Prediction of neonatal outcome in congenital cytomegalovirus infection at the time of prenatal diagnosis

Enrico David, 2014, « The Assumption of Wee »
Prediction of neonatal outcome in congenital cytomegalovirus infection at the time of prenatal diagnosis

Rationale

• Need for improvement of Positive and Negative Predictive Value
• Early reassurance
• Early access to TOP
• Opportunity for treatment
Prognosis based upon clinical neonatal evaluation

This sets the goal of prenatal management by extrapolating neonatal symptoms to prenatal evaluation

5-10% Severe  5-10% Moderate  90% Asymptomatic

- IUGR
- Microcephaly
- Ventriculomegaly
- Seizures
- Spasticity
- Meconial peritonitis
- Hepatomegaly
- Splenomegaly
- Hepatitis
- Thrombocytopenia
- No clinical sign

Neonatal Death 30%  Sequelae 30%  Neurosensory Hearing loss 60%  Neurosensory Hearing loss 5-15%

Modified from Fowler et al N Eng J Med 1992
Extra-cerebral ultrasound features of fetal CMV infection

Presented in the theoretical chronological order of their development

Placentitis
Oligohydramnios
Polyhydramnios

Ileus
Meconial peritonitis / Ascites
Liver & Spleen enlargement

Ubiquitous Calcifications

Pericardial / Pleural Effusion
Dilated Myocarditis
Heart Calcifications
Hydrops

Growth Restriction / Small for GA

Django Hernandez, 2008
Ultrasound to my mother history-we got twins!
Hyperechogenic bowel

Figure 2. Flow chart showing the approach to the analysis. *Sequential subanalysis with serial

260 cases of echogenic bowel, (0.4%)

13 cases (5%) of trisomy 21,
1 case (0.4%) of trisomy 18,
2 cases (0.8%) of trisomy 13,
1 case (0.4%) of chromosomal mosaicism,
5 documented cases (1.9%) of CMV infection,
6 documented cases (2.3%) of CF,
1 case (0.4%) of both documented CF and chromosomal mosaicism.
43 cases had associated anomalies,

<table>
<thead>
<tr>
<th>Authors</th>
<th>n</th>
<th>Term (weeks)</th>
<th>Poor perinatal outcome (%)</th>
<th>Chromosomal abnormality (%)</th>
<th>Cystic fibrosis (%)</th>
<th>Infection (%)</th>
<th>IUGR (%)</th>
<th>Perinatal mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dicke and Crane (1992)</td>
<td>30</td>
<td>15–34</td>
<td>12 (40)</td>
<td>1 (3)</td>
<td>4 (14)</td>
<td>0</td>
<td>6 (21)</td>
<td>4 (14)</td>
</tr>
<tr>
<td>Nyberg et al. (1993a)</td>
<td>95</td>
<td>15–24</td>
<td>45 (47)</td>
<td>24 (25)</td>
<td>0</td>
<td>1 (1)</td>
<td>13 (18)</td>
<td>6 (8)</td>
</tr>
<tr>
<td>Bromley et al. (1994)</td>
<td>50</td>
<td>14–24</td>
<td>21 (42)</td>
<td>8 (16)</td>
<td>0</td>
<td>0</td>
<td>8 (19)</td>
<td>5 (12)</td>
</tr>
<tr>
<td>Hill et al. (1994)</td>
<td>32</td>
<td>15–21</td>
<td>11 (34)</td>
<td>2 (6)</td>
<td>0</td>
<td>2 (6)</td>
<td>4 (13)</td>
<td>5 (17)</td>
</tr>
<tr>
<td>Muller et al. (1995)</td>
<td>182</td>
<td>14–34</td>
<td>71 (39)</td>
<td>8 (4)</td>
<td>1 (1)</td>
<td>7 (4)</td>
<td>12 (7)</td>
<td>23 (13)</td>
</tr>
<tr>
<td>Slotnick and Abuhamad (1996)</td>
<td>145</td>
<td>16–20</td>
<td>20 (14)</td>
<td>8 (6)</td>
<td>7 (5)</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Yaron et al. (1999)</td>
<td>79</td>
<td>14–23</td>
<td>36 (46)</td>
<td>5 (6)</td>
<td>2 (3)</td>
<td>5 (6)</td>
<td>5 (7)</td>
<td>6 (8)</td>
</tr>
<tr>
<td>Ghose et al. (2000)</td>
<td>60</td>
<td>16–22</td>
<td>17 (28)</td>
<td>3 (5)</td>
<td>3 (5)</td>
<td>0</td>
<td>6 (11)</td>
<td>6 (11)</td>
</tr>
<tr>
<td>Strocker et al. (2000)</td>
<td>131</td>
<td>15–23</td>
<td>38 (29)</td>
<td>15 (11)</td>
<td>0</td>
<td>13 (10)</td>
<td>8 (7)</td>
<td>9 (8)</td>
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<tr>
<td>Simon-Bouy and Muller (2002)</td>
<td>682</td>
<td>15–34</td>
<td>209 (30.6)</td>
<td>24 (3.5)</td>
<td>20 (3)</td>
<td>19 (2.8)</td>
<td>28 (4.1)</td>
<td>24 (3.5)</td>
</tr>
<tr>
<td>Kesrouani et al. (2003)</td>
<td>196</td>
<td>14–24</td>
<td>80 (40.8)</td>
<td>14 (7.1)</td>
<td>3 (1.5)</td>
<td>8 (4)</td>
<td>13 (6.6)</td>
<td>4 (2)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>1682</td>
<td>14–34</td>
<td>560 (33.3)</td>
<td>112 (6.7)</td>
<td>40 (2.4)</td>
<td>55 (3.3)</td>
<td>103 (6.1)</td>
<td>92 (5.5)</td>
</tr>
</tbody>
</table>

