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Objectives

• Review the current state of knowledge about preeclampsia and other hypertensive disorders in pregnancy

• Understand the new practice guidelines from the ACOG Task Force for the diagnosis and management of preeclampsia

• Identify areas of research to bridge gaps in our current knowledge
Disclosure of Relevant Financial Relationships

• None
Disclaimer
Presidental Initiative

- Hypertensive disorders of pregnancies are worldwide issues, with increasing incidence
- Hypertensive disorders of pregnancy are major contributors to prematurity, future CV disease
- For every preeclampsia related death, approximately 50-100 women at risk from “near miss”
- Despite considerable research, the etiology of preeclampsia remains unclear
Task Force

- Composed of 17 member panel
- Experts in OB, MFM, Hypertension, Internal Medicine, Nephrology, Anesthesiology, Physiology, and Patient Advocacy
Task Force Members

- James Roberts, MD, Chair
- Phyllis August, MD, MPH
- George Bakris, MD
- John Barton, MD
- Ira Bernstein, MD
- Maurice Druzin, MD
- Robert Gasier, MD
- Joey Granger, MD
- Arun Jeyabalan, MD, MS
- Donna Johnson, MD
- S. Ananth Karumanchi, MD
- Marshall Leinheimer, MD
- Michelle Owens, MD, MS
- George Saade, MD
- Baha Sabai, MD
- Catherine Spong, MD
- Eleni Tsigas
- James Martin Jr, MD

University of Minnesota
Driven to Discover™
Grading Recommendations

• Used evidence assessment and recommendation strategy developed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group
  – Quality of evidence
  – Strength of recommendation

www.gradeworkinggroup.org/index.htm
Classification

- Preeclampsia-Eclampsia
- Gestational Hypertension
- Chronic Hypertension
- Chronic Hypertension with Superimposed Preeclampsia
Preeclampsia/Gestational Hypertension
Invasion Defects in Preeclampsia

http://iahealth.net/pre-eclampsia/
Preeclampsia-Eclampsia

- Hypertensive disorder of pregnancy with multisystem involvement
- Typically diagnosed after 20 weeks’ GA
- Can be superimposed
- Most common form = new-onset hypertension and proteinuria or,
- Hypertension and multisystem involvement in the absence of proteinuria
Multisystemic Involvement

Preeclampsia
+/- proteinuria
Terminology

• Mild preeclampsia
• Preeclampsia without severe features
  – Avoid rigid classification
  – Dynamic and progressive
Diagnosing Hypertension

- Mild > 140/90 mmHg
- Severe > 160/110 mmHg
- 2 determinations four hours apart*
Measuring BP

• Patient comfortably seated, legs uncrossed
• Back and arm supported so the middle of the cuff on the upper arm is at the level of the right atrium (midpoint of the sternum)
• Instruct patient to relax, not talk for 5 minutes before 1st reading
• If elevated, wait several minutes and repeat to exclude spurious elevation
Diagnosing Proteinuria

- 24-hour urine protein $\geq 300$ mg
- Urine protein/creatinine ratio $\geq 3.0$ mg/dL
- Qualitative dipstick 1+ or greater

*Not required for diagnosis of preeclampsia*
Gestational Hypertension

• New onset elevations of BP after 20 weeks, often near term, in absence of proteinuria

• Many women with this diagnosis have preeclampsia without proteinuria or other organ involvement

• If severe hypertension develops, outcomes similar to SPE
Gestational Hypertension

- Failure of BP to normalize in the postpartum period = chronic HTN
- Risk factor for future chronic hypertension
Features Warranting Close Observation for Development of Preeclampsia

- Visual disturbances
- Severe headaches
- Fetal growth restriction
- New-onset proteinuria in second half of pregnancy
- Change in SBP \( \geq 30 \) or DBP \( \geq 15 \) mmHg
Initial Evaluation

- CBC with platelet count
- Serum creatinine
- Liver enzyme levels
- Urine protein (24 hour or protein/creatinine ratio)
- Assess for symptoms of SPE
- Ultrasound for EFW and AFV
- Nonstress test
Maternal and Fetal Findings

- 37 0/7 weeks or more of gestation or
- 34 0/7 weeks or more of gestation with:
  - Labor or rupture of membranes
  - Abnormal maternal-fetal test results
  - Ultrasonographic estimate of fetal weight less than fifth percentile
  - Suspected abruptio placentae

Yes

- Delivery
- Prostaglandins if needed for induction

No

- Less than 37 0/7 weeks of gestation
- Inpatient or outpatient management
  Maternal evaluation: twice weekly
  Fetal evaluation:
  - With preeclampsia: twice weekly nonstress test
  - With gestational hypertension: weekly nonstress test

37 0/7 weeks or more of gestation
- Worsening maternal or fetal condition*
- Labor or premature rupture of membranes

Yes

*Fig 5-1. Management of mild gestational hypertension or preeclampsia without severe features.
≥ 37 weeks or
≥ 34 weeks and labor or PROM, FGR < 5th%,
abruption

NO

< 37 0/7 weeks
Inpatient or outpatient management

37 0/7 weeks or more
Worsening maternal or fetal condition
Labor or premature rupture of membranes

DELIVERY

ACOG Hypertension in Pregnancy Task Force 2013
Hospitalization for Delivery

• 37 and 0/7
• Suspected placental abruption
• 34 and 0/7 and
  – Progressive labor or rupture of membranes
  – EFW < 5th%
  – Oligohydramnios (persistent AFI < 5 cm)
  – Persistent BPP 6/10 or less
Outpatient Management of Mild Preeclampsia/Gest HTN

- Daily kick counts
- US for fetal growth every 3 weeks
- AFV assessment weekly
- Antepartum fetal testing
- Twice weekly BP assessment
- For GHTN: Weekly protein assessment
- Weekly labs (CBC, Scr, liver enzymes)
Outpatient Management of Mild Preeclampsia/Gest HTN

• Education and monitoring of symptoms of preeclampsia
• Immediate assessment of size/date discrepancy and/or decreased fetal movement
• Hospitalization for severe BPs, lab abnormalities, or abnormal surveillance
Task Force Recommendation

• For women with preeclampsia without severe features, use of ultrasonography to assess fetal growth and antenatal testing to assess fetal status is suggested.
  – Quality of evidence: Moderate
  – Strength of recommendation: Qualified
Assessing Severity of Preeclampsia

- SBP ≥ 160 or DBP ≥ 110
  - 2 occasions
  - at least 4 hrs. apart
  - patient on bedrest or on antihypertensive therapy
- Thrombocytopenia
- Impaired liver function
- Progressive renal insufficiency
- Pulmonary edema
- Cerebral or visual disturbances
Items removed for classification of SPE

- Proteinuria $\geq 5$ grams
- Fetal growth restriction
Antihypertensive therapy in mild to moderate Gestational HTN

• Used to prevent severe GHTN and maternal hemorrhagic CVA
• No consensus regarding mgmt of nonsevere HTN
Treatment of Mild to Moderate Hypertension

• Cochrane review 2014
  – 49 trials, n=4723 women with mild-mod HTN in pregnancy
  – Reduced risk of developing severe HTN (RR, 0.49; 95% CI 0.40-0.60) but no effect on incidence of preeclampsia

• No improvement in maternal or perinatal outcomes with antihypertensive therapy

Abalos E et al. Cochrane Database 2014;2: CD002252
Fetal harm?

