Pharmacology Review:

Medications for Managing Hypertensive Conditions in Pregnancy and Postpartum

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Disclosure

- I have no disclosures

Objectives

- To discuss chronic mild to moderate hypertension control and goal levels based on the CHIPs and CHAPs studies
- To discuss the pharmacology of mild to moderate hypertension control
- Review preeclampsia pharmacological control
- Demonstrate order sets and protocols utilized at Billings Clinic to address acute preeclampsia control
- Review information about possible future states of hypertension control in pregnancy

Pregnancy Hypertension and Complications

- 10% of pregnancies have hypertension
- 1% have preexisting hypertension
- 5-6% of pregnancies with hypertension will not have proteinuria
- 2-8% of pregnancies will develop preeclampsia
- 20-50% of pregnancies with chronic hypertension may develop superimposed preeclampsia
- 16% of maternal deaths associated with hypertension
- Hypertension in pregnancy is associated with 3-5x risk for:
  - Placental abruption, preeclampsia, preterm birth, small for gestational age birth weight, and perinatal death
- Hypertension is pregnancy is also associated with 5-10x risk for:
  - Maternal heart failure, death, pulmonary edema, acute kidney injury/failure and stroke
- In non-pregnant patients, treatment is recommended when BP exceeds 140/90 (2017 ACC/AHA)
- Treatment in pregnancy has shown reduction of severe hypertension, but fails to improve maternal, fetal, or neonatal outcomes
- Tight control of BP has been associated with poor fetal growth and well being, especially when atenolol is utilized as a treatment
- Consensus to treat pregnancy with severe hypertension (>160/110)

Pregnancy Hypertension and Complications

- Most recent ACOG bulletin on chronic hypertension #203(2019) recommends:
  - If pt meets ACC and AHA criteria for stage 1 hypertension (systolic 130-139, diastolic 80-89) prior to pregnancy, patient should continue appropriate therapy
  - For patients who have not previously met this level consider a conservative approach and utilize higher degree of observation
  - New diagnosis stage 1 hypertension in pregnancy doesn't require medications based on this bulletin
- There has been a 20 week cutoff in pregnancy
  - Hypertension prior to this has been attributed to chronic hypertension
  - Hypertension after 20 weeks is attributed to preeclampsia or gestational hypertension
- A confounder in the diagnosis of hypertension during pregnancy
  - A physiologic decrease in vascular resistance(30%) begins at 7wks, it peaks at 16-18wks
  - This reduction in vascular resistance can cause a 10% reduction in BP
  - BP typically returns to pre-pregnancy levels in the 3rd trimester

Recent Studies and Literature

- CHIPS - Control of hypertension in pregnancy – Magee, L.A., et.al NEJM 2015 paper
  - Less tight vs tight control of hypertension in pregnancy – paper looked at 987 women, singleton pregnancy, with gest age of 14-34wks, less tight (control group) diastolic goal was 100mmHG, while tight control (experimental group) had a diastolic goal of 85mmHG.
  - Primary outcome – pregnancy loss or NICU care required for more than 48 hours – no difference
  - Secondary outcomes – no difference in SGA, Severe hypertension was found less often in tight control group
  - Observed BP mean, Less tight vs tight from randomization to delivery 138.8/89.9 vs 133.1/85.3, Primary medication was labetalol (~69%)

Table 2. Primary and Other Perinatal Outcomes.*

Variable	Less-Tight Control (N=493)	Tight Control (N=488)	Adjusted Odds Ratio (95% CI)†
Primary outcome — no. (%)	155 (31.4)	150 (30.7)	1.02 (0.77–1.35)
Pregnancy loss — no. (%)	15 (3.0)	13 (2.7)	1.14 (0.53–2.45)
Miscarriage	0	1 (0.2)	
Ectopic pregnancy	0	0	
Elective termination‡	1 (0.2)	1 (0.2)	
Perinatal death	14 (2.8)	11 (2.3)	1.25 (0.56–2.81)
Stillbirth	12 (2.4)	7 (1.4)	
Neonatal death	2 (0.4)	4 (0.8)	
High-level neonatal care for >48 hr — no./total no. (%)§	141/480 (29.4)	139/479 (29.0)	1.00 (0.75–1.33)
Gestational age at delivery — wk	36.8±3.4	37.2±3.1	
Small-for-gestational-age newborns — no./total no. (%)¶			
Birth weight <10th percentile	79/491 (16.1)	96/488 (19.7)	0.78 (0.56–1.08)
Birth weight <3rd percentile	23/491 (4.7)	26/488 (5.3)	0.92 (0.51–1.63)
Other perinatal outcomes of liveborn infants			
Respiratory complications — no./total no. (%)			
Clinical respiratory problem	82/480 (17.1)	67/479 (14.0)	1.19 (0.83–1.71)
Administration of oxygen beyond the first 10 min of life	34/479 (7.1)	25/477 (5.2)	1.24 (0.72–2.14)
Ventilatory support (with or without intubation) beyond the first 10 min of life	35/478 (7.3)	38/479 (7.9)	0.86 (0.53–1.40)
Use of surfactant	28/480 (5.8)	26/479 (5.4)	0.97 (0.55–1.69)
At least one serious neonatal complication — no./total no. (%)‖	40/480 (8.3)	40/479 (8.4)	0.96 (0.60–1.52)

Table 3. Secondary and Other Maternal Outcomes.*

Variable	Less-Tight Control (N=493)	Tight Control (N=488)	Adjusted Odds Ratio (95% CI)†
Serious maternal complications — no. (%)‡	18 (3.7)	10 (2.0)	1.74 (0.79–3.84)
Uncontrolled hypertension	0	0	
Transient ischemic attack or stroke	0	1 (0.2)	
Pulmonary edema	2 (0.4)	1 (0.2)	
Renal failure	0	1 (0.2)	
Transfusion§	16 (3.2)	8 (1.6)	
Placental abruption — no. (%)	11 (2.2)	11 (2.3)	0.94 (0.40–2.21)
Severe hypertension — no. (%)	200 (40.6)	134 (27.5)	1.80 (1.34–2.38)
Preeclampsia — no./total no. (%)	241/493 (48.9)	223/488 (45.7)	1.14 (0.88–1.47)
Defined only by new proteinuria¶	148/493 (30.0)	132/488 (27.0)	1.08 (0.74–1.59)
At least one symptom of preeclampsia‖	171/493 (34.7)	156/488 (32.0)	1.11 (0.84–1.46)
Abnormal laboratory test results			
Platelet count <100×10^9/liter	21/493 (4.3)	8/488 (1.6)	2.63 (1.15–6.05)
Elevated AST or ALT level, with symptoms	21/492 (4.3)	9/488 (1.8)	2.33 (1.05–5.16)
Elevated LDH level, with symptoms	16/491 (3.3)	9/488 (1.8)	1.78 (0.77–4.11)
HELLP syndrome**	9/493 (1.8)	2/488 (0.4)	4.35 (0.93–20.35)
Serum creatinine level >2.3 mg/dl	0	1/488 (0.2)	

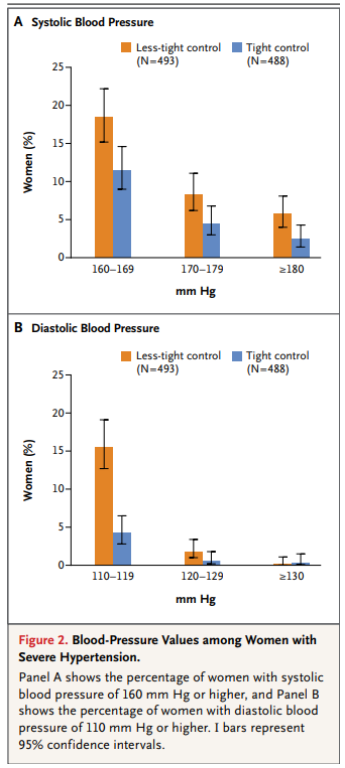

Figure 2. Blood-Pressure Values among Women with Severe Hypertension.
Panel A shows the percentage of women with systolic blood pressure of 160 mm Hg or higher, and Panel B shows the percentage of women with diastolic blood pressure of 110 mm Hg or higher. I bars represent 95% confidence intervals.

