Pre-eclampsia Clinical Guidelines

INTRODUCTION: Hypertensive disorders of pregnancy are arranged into four categories: chronic hypertension, gestational hypertension, pre-eclampsia, and pre-eclampsia superimposed on chronic hypertension. Hypertensive disorders are one of the leading causes of significant maternal and neonatal morbidity and mortality globally. Of these, pre-eclampsia is found in 3-8% of all pregnancies. In addition, it is found in 14% of multi-fetal gestations and is a recurrence in 18% of all diagnoses. More commonly, late onset of pre-eclampsia > 34 weeks complicates pregnancies, however 10% present before 34 weeks and 5% present after delivery (usually within 48 hrs). Serious complications of pre-eclampsia include placental abruption, pulmonary edema, DIC, posterior reversible encephalopathy syndrome (PRES), eclampsia, stroke, and acute renal or liver failure. Acute fatty liver of pregnancy, TTP-HUS, and exacerbation of systemic SLE or other preexisting renal disease should be considered in the differential diagnosis and excluded.

I. DEFINITIONS

1. Hypertension
   a. Elevated blood pressure (BP) ≥ 140 mmHg systolic and/or ≥ 90 mmHg diastolic on at least 2 occasions at least 4 hours apart but within 1 week

2. Proteinuria
   a. Proteinuria ≥ 300 mg in 24 hour urine collection
   b. Protein: creatinine ratio ≥0.3 mg/dL or >30 mg/mmol
      i. P:C ratio ≥0.3 mg/dL or >30 mg/mmol with elevated BP needs reflex 24 hr urine as an inpatient
      ii. P:C ratio< 0.3 mg/dL with elevated BP needs reflex 24 hr urine on outpatient basis
   Note: Proteinuria is no longer a requirement for diagnosis of pre-eclampsia if severe features are present (listed below)
   (Reflex 24-hour urine should be returned to primary OB provider)

3. Severe features:
   a) Persistent SBP > 160 mm Hg and/or DBP > 110 mm Hg on two occasions at least 4 hours apart or after treatment with IV hypertensive medications
   b) Persistent and/or severe cerebral or visual disturbances (i.e. headache, seizures, scotomata)
   c) Any sign of end-organ dysfunction
      o Thrombocytopenia (platelet count < 100,000 platelets/mL)
      o Progressive renal insufficiency (serum creatinine doubling or > 1.1 mg/dL)
      o Hepatic abnormality (severe persistent right upper quadrant (RUQ) or epigastric pain nonresponsive to medications or elevated serum transaminases to twice normal concentrations)
   d) Pulmonary edema
   (Note: Oliguria (<500 ml/24 hrs.) and massive proteinuria >5g/24 hr are no longer included in the classification, but may have clinical implications. Fetal growth restriction is managed according to protocol and likely poses an additional risk factor to the diagnosis of pre-eclampsia)

I. Classification/Diagnosis

a. Gestational hypertension (GHTN) 6-17% nulliparous and 2-4% multiparous
b. Chronic hypertension (CHTN)  
c. Chronic hypertension with superimposed pre-eclampsia  
d. Pre-eclampsia  
e. Eclampsia

| Pre-Eclampsia | A. New onset of hypertension with proteinuria or end-organ dysfunction > 20 wks EGA in previously normotensive women. (See above criteria for severe features and definition of end-organ dysfunction)  
| B. GHTN associated with persistent neurologic symptoms, epigastric or right upper quadrant (RUQ) pain with nausea (N) and vomiting (V), thrombocytopenia (platelets ≤ 100,000/mm³), or abnormal liver enzymes

| Chronic Hypertension | A. Hypertension as defined above diagnosed prior to pregnancy or 20th wks EGA, may be diagnosed if gestational HTN persist after 12wks postpartum  
| B. Chronic hypertension with superimposed preeclampsia  
a) Patients with chronic HTN without proteinuria at <20 weeks gestation, defined as new onset proteinuria of ≥ 0.3 g in 24-hour specimen)  
b) Patients with chronic HTN and pre-existing proteinuria before 20 weeks gestation, defined as severe range BP in a previously well controlled patient or onset of new signs or symptoms consistent with end-organ involvement

| Gestational Hypertension | Hypertension as defined above developing after 20 wks EGA in the absence of proteinuria or severe features.  
***Definitive diagnose made postpartum: Resolution prior to 12 wks postpartum (transient hypertension of pregnancy) or persistent beyond 12 wks (chronic hypertension)

| Eclampsia | Development of convulsions and/or unexplained coma during pregnancy or postpartum in patients with signs and symptoms of preeclampsia, in the absence of other seizure etiologies.

