Update on Hypertensive Diseases in Pregnancy

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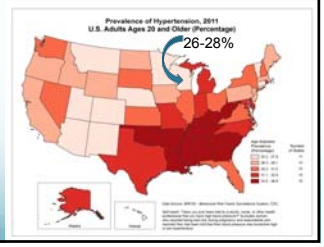
CHTN Burden

- 1 in 3 (31%) American adults
- 30% prehypertension
- 348,000 deaths due to HTN
- $47.5 billion annually
- 47% BP controlled



New criteria for control of BP in Pregnancy

- American Society of Hypertension
- National Institute for Health and Clinical Excellence: United Kingdom
- 7th Report JNC
  - Initiate Rx: 150-160/100-110
  - Target BP: < 150/100
- Society of Ob & Gyn of Canada
- Society of OB Medicine of Australia and NZ
  - Initiate Rx: 140-159/90-109
- End-organ disease: BP in normal range

Lower criteria for severe HTN and initiating treatment

- Concern for CVA's, death
  - Martin et al 2005
  - UK 2007: NICE Confidential Enquiries in Maternal Deaths
- Lower criteria for initiating Rx, maintenance of BP

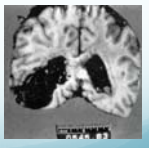
Decrease risk of:

Cerebral hemorrhage

Cardiac failure

Myocardial infarction

Perinatal morbidity and mortality



ACOG Task Force on HTN in Pregnancy Classification

- No change: same 4 categories introduced 1972, components modified 1990, 2000

- **Preeclampsia-Eclampsia**
- **Chronic HTN**
- **Chronic HTN with superimposed Preeclampsia**
- **Gestational HTN**

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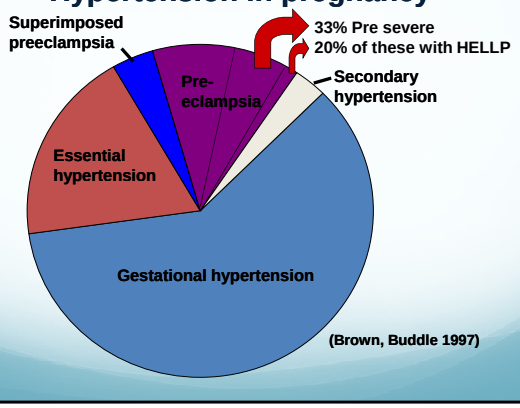
Hypertension in pregnancy



ACOG Task Force: Reasons for changes

- Maternal deaths could be prevented if providers alert that Preeclampsia **will progress**
- Intervention in acutely ill women with multiple organ dysfunction **delayed due to absence of proteinuria**
- Amount of proteinuria **does not predict maternal or fetal outcome**

***Trying to eliminate term "mild Pre" and replace with "Pre without severe features"**

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Case: CJ

- 33 y/o G3 P2002, nl PN, labored at 40 2/7 wks, NSVD. C/o severe HA 1 hr later and BP 158/92; repeat 162/88. Neg urine protein, No labs sent; observe.
- 30 min later grand mal seizures
- MgSO4 initiated
- 10 min later BP 112/70, P 120; repeat BP 90/40, P 144; BP 70/0
- Abdomen distended, painful and rigid; to OR
- Laparotomy: ruptured liver, hemorrhage, transfused, packed abdomen
- Transported to Tertiary Center
- Eclampsia/HELLP and liver rupture
  - 5 laparotomies
  - 44 u blood products
  - ARDS, 2 wks ventilatory support
  - Renal failure
  - Full recovery over several months

Component change for Preeclampsia

- Proteinuria eliminated as requirement: does not predict outcome
- Diagnosis of Preeclampsia:
  - **HTN with Proteinuria**

    OR
  - **HTN with**
    - Thrombocytopenia (< 100,000 platelets/ml)
    - Impaired liver function (≥ 2X normal)
    - New renal insufficiency (creat > 1.1 mg/dl or 2X creat)
    - Pulmonary edema
    - New-onset cerebral or visual disturbances

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Diagnostic criteria for Preeclampsia