- In 29 trials evaluating oral β-blocker therapy vs placebo in mild-mod HTN, decrease in risk of severe HTN but increase in SGA infants (RR, 1.36; 95% CI, 1.02-1.82)

Magee L et al. Cochrane Database 2003;3: CD002863
Task Force Recommendation

• For women with mild gestational hypertension or preeclampsia with a persistent BP of less than 160 mm Hg systolic or 110 mm Hg diastolic, it is suggested that antihypertensive medications **not** be administered.
  – *Quality of Evidence*: Moderate
  – *Strength of Recommendation*: Qualified
Bed Rest
Task Force Recommendation

• For women with gestational hypertension or preeclampsia without severe features, strict bed rest not recommended
  – Modification of work or activity and hospitalization should be individualized
    • Quality of evidence: low
    • Strength of recommendation: Qualified
Timing of Delivery

Maternal Risk

Gestational Age

Fetal Risk
HYPITAT I

- Multicenter, randomized trial, n=756
- Women with gestational hypertension or mild preeclampsia between 36-41 0/7 weeks gestation were randomized to induction of labor (n=377) or expectant management (n=379)
  - Primary outcome: adverse maternal outcome: severe preeclampsia, HELLP, eclampsia, pulmonary edema, abruption
  - Secondary outcome: neonatal morbidities and rate of cesarean delivery

Koopmans CM et al Lancet 2009; 374: 979-088
HYPITAT I

- Gestational hypertension
  - DBP ≥ 95 mmHg
- Mild preeclampsia
  - DBP ≥ 90 mmHg + proteinuria (> 300 mg on 24h urine collection, or protein/creatinine ratio > 30 mg/mmol, 2+ occurrences of protein on dipstick)
- Exclusion criteria
  - Severe gestation hypertension or severe preeclampsia, SBP ≥ 170 mmHg or DBP ≥ 110 mmHg, proteinuria of 5 grams or higher per 24 hour urine
  - Hypertension treated with antihypertensive drugs, diabetes mellitus, gestational diabetes requiring insulin, renal disease, heart disease, previous cesarean delivery, HELLP syndrome, oliguria, pulmonary edema, HIV, use of IV antihypertensive medications, fetal anomalies, suspected FGR, nonreassuring fetal heart rate tracing

Koopmans CM et al Lancet 2009; 374: 979-088
<table>
<thead>
<tr>
<th></th>
<th>Induction of labor (n=377)</th>
<th>Expectant monitoring (n=379)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nulliparous</td>
<td>269 (71%)</td>
<td>272 (72%)</td>
</tr>
<tr>
<td>Maternal age (years)</td>
<td>29 (26-33)</td>
<td>29 (26-33)</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>38.4 (37.6-39.4)</td>
<td>38.6 (37.6-39.4)</td>
</tr>
<tr>
<td>Ethnic origin – White</td>
<td>317 (84%)</td>
<td>298 (79%)</td>
</tr>
<tr>
<td>BMI – baseline</td>
<td>32.5 (28.7-36.4)</td>
<td>32.3 (28.5-35.9)</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gestational hypertension</td>
<td>244 (65%)</td>
<td>252 (66%)</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>123 (33%)</td>
<td>123 (32%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>10 (3%)</td>
<td>4 (1%)</td>
</tr>
</tbody>
</table>

Adapted from Table 1, Koopmans CM et al Lancet 2009; 374: 979-088
<table>
<thead>
<tr>
<th>Time between randomisation and onset of labour (days)</th>
<th>Induction of labour (n=377)</th>
<th>Expectant monitoring (n=379)</th>
<th>Relative risk (95% CI; p value)</th>
<th>Absolute risk reduction (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.79 (0.67–1.0)</td>
<td>6.3 (3.7–10.9)</td>
<td>&lt;0.0001*</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

| Gestational age at delivery (weeks)                  | 38.7 (37.9–39.8)            | 39.9 (38.9–40.4)            | <0.0001*                      | NA                              |

<table>
<thead>
<tr>
<th>Onset of labour</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous</td>
<td>10 (3%)</td>
<td>200 (53%)</td>
<td>0.05 (0.03–0.09; &lt;0.0001)</td>
<td>50.12% (44.64 to 55.24)</td>
</tr>
<tr>
<td>Planned caesarean section</td>
<td>1 (&lt;1%)</td>
<td>6 (2%)</td>
<td>0.17 (0.02–1.39; 0.059)</td>
<td>NS</td>
</tr>
<tr>
<td>Induction</td>
<td>366 (97%)</td>
<td>173 (46%)</td>
<td>2.13 (1.90–2.38; &lt;0.0001)</td>
<td>−51.44% (−55.54 to −45.93)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Indications that induction of labour was needed†</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomised to treatment</td>
<td>366 (100%)</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Maternal indications</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe hypertension (mm Hg)</td>
<td>NA</td>
<td>78 (45%)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Severe proteinuria</td>
<td>NA</td>
<td>3 (2%)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>HELLP syndrome</td>
<td>NA</td>
<td>7 (4%)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Use of anticonvulsive drugs</td>
<td>NA</td>
<td>37 (21%)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Use of intravenous antihypertensive drugs</td>
<td>NA</td>
<td>28 (16%)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Suspected fetal distress</td>
<td>0</td>
<td>18 (10%)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Time since prelabour rupture of membranes &gt;48 h</td>
<td>0</td>
<td>9 (5%)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Gestational age &gt;41 weeks</td>
<td>0</td>
<td>24 (14%)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Chose induction</td>
<td>0</td>
<td>48 (28%)</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Data are median (IQR) or number of patients (%), unless otherwise indicated. NA = not applicable. NS = not stated because indicator was not significantly associated. HELLP = haemolysis, elevated liver enzymes, and low platelet count. *Relative risk and absolute risk reduction not stated because not clinically relevant. †Some patients had more than one clinical feature; percentages are given for women who were induced (366 patients randomised to induction of labour, 173 patients randomised to expectant monitoring).

