Virus screening before and during pregnancy; guidelines and controversies

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Sheila Handbury Chair, Maternal Fetal Medicine
University of Melbourne

Viruses in May, Katoomba, 2014
OBSERVATIONS

ON

SOME OF THE CAUSES WHICH DESTROY THE

FŒTUS IN UTERO;

WITH THE ACCOUNT OF A CASE IN WHICH A SUCCESSFUL
MODE OF TREATMENT WAS EMPLOYED IN PREVENTING
THAT ACCIDENT.

By D. STEWART, M.D.

LECTURER ON MIDWIFERY.

COMMUNICATED BY

MR. WARDROP.

Read July 19, 1814.
Although no direct vascular or nervous connection has hitherto been traced between the maternal and foetal systems; yet it is certain, that there are some diseases, which are communicated from the mother to the foetus;

Congenital syphilis

The invariable premature death of the offspring of this woman, together with the sloughing of the cuticle at the umbilicus of the foetus, led me to suspect the existence of a venereal taint in one of the parents; and on inquiry my suspicions were farther confirmed by learning that the father had an incurable sore on one of his ankles, the appearances of which were very suspicious.
Perinatal Infections in Pregnancy...200 years on

**Which are associated with significant fetal / infant risks?**

<table>
<thead>
<tr>
<th>Viral Infections......</th>
<th>Is it amenable to primary prevention?</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Rubella</em></td>
<td>Can we reduce the risk of maternal infection?</td>
</tr>
<tr>
<td><em>Influenza</em></td>
<td></td>
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<tr>
<td><em>Hepatitis B</em></td>
<td></td>
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<tr>
<td><em>HIV</em></td>
<td></td>
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<tr>
<td><em>Hepatitis C</em></td>
<td></td>
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<tr>
<td><em>Varicella</em></td>
<td></td>
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<tr>
<td><em>Measles</em></td>
<td></td>
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<tr>
<td><em>Herpes Simplex</em></td>
<td></td>
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<tr>
<td><em>Parvovirus</em></td>
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<tr>
<td><em>CMV</em></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Other Infections......</th>
<th>Is it amenable to secondary prevention?</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Syphilis</em></td>
<td>Can we minimise the risk of fetal transmission?</td>
</tr>
<tr>
<td><em>Listeria</em></td>
<td></td>
</tr>
<tr>
<td><em>Group B Strep</em></td>
<td></td>
</tr>
<tr>
<td><em>Pertussis</em></td>
<td></td>
</tr>
<tr>
<td><em>Toxoplasmosis</em></td>
<td></td>
</tr>
<tr>
<td><em>Malaria</em></td>
<td></td>
</tr>
</tbody>
</table>
Viral Screening in Pregnancy

**What type of screening?**

**Population screening**

*All pregnant women; primary prevention through vaccination, before or during pregnancy*

- **Rubella**
- **Varicella**
- **(Influenza)**

*All pregnant women; secondary prevention to minimize risk of perinatal transmission*

- **Hepatitis B**
- **Hepatitis C**
- **HIV**
Viral Screening in Pregnancy

What type of screening?

Targeted screening

Abnormal finding prompts secondary screening

- **Rubella**: Intrauterine growth restriction; particularly symmetric I/early onset
- **Herpes Simplex**: Abnormal findings on mid trimester anatomy survey, particularly brain (e.g., Ventriculomegaly, microcephaly)
- **Parvovirus**: Investigation of fetal hydrops
- **CMV**: Investigation of unexplained stillbirth

Focus is on aetiology of findings, better define prognosis, potential for tertiary prevention to minimize fetal damage
Viral Screening in Pregnancy

Guidelines and Controversies: Can we do better?