| HELLP (Hemolysis, Elevated Liver enzymes, and Low Platelets) | A suspected variant of Pre-E (see complications for diagnosis and management)  
***15-20% present without hypertension or proteinuria

II. RISK FACTORS
1. Previous pregnancy complicated by preeclampsia (RR 7.19, CI 5.85-8.83)  
2. Presence of antiphospholipid antibody syndrome (RR 9.72, CI 4.34-21.75)  
3. Pregestational diabetes mellitus (RR 3.56, CI 2.54-4.99)  
4. Gestational diabetes mellitus (RR 1.5, CI 1.3-1.8)  
5. CHTN/Renal disease/Autoimmune disorders  
6. Multifetal gestation (RR 2.93, CI 2.04-4.21)  
7. Obesity prior to pregnancy (2.47 CI 1.66-3.67)
8. Family history of Pre-eclampsia or eclampsia (2.90, CI 1.70-4.93)
9. AMA > 40 (RR 1.96 CI 1.34-2.87)
10. Nulliparity (RR 2.91, CI 1.28-6.61)
11. Other factors: Black Race, Interpregnancy interval of ≥ 10 yrs, Abnormal uterine Doppler studies at 18 and 24 weeks, Infertility, and Polycystic ovarian syndrome (PCOS)

III. MANAGEMENT
1. The only definitive cure for pre-eclampsia is delivery.
2. The primary objective of management of pre-eclampsia is always maternal safety.
3. The secondary objective, when possible, is delivery of a mature newborn that will not require intensive and prolonged neonatal care.
4. For the patient who is preterm (< 37 weeks), expectant management is warranted in the absence of severe disease, but delivery is generally recommended at 37 0/7 weeks.
   a. Cervical ripening agents should be used for unfavorable cervices.

Management considerations in hypertensive disorders of pregnancy
   a) Outpatients should be advised to come immediately to triage for any signs or symptoms of severe pre-eclampsia (New onset HA, vision changes or scotomata, epigastric or right upper quadrant abdominal pain).
   b) If there is any evidence of significant worsening of maternal or fetal status, or new onset features of severe disease, outpatients should be hospitalized and evaluated for delivery.
   c) Vaginal delivery may be attempted in the absence of typical obstetrical indications for cesarean delivery.
      a. Cesarean delivery without a trial of labor is reasonable in those < 30 weeks with an unfavorable cervix.
   d) Evidence does not mandate magnesium sulfate for pre-eclampsia without severe disease; individualization of care may be necessary in cases with diagnostic confounders.

Maternal and fetal outpatient expectant management of pre-eclampsia
Outpatient management of pre-eclampsia is not routinely performed and should only be undertaken with MFM consultation. After the initial inpatient evaluation for pre-eclampsia, there is the potential to consider patients as candidates for outpatient management on a case-by-case basis.

Patients undergoing outpatient management should receive fetal surveillance at least twice per week, twice weekly measurement of blood pressure, weekly assessment of protein, platelet counts, and liver enzymes, ultrasound for EFW every 3 weeks, as well as be able to comply with recommendations and testing. Patient is NOT an outpatient candidate in the following settings: SBP >150 mmHg or DBP >100 mmHg, severe features, abnormal platelet count or liver enzymes, presence of maternal symptoms suggestive of severe disease, abnormal fetal growth profile, or non-reassuring fetal testing.

Maternal and fetal inpatient expectant management of pre-eclampsia without severe disease
Maternal Evaluation
   a) Daily weight
   b) Monitoring for severe pre-eclampsia symptoms
   c) Twice-weekly lab tests: CBC, uric acid, Cr, LDH, AST, ALT
Fetal Evaluation
a) Daily fetal movement
b) Antenatal fetal testing as specified in applicable guidelines
c) Ultrasound for growth every 3 weeks.