Table 2: Pregnancy outcome and onset of labour in randomised patients

Koopmans CM et al Lancet 2009; 374: 979-088
<table>
<thead>
<tr>
<th>Composite adverse maternal outcome</th>
<th>Induction of labour (n=377)</th>
<th>Expectant monitoring (n=379)</th>
<th>Relative risk (95% CI; p value)</th>
<th>Absolute risk reduction (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal death</td>
<td>0</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Severe hypertension (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP</td>
<td>55 (15%)</td>
<td>88 (22%)</td>
<td>0.63 (0.46-0.86; &lt;0.0003)</td>
<td>8.62% (2.05-14.16)</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>62 (16%)</td>
<td>103 (27%)</td>
<td>0.61 (0.46-0.80; &lt;0.0001)</td>
<td>10.73% (4.85-16.52)</td>
</tr>
<tr>
<td>Severe proteinuria*</td>
<td>3 (2%)</td>
<td>4 (2%)</td>
<td>0.91 (0.21-4.02; 0.90)</td>
<td>NS</td>
</tr>
<tr>
<td>HELLP syndrome</td>
<td>4 (1%)</td>
<td>11 (3%)</td>
<td>0.37 (0.12-1.14; 0.07)</td>
<td>NS</td>
</tr>
<tr>
<td>Eclampsia</td>
<td>0</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Lung oedema</td>
<td>0</td>
<td>2 (1%)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Postpartum haemorrhage</td>
<td>35 (9%)</td>
<td>40 (11%)</td>
<td>0.88 (0.57-1.35; 0.55)</td>
<td>NS</td>
</tr>
<tr>
<td>Thromboembolic disease</td>
<td>1 (&lt;1%)</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Placental abruption</td>
<td>0</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Severe hypertension measured twice (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP</td>
<td>26 (7%)</td>
<td>44 (12%)</td>
<td>0.60 (0.38-0.95; 0.03)</td>
<td>4.71% (0.57-8.92)</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>28 (7%)</td>
<td>50 (13%)</td>
<td>0.56 (0.36-0.87; 0.01)</td>
<td>5.77% (1.42-10.16)</td>
</tr>
<tr>
<td>Drugs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral antihypertensive</td>
<td>67 (18%)</td>
<td>111 (29%)</td>
<td>0.61 (0.47-0.80; &lt;0.0001)</td>
<td>11.52% (5.48-17.45)</td>
</tr>
<tr>
<td>Intravenous antihypertensive</td>
<td>13 (3%)</td>
<td>39 (10%)</td>
<td>0.34 (0.18-0.62; &lt;0.0001)</td>
<td>6.84% (3.28-10.59)</td>
</tr>
<tr>
<td>Intravenous anticonvulsive</td>
<td>24 (6%)</td>
<td>46 (12%)</td>
<td>0.53 (0.33-0.84; 0.01)</td>
<td>5.77% (1.64-9.98)</td>
</tr>
<tr>
<td>Maternal hospital care</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intensive care</td>
<td>6 (2%)</td>
<td>14 (4%)</td>
<td>0.41 (0.16-1.07; 0.059)</td>
<td>NS</td>
</tr>
<tr>
<td>Medium care</td>
<td>14 (4%)</td>
<td>15 (4%)</td>
<td>0.90 (0.44-1.84; 0.777)</td>
<td>NS</td>
</tr>
<tr>
<td>Maternal ward</td>
<td>340 (90%)</td>
<td>319 (84%)</td>
<td>1.03 (0.99-1.07; 0.145)</td>
<td>NS</td>
</tr>
<tr>
<td>Unknown</td>
<td>17 (5%)</td>
<td>31 (8%)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Duration of hospital stay (days)</td>
<td>2.0 (1.0-3.0)</td>
<td>2.0 (1.0-4.0)</td>
<td>0.12†</td>
<td>NA</td>
</tr>
</tbody>
</table>

Data are number of patients (%) or median (IQR), unless otherwise indicated. NA= not applicable. BP=blood pressure. NS= not stated because indicator was not significantly associated. HELLP= haemolysis, elevated liver enzymes, and low platelet count. *Data are missing for some participants: n=157 for induction of labour, and n=191 for expectant monitoring. †Relative risk and absolute risk reduction not stated because not clinically relevant.

Table 3: Maternal outcome

Koopmans CM et al Lancet 2009; 374: 979-088
<table>
<thead>
<tr>
<th>Clinical feature</th>
<th>Induction of labour (n=377)</th>
<th>Expectant monitoring (n=379)</th>
<th>Relative risk (95% CI; p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous</td>
<td>273 (72%)</td>
<td>253 (67%)</td>
<td>1.09 (0.99—1.19; 0.091)</td>
</tr>
<tr>
<td>Vaginal instrumental delivery</td>
<td>50 (13%)</td>
<td>54 (14%)</td>
<td>0.93 (0.65—1.33; 0.694)</td>
</tr>
<tr>
<td>Caesarean section</td>
<td>54 (14%)</td>
<td>72 (19%)</td>
<td>0.75 (0.55—1.0; 0.085)*</td>
</tr>
</tbody>
</table>

Clinical features indicating that caesarean section was needed:

<table>
<thead>
<tr>
<th>Clinical feature</th>
<th>Induction of labour (n=377)</th>
<th>Expectant monitoring (n=379)</th>
<th>Relative risk (95% CI; p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arrest of first stage of labour</td>
<td>15 (28%)</td>
<td>24 (33%)</td>
<td>NA</td>
</tr>
<tr>
<td>Arrest of second stage of labour</td>
<td>3 (6%)</td>
<td>7 (10%)</td>
<td>NA</td>
</tr>
<tr>
<td>Failed instrumental delivery</td>
<td>4 (7%)</td>
<td>2 (3%)</td>
<td>NA</td>
</tr>
<tr>
<td>Fetal distress</td>
<td>17 (31%)</td>
<td>20 (27%)</td>
<td>NA</td>
</tr>
<tr>
<td>Failure to progress and fetal distress</td>
<td>12 (22%)</td>
<td>8 (11%)</td>
<td>NA</td>
</tr>
<tr>
<td>Maternal complication</td>
<td>2 (4%)</td>
<td>7 (10%)</td>
<td>NA</td>
</tr>
<tr>
<td>Elective</td>
<td>1 (2%)</td>
<td>4 (6%)</td>
<td>NA</td>
</tr>
</tbody>
</table>

Data are number of patients (%), unless otherwise indicated. NA = not applicable. *Absolute risk reduction is 4.67% (95% CI—0.65 to 9.98).

Table 4: Method of delivery

Koopmans CM et al Lancet 2009; 374: 979-088
<table>
<thead>
<tr>
<th></th>
<th>Induction of labour (n=377)</th>
<th>Expectant monitoring (n=379)</th>
<th>Relative risk (95% CI; p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birthweight (g)</td>
<td>3220 (2890-3565)</td>
<td>3490 (3080-3810)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Composite adverse neonatal outcome</td>
<td>24 (6%)</td>
<td>32 (8%)</td>
<td>0.75 (0.45-1.26; 0.276)†</td>
</tr>
<tr>
<td>Fetal deaths</td>
<td>0</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Apgar score of &lt;7 after 5 min</td>
<td>7 (2%)</td>
<td>9 (2%)</td>
<td>0.79 (0.30-2.09; 0.632)</td>
</tr>
<tr>
<td>Arterial pH &lt;7-05‡</td>
<td>9 (3%)</td>
<td>19 (6%)</td>
<td>0.46 (0.21-1.00; 0.043)</td>
</tr>
<tr>
<td>Admission to intensive care</td>
<td>10 (3%)</td>
<td>8 (2%)</td>
<td>1.26 (0.50-3.15; 0.625)</td>
</tr>
<tr>
<td>Neonatal hospital care</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medium care</td>
<td>68 (18%)</td>
<td>69 (18%)</td>
<td>0.99 (0.73-1.34; 0.952)</td>
</tr>
<tr>
<td>High care</td>
<td>12 (3%)</td>
<td>10 (3%)</td>
<td>1.21 (0.53-2.76; 0.656)</td>
</tr>
<tr>
<td>Intensive care</td>
<td>10 (3%)</td>
<td>8 (2%)</td>
<td>1.26 (0.50-3.15; 0.625)</td>
</tr>
<tr>
<td>Duration of stay in a neonatal medium, high, or intensive care unit (days)</td>
<td>3.0 (2.0-6.0)</td>
<td>4.0 (2.8-7.0)</td>
<td>0.077*</td>
</tr>
</tbody>
</table>

Koopmans CM et al Lancet 2009; 374: 979-088
### Figure 2: Risk of composite poor maternal outcome

*Data are missing for some participants.