Recent Studies and Literature

- ACOG Bulletin #203– Chronic Hypertension in Pregnancy, Vidaeff, A., et. Al 2019
  - Review article discussing management of chronic hypertension in pregnancy considering the 2017 ACC/AHA recommendations of treating non-pregnant patients with stage 1 hypertension = BP >130/80, Stage 2 hypertension =BP>140/90, but less than severe hypertension = BP >160/110
  - Article discusses the lack of evidence for treating BP in chronic hypertension < severe range = BP >/= 160/110
  - If a woman has been started on medications prior to pregnancy it is reasonable to continue treatment, it may also be reasonable to stop therapy especially during the first 2 trimesters if BP is not within severe range
  - Noted CHIPS study and that the only difference between tight and less tight was higher incidence of severe range BP in the less tight control group. Mentioned the CHAPS study was in progress. Noted 2014 Cochrane review showing evidence for treatment of mild to moderate hypertension remains unclear
  - States initiation of medication is recommended for chronic hypertension with BP > 160/110, but allows for initiation with lower BP with comorbidities
  - Recommends:
    - BP correction to target BP >120/80 for maintenance of uteroplacental blood flow
    - Initiation of 81 mg aspirin for those at risk of preeclampsia with gestational age between 12-28 wks

Recent Studies and Literature

- ACOG Bulletin #203– Chronic Hypertension in Pregnancy, Vidaeff, A., et. Al 2019

AHA/ACC 2017 Hypertension Diagnostic Criteria	
Normal	**Systolic/diastolic <120/80**
Elevated	**Systolic/diastolic = 120-129/80**
Stage 1 Hypertension	**Systolic/diastolic = 130-139/80-89**
Stage 2 Hypertension	**Systolic/diastolic >140/90**

Table 1. American College of Obstetricians and Gynecologists Definitions of Hypertensive Disorders

Disorder	Definition
Hypertension in pregnancy	Systolic blood pressure ≥140 mm Hg or diastolic BP ≥90 mm Hg, or both, measured on two occasions at least 4 hours apart
Severe-range hypertension	Systolic blood pressure ≥160 mm Hg or diastolic BP ≥110 mm Hg, or both, measured on two occasions at least 4 hours apart
Chronic hypertension	Hypertension diagnosed or present before pregnancy or before 20 weeks of gestation; or hypertension that is diagnosed for the first time during pregnancy and that does not resolve it the postpartum period
Chronic hypertension with superimposed preeclampsia	Preeclampsia in a woman with a history of hypertension before pregnancy or before 20 weeks of gestation

Risks of chronic hypertension in pregnancy	
Maternal Risks	**Fetal Risks**
Death	Stillbirth or perinatal death
Stroke	Growth restriction
Pulmonary Edema	Preterm birth
Renal insufficiency and failure	Congenital anomalies
Myocardial infarction	
Preeclampsia	
Placental abruption	
Cesarean delivery	
Postpartum hemorrhage	
Gestational diabetes	

Recent Studies and Literature

- ACOG Bulletin #203– Chronic Hypertension in Pregnancy, Vidaeff, A., et. Al 2019

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

Table 3. Antihypertensive Agents Used for Urgent Blood Pressure Control in Pregnancy

Drug	Dosage	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 and fewer adverse effects than other agents. 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.

Recent Studies and Literature

- ACOG Bulletin #203– Chronic Hypertension in Pregnancy, Vidaeff, A., et. Al 2019

Box 4. Sample Order Set for Severe Intrapartum or Postpartum Hypertension Initial First-line Management With Immediate-Release Oral Nifedipine*†

- Notify physician if systolic blood pressure (BP) is greater than or equal to 160 mm Hg or if diastolic BP is greater than or equal to 110 mm Hg.
- Institute fetal surveillance if undelivered and fetus is viable.
- If severe BP elevations persist for 15 minutes or more, administer immediate-release nifedipine capsules (10 mg orally).‡
- Repeat BP measurement in 20 minutes and record results.
- If either BP threshold is still exceeded, administer immediate-release nifedipine capsules (20 mg orally). If BP is below threshold, continue to monitor BP closely.
- Repeat BP measurement in 20 minutes and record results.
- If either BP threshold is still exceeded, administer nifedipine immediate release capsule (20 mg orally). If BP is below threshold, continue to monitor BP closely.
- Repeat BP measurement in 20 minutes and record results.
- If either BP threshold is still exceeded, administer labetalol (20 mg intravenously for more than 2 minutes) and obtain emergency consultation from maternal–fetal medicine, internal medicine, anesthesia, or critical care subspecialists.
- Give additional antihypertensive medication per specific order.
- Once the aforementioned BP thresholds are achieved, repeat BP measurement every 10 minutes for 1 hour, then every 15 minutes for 1 hour, then every 30 minutes for 1 hour, and then every hour for 4 hours.
- Institute additional BP timing per specific order.

Box 5. Sample Order Set for Severe Intrapartum or Postpartum Hypertension Initial First-line Management With Hydralazine*

- Notify physician if systolic BP is 160 mm Hg or more or if diastolic BP is 110 mm Hg or more.
- Institute fetal surveillance if undelivered and fetus is viable.
- If severe BP elevations persist for 15 minutes or more, administer hydralazine (5 mg or 10 mg IV for more than 2 minutes).
- Repeat BP measurement in 20 minutes and record results.
- If either BP threshold is still exceeded, administer hydralazine (10 mg IV for more than 2 minutes). If BP is below threshold, continue to monitor BP closely.
- Repeat BP measurement in 20 minutes and record results.
- If either BP threshold is still exceeded, administer labetalol (20 mg IV for more than 2 minutes). If BP is below threshold, continue to monitor BP closely.
- Repeat BP measurement in 10 minutes and record results.
- If either BP threshold is still exceeded, administer labetalol (40 mg IV for more than 2 minutes) and obtain emergency consultation from maternal–fetal medicine, internal medicine, anesthesia, or critical care subspecialists.
- Give additional antihypertensive medication per specific order.
- Once the aforementioned BP thresholds are achieved, repeat BP measurement every 10 minutes for 1 hour, then every 15 minutes for 1 hour, then every 30 minutes for 1 hour, and then every hour for 4 hours.
- Institute additional BP timing per specific order.

Abbreviations: BP, blood pressure; IV, intravenously.

*Please note there may be adverse effects and contraindications.

Box 6. Sample Order Set for Severe Intrapartum or Postpartum Hypertension, Initial First-line Management With Labetalol*

- Notify physician if systolic BP measurement 160 mm Hg or more or if diastolic BP measurement is 110 mm Hg or more.
- Institute fetal surveillance if undelivered and fetus is viable.
- If severe BP elevations persist for 15 minutes or more, administer labetalol (20 mg IV for more than 2 minutes).
- Repeat BP measurement in 10 minutes and record results.
- If either BP threshold is still exceeded, administer labetalol (40 mg IV for more than 2 minutes). If BP is below threshold, continue to monitor BP closely.
- Repeat BP measurement in 10 minutes and record results.
- If either BP threshold is still exceeded, administer labetalol (80 mg IV for more than 2 minutes). If BP is below threshold, continue to monitor BP closely.
- Repeat BP measurement in 10 minutes and record results.
- If either BP threshold is still exceeded, administer hydralazine (10 mg IV for more than 2 minutes). If BP is below threshold, continue to monitor BP closely.
- Repeat BP measurement in 20 minutes and record results.
- If either BP threshold is still exceeded, obtain emergency consultation from maternal–fetal medicine, internal medicine, anesthesia, or critical care subspecialists.
- Give additional antihypertensive medication per specific order.
- Once the aforementioned BP thresholds are achieved, repeat BP measurement every 10 minutes for 1 hour, then every 15 minutes for 1 hour, then every 30 minutes for 1 hour, and then every hour for 4 hours.
- Institute additional BP timing per specific order.

Abbreviations: BP, blood pressure; IV, intravenously.

*Please note there may be adverse effects and contraindications.