Maternal and fetal inpatient management of Severe Pre-eclampsia (Fig. 2)
a) Initial assessment and observation on antepartum service (OBSCU)
   a. Maternal stabilization
   b. Prolonged maternal BP and symptomatology monitoring
   c. Admission laboratory evaluation
      i. P: C ratio screening, with microscopic urinalysis. Reflex 24 hr urine (See above proteinuria section)
      ii. CBC +/- peripheral smear, CMP (Cr, AST, ALT), Uric Acid, LDH, Direct bilirubin, Coagulation profile (not typically indicated in the absence of abruption, severe thrombocytopenia, or liver dysfunction)
   d) Fetal U/S for EFW, AFI
   e) Intravenous magnesium sulfate should be initiated at time of admission (6 gram bolus followed by 2gm/hr)
      a. Clinical assessments should be performed and documented on hourly basis while magnesium is infusing.
      b. Clinical suspicion for magnesium toxicity, serum magnesium level should be measured with clinical suspicion (please see section for management of magnesium toxicity
      c. Renal dosing (6gm load and 1 g/hr maintenance) and more frequent serum monitoring should be considered in those with renal insufficiency
   d) Steroids should be administered to patients <34 weeks (See Antenatal Steroid protocol). Betamethasone 12 mg IM q 24 hours x 2 doses is the preferred regimen.
   e) Correction of coagulopathy if present.
   f) Expectant management is a reasonable alternative for women <34 weeks gestation if clinical maternal and fetal courses are stable and maintained. MFM consultation should be obtained.
   g) Delivery should be considered in all women who meet criteria for severe pre-eclampsia at > 34 0/7 weeks.

Maternal and fetal inpatient expectant management of severe pre-eclampsia (24 0/7** wks-33 6/7 wks)

Maternal Evaluation
a) Daily weight
b) Monitor blood pressure, urine output, cerebral status, epigastric pain/tenderness or vaginal bleeding
   c) Antihypertensive drugs to maintain blood pressure between 140/90 and 150/100 mmHg
   d) Twice-weekly labs. Frequency of labs maybe adjusted on an individual basis

Fetal Evaluation
a) Continuous fetal monitoring for the first 24 hours then daily NST
b) BPP twice per week
c) Doppler studies as indicated per IUGR protocol
d) Ultrasound for growth at least every 3 weeks
Criteria for immediate delivery (within 48 to 72 hours) in pre-eclampsia

Maternal

a. Uncontrolled severe hypertension (SBP ≥ 160 mmHg, DBP ≥ 110 mmHg) despite maximum doses of antihypertensive therapy (IV labetalol, hydralazine and/or oral nifedipine).

b. Eclampsia or persistent cerebral symptoms

c. Pulmonary edema

d. Placenta abruption

e. HELLP syndrome

f. Renal failure (Serum creatinine of 1.5 mg/dl in patient with previously normal creatinine)

Fetal

a. Persistent non-reassuring fetal status

b. Lethal fetal anomalies

***Delivery timing may be individualized based on maternal stability

Intrapartum management

a) Blood pressure control, then increased level of observation for the immediate postpartum period (24 hrs) to monitor BP, neurologic exam, and fluid status

b) Continuous fetal monitoring

c) Intravenous magnesium sulfate administration and should continue for 24 hours postpartum (postpartum infusion maybe adjusted with definitive evidence of maternal clinical improvement)

a. Clinical assessments (Cardiovascular and pulmonary exam, patellar reflexes, urinary output) should be performed and documented on hourly basis while magnesium is infusing.

d) Indwelling urinary catheter for hourly assessment of urine output while receiving magnesium sulfate

Postpartum management

a) Patients with HELLP syndrome should have CBC and liver enzymes monitored daily until improvement noted.

b) If hypertension persists after delivery, antihypertensive medication may need to be prescribed prior to hospital discharge.

c) NSAIDs should be used cautiously with poor BP control, oliguria, renal insufficiency, or thrombocytopenia.