<table>
<thead>
<tr>
<th>Gestational age at randomisation (weeks)</th>
<th>Induction of labour (N=377) Event/n</th>
<th>Expectant monitoring (N=379) Event/n</th>
<th>Relative risk (95% CI)</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>36-37</td>
<td>18/40 (45%)</td>
<td>15/35 (43%)</td>
<td>1.05 (0.63-1.76)</td>
<td></td>
</tr>
<tr>
<td>37-38</td>
<td>32/96 (33%)</td>
<td>41/92 (45%)</td>
<td>0.75 (0.52-1.08)</td>
<td></td>
</tr>
<tr>
<td>38-39</td>
<td>27/99 (27%)</td>
<td>40/93 (43%)</td>
<td>0.63 (0.43-0.94)</td>
<td></td>
</tr>
<tr>
<td>39-40</td>
<td>27/83 (33%)</td>
<td>42/103 (42%)</td>
<td>0.78 (0.53-1.15)</td>
<td></td>
</tr>
<tr>
<td>40-41</td>
<td>13/59 (22%)</td>
<td>27/56 (48%)</td>
<td>0.46 (0.26-0.79)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cervical consistency at baseline*</th>
<th>Induction of labour</th>
<th>Expectant monitoring</th>
<th>Relative risk (95% CI)</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUFF</td>
<td>22/61 (36%)</td>
<td>36/65 (53%)</td>
<td>0.55 (0.44-0.69)</td>
<td></td>
</tr>
<tr>
<td>Moderate to very weak</td>
<td>92/301 (31%)</td>
<td>125/297 (42%)</td>
<td>0.73 (0.59-0.90)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cervical dilatation at baseline (cm)*</th>
<th>Induction of labour</th>
<th>Expectant monitoring</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>62/174 (36%)</td>
<td>86/163 (53%)</td>
<td>0.68 (0.53-0.87)</td>
</tr>
<tr>
<td>1</td>
<td>34/121 (28%)</td>
<td>48/131 (37%)</td>
<td>0.77 (0.53-1.10)</td>
</tr>
<tr>
<td>2</td>
<td>16/53 (30%)</td>
<td>25/55 (45%)</td>
<td>0.66 (0.40-1.10)</td>
</tr>
<tr>
<td>&gt;2</td>
<td>4/16 (25%)</td>
<td>3/17 (18%)</td>
<td>1.41 (0.37-5.37)</td>
</tr>
</tbody>
</table>

Koopmans CM et al Lancet 2009; 374: 979-088
HYPITAT I

- Induction of labor was associated with significant reduction in composite adverse maternal outcome (RR 0.71; 95% CI, 0.59-0.86), with a NNT of 8
- No difference in rates of neonatal complications or cesarean delivery
- Conclusion: Induction of labor should be advised for women with gestational hypertension and a diastolic BP of 95 mmHg or higher or mild preeclampsia at a gestational age of beyond 37 weeks

Koopmans CM et al Lancet 2009; 374: 979-088
Task Force Recommendation

• For women with mild gestational hypertension or preeclampsia without severe features at or beyond 37 0/7 weeks of gestation, delivery rather than continued observation is suggested.
  – Quality of evidence: Moderate
  – Strength of Recommendation: Qualified
What do the Critics Say?

“Doesn’t apply to my population – performed in Netherlands and definitions used to diagnose GHTN are different”

“In statistical analysis, a true significant relative risk is not seen until 38 weeks”

“In a time when late preterm birth and early term birth is closely regulated, recommendation makes me uncomfortable.”
Gestational hypertension ≠
mild form of preeclampsia

- 25% of women diagnosed at 34 weeks will later develop proteinuria\(^1\)
- Portion of women with GHTN have chronic HTN masked by decrease in BP in early pregnancy
- Portion of women have similar outcomes to normotensive women\(^2,3\)

\(^2\) Roberts JM et al. Hypertension 2005;46:1263-9
\(^3\) Powers RW. Reprod Sci 2008;15:374-81
Traditional Preeclampsia vs NP Preeclampsia (or GHTN)

- Prospective multicenter cohort
- Enrolled women with sign or symptoms of preeclampsia between 20-41 weeks
- 1223 subjects, 661 diagnosed with TP (54%) vs 837 with new criteria (68%)

Woelkers D. AJOG 210(1);S50 2014
<table>
<thead>
<tr>
<th>Weeks</th>
<th>Traditional Preeclampsia (N=465)</th>
<th>Nonproteinuric Preeclampsia (N=76)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 35+0 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(N=757)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-section</td>
<td>329 (70.8)</td>
<td>55 (72.3)</td>
</tr>
<tr>
<td>Preterm &lt;37 wk</td>
<td>400 (86.0)</td>
<td>65 (85.5)</td>
</tr>
<tr>
<td>Early preterm &lt;34 wk</td>
<td>281 (60.4)</td>
<td>34 (44.7) *</td>
</tr>
<tr>
<td>SGA</td>
<td>204 (43.9)</td>
<td>31 (40.8)</td>
</tr>
<tr>
<td>Stillbirth</td>
<td>7 (1.5)</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Neonatal death</td>
<td>10 (2.2)</td>
<td>2 (2.6)</td>
</tr>
<tr>
<td>Maternal adverse outcome</td>
<td>17 (3.7)</td>
<td>3 (3.9)</td>
</tr>
<tr>
<td>MAO or perinatal mortality</td>
<td>34 (7.3)</td>
<td>6 (7.9)</td>
</tr>
<tr>
<td>35-37 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(N=224)</td>
<td>(N=115)</td>
<td>(N=49)</td>
</tr>
<tr>
<td>C-section</td>
<td>55 (47.8)</td>
<td>27 (55.1)</td>
</tr>
<tr>
<td>Preterm &lt;37 wk</td>
<td>78 (67.8)</td>
<td>38 (57.1)</td>
</tr>
<tr>
<td>SGA</td>
<td>30 (26.1)</td>
<td>14 (28.6)</td>
</tr>
<tr>
<td>Maternal adverse outcome</td>
<td>2 (1.7)</td>
<td>1 (2.0)</td>
</tr>
<tr>
<td>≥ 37 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(N=242)</td>
<td>(N=81)</td>
<td>(N=51)</td>
</tr>
<tr>
<td>C-section</td>
<td>33 (40.7)</td>
<td>25 (49.0)</td>
</tr>
<tr>
<td>SGA</td>
<td>15 (18.5)</td>
<td>12 (23.5)</td>
</tr>
<tr>
<td>Maternal adverse outcome</td>
<td>1 (1.2)</td>
<td>1 (1.9)</td>
</tr>
</tbody>
</table>

Data reported as N (%). *p<0.05 by X². SGA, BW < 10%; MAO-maternal adverse outcome (abruption, renal failure, pulmonary edema/distress, fatty liver, TTP, DIC, stroke, and retinal detachment).
Timing of Delivery – 34-37 weeks

- **Risks**
  - Severe hypertension (10-15%)
  - Eclampsia (0.2-0.5%)
  - HELLP (1-2%)
  - Abruption (0.2-2%)
  - FGR (10-12%)
  - IUFD (0.2-0.5%)

- **Benefits**
  - Decreased rates of admission to NICU
  - Decreased neonatal respiratory distress
  - Decreased risk of neonatal death

Sibai, et al. Semin Perinatol 2011
HYPITAT II*

- Multicenter, randomized trial, n=704
- Women with gestational HTN, preeclampsia, or worsening chronic HTN between 34-37 weeks’ gestation randomized to delivery (n=353) versus expectant management (n=351)
  - Adverse maternal outcomes in 0.9% of delivery group versus 2.8% expectant group (RR 0.3, 95% CI 0.08-1.08, NNT 51)
  - RDS in 6% in delivery group, versus 2% in expectant group (RR 3.01, 95% CI 1.30-6.99, NNH 25)

*Broekhuijsen, et al. SMFM Annual Meeting 2014
Task Force Recommendation

- For women with mild gestational hypertension or preeclampsia without severe features and no indication for delivery at less than 37 0/7 weeks of gestation, expectant management with maternal and fetal monitoring is suggested.

