Postpartum Hypertension: Etiology, Diagnosis, and Management

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Objectives

1. To assist providers in identifying postpartum HTN.
2. To provide guidance in the evaluation of postpartum HTN.
3. To provide instructions for the management of acute severe and persistent postpartum HTN.

Background: Hypertension in Pregnancy

- Affects up to 10% of pregnancies
- Can have devastating consequences including
  - Maternal stroke
  - Maternal death
- Risk of maternal stroke increases around pregnancy
  - Greatest risk during delivery and postpartum (2 wk)
  - 3-fold increased risk compared controls

Taskforce on Hypertension in Pregnancy. *Obstet Gynecol*, 2013.
Magee L et al. *Cochrane Database Syst Rev*, 2013.

Postpartum Physiology

- BP initially decreases postpartum
  - Then peaks 3-6 days postpartum
  - Secondary to mobilization of sodium and free water to intravascular compartment

- Antepartum preeclampsia managed with delivery
  - Is postpartum preeclampsia a separate entity?

Taskforce on Hypertension in Pregnancy. *Obstet Gynecol*, 2013.
Magee L et al. *Cochrane Database Syst Rev*, 2013.

Background Continued

- True incidence postpartum HTN not known
  - best estimates: 0.3-27.5% of all HTN complicating pregnancy

- Up to 44% of eclampsia occurs postpartum
  - most often within 48hrs of delivery.

Taskforce on Hypertension in Pregnancy. *Obstet Gynecol*, 2013.
Sibai et al. *Am J Obstet Gynecol*, 2012.
Douglas et al. *BMJ*, 1994.

Definitions

- **Definition HTN complicating pregnancy:**
  - SBP ≥ 140 mmHg and/or
  - DBP ≥ 90 mmHg
  - ≥ 2 readings 4hr apart

- **Severe HTN :**
  - SBP ≥ 160 mmHg and/or
  - DBP ≥ 110 mmHg
  - ≥ 2 readings repeated at a short interval (minutes)

Taskforce on Hypertension in Pregnancy. *Obstet Gynecol*, 2013.

Diagnostic Evaluation

- Discontinue all medications associated with HTN:
  - NSAIDS (ibuprofen, Toradol)
  - Methylergonovine (Methergine)

- Exclude HTN complicating pregnancy (GHTN and preeclampsia) from secondary causes for maternal HTN

Makris et al. *Am J Obstet Gynecol*, 2004.

Diagnosis of HTN Complicating Pregnancy

- Diagnostic categories:
  - Gestational HTN
  - Preeclampsia with severe features
  - Preeclampsia without severe features
  - Worsening CHTN
  - Superimposed preeclampsia
    - Further classified into with and without severe features

- HTN complicating pregnancy can persist 6-12 wks postpartum

Sibai et al. *Am J Obstet Gynecol*, 2012.
Mikami et al. *J Obstet Gynecol Res*, 2014.

Hypertensive Disorders of Pregnancy

TABLE 2-1. Diagnostic Criteria for Preeclampsia ⇦

Blood pressure	• Greater than or equal to 140 mm Hg systolic or greater than or equal to 90 mm Hg diastolic on two occasions at least 4 hours apart after 20 weeks of gestation in a woman with a previously normal blood pressure • Greater than or equal to 160 mm Hg systolic or greater than or equal to 110 mm Hg diastolic, hypertension can be confirmed within a short interval (minutes) to facilitate timely antihypertensive therapy
and	
Proteinuria	• Greater than or equal to 300 mg per 24 hour urine collection (or this amount extrapolated from a timed collection) or • Protein/creatinine ratio greater than or equal to 0.3* • Dipstick reading of 1+ (used only if other quantitative methods not available)
Or in the absence of proteinuria, new-onset hypertension with the new onset of any of the following:	
Thrombocytopenia	• Platelet count less than 100,000/microliter
Renal insufficiency	• Serum creatinine concentrations greater than 1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease
Impaired liver function	• Elevated blood concentrations of liver transaminases to twice normal concentration
Pulmonary edema	
Cerebral or visual symptoms	

Hyperten

Taskforce on Hypertension in Pregnancy. *Obstet Gynecol*, 2013.