- BP > 20 wks
  - ≥ 140 systolic or ≥ 90 diastolic 2X 4 hrs apart

    OR
  - **≥ 160 systolic or ≥ 110 diastolic 2X minutes apart***
- Proteinuria
  - ≥ 300 mg/24 hr (**or other timed collection***)
  - **Protein/Creatinine ratio ≥ 0.3***
  - 1+ dipstick **(only if other not available*)**

  OR
- **BP (above), no proteinuria, but any severe component***

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Preeclampsia with Severe Features

- BP ≥ 160 systolic or BP ≥ 110 diastolic 2X ≥ 4 hrs apart while on bedrest (unless Rx initiated)
- Thrombocytopenia (platelets < 100,000/ml)
- Abnormal LFT >2X nl, severe RUQ or epigastric pain unresponsive to Rx, no other diagnosis
- Renal insufficiency, creat > 1.1 or 2X baseline
- Pulmonary edema
- Cerebral or visual disturbances

No proteinuria criteria*

No IUGR criteria*

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Proteinuria not required

- Did NOT say: stop checking for proteinuria
- Did say: it is NOT REQUIRED for the diagnosis of Preeclampsia
- Urine dip for protein at each PN visit still recommended!

Protein/Creatinine Ratio

- Spot urine
- No special timing
- Rapid results
- Inexpensive
- No compliance issues

Protein/Creatinine Ratio

- Cote et al meta-analysis
  - P/C ratio accurate at low levels protein
  - Reasonable "rule out" test for proteinuria ≥0.3g/d
  - Cut-off 30 mg/mmol (~0.3): 84% sensitive, 76% specific
- Cote et al accuracy of 24 hr urine
  - 24 hr collections: 13-68% are inaccurate
  - Recommend validation P/C against adverse outcomes, not against 24 hr collections
  - Recommend using P/C

Cote et al, BMJ 2008;336:1003-6
Cote et al, AJOG 2008;199:625-31

Prediction of Preeclampsia

- **Use risk factors from history**
- Not demographics
- Not biochemical analytes
  - Angiogenic factors
- Not biophysical findings
  - Uterine artery Doppler
- No combination of above

Only useful if effective preventive treatment and therapeutic interventions available

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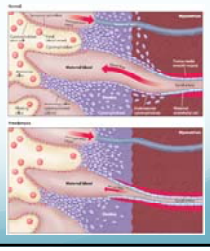
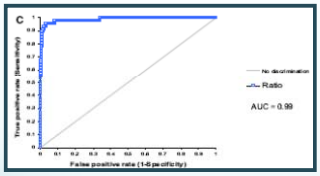
Angiogenic factors to predict Preeclampsia

- s-Flt1 and sEng ↑
  - Elevated in serum of gravidas with PRE
  - Elevated 5 weeks before clinical onset PRE
  - s-Flt-1 levels correlate with PRE severity
  - sEng correlates with HELLP
- VEGF and PlGF ↓ in PRE
- Results in endothelial dysfunction that manifests as clinical symptoms



Angiogenic factors to predict Preeclampsia: ROC curve sFlt1/PlGF



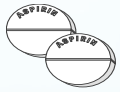
- Clinical lab platform
- All preeclampsia
  - Sensitivity 96%
  - Specificity 97%
- Not FDA approved
- Not available in US

What do you do if + ???

Sunderji AJOG 2010;202:40.e1-7
Beckman Coulter, Chaska MN

Prevention of Preeclampsia

- Hx Pre ≤ 34 wks with PTD: low dose ASA QD
- Hx Pre ≥ 2 pregnancies: low dose ASA QD
- NOT Recommended
  - Vit C or Vit E
  - Salt restricted diet
  - Bedrest or restriction of physical activity
  - Calcium
  - Vit D
  - Fish oil



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Low dose ASA to Prevent Preeclampsia

- Low dose ASA (≤ 81 mg QD)
  - Cochrane meta-analysis 59 trials, >37,000 women
  - 17% reduction in high risk women
  - NNT in high risk women to prevent 1 case: 50
  - NNT in low risk women to prevent 1 case: 500
- High risk
  - Hx Pre ≤ 34 wks with PTD
  - Hx Pre in ≥2 previous pregancies