Recent Studies and Literature

- ACOG Bulletin #222– Gestational Hypertension and Preeclampsia, Espinoza, J., et. Al 2020
  - Many risk factors for developing preeclampsia (box1) but important to realize that preeclampsia most often occurs in nulliparous pregnancies with no obvious risk factors
  - Preeclampsia often involves new onset hypertension after 20 weeks. It often presents with proteinuria (300mg/24hr, Protein to creatine ratio of 0.3, dipstick reading of 2+) but not always as some cases have other signs and symptoms without proteinuria
  - In the setting of a BP > 140/90 any of the symptoms of HELLP syndrome are predictive of preeclampsia, other signs and symptoms include; right upper quadrant or epigastric pain, serum creatinine >1.1mg/dL or doubling of it, pulmonary edema, new headache unresponsive to medication and can't be attributed to other etiologies

Box 1. Risk Factors for Preeclampsia

Nulliparity
Multifetal gestations
Preeclampsia in a previous pregnancy
Chronic hypertension
Pregestational diabetes
Gestational diabetes
Thrombophilia
Systemic lupus erythematosus
Prepregnancy body mass index greater than 30
Antiphospholipid antibody syndrome
Maternal age 35 years or older
Kidney disease
Assisted reproductive technology
Obstructive sleep apnea

Box 2. Diagnostic Criteria for Preeclampsia

Blood pressure

- Systolic blood pressure of 140 mm Hg or more or diastolic blood pressure of 90 mm Hg or more on two occasions at least 4 hours apart after 20 weeks of gestation in a woman with a previously normal blood pressure
- Systolic blood pressure of 160 mm Hg or more or diastolic blood pressure of 110 mm Hg or more. (Severe hypertension can be confirmed within a short interval (minutes) to facilitate timely antihypertensive therapy).

Box 2. Diagnostic Criteria for Preeclampsia

and

Proteinuria

- 300 mg or more per 24 hour urine collection (or this amount extrapolated from a timed collection) or
- Protein/creatinine ratio of 0.3 ~~mg/dL~~ or more or
- Dipstick reading of 2+ (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~~ $\times 10^9$/L
- 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
- New-onset headache unresponsive to medication and not accounted for by alternative diagnoses or visual symptoms

Box 3. Preeclampsia with Severe Features

- Systolic blood pressure of 160 mm Hg or more, or diastolic blood pressure of 110 mm Hg or more on two occasions at least 4 hours apart (unless antihypertensive therapy is initiated before this time)
- Thrombocytopenia (platelet count less than 100,~~000~~ $\times 10^9$/L
- Impaired liver function that is not accounted for by alternative diagnoses and as indicated by abnormally elevated blood concentrations of liver enzymes (to more than twice the upper limit normal concentrations), or by severe persistent right upper quadrant or epigastric pain unresponsive to medications
- Renal insufficiency (serum creatinine concentration more than 1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease)
- Pulmonary edema
- New-onset headache unresponsive to medication and not accounted for by alternative diagnoses
- Visual disturbances

Recent Studies and Literature

- ACOG Bulletin #222– Gestational Hypertension and Preeclampsia, Espinoza, J., et. Al 2020
  - Gestational hypertension – BP >/=140/90 after 20 weeks and resolves in the postpartum period
  - Similar therapy and management to preeclampsia without severe features
  - Outcomes generally good still an area of concern:
    - Associated with adverse outcomes
    - 50% of those with gestational hypertension will develop proteinuria or other organ dysfunction
    - Progression is more likely when hypertension occurs prior to 32 wks
  - Aspirin use in women at risk for preeclampsia
    - Low dose aspirin (81mg qday) should be started when pregnancy is between 12-28wk
    - Some studies question the utility of aspirin when started after 16 wks, many other studies have found utility regardless of when it started if it was prior to 28wks
    - Higher doses of 150 mg have been tried in pt between 11-36 weeks, preeclampsia was seen in 1.6% of test group and in 4.3% of the control group

Table 1. Clinical Risk Factors and Aspirin Use*

Level of Risk	Risk Factors	Recommendation
High†	• History of preeclampsia, especially when accompanied by an adverse outcome • Multifetal gestation • Chronic hypertension • Type 1 or 2 diabetes • Renal disease • Autoimmune disease (ie, systemic lupus erythematosus, the antiphospholipid syndrome)	Recommend low-dose aspirin if the patient has one or more of these high-risk factors
Moderate‡	• Nulliparity • Obesity (body mass index greater than 30) • Family history of preeclampsia (mother or sister) • Sociodemographic characteristics (African American race, low socioeconomic status) • Age 35 years or older • Personal history factors (eg, low birth weight or small for gestational age, previous adverse pregnancy outcome, more than 10-year pregnancy interval)	Consider low-dose aspirin if the patient has more than one of these moderate-risk factors§
Low	• Previous uncomplicated full-term delivery	Do not recommend low-dose aspirin

Recent Studies and Literature

- CHAPS - Chronic hypertension and pregnancy – Tita, A.T., et. al NEJM 2022 paper
  - Treatment for mild chronic hypertension during pregnancy. Study looking at 2408 women with an experimental group with mild chronic hypertension (Systolic>140, and/or diastolic >90) and a control group who was not treated unless they experienced severe hypertension(systolic>160, and/or diastolic>110).
  - Patients in treatment group were prescribed labetalol or ER nifedipine, other agents were available if preferred by patient (amlodipine or methyldopa), dose was escalated to maximum tolerable dose prior to starting a second medication
  - Primary outcome was a composite of preeclampsia with severe features occurring up to 2 weeks postpartum, preterm birth prior to 35 wks, placental abruption, fetal or neonatal death
  - Secondary outcomes were; composite of maternal death, admission to ICU, birth prior to 37wks

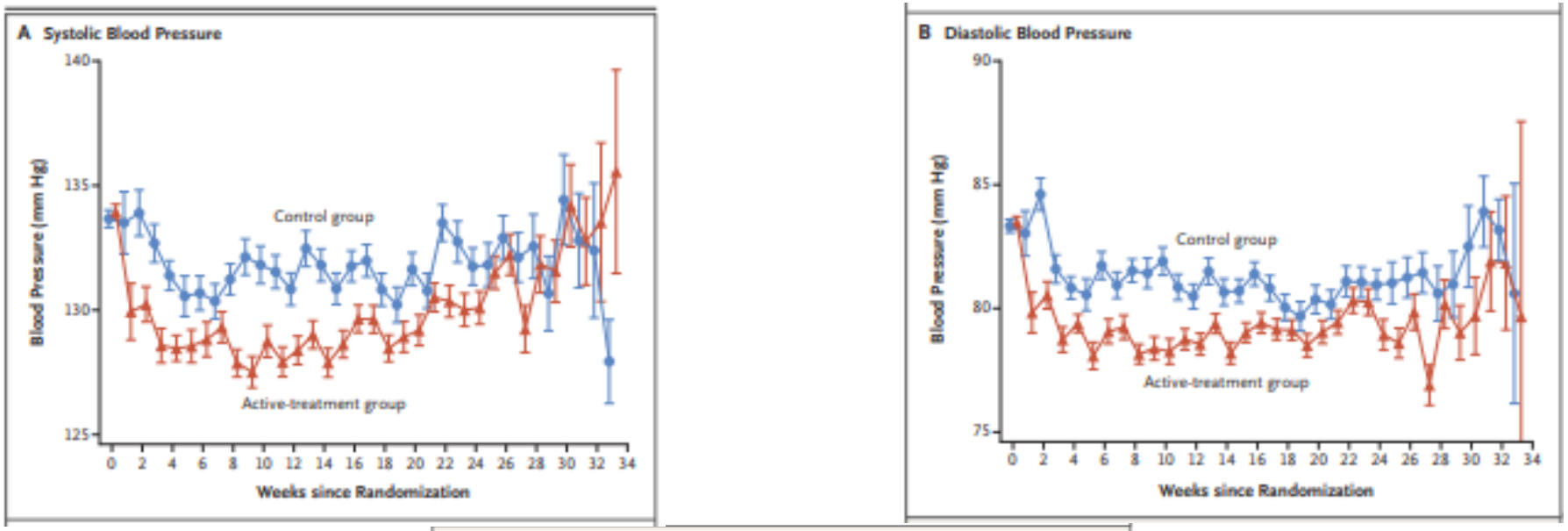

Figure 1. Mean Blood Pressure after Randomization.
Between randomization and delivery, the overall mean blood-pressure level was lower in the active-treatment group than in the control group, both for systolic pressure (129.5 mm Hg vs. 132.6 mm Hg) and for diastolic pressure (79.1 mm Hg vs. 81.5 mm Hg). I bars indicate standard errors.

