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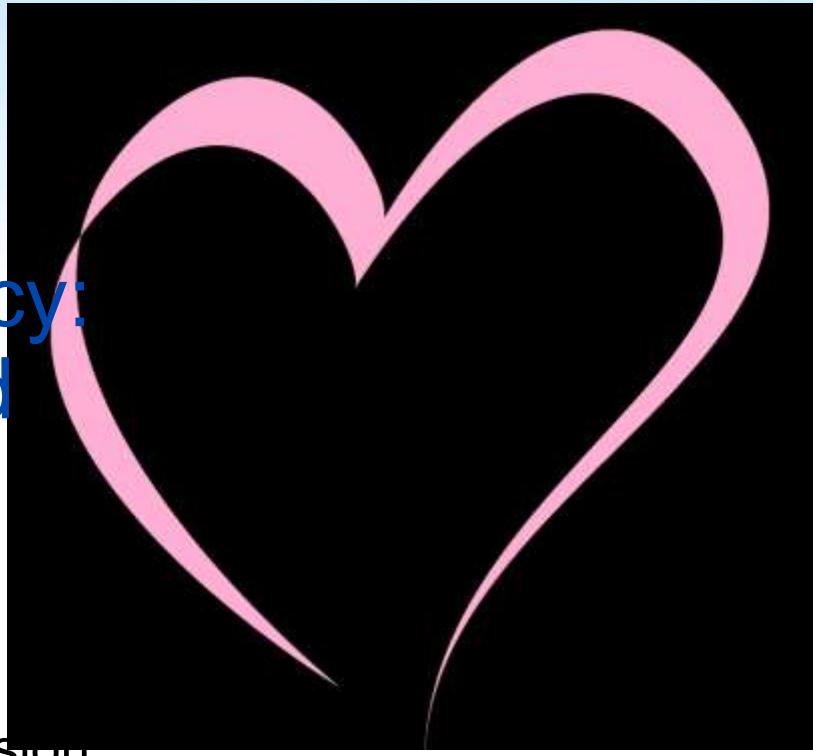

Hypertension in Pregnancy: Diagnosis, Treatment and Outcomes

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Disclosures

No conflicts of interest

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Objectives

Determine the most appropriate treatments and medication choices in the pregnant patient with hypertension

Hypertensive Disorders in Pregnancy

- Preeclampsia-eclampsia
- Preeclampsia superimposed on chronic HTN
- Chronic HTN
- Gestational HTN

National High Blood Pressure Education Program Working Group Report on High Blood Pressure in Pregnancy. AJOG 2000
ACOG, Task force on HTN in pregnancy. Obstet Gynecol 2013

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Preeclampsia-eclampsia

- Affects 5% of all pregnancies worldwide
- Remains a leading cause of maternal and fetal morbidity and mortality
- In USA, pregnancy-related mortality 14.5/100,000 livebirths (1998-2005); 12% due to pregnancy HTN

Berg et al. Obstet Gynecol 2010

- Increasing trend in USA for pregnancy related-hospitalizations with stroke, ↑54% ('94→'07)
  - with HTN disorders as a leading cause

Kuklina et al. Stroke 2011

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Preeclampsia: diagnostic criteria

- BP≥140/90 mm Hg on 2 occasions 4 hours apart, or ≥160/110 mm Hg within short interval
- Proteinuria ≥ 300 mg/24 hour urine
  - Protein/Cr ratio ≥ 0.3
  - Dipstick ≥ 1+

In the absence of proteinuria

- Serum Cr >1.1 mg/dL or doubling
- Thrombocytopenia < 100,000/μL
- Elevated AST and ALT (2x normal)
  - HELLP

American College of Obstetrics &Gynecology, Task force on HTN in pregnancy. Obstet Gynecol 2013

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Placental ischemia in preeclampsia

- Normal placental vascular structure: an intricately choreographed interaction between fetal and maternal circulatory systems
- Fetal cytotrophoblasts invade maternal spiral arteries →low resistance, high capacitance vessels
- Preeclampsia: Abnormalities in this process result in maintenance of high resistance, low capacitance maternal spiral arteries and consequent placental ischemia

