Hypertensive Disorders of Pregnancy Clinical Guidelines

These clinical guidelines are intended to given general guidelines on the care of patients with hypertensive disorders. Individual patient care may require alternative management and MFM Consultation is recommended for atypical/complex patients.

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 2-8% of all pregnancies. In addition, it is found in 14% of multi-fetal gestations and is a recurrence in 18% of all diagnoses. 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.
    b. American College of Cardiology and American Heart Association have changed their criteria for diagnosing hypertension to BP ≥ 130 mmHg systolic and/or ≥ 80 mmHg diastolic. It is reasonable to continue to manage patients in pregnancy as hypertensive based on these definitions if they were previously diagnosed.

2. Proteinuria
    a. Proteinuria ≥ 300 mg in 24 hour urine collection
    b. Protein: creatinine ratio ≥0.3
    Note: Proteinuria is no longer a requirement for diagnosis of pre-eclampsia if severe features are present (listed below) but may be an indicator for further evaluation or a way to distinguish chronic hypertension from superimposed pre-eclampsia if there is new-onset proteinuria.
    ***A spot P:C ratio of <0.15 safely indicates a level of proteinuria <300mg/24hrs. For patients with a P:C >0.15 or abnormal serum creatinine values, a 24hr urine collection is recommended.

3. Severe features:
    a) SBP > 160 mm Hg and/or DBP > 110 mm Hg on two occasions at least 4 hours apart unless IV hypertensive medications are initiated before this time
    b) New onset headache unresponsive to medications or visual disturbances not accounted for by alternative diagnoses
    c) Any sign of end-organ dysfunction
        - Thrombocytopenia- platelet count < 100,000 platelets/mL)
        - Renal insufficiency-serum creatinine doubling or > 1.1 mg/dL in the absence of other renal disease
        - Impaired liver function -severe persistent right upper quadrant (RUQ) or epigastric pain nonresponsive to medications, or elevated serum transaminases to twice upper limit of normal concentrations not accounted for by alternative diagnoses

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)

Classification/Diagnosis

a. Chronic hypertension (CHTN)
    1. Chronic hypertension with super-imposed pre-eclampsia
b. Gestational hypertension (GHTN)
c. Pre-eclampsia
    1. Without severe features
    2. With severe features
d. Eclampsia
e. HELLP

Chronic Hypertension	A. 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 super-imposed 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 diagnosis made postpartum: Resolution prior to 12 wks postpartum (transient hypertension of pregnancy) or persistent beyond 12 wks (chronic hypertension)
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/mm^3), or abnormal liver enzymes
Eclampsia	Development of seizures, 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), with approximately 30% of cases presenting or progressing postpartum. ***up to 15% 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 (BMI>30) (2.47 CI 1.66-3.67)
8. Family history of Pre-eclampsia or eclampsia (2.90, CI 1.70-4.93)
9. AMA > 35
10. Nulliparity (RR 2.91, CI 1.28-6.61)
11. Assisted Reproductive Technology
12. Obstructive Sleep Apnea
13. Black Race
14. Interpregnancy interval of $\geq$ 10 yrs,

III. MANAGEMENT The only definitive cure for pre-eclampsia is delivery. The primary objective of management of pre-eclampsia is always maternal safety. The secondary objective, when possible, is delivery of a mature newborn that will not require intensive and prolonged neonatal care.

Indicated delivery timing:

a. Chronic hypertension not on medications – 38w0d – 39w6d
b. Chronic hypertension controlled on medications – 37w0d – 39w6d
c. Chronic hypertension not well controlled on medications – 36w0d – 37w6d
d. Gestational hypertension – 37w0d
e. Pre-eclampsia without severe features – 37w0d
f. Pre-eclampsia and Gestational Hypertension with severe features and otherwise stable maternal and fetal conditions – 34w0d
g. Pre-eclampsia with severe features, unstable, complicated, or prior to viability – delivery after maternal stabilization

Management Considerations

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) Consider secondary causes of sudden-onset or treatment-refractory hypertension (renal, cardiac, endocrine, medication/substance use, habitus)
d) Vaginal delivery may be attempted in the absence of typical obstetrical indications for cesarean delivery. Cesarean delivery without a trial of labor is reasonable in those < 30 weeks with an unfavorable cervix.
e) Evidence does not mandate magnesium sulfate for pre-eclampsia without severe disease; individualization of care may be necessary in cases with diagnostic confounders.