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Active Treatment (N=1208)	Control (N=1200)
Age — yr	32.3±5.6	32.3±5.8
Race or ethnic group — no. (%)†		
Non-Hispanic White	347 (28.7)	326 (27.2)
Non-Hispanic Black	574 (47.5)	570 (47.5)
Hispanic	238 (19.7)	250 (20.8)
Other	49 (4.1)	54 (4.5)
Mother's type of insurance — no. (%)		
Government-assisted insurance or Medicaid	673 (55.7)	656 (54.7)
Private insurance	459 (38.0)	463 (38.6)
None	60 (5.0)	65 (5.4)
Missing data	16 (1.3)	16 (1.3)
Type of chronic hypertension — no. (%)		
Newly diagnosed	263 (21.8)	258 (21.5)
Diagnosed and receiving medication	677 (56.0)	681 (56.8)
Diagnosed and not receiving medication	268 (22.2)	261 (21.8)
Blood pressure — mm Hg		
Systolic	134.3±12.7	133.7±12.4
Diastolic	83.9±9.5	83.4±9.6
Previous pregnancy — no. (%)	1007 (83.4)	989 (82.4)
Body-mass index‡		
Mean	37.7±10.0	37.5±9.6
Distribution — no. (%)		
<30	295 (24.4)	259 (21.6)
30 to <40	460 (38.1)	517 (43.1)
≥40	434 (35.9)	402 (33.5)
Gestational age <14 wk — no. (%)	496 (41.1)	481 (40.1)
Coexisting illness or lifestyle factor — no. (%)		
Diabetes mellitus	191 (15.8)	189 (15.8)
Current smoker	92 (7.6)	82 (6.8)
Aspirin use	539 (44.6)	536 (44.7)

Recent Studies and Literature

- CHAPS - Chronic hypertension and pregnancy – Tita, A.T., et. al NEJM 2022 paper
  - Primary event in 30.2% of the treatment group, and 37% of the control, p<0.001, adjusted risk ratio was 0.82 this leads to a number needed to treat of 15 to prevent a single outcome
  - Preeclampsia with severe features 23.3% in treatment and 29.1% in control
  - Of note fetal size of less than 10th percentile was 11.2% in treatment and 10.4% in control similar findings for infants found in the 5th percentile of weight for gestational age

Table 2. Primary and Safety Outcomes.

Outcome	Imputation Analysis (N=2408)*		Complete-Case Analysis (N=2325)†			
	Adjusted Risk Ratio (95% CI)	P Value	Active Treatment	Control	Risk Ratio (95% CI)	P Value
			no./total no. (%)			
Primary composite outcome	0.82 (0.74–0.92)	<0.001	353/1170 (30.2)	427/1155 (37.0)	0.82 (0.73–0.92)	<0.001
Preeclampsia with severe features	0.80 (0.70–0.92)		272/1170 (23.3)	336/1155 (29.1)	0.80 (0.70–0.92)	
Medically indicated preterm birth at <35 wk	0.73 (0.60–0.89)		143/1170 (12.2)	193/1155 (16.7)	0.73 (0.60–0.89)	
Placental abruption	0.88 (0.49–1.59)		20/1170 (1.7)	22/1155 (1.9)	0.90 (0.49–1.64)	
Fetal or neonatal death at <28 days	0.81 (0.54–1.22)		41/1170 (3.5)	50/1155 (4.3)	0.81 (0.54–1.21)	
Safety outcome						
Small for gestational age						
<10th percentile	1.04 (0.82–1.31)	0.76	128/1146 (11.2)	117/1124 (10.4)	1.07 (0.85–1.36)	0.56
<5th percentile	0.89 (0.62–1.26)	0.51	58/1146 (5.1)	62/1124 (5.5)	0.92 (0.65–1.30)	0.63

* Shown are the results of multiple imputation analysis performed with the use of multivariable log-binomial regression models to calculate adjusted risk ratios. The missing values were modeled within treatment group with the use of baseline characteristics that included diabetes status (yes or no), treatment status at enrollment (receiving or not receiving blood-pressure medication), age, body-mass index, and elevated blood pressure (≥150 mm Hg systolic or ≥100 mm Hg diastolic) at the first visit.

† Complete-case analysis of the primary outcome included 2325 patients with sufficient data (1170 in the active-treatment group and 1155 in the control group). Complete-case analysis of the safety outcome included 2270 patients with sufficient data (1146 in the active-treatment group and 1124 in the control group); included in this analysis were assessments of data obtained during delivery.

Recent Studies and Literature

- CHAPS - Chronic hypertension and pregnancy – Tita, A.T., et. al NEJM 2022 paper
  - This study confirms the findings of the CHIPS study finding there no differences between group difference in NICU admission, neonatal weight differences or pregnancy loss
  - Of note in CHAPS 47.5% of patients were black whereas in CHIPS only 12.5% were black
  - CHAPS potentially had longer duration of therapy - CHAPS 15.4 wks with tx duration of 21 weeks vs CHIPS 24wks and 12 weeks of treatment duration

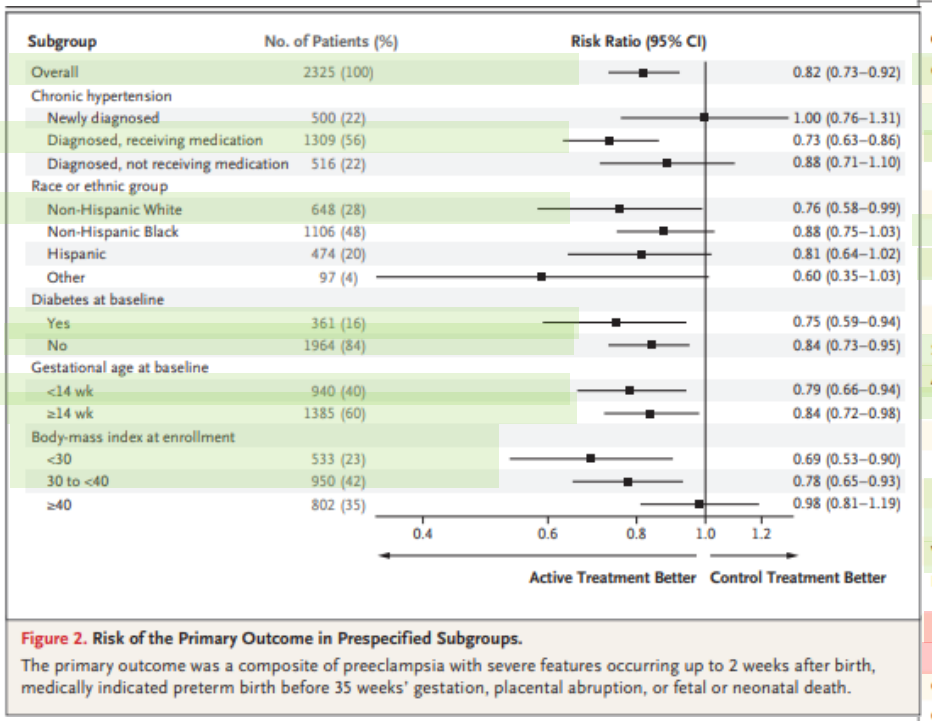

Figure 2. Risk of the Primary Outcome in Prespecified Subgroups.
The primary outcome was a composite of preeclampsia with severe features occurring up to 2 weeks after birth, medically indicated preterm birth before 35 weeks' gestation, placental abruption, or fetal or neonatal death.