IUGR, intrauterine growth retardation.

a Fetuses with chromosomal abnormality are excluded.

b Fetuses with chromosomal abnormality and terminations of pregnancy are excluded.

Decrease the gain and switch off the harmonics to compare the echogenicity of the bowel to that of the bones (Grade 3 : > ou = bone)
Liver and Spleen Measurement and Biometry

Right liver lobe in a sagittal plane

**Figure 1.** Longitudinal scan showing the fetal liver length as measured from the right hemidiaphragm to the tip of the right lobe. L = fetal liver, B = fetal bowel, and H = fetal heart.

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In an axial plane

**Figure 2.** Relationship (along with 95% confidence limits) of fetal liver length and gestational age from 20 to 41 weeks' gestation. *Obstet Gynecol 1985*

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**Table 1.** Ultrasound Measurement* of the Fetal Liver and Spleen From 20 Weeks' Gestation to Term

<table>
<thead>
<tr>
<th>Gestational age (wks)</th>
<th>No. of measurements</th>
<th>Arithmetic mean (mm)</th>
<th>± 2 SD (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>8</td>
<td>27.3</td>
<td>6.4</td>
</tr>
<tr>
<td>21</td>
<td>2</td>
<td>28.0</td>
<td>1.5</td>
</tr>
<tr>
<td>22</td>
<td>4</td>
<td>30.6</td>
<td>6.7</td>
</tr>
<tr>
<td>23</td>
<td>13</td>
<td>30.9</td>
<td>4.5</td>
</tr>
<tr>
<td>24</td>
<td>10</td>
<td>32.9</td>
<td>6.7</td>
</tr>
<tr>
<td>25</td>
<td>14</td>
<td>33.6</td>
<td>5.3</td>
</tr>
<tr>
<td>26</td>
<td>10</td>
<td>35.7</td>
<td>6.3</td>
</tr>
<tr>
<td>27</td>
<td>20</td>
<td>36.6</td>
<td>3.3</td>
</tr>
<tr>
<td>28</td>
<td>14</td>
<td>38.4</td>
<td>4.0</td>
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<td>29</td>
<td>13</td>
<td>39.1</td>
<td>5.0</td>
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<td>30</td>
<td>10</td>
<td>38.7</td>
<td>5.0</td>
</tr>
<tr>
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<td>32</td>
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<td>33</td>
<td>14</td>
<td>43.8</td>
<td>6.6</td>
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<tr>
<td>34</td>
<td>11</td>
<td>44.8</td>
<td>7.1</td>
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<tr>
<td>35</td>
<td>14</td>
<td>47.8</td>
<td>9.1</td>
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<tr>
<td>36</td>
<td>10</td>
<td>49.0</td>
<td>8.4</td>
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<tr>
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<td>10</td>
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</tr>
<tr>
<td>38</td>
<td>12</td>
<td>52.9</td>
<td>4.2</td>
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<tr>
<td>39</td>
<td>5</td>
<td>55.4</td>
<td>6.7</td>
</tr>
<tr>
<td>40</td>
<td>1</td>
<td>59.0</td>
<td>2.4</td>
</tr>
<tr>
<td>41</td>
<td>2</td>
<td>69.3</td>
<td>2.4</td>
</tr>
</tbody>
</table>