Expectant Management of Pre-eclampsia

Outpatient management is an option only for women with gestational hypertension or preeclampsia without severe features. Hospitalization is appropriate for women with severe features and for women in whom adherence to frequent monitoring is a concern. 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, and at least weekly measurement of blood pressure and labs to include assessment of protein, platelet counts, and liver enzymes. Ultrasound for EFW should be performed every 2-4 weeks

Maternal and Fetal Inpatient Management of Pre-eclampsia

a) Initial assessment and observation on labor and delivery or antepartum service to determine candidacy for expectant management.
    a. Maternal stabilization
    b. Prolonged maternal BP and symptomatology monitoring
    c. Admission laboratory evaluation
        i. Evaluation of proteinuria with P:C ratio and/or 24hr urine protein.
        ii. CBC, CMP (Cr, AST, ALT), LDH
        iii. Consider uric acid

b) Fetal U/S for EFW if not performed recently. Continuous fetal monitoring until patient stability and candidacy for expectant management confirmed.

c) For patients with severe features, intravenous magnesium sulfate should be initiated at time of admission (6 g bolus followed by 2gm/hr)
    a. Clinical assessments should be performed and documented on hourly basis while magnesium is infusing.
    b. Serum magnesium level should be measured with clinical suspicion for magnesium toxicity (please see section for management of magnesium toxicity
    c. Renal dosing: alternative magnesium dosing and more frequent serum monitoring should be considered in those with renal insufficiency (consider 6gm load only or decreased maintenance infusion)

d) Persistent severe hypertension (>15 minutes) should be treated expeditiously as soon as possible and within 30-60min. *(See Table 1 for Antihypertensive Agents used for urgent blood pressure control)*.

e) Steroids should be administered to patients <34 weeks and patients <37 weeks who meet criteria (See Antenatal Steroid protocol). Betamethasone 12 mg IM q 24 hours x 2 doses is the preferred regimen. Alternatively, dexamethasone 6mg IM q12hrs x 4 doses may be used.

f) Correction of coagulopathy if present.

g) Expectant management is reasonable for women with severe features < 34w0d gestation if clinical maternal and fetal courses are stable and maintained. MFM consultation should be obtained.

h) Delivery is recommended in all women who meet criteria for pre-eclampsia with severe features at ≥ 34w0d. Expectant management of patients with preeclampsia without severe features and reassuring fetal well-being is appropriate until 37 0/7 weeks gestation.

Table 1. Antihypertensive Agents Used for Urgent Blood Pressure Control in Pregnancy

Drug	Dose	Comments	Onset of Action
Labetalol	10–20 mg IV, then 20–80 mg every 10–30 minutes to a maximum cumulative dosage of 300 mg; or constant infusion 1–2 mg/min IV	Tachycardia is less common with fewer adverse effects. Avoid in women with asthma, preexisting myocardial disease, decompensated cardiac function, and heart block and bradycardia.	1–2 minutes
Hydralazine	5 mg IV or IM, then 5–10 mg IV every 20–40 minutes to a maximum cumulative dosage of 20 mg; or constant infusion of 0.5–10 mg/hr	Higher or frequent dosage associated with maternal hypotension, headaches, and abnormal fetal heart rate tracings; may be more common than other agents.	10–20 minutes
Nifedipine (immediate release)	10–20 mg orally, repeat in 20 minutes if needed; then 10–20 mg every 2–6 hours; maximum daily dose is 180 mg	May observe reflex tachycardia and headaches	5–10 minutes

Abbreviations: IM, intramuscularly; IV, intravenously.

Table 2. Common Oral Antihypertensive Agents in Pregnancy

Drug	Dosage	Comments
Labetalol	200–2,400 mg/d orally in two to three divided doses. Commonly initiated at 100–200 mg twice daily	Potential bronchoconstrictive effects. Avoid in women with asthma, preexisting myocardial disease, decompensated cardiac function, and heart block and bradycardia.
Nifedipine	30–120 mg/d orally of an extended-release preparation. Commonly initiated at 30–60 mg once daily (extended-release)	Do not use sublingual form. Immediate-release formulation should generally be reserved for control of severe, acutely elevated blood pressures in hospitalized patients. Should be avoided in tachycardia.
Methyldopa	500–3,000 mg/d orally in two to four divided doses. Commonly initiated at 250 mg twice or three times daily	Safety data up to 7 years of age in offspring. May not be as effective as other medications, especially in control of severe hypertension. Use limited by side effect profile (sedation, depression, dizziness).
Hydrochlorothiazide	12.5–50 mg daily	Second-line or third-line agent

Monitoring of inpatients undergoing expectant management of pre-eclampsia

Maternal Evaluation

a) Monitor blood pressures and symptoms suggestive of severe disease including headaches, visual disturbances, epigastric pain/tenderness.
b) Antihypertensive drugs to maintain blood pressure <160/110.
c) At least weekly labs. Frequency of labs may be adjusted on an individual basis