d) Patients need blood pressure monitoring for the initial 72 hours postpartum. If discharged prior to 72 hours, an outpatient appointment for blood pressure check should be scheduled for postpartum day 3. Then, patients should return for a blood pressure 7-10 days post-delivery.

e) If the hypertension persists beyond 12 weeks postpartum, the diagnosis of chronic hypertension should be entertained and the patient be referred to their primary care physician.
Figure 1. Management recommendations for pre-eclampsia and gestational hypertension

Maternal and Fetal Evaluation

≥34 weeks’ gestation WITH
- Spontaneous labor
- Rupture of membranes
- Non-reassuring fetal testing

NO

Inpatient
- Daily maternal assessment
- Daily NST/Twice weekly BPPs
- Weekly labs or as clinically indicated

Outpatient
- Twice weekly BP check
- Weekly MD clinic visit
- Twice/week antenatal testing
- Weekly Labs
- Readmit for change in clinical or lab status

Inpatient or outpatient management
- Maternal and fetal evaluation

Worsening Maternal or Fetal Condition
- 37 0/7 weeks gestation
- Spontaneous Labor

Delivery

YES
Severe Pre-eclampsia < 34 weeks
Superimposed Pre-eclampsia with severe features

Admit to Labor & Delivery area
Maternal & Fetal Evaluation x 24 hours
IV Magnesium Sulfate
Antihypertensives if SBP ≥ 160 mm Hg
DBP ≥ 105 or mean arterial pressure > 125 mm Hg
Corticosteroids for lung maturity

Eclampsia
Pulmonary edema
Acute renal failure
Disseminated Coagulopathy
Persistent neurologic symptoms
Severe hypertension unresponsive to therapy
Non-reassuring fetal status

Yes
Deliver before completion of steroids

No

HELLP syndrome
Thrombocytopenia

Yes
May consider expectant mgt for 48 hours with antenatal corticosteroids administration then delivery

No

23 0/7-23 6/7 wks
AND/OR
NICU CONSULT

Antihypertensive as needed
Daily evaluations of maternal-fetal conditions
Delivery at 34 weeks

24 0/7-34 0/7 wks

DELIVERY
IV. COMPLICATIONS OF PRE-ECLAMPSIA

1. HELLP (Hemolysis, Elevated Liver enzymes, and Low Platelets)
   a. Hemolysis (Schitocytes or helmet cells on peripheral smear, lactate dehydrogenase (LDH) >600 U/L or bilirubin >1.2 mg/dL)
   b. Elevated Liver Enzyme Levels: Twice normal values
   c. Low Platelets: Platelet count <100,000/mm3

Management of HELLP Syndrome
   a) Transfer or admission to a tertiary care center
   b) Initial assessment and management as severe pre-eclampsia (See above).
   c) Immediate delivery should be performed in patients at or beyond 34 weeks gestation.
   d) In patients < 34 0/7 wks, glucocorticoids should be given for fetal benefits and delivery planned 24 hours after the second dose if maternal and fetal status remain stable.
   e) Mode of delivery is individualized based on maternal condition and cervix status

Perioperative management of a patient with HELLP syndrome requiring cesarean section:
   a) Control severe hypertension
   b) Initiate intravenous magnesium sulfate infusion
   c) Glucocorticoids for 24–48 hours for fetal benefit if <34 wks
   d) General anesthesia for platelet count <80,000/mm3
   e) Platelet transfusion 5–10 units before surgery if platelet count <50,000/mm3
   f) Postoperative transfusions as needed
   g) Inpatient monitoring for at least 72 hours postpartum

Management of Eclampsia
   a) The main therapy is supportive care and initiate safety measures to avoid maternal injury.
   b) Maintain oxygenation to mother and fetus
      a. Oxygen
      b. Pulse oximetry or arterial blood gas measurements
   c) Minimize aspiration
      a) Lateral decubitus position
      b) Suctioning of vomitus and oral secretions
      c) Obtain chest x-ray after cessation of convulsion to rule out aspiration
      d) Avoid administration of benzodiazepines except for prolonged seizures (see below)
   d) Initiate MgSO4 to prevent recurrent seizures
   e) Control severe hypertension
   f) Deliver once maternal status is stabilized
      a. Vaginal delivery is the preferred route after an eclamptic seizure. Cesarean delivery should be performed for obstetric indications only.