Classification

Diagnosis	Criteria
Gestational hypertension	New onset blood pressure elevation after 20 week gestation ***without*** ▪ Proteinuria ▪ "Atypical (severe) features"
Preeclampsia	New onset blood pressure elevation after 20 week gestation ***and proteinuria*** ▪ With or without severe features
Worsening chronic hypertension	Does not meet criteria for superimposed preeclam
Superimposed preeclampsia	Meets diagnostic criteria for superimposed preeclampsia: • Increase in BP from baseline • New onset or sudden change in proteinu • New onset laboratory findings • New onset symptoms

Severe Features

- SBP ≥160 mmHg or DBP ≥110 mmHg
- Thrombocytopenia (platelets <100,000/microliter)
- Impaired liver function (LFTs 2x normal or symptoms)
- Renal insufficiency (Cr ≥ 1.1mg/dL or 2x normal)
- Pulmonary edema
- Cerebral or visual disturbances

Superimposed Preeclampsia Diagnosis

- Increase in BP from baseline
- New onset proteinuria or sudden increase
- New onset laboratory findings
- New onset symptoms

Secondary Causes of Hypertension

- Secondary hypertension
  - Attributable to an underlying medical condition
  - Can present initially postpartum

- Work-up for secondary causes should be pursued if HTN is
  - Severe
  - Resistant
  - Hypokalemia (K <3mEq/L)
  - Abnormal Cr (≥ 1.1mg/dL)
  - Strong family history of kidney disease

Secondary Causes of Hypertension

Diagnosis	Diagnostic clues
Hypertensive disorder of pregnancy	Blood pressure peaks days 3-6 postpartum, absence of other signs/symptoms below
Renovascular hypertension	Abdominal bruit
Primary kidney disease	Elevated creatinine or abnormal UA
Primary aldosteronism	Hypernatremia or hypokalemia
Sleep apnea	Obese patient who snores
Pheochromocytoma	Paroxysmal hypertension
Cushing's disease	Classic signs of Cushing's (buffalo hump, moon facies, striae, acne, abdominal obesity)
Hyperthyroidism	Vascular reactivity

Diagnosis of Secondary Hypertension

- ***Diagnostic Testing***
  - TSH with reflex FT4
  - CMP = Electrolytes (Na, K) and creatinine
  - Renal US with Doppler flow
  - 24-hour urine for catecholamines/metanephrines
    - Alternative serum plasma fractionated metanephrines
  - 24-hour urinary free cortisol (only if clinical sx)
  - Polysomnography ("sleep study")

Management

- Management often required before diagnosis established
  - Severe HTN can cause maternal stroke

CO. 623. *Obstet Gynecol*, 2015

Management

- ACOG: Treat severe HTN sustained over 15 min
  - During pregnancy or in the postpartum period

CO. 623. *Obstet Gynecol*, 2015

ACOG Committee Opinion 623 (February 2015)

Emergent Therapy for Acute-Onset, Severe Hypertension During Pregnancy and the Postpartum Period

- Provide 3 "order sets" for agent as first-line acute Rx
  - IV labetalol
  - IV hydralazine
  - PO nifedipine

Labetalol for Initial First-Line Management

1. Monitor fetus if viable
2. BP ≥ 160/110 mmHg on 2 occasions over 15 min
3. Labetalol 20mg IV over 2 min
4. Repeat BP in 10 min
5. If continues to exceed threshold, labetalol 40mg IV (2 min)
6. Repeat BP in 10 min
7. If continues to exceed threshold, labetalol 80mg IV (2 min)
8. Repeat BP in 10 min
9. **If continues to exceed threshold, transition to hydralazine**