  - Quality of Evidence: Low*
  - Strength of Recommendation: Qualified
Magnesium sulfate for Preeclampsia without Severe Features?

• Two double-blind, placebo controlled trials evaluating use of magnesium sulfate in preeclampsia without severe features

• No instances of eclampsia in placebo group (n=181), no difference in women who progressed to SPE (12.5% in treated vs. 13.8% in placebo, RR, 0.90; 95%CI, 0.52-1.54)

• Numbers too small to draw meaningful conclusions
Task Force Recommendation

• For women with preeclampsia with systolic BP < 160 mmHg and diastolic BP < 110 mm Hg and no maternal symptoms, it is suggested that magnesium sulfate not be administered universally for the prevention of eclampsia.
  – Quality of evidence: Low
  – Strength of recommendation: Qualified
When to Initiate Intrapartum Magnesium Sulfate

- Signs and symptoms concerning for development of seizures
  - Headache
  - Blurred vision
  - Altered mental state
  - Scotomata
  - Clonus
  - RUQ pain
- Progression to severe disease
Preeclampsia with Severe Features
Preeclampsia with Severe Features

DELIVERY

Patients may require blood transfusions prior to and/or during surgery.
Task Force Recommendation

• For women with severe preeclampsia at or beyond 34 0/7 weeks of gestation, and in those with unstable maternal-fetal conditions irrespective of gestational age, delivery soon after maternal stabilization is recommended.
  – Quality of data: Moderate
  – Strength of recommendation: Strong
Preeclampsia with Severe Features

- Persistent severe hypertension only
  - SBP ≥ 160 mm Hg or DBP ≥ 110 mm Hg
Expectant Management

• Odendaal et al
  – n=38 women, 28-34 weeks
  – Expectant management (n=18) resulted in:
    • greater latency to delivery (7.1 d vs 1.3 d; P<.05)
    • later gestational age at delivery (223 d vs 221 d; P<.05)
    • reduced neonatal complications (33% vs 75%; P<.05)

Odendaal et al Obstet Gynecol 1990
Expectant Management

- Sibai et al
  - N=95, 28-32 weeks
  - Expectant management group vs immediate delivery:
    - greater gestational age (32.9 wks vs 30.8 wks); p=.01
    - less frequency NICU admission (76% vs 100%; P< .01)
    - less frequent RDS (22.4% vs 50%; P=.002)
    - less frequent NEC (0% vs 10.9%;p=.02)
    - more frequent SGA birth wt (30.1% vs 10.9%; p=-.04)
    - No cases of maternal eclampsia or pulmonary edema
    - Similar rates of abruption, HELLP (4.1% vs 2.1%)

Sibai et al AJOG 1994
Expectant Management

• MEXPRE RCT
  – N=425, 28-33 weeks
  – Expectant management group vs immediate delivery:
    • No statistical difference in composite morbidity/mortality of infants, length of NICU stay
    • Trend towards decreased total morbidity and mortality in < 31 weeks of gestation

Gracia VP et al. AJOG 2013;209;425e1-8
Maternal and Perinatal Outcome by Gestational Age at Expectant Management

Bombrays AE et al AJOG 2008;199:247e1-6
Expectant Management in Preeclampsia and Fetal Growth Restriction

- Chammas Shorter: Prolongation (3.1 vs 6.6 days)
- Ganzevoort: Similar prolongation (7 days in each)
  Increased perinatal deaths in FGR (23.2 vs. 10%)
- Visser: Similar prolongation (10 days in each)
  All fetal deaths with FGR at <30 wks
- Shear: Increased maternal complications in FGR
- Haddad: Similar days of prolongation
  Increased fetal death in FGR (7% vs 1%)
Indications of Delivery
Expectant Management (39 studies, 4650 pts)

- Maternal 40%
- Fetal 36%
- Maternal and Fetal 9%
- Spontaneous labor 6%
- GA ≥ 34 weeks 16%
- Other 6%

Magee LA et al. Hypertens Pregnancy 2009
<table>
<thead>
<tr>
<th>Maternal</th>
<th>Fetal/Neonatal</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU admission</td>
<td>27.6 (1.5, 52.6)</td>
</tr>
<tr>
<td>HELLP syndrome</td>
<td>Stillbirth</td>
</tr>
<tr>
<td>Recurrent severe HTN</td>
<td>Neonatal death</td>
</tr>
<tr>
<td>Abuptio placentae</td>
<td>Perinatal asphyxia</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>Any neonatal complication</td>
</tr>
<tr>
<td>Eclampsia</td>
<td>Small-for-gestational age</td>
</tr>
<tr>
<td>Subcapsular liver hematoma</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
</tr>
</tbody>
</table>

Magee LA et al Hypertens Pregnancy 2009
Task Force Recommendation

• For women with severe preeclampsia at less than 34 0/7 weeks of gestation with stable maternal and fetal conditions, it is recommended that continued pregnancy be undertaken only at facilities with adequate maternal and neonatal intensive care resources.
  – Quality of evidence: Moderate
  – Strength of recommendation: Strong
Management before the limit of Fetal Viability

• Poor prognosis – survival rates$^{1,2,3}$
  – <23 0/7 0/34
  – @23 0/7 4/22
  – @24 0/7 15/26

• If FGR present < 23 weeks, mortality approaches 100%$^{3,4}$

$^{1}$Sibai AJOG 2007; $^{2}$Sibai AJOG 2011; $^{3}$Bombr ys et al AJOG 2008; $^{4}$Belghiti et al AJOG 2011
Task Force Recommendation

• For women with severe preeclampsia and before fetal viability, delivery after maternal stabilization is recommended. Expectant management is not recommended.
  – Quality of evidence: Moderate
  – Strength of recommendation: Strong
Maternal and Fetal Monitoring

• Maternal
  – VS, I/Os q 8 hrs
  – ✓ symptoms q 8 hrs
  – ✓ contractions, ROM, abdominal pain, bleeding q 8 hrs
  – Labs qd, can be spaced to qod if stable

• Fetal
  – Kick counts and NST with toco daily
  – BPP twice weekly
  – Serial fetal growth every 2 weeks with UARs if FGR suspected
Corticosteroids in Severe Preeclampsia

- RCTs involving pregnancies with hypertension show that giving ACS results in less frequent:
  - RDS (RR 0.50; 95% CI, 0.35-0.72)
  - Neonatal death (RR 0.50; 95% CI, 0.29-0.87)
  - IVH (RR, 0.38; 95% CI, 0.17-0.87)

Roberts et al Cochrane Database 2006
Task Force Recommendation

• For women with severe preeclampsia receiving expectant management at 34 0/7 weeks or less of gestation, the administration of corticosteroids for fetal lung maturity benefit is recommended.
  – Quality of evidence: High
  – Strength of recommendation: Strong
Severe Proteinuria