Population screening
- All pregnant women
- Rubella
- Varicella
- (Influenza)
- Hepatitis B
- Hepatitis C
- HIV

Targeted screening
- Abnormal finding prompts screening
- Rubella
- Herpes Simplex
- Parvovirus
- CMV
Hepatitis B Infection
Prevention of mother to child transmission of Hepatitis B

Every 30-45 seconds, someone dies from Hepatitis B: 90% Hep B deaths relate to chronic Hep B (cirrhosis or liver cancer)

**Infected newborns** most likely to develop chronic Hepatitis B

**Post exposure prophylaxis** (vaccine and HIG) can reduce neonatal infection by 90-95%
Screening Recommendations to Minimise the Risk of Failed Prophylaxis

Timely HBIG and vaccine

Assessment of viral replicative status

Minimise invasive procedures

Prevention of mother-to-child transmission of hepatitis B virus (HBV) during pregnancy and the puerperium: Current standards of care

Michelle L. GILES,1 Ruth GRACE,2 Amy TAI,3 Katarzyna MICHALAK2 and Susan P. WALKER3


5 year retrospective cohort study

N = 46,855 births; 3 Victorian public hospitals

N = 398 (0.9%) Hep B positive

Timing of HBIG and vaccine at delivery

Assessment of viral load

Management of AN invasive procedures
Risk Factors for Failed Prophylaxis….

Invasive procedures

Recommendations to avoid invasive *intrapartum* procedures are well followed

What about *antenatal* procedures, particularly those for prenatal diagnosis?

Uptake of genetic screening for Trisomy 21 in Australia is extremely high
All screening tests report detection rates for T21 at a 5% false positive
Amniocentesis....
Chorionic Villus Sampling...
Minimally invasive fetal surgery.....
Open Fetal Surgery.....
What are the risks? ...

Risk of vertical transmission of hepatitis B after amniocentesis in HBs antigen-positive mothers

Wei Yi¹, Calvin Q. Pan²,*, Jianzhen Hao¹, Yuhong Hu¹, Min Liu¹, Li Li¹, Dongzhu Liang¹

Journal of Hepatology 2014 vol. 60 | 523–529

63 amniocentesis; 198 matched no amniocentesis; VT 6.4% vs 2.5%

Stratification by VL: ≥ 7 log 10 copies/mL: VT 50% vs 4.5%; OR 21.3

Hep B sAg + women should have viral load performed prior to amniocentesis to evaluate their risk of VT, and be counselled accordingly
Is there an alternative to invasive testing?

We have entered the era of non invasive prenatal testing.....

99% sensitivity; <0.1% false positive rate; cost $500-$1000, no rebate

Recommend NIPT as advanced screening in women with high risk result and high VL
Summary...

Compliance with existing guidelines is poor
- assessment VL; stratification of risk
- minimise antenatal invasive procedures

Potential Reasons:
- 87% non Australian born; nearly half emigrated within last 5 years
  Over 40% required interpreter for antenatal care

Solution:
- Designated clinics for pregnant women with Hepatitis B
- Guidelines need to reinforce VL as single most important triage
  Decision for antivirals
  ?mode of delivery
  Support NIPT for screening in high risk groups
Parvovirus infection
Parvovirus.....

Not part of routine screening....

At Risk
40% of pregnant women are seronegative

Seroconversion
- 20% of women will seroconvert after community/school exposure
- 50% of women will seroconvert after household contact
- 1% of pregnant women will seroconvert without known contact

Fetal Risks Following Seroconversion
- 50% risk of transmission
- 15% risk of hydrops <20 weeks; <5% > 20 weeks

May present with seroconversion or picked up following Ix for fetal hydrops ....
1. Management of Fetal Hydrops.....

**Description, not a diagnosis....**

| Two or more: pleural fluid, pericardial fluid, ascites, skin oedema |

**Investigate for Aetiology.....**

<table>
<thead>
<tr>
<th>Cardiac</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
</tr>
<tr>
<td>Chest mass/ mediastinal compression</td>
</tr>
<tr>
<td>Infections: TORCH, parvovirus</td>
</tr>
<tr>
<td>Chromosomal/ Genetic</td>
</tr>
</tbody>
</table>

*In parvovirus, mostly anemia +/- cardiomyopathy +/- hepatitis.....*
2. Management of seroconversion...