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Clinical Presentation

- Different clinical subtypes
  - Early versus late (before or after 34 GW)
  - Mild versus severe
  - Placental versus maternal
  - **Placental**→ impaired angiogenesis→ endothelial dysfunction →early and severe preeclampsia
  - **Maternal**→ endothelial dysfunction predating pregnancy

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Early-onset vs Term Preeclampsia

- Placental pathology, more IUGR
- ↑ Perinatal and maternal mortality, recurrence rate
- ↑ Rates of long-term medical complications
  - CVD, HTN
  - CKD, ESRD
  - CVD in offspring
- Term preeclampsia
  - Placental dysfunction rare
  - 20% HELLP and 55% eclampsia cases at term

Staff et al. Hypertension, 2013

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Angiogenic factors and preeclampsia

- Abnormal in early, severe preeclampsia, but not in late disease
- Different clinical subtypes
  - Early versus late (before or after 34 GW)
  - Mild versus severe
  - Placental versus maternal
- Angiogenic factor abnormalities
  - Abnormal placentation→ impaired angiogenesis→ early and severe preeclampsia (in ~10-20 % of PE cases)
- Not informative for
  - term preeclampsia

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Preeclampsia: Short-term outcomes

- Maternal
  - Neurological problems (seizures and stroke)
  - Pulmonary edema
- Fetal
  - Intrauterine growth restriction (IUGR)
  - Prematurity
  - Intrauterine fetal death

Chronic Hypertension

- BP≥140/90 mm Hg before 20th week of gestation
- Indicators of poor prognosis:
  - Failure of BP to ↓ in mid-gestation
  - Secondary hypertension
- ↑ risk for preeclampsia

Treatment of Preeclampsia

Balance between

- Pregnancy termination to prevent maternal complications related to systemic disease and HTN
- Pregnancy continuation to prevent fetal immaturity and related complications

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Treatment of Preeclampsia

Delivery

- Mild PE at ≥ 37 GW
- Severe PE ≥ 34 GW
  - Expectant management only at tertiary facilities

    Magnesium for seizure prophylaxis
- Eclampsia
- Severe PE

    Corticosteroids for lung maturation
- Severe PE < 34 GW
  - Wait for 48 hours if maternal and fetal conditions remain stable

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Treatment of Hypertension in Pregnancy

- Different approach than in non-pregnant patients
- **Assumption**: HTN of 5-6 months duration in a young premenopausal woman without other risk factors does not increase her overall risk for CVD
- **Concern**: Decrease BP in mother can compromise feto-placental unit

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Treatment of Hypertension in Pregnancy

- Poorly controlled, retrospective observations of different types of HTN
- Great divergence of opinion
- “Shamefully few” well-designed studies
- Results of well-designed adequately powered studies are pending

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Treatment of Hypertension

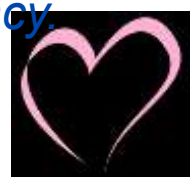
Preeclampsia

- Established benefit for treating SBP≥ 160 mm Hg or DBP≥110 mm Hg

Chronic HTN

- Initiate therapy for SBP≥160 mm Hg or DBP≥105 mm Hg
  - SBP 120-160 mm Hg
  - DBP 80-105 mm Hg

ACOG, Task force on HTN in pregnancy. Obstet Gynecol 2013



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Less-Tight versus Tight Control of Hypertension in Pregnancy

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The Control of Hypertension In Pregnancy Study CHIPS

- Trial comparing less-tight control of HTN (target DBP, 100 mm Hg) with tight control (85 mm Hg) among pregnant women
- Outcomes: pregnancy loss, high-level neonatal care, serious maternal complications (preeclampsia, severe maternal hypertension >160/110 mm Hg)

Enrollment and Randomization

- Chronic or gestational HTN
  - Office DBP 90-105 if NOT on antihypertensives
  - Office DBP 85-105 if they were
  - Live singleton 14^{+0} to 33^{+6} weeks
- Exclusion
  - Proteinuria, ACEI use at ≥14 weeks, known multiple gestations, major fetal anomaly

