New Concepts in the Management of Preeclampsia with Severe features

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Objectives:

• Discuss the management of preeclampsia with severe features remote from term

• Discuss the role of Magnesium Sulfate post-partum in preeclampsia with severe features

Disclosure: No conflict of interest to declare

Maternal Mortality: Causes

Hypertensive disorders continue to be significant cause for maternal mortality in both developing and developed countries

Lancet, 2014
Preeclampsia with Severe Features: ACOG Task Force on Hypertension in Pregnancy
Nov 2013

- Blood pressure of 160 mm Hg systolic or higher or 110 mm Hg diastolic or higher on two occasions at least 4 hours apart while the patient is on bed rest
- New onset cerebral or visual disturbances
- Pulmonary edema
- Epigastric or right upper-quadrant pain unresponsive to medication
- Impaired liver function (elevated LFTs twice normal concentration)
- Thrombocytopenia (platelets < 100,000)
- Progressive renal insufficiency (serum creatinine > 1.1 mg/dl or doubling of the serum creatinine in the absence of other renal disease)

KEY: Fetal growth restriction and proteinuria > 5gm/24 no longer features of severe disease

Severe Preeclampsia Remote from Term: Concerns

Maternal risks

Fetal risks

Severe Preeclampsia 34 weeks: Studies

<table>
<thead>
<tr>
<th>Maternal complications during expectant management of severe preeclampsia</th>
<th>HELLP syndrome (%)</th>
<th>Pulmonary edema (%)</th>
<th>Renal failure (%)</th>
<th>Eclampsia (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized trials</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Sibai et al. (n = 10)</td>
<td>41.0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Sibai et al. (n = 45)</td>
<td>4.1</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Observational studies</td>
<td></td>
<td></td>
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<tr>
<td>Sibai et al. (n = 120)</td>
<td>55.9</td>
<td>0</td>
<td>0</td>
<td>5.6</td>
</tr>
<tr>
<td>D’Alton et al. (n = 20)</td>
<td>14.3</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hall et al. (n = 345)</td>
<td>5.2</td>
<td>2.1</td>
<td>1.7</td>
<td>1.2</td>
</tr>
<tr>
<td>Lasko-Dobrzanska et al. (n = 120)</td>
<td>5.5</td>
<td>2.3</td>
<td>1.4</td>
<td>0</td>
</tr>
<tr>
<td>Ohlsson et al. (n = 47)</td>
<td>17.0*</td>
<td>0.5</td>
<td>17.0*</td>
<td>0</td>
</tr>
<tr>
<td>Haddad et al. (n = 236)</td>
<td>14.2</td>
<td>0.3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Defes et al. (n = 131)</td>
<td>4.8</td>
<td>0.8</td>
<td>2.3</td>
<td>2.3</td>
</tr>
<tr>
<td>Shear et al. (n = 115)</td>
<td>27.1</td>
<td>3.9</td>
<td>Not reported</td>
<td>1.8</td>
</tr>
</tbody>
</table>

No maternal mortality

Severe Preeclampsia <34 weeks: Studies

| Perinatal complications during expectant management of severe preeclampsia |
|---|---|---|---|---|
| HELLP syndrome (%) | Pulmonary edema (%) | Renal failure (%) | Eclampsia (%) |
| Randomized trials |
| Sibai et al. (n = 10) | Not reported | 38.9 | 10.6 |
| Sibai et al. (n = 49) | 4.1 | 30.1 | 20.5 |
| Observational studies |
| Ohlsson et al. (n = 47) | 7.1 | 35.7 | 7.1 |
| Vulliez et al. (n = 206) | 5.1 | 58.1 | 74.0 |
| Hajj et al. (n = 340) | 20 | 36 | 44.6 |
| Veppala-Shanmugaratnam et al. (n = 120) | 8.9 | 21.7 | 7.4 |
| Chow et al. (n = 108) | 12.7 | 51.1 | 44.7 |
| Haddad et al. (n = 236) | 8.7 | 24.3 | 52.4 |
| Defes et al. (n = 131) | 22.9 | 0.3 | 65.2 |
| Shear et al. (n = 115) | 5.6 | 63.9 | 18.3 |