Mean interval from *maternal exposure to fetal infection* 7 weeks

Marrow suppression takes *3-4 weeks* to result in fetal anemia

Surveillance for fetal anemia for 12 weeks post exposure
Monitoring for anemia....

Hypoxic Fetuses redistribute their circulation to critical vascular beds;
• ‘brain sparing’

Anemic Fetuses have an increased cardiac output and low blood viscosity

Middle cerebral artery peak systolic velocity is mainstay of surveillance for fetal anemia

MCA = Middle cerebral artery, MOM = Multiples of the median
A: moderate to severe anemia; B: mild anemia; C: no anemia.
MCA PSV for anemia surveillance
Intra Uterine Transfusion

Pre transfusion

- Estimated fetal weight calculation
- Estimate likely transfusion volume
- Maternal sedation
- >24 weeks steroids for fetal lung maturity
- Washed, filtered, irradiated, fresh, CMV negative red cell unit
- Preliminary paralysis with IM or IV vecuronium / pancuronium
Technique for Intra uterine transfusion...

Fetal Transfusion

- aseptic technique with local infiltration
  - 2% xylocaine
- 20-22G Echo-tip Cook FBS needle into
  - placental cord insertion (anterior placenta) or
  - intra-hepatic portion of umbilical vein (posterior placenta)
- FBS taken
  - Hb, MCV, plt count
Table 2  Long-term neurodevelopmental outcome after intrauterine transfusions for parvovirus B19 infection; summary of the literature

<table>
<thead>
<tr>
<th>First author (year)</th>
<th>Patient number</th>
<th>Major neurodevelopmental impairment (%)</th>
<th>Minor neurodevelopmental impairment (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miller (1998)</td>
<td>8</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dembinski (2002)</td>
<td>20</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nagel (2007)</td>
<td>18</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>de Jong (2012)</td>
<td>28</td>
<td>11</td>
<td>2.5</td>
</tr>
</tbody>
</table>

Overall, severe neurodevelopmental problems after IUT for parvovirus B19 infection in pregnancy is not a rare finding and may occur in up to 12.5% of children. The causes for a possible increased rate of cerebral injury and adverse neurodevelopmental outcome in parvovirus B19 infection are still not fully understood. Adverse outcome may be directly related to either viral infection itself or, alternatively, the compromised condition of the fetus with severe anaemia and hydrops.
### Summary: Parvovirus.....

<table>
<thead>
<tr>
<th>Universal screening not routine</th>
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<tbody>
<tr>
<td>May be requested by high risk groups...</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Is it amenable to primary prevention?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes:</td>
</tr>
<tr>
<td>• Hygiene advice; avoid contacts during endemics</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Is it amenable to tertiary prevention?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes:</td>
</tr>
<tr>
<td>• Fetal transfusion for severe fetal anemia reduces fetal mortality; justifies 12 weeks middle cerebral artery peak systolic velocity surveillance post maternal infection</td>
</tr>
</tbody>
</table>

**Long term follow up is crucial to better inform parents of likely outcome**
Cytomegalovirus infection

Universal screening? when?

Targeted Screening? who?
**CMV: Is it time to screen?**

**Yes!**
‘Most prevalent infection related cause of neurological handicap since introduction of rubella vaccine...’

**No!!**
‘Opening Pandora’s box...’
‘There are known knowns. These are things we know that we know. There are known unknowns. That is to say, there are things that we know we don't know. But there are also unknown unknowns. There are things we don't know we don't know.’

• Donald Rumsfeld, US Secretary of Defence
The scope of the problem...

<table>
<thead>
<tr>
<th>Event</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>50% pregnant women CMV IgG negative</td>
<td>500/1000</td>
</tr>
<tr>
<td>1% will seroconvert during pregnancy</td>
<td>5/1000</td>
</tr>
<tr>
<td>40% of their infants will get infected</td>
<td>2/1000</td>
</tr>
<tr>
<td>Secondary infection</td>
<td>4/1000</td>
</tr>
<tr>
<td>Seroprevalence at birth</td>
<td>6/1000</td>
</tr>
</tbody>
</table>
Congenital Infection

Risk factors for transmission:
- primary infection > recurrent infection
- advancing gestational age