SD = standard deviation.  
*Mean length ± 2 SD.
Extra-cerebral ultrasound features of fetal CMV infection
The Unclear prognostic value of Growth restriction in fetal CMV Infection

### Congenital CMV: Adjusted\(^a\) Odds Ratios of Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Odds ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>1.2</td>
<td>0.2-9.0</td>
</tr>
<tr>
<td>Abnormal neuroimaging</td>
<td>7.8</td>
<td>2.2-28.1</td>
</tr>
<tr>
<td>Suspected SNHL(^b)</td>
<td>87.6</td>
<td>11.8-633.4</td>
</tr>
<tr>
<td>Suspected SNHL and death(^c)</td>
<td>40.6</td>
<td>7.1-231.1</td>
</tr>
</tbody>
</table>

\(^a\)Adjusted for maternal age and race, antenatal steroids, gestational age and small for gestational age, \(^b\)N=148 (excluding deaths and hearing screen results unknown) \(^c\) N=188 (excluding screening results unknown)

*Pediatrics* 2014;133:e609–e615

### Prevalence of hypotrophy in 131 infected neonates (N=131) in relation with neurological assessment

<table>
<thead>
<tr>
<th>NORMAL Neurological examination CT scan</th>
<th>42 / 114 (37%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABNORMAL Neurological examination Or CT scan</td>
<td>8 / 17 (51%)</td>
</tr>
</tbody>
</table>

# Prognosis of fetal infection with non-cerebral features on ultrasound

<table>
<thead>
<tr>
<th>Study</th>
<th>Total</th>
<th>Asymptomatic</th>
<th>Proportion</th>
<th>95%-CI</th>
<th>W(random)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guerra B, Am J Obs Gyne, 2008</td>
<td>14</td>
<td>6</td>
<td>0.43</td>
<td>[0.18; 0.71]</td>
<td>23.0%</td>
</tr>
<tr>
<td>jacquemard , BJOG, 2007</td>
<td>20</td>
<td>10</td>
<td>0.50</td>
<td>[0.27; 0.73]</td>
<td>33.5%</td>
</tr>
<tr>
<td>Liesnard Obstet Gynecol, 2000</td>
<td>9</td>
<td>3</td>
<td>0.33</td>
<td>[0.07; 0.70]</td>
<td>13.4%</td>
</tr>
<tr>
<td>Lipitz, Ultrasound Obs Gyne , 2010</td>
<td>7</td>
<td>4</td>
<td>0.57</td>
<td>[0.18; 0.90]</td>
<td>11.5%</td>
</tr>
<tr>
<td>Picone, Prenat Diag, 2008</td>
<td>13</td>
<td>4</td>
<td>0.31</td>
<td>[0.09; 0.61]</td>
<td>18.6%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>63</strong></td>
<td><strong>27</strong></td>
<td><strong>0.43</strong></td>
<td><strong>[0.31; 0.56]</strong></td>
<td><strong>100%</strong></td>
</tr>
</tbody>
</table>
Prognosis of fetal infection by ultrasound throughout pregnancy

