strain specific effects e.g CMV
- Immunomodulating effects of the virus on the host's immune response
 - CMV, HSV, HIV



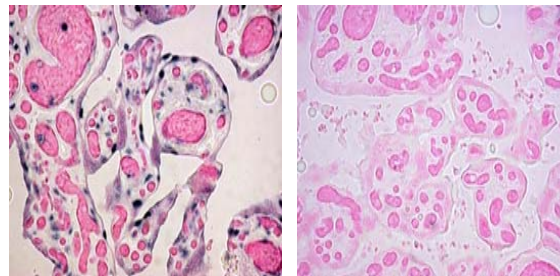
CMV -DNA infected placental tissue



gB



MIE



UL21.5





virology
division
diagnosis.research.teaching



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Clinical manifestations

- Jaundice
 - CMV, Toxo, Rubella, HSV, Syphilis, Hep B
- Purpura
 - usually appears on the first day
 - CMV, Toxo, Rubella, HSV, Syphilis,
- Hepatosplenomegaly
 - CMV, Toxo, HSV, Syphilis, Coxsackie



Eye abnormalities

- Cataracts
 - Rubella, VZV, toxo, CMV & HSV (rare)
- Chorioretinitis
 - Rubella (generalised), toxo, CMV, HSV, VZV, syphilis
- Glaucoma
 - rubella, syphilis
- Keratoconjunctivitis
 - HSV



Microphthalmia

- Toxo, Rubella CMV (rare)



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Vaccines for CMV

- Multiple tried
- CMV indicated as a major target for prevention strategies by international agencies
- Vaccine strategies could be
 - Vaccinate all before pregnancy
 - Vaccinate all
 - Vaccinate if seronegative
 - Vaccinate before immunosuppression
 - Therapeutic vaccine , results of IVIG studies [Nigro, 2005]



Types of CMV vaccine

- Peptide subunit
 - Based on CTL epitopes
 - Targets pp65 (coat protein), IE1 (nonstructural)
 - gB as immunodominant target for neutralising Ab
 - Methods transgenic mice with HLA-A*0201 gene
- Live attenuated (Ad169, Towne)
- Multiple antigen
 - Overlapping peptides
 - gB plus pp65/other antigens



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IVIG for congenital CMV infection/disease - therapy

- Counselling and support
- Termination
 - 20% clinical sequelae
- Clinical identification
 - Ultrasound of little use
- Antivirals
 - Ganciclovir toxic, teratogenic
 - Foscarnet toxic





ALTERNATIVE THERAPIES



Alternative therapies

- Hygiene
- Antivirals
 - Ganciclovir
 - Foscarnet
 - Cidofivir



IVIg during pregnancy for congenital CMV therapy

- Pregnant women +1° CMV + AF CMV pos
Therapy 200 v/kg IVIg
31 → 1 (3%) CMV disease
- Pregnant women + 1° CMV
Therapy nil
14 → 7 (50%) CMV disease
- IVIg – Cytotect Biotest anti-CMV hyper Ig



IVIG during pregnancy for congenital CMV-groups

- Therapy

- 1° infection >6 week prior
- Amniocentesis (n=79) usually >wga
- IVIG 200u/kg ± 400u/kg fetal wt intra AF

- Prevention

- 1° infection <6 week prior/decline
- No amniocentesis
- IVIG 100u/kg monthly



IVIG during pregnancy for congenital CMV - study

- Prospective 1995 to 2003
- 157 women, 127 Rome, 7 Cities
 - 148 asymptomatic 1° CMV
 - 28 Top
- Serology
 - 157 – 131 seroconversion
 - 4 IgM (pre-conception infection?)
 - 22 IgM + low avidity
- Infection T_1 42%
 T_2 50%



QuickTime™ and a
TIFF (Uncompressed) decompressor
are needed to see this picture.



- Neonatal follow up
 - FBC, LFT, Ophthalmology, U/S Abdo, U/S CNS, BAER, urine CMV \leq 2 weeks
- Affected neonates follow up
 - As above
 - CSF
 - EEG
 - Cerebral CT, MRI
 - Gesell, Bayley, Stanford-Binet IG
- IUGR = head and abdo $<10^{\text{th}}$ centile



Prevention

- Pregnant women + 1° CMV <21 wga + No AF

Therapy 100 u/kg IVIG

37 → 6 (16%) CMV disease

2-11 weeks post-seroconversion

- Pregnant women +1° CMV

Therapy nil

47 → 19 (40%) CMV disease

[Nigro, 2005]



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IVIG for congenital CMV infection/disease

- CMV immunoglobulin
 - There is a paucity of evidence to guide clinical practice in this area and there is currently variation in practice. There is a non-randomised, case-controlled series where CMV immunoglobulin was used during pregnancy. With currently available information CMV immunoglobulin cannot be recommended as routine treatment. Expectation of the clinical benefit would be even less where there is sonographic evidence of fetal disease.
- Use during pregnancy is not currently a TGA approved indication for CMV immunoglobulin.

[Guidelines, 2007]



Criteria for access to CMV immunoglobulin

- The patient must have a proven primary CMV infection and a CMV congenitally infected fetus as evidenced by a positive PCR or culture for CMV on amniocentesis and documented serological primary maternal CMV infection.
- The administering centre should abide by recommendations contained within this paper and agree to obtain consent from the mother for collection of the following data:
 - Data at entry, Data at birth, Annual follow-up to 5yrs (Neurodevelopmental and hearing assessments, viral shedding)



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IVIG for Congenital CMV Infection/Disease - Testing

- CMV IgG ideally pre-pregnancy
- CMV IgG seronegative
 - Counselling
 - Handwashing etc
 - Repeat testing during pregnancy with counselling

[Guidelines, 2008]



IVIG for Congenital CMV Infection/Disease – testing during pregnancy

- Routine screening for CMV currently not recommended
- Some problems
 - Anxiety
 - Resources for testing, counselling amniocentesis
 - Early seropositives with IgM, IgG avidity

[Guidelines, 2008]



Benefits

- Seronegatives identified
- Potential for therapy, although of uncertain value
- Seroconversion can be monitored
- May direct need for amniocentesis (>6 weeks post-seroconversion)



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CMV IVIG - Issues

- IVIG did not reduce CMV levels
 - Compare other studies CMV hyper IG
- Changes in placental size with IVIG
- Controls did not receive seronegative IVIG
- Alternate therapies (GCV in symptomatic CNS disease)

[Smets, 2007]





ROBIN NOTICED THE PROBLEM
ALMOST IMMEDIATELY