• Although the amount of proteinuria increases over time with expectant management, this change is not predictive of pregnancy prolongation or perinatal outcomes\(^1,2\)

\(^1\)Newman et al  Am J Obstet Gynecol 2003
\(^2\)Schiff et al  Am J Obstet Gynecol 1996
Task Force Recommendation

• For women with preeclampsia, it is suggested that a delivery decision should not be based on the amount of proteinuria or change in the amount of proteinuria
  – Quality of evidence: Moderate
  – Strength of recommendation: Strong
Maternal Indications for Delivery

- Persistent headache, visual changes or epigastric or RUQ pain
- Persistent N/V
- PTL, PPROM*
- Recurrent severe HTN
- Progressive renal insufficiency*
- Persistent thrombocytopenia*
- Pulmonary edema
- Eclampsia
- Suspected placental abruption

*Delay delivery for 48 hours to give ACS
Fetal Indications for Delivery

- 34 0/7 weeks
- Severe FGR < 5th%*
- Persistent oligohydramnios (SDP < 2 cm)*
- BPP 4/10 or less on two occasions 6 hrs apart
- Reversed EDF on UARs*
- Recurrent variable or late decelerations during NST
- Fetal death

*Delay delivery for 48 hours to give ACS
It is suggested that corticosteroids be administered and delivery be deferred for 48 hours if maternal and fetal conditions remain stable for women with severe preeclampsia and a viable fetus at 33 6/7 weeks or less of gestation with previously listed conditions*

- Quality of evidence: Moderate
- Strength of recommendation: Qualified
Expectant Management of Severe Preeclampsia Algorithm

- Evidence based
- Easy to understand
- Have available on birthing units to help guide management
Route of Delivery in Preeclampsia

- Vaginal delivery is preferred, but less likely with decreasing gestational age

<table>
<thead>
<tr>
<th>Weeks</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;28 weeks</td>
<td>93-97%</td>
</tr>
<tr>
<td>28-32 weeks</td>
<td>53-65%</td>
</tr>
<tr>
<td>32-34 weeks</td>
<td>31-38%</td>
</tr>
</tbody>
</table>

Rates of c-section after labor induction for preeclampsia.

Task Force Recommendation

• For women with preeclampsia, it is suggested that the mode of delivery does not need to be cesarean delivery. The mode of delivery should be determined by gestational age, fetal presentation, cervical status and maternal-fetal condition.
  – Quality of evidence: Moderate
  – Strength of recommendation: Qualified
Anesthesia Considerations

• Neuraxial anesthesia is recommended for women with preeclampsia
• No studies have examined the safe limit for platelet count and neuraxial anesthesia
• Invasive hemodynamic monitoring is not routinely recommended in preeclampsia with severe features
Acute Control of Severe Hypertension

• To prevent CV, renal, or cerebrovascular complications

• No randomized trials in pregnancy to determine level of hypertension to treat to prevent these complications

• Data from case series reveal increased rates of heart failure, pulmonary edema and death

• Systolic hypertension most important predictor of cerebral injury
Acute Control of Severe Hypertension

- BP goal: 140-160/90-100
  - prevents repeated, prolonged exposure of the patient to severe systolic HTN → loss of cerebral autoregulation

- Maternal stabilization should occur prior to delivery
  - intubation places patient at risk for increase in BP

- Judicious fluid administration in oliguric patient

ACOG Committee Opinion 514; 2011
# Antihypertensive Agents

## TABLE 7-1. Antihypertensive Agents Used for Urgent Blood Pressure Control in Pregnancy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Labetalol</td>
<td>10–20 mg IV, then 20–80 mg every 20–30 min to a maximum dose of 300 mg or Constant infusion 1–2 mg/min IV</td>
<td>Considered a first-line agent&lt;br&gt;Tachycardia is less common and fewer adverse effects&lt;br&gt;Contraindicated in patients with asthma, heart disease, or congestive heart failure</td>
</tr>
<tr>
<td>Hydralazine</td>
<td>5 mg IV or IM, then 5–10 mg IV every 20–40 min or Constant infusion 0.5–10 mg/h</td>
<td>Higher or frequent dosage associated with maternal hypotension, headaches, and fetal distress—may be more common than other agents</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>10–20 mg orally, repeat in 30 minutes if needed; then 10–20 mg every 2–6 hours</td>
<td>May observe reflex tachycardia and headaches</td>
</tr>
</tbody>
</table>

Abbreviations: IM, intramuscularly; IV, intravenously.
Antihypertensive medications to treat severe BP in pregnancy

- No superior drug in several randomized trials comparing labetalol, hydralazine or oral nifedipine
- 35 trials, n=3,573 women\(^1\)
  - No differences in efficacy or safety between hydralazine and labetalol or hydralazine and calcium channel blockers
  - Can use any of these agents to treat acute, severe hypertension

\(^1\)Duley L et al. Cochrane Data Syst Rev 2013
Acute Control of Severe Hypertension

• Persistent BP systolic BP ≥ 160 or diastolic BP ≥ 110
• IV labetalol bolus
  – 20, 40, 80 mg q 10 min (max 300/hr)
  – Continuous IV infusion (1-2 mg/min)
  – If no IV access, give 200 mg orally, repeat in 30 min
• IV hydralazine bolus
  – 5, 10, 10 mg q 20 min (max 25 mg)
• Oral nifedipine
  – 10-20 mg q 30 min (max 60 mg)
• IV sodium nitroprusside

ACOG Committee Opinion 514; 2011
Task Force Recommendation

- For women with preeclampsia with severe hypertension during pregnancy (sustained SBP > 160 mm Hg or DBP > 110 mm Hg) the use of antihypertensive therapy is recommended.
  - Quality of evidence: Moderate
  - Strength of recommendation: Strong
Calcium channel blockers and intravenous magnesium?

- Theoretical risk of hypotension and neuromuscular blockade
- One review concluded that combined use of these drugs does not increase risk\(^1\)
- However, given that both are calcium antagonists, careful monitoring is advised

\(^1\)Magee LA Am J Obstet Gynecol 2007;196:514e1-9
Eclampsia
Eclampsia

- Presence of new-onset grand mal seizures in women with preeclampsia
- Can occur before, during or after labor
- If occurs 48-72 hours postpartum or while on magnesium therapy, consider:
  - Bleeding AVM
  - Ruptured aneurysm
  - Idiopathic seizure disorder
Anticonvulsant Therapy for Eclampsia

• Magnesium sulfate superior to other anticonvulsants for treatment of eclampsia\(^1\)

• Systemic review of 11,000 women in 6 trials shows magnesium sulfate works in prevention of eclampsia\(^2\)
  – Intravenous loading dose of 4-6 grams/hours followed by 1-2 grams/hour for at least 24 hours
  – ↓ eclampsia by 50% (RR, 0.41, 95% CI 0.29-0.58)

• Treat for at least 24 hours after last convulsion

\(^1\)Duley L et al Cochrane Database 2010;12:CD000127
\(^2\)Duley L et al Cochrane Database 2010;11:CD000025
Expectant Management of Eclampsia?

- Expectant management can be associated with significant maternal and perinatal morbidity and mortality
- Expectant management prior to 34 weeks for 24-48 hours to administer corticosteroids can be undertaken with meticulous maternal and fetal monitoring, continuous magnesium sulfate and antihypertensive therapy
- In most situations, there is general agreement that women should undergo delivery following stabilization
Should Magnesium Sulfate be continued during Surgery?