Hydralazine for Initial First-Line Management

1. Monitor fetus if viable
2. BP ≥ 160/110 mmHg on 2 occasions over 15 min
3. Hydralazine 5 or 10 mg IV over 2 min
4. Repeat BP in 20 min
5. If continues to exceed threshold, hydralazine 10mg (2 min)
6. Repeat BP in 20 min
7. If continues to exceed threshold, hydralazine 10mg (2 min)
8. Repeat BP in 20 min
9. **If continues to exceed threshold, transition to labetalol**

Nifedipine for Initial First-Line Management

1. Monitor fetus if viable
2. BP ≥ 160/110 mmHg on 2 occasions over 15 min
3. Nifedipine 10 mg PO
4. Repeat BP in 20 min
5. If continues to exceed threshold, nifedipine 20 mg PO
6. Repeat BP in 20 min
7. If continues to exceed threshold, nifedipine 20 mg PO
8. Repeat BP in 20 min
9. **If continues to exceed threshold, transition to labetalol**

Acute Severe HTN Control

- Maximum dose (short-acting)
  - Labetalol = 300mg
  - Hydralazine = 25mg
  - Nifedipine = 120mg
- Labetalol and hydralazine first line
  - Nifedipine may also be used
- Nifedipine may be safely used in women on MgSO4 seizure PPX

CO. 623. *Obstet Gynecol*, 2015

So which is better postpartum?

- Only one prospective trial looked specifically postpartum.

Management of Severe Hypertension in the Postpartum Period with Intravenous Hydralazine or Labetalol: A Randomized Clinical Trial

Paulino Vigil-De Gracia M.D., MSPOG, FACOG,
Esteban Ruiz M.D., Juan C. López M.D.,
Ilka Alveo de Jaramillo, Juan C. Vega-Maleck M.D., and
Jaime Pinzón M.D., MSPOG, FACOG, For the HYLA
treatment investigators

Vigil de Garcia. *Hypertens Pregnancy*, 2007.

Vigil de Garcia et al

- **Objective**
  - Determine safety and efficacy for IV hydralazine and IV labetalol postpartum

- Randomized 82 women with severe postpartum HTN
  - IV hydralazine (N=42)
  - IV labetalol (N=40)

- **Primary endpoint**
  - Successful lowering of maternal BP
  - Other secondary outcomes

Methods

- Hydralazine
  - 5 mg slow IV bolus
  - Repeated Q 20 min
  - Max 5 doses (25 mg)

- Labetalol
  - 20mg IV bolus
  - 40mg IV bolus if not effective (20 min)
  - 80mg IV bolus if not effective (Q 20 min to total 300 mg)

Results

Table 2: Maternal outcome.

Variable	Hydralazine (N = 42)	Labetalol (N = 40)
Symptoms		
Women with symptoms*, n(%)	9 (21.4)	7 (17.5)
Palpitations	3 (7.1)	1 (2.5)
Headache	2 (4.7)	1 (2.5)
Tachycardia ≥ 100 beats/min, n(%)	2 (4.7)	2 (5.0)
1–2 doses for effective BP control, n(%)	35 (83.3)	35 (87.5)
3–4 doses for effective BP control, n(%)	7 (16.7)	4 (10.0)
Persistent severe hypertension, n(%)	0 (0)	1 (2.5)
HELLP syndrome, n(%)	2 (4.7)	1 (2.5)
Eclampsia, n(%)	0 (0)	1 (2.5)
Oliguria, n(%)	3 (7.1)	2 (5.0)

BP = Blood pressure, SBP = systolic blood pressure. *Some women had more than one symptom.
All p values > 0.05.

Conclusions

- No significant differences for severe HTN or maternal effects
- Only one case of persistent HTN (labetalol group)
- ***IV hydralazine and labetalol both safe and effective***

Indirect Evidence?

A randomized, double-blind trial of oral nifedipine and intravenous labetalol in hypertensive emergencies of pregnancy

Stephen T. Vermillion, MD, James A. Scardo, MD, Roger B. Newman, MD, and Suneet P. Chauhan, MD

Charleston, South Carolina

- Randomized double-blind trial in 50 peripartum women
- Fewer than half patients enrolled were postpartum

Vermillion. *Am J Obstet Gynecol*, 1999.