Risk factors for sequelae:
- Primary infection > recurrent infection
- Earlier gestational age (30% T1)

Among newborns with primary congenital CMV

10% symptomatic at birth:
- Up to 10% perinatal mortality
- 40-60% major neurological sequelae

90% asymptomatic at birth;
- 10-15% symptomatic later (progressive SNHL)
<table>
<thead>
<tr>
<th>Event</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>50% pregnant women CMV IgG negative</td>
<td>148,000</td>
</tr>
<tr>
<td>1% will seroconvert during pregnancy</td>
<td>1480</td>
</tr>
<tr>
<td>40% of their infants will get infected</td>
<td>592</td>
</tr>
<tr>
<td>10% symptomatic at birth</td>
<td>59</td>
</tr>
<tr>
<td>10% symptomatic later</td>
<td>59</td>
</tr>
</tbody>
</table>
Pandora’s algorithm: universal screening

If seronegative pre pregnancy/ early pregnancy....

Vaccination
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.

Identified by Institute of Medicine as highest priority in congenital infectious diseases in the developed world

Phase 2 trials ongoing; no effective vaccine imminent
If seronegative pre pregnancy/ early pregnancy....

Advice to avoid primary infection in pregnancy
BOX. CDC and American College of Obstetricians (ACOG) recommendations for reducing risk for cytomegalovirus (CMV) Infection

**CDC recommendations for women who are pregnant or might become pregnant**

- Wash hands often with soap and water, especially after contact with saliva of or diapers from young children. Wash well for 15-20 seconds.
- Do not kiss children aged <6 years on the mouth or cheek. Instead, kiss them on the head or give them a hug.
- Do not share food, drinks, or utensils (spoons or forks) with young children.

**ACOG recommendations for obstetricians and gynecologists on counseling pregnant women**

- Advise careful handling of potentially infected articles, such as diapers.
- Advise thorough handwashing when around young children or immunocompromised persons.
- Explain that careful attention to hygiene is effective in helping prevent CMV transmission.

*Available at [http://www.cdc.gov/cmv](http://www.cdc.gov/cmv).
Picome et al, BJOG 2009
n=3792 French women seronegative 12 weeks

Intervention: advice at 12 weeks
• Frequent hand washing for 15-20 seconds
• Avoid intimate contact <6 y.o.
• Didn’t recommend gloves

Diagnosis
• Rescreened at 36 weeks

Results
• Seroconversion rate 0.26% (cf expected 1%)
Pandora’s Algorithm: universal screening

If seronegative pre pregnancy/ early pregnancy....

Advice to avoid primary infection in pregnancy

? Rescreen during pregnancy
When and how to rescreen?

**Symptomatic (25%)**
- Clinical diagnosis unreliable

**Asymptomatic**
- ?when: *Aggressive*: monthly? *Conservative*: 16 weeks and late third trimester

**Challenges with interpretation of serology**
- CMV IgM: problems with false positive
- Need to be able to access serial serology and interpret IgG avidity
  - low avidity usually seen in first 12-16 weeks of infection

**Diagnosis**
Seroconversion or presence of IgM combined with low avidity IgG
Most important infections are early...
If seronegative pre pregnancy/ early pregnancy:....

Advice to avoid primary infection in pregnancy

Rescreen during pregnancy

Fetal diagnosis following maternal seroconversion
<table>
<thead>
<tr>
<th>Confirmation of fetal diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Counsel regarding vertical transmission rate 40%</strong></td>
</tr>
<tr>
<td><strong>Need to establish fetal diagnosis</strong></td>
</tr>
</tbody>
</table>
| **How?**  
Amniocentesis for CMV PCR |
| **When?**  
≥ 21 week’s gestation and ≥ 7 weeks post maternal infection |
| **Indications?**  
Serological evidence seroconversion  
US abnormalities consistent with CMV infection |
| **Result?**  
Viral DNA detected: **fetal infection confirmed; PPV 100%**  
No viral DNA: **infection can be ruled out: NPV 95%**  
(....so still need to screen newborns...) |
Is there an effective secondary prevention to avoid fetal infection?