Table 3. Maternal Outcomes.*

Outcome	Active Treatment (N=1208)	Control (N=1200)	Treatment Effect (95% CI)†
Composite cardiovascular complications — no. (%)	25 (2.1)	33 (2.8)	0.75 (0.45 to 1.26)
Maternal death	1 (0.1)	2 (0.2)	0.50 (0.05 to 5.47)
Heart failure	1 (0.1)	1 (0.1)	0.99 (0.06 to 15.9)
Stroke	0	0	NA
Myocardial infarction or angina	0	0	NA
Pulmonary edema	5 (0.4)	11 (0.9)	0.45 (0.16 to 1.30)
ICU admission or intubation	12 (1.0)	16 (1.3)	0.75 (0.35 to 1.57)
Encephalopathy	1 (0.1)	0	1.00 (1.00 to 1.00)
Renal failure	9 (0.8)	14 (1.2)	0.64 (0.28 to 1.47)
Severe hypertension — no. (%)	436 (36.1)	531 (44.3)	0.82 (0.74 to 0.90)
Any preeclampsia — no. (%)	295 (24.4)	373 (31.1)	0.79 (0.69 to 0.89)
Severe hypertension plus proteinuria	189 (15.7)	215 (17.9)	0.87 (0.73 to 1.04)
Eclampsia	0	1 (0.1)	NA
HELLP	0	3 (0.3)	NA
Hypertension plus end-organ dysfunction	136 (11.3)	181 (15.1)	0.75 (0.61 to 0.92)
Nonsevere preeclampsia	23 (1.9)	37 (3.1)	0.62 (0.37 to 1.03)
Worsening chronic hypertension — no. (%)	132 (10.9)	156 (13.0)	0.84 (0.68 to 1.04)
Mean blood pressure during prenatal visits — mm Hg‡			
Systolic	129.5±10.0	132.6±10.1	−3.11 (−3.95 to 2.28)
Diastolic	79.1±7.4	81.5±8.0	−2.33 (−2.97 to 0.04)
Gestational age at delivery — wk§	36.6±4.3	36.3±5.1	0.24 (−0.15 to 0.62)
Cesarean delivery — no. (%)	592 (49.0)	582 (48.5)	1.01 (0.93 to 1.10)
Any blood transfusion — no. (%)	46 (3.8)	53 (4.4)	0.86 (0.59 to 1.27)

Table 4. Neonatal Outcomes.*

Outcome	Active Treatment (N=1208)	Control (N=1200)	Treatment Effect (95% CI)†
Composite of severe neonatal complications — no. (%)	24 (2.0)	31 (2.6)	0.77 (0.45 to 1.30)
Bronchopulmonary dysplasia	8 (0.7)	14 (1.2)	0.57 (0.24 to 1.35)
Retinopathy of prematurity	16 (1.3)	20 (1.7)	0.79 (0.41 to 1.53)
Necrotizing enterocolitis	2 (0.2)	2 (0.2)	0.99 (0.14 to 7.06)
Intraventricular hemorrhage, grade 3 or 4	3 (0.3)	4 (0.3)	0.75 (0.17 to 3.32)
Preterm birth at <37 wk — no. (%)	332 (27.5)	377 (31.4)	0.87 (0.77 to 0.99)
Birth weight <2500 g — no. (%)	232 (19.2)	277 (23.1)	0.83 (0.71 to 0.97)
NICU admission — no. (%)	368 (30.5)	402 (33.5)	0.91 (0.81 to 1.02)
Neonatal hospital stay			
Mean no. of days‡	2.8±1.7	2.9±1.7	−0.05 (−0.18 to 0.09)§
≥3 days — no. (%)	590 (48.8)	592 (49.3)	0.98 (0.90 to 1.06)
Ponderal index — g/cm³¶	2.9±3.7	2.7±2.8	0.16 (−0.11 to 0.43)§
Head circumference — cm‖	33.3±3.0	33.0±3.2	0.31 (0.05 to 0.56)§
Placental weight — g**	466.3±177.6	464.6±175.6	1.67 (−17.57 to 20.91)§
Hypoglycemia — no. (%)	191 (15.8)	195 (16.3)	0.97 (0.81 to 1.17)
Bradycardia — no. (%)	31 (2.6)	35 (2.9)	0.88 (0.55 to 1.42)
Hypotension — no. (%)	7 (0.6)	16 (1.3)	0.43 (0.18 to 1.05)
Any respiratory support — no. (%)	219 (18.1)	243 (20.3)	0.90 (0.76 to 1.06)
Respiratory distress syndrome — no. (%)	149 (12.3)	171 (14.3)	0.87 (0.71 to 1.06)
Transient tachypnea — no. (%)	70 (5.8)	63 (5.3)	1.10 (0.79 to 1.54)
Seizures — no. (%)	3 (0.3)	1 (0.1)	2.98 (0.31 to 28.6)
Hyperbilirubinemia — no. (%)	266 (22.0)	283 (23.6)	0.93 (0.81 to 1.08)
Apgar score of <7 at 5 min — no. (%)††	68 (5.6)	80 (6.7)	0.84 (0.62 to 1.16)
Sepsis — no. (%)			
Suspected or proven	138 (11.4)	163 (13.8)	0.84 (0.68 to 1.04)
Proven	21 (1.7)	34 (2.8)	0.61 (0.36 to 1.05)

Recent Studies and Literature

- Oral antihypertensives for non-severe pregnancy hypertension: systematic review network meta- and trial Sequential analysis – Bone, J.N., et. Al Hypertension 2022
  - The study had two aims; 1 to perform a large meta-analysis for non- severe hypertension in pregnancy and to perform analysis to estimate future sample sizes to determine differences in outcomes of incidence of severe hypertension, safety related outcomes, fetal outcomes and fetal death
  - The meta-analysis involved 61 studies with 6923 women. Outcomes were risk reduction of severe hypertension, reduction in proteinuria or preeclampsia, reduction in fetal or newborn death, non-severe hypertension was 140-159/90-109
  - Outcomes: Labetalol – less severe hypertension, proteinuria, perinatal death. Methyldopa – less severe hypertension. Other antihypertension medications (B-Blockers, calcium channel blockers) less severe hypertension. Labetalol better prevent severe hypertension compared to methyldopa. Labetalol and CCB require fewer secondary agents
  - Study population findings – for superiority studies on two different medications and their impact on severe hypertension reductions studies, may require 2500-10000/arm for a 20% relative risk reduction

Recent Studies and Literature

- Hypertension in pregnancy: Diagnosis, blood pressure goals and pharmacotherapy: scientific statement from AHA. Garovic V.D., et. Al 2022 Hypertension
  - Paper argues that ACOG BP guidelines are possibly too high and leaves many women untreated, It compares ACOG guidelines with other institutions and countries guidelines
  - Authors state this is because of 3 reasons:
    - No measurable immediate or long-term health benefits of stricter BP treatment for a short duration
    - Lower BP may compromise utero-placental circulation impairing fetal well being and growth
    - Lack of therapeutic options with low risk of fetal adverse effects
  - Authors state there are good reasons for changing the BP thresholds in the US
    - Prevents the development of severe hypertension
      - May prevent preeclampsia especially in populations at high risk for hypertension related adverse outcomes
    - May decrease risk for neurological manifestations (headache, visual disturbance, seizure and stroke)
      - Women may be at risk for these at a lower BP than the non-pregnant population
    - May prolong pregnancy in women with less severe preeclampsia
    - Decreasing treatment thresholds may decrease number of rushed preterm deliveries caused by high BP with preeclampsia
    - More literature is emerging that exposure to high BP with first pregnancy may increase cardiovascular disease risk and that this is compounded by more time spent pregnant with multiple pregnancies
      - This is compounded with comorbid disease states (diabetes, heart disease kidney disease, PCOS)
    - Hypertension disorders of pregnancy are associated with increased postpartum risk of both cardiovascular and neurological disease

Recent Studies and Literature

- Hypertension in pregnancy: Garovic V.D., et. Al 2022 Hypertension

Summary of and key discrepancies between published guidelines for the diagnosis and treatment of hypertensive disorders of pregnancy

Guideline		HYPERTENSION IN PREGNANCY Diagnosis*	Treatment threshold (mm Hg)	Treatment target (mm Hg)	Continuation of anti-hypertensive therapy
American College of Obstetricians and Gynecologists	2013[1] 2019[2] 2020[3]		≥ 160/105 with diagnosis of chronic hypertension[1] ≥ 160/110 if acute[3]/chronic hypertension[2] †	120–159/80–105[1] 120–159/80–109 if chronic[2] †	Guided by informed discussion with women
World Health Organisation	2018[144] 2020[145]	Not defined	Not specified †	Above lower limits of normal[145]	Not specified
National Institute for Health and Clinical Excellence	2019[146]		≥ 140/90	≤135/85	Continue treatment unless <110/70 mm Hg or symptomatic hypotension
Society of Obstetricians and Gynaecologists, Canada	2018[147] 2020[148]		≥ 140/90[148, 149]	DBP 85[148, 149] <140/90 + comorbidities[149]	Not specified
International Society for the Study of Hypertension in Pregnancy	2018[112]	+ the absence of preeclampsia features	≥ 140/90 in office ≥ 135/85 at home	110–140/85	Not specified
European Society of Cardiology	2018[150]	"Antenatally unclassified" if first BP measure > 20 weeks of gestation	≥ 150/95 ≥ 140/90 + end-organ damage / gestational hypertension	Not specified	Consider discontinuation if BP 140–159/90–109 mm Hg + normal renal function
Society of Obstetric Medicine of Australia and New Zealand	2014[151]		≥ 160/100 ≥ 140/90, optional	Based on clinician assessment	Consider discontinuation if BP fall<20 weeks of gestation

