The Management of Preeclampsia

Summary of the Hypertension in Pregnancy Task Force

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Disclosure of Relevant Financial Relationships

Research support

- Alere, San Diego (BIOSITE)
- Beckman Coulter
  (Biomarkers for preeclampsia)

Consultation

- GTC Biotherapeutics
2012 ACOG Presidential Initiative

Preeclampsia

- Summarize the current state of knowledge
- Develop practice guidelines and checklists
- Identify the most compelling areas for research
Hypertension in Pregnancy Working Group

- JM Roberts (Chair)
- PA August
- G Bakris
- JR Barton
- IM Bernstein
- ML Druzin
- RR Gaiser
- JP Granger
- A Jeyabalan

- DD Johnson
- SA Karumanchi
- M Lindheimer
- MY Owens
- GR Saade
- BM Sibai
- CY Spong
- EZ Tsigas
- JN Martin (Ex Officio)
DON'T SHOOT THE MESSENGER
(OR ANYONE ELSE)
Pathogenesis of Preeclampsia

Vascular disease  Idiopathic  Excessive trophoblast

Reduced trophoblastic perfusion
Placental bed vascular remodeling is abnormal in preeclampsia

Putting a “funnel at the end of a hose” reduces velocity of flow (1-2 m/sec to 10 cm/sec). Minimal (50%) affect on volume of flow

NK = natural killer
EVT = extravillous trophoblast cell
ENVT = endovascular trophoblast

P Parham 2004
Pathogenesis of Preeclampsia

Vascular disease
Idiopathic
Excessive trophoblast

Reduced trophoblastic perfusion

? Endothelial injury
Preeclampsia is **NOT** just hypertension.
Fetal Manifestations in Preeclampsia

- Abruption
- Vascular Stillbirth
- Abnormal UA Doppler
- FGR
- Oligohydramnios
Proteinuria
Facial edema
Pulmonary edema
Ascites
Pleural effusions
HELLP
Renal failure
Epigastric pain
CNS bleeding
Nausea/vomiting
Blood Pressure
Capillary Leak
Symptoms
Fibrinolysis Hemolysis
Low platelets
Liver enzymes
DIC
Normal
Mild
Severe

Maternal
Current Clinical Issues

• Atypical preeclampsia
• Targets of BP control
• Timing of delivery
  – Severity of disease
  – Degree of proteinuria
• Magnesium sulfate
  – Indications
  – Intra-operative use
• Postpartum presentation
Fetal / Maternal Risk

Newborn Benefit
Gestational Hypertension

- Development of hypertension after 20 wks
  - Previously normotensive
  - SBP $\geq$ 140 mmHg
    - or (not and/or)
  - DBP $\geq$ 90 mmHg
  - Persistent for 4 hrs
- BP returns to normal by 6 wks postpartum
Preeclampsia

- **Gestational hypertension** + new onset of any of the following:
  - **Proteinuria**
    - $\geq 300 \text{ mg/day}$ or
    - Protein/Cr $\geq 0.3 \text{ mg/mg}$
    - Dipstick $\geq 1+$
  - **Thrombocytopenia**
  - **Impaired liver function**
  - **Renal insufficiency**
  - **Pulmonary edema**
  - **Cerebral disturbances**
  - **Visual impairment**
“Suspected” Superimposed Preeclampsia

- New onset proteinuria

- Sudden ↑ in pre-existing proteinuria

- Sudden ↑ in blood pressure if
  - Previously well controlled or
  - Escalation of BP medications
Superimposed Preeclampsia with Severe Features

- Severe hypertension despite maximum doses
- Cerebral / visual symptoms
- Pulmonary edema
- Low platelets or elevated liver enzymes
- Serum creatinine $\geq 1.1\text{mg (new onset)}$
“HELLP” Syndrome
A Subset of Severe Preeclampsia-Eclampsia

Hemolysis
Elevated Liver Functions
Low Platelets

Weinstein L, AJOG 1982;142:159
Sibai’s Criteria for HELLP

- **Hemolysis**
  - Abnormal peripheral smear
  - Serum total bilirubin $\geq 1.2$ mg/dl

- **Elevated liver enzymes (2x upper limits of normal)**
  - Serum AST $\geq 70$ U/L
  - Serum LDH $> 600$ U/L