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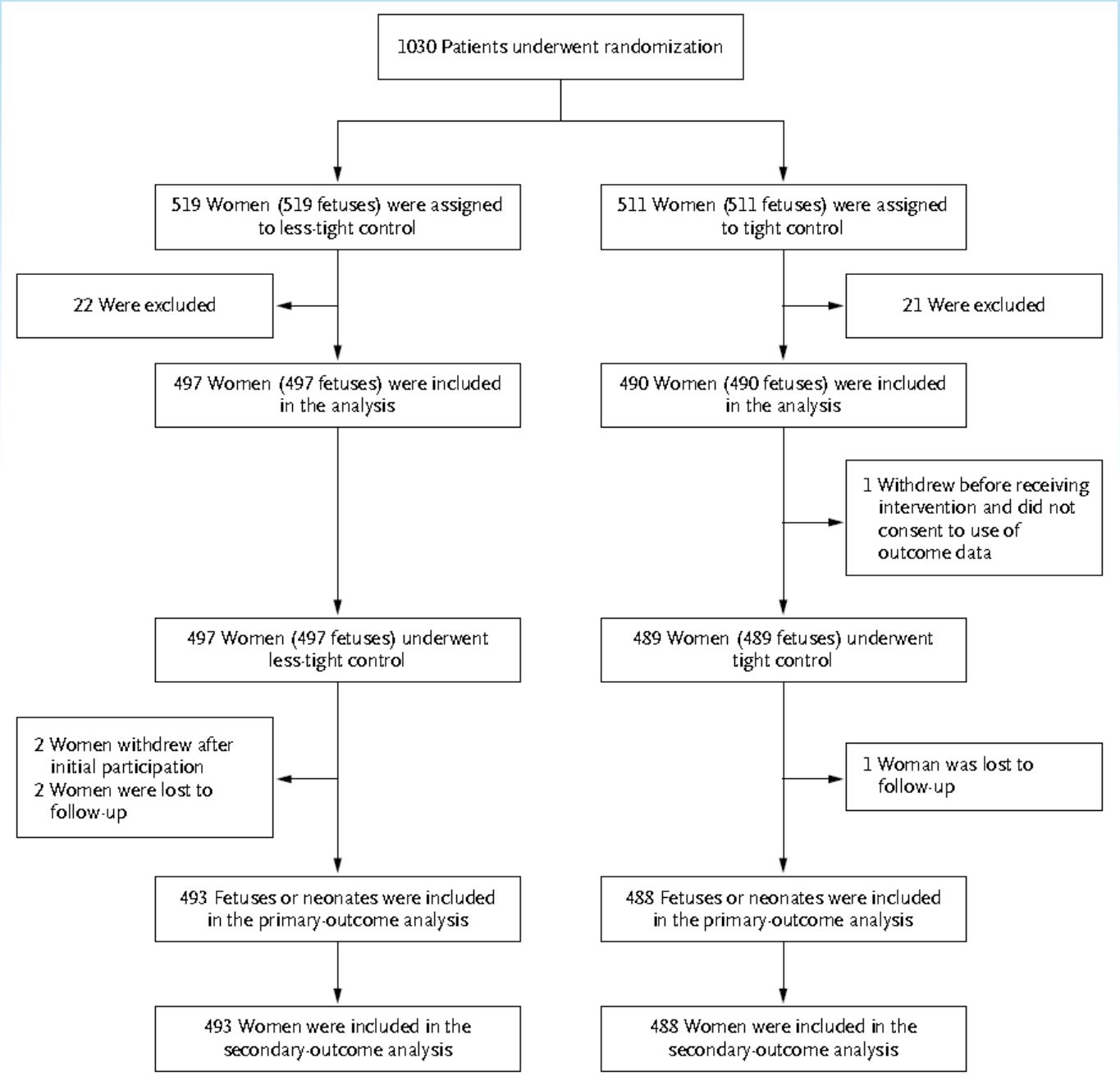
45 sites