Recent Studies and Literature

- Hypertension in pregnancy: Garovic V.D., et. Al 2022 Hypertension

Guideline		PREECLAMPSIA Diagnosis §	SUPERIMPOSED PREECLAMPSIA ON CHRONIC HYPERTENSION Diagnosis §	Treatment threshold (mm Hg)	Treatment target (mm Hg)
American College of Obstetricians and Gynecologists	2019[1]		Chronic hypertension + a sudden change in preeclampsia diagnostic parameters	≥ 160/110[1]	Not specified
National Institute for Health and Clinical Excellence	2019[146]	Symptoms include utero-placental dysfunction ‖	Not specified	≥ 140/90	≤ 135/85
Society of Obstetricians and Gynaecologists, Canada	2014[149] 2018[152]	Symptoms include ≥1 severe complication	≥ 20 weeks of gestation + resistant hypertension + new or worsening proteinuria or ≥1 adverse conditions or severe complications of preeclampsia	≥ 140/90[152]	DBP 85[152]
International Society for the Study of Hypertension in Pregnancy	2018[112]	Symptoms include utero-placental dysfunction ‡	Chronic essential hypertension + ≥ 1 sign of maternal organ dysfunction consistent with preeclampsia, or new-onset proteinuria in the setting of a rise in BP	≥ 140/90	110–140/85
European Society of Cardiology	2018[150]	Proteinuria necessary, only high suspicion if hypertension + abnormal biochemistry / symptomatic	Hypertension <20 weeks of gestation + superimposed gestational hypertension + proteinuria	≥ 140/90	Not specified
Society of Obstetric Medicine of Australia and New Zealand	2014[151]	Symptoms include fetal growth restriction	Pre-existing hypertension with proteinuria or ≥1 systemic feature of preeclampsia	160/100 140–160 / 90–100, optional	Individual assessment

Recent Studies and Literature

- Hypertension in pregnancy: Garovic V.D., et. Al 2022 Hypertension

Guideline		Future cardiovascular disease risk management
American College of Obstetricians and Gynecologists	2019[1,53]	Postpartum follow-up visit (early postpartum visit) with either the primary care provider or cardiologist is recommended within 7–10 days of delivery for women with hypertensive disorders
National Institute for Health and Clinical Excellence	2019[1,46]	Referral to family care doctor for CVD risk prevention
Society of Obstetricians and Gynaecologists, Canada	2014[1,49]	All women who have had a hypertensive disorder of pregnancy should pursue a healthy diet and lifestyle
International Society for the Study of Hypertension in Pregnancy	2018[1,12]	Regular general practitioner follow-up to monitor BP + periodic measurement of fasting lipids and blood sugar. Adopt healthy lifestyle with maintenance of ideal weight and regular aerobic exercise
European Society of Cardiology	2018[1,50]	Annual primary care physician CVD risk screen
Society of Obstetric Medicine of Australia and New Zealand	2014[1,51]	Advise optimization of CVD risk factors

Billings Clinic Order Sets

Magnesium

And

Preeclampsia

Billings Clinic Order Sets - Magnesium

FBC ADULT Magnesium Sulfate Orders (Initiated Pending)		
Nursing Orders		
☑	Vital Signs, routine (Vital Signs)	T;N, Routine, q5Min, for 30 min, while magnesium bolus infusing
☑	Vital Signs, routine (Vital Signs)	T;N, Routine, q15Min, for 1 HR, for first hour of magnesium infusion
☑	Vital Signs, routine (Vital Signs)	T;N, Routine, q1H, until magnesium infusion complete
Continuous Infusions		
	ADULT Medication Orders	
	Choose one of the following orders	
	Rate: 2gm/hr(50mL/hr)	
☐	FBC Magnesium 40mg/mL in SWFI	IV Infusion
	Rate: 1gm/hr(25mL/hr)	
☐	FBC Magnesium 40mg/mL in SWFI	IV Infusion
Medications		
☑	magnesium sulfate (magnesium sulfate IV BOLUS)	4 gm IV Bolus ONE TIME, Infuse over 20 min - Administer bolus from 40mg/mL continuous infusion. (Pharmacy will not send IVPB unless requested)
☑	calcium chloride	1,000 mg IV Push q1H PRN Other - see comment x 8 dose(s)/time(s), Syringe, Routine - PRN signs/symptoms of magnesium toxicity (per FBC Preeclampsia Protocol)

Billings Clinic Order Sets – Preeclampsia

	$		Component	Status	Dose ...		Details
FBC ADULT Preeclampsia Orders (Planned Pending)							
Vital Signs							
☑			Vital Signs, routine (Vital Signs)				T;N, Routine, q30Min, for 2 HR
☑			Vital Signs, routine (Vital Signs)				T;N, Routine, q1H, while awake. Every 4 hours while sleeping.
Nursing Orders							
☑			Intake and Output				T;N, Routine
☐			Insert Indwelling Urinary Catheter (Foley Catheter, Urometer)				T;N, Routine, Managed By Provider, Catheter Type Foley, Urometer for strict measurement
☑			Notify Provider (Notify Physician)				T;N, For systolic BP > 160mmHg or diastolic BP > 110mmHg
☐			Nursing Communication Order				T;N, Keep total intake (IV + PO) < or = to 150 mL/hr
Medications							
			ADULT Medication Orders				
Blood Pressure							
			Select only ONE BLOOD PRESSURE medication for Intrapartum and Immediate Postpartum				
☐			yyFBC hydrALAZine Hypertension Orders				
☐			yyFBC Labetalol Hypertension Orders				
☐			yyFBC Nifedipine Hypertension Orders				

Billings Clinic Order Sets – Preeclampsia Reference Document

Labetalol 20-80 mg IV q10 min PRN other
Comments: administer by slow IV push over 2 min for SBP≥160 mm Hg and/or DBP≥110 mm Hg
Patient dose to = 20mg, 40mg, or 80mg x2 doses, Maximum cumulative dose in 24 hours = 300mg
If patient's blood pressure remains elevated between 10-60 minutes since last dose administer next highest dose, contact MD when 80 mg dose is utilized
If it has been ≥60 min since last dose administer same dose as previous dose and contact MD
If it has been ≥ 24hr since the last dose restart dosing at 20 mg, contact MD and follow above instructions
If patient has reached 80 mg dose and continues to have SBP≥160 mm Hg and/or DBP≥110 mm Hg within 60 minutes of previous dose contact MD and administer second dose of 80 mg of labetalol
If heart rate <60 BPM contact MD prior to administration

Labetalol Reference Table

Maximum cumulative dose in 24 hours = 300mg

10 -60 min since last dose	≥60min since last dose	≥24 hours since last dose
Progress to next dose 20-40-80mg	Remain at previous dose	Start at 20 mg
Contact MD if 80 mg dose used	Contact MD	Contact MD
Example: 20 mg given 30 min ago	**Example:** 20 mg given 2 hours ago	**Example:** 40 mg given 26 hours ago
Administer 40 mg	Administer 20 mg and contact MD	Administer 20 mg and contact MD

Contact MD For SBP≥160 mm Hg and/or DBP≥110 mm Hg after 2nd 80 mg labetalol dose, administer Hydralazine 10mg IV x one time

Hydralazine 10 mg IV q 20 min PRN other – 3 dose limit in 24 hour period
Comments: administer by slow IV push over 2 min for SBP≥160 mm Hg and/or DBP≥110 mm Hg
May be administered up to 3 doses, Contact MD after 3rd dose
Contact MD For SBP≥160 mm Hg and/or DBP≥110 mm Hg ≥ 10 min after 3rd hydralazine dose contact MD and administer labetalol 40 mg IV x one time

Nifedipine 10mg PO one time PRN other
Comments: for SBP≥160 mm Hg and/or DBP≥110 mm Hg
Administer 10 mg dose 1st
If patient continues to be hypertensive ≥20 min after 1st dose of nifedipine begin utilizing 20 mg doses

Nifedipine 20 mg PO q20min PRN other – 2 dose limit
Comments: SBP≥160 mm Hg and/or DBP≥110 mm Hg
Administer 20 mg dose 2nd and 3rd, Contact MD with third dose
Contact MD for SBP≥160 mm Hg and/or DBP≥110 mm Hg ≥ 20 min after 2nd 20 mg nifedipine dose, administer Labetalol 40 mg IV x one time