Methods

- Oral nifedipine
  - 10 mg PO initial dose
  - 20 mg PO Q 20 min x 5 doses
- IV labetalol
  - 20 mg IV
  - 40 mg IV
  - 80 mg IV x 3 doses
- Blind cross-over if necessary

Results

- Time to achieve the blood pressure goal
  - Shorter with nifedipine (P=0.002)
    - Nifedepine (mean ± SD, 25 ± 13.6 minutes)
    - Labetalol (43.6 ± 25.4 minutes)

- No need for cross-over (use of other drug) in either group

- Both safe and effective but **nifedipine works faster**

Oral Nifedipine or Intravenous Labetalol for Hypertensive Emergency in Pregnancy

A Randomized Controlled Trial

- Third prospective trial comparing these meds
- Performed entirely antepartum
- Enrolled 60 women with severe HTN

Shekhar. *Obstet Gynecol*, 2013.

Methods and Results

- Randomized to either
  - Nifedipine 10 mg PO Q 20 min x 5 doses
  - Labetalol 20 mg, 40 mg, 80 mg, 80 mg, 80 mg IV

- Time to achieve BP control faster with nifedipine (p=0.008)
  - Nifedipine = 40 min
  - Labetalol = 60 min

- Conclusions: Nifedipine superior to labetalol

When to use MgSO4 seizure prophylaxis?

- No studies have investigated de novo postpartum preeclampsia
  - Does magnesium prevent seizures in this group?

- What is the evidence?

Do women with pre-eclampsia, and their babies, benefit from magnesium sulphate? The Magpie Trial: a randomised placebo-controlled trial

*The Magpie Trial Collaborative Group**

- Multinational placebo controlled trial involving >10,000 women
- Included women with preeclampsia in labor or <24 hours PP
- Objective: Determine whether MgSO4 reduces risk seizure?
- 1300+ were enrolled postpartum

Duley. *Lancet*, 2002.

Results

- Risk of seizure reduced in all women receiving MgSO4
  - 0.8% versus 1.9% ($p<0.001$)

- Number needed to treat for all types HTN 91
  - NNT for severe preeclampsia 63
  - NNT for those without severe 109

Results

- MgSO4 did not lower seizure risk in women randomized PP
  - 0.62% versus 1.14% (p >0.10)

- Study not powered for this outcome

In women diagnosed with eclampsia postpartum?

- The Collaborative Eclampsia Trial
  - Involved 1667 women with eclampsia
  - Randomized to MgSO4 vs diazepam, MgSO4 vs phenytoin

- 419 women diagnosed postpartum

The Eclampsia Trial Collaborative Group. *Lancet*, 1995.

Results

- MgSO4 decreased risk of recurrent sz compared to diazepam
  - 10.9% versus 29.9% (RR: 0.37, 95% CI: 0.21–0.64)

- No difference between MgSO4 and phenytoin
  - 6.3% versus 14.7% (RR 0.43, 95% CI: 0.15–1.20)

How long postpartum should we treat?

- New onset preeclampsia with severe features or severe GHTN
  - Can be diagnosed several weeks PP (up to 6-12 weeks)
- How far out postpartum should we initiate $MgSO_4$ therapy?
  - The answer is unknown
- Risk of eclampsia highest in first week postpartum
  - **Prudent to treat at least for the first postpartum week**

Persistent Postpartum HTN

- Persistent postpartum HTN
  - ≥ 2 BPs ≥ 150 mmHg SBP and/or ≥ 100 mmHg DBP

- ACOG recommendation
  - Start a long acting oral antihypertensive agent

So which is better?

- Oral nifedipine versus oral labetalol
  - Both are commonly used for this purpose
  - Both are considered compatible with breastfeeding

Persistent Postpartum Hypertension

- Only one randomized prospective trial
  - Investigated the management of persistent postpartum HTN
- Sharma et al
  - Randomized 50 women with persistent HTN
  - Received oral labetalol or oral nifedipine
- Objective:
  - Determine which results in shorter time to achieve BP control

Outcomes

- Primary outcome: **Time to sustained BP control**
  - Defined as the absence of severe HTN for ≥ 12 hours.