Odd ratio to be found symptomatic at birth or at Termination of Pregnancy:

- **4.4** if for **extra-cerebral** ultrasound anomalies
- **40.6** for **cerebral** ultrasound anomalies

E. Munch, *Le cri*, 1893, National Gallery, Oslo

Benoist G et al., 2008, British J Obstet Gynaecol, 115: 823-9
Prognostic value of prenatal imaging

- PPV of isolated extra-cerebral US features at any time during the pregnancy for being symptomatic at birth is $\sim 55\%$

- NPV of normal imaging (US + MRI)* throughout the pregnancy is $\sim 90\%$

* Cumulative performance of US and MRI up to 3rd T

Cerebral ultrasound features of fetal CMV infection

Presented in order of increasing severity

• Ventriculomegaly (A)
• Parenchymal calcifications (B)
• Subependymal Cysts (C)
• Calcifications of the lenticulostriate vessels (D)
• Intraventricular septation (E)
• Periventricular Hyperechogenicity (F,G)
• Periventricular Cysts (G)
• Cystic Periventricular leukomalacia (I)
• Abnormal Gyration / Lisencephaly (J/30 w)
• Enlarged pericerebral spaces (J,K,L)
• Polymicrogyria (K)
• Microencephaly (L)
• Microcephaly (M)

Prenatal Imaging: Posters # 8, 59, 71, 72, 73, 74

**Introduction**

Congenital Cytomegalovirus (CMV) has an incidence of 0.5 to 1.0% of all live births and is the leading infectious cause of hearing loss and mental retardation.

**Materials and Methods**

Patient with serological evidence of maternal primary CMV infection and proven vertical transmission to the fetus were recruited in a prospective observational study between 1996-2016. Termination of the pregnancy (TOP) was presented as an option for CMV-infected fetuses after ultrasound evaluation. Hearing and neurological clinical assessments were performed for all neonates with a CMV-positive urine sampling.

**Results**

67 patients (69 fetuses) were included in this study. Fetuses were excluded from the analysis because of insufficient data on the outcomes. TOP was performed for 26 fetuses. 11 fetuses had US anomalies confirmed by autopsy. Histological evidence of fetal infection damage was detected in 13 cases without US anomalies. 12 live born infants out of 39 had prenatal imaging suggestive for a CMV infection. 6 infants presented clinical anomalies from whom 4 cases were considered as severe. 6 live born infants of 23 with normal fetal US showed hearing impairments and 2 cases were associated with mid-neurological sequelae.

**Conclusions**

In a group of early maternal primary CMV infections, proven fetal infection, fetal US anomalies were detected in 37.7% and were confirmed in autopsy or clinical evaluation after birth in 73.9%. In patients with normal fetal US evaluation, autopsy or clinical evaluation after birth could detect CMV-related anomalies in 55% of fetuses.
Targetted ultrasound v. MRI to depict brain lesions in infected fetuses

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>US+</strong></td>
<td>63.6</td>
<td>94.4</td>
<td>77.8</td>
<td>89.5</td>
</tr>
<tr>
<td><strong>MRI+</strong></td>
<td>51</td>
<td>100</td>
<td>81</td>
<td>67</td>
</tr>
<tr>
<td><strong>US+ and MRI+</strong></td>
<td>54.5</td>
<td>100</td>
<td><strong>100</strong></td>
<td><strong>87.8</strong></td>
</tr>
<tr>
<td><strong>US+ and/or MRI+</strong></td>
<td>72.7</td>
<td>88.9</td>
<td>66.7</td>
<td>91.4</td>
</tr>
</tbody>
</table>