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Magee LA et al. N Engl J Med 2015;372:407-417

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Table 1. Baseline Characteristics at Enrollment.*

Characteristic	Less-Tight Control (N=497)	Tight Control (N=490)
Maternal age at expected date of delivery — yr	34.0±5.7	33.7±5.8
Body-mass index — no./total no. (%)†		
<18.5	1/493 (0.2)	2/485 (0.4)
18.5–24.9	116/493 (23.5)	112/485 (23.1)
25.0–29.9	131/493 (26.6)	135/485 (27.8)
≥30.0	245/493 (49.7)	236/485 (48.7)
Cigarette smoking during this pregnancy — no. (%)	35 (7.0)	28 (5.7)
Nulliparous — no. (%)	161 (32.4)	168 (34.3)
Weeks of gestation	23.7±6.3	24.2±6.3
Type of nonproteinuric hypertension — no. (%)		
Preexisting hypertension	371 (74.6)	365 (74.5)
Gestational hypertension	126 (25.4)	125 (25.5)
Prior blood pressure ≥160 mm Hg systolic or ≥110 mm Hg diastolic during this pregnancy — no. (%)	82 (16.5)	59 (12.0)
Antihypertensive medication at enrollment — no. (%)	279 (56.1)	287 (58.6)
Blood pressure within 1 wk before randomization — mm Hg		
Systolic	140.4±9.7	139.7±9.8
Diastolic	92.6±4.8	92.2±5.2
Currently monitoring blood pressure at home — no. (%)	185 (37.2)	194 (39.6)
Gestational diabetes at enrollment — no. (%)	32 (6.4)	31 (6.3)

* Plus–minus values are means ±SD. There were no significant differences between the groups except with respect to prior blood pressure of 160 mm Hg or higher systolic or 110 mm Hg or higher diastolic during this pregnancy (P=0.049).
† Body-mass index is the weight in kilograms divided by the square of the height in meters.

Groups: BP control

- From randomization until delivery, BP was higher among women in ‘less tight’ vs. ‘tight’ control group
  - Mean difference of 5.8 mm Hg for SBP
  - Mean difference 4.6 mm Hg for DBP (both $p<0.001$)

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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)

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Magee LA et al. N Engl J Med 2015;372:407-417

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 $<100\times10^9$/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)	

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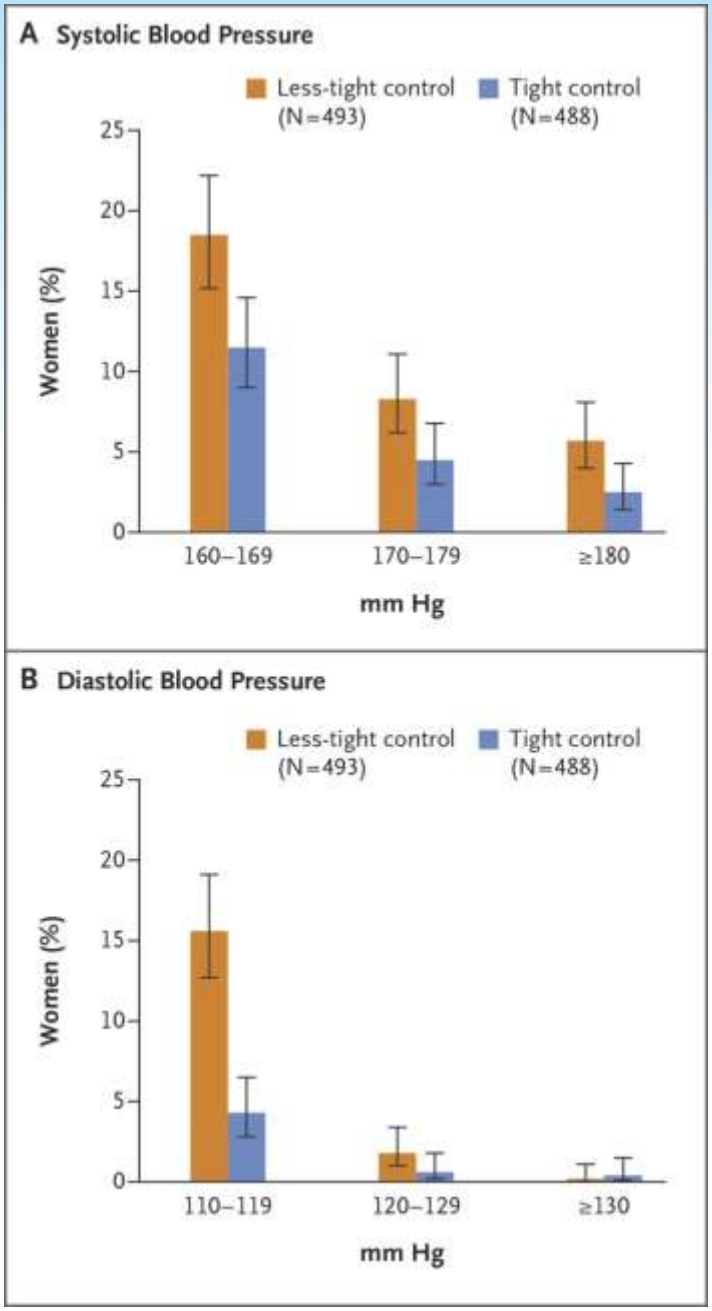
Blood-Pressure Values among Women with Severe Hypertension