- Secondary outcomes:
  - Postpartum length of stay
  - Need for increased drug dosing
  - Need for additional oral antihypertensive agents
  - Patient reported side effects

Methods

- Conducted a randomized controlled trial
  - Between June 2014 and June 2015
  - Cedars-Sinai Medical Center in Los Angeles, CA

- Included women who
  - Delivered at ≥ 32 weeks gestation
  - With persistent postpartum HTN (BP ≥ 150/100 mmHg)
  - Requiring an oral antihypertensive agent

Methods

- Included women with
  - Gestational HTN
  - Preeclampsia
  - Chronic HTN not previously on medication.
- Permission granted by Primary OB for enrollment
- Written informed patient consent was obtained

Medication Titration

- Patients randomized to
  - Procardia 30mg PO XL daily
  - Labetalol 200mg PO BID

- Medication was increased to achieve BP control
  - Procardia: 30 -> 60 -> 90 mg daily
  - Labetalol: 200 -> 400 -> 800 mg BID

- If maximum dose of one med was achieved without control,
  - Alternative med added at the lowest dose
  - Alternative med increased to achieve control

Results

	Labetalol (N=25)	Nifedipine (N=25)	P-value
Time to control (hours)	37.6 (32.5)	38.2 (27.6)	0.51
Required additional oral agent for control	3 (12%)	2 (8%)	0.64
Required increased dose for control	9/27 (33%)	16/28 (57%)	0.08
Discharged at starting medication dosage	16/21 (76%)	10/22 (46%)	0.04

Persistent Postpartum Hypertension

- No difference was detected in
  - Time to blood pressure control
  - Length of postpartum stay.
- Labetalol achieved control
  - At a lower dose
  - With fewer side effects.
- **Labetalol may be the preferred initial oral antihypertensive agent for postpartum HTN management.**

Outpatient Follow-up

- Office visit
- Home BP monitoring

Can we prevent postpartum HTN?

- Several studies have investigated the prophylactic treatment
  - Women with antepartum HTN
  - Prevent severe HTN and shorten hospital stay

- These studies demonstrate mixed results

Postpartum Preeclampsia Management With Furosemide: A Randomized Clinical Trial

- 264 postpartum women with preeclampsia
  - Had completed MgSO4 therapy
  - Began to diurese
- Randomized to either furosemide 20mg PO daily or no therapy.
- Furosemide treatment resulted in:
  - More rapid resolution of HTN
  - Decreased need for antihypertensive therapy

Ascarelli et al. *Obstet Gynecol*, 2005.

A randomised placebo controlled trial of loop diuretics in moderate/severe pre-eclampsia, following delivery

:

- 19 women with preeclampsia

- Randomized: furosemide 40mg PO daily for 7 days or placebo

- No difference in the need for antihypertensive therapy use PP
  - Type II error?

Matthews et al. *J Obstet Gynecol*, 1997.

The use of nifedipine during the postpartum period in patients with severe preeclampsia

- 31 women with an antenatal diagnosis of preeclampsia
- Randomized to
  - Nifedipine 10mg orally Q 4hrs post-delivery
  - Placebo

Barton et al. *Am J Obstet Gynecol*, 1990.

Results

- Nifedipine group had
  - Higher UOP in the first 24hrs postpartum
  - Reduction in MAP from 18 to 24 hours postpartum.

- Clinical utility of these findings?

The Verdict for Prevention

- Inconsistencies in these results
- Prophylactic treatment not recommended

Conclusions

- Postpartum HTN is likely common common
- Postpartum HTN can have devastating consequences:
  - Maternal stroke and death
- Providers must to be aware of this and educate patients

Conclusions

- Postpartum severe acute HTN should be treated
  - First line ?oral nifedipine
  - Alternative IV hydralazine or labetalol

Conclusions

- Women with persistent postpartum HTN should be treated
  - Preferably with oral labetalol or oral nifedipine