Expectant Management of Severe Preeclampsia Remote from Term

- 72 publications, primarily from tertiary care centers in Dutch and developed world sites.
- Expectant care of severe preeclampsia <34 wk (39 cohorts, 4,650 women), for which 40% of women are eligible, is associated with pregnancy prolongation of 7-14 days.
- Few serious maternal complications (median <5%), similar to interventionist care (2 studies, 42 women)

Magee et al. Hyperten Pregnan 2009

Expectant Management: Magee Review 2009

Cochrane Review: 2013

- 4 studies reviewed with a total of 425 patients
- Insufficient data to reach conclusions regarding risks for the mother
- Insufficient evidence to reach conclusions regarding perinatal mortality
- Expectant management appears to reduce neonatal morbidity (RDS)
- Need for randomized studies with enough power to make valid conclusions

SMFM Clinical Opinion www.AIOG.org

Evaluation and management of severe preeclampsia before 34 weeks’ gestation

Am J Obstet Gynecol 2011
Contraindications for Expectant Management of Severe Preeclampsia after initial observation

- Persistent symptoms of severe preeclampsia
- Eclampsia
- Pulmonary edema
- Persistent severe hypertension despite treatment
- HELLP syndrome
- DIC
- Significant renal dysfunction
- Non-reassuring fetal status
- Abruption
- Previability

Short term evaluation 24-48 hours Severe Preeclampsia < 34 weeks

- Steroids for fetal lung maturity
- Daily evaluation for maternal symptoms
- BP control with antihypertensives
- Daily monitoring of labs: LFTs, renal, platelets
- 24 hour urine collection
- Fetal assessment
- Delivery for reasons stated before or reaching 34 weeks

Long Term Management of Severe Preeclampsia < 34 weeks

- Daily assessment of maternal symptoms
- Frequent assessment of maternal labs (HELLP and renal function)
- Daily evaluation of fetal status
- Scans for growth and fluid assessment
- Delivery for worsening symptoms, eclampsia, abruption, EFW <5%, oligohydramnios, intractable hypertension, HELLP syndrome or reaching 34 weeks

What are the implications of expectant management of severe preeclampsia for developing countries?

- Lack of resources such as blood bank, anesthesia 24 hours a day, 7 days a week
- Ability to intervene expeditiously in cases of abruption
- Concern for increase maternal or fetal mortality while waiting
- Limited ICU resources putting in jeopardy premature infants
Expectant Management of Severe Preeclampsia in Developing World

- Can the criteria established by only 2 randomized studies with limited numbers and the SMFM recommendations apply to developing countries with limited resources?

- Need for randomized study in the developing world such as in Latin America, in which Preeclampsia is the number one reason for maternal mortality

**MEXPRE LATIN**

- **Purpose:** To determine whether expectant management of severe preeclampsia prior to 34 weeks gestation results in better outcome compared with prompt delivery after steroid administration in Latin American countries

- Randomized, multicenter, parallel, open-label clinical trial in 8 tertiary teaching hospitals (6 countries) in Latin America with experience in the management of severe preeclampsia and selected among 21 centers, because of their ability to respond to emergencies and with experience in conducting clinical studies

- Primary Objective: Perinatal mortality (fetal and neonatal death)

- Secondary outcomes: Composite neonatal morbidities, and maternal morbidities and death.

- Criteria for severe preeclampsia similar to the ones defined by SMFM and ACOG prior to Nov 2013

- Exclusion: eclampsia, HELLP syndrome, renal failure, pulmonary edema, active vaginal bleeding, rupture membranes, IU GR, oligo and reverse umb art Doppler.
MEXPRE LATIN Study

MEXPRE LATIN: Patient characteristics

Reasons for delivery in the expectant group

- Uncontrollable blood pressure 40.4%
- Fetal compromise: 29%
- Persistent symptoms: 28.2%
- Attainment of 34 weeks: 26%
- Maternal complications (eclampsia, HELLP, others): 21.3%
**MEXPRE LATIN Results**