Duley, Cochrane 2007 (2): CD004659

Preeclampsia without severe features, mild GHTN: Management

- Labs: urine protein, CBC, platelets, LFT's, creatinine
- US to evaluate fetal growth
- BP < 160 systolic, < 110 diastolic: NO Rx
- Serial assessment symptoms, fetal movement
- Twice weekly BP (at least once in office BP)
- Platelets, LFT's, creat, urine P/C (if GHTN) weekly
- Antenatal testing
- IUGR: add umbilical artery Dopplers

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Preeclampsia without severe features, mild GHTN: Management

- Delivery 37 0/7 weeks
- Suspected abruptio placenta: deliver any GA
- Delivery ≥ 34 0/7 weeks
  - IUGR < 5th %tile
  - AFI < 5 cm
  - BPP's persistently ≤ 6/10
  - PROM or progressive labor
- **$MgSO_4$ not universally required**

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Preeclampsia without severe features: $MgSO_4$

- **Did not say** completely stop using MgSO4 in Pre without severe features
- Pre without severe features and no maternal symptoms MgSO4 not universally recommended
- Consider MgSO4 if:
  - Headache
  - Blurred vision
  - Altered mental state
  - Scotomata
  - Clonus
  - RUQ pain

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$MgSO_4$

- Recommended
  - Eclampsia
  - Preeclampsia with severe features
  - Intraoperatively if CS
- Use judgment (not universally required)
  - Preeclampsia without severe features

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$MgSO_4$ for Preeclampsia

- Magnesium side effects vs placebo
  - Respiratory depression 1% vs 0.46%
  - Postpartum hemorrhage 2.4% vs 1%
- Seizures with mild Pre: 0.6% or 1/200
  - If $MgSO_4$ decreases seizures 50%, NNT to prevent 1 seizure = 400
- Seizures with severe Pre: 2% or 1/50
  - NNT to prevent 1 seizure = 76
  - NNT with imminent eclampsia (HA, visual changes, epigastric pain, hyper-reflexia) = 36

Is $MgSO_4$ required for preeclampsia without severe features and what duration?

- Not required
- If used, consider shorter therapy
- Use good clinical judgment
- Know your patient population: CHTN? DM?
- Ominous signs longer duration: HA, blurred vision, epigastric pain, hyper-reflexia
- Reassuring signs pp: diuresis, low BP, no HA or visual symptoms, nl labs

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Preeclampsia with severe features

- Delivery
  - ≥ 34 0/7 weeks
  - < 34 0/7 weeks and unstable
  - < viability (?24, ?23, ?22 weeks)
    - **EXPECTANT MANAGEMENT NOT RECOMMENDED**
- < 34 weeks and stable: Expectant management

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Case: DS

30 y/o G1 IVF pt transported to tertiary center at 23 0/7 wks with severe preeclampsia.

BP 160-180/100-120, 4+ protein.

$MgSO_4$, betamethasone and 2 doses IV hydralazine

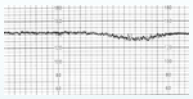
Labs: no evidence of HELLP, 24 hr urine 7.5 g protein.

Fetus: severe IUGR, EFW 380 g, FHR decreased variability, AFI 6.2 and absent EDF.

How should you counsel and manage her?

Case: DS

- Pt was advised of bleak prognosis for fetus, but desperately wanted the pregnancy, declined delivery
- po labetalol: BP improved to 150-160/100
- $MgSO_4$ stopped HD 2
- HD 7 Fetus developed late decels, poor LTV, REDF



- Classical CS 24 0/7 wk: infant 440 g, died DOL 3 from complications of prematurity and IUGR
- Mother did well, d/c home on labetalol, f/u 1 week

Preeclampsia with severe features Expectant management

- Viability to 33 6/7 weeks and stable:
  - Only at center with maternal and neonatal intensive care resources
  - Inpatient only
  - MgSO4 can be d/c when stable
  - Steroids for fetal lung maturity
  - Vitals, symptoms (Q 8 hr) and labs (QD)
  - Antihypertensives if BP ≥ 160 syst, ≥110 diast
  - Antenatal testing
  - US for growth Q 2 wks