Billings Clinic Order Sets – Preeclampsia with Labetalol

	$		Component	Status	Dose ...		Details
FBC ADULT Preeclampsia Orders, yyFBC Labetalol Hypertension Orders (Planned Pending)							
Vital Signs							
☑			Vital Signs, routine (Vital Signs)				T;N, Routine, PRN, q10Min, for 1 HR - Monitor blood pressure every 10 minutes for 1 hour after last dose of labetalol. If blood pressure remains normal revert to either standard monitoring or magnesium infusion monitoring.
Nursing Orders							
Fetal Monitoring							
☑			Fetal Monitoring				T;N, Routine, for 1 HR, PRN, Continuous fetal monitoring - Continuous fetal monitoring for 1 hour after last dose of labetalol. After an hour without medication revert to either standard monitoring or magnesium infusion monitoring.
Medications							
☑			labetalol				20 mg IV Push q10Min PRN Blood Pressure, Soln Administer by slow IV push over 2 min for SBP>160 mm Hg and/or DBP>110 mm Hg Patient dose to = 20, 40mg or 80 mg, Maximum cumulative dose in 24 hours = 300mg -If patient's blood pressure remains elevated between 10-60 minutes of last dose admini...
☑			labetalol				40 mg IV Push q10Min PRN Blood Pressure, Soln Administer by slow IV push over 2 min for SBP>160 mm Hg and/or DBP>110 mm Hg Patient dose to = 20, 40mg or 80 mg, Maximum cumulative dose in 24 hours = 300mg -If patient's blood pressure remains elevated between 10-60 minutes of last dose admini...
☑			labetalol				80 mg IV Push q10Min PRN Blood Pressure x 2 dose(s)/time(s), Soln Administer by slow IV push over 2 min for SBP>160 mm Hg and/or DBP>110 mm Hg Patient dose to = 20, 40mg or 80 mg, Maximum cumulative dose in 24 hours = 300mg -If patient's blood pressure remains elevated between 10-60 minutes of last dose admini...
☑			hydrALAZINE				10 mg IV Push ONE TIME PRN Blood Pressure x 1 dose(s)/time(s), Soln If systolic blood pressure is greater than 160 or diastolic blood pressure is greater than 100 after 2nd 80mg dose of labetalol. Administer by slow IV push over 2 min. Contact MD if hydrALAZINE is administered.

Billings Clinic Order Sets – Preeclampsia with Nifedipine

	$		Component	Status	Dose ...	Details
FBC ADULT Preeclampsia Orders, yyFBC Nifedipine Hypertension Orders (Planned Pending)						
Vital Signs						
☑			Vital Signs, routine (Vital Signs)			T;N, Routine, PRN, q20Min, for 1 HR - Monitor blood pressure every 20 minutes for 1 hour after last dose of NIFEdipine. If blood pressure remains normal revert to either standard monitoring or magnesium infusion monitoring.
Nursing Orders						
Fetal Monitoring						
☑			Fetal Monitoring			T;N, Routine, Continuous fetal monitoring - Continuous fetal monitoring for 1 hour after last dose of NIFEdipine. After an hour without medication revert to either standard monitoring or magnesium infusion monitoring.
Medications						
☑			NIFEdipine			10 mg PO ONE TIME PRN Blood Pressure, Cap Administer for SBP>160 mm Hg and/or DBP>110 mm Hg. If patient continues to be hypertensive 20 min after 10mg dose begin utilizing 20mg doses.
☑			NIFEdipine			20 mg PO q20Min PRN Blood Pressure x 2 dose(s)/time(s), Cap Administer for SBP>160 mm Hg and/or DBP>110 mm Hg >/= 20 min after 10mg dose. Contact MD with 2nd dose of 20mg.
☑			labetalol			40 mg IV Push ONE TIME PRN Blood Pressure, Soln For SBP>160 mm Hg and/or DBP>110 mm Hg after 2nd dose of 20mg NIFEdipine administer by slow IV push over 2 min. If labetalol is given, contact MD -If heart rate <60 BPM contact MD prior to administration

Billings Clinic Order Sets – Preeclampsia with Hydralazine

	$		Component	Status	Dose ...	Details
FBC ADULT Preeclampsia Orders, yyFBC hydrALAZine Hypertension Orders (Planned Pending)						
Vital Signs						
☑			Vital Signs, routine (Vital Signs)			T;N, Routine, PRN, q20Min, for 1 HR - Monitor blood pressure every 20 minutes for 1 hour after last dose of hydrALAZINE. If blood pressure remains normal revert to either standard monitoring or magnesium infusion monitoring.
Nursing Orders						
Fetal Monitoring						
☑			Fetal Monitoring			T;N, Routine, Continuous fetal monitoring - Continuous fetal monitoring for 1 hour after last dose of hydrALAZINE. After an hour without medication revert to either standard monitoring or magnesium infusion monitoring.
Medications						
☑			hydrALAZINE			10 mg IV Push q20Min PRN Blood Pressure x 3 dose(s)/time(s), Soln Administer by slow IV push over 2 min for SBP>160 mm Hg and/or DBP>110 mm Hg May be administered up to 3 doses Contact MD after 3rd dose
☑			labetalol			40 mg IV Push ONE TIME PRN Blood Pressure x 1 dose(s)/time(s), Soln For systolic blood pressure is greater than 160 or diastolic blood pressure is greater than 110 after the 3rd dose of hydrALAZINE contact MD and administer labetalol. -If heart rate <60 BPM contact MD prior to administration

Billings Clinic Order Sets – Postpartum Medication orders

		Postpartum Medications	
☑		hydroCHLOROthiazide	25 mg PO qDay, Tab, Routine
☑		carvedilol	12.5 mg PO BID, Tab, Routine
☑		labetalol	200 mg PO BID, Tab, Routine
☑		furosemide (Lasix)	20 mg PO BID, Tab, Routine
☑		lisinopril	20 mg PO qDay, Tab, Routine
☑		metoprolol (metoprolol tartrat...	50 mg PO BID, Tab, Routine
☑		metoprolol (metoprolol succi...	100 mg PO qDay, ER Tablet, Routine
☑		NIFEdipine	10 mg PO TID, Routine
☑		NIFEdipine (NIFEdipine exten...	30 mg PO qDay, ER Tablet, Routine

Possible Future Directions

- Phenotype directed management of hypertension in pregnancy, McLaughlin K. et. Al 2022 J. of Amer. Heart Association
  - Paper looks at potential new markers of preeclampsia, and the type of cardiovascular change to potentially better treat preeclampsia and better guide medication selection
  - Noninvasive hemodynamic
    - First type – high cardiac output low total peripheral resistance – increase HR, SV and CO, decreased TPR – more common in late onset preeclampsia
    - Second type – low cardiac output high TPR – decreased HR, SV, and CO increased TPR – more common in early onset preeclampsia
  - Placental growth factor real time serum testing
    - Finds the lower the circulating levels of PIGF are the more likely the patient is to develop preeclampsia during the pregnancy
    - Patients with low PIGF also demonstrate and increased risk of preterm delivery and stillbirth
- Hypertensive disorders of pregnancy and future maternal health, Hauspurg A., 2019 Current Hypertension Reports
  - Paper advocates for better more frequent postpartum maternal management and handoff to primary care provider
  - Potentially extend Medicaid coverage(many states stop at 60 days postpartum) to help with persistent hypertension monitoring and management
  - US is one of few developed countries without paid parental leave

Possible Future Directions

- Phenotype directed management of hypertension in pregnancy, McLaughlin K. et. Al 2022 J. of Amer. Heart Association

Table 1. Mechanism of Action of Standardly Used Medications

Drug name	Usual oral starting dose (Maximum dose)	Mechanism of action	Appropriate hemodynamic profile for therapy use
Atenolol	12.5–25 mg twice a day (75 mg 3 times a day)	Competitively blocks response to beta-adrenergic stimulation, selectively blocks $beta_1$-receptors with little or no effect on $beta_2$-receptors except at high doses	High CO
Labetalol	200 mg twice a day (400 mg 3 times a day)	1. Blocks $alpha_1$-, $beta_1$-, and $beta_2$-adrenergic receptor sites; suppresses elevated renin. Beta-specific isomer more rapidly metabolized in pregnancy than alpha-specific isomer. The ratio of alpha- to beta-blockade for oral administration is 1:3 and for intravenous administration is 1:7[72,73]	High CO
Hydralazine	5 mg 3 times a day (20 mg 4 times a day)	1. Direct vasodilation of arterioles (with little effect on veins) reduces systemic resistance. Although exact mechanism unknown, arterial vasodilation occurs independent of the overlying presumably damaged endothelium, within the vascular smooth muscle. Mechanisms of action include inhibition of calcium release from the sarcoplasmic reticulum and inhibition of myosin phosphorylation[74]	High TPR
Nifedipine XL	30 mg daily (60 mg twice a day)	Inhibits calcium ion entry into the "slow channels" or select voltage-sensitive areas of vascular smooth muscle and myocardium during depolarization, producing a relaxation of coronary vascular smooth muscle and coronary vasodilation; reduces peripheral vascular resistance, producing a reduction in arterial blood pressure	High TPR

CO indicates cardiac output; and TPR, total peripheral resistance.