• **YES!**
  • Will not abate potential interactions with anesthetic agents (half life of 5 hours)
  • Increases likelihood of subtherapeutic magnesium levels in recovery room or postpartum suite
  • Induction of anesthesia and stress of delivery may reduce seizure threshold
Task Force Recommendation

• For women with eclampsia, the administration of parenteral magnesium sulfate is recommended

• For women with severe preeclampsia, the administration of intrapartum-postpartum magnesium sulfate to prevent eclampsia is recommended
  – Quality of evidence: High
  – Strength of recommendation: Strong

• For women with preeclampsia undergoing cesarean delivery, the continued intraoperative administration of parenteral magnesium to prevent magnesium sulfate is recommended.
  – Quality of evidence: Moderate
  – Strength of recommendation: Strong
HELLP Syndrome

**Hemolysis** abnormal peripheral smear, bilirubin ≥ 1.2 mg/dL, serum LDH > 600 U/L

**Elevated**

**Liver Enzymes** > 2x normal, AST ≥ 70 U/L

**Low**

**Platelets** < 100,000

Weinstein L, AJOG 1982;142:159
HELLP Syndrome

<34 weeks*
- Delay delivery for 24-48 hours*
- Steroids for fetal lung maturity

≥34 weeks
- Magnesium sulfate therapy and Antihypertensive therapy

Delivery
- DIC
- ARF
- liver infarction or hemorrhage abruption
- pulmonary edema
- nonreassuring fetal status
Corticosteroids in HELLP for Maternal Benefit

- Benefits of dexamethasone in women with HELLP is conflicting
- 11 randomized controlled trials evaluating perinatal outcome in women given steroids during expectant management
  - Significantly improved maternal platelet counts
  - No significant improvements in maternal mortality or severe maternal morbidities

Woudstra DM et al Cochrane Database 2010, Issue 9
Postpartum Hypertension
Postpartum Hypertension

• Severe features, including seizures, can present for the first time postpartum
  – At risk up to 4 weeks postpartum
• Due to early hospital discharge, important to educate patients on signs to report (epigastric pain, severe headaches, visual disturbances)
  – Unclear if educating patients on symptoms that precede eclampsia, stroke will reduce morbidity related to these conditions
Postpartum Hypertension and Preeclampsia

Percentage of Hypertension and Proteinuria

- Severe Pree
- HELLP
- GH
- Proteinuria

Stepan H et al J Hum Hypert 2006
Management of Postpartum Hypertension

- Antihypertensive administration for persistent SBP >150 or DBP > 100
- NSAIDS increase BP; consider alternative analgesics in these patients
- Magnesium sulfate for at least 24 hours from time of diagnosis for women with preeclampsia or severe hypertension and symptoms
  - Severe headache, visual changes, altered mental status, epigastric pain, shortness of breath
Task Force Recommendations

- For all women in the postpartum period, it is suggested that discharge instructions include information about the signs and symptoms of preeclampsia as well as the importance of prompt reporting of this information to their health care providers
  - Quality of evidence: Low
  - Strength of recommendation: Qualified
## Antihypertensive Therapy

### TABLE 7-2. Common Oral Antihypertensive Agents in Pregnancy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Comments</th>
</tr>
</thead>
</table>
| Labetalol                   | 200–2,400 mg/d orally in two to three divided doses | Well tolerated  
Potential bronchoconstrictive effects  
Avoid in patients with asthma and congestive heart failure |
| Nifedipine                  | 30–120 mg/d orally of a slow-release preparation | Do not use sublingual form |
| Metyldopa                   | 0.5–3 g/d orally in two to three divided doses | Childhood safety data up to 7 years of age  
May not be as effective in control of severe hypertension |
| Thiazide diuretics          | Depends on agent                             | Second-line agent |
| Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers | Associated with fetal anomalies  
Contraindicated in pregnancy and preconception period |
For women in whom gestational hypertension, preeclampsia, or superimposed preeclampsia is diagnosed, it is suggested that BP be monitored in the hospital or that equivalent outpatient surveillance be performed for at least 72 hours postpartum and again 7-10 days after delivery or earlier in women with symptoms

– Quality of evidence: Moderate
– Strength of recommendation: Qualified
Long-term Risks

• Women with preeclampsia have a 2-fold increase in CV disease

• Highest risk
  – Preeclampsia < 34 weeks or FGR, 8-10 fold increased risk
  – If recurrent, increase in death from CV disease earlier in life compared with women who only had PE in first pregnancy

• AHA recognizes hx of preeclampsia as part of risk score for CV disease
Model for pregnancy as a stress test for long-term cardiovascular disease.

- Red line: Population with complicated pregnancy, e.g. pre-eclampsia
- Blue line: Healthy population
- Green line: Threshold for vascular or metabolic disease

Task Force Recommendations

• For women with a medical history of preeclampsia who gave birth preterm (< 37 0/7 weeks of gestation) or who have recurrent preeclampsia, yearly assessment of blood pressure, lipids, fasting blood glucose, and body mass index is suggested
  – Quality of evidence: Low
  – Strength of recommendation: Qualified
Prediction and Prevention of Preeclampsia
Prediction of Preeclampsia

• Requires high likelihood ratio (LR) + preventative approach or therapeutic intervention reduces adverse maternal/fetal outcomes

• LR > 10
## Prediction of preeclampsia

<table>
<thead>
<tr>
<th>Predictive Test</th>
<th>Likelihood ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Risk Factors</td>
<td>3.6</td>
</tr>
<tr>
<td>Uterine Artery Doppler</td>
<td>5.0-20</td>
</tr>
<tr>
<td>Angiogenesis related biomarkers</td>
<td>low</td>
</tr>
<tr>
<td>Uterine PI + MAP + PAPP-a + serum free P1GF + BMI + history</td>
<td>16.5*</td>
</tr>
<tr>
<td>P1GF/soluble endoglin ratio</td>
<td>57.6*</td>
</tr>
</tbody>
</table>

North, et al BMJ 2011
Prediction of Adverse Outcome in Patients with PE

• Biomarkers for PE/GHTN with high risk of progressing to multisystem involvement
  – Elevated uric acid $\geq$ 5.2 mg/dL, PPV 91.4%
  – At < 34 wks GA, P1GF ratio = 85, PPV 86%, positive LR 12.2 for predicting adverse maternal outcome within 2 weeks

Kenny et al Hypertension 2010
Prediction of Adverse Outcome in Patients with PE

- Biomarkers to rule out progression of GHTN to PE or adverse outcomes
  - n=176, plasma sFlt-1/P1GF ratio < 85, NPV 87.3%, negative LR 0.29
  - 6/16 with FN and AO related to PE

Rana et al Circulation 2012
Prediction of Preeclampsia

• No biomarkers clinically approved for use
• sFlt-1, P1GF, and soluble endoglin in early second trimester +/- uterine artery dopplers show promise
• Large prospective trials evaluating the clinical utility of biomarkers are needed
Task Force Recommendation

• Screening to predict preeclampsia beyond obtaining an appropriate medical history to evaluate for risk factors is not recommended
  – Quality of evidence: Moderate
  – Strength of recommendations: Strong
Early Administration of Low-Dose Aspirin for the Prevention of Severe and Mild Preeclampsia: A Systematic Review and Meta-Analysis