- Largest randomized study of severe preeclampsia to date
- No difference in composite neonatal morbidity despite a gain of 8 days in utero
- Abruptions: 5.41 OR (1.16-25.2) for expectant group
- SGA: 2.64 OR (1.31-5.33) for expectant group
- Suggests that no reason to wait in a "hostile intrauterine environment"


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**Editorial: Pregnancy outcomes in developed vs developing countries**

- The results of this trial suggest that severe preeclampsia < 34 weeks in Latin America countries and countries with limited resources should be managed with delivery after steroid administration.
- Need for randomized studies with enough power should be done in developed countries

Sibai, Am J Obstet Gynecol 2013

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**Neonatal Outcome Severe Preeclampsia PAH**

<table>
<thead>
<tr>
<th></th>
<th>Delivered &lt;72 Hours N=92</th>
<th>Conservative Management* N=42</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birthweight (gm)</td>
<td>1203 ± 456</td>
<td>1121 ± 349</td>
<td>.10</td>
</tr>
<tr>
<td>RDS</td>
<td>69 (74%)</td>
<td>30 (71%)</td>
<td>.45</td>
</tr>
<tr>
<td>BPD</td>
<td>15 (16%)</td>
<td>8 (20%)</td>
<td>.38</td>
</tr>
<tr>
<td>NEC</td>
<td>9 (9.8%)</td>
<td>7 (18%)</td>
<td>.17</td>
</tr>
<tr>
<td>Grade 3 or 4 IVH</td>
<td>1 (1.1%)</td>
<td>1 (2.4%)</td>
<td>.51</td>
</tr>
<tr>
<td>Sepsis</td>
<td>13 (14%)</td>
<td>5 (13%)</td>
<td>.52</td>
</tr>
<tr>
<td>Neonatal Death</td>
<td>2 (2.2%)</td>
<td>1 (2.4%)</td>
<td>.67</td>
</tr>
<tr>
<td>Days in Neonatal ICU</td>
<td>47.9 ± 26.0</td>
<td>56.9 ± 44.4</td>
<td>.145</td>
</tr>
<tr>
<td>SGA</td>
<td>21 (23%)</td>
<td>12 (23%)</td>
<td>.29</td>
</tr>
</tbody>
</table>

* Gain of 7.1 days in the conservative group

Sehdev, Abbasi, Ludmir, SGI 2004

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**Additional Studies**

- No difference in RDS, greater risk for pulmonary edema in expectant group

J Matern Fetal Neonatal Med 2014
Temporizing management vs. termination of pregnancy in women with severe preeclampsia at 28-34 weeks (TOTEM-Trial)

- Multicenter RCT women between 28 to 34 wks
- Severe preeclampsia with or without HELLP syndrome
- Delivery 48 hours after steroid v. Expectant management
- Primary outcome: adverse perinatal outcome: perinatal death, RDS, BPD, sepsis, IVH, PVL and NEC
- Major maternal complications secondary outcome

Duvekot et al, SMFM 2015

TOTEM-Trial

- Trial closed after 24 months because of low recruitment
- 56 women from 9 hospitals randomized
- 30 to temporizing group, 26 to immediate delivery
- GA at randomization 30 wks for both groups
- Adverse perinatal outcome 55% (immediate) v. 50% (expectant)
- Median prolongation in the temporizing group 3 days (3.5 days)
- Reasons for delivery in the expectant group: Maternal 63%, fetal 37%
- 1 fetal death in both groups
- BW 1417g (immediate) v. 1289 g (expectant)
- No maternal deaths

Long Term Outcome for Offspring

- What are the long term consequences related to IUGR?
- Can we improve IUGR with bedrest?

Meta-analysis of 3 RCTs: Vigil de-Gracia 2015
**Conclusions**

- Based on our randomized study, management of severe preeclampsia prior to 34 weeks gestation should be done in a tertiary care center with adequate personnel, ready for immediate delivery in case of abruption.
- The most important intervention to improve neonatal outcome is the prompt administration of steroids and the ability to provide intensive neonatal care.
- Our data suggest that severe preeclampsia prior to 34 weeks should be managed with prompt delivery after steroid administration.
- The long term implications of IUGR in the face of severe preeclampsia remains to be determined.

