The Use of Magnesium Sulfate to Reduce Cerebral Palsy

Kendra Gray, DO
Banner University Medical Center Phoenix
kendramgray@gmail.com
Objectives

• Understand the historical unfolding of Cerebral Palsy as we know it today
• Define Cerebral Palsy
• Understand hypoxemic-ischemic injury at a neuronal level
• Discuss role of magnesium sulfate as a potential neuroprotective agent
• Review current literature regarding antenatal magnesium sulfate
• Propose a policy for administration of magnesium based on the literature
Disclosures

I have no relevant financial relationships to disclose or conflicts of interest to resolve.

I will not discuss any unapproved or off label, experimental or investigational use of a product, drug, or device.
1861: scribed disorder that was crippling ME children’s muscles weak, stiff, and prone to twitching.

Followed a complicated delivery yielding lack of oxygen yielding brain damage.
1889: “The Cerebral Palsies of Children”

“The young physician starts life with 20 drugs for each disease, and the old physician ends life with one drug for 20 diseases.”
Challenging the Status Quo...

• 1897: Challenged Little stating that the disorder began before birth.

• Development of the brain and nervous system was altered based on the fetal environment

Sigmund Freud
Cerebral Palsy Defined

Cerebral palsy is a physical disability that affects movement and posture.

- **Spastic cerebral palsy** — causes stiffness and movement difficulties
- **Athetoid cerebral palsy** — leads to involuntary and uncontrolled movements
- **Ataxic cerebral palsy** — causes a problem with balance and depth perception
Majority of CP (85%–90%) is congenital

Risk Factors
- Low birth weight
- Infections during pregnancy
- Multiples
- Pregnancies resulting from assisted reproductive technology
- Hyperbilirubenemia and kernicterus
- Medical conditions in the mother
- Birth complications
Most prevalent pathologic lesion in CP is peri ventricular white matter (PVWM) injury resulting from vulnerability of immature preoligodendrocytes (POD) <32 weeks.

POD are precursors of myelinating oligidendrocytes which constitute a major glial population in white matter.

Oxidative stress & excitotoxicity from excessive stimulation of ionotopic glutamate receptors on POD are the most prominent molecular mechanism for PVWM injury.
Stabilization of cerebral circulation by stabilizing blood pressure and normalizing cerebral blood flow

Prevention of excitatory injury by stabilization of neuronal membranes and blockade of excitatory neurotransmitters, such as glutamate

Protection against oxidative injury via antioxidant effects

Protection against inflammatory injury via anti-inflammatory effects
Literature Review

Most commonly cited trials...

1. MagNET
2. ACTOMgSO$_4$
3. MAGPIE
4. PREMAG
5. BEAM
MagNET - Magnesium and Neurologic Endpoints Trial


**Objective:** Determine whether antenatal magnesium sulfate for infants had adverse outcomes such as interventricular hemorrhage, periventricular leukomalacia, cerebral palsy, or death.
Study Design:

- RCT: 149 women, singleton or twin 24-34 weeks with PPROM or PTL. Randomized to one of 2 protocols including placebo.
- MgSO4 for CP prevention vs MgSO4 as a tocolytic
- Prevention group: >4cm, received 4 gm load
**MagNET - Magnesium and Neurologic Endpoints Trial**

**Results:**

- 37% (11/30) had an adverse event in neuroprophylaxis arm
- 21% (6/29) of those that received placebo.
- Combined: 32% of infants that received MgSO4 had an adverse event compared to 19% of the infants of mothers that received placebo.
- The findings were not statistically significant (p=.07)
- Children with adverse outcomes had higher umbilical cord magnesium levels at delivery.

*Might MgSO4 be harmful to neonates?*
Can my boyfriend come along?

I'm not your boyfriend! You totally are. I'm casually dating a number of people.

But you spend twice as much time with me as with anyone else. I'm a clear outlier.

Your math is irrefutable.