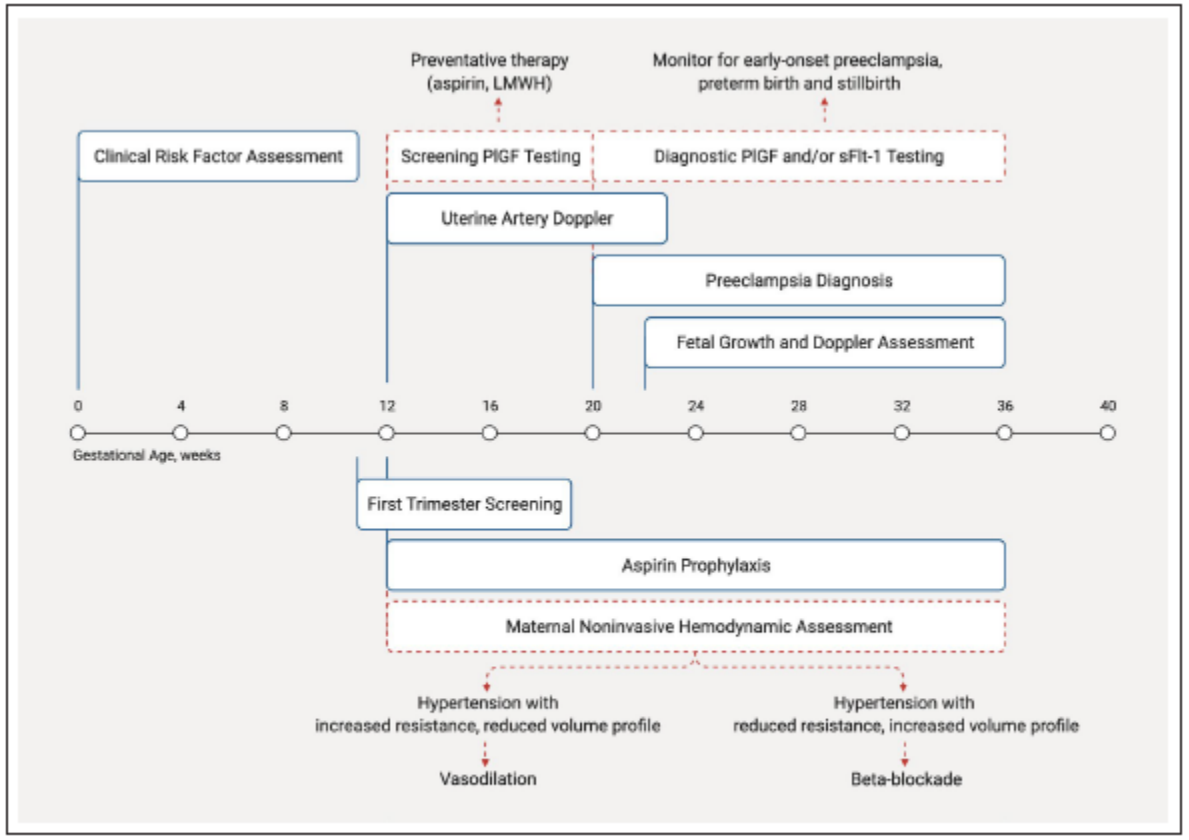

Figure 6. Proposed recommendations for phenotype-driven clinical care of hypertensive pregnant patients.
LMWH indicates low molecular weight heparin; PlGF, placental growth factor; and sFlt1, soluble fms-like tyrosine kinase.

Oral Medications

- Oral Labetalol
  - MOA – non-selective $beta_1$ and $beta_2$ blocker, with $alpha_1$ antagonism, decreased heart rate, decrease systemic vascular resistance
  - ADME – tmax 1-2hr, 25% bioavail, hepatic metab, t1/2 5-8hr
  - Dose – 100mg po bid, max 2400mg/day
  - Adverse effects – dizziness, fatigue, decreased CO,
  - Contraindications – Asthma, diabetes (masking of hyper/hypoglycemia symptoms)

Oral Medications

- Oral Nifedipine
  - MOA – dihydropryridine calcium channel blocker – caused smooth muscle relaxation decreasing SVR
  - ADME – Tmax 30 min IR 6hr ER, liver metab, t1/2 2 hr
  - Dose – xl -10-180 mg/day
  - Adverse effects – hypotension, dizziness headache
  - Contraindications – N/A

Oral Medications

- Oral hydralazine
  - MOA – Vasodilator – may interfere with calcium, indirectly increases renin secretion
  - ADME – peak 1-2h, metab hepatic, excretion renal, t1/2 3-7hr
  - Dose – oral dosing rare – start 10mg q6h titrate to 50mg q6h
  - Adverse effects – tachycardia, headache,
  - Contraindications –

Oral Medications

- Oral Aspirin
  - MOA - decreases prostaglandin synthesis and platelet aggregation
  - ADME – cmax 20 min-2hr, metab systemic, excretion renal, t1/2 20-60min
  - Dose – for prevention of preeclampsia 81-162mg qday
  - Adverse effects – ulcer, hemorrhage, tinnitus, brochospasm
  - Contraindications –

Oral Medications

- Hydrochlorothiazide
  - MOA – thiazide diuretic with majority of action at distal convoluted tubule
  - ADME – excretion renal, t1/2 6-15hrs
  - Dose – 12.5-50mg/day
  - Adverse effects – hypotension, vertigo, hyponatremia
  - Contraindications – anuria

Oral Medications

- Methyldopa
  - MOA – A_2 agonist causing down regulation of sympathetic tone, this decreases BP
  - ADME – metab – hepatic, excretion renal
  - Dose – 500-3000 mg/day, in 2-4 divided doses
  - Adverse effects – dizziness, headache, sedation, heart block, hepatotoxicity elevated LFT
  - Contraindications – liver disease

IV/oral preeclampsia Medications

- Labetalol
  - MOA – non-selective $beta_1$ and $beta_2$ blocker, with $alpha_1$ antagonism, decreased heart rate, decrease systemic vascular resistance
  - ADME –hepatic metab, t1/2 5-8hr
  - Dose – 20-80mg/dose, max daily dose 300mg
  - Adverse effects – dizziness, fatigue, decreased CO,
  - Contraindications – Asthma, diabetes (masking of hyper/hypoglycemia symptoms)

IV/oral preeclampsia Medications

- Nifedipine
  - MOA – dihydropryridine calcium channel blocker – caused smooth muscle relaxation decreasing SVR
  - ADME – Tmax 30 min IR 6hr ER, liver metab, t1/2 2 hr
  - Dose – xl -10-180 mg/day
  - Adverse effects – hypotension, dizziness headache
  - Contraindications – do not administer sublingual

IV/oral preeclampsia Medications

- MOA – Vasodilator – may interfere with calcium, indirectly increases renin secretion
- ADME –metab hepatic, excretion renal, t1/2 3-7hr
- Dose – 5-10mg with max of 30mg/24hr – increased risk of maternal/fetal tachycardia
- Adverse effects – tachycardia, headache,
- Contraindications –

IV/oral preeclampsia Medications

- Magnesium
  - MOA - antagonism of calcium channels preventing neuron/muscle signal propagation/ contraction -
  - Dose – 4-6 gm load followed by 1-2gm/hour infusion
  - Adverse effects – Magnesium toxicity – peripheral tingling, hyporeflexia, smooth muscle/ diaphragm paralysis
  - Contraindications –