Recommended regimens of magnesium sulfate in the treatment of eclamptic convulsions
   1. Loading dose: 6 g IV over 30 min (6 g of 50% solution diluted in 150 cc D5W)
   2. Maintenance dose: 2 g IV per hr (40 g in 1 L D5LR at 50 cc/h)
   3. Additional 2 g over 5–10 min can be given with persistent convulsions and may be repeated if necessary.
   4. If no IV access: 5 g IM x 2 (1 injection in each buttock)
5. If convulsions persist (2% of cases) defined as a seizure lasting for more than 5 minutes, may give other agents to control seizure. Consider imaging for other intracranial pathology in the patient with recurrent seizures or other findings.

6. In refractory seizures consider alternative treatments (intubation and muscular paralysis may be necessary)

<table>
<thead>
<tr>
<th>Serum magnesium levels and associated clinical findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss of patellar reflex</td>
</tr>
<tr>
<td>Feeling of warmth, flushing</td>
</tr>
<tr>
<td>Double vision</td>
</tr>
<tr>
<td>Somnolence</td>
</tr>
<tr>
<td>Slurred speech</td>
</tr>
<tr>
<td>Muscular paralysis</td>
</tr>
<tr>
<td>Respiratory difficulty</td>
</tr>
<tr>
<td>Cardiac arrest</td>
</tr>
</tbody>
</table>

Management of magnesium toxicity
1. Discontinue magnesium sulfate infusion
2. Begin supplemental oxygen administration
3. Obtain serum magnesium level
4. Administer 1 g calcium gluconate (10 cc of 10% calcium gluconate) by slow intravenous push over 5-10 minutes
   a. Repeat calcium gluconate administration if necessary
5. If respiratory arrest occurs, begin cardiopulmonary resuscitation

** Special consideration: 23 0/7-23 6/7 weeks EGA
1. Neonatal consultation
2. If patient desires intervention in the 23rd week following neonatal consultation, then individualized therapies for expectant management of pre-eclampsia may be elected (see expectant management portion of protocol)
<table>
<thead>
<tr>
<th>Drug</th>
<th>Starting dose</th>
<th>Maximum dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute treatment of severe hypertension</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydralazine</td>
<td>5-10 mg IV every 20 min.</td>
<td>30 mg*</td>
<td></td>
</tr>
<tr>
<td>Labetalol</td>
<td>20-40 mg IV every 10-15 min.</td>
<td>220 mg*</td>
<td>Avoid in women with asthma/CHF</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>10-20 mg oral every 30 min.</td>
<td>50 mg*</td>
<td></td>
</tr>
<tr>
<td><strong>Long term treatment of hypertension</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methyldopa</td>
<td>250 mg BID</td>
<td>2 gram/day</td>
<td>Rarely indicated</td>
</tr>
<tr>
<td>Labetalol</td>
<td>100 mg BID</td>
<td>2400 mg/day</td>
<td></td>
</tr>
<tr>
<td>Atenolol</td>
<td>50 mg QD</td>
<td>100 mg/day</td>
<td>May be associated with IUGR</td>
</tr>
<tr>
<td>Propranolol</td>
<td>40 mg BID</td>
<td>640 mg/day</td>
<td></td>
</tr>
<tr>
<td>Hydralazine</td>
<td>10 mg TID</td>
<td>100 mg/day</td>
<td></td>
</tr>
<tr>
<td>Nifedipine XR</td>
<td>30-60 mg QD</td>
<td>120 mg/day</td>
<td></td>
</tr>
<tr>
<td>Amlodipine</td>
<td>5 mg Daily</td>
<td>10 mg/day</td>
<td>Avoid high dosing in patients with hepatic insufficiency</td>
</tr>
<tr>
<td>Thiazide diuretic</td>
<td>12.5 mg BID</td>
<td>50 mg/day</td>
<td>Use in previously established salt-sensitive hypertension and/or CHF. May be added as second agent</td>
</tr>
<tr>
<td>ACE inhibitors/ARB</td>
<td></td>
<td></td>
<td>Generally not used in pregnancy</td>
</tr>
</tbody>
</table>