Prediction of a good outcome

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MRI- US-</strong></td>
<td>89.2</td>
<td>80</td>
<td><strong>94.3</strong></td>
<td>80</td>
</tr>
</tbody>
</table>
Maud Dale by Fernand Leger (1935) and by Paul Bellows (1919) @ The Smithsonian
Quantitative/Objective Assessment of T2 Hyper Signal Intensity

- Single-shot fast spin echo (SSFSE) T2-weighted sequence (TE=90 ms, TR=1298 ms) slice thickness of 3 or 4 mm
- Region of interest in the areas of higher intensity or in the temporal region if there were no HSI
- **SI ratio** = SI Temporal / SI Basal Ganglia

*Deloison et al 2013*
Infections with an impact on the fetal brain directly or indirectly

Malformative Sequence / Cascade $f$ (Gestational Age - ?)

- Polymicrogyria
- Pachygyria
- Lissencephaly
- Microencephaly / Microcephaly
- Hydrocephalus
- Encephalomalacia
- Schizencephaly

Inflammatory Response

- Proinflammatory cytokines + lack of modulating proteins

Viral lesion

- Hypoxia
- Vasculitis
- Apoptosis
- Necrosis
- Hemorrhage
- Periventricular Leukomalacia
- Gliosis
- Clastic Dysgenesis
- Abnormal Neuronal Migration
Impact on the fetal brain with gestational age at fetal infection

Malformative Sequence / Cascade \( f \) (Gestational Age - ?)

First & Early Second Trimester (< 18 w)
- Loss of neurons and glia
- Lissencephaly with a thin cortex, cerebellar hypoplasia, and ventriculomegaly
- Delayed myelination and periventricular calcification

Third Trimester (after 26 Weeks)
- Delayed myelination, dysmyelination, and white matter disease
- Gyration tends to be normal

Late Second Trimester (18–24 W)
- Migrational abnormalities such as polymicrogyria,
**Prognosis of Fetal CMV Infection at 23 (22-28) weeks**

- **82 infected fetuses**
  - **Severe brain ultrasound anomalies**
    - N=19
  - **No severe brain ultrasound anomalies**
    - N=63

### Severe brain ultrasound anomalies
- TOP (severe) n=18
- Symptomatic babies n=1
- Asymptomatic babies n=0

### Non-severe ultrasound anomalies
- TOP (severe) * n=3 (14%)
  - Symptomatic babies** n=11 (60%)
    - Deafness n=3 (14%)
    - Hearing loss n=4 (18%)
    - Others n=4 (18%)
  - Asymptomatic babies n=8 (36%)

### No ultrasound anomalies
- TOP (severe) * n=3 (7%)
  - Symptomatic babies n=0 (0%)
  - Asymptomatic babies n=38 (93%)

---

**Median follow-up:**
- **TOP**: 18 (5-48) Mo
- **Symptomatic children*** n=9 (41%)
  - Deafness n=9 (9%)
  - Hearing loss n=7 (32%)
  - Neurodevelopmental delay n=0
- **Asymptomatic children** n=10 (45%)

**Postnatal Follow-up**: Median follow-up: 12 (1-53) Mo
- **Symptomatic children*** n=2 (5%)
  - Deafness n=0
  - Hearing loss n=2 (5%)
  - Neurodevelopmental delay n=0
  - Asymptomatic children n=36 (88%)

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* TOP because of severe brain features at follow-up

**3 with deafness, 2 with profound UHL, 1 with severe UHL, 1 with mild UHL, 4 with thrombocytopenia or IUGR or both

***2 with profound BHL, 2 with profound UHL, 1 with severe UHL and monoparesia of 1 arm, 1 with severe UHL, 2 with mild UHL, 1 with vestibulopathy without HL

****2 with mild UHL

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L. Bourgeois, Femme 2005
**Prognostic factors of a symptomatic status at birth or at Termination**

In 63 fetuses presenting with no US features or non-severe US features at the time of prenatal diagnosis at 23 (IQ: 22-28) weeks’