Fetal Evaluation

a) At least daily NST
b) BPP twice weekly
c) Doppler studies if indicated per FGR protocol
d) Ultrasound for growth every 2-4 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
c. persistent cerebral symptoms, epigastric pain, or RUQ pain refractory/unresponsive to treatment
d. Pulmonary edema
e. Placenta abruption
f. HELLP syndrome
g. Renal failure (Serum creatinine of 1.5 mg/dl in patient with previously normal creatinine)
h. Stroke or Myocardial infarction

Fetal

a. Persistent non-reassuring fetal status
b. Lethal fetal anomalies
c. Fetal death
d. Pre-viable fetus

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

Intrapartum management

a) Monitor BP, neurologic exam, pulse oximetry, and fluid status
b) Continuous fetal monitoring
c) Intravenous magnesium sulfate administration for severe features and should continue for 24 hours postpartum in most cases
    a. Clinical assessments (Cardiovascular and pulmonary exam, deep tendon reflexes, urinary output) should be performed and documented while magnesium is infusing.
d) Indwelling urinary catheter for hourly assessment of urine output while receiving magnesium sulfate

Postpartum management

a) Continue to monitor BPs and symptoms in the postpartum period.
b) Patients with HELLP syndrome should have CBC and liver enzymes monitored at least at 12-hour intervals until improvement noted.
c) If hypertension persists after delivery, antihypertensive medication may need to be prescribed prior to hospital discharge.
d) NSAIDs should continue to be used preferentially over opioid analgesics.
e) Patients should return for blood pressure check in clinic 3-10 days post-delivery. For patients sent home on medications, return visit in 3 days is recommended and for those without medications, 7-10 days.
f) If the hypertension persists beyond 12 weeks postpartum, the diagnosis of chronic hypertension should be considered and the patient referred to their primary care physician.

IV. COMPLICATIONS OF PRE-ECLAMPSIA

HELLP (Hemolysis, Elevated Liver enzymes, and Low Platelets)

Diagnostic criteria:

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:

a) Transfer or admission to a tertiary care center
b) Initial assessment and management as severe pre-eclampsia (See above).
c) Control severe hypertension and initiate magnesium sulfate infusion.
d) Immediate delivery should be performed in patients at or beyond 34 weeks gestation
e) In patients < 34 0/7 wks, expectant management x 48 hours can be considered in stable patients to administer glucocorticoids for fetal benefits
f) Mode of delivery is individualized based on maternal condition and cervical exam.
g) For patients requiring cesarean delivery, general anesthesia likely for patients with platelet count <80,000/mm3 or rapidly down-trending platelets.
h) Platelet transfusion prior to surgery if platelet count <50,000/mm3
i) Postoperative platelet transfusions as needed
j) CBC and liver enzymes monitored at least at 12-hour intervals until improvement noted
k) Inpatient monitoring for at least 72 hours postpartum.

Eclampsia Management

The main therapy is supportive care and initiation of safety measures to avoid maternal injury.

a) Monitor VS and Maintain oxygenation to mother and fetus
    a. Oxygen
    b. Pulse oximetry
    c. Control severe hypertension
b) Minimize aspiration
    a) Lateral decubitus position
    b) Suctioning of vomitus and oral secretions
c) Initiate MgSO4 to prevent recurrent seizures
d) Fetal heartrate decelerations, even bradycardia, may occur during and after eclamptic seizures due to hypoxia and hypercarbia. Delivery should not be attempted until maternal stabilization, and often maternal resuscitation is followed by normalization of the fetal tracing.
e) Delivery should occur in a timely fashion after maternal stabilization
    a. Eclampsia by itself is not an indication for cesarean delivery.

b. The method of delivery should depend on factors such as gestational age, fetal presentation, and cervical exam
c. A high rate of failure may be anticipated with induction or augmentation in pregnancies less than 30 weeks gestation if the patient is not in labor and Bishop score is unfavorable. In these cases, it may be preferable to opt for cesarean delivery without further delay.

g) Consider head imaging and intubation in cases refractory to magnesium sulfate

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)
    a. Goal therapeutic range of 4.8-9.6 mg/dL (4-8 mEq/L)
3. Additional 2-4 g IV over 5–10 min can be given with persistent convulsions and may be repeated if necessary.
4. If no IV access is anticipated for a prolonged period: 10g IM loading dose can be given divided in 2 doses (5g injection into 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 (sodium amobarbital (250mg IV in 3 minutes), thiopental, or phenytoin (1250mg IV at a rate of 50mg/minute).

Serum magnesium levels and associated clinical findings

Loss of patellar reflex	8–12 mg/dL
Feeling of warmth, flushing	9–12 mg/dL
Double vision	10–12 mg/dL
Somnolence	10–12 mg/dL
Slurred speech	10–12 mg/dL
Muscular paralysis	15–17 mg/dL
Respiratory paralysis	>12 mg/dL
Cardiac arrest	24-30 mg/dL

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

References:

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Updated August 2022

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