2005; Non randomized study

Reduction in vertical transmission from 40% (19/47) to 16% (6/37)

Presumed efficacy: high IgG avidity (neutralizing/immunomodulating activity)
Is there an effective secondary prevention to avoid fetal infection?

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 Klerys, M.D., and Giuseppe Gerna, M.D., for the CHIP Study Group

N=123; powered for the same reduction seen in Nigro, 2005

Primary CMV between 5 and 26 weeks

Treatment commenced within 6 weeks of presumed infection

Intervention: 100U/kg IV or placebo every 4 weeks until 36 weeks (or + amnio)
Is there an effective secondary prevention to avoid fetal infection?

A Randomized Trial of Hyperimmune Globulin to Prevent Congenital Cytomegalovirus

Preterm birth;  
15% in CMVHIG; 2% in placebo; p=0.06

AbN cranial US;  
11% in CMVHIG; 16% in placebo

Viral load (placenta/blood);  
No difference

Primary outcome: 30% CMV HIG vs 44%; p=0.13
Pandora’s Algorithm: universal screening

| If seronegative pre pregnancy/ early pregnancy.... |
| Advice to avoid primary infection in pregnancy |
| Rescreen during pregnancy |
| Fetal diagnosis following maternal serovconversion |
| The search for the affected fetus |
The search for the affected fetus....

Ultrasound ?every 2-4 weeks

Features of placental infection:
• Intrauterine growth restriction, oligohydramnios
• Hepatosplanomegaly
• Hydrops
• stillbirth
The search for the affected fetus...

Ultrasound every 2-4 weeks:

**CNS injury (direct cytopathic damage):**

- Ventriculomegaly, intraventricular adhesions, periventricular calcifications +/- cysts,
- cortical abnormalities, hypoplastic CC, cerebellar abnormalities, brain atrophy or haemorrhage

Value of transfontanellar US

Need for targetted, skilled, serial assessment
The search for the affected fetus....

1. Ultrasound

2. MRI

- Provides better evaluation of white matter, posterior fossa and cerebral cortex than US

Value of late US/ MRI will partly depend on gestation at which TOP is accessible
The Search for Affected Fetus:
Searching for Brain Abnormalities vs. .......

Almost all retrospective studies
Variable length of follow up
Small numbers of infected fetuses
"Fetal infection" = amnio or neonatal urine PRCR
Confounding effect of prenatal therapies
Bias in tertiary referral population vs screening
Variable detail on timing of maternal infection
Different imaging regimes
High TOP in some studies = “adverse outcome”
Wide range in results

Prediction of Outcome Based on Ultrasound:
Limitations of the Literature
## Prenatal imaging studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Prospective</th>
<th>GA at infection</th>
<th>Amnio pos (n)</th>
<th>Abn US in pos fetuses/neonates</th>
<th>TOP (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipitz 2002</td>
<td>Yes</td>
<td>Not stated</td>
<td>51</td>
<td>11 (21%) *</td>
<td>33</td>
</tr>
<tr>
<td>Guerra 2008</td>
<td>No</td>
<td>Not stated</td>
<td>154</td>
<td>23 (15%)</td>
<td>9</td>
</tr>
<tr>
<td>Benoist 2008a</td>
<td>no</td>
<td>Not stated</td>
<td>49**</td>
<td>19 (39%)</td>
<td>10</td>
</tr>
<tr>
<td>Benoist 2008b***</td>
<td>no</td>
<td>T1-3, 8 unknown</td>
<td>73</td>
<td>38 (52%)</td>
<td>32</td>
</tr>
<tr>
<td>Farkas 2011</td>
<td>no</td>
<td>7-31w</td>
<td>69</td>
<td>32 (46%)</td>
<td>29</td>
</tr>
<tr>
<td>Lipitz 2010</td>
<td>no</td>
<td>T1-T2 (T3)</td>
<td>29 (9)</td>
<td>6 (21%)</td>
<td>5</td>
</tr>
<tr>
<td>Picone 2013</td>
<td>no</td>
<td>T1/2/3</td>
<td>32</td>
<td>23/60 pos total newborns (38%)</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>19/37 T1 (51%)</td>
<td></td>
</tr>
<tr>
<td>Lipitz 2013</td>
<td>yes</td>
<td>T1/2</td>
<td>145</td>
<td>20/137 (15%) 20% in T1</td>
<td>7</td>
</tr>
</tbody>
</table>
• Prospective study n = 145 with CMV infection in T1 or T2
• Strict criteria for dating and serological diagnosis
• All cases diagnosed by amnio > 20 w
• Counselling by fetal medicine specialist
• Serial ultrasounds every 3-4 weeks
• Fetal MRI at 31-32 weeks in 84%
• Low TOP rate (n=7, most had ab US findings)
• No prenatal therapy given
• Standardized paediatric follow up to median 27m
US prediction of severe sequelae in survivors of T1 infection