Women receiving 'less tight' (vs. 'tight') control experienced significantly more severe hypertension antenatally (189, 95.0% vs. 111, 82.8%, p<0.001)

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Antihypertensive agents used antenatally

	Less-tight	Tight
Labetalol	242/362 (66.9%)	304/452 (67.3%)
Methyldopa	154/362 (42.5%)	182/452 (40.3%)
Nifedipine	115/362 (31.8%)	136/452 (30.1%)
Other	52/362 (14.4%)	55/452 (12.2%)

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Results - Maternal

- No difference in 1^{o} outcomes
- No difference in serious and other maternal complications, including PE
- Severe HTN (>160/110 mm Hg) more common in less-tight control group
- Thrombocytopenia and elevated LFTs more common in the less-tight-control, but not statistically different
- No difference between chronic vs. gestational HTN

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Results – Fetal

- IUGR slightly (not significantly) lower in less-tight-control group (16 vs. 20%), but study was not powered for this outcome
- Not powered to detect differences in frequencies of fetal or maternal deaths
- Perinatal mortality 2.8% in less tight and 2.3% in tight

CHIPS-Conclusions

- Tight control of HTN in pregnancy confers no apparent benefit to the fetus, but also does not pose a risk to fetus or newborn
- Tight control shows moderate benefit in preventing progression to severe HTN for the mother

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Cochrane Review 2014

- Review of anti-hypertensive therapy for mild-moderate HTN in pregnancy
- Included 49 trials (4723 patients)
- Conclusion: treatment reduced the risk (by half) of developing severe HTN, but had little effect on the incidence of PE

Abalos et al., 2014

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Medical Therapy

		Benefits	Risks
Central agents			
Preferred	Methyldopa	Proven safety and efficacy	Neuro-depressant side effects
Alternative	Clonidine	Efficacy similar to methyldopa	Unproven safety
Beta blockers			
Preferred	Labetalol	Safety and efficacy similar to methyldopa	Fetal bradycardia, neonatal hypoglycemia, decreased u/p flow
Contraindicated	Atenolol	None compared to Labetalol	Intrauterine growth retardation
Calcium channel blockers			
Preferred	Nifedipine	Lowers BP without affecting umbilical artery flow	Fetal distress, profound hypotension with magnesium
Alternative	Verapamil	Similar efficacy to other oral agents	Untested safety profile, risk of interaction with magnesium
Direct vasodilators			
Preferred	Hydralazine	Most efficacious IV agent	Maternal neuropathy, drug-induced SLE
Alternative	Nitroprusside	Effective in severe HTN	Cyanide and thiocyanate toxicity
Diuretics			
Preferred	Thiazide	Useful in chronic HTN	Volume contraction, electrolyte pro[illegible]
Contraindicated	Spironolactone	None	Possible fetal anti-androgen effect