**Background:**

- Preeclampsia/Eclampsia continues to be one of the principal reasons for maternal mortality in Latin America.
- The incidence of eclampsia in patients with severe preeclampsia varies between 1-3% and is more common in developing countries.
- Magnesium Sulfate is recommended for patients with severe preeclampsia in labor and for the first 12-24 hours post partum to prevent eclampsia.
- No randomized study has studied the value of post partum Magnesium Sulfate in patients with severe preeclampsia that have received Magnesium Sulfate prior to delivery.

**Eclampsia in Patients with Severe Preeclampsia: Rate of Seizures**

<table>
<thead>
<tr>
<th>Authors</th>
<th>Magnesium Sulfate N (%)</th>
<th>Control N (%)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moodley and Moodley</td>
<td>1/112 (0.9)</td>
<td>0/116</td>
<td>N/A</td>
</tr>
<tr>
<td>Coetzee et al.</td>
<td>1/345 (0.3)</td>
<td>11/340 (3.2%)</td>
<td>0.09 (0.01-0.69)</td>
</tr>
<tr>
<td>MAGPIE Trial</td>
<td>40/5055 (0.8)</td>
<td>96/5055 (1.9)</td>
<td>0.42 (0.26-0.60)</td>
</tr>
<tr>
<td>Belfort et al.</td>
<td>7/831 (0.8)</td>
<td>21/819 (2.6)</td>
<td>0.33 (0.14-0.77)</td>
</tr>
<tr>
<td>Total</td>
<td>49/6343 (0.6)</td>
<td>128/6330 (2.0)</td>
<td>0.39 (0.28-0.55)</td>
</tr>
</tbody>
</table>

**References:**
2. The MAGPIE Trial. Lancet 2002
Objectives:

**Primary:** to determine the incidence of post partum eclampsia (first 24 hours) in patients with severe preeclampsia that received at least 8 hours (1gm/hour = 8 gms) of Magnesium Sulfate prior to delivery.

**Secondary:**
- Maternal death
- Hemorrhage
- Respiratory depression
- ICU admission
- Hypertensive crisis
- Time to convulsion
- Number of convulsions
- Eclampsia after first 24 hours
- Time to ambulation
- Time to breast feeding

Methods:

RCT
9 maternities in 5 countries in Latin America

Inclusion criteria:
- Severe preeclampsia
- 8 hours of Magnesium Sulfate exposure prior to delivery

Exclusion criteria:
- Eclampsia
- HELLP syndrome
- Epilepsy
- Renal Insufficiency
- Pulmonary edema
- Uncontrolled diabetes
- Hypertensive encephalopathy.

8 hours of Magnesium Sulfate prior to delivery as criteria for randomization
- Randomized study comparing Magnesium Sulfate to Nimodipine for the prevention of eclampsia.
  - No patients that received 8 hours of Magnesium Sulfate antepartum and 24 hours of Magnesium Sulfate post partum had a convulsion post partum (0/831)
    Belfort et al, NEJM 2003

- Post partum arm of the MAGPIE trial, 1335 women randomized to Magnesium Sulfate vs. Placebo during post partum period.
  Magnesium: 4/639(0.62%) vs. Placebo 8/696 (1.14%)
  RR: 0.54, 95%CI: 0.16 - 1.80
  The MAGPIE Trial, Lancet 2002
Post Partum Care

- All patients observed closely with continuous monitoring of vital signs and symptoms
- Patients randomized to Magnesium Sulfate had a Foley catheter and were on strict bedrest
- Patients randomized to No Magnesium Sulfate were allowed to ambulate and breastfeed as tolerated and if stable
- If SBP ≥ 160 mmHg or DBP ≥ 110 mmHg IV Hydralazine or IV Labetalol given with incremental doses as necessary