- **Low platelets**
  - Platelet count $< 100,000/\mu$L

Antepartum Management of Gestational Hypertension

- No bed rest
- No anti-hypertensive medications
- Daily monitoring of Sn/Sxs and fetal movement
- Twice weekly office/clinic (BP, proteinuria)
- Fetal testing at diagnosis, then
  - NST and AFI every week
  - EFW every 3 weeks
- CBC, liver enzymes, creatinine every week
Antepartum Management of Preeclampsia

- No bed rest
- No anti-hypertensive medications
- No proteinuria assessment
- Daily monitoring of Sn/Sxs and fetal movement
- Twice weekly office/clinic evaluation
- Fetal testing at diagnosis, then
  - NST and AFI twice per week
  - EFW every 3 weeks
- CBC, liver enzymes, creatinine every week
## Induction versus Expectant Management in Mild GHTN–Preeclampsia after 36 wk

*(HYPITAT randomized trial)*

<table>
<thead>
<tr>
<th></th>
<th>Induction (n=377)</th>
<th>Expectant (n=379)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GA (wk)</td>
<td>38.4 (36°-41°)</td>
<td>38.6 (36°-41°)</td>
</tr>
<tr>
<td>GHTN</td>
<td>65%</td>
<td>66%</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>33%</td>
<td>32%</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>450 (300 - &lt;5g)</td>
<td>600 (300- &lt;5g)</td>
</tr>
<tr>
<td>Bishop score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 2</td>
<td>25%</td>
<td>22%</td>
</tr>
<tr>
<td>2-6</td>
<td>60%</td>
<td>64%</td>
</tr>
</tbody>
</table>

*Koopmans et al, Lancet 2009*
<table>
<thead>
<tr>
<th>Maternal Outcome</th>
<th>Induction n=377</th>
<th>Expectant n=379</th>
<th>RR (95% C.I.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite adverse outcome</td>
<td>31%</td>
<td>44%</td>
<td>0.71 (0.59-0.86)</td>
</tr>
<tr>
<td>HELLP</td>
<td>1%</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>0</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>Abruptio</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Eclampsia</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Maternal ICU</td>
<td>2%</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Severe systolic HTN</td>
<td>15%</td>
<td>23%</td>
<td>0.63 (0.46-0.86)</td>
</tr>
<tr>
<td>Cesarean section</td>
<td>14%</td>
<td>19%</td>
<td>0.75 (0.55-1.04)</td>
</tr>
</tbody>
</table>
Mild GHTH - Preeclampsia

Maternal & Fetal Evaluation

- ≥ 37 weeks’ gestation
- ≥ 34 weeks’ gestation
  - Labor, PPROM
- Suspected Abruptio
- Abnormal M/F testing

Yes → Delivery

No →

- Inpatient / outpatient
- Maternal / fetal testing

Yes → Worsening M/F condition
- Labor / PPROM
- ≥ 37 weeks’ gestation
Management of severe preeclampsia

- Term
  - Delivery
- Remote from term
  - Individualize
Lifetime of Care

- Chronic Lung Disease
- Chronic Heart Disease
- Hearing Disorders
- Retrolental Fibroplasia (Vision Disorders)
- Cerebral Palsy
- Other Severe Neurological Disorders
## Neonatal Complications with Betamethasone vs. Placebo in Severe Preeclampsia 26-34 wks*

<table>
<thead>
<tr>
<th></th>
<th>Rx</th>
<th>Placebo</th>
<th>RR</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RDS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• All</td>
<td>23%</td>
<td>43%</td>
<td>0.53</td>
<td>(0.35-0.82)</td>
</tr>
<tr>
<td>• Severe</td>
<td>9</td>
<td>23</td>
<td>0.39</td>
<td></td>
</tr>
<tr>
<td>• 33-34 wk</td>
<td>14</td>
<td>32</td>
<td>0.44</td>
<td></td>
</tr>
<tr>
<td><strong>IVH</strong></td>
<td>6</td>
<td>17</td>
<td>0.35</td>
<td>(0.15-0.85)</td>
</tr>
<tr>
<td><strong>Infection</strong></td>
<td>19</td>
<td>32</td>
<td>0.59</td>
<td>(0.36-0.97)</td>
</tr>
<tr>
<td><strong>Death</strong></td>
<td>14%</td>
<td>28%</td>
<td>0.5</td>
<td>(0.28-0.89)</td>
</tr>
</tbody>
</table>