Pharmacological therapies

- Safe for fetus
- Labetalol, nifedipine, methyldopa
- ACEI, ARB, renin inhibitors, ARA contraindicated
- Atenolol associated with IUGR
- Spironolactone with ambiguous genitalia
- Avoid NSAIDs for pain control

Non-pharmacological therapies

- Strict bed rest not recommended
- Weight loss and extremely low sodium diets (less than 100 mEq/day) not recommended
- Moderate exercise for women with chronic HTN with well-controlled BP

ACOG, Task force on HTN in pregnancy. Obstet Gynecol 2013

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Preeclampsia prevention

- Antioxidants (vitamin C and vitamin E) are not effective
- Calcium may be useful in populations with low calcium intake
- Bed rest and low-salt diet don't prevent preeclampsia

ACOG, Task force on HTN in pregnancy. Obstet Gynecol 2013

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Preeclampsia prevention

- ASA started prior to 14 weeks: PARIS collaboration- meta analysis of >30,000 women: 10% reduction in the RR of PE and birth <34 weeks' gestation

Lancet, 2007

Recommended

- Early-onset PE and preterm delivery (<34 GW)
- Recurrent PE
- 60-80 mg daily prior to 36 weeks

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Postpartum care

- HTN or PE: follow up BP postpartum
- ALL women: discharge instructions should include signs and symptoms of PE
- BP treatment for persistent postpartum HTN ≥150/100 mm Hg
- New-onset HTN postpartum with neurological symptoms: Mg prophylaxis

Meta-analysis

- The relative risks (95% CI)
- HTN 3.70 (2.70 to 5.05) after 14.1 years
- CHD 2.16 (1.86 to 2.52) after 11.7 years
- Stroke 1.81 (1.45 to 2.27) after 10.4 years
- Venous thromboembolism 1.79 (1.37 to 2.33) after 4.7 years
- Overall mortality after PE: 1.49 (1.05 to 2.14) after 14.5 years

Bellamy et al. BMJ,2007

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2011 AHA Guidelines for the Prevention of CVD in women

- Postpartum: monitored and treated for modifiable risk factors
- Questions regarding HTN in pregnancy should become a routine part of medical history
- Future studies of exposures and events across a woman's lifespan-need for population based studies

Mosca et al. Circulation, 2011

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2014 AHA Guidelines for the Prevention of Stroke in women

- Increased risk during pregnancy, postpartum, and years after
- Prospective studies on the pathophysiology underlying the association, especially in diverse populations
- These studies will provide evidence to inform screening, prevention, and treatment strategies in women with a history of HTN in pregnancy

Bushnell et al. Stroke, 2014

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Postpartum Care

Table.
CVD risk factor screening in women with adverse pregnancy outcomes.

	Time interval for screening post-partum	Time interval for subsequent screening
Hypertension	Screen within 6 months to 1 year post-partum[21]	For SBP 120–139 mmHg or DBP 80–90 mmHg: screen annually; for BP <120/80: screen every 2 years[14 and 17]
		If history of hypertensive disorder during pregnancy, screen annually[19]
Hyperlipidemia	Reasonable to screen within 12 weeks post-partum and post-lactation	Screen annually depending on ASCVD risk[11]
		If history of hypertensive disorder during pregnancy, screen annually[19]
Diabetes	Screen within 6 weeks if GDM[42 and 44]	If impaired fasting glucose at 6 weeks post-partum, screen annually[42]
		Screen every 3 years, with more frequent testing depending on risk and if initial screen abnormal[72]
		If history of hypertensive disorder during pregnancy, screen annually[19]
Obesity/BMI	Screen annually[59]	Screen annually[19 and 59]
Tobacco use	Screen at first post-partum visit[49]	Screen at each visit[50]
Nutrition	Assess at first post-partum visit	Assess at each visit depending on risk[53]
Physical activity	Assess at first post-partum visit[73]	Assess at each visit depending on risk[53]