Stéphanie Roberge, M.Sc. 1  Yves Giguère, M.D., Ph.D. 2  Pia Villa, M.D. 3  Kypros Nicolaides, M.D. 4  Merja Vainio, M.D. 5  Jean-Claude Forest, M.D., Ph.D. 2  Peter von Dadelzen, M.B.Ch.B., D.Phil. 6  Daniel Vaiman, Ph.D. 7  Sylvie Tapp, B.Sc. 1  Emmanuel Bujold, M.D., M.Sc., F.R.C.S.C. 8

Prevention of Preeclampsia and Intrauterine Growth Restriction With Aspirin Started in Early Pregnancy
A Meta-Analysis

Emmanuel Bujold, MD, MSc, Stéphanie Roberge, MSc, Yves Lacasse, MD, MSc, Marc Bureau, MD, François Audibert, MD, MSc, Sylvie Marcoux, MD, PhD, Jean-Claude Forest, MD, PhD, and Yves Giguère, MD, PhD
Prevention of Preeclampsia

• Antiplatelet Agents
  – 30,000 women, 31 trials, varying risk, RR of PE 0.9 (CI, 0.84-0.97)
  – 37,000 women, 59 trials, 17% reduction in risk of PE, significant absolute risk reduction in women at high risk for PE
  – Limitations: positive trial more likely to be published than negative trial, largest trials did not show significant protective effect

Bujold, et al Obstet Gyn 2010
TABLE 4-1. PARIS number needed-to-treat with sample baseline event rates

<table>
<thead>
<tr>
<th>Condition</th>
<th>Sample baseline event rate</th>
<th>PARIS relative risk (95%CI)</th>
<th>Number needed-to-treat (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-eclampsia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>18%</td>
<td>0.90 (0.84–0.97)</td>
<td>56 (35–185)</td>
</tr>
<tr>
<td></td>
<td>6%</td>
<td></td>
<td>167 (104–556)</td>
</tr>
<tr>
<td></td>
<td>2%</td>
<td></td>
<td>500 (313–1667)</td>
</tr>
<tr>
<td>Preterm &lt;34 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>20%</td>
<td>0.90 (0.83–0.98)</td>
<td>50 (29–250)</td>
</tr>
<tr>
<td></td>
<td>10%</td>
<td></td>
<td>100 (59–500)</td>
</tr>
<tr>
<td></td>
<td>2%</td>
<td></td>
<td>500 (294–2500)</td>
</tr>
<tr>
<td>Perinatal death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>7%</td>
<td>0.91 (0.81–1.03)</td>
<td>159 (75–476)</td>
</tr>
<tr>
<td></td>
<td>4%</td>
<td></td>
<td>278 (132–833)</td>
</tr>
<tr>
<td></td>
<td>1%</td>
<td></td>
<td>1111 (526–3333)</td>
</tr>
<tr>
<td>Small for gestational age baby</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>15%</td>
<td>0.90 (0.81–1.01)</td>
<td>67 (35–667)</td>
</tr>
<tr>
<td></td>
<td>10%</td>
<td></td>
<td>100 (53–1000)</td>
</tr>
<tr>
<td></td>
<td>1%</td>
<td></td>
<td>1000 (526–10 000)</td>
</tr>
<tr>
<td>Pregnancy with serious adverse outcome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>25%</td>
<td>0.90 (0.85–0.96)</td>
<td>40 (27–100)</td>
</tr>
<tr>
<td></td>
<td>15%</td>
<td></td>
<td>67 (44–167)</td>
</tr>
<tr>
<td></td>
<td>7%</td>
<td></td>
<td>143 (95–357)</td>
</tr>
</tbody>
</table>

Task Force Recommendation

- For women with medical history of early-onset preeclampsia and preterm delivery < 34 0/7 weeks of gestation or preeclampsia in more than one prior pregnancy, initiating the administration of daily low-dose (60-80 mg) aspirin beginning in the late first trimester is suggested
  - Quality of evidence: Moderate
  - Strength of Recommendation: Qualified
Other Nutritional Interventions

• 15 randomized trials, 20,748 women on vitamin C and vitamin E for prevention of PE
  – No benefit, RR 0.94 (95% CI, 0.82-1.07)

• Calcium supplementation
  – 13 trials, 15,730 women
  – Significant reduction of preeclampsia, RR 0.45 (95% CI, 0.31-0.65), with greatest effect among women with low baseline calcium intake
  – Consider in women from population with low baseline calcium intake (< 600 mg/d)
Other Nutritional Interventions

• Vitamin D deficiency, fish oil, garlic
  – Unknown if supplementation is beneficial

• Protein and calorie restriction in obese pregnant women
  – No reduction in risk of PE or GHTN, may increase risk of FGR

• Dietary salt intake and diuretics
  – No significant benefit
Lifestyle Modifications

• Bedrest
  – Small trials did not look at perinatal and maternal outcomes

• Exercise
  – In pregnancy, moderate exercise stimulates placental angiogenesis and improves maternal endothelial dysfunction
  – Small studies, CIs too wide to draw meaningful conclusions
Preeclampsia
Hypertension, proteinuria

Anti-angiogenic response
↑ sFLT1, sEnd
↓ PLGF

Altered immune response
↑ Inflammatory cytokines (IL-6, TNF-α)
↓ Anti-inflammatory cytokines (IL-10)

Abnormal trophoblast invasion
Poor spiral artery remodeling

Oxygen disruption
↑ HIF1α
↑ Placental oxidative stress

Image courtesy of The Curators of the University of Missouri (2011), a public corporation.
Advances in Understanding of Preeclampsia

Perivascular and endovascular cytotrophoblasts fail to express the Notch ligand JAG1.

Variability in immune system genes that code MHC molecular and NK receptors.

Image courtesy of The Curators of the University of Missouri (2011), a public corporation.
Pathways by which reduced uterine perfusion pressure (RUPP) and placental ischemia may lead to endothelial and cardiovascular dysfunction during pregnancy.

Angiogenic Factors: Molecular mechanisms involved in regulation of sFlt-1 production, inhibitors of sFlt-1 production or stimulators of VEGF and PIGF production for therapy

Immune Factors: Pathogenic importance of AT1-AA, how they are produced and how they interact with other pathogenic agents

Relative importance of NO deficiency in pathogenesis of preeclampsia

ET-1 as potential therapeutic target

Angiogenic Factors

With sFlt1

VEGF

↓

VEGF

sFlt1

VEGF receptors

No Angiogenesis

Without sFlt1

VEGF

↓

VEGF receptors

Pro Angiogenesis signal

Xu et al. Fibrogenesis & Tissue Repair 2012 5:13
Hemeoxygenase

• Stress response gene, HO-1
  – Catalytic product, carbon monoxide

↑ HO-1 enzyme activity decreases TNF-alpha mediated cellular damage

• Induction or administration of HO-1 enzyme or metabolites ameliorate HTN

• StAmP – Statins to Ameliorate early onset Preeclampsia
Task Force Recommendations

• Study of placentation, including immunological and angiogenic signaling pathways abnormalities
• Role of genetic and epigenetic factors in preeclampsia
• Molecular mechanisms involved in regulation of proangiogenic and antiangiogenic factors
• Further development of animal models
Task Force Recommendations for Clinical Research

- Prediction and Risk Stratification
- Therapy and Prevention of Preeclampsia, Eclampsia and HELLP syndrome
- Management of Preeclampsia, Eclampsia and HELLP syndrome
- Chronic Hypertension
- Education
Andrea D. Shields, MD

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