Acute Control of Severe Hypertension

- Persistent (> 60 min) SBP ≥ 160 mmHg or
- Persistent DBP ≥ 110 mmHg
- IV labetalol
  - bolus doses 20-40 mg (max 300/hr)
  - continuous IV infusion (1-2 mg/min)
- IV bolus doses of hydralazine
  - 5, 10, 10 mg q 20 min (max 25 mg)
- Oral nifedipine
  - 10-20 mg q 20 min (max 60 mg)
- IV Sodium nitroprusside
Prevention of Convulsions

• Magnesium sulfate

  Intravenous regimen
  Loading dose: 4 or 6 g IV over 20 mins
  Maintenance: 2 g IV per hr

• If convulsions recur

  2 g dose of magnesium sulfate

• Treat: Eclampsia, Severe preeclampsia, HELLP
Maternal & Perinatal Outcome by GA at Expectant Management

- <23 wk: n=27, Perinatal Survival: 0%
- 23-23.6/7 wk: n=20, Perinatal Survival: 18%
- 24-24.6/7 wk: n=25, Perinatal Survival: 36%
- 25-25.6/7 wk: n=26, Perinatal Survival: 52%
- 26-26.6/7 wk: n=36, Perinatal Survival: 70%

Bombrys et al, Am J Ob Gyn 2007
## Expectant Management in Preeclampsia & FGR

<table>
<thead>
<tr>
<th>Authors</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chammas</td>
<td>Shorter prolongation (3.1 vs 6.6 days)</td>
</tr>
<tr>
<td>Ganzevoort</td>
<td>Similar prolongation (7 days in each)</td>
</tr>
<tr>
<td></td>
<td>Increased perinatal deaths in FGR (23.2 vs. 10%)</td>
</tr>
<tr>
<td>Visser</td>
<td>Similar prolongation (10 days in each)</td>
</tr>
<tr>
<td></td>
<td>All fetal deaths with FGR at &lt;30 wks</td>
</tr>
<tr>
<td>Shear</td>
<td>Increased maternal complications in FGR</td>
</tr>
<tr>
<td>Haddad</td>
<td>Similar days of prolongation</td>
</tr>
<tr>
<td></td>
<td>Increased fetal death in FGR (7% vs 1%)</td>
</tr>
</tbody>
</table>
Fetal Guidelines

- Expedited delivery (within 72 hrs)
  - Fetal distress by FHR tracing or BPP ≤ 4
  - Amniotic fluid index < 5 cm
  - Ultrasound EFW < 5\textsuperscript{th} percentile
  - Reverse umbilical artery diastolic flow
  - Labor/ROM
  - ≥ 34 weeks’ gestation
Abruptio Placentae
John M. Harlan
Supreme Court Justice
1877-1911

“Let it be said that I am right rather than consistent”
Proteinuria in Preeclampsia

Does the amount matter?

• No differences in outcomes (< 5 vs ≥ 5 g)
  • Renal function
  • Latency

• Similar outcomes (< 5, 5-9.99, ≥ 10 g/24h)

• Delivery decision should not be based on:
  • Amount of proteinuria
  • Change in amount of proteinuria
Severe Preeclampsia < 34 wks

- Admit to L&D 24-48 hrs.
- Corticosteroids, MgSO4 prophylaxis, antihypertensives
- Ultrasound, FHR monitoring, symptoms, laboratory tests

**Contraindications to continued expectant management?**

- Eclampsia
- < 23\(^{0/7}\) wks
- Pulmonary edema
- Abnormal fetal testing
- ARF, DIC
- Abruptio placentae

Delivery

- Yes
- No
Severe Preeclampsia < 34 wks

Offer continued expectant management
• Inpatient only, D/C MgSO4
• Daily maternal / fetal testing, sxs, BP, labs

Are there additional complications?
• Persistent symptoms
• HELLP / partial HELLP syndrome
• REDF (umbilical artery)
• Labor / PROM, 33\(^{0/7}\) – 33\(^{6/7}\)

Deliver after 48 hrs

24-32 wks
Expectant Rx
Deliver @ 33\(^{6/7}\)
Indications for Delivery
Expectant management (39 studies, 4,650 pts)

- Maternal: 40%
- Fetal: 36%
- Maternal & fetal: 9%
- Spontaneous labor: 6%
- GA of ≥ 34 weeks: 16%
- Other: 6%