Face it—I'm your statistically significant other.
Objective: Determine the effectiveness of magnesium sulfate given for neuroprotection treatment in infants at risk for preterm delivery before 30 weeks
ACTOMgSO4 The Australasian Collaborative Trial of Magnesium Sulfate

Study Design:

• RCT, 1062 women, singleton to quads, <30 weeks.
• Birth expected within 24 hours. 4g load with 2g to follow
Results:
Data were analyzed for 1047 (99%) 2-year survivors.

- **Total pediatric mortality 13.8% vs 17.1%;**
  \[\text{RR}, 0.83; 95\% \text{ CI}, 0.64-1.09\]
- **Cerebral palsy in survivors 6.8% vs 8.2%;**
  \[\text{RR}, 0.83; 95\% \text{ CI}, 0.54-1.27\]
- **Combined death or cerebral palsy 19.8% vs 24.0%;**
  \[\text{RR}, 0.83; 95\% \text{ CI}, 0.66-1.03\]
- **Substantial gross motor dysfunction 3.4% vs 6.6%;**
  \[\text{RR}, 0.51; 95\% \text{ CI}, 0.29-0.91\]
- **Combined death or substantial gross motor dysfunction 17.0% vs 22.7%;**
  \[\text{RR}, 0.75; 95\% \text{ CI}, 0.59-0.96\]
YOU'RE THREE STANDARD DEVIATIONS ABOVE THE NORM

UM...THANKS?

LOVE LETTER FROM A STATISTICIAN
THE MAGPIE TRIAL: A RANDOMISED TRIAL COMPARING MAGNESIUM SULPHATE WITH PLACEBO FOR PRE-ECLAMPSIA
2007: Secondary analysis of MAGPIE that looked at 2895 children at 18 months of age for the primary outcome of death or neurosensory disability

Objective: to assess long-term effects of in-utero exposure to MgSO4 for children whose mothers had preeclampsia
Results:

- No substantive harmful effects were apparent in the short term, for either mother or baby.
- Exposure to MgSO4 while in-utero was not associated with a clear difference in the risk of death or disability for children at 18 months.
PREMAG

Marret, et al 2007. Magnesium sulphate given before very-preterm birth to protect infant brain: the randomised controlled PREMAG trial

Objective: To evaluate whether MgSO$_4$ given to women at risk of very-preterm birth would be neuroprotective in preterm newborns and would prevent neonatal mortality and severe white-matter injury (WMI).
Study Design:

- RCT, 573 women, <33 weeks GA
- Birth expected within 24 hours
- 4g MgSO4 vs Isotonic saline over 30 minutes
Results:
MgSO₄ vs Placebo

- Total mortality (9.4 versus 10.4%; OR: 0.79, 95% CI 0.44-1.44)
- Severe WMI (10.0 versus 11.7%; OR: 0.78, 95% CI 0.47-1.31)
- Combined outcomes (16.5 versus 17.9%; OR: 0.86, 95% CI 0.55-1.34)
- Less frequent with MgSO₄, but differences were not statistically significant.

Conclusion: More research is needed
WHY IS THAT WOMAN SCOWLING AT ME? DO I KNOW HER?

If she loves you more each and every day, by linear regression she hated you before you met.
Objective: To test the hypothesis that the administration of magnesium sulfate to women at high risk for early preterm delivery would reduce the risk of cerebral palsy in their children.
Study Design:

- Multicenter RCT, 2241 women, singleton or twins
- 24 through 31 weeks
- Birth expected within 2 to 24 hours.
- Protocol 6 g infused for 20 to 30 min -> 2 g/hr or identical-appearing placebo.
- DC’d if not delivered within 12hrs and delivery no longer imminent
- Restarted if delivery imminent and rebolused if at least 6 hours had passed since the discontinuation medication
Results:
The rate of the primary outcome, composite of stillbirth or infant death by 1 year or moderate to severe CP at or beyond 2 years was not significantly different in the MgSO4 group and the placebo group.
• 11.3% vs 11.7%, respectively
• RR 0.97 95% CI 0.77-1.2