### Post Partum results according to treatment group

<table>
<thead>
<tr>
<th></th>
<th>Magnesium Sulfate Post Partum N=555</th>
<th>No Magnesium Sulfate Post Partum N=558</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cesarean, N (%)</td>
<td>337 (61.0)</td>
<td>345 (61.4)</td>
<td>0.86</td>
</tr>
<tr>
<td>Total hours of leg prior to delivery mean (SD)</td>
<td>18 ± 11.3</td>
<td>16.8 ± 9.7</td>
<td>0.48</td>
</tr>
<tr>
<td>Drugs for HTN, N (%)</td>
<td>190 (34.2)</td>
<td>179 (32.2)</td>
<td>0.73</td>
</tr>
<tr>
<td>Abruptio, N (%)</td>
<td>18 (3.3)</td>
<td>14 (2.5)</td>
<td>0.42</td>
</tr>
<tr>
<td>UGAE, N (%)</td>
<td>134 (24.1)</td>
<td>127 (22.7)</td>
<td>0.97</td>
</tr>
<tr>
<td>Steroids for PFM, N (%)</td>
<td>102 (18.3)</td>
<td>105 (18.8)</td>
<td>0.46</td>
</tr>
</tbody>
</table>

### Maternal Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Magnesium Sulfate Post Partum N=555</th>
<th>No Magnesium Sulfate Post Partum N=558</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe Preeclampsia N (%)</td>
<td>307 (55.0)</td>
<td>307 (55.0)</td>
<td>0.66</td>
</tr>
<tr>
<td>Superimposed Preeclampsia N (%)</td>
<td>55 (10.0)</td>
<td>51 (9.1)</td>
<td>0.71</td>
</tr>
<tr>
<td>Age (mean ± SD)</td>
<td>26.8 ± 7.1</td>
<td>26.4 ± 7.0</td>
<td>0.82</td>
</tr>
<tr>
<td>Urinary protein 24-h mg (median ± SD)</td>
<td>325 (18.6)</td>
<td>327 (18.6)</td>
<td>0.99</td>
</tr>
<tr>
<td>Total complications N (%)</td>
<td>76 (13.7)</td>
<td>73 (13.0)</td>
<td>0.76</td>
</tr>
<tr>
<td>Hemorrhage N (%)</td>
<td>11 (2.0)</td>
<td>13 (2.3)</td>
<td>0.76</td>
</tr>
<tr>
<td>Respiratory depression N (%)</td>
<td>5 (0.9)</td>
<td>4 (0.7)</td>
<td>0.67</td>
</tr>
<tr>
<td>Severe HTN N (%)</td>
<td>52 (9.5)</td>
<td>50 (9.0)</td>
<td>0.60</td>
</tr>
<tr>
<td>Drugs for Hypertension N (%)</td>
<td>383 (69.0)</td>
<td>300 (53.7)</td>
<td>0.35</td>
</tr>
<tr>
<td>Time to amb (hours)</td>
<td>18.1 ± 10.6</td>
<td>11.8 ± 10.8</td>
<td>0.0001</td>
</tr>
<tr>
<td>Time to lact (hours)</td>
<td>24.1 ± 17.1</td>
<td>17.1 ± 16.8</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

No maternal deaths in either group.

Note: All data is mean ± SD.
Characteristics of the patients with Eclampsia Post Partum

**Magnesium Sulfate post partum 1 of 555:**
26 year old multiparous at 28 weeks. One convulsion 6 hours post partum. No other complications.

**No Magnesium Sulfate post partum 2 of 558:**
1) 16 year old primigravid at 36 weeks. One convulsion 6 hours post cesarean. No other complications.
2) 34 year old multiparous at 37 weeks. One convulsion 3 hours post partum. No other complications.

**Strengths**
- RCT
- Primary Objective eclampsia is easy to evaluate
- Power of the study > 90%
- Multicenter study in countries with high frequency of preeclampsia/eclampsia

**Limitations**
Open and not double blinded

**Conclusions**
- Not using Magnesium Sulfate for 24 hours post partum in patients with severe preeclampsia that had received at least 8 hours of Magnesium Sulfate prior to delivery, did not result in an increase in eclampsia.
- The use of Magnesium Sulfate post partum did not increase nor improve any maternal complications.
- The use of Magnesium Sulfate post partum resulted in less time to ambulation and to breast feeding.
- The use of post partum Magnesium Sulfate in patients with severe preeclampsia that had received at least 8 hours of Magnesium Sulfate prior to delivery does not seem to be justified. Additional studies are necessary to confirm these findings.

**Thank you**
- Jack.ludmir@Jefferson.edu