<table>
<thead>
<tr>
<th>Logistic regression</th>
<th>OR</th>
<th>IC95%</th>
<th>p. value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMV DNA in fetal blood (for each 1 log of IU/ml increase) N=54</td>
<td>5.77</td>
<td>2.02-16.53</td>
<td>0.001</td>
</tr>
<tr>
<td>Thrombocytopenia (for each 10 000/mm³ decrease) N=49</td>
<td>0.74</td>
<td>0.60-0.89</td>
<td>0.002</td>
</tr>
<tr>
<td>Presence of non-severe US symptoms N=63</td>
<td>18.29</td>
<td>4.29-78.04</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Abnormal fetal blood results N=50</td>
<td>40.44</td>
<td>4.64-352.72</td>
<td>0.001</td>
</tr>
<tr>
<td>Adjusted CMV DNA in amniotic fluid (for each 1 log of IU/ml increase) N=48</td>
<td>2.31</td>
<td>1.15-4.64</td>
<td>0.018</td>
</tr>
<tr>
<td>Presence of non-severe US symptoms Adjusted CMV DNA in amniotic fluid (for each 1 log of IU/ml increase) N=48</td>
<td>10.45</td>
<td>1.96-55.63</td>
<td>0.006</td>
</tr>
<tr>
<td>Abnormal fetal blood results Presence of non-severe US symptoms N=50</td>
<td>17.76</td>
<td>1.92-164.02</td>
<td>0.011</td>
</tr>
</tbody>
</table>

. Complete laboratory data were not available for all cases. Some amniocenteses were done in another centre and therefore the amniotic fluid sample was not tested in Necker laboratory. Some women declined having cordocentesis.

US= ultrasound

Abnormal fetal blood results = platelets count ≤ 114,000/ mm³ and/or CMV DNA load ≥ 4.93 log₁₀ IU/ml.
### Predictive values (PPV, NPP) of non-severe ultrasound features alone or combined with fetal laboratory parameters

For any symptom at birth or Termination of Pregnancy

<table>
<thead>
<tr>
<th>Description</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-severe US features alone</td>
<td>60%</td>
<td>93%</td>
</tr>
<tr>
<td>Non-severe US features AND adjusted CMV DNA in amniotic fluid &gt; 1MoM</td>
<td>78%</td>
<td>90%</td>
</tr>
<tr>
<td>Non-severe US features OR adjusted CMV DNA in amniotic fluid &gt; 1MoM</td>
<td>44%</td>
<td>95%</td>
</tr>
<tr>
<td>Non-severe US features AND abnormal fetal blood results</td>
<td>79%</td>
<td>91%</td>
</tr>
<tr>
<td>Non-severe US features OR abnormal fetal blood results</td>
<td>50%</td>
<td>100%</td>
</tr>
</tbody>
</table>

*PPV: positive predictive value, NPV: Negative predictive value*

*S. Dali, «Jaune d’œuf Soleil» 1946*
Area Under the Curve for CMV DNA load in amniotic fluid and fetal blood and of fetal platelet count

for a symptomatic status at birth or at TOP

ROC curves. The small hatched line shows the CMV DNA loads in fetal blood. The bold line shows the fetal platelets counts and the large hatched line shows the CMV DNA loads in amniotic fluid.
Prognostic value of amniotic fluid viral load

Symptomatic V.
Asymptomatic
CMV DNA loads in fetal blood and as fetal platelets counts in relation to the asymptomatic or symptomatic status at birth or at termination of pregnancy.

Scatter plot. Empty dots are cases asymptomatic at birth; full dots are cases symptomatic at birth or at TOP (TOP: termination of pregnancy)
Contribution of CMV DNA load in fetal blood and of fetal platelet count in establishing the prognosis of an infected fetus

(Algorithm based on recursive partitioning model)
Predictive model based on the peptidome analysis in the amniotic fluid

89% sensitivity and 75% specificity\textsuperscript{1}

Prediction of neonatal outcome in congenital cytomegalovirus infection at the time of prenatal diagnosis

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