Prespecified secondary analysis:
• When mortality and CP looked at separately, CP occurred significantly less frequently in the MgSO4 group than the placebo group among surviving children
• 1.9% vs 3.5%
• RR 0.55, 95% CI 0.32-0.95
Number Needed to Treat

63 women to prevent one case of moderate to severe Cerebral Palsy in all-comers but only 29 women to prevent one case among infants ≤ 28 weeks
Criticisms of BEAM

- The composite outcomes are competing risk for the outcome of interest, CP.
  Infants who die before their first birthday cannot be evaluated for CP.
  Does not account for infants that died at their first birthday who had CP.
- Only 2 additional infants from the group who died in those who received MgSO₄ would have had to have survived and been diagnosed with CP to lose statistical significance.
- Cord magnesium levels were not sampled.
Cost Effectiveness

• Confirmatory trial would require >8000 women <32 weeks and 100% F/U of children
• Enrollment of 2241 mothers in the 20 center NICHD/MFMU Network trial took 10 years and cost $25 million
FIGURE 2
Effect of magnesium sulfate on cerebral palsy

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative risk (fixed) (95% CI)</th>
<th>Magnesium n/N</th>
<th>Control n/N</th>
<th>Weight (%)</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mittendorf et al&lt;sup&gt;29.a&lt;/sup&gt;</td>
<td></td>
<td>3/30</td>
<td>0/29</td>
<td>0.3</td>
<td>6.77 (0.37-125.7)</td>
</tr>
<tr>
<td>Mittendorf et al&lt;sup&gt;29.b&lt;/sup&gt;</td>
<td></td>
<td>0/55</td>
<td>3/51</td>
<td>2.4</td>
<td>0.13 (0.01-2.51)</td>
</tr>
<tr>
<td>Crowther et al&lt;sup&gt;31&lt;/sup&gt;</td>
<td></td>
<td>36/629</td>
<td>42/626</td>
<td>27.7</td>
<td>0.85 (0.56-1.31)</td>
</tr>
<tr>
<td>Magpie&lt;sup&gt;32&lt;/sup&gt;</td>
<td></td>
<td>2/404</td>
<td>3/401</td>
<td>2.0</td>
<td>0.66 (0.11-3.94)</td>
</tr>
<tr>
<td>Marret et al&lt;sup&gt;34&lt;/sup&gt;</td>
<td></td>
<td>22/352</td>
<td>30/336</td>
<td>20.2</td>
<td>0.70 (0.41-1.19)</td>
</tr>
<tr>
<td>Rouse et al&lt;sup&gt;35&lt;/sup&gt;</td>
<td></td>
<td>41/1188</td>
<td>74/1256</td>
<td>47.4</td>
<td>0.59 (0.40-0.85)</td>
</tr>
<tr>
<td>Combined</td>
<td></td>
<td>104/2658</td>
<td>152/2699</td>
<td>100.0</td>
<td>0.69 (0.55-0.88)</td>
</tr>
</tbody>
</table>