Mehta et al. Seminars in Perinatology, 2015

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Future Questions

- In women with chronic HTN in pregnancy, does early (i.e., <14 week GA) BP control prevent PE?
- Is there any subgroup of women with chronic HTN that may derive benefit from tight control?
  - e.g., the fourth quartile age group?
- HTN in pregnancy is associated with future cardiovascular risk. Will the women in the tight-control group have a lowered risk in the future?

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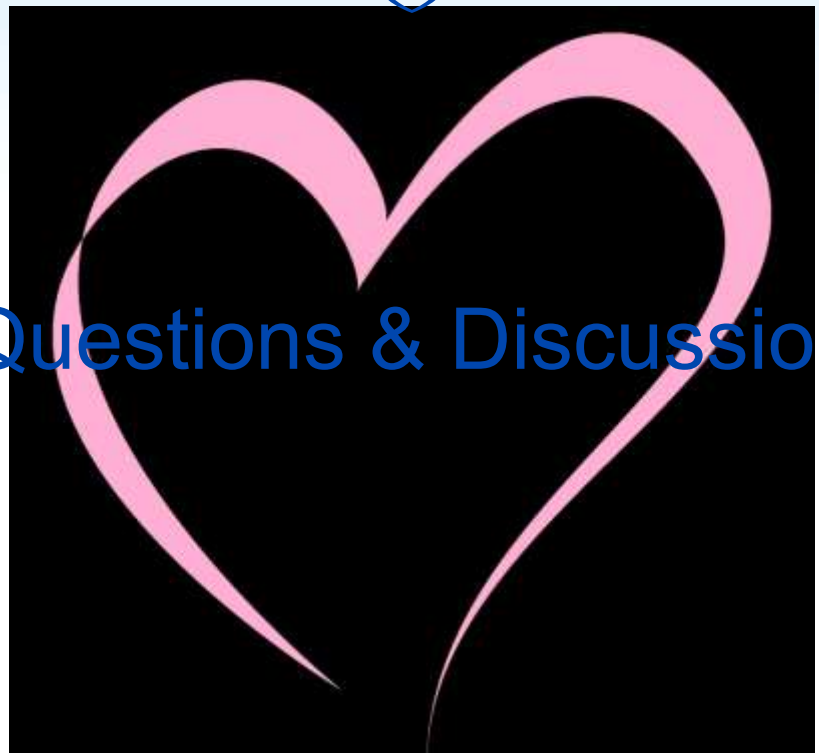

Questions & Discussion

Case 1

- A 29-year old presents at 33 GW with BP165/100 mm Hg, headache, and proteinuria of 22.6 grams/24 h
- Diagnostic criteria of specific HTN pregnancy disorders
- **Blood pressure treatment: goals and choice of medications**
- Immediate outcomes: maternal and fetal morbidity and mortality
- Long-term maternal outcomes

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Question #1
Treatment of Preeclampsia

Treatment of HTN (either chronic or gestational) prevents progression to PE

1. True
2. False

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Question #2
Treatment of HTN in pregnancy

Which of the below hypertension medications is safe during pregnancy?

1. Enalapril
2. Spironolactone
3. Losartan
4. Hydrochlorothiazide

Case 1

- A 29-year at 33 GW presented with BP165/100 mm Hg, and acute-onset proteinuria of 22.6 grams/24 hours
- Labetalol, BP of150/90 mm Hg
- Corticosteroids for lung maturation
- C-section with delivery of a SGA baby-girl
- Three months later, BP controlled on nifedipine; microalbuminuria of 260 mg/24 hour urine

Case 1: Postpartum Care

- Yearly assessment of BP, lipids, FBG, and BMI

ACOG, Task force on HTN in pregnancy. Obstet Gynecol 2013

- Treatment according to current guidelines
- Life-style modifications

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