T1 infection: overall 10% risk neurodev delay

- Normal US
  - 6% risk NDD
- AbN US
  - 23% risk NDD

Lipitz 2013, excludes 4 TOP/1 NND
Pandora’s Algorithm: universal screening

If seronegative pre pregnancy/ early pregnancy....

Advice to avoid primary infection in pregnancy

Rescreen during pregnancy

Fetal diagnosis following maternal serovconversion

Detection of the affected fetus

?access to TOP

Is there any effective treatment?

?CMV HIG

?antivirals
Is there an effective tertiary prevention to prevent neonatal sequelae?

1/31 infants born with CMV disease (3%)

7/14 infants born with CMV disease (50%)

14 fetuses with US evidence of severe disease resolved (?)

Non randomised clinical trial

TREATMENT group
Positive amniocentesis (ie infected fetus)
Is there an effective tertiary prevention to prevent neonatal sequelae?

**CMV HIG**

- among congenitally infected newborns, infants whose mothers did not receive CMV HIG were more likely to have hearing or neurological impairment at follow up (43% vs 13%, p<0.01)
  - *Visentin 2012*

- No ongoing trials; CMV HIG available to women in Australia with known infected fetus


**Valacyclovir**

**DB RCT: valacyclovir for extracerebral signs of CMV infection**

- Completion expected 2014
So...where are we exactly?
Congenital CMV is a significant contributor to long-term disability

Hygiene measures to reduce transmission in seronegative women appear effective

Screening would enable primary infection to be diagnosed reliably in pregnancy

Fetal infection can be diagnosed reliably with amniocentesis

Improving ability to identify the affected fetus who is likely to suffer severe sequelae

No country has implemented universal screening for CMV in pregnancy

Tertiary prevention of CMV may involve access to late termination of pregnancy
The known unknowns...

<table>
<thead>
<tr>
<th>The known unknowns....</th>
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<tbody>
<tr>
<td>Diagnosis of non-primary infection in pregnancy can be difficult</td>
</tr>
<tr>
<td>Optimal frequency for rescreening seronegative women remains to be determined</td>
</tr>
<tr>
<td>The role of CMV HIG to reduce fetal infection = subject of ongoing trials</td>
</tr>
<tr>
<td>Role of CMV HIG or antivirals to reduce fetal sequelae is uncertain</td>
</tr>
<tr>
<td>Estimates of risk for long term sequelae with normal imaging remains imprecise</td>
</tr>
</tbody>
</table>
The unknown unknowns....

| Attitudes of Australian women and clinicians to CMV screening |
| Cost effectiveness |
| The resources required for screening, fetal diagnosis, fetal surveillance +/- therapy |
Where we are: Viruses in May, 2014...

**Congenital CMV**

- Significant and important contributor to long term handicap
- Measures to reduce transmission in seronegative high risk women appear effective
- Reliable serological diagnosis of primary infection, and fetal infection
- Improving data on identifying the affected fetus at risk of long term sequelae
- No country has implemented universal screening for CMV
- This position is likely to change if primary, secondary or tertiary prevention of fetal disease is confirmed
May 2, 2014

Thank you!