Test for heterogeneity $I^2 = 4.4\%$

<sup>a</sup>Neuroprotective arm
<sup>b</sup>Tocolytic arm

## Number Needed to Treat

<table>
<thead>
<tr>
<th>Gestational age (weeks)</th>
<th>Baseline risk CP (%)</th>
<th>Risk CP with MgSO4 (%)</th>
<th>Risk Difference (%)</th>
<th>Number Needed to Treat</th>
</tr>
</thead>
<tbody>
<tr>
<td>22-27</td>
<td>14.6</td>
<td>8.0</td>
<td>6.6</td>
<td>15</td>
</tr>
<tr>
<td>28-31</td>
<td>6.1</td>
<td>3.4</td>
<td>2.8</td>
<td>35</td>
</tr>
<tr>
<td>32-36</td>
<td>0.7</td>
<td>0.4</td>
<td>0.3</td>
<td>333</td>
</tr>
<tr>
<td>&gt;37</td>
<td>0.11</td>
<td>0.06</td>
<td>0.05</td>
<td>2000</td>
</tr>
</tbody>
</table>
“None of the individual studies found a benefit with regard to their primary outcome. However, the available evidence suggests that magnesium sulfate given before anticipated early preterm birth reduces the risk of cerebral palsy in surviving infants. Physicians electing to use magnesium sulfate for fetal neuroprotection should develop specific guidelines regarding inclusion criteria, treatment regimens, concurrent tocolysis, and monitoring in accordance with one of the larger trials...”
<table>
<thead>
<tr>
<th>Study</th>
<th>Total #</th>
<th>Inclusion</th>
<th>Dose</th>
<th>Duration</th>
<th>Death &amp; CP</th>
<th>Death</th>
<th>CP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crowther</td>
<td>1,255</td>
<td>&lt;30 wks likely deliv 24h</td>
<td>4 g load 1 g/hr</td>
<td>Up to 24 hr</td>
<td>RR 0.83</td>
<td>RR 0.83</td>
<td>RR 0.83</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.66-1.03</td>
<td>0.64-1.09</td>
<td>0.54-1.27</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marret</td>
<td>688</td>
<td>&lt;33 wks</td>
<td>4 g load only</td>
<td>Loading dose only</td>
<td>OR 0.80</td>
<td>OR 0.85</td>
<td>RR 0.70</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.58-1.10</td>
<td>0.55-1.32</td>
<td>0.41-1.19</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rouse</td>
<td>2,241</td>
<td>24-31 wks high risk SPTB</td>
<td>6 g load 2 g/hr</td>
<td>Up to 12 hrs; retreat</td>
<td>RR 0.97</td>
<td>RR 1.12</td>
<td>RR 0.55</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>when deliv imminent</td>
<td>0.77-1.23</td>
<td>0.85-1.47</td>
<td>0.32-0.95</td>
</tr>
</tbody>
</table>
The risks and benefits of magnesium neuroprophylaxis were reviewed – patient accepts or declines treatment.

The risks for disabilities, and even death, are significant for infants born at this early gestational age.

Recent data suggest that magnesium decreases, but does not eliminate, the risk of cerebral palsy in children who survive. Given this, we would like to offer you magnesium therapy.

We monitor women who receive magnesium closely to minimize side effects of magnesium, which are commonly mild.

NICU will be informed of the use of magnesium sulfate prior to delivery of preterm infant.
A FEW POINTS TO CONSIDER

• Long Term Magnesium Sulfate Use

• Possible Side Effects:
  • Circulatory collapse, Respiratory paralysis, Hypothermia, Pulmonary edema, Depressed reflexes, Hypotension, Flushing, Drowsiness, Depressed cardiac function, Diaphoresis, Hypocalcemia, Hypophosphatemia, Hyperkalemia, Visual changes

• Caution with:
  • Renal Impairment
  • Myasthenia gravis or other neuromuscular disease
  • Pulmonary Hypertension
  • Patients on Digoxin
# Table 2. Univariate Risks For Cerebral Palsy in Singleton Term Infants