MgSO₄ Prophylaxis Guidelines

- Mild GHTN / preeclampsia (No)
- Superimposed preeclampsia (No)
- Severe GHTN / preeclampsia (Yes)
- Superimposed with severe features (Yes)
- HELLP / eclampsia (Yes)
Magnesium Sulfate during Cesarean Delivery

- Half-life of 5 hours
- Discontinuing magnesium will not change drug interactions
- Increase risk for seizure outside the operative suite
Management of HELLP Syndrome

- Similar to preeclampsia with severe features
  - Corticosteroids for fetal benefit only < 34 wk
  - If condition stable, delay delivery for 48 hrs
- No dexamethasone for maternal benefit
  - Antepartum
  - Postpartum
Rate of Persistent Diastolic Hypertension & Proteinuria in Postpartum Period

H Stepan et al., J Hum Hypert 2006
Physiologic Adaptations PP that Predispose to Hypertension-Preeclampsia

- Fluid mobilization from interstitium
  - Volume load
  - Sodium load
- Reduced colloid oncotic pressure
- Withdrawal of vasodilating factors
  - PlGF, prostacyclin, NO
- Use of vasoactive medications
  - Ibuprofen (Lapi et al, BMJ 2013)
  - Methergine
Postpartum Management

- BP monitored a minimum 72 hours postpartum
- Repeat BP assessment 7-10 days postpartum
  - Office / clinic
  - Home health
- Specific written discharge instructions
  - Headache
  - RUQ or chest pain
  - Vision impairment
  - Office and L&D telephone numbers
Primary Prevention of Preeclampsia
Preeclampsia Pharmacopoeia

What works?
Prevention of Recurrent Preeclampsia

- Prepregnancy
  - Weight loss to ideal BMI
  - Control of glucose in diabetes
  - Control of BP in CHTN (diet, exercise)
- Low dose aspirin in select patients (from 12 wks)
- Not recommended
  - Vitamins C & E
  - Fish oil
  - Dietary salt restriction
  - Anti-HTN therapy to prevent preeclampsia
Coming soon from your ACOG

- Executive summary of HIP task force
- Downloadable outpatient instructions
  - Antepartum
  - Postpartum
  - Long term health risk assessment
References


References


Rate of Persistent Hypertension & Proteinuria after Expectant Management of Preeclampsia, HELLP, Eclampsia

Berks et al. Obstet Gynecol 2009;114:1307
Interpregnancy Weight Change and Risk of Adverse Pregnancy Outcomes

Swedish Birth Register

Villamor et al. Lancet 2006, 368;1164
Long term maternal outcome

- Recurrent preeclampsia
- CHTN (4-fold*)
- Ischemic heart disease (2-fold*)
- Stroke (2-fold*)
- Venous thromboembolism (2-fold*)
- All-cause mortality (1.5-fold*)

Preeclampsia is a screening test for future health

* Barton, Sibai 2008
* Craici et al 2008
Cardiovascular Risk Management After Early Onset-Preeclampsia

- 6 weeks postpartum
  - BP, BMI

- 3 to 6 months postpartum
  - BP, BMI
  - Screen for metabolic abnormalities (glucose, lipids)
  - Dipstick albuminuria
  - Refer if persistent albuminuria or secondary HTN

- Ongoing care
  - Yearly BP, BMI; every other year glucose, cholesterol

Spaan J et al. Hypertension 2012
Perinatal Survival & Maternal Complications in Expectant Management at < 25\(^{0/7}\) Wks

- < 23 Wks: n=51 (52)
  - Perinatal Survival: 37
  - Maternal Complications: 0

- 23\(^{0/7}\) - 23\(^{6/7}\) Wks: n=62 (66)
  - Perinatal Survival: 20
  - Maternal Complications: 20

- 24\(^{0/7}\) - 24\(^{6/7}\) Wks: n=40 (41)
  - Perinatal Survival: 43
  - Maternal Complications: 35

B. Sibai
Maternal & Perinatal Outcome by GA at Expectant Management

- Perinatal Survival
- Maternal Complications

**Perinatal Survival**

- 25-25\(^{6/7}\) % 70
- 26-26\(^{6/7}\) % 97

**Maternal Complications**

- 25-25\(^{6/7}\) n=26
- 26-26\(^{6/7}\) n=36

B. Sibai