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cases (n = 109)</th>
<th>Controls (n = 216)</th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>20/109 (18)</td>
<td>60/218 (28)</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>25-35</td>
<td>66/109 (61)</td>
<td>119/218 (54)</td>
<td>1.7 (0.9-3.2)</td>
<td>0.09</td>
</tr>
<tr>
<td>&gt;35</td>
<td>22/109 (20)</td>
<td>39/218 (18)</td>
<td>1.7 (0.8-3.7)</td>
<td>0.15</td>
</tr>
<tr>
<td>Maternal race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>52/109 (48)</td>
<td>125/218 (57)</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>11/109 (10)</td>
<td>12/218 (8)</td>
<td>2.2 (0.8-5.8)</td>
<td>0.07</td>
</tr>
<tr>
<td>Hispanic</td>
<td>19/109 (17)</td>
<td>33/218 (15)</td>
<td>1.4 (0.7-2.9)</td>
<td>0.30</td>
</tr>
<tr>
<td>Asian</td>
<td>13/109 (12)</td>
<td>32/218 (15)</td>
<td>1.0 (0.4-2.1)</td>
<td>0.90</td>
</tr>
<tr>
<td>Other</td>
<td>4/109 (4)</td>
<td>5/218 (2)</td>
<td>1.9 (0.4-3.9)</td>
<td>0.34</td>
</tr>
<tr>
<td>Unknown</td>
<td>10/109 (9)</td>
<td>11/218 (5)</td>
<td>2.2 (0.8-6.0)</td>
<td>0.09</td>
</tr>
<tr>
<td>Nulliparity</td>
<td>52/109 (48)</td>
<td>80/218 (37)</td>
<td>1.6 (1.0-2.7)</td>
<td>0.04</td>
</tr>
<tr>
<td>Preterm complications</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of infertility</td>
<td>3/109 (3)</td>
<td>8/215 (4)</td>
<td>0.7 (0.1-3.2)</td>
<td>0.68</td>
</tr>
<tr>
<td>Intrauterine growth restriction</td>
<td>11/105 (10)</td>
<td>6/207 (3)</td>
<td>3.9 (1.3-13.3)</td>
<td>0.01</td>
</tr>
<tr>
<td>Gestational diabetes</td>
<td>10/109 (9)</td>
<td>10/215 (5)</td>
<td>2.1 (0.8-5.9)</td>
<td>0.10</td>
</tr>
<tr>
<td>Preeclampsia/pregnancy-induced hypertension</td>
<td>6/109 (6)</td>
<td>10/215 (5)</td>
<td>1.2 (0.4-3.9)</td>
<td>0.70</td>
</tr>
<tr>
<td>Intrapartum complications</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical chorioamnionitis</td>
<td>15/109 (14)</td>
<td>9/215 (4)</td>
<td>3.8 (1.5-10.1)</td>
<td>0.001</td>
</tr>
<tr>
<td>Hemorrhagic chorioamnionitis</td>
<td>5/109 (5)</td>
<td>1/215 (1)</td>
<td>2.5 (0.2-13.8)</td>
<td>0.36</td>
</tr>
<tr>
<td>Maternal fever (temperature &gt;100.8°C)</td>
<td>21/109 (20)</td>
<td>15/215 (7)</td>
<td>3.3 (1.5-7.2)</td>
<td>0.001</td>
</tr>
<tr>
<td>Highest documented maternal temperature, °C</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;37.8</td>
<td>85/109 (78)</td>
<td>200/215 (92)</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>37.8-38.1</td>
<td>10/109 (9)</td>
<td>8/215 (4)</td>
<td>3.9 (1.2-13.9)</td>
<td>0.01</td>
</tr>
<tr>
<td>&gt;38.1</td>
<td>11/109 (10)</td>
<td>9/215 (4)</td>
<td>2.9 (1.0-8.1)</td>
<td>0.02</td>
</tr>
<tr>
<td>Rupture of membranes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;24 h</td>
<td>84/109 (77)</td>
<td>189/202 (94)</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>24-35.9 h</td>
<td>5/109 (5)</td>
<td>8/202 (4)</td>
<td>1.4 (0.4-5.0)</td>
<td>0.55</td>
</tr>
<tr>
<td>&gt;36 h</td>
<td>9/109 (9)</td>
<td>2/202 (2)</td>
<td>4.1 (1.1-15.2)</td>
<td>0.02</td>
</tr>
<tr>
<td>Delivery variables</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breech presentation</td>
<td>5/109 (5)</td>
<td>5/215 (2)</td>
<td>4.1 (0.9-16.2)</td>
<td>0.01</td>
</tr>
<tr>
<td>Cesarean delivery (urgent or emergency)</td>
<td>38/109 (35)</td>
<td>17/215 (8)</td>
<td>6.5 (3.3-13.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Forceps used</td>
<td>6/109 (6)</td>
<td>2/215 (1)</td>
<td>6.4 (1.1-68.1)</td>
<td>0.02</td>
</tr>
<tr>
<td>Vacuum used</td>
<td>20/109 (19)</td>
<td>17/215 (8)</td>
<td>2.8 (0.9-7.9)</td>
<td>0.05</td>
</tr>
<tr>
<td>Meconium (mild or trace)</td>
<td>13/109 (12)</td>
<td>31/215 (14)</td>
<td>0.8 (0.4-1.7)</td>
<td>0.60</td>
</tr>
<tr>
<td>Meconium (moderate or severe)</td>
<td>24/109 (22)</td>
<td>20/215 (9)</td>
<td>2.9 (1.4-5.9)</td>
<td>0.001</td>
</tr>
<tr>
<td>Birth canal</td>
<td>3/109 (3)</td>
<td>6/215 (3)</td>
<td>1.9 (0.4-8.9)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Infant characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td>57/107 (53)</td>
<td>115/211 (54)</td>
<td>1.0 (0.8-1.1)</td>
<td>0.84</td>
</tr>
<tr>
<td>Gestational age, mean (SD), wk</td>
<td>36.9 (1.2)</td>
<td>36.6 (1.3)</td>
<td>NA</td>
<td>0.54</td>
</tr>
<tr>
<td>Birthweight, mean (SD), g</td>
<td>3311 (628)</td>
<td>3477 (429)</td>
<td>NA</td>
<td>0.04</td>
</tr>
<tr>
<td>Apgar score &lt;7</td>
<td>26/107 (24)</td>
<td>2/211 (1)</td>
<td>33.5 (8.0-294)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cord pH &lt;7.0</td>
<td>5/42 (12)</td>
<td>0/26 (0)</td>
<td>NA</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Admitted to neonatal intensive care unit</td>
<td>62/107 (58)</td>
<td>17/210 (8)</td>
<td>10.7 (5.5-21.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diagnosis of &quot;birth asphyxia&quot;</td>
<td>27/107 (25)</td>
<td>0/211 (0)</td>
<td>NA</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Neonatal seizures</td>
<td>31/107 (30)</td>
<td>3/211 (1)</td>
<td>42.6 (10.3-372)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Abbreviations:** CI, confidence interval; NA, not applicable; OR, odds ratio.

*Only the study participants with data available for the specified risk factor are included in each row.

*Odds ratio and upper confidence limit cannot be calculated due to zero cells. Lower confidence limit = 3.5.

*Diagnosis of birth asphyxia or hypoventilation with hypoxia made by treating physician. Odds ratio and upper confidence limit cannot be calculated due to zero cells. Lower confidence limit = 18.4.
LOOKING FORWARD

BRAIN DAMAGE IN PRETERM NEWBORNS AND MATERNAL MEDICATION: THE ELGAN STUDY EXTREMELY LOW GESTATIONAL AGE NEWBORN
Questions? Comments?

[SORRY, WE JUST CAN'T TRUST YOU...]
References

• Magpie Trial Follow-Up Study Collaborative Group. The Magpie Trial: a randomised trial comparing magnesium sulphate with placebo for pre-eclampsia. Outcome for children at 18 months. BJOG 2007;114:289-299
• Marret S, Marpeau L, Follet-Bouhamed C, et al. [Effect of magnesium sulphate on mortality and neurologic morbidity of the very-preterm newborn (of less than 33 weeks) with two-year neurological outcome: results of the prospective PREMAG trial]. Gynecol Obstet Fertil 2008; 36:278.
• https://www.cdc.gov/ncbddd/cp/data.html