Treatment of acute severe HTN

- Hydralazine: 5-10 mg IV or 10 mg IM Q 20-40 min; if no response after 3 doses use second agent
- Labetalol: 20 mg IV, additional 40 mg 10 minutes later, then 80 mg every 10 minutes for 2 additional doses (220 mg max); if no response use second agent
- Nifedipine: 10 mg orally, repeat in 30 minutes
  - May synergize with $MgSO_4$ causing hypotension
- Na nitroprusside drip: 0.25 mcg/kg/min

  (treat no more than 4 hours)
- Decrease, do not normalize BP (maintain fetal and maternal perfusion)
- Target: 150-160/90-105 mmHg

Preeclampsia with severe features < 34 wks: steroids and deliver in 48 hrs

- PPROM
- Labor
- Platelets < 100,000
- IUGR < 5th %tile
- AFI < 5 cm
- UA reversed end-diastolic flow
- Renal dysfunction (new or increasing)
- Stable HELLP

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Preeclampsia with severe features < 34 wks: Deliver immediately

- Uncontrollable severe HTN
- Eclampsia
- Unstable HELLP
- Pulmonary edema
- Abruptio placentae
- DIC
- Nonreassuring fetal status
- Fetal demise

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Case TD

- 30 y/o G 7 P 1142 seen in clinic at 28 6/7 wks. Sent to triage for BP 152/96, P/C 0.23
- History of severe PRE with elevated LFT's last pregnancy at 33 weeks: $MgSO_4$, betamethasone, RCS. Mother and infant did well.
- Baby ASA QD, baseline labs, growth US's in current pregnancy.
- Fetus with normal growth; NST good LTV, no decels

Case TD

- Serial BP's, TID NST's, Labs Q 24 hrs
- Betamethasone
- Labs all in normal range except:

SGOT	12	74
SGPT	21	293

- Increased frequency of labs:

SGOT	12	74	254	418	518
SGPT	21	293	390	575	737

What should you do now?

Case TD

- $MgSO_4$
- 24 hrs after admission: RCS for atypical unstable preeclampsia/HELLP
- Post op BP and LFT's returned to normal, no other lab abnormalities, no proteinuria
- Mother and baby did well

Prior Preeclampsia

- Preconception visit
  - Discuss prognosis
  - Modify lifestyle
  - Assess medical problems
  - Review and modify medications
- Low dose ASA in next pregnancy
  - Preterm delivery with preeclampsia (<34 wks)
  - Preeclampsia in more than one pregnancy

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Case: CJ cont.

- 37 y/o G4 P3003 presents at 6 wks with unplanned pregnancy
- History eclampsia/HELLP and liver rupture 4 yrs ago
  - 5 laparotomies
  - 44 u blood products
  - ARDS, 2 wks ventilatory support
  - Renal failure
  - Full recovery over several months
- What do you advise her to do?

Future pregnancy after HELLP?

Table 3. Pregnancy Outcome After HELLP

	Normotensive women			
	Women (n)	Pregnancies (n)	HELLP (%)	Preeclampsia (%)
Sibai et al[47]	139	192	3	19
Sullivan et al[45]	122	161	19	23
Van Pampus et al[49]	77	92	2	16
Chames et al[50]*	40	42	6	52

HELLP, hemolysis, elevated liver enzymes, and low platelets.
* HELLP at or before 28 weeks of gestation in a previous pregnancy.

Outcomes of subsequent pregnancies in women with HELLP syndrome

Outcome (n = 53)	n (%)
Spontaneous abortion (<20 wks)	5 (9)
Preterm (<37 wks)	26 (49)
Preeclampsia	15 (28)
HELLP	13 (24.5)
Birthweight <10th percentile	2 (4)
Abruptio placentae	1 (1.8)

Sibai Obstet Gynecol 2004;103:981-91

Habli AJOG 2009;201:385 e1-e5

Case: CJ cont.

- Recurrence of Pre and HELLP: 25%
- No data on recurrence of liver rupture
- Low dose ASA
- Home BP monitoring
- Frequent PN visits
- Monthly LFT's, platelets

Case: CJ cont.

- 37 5/7 week office visit
- BP's 142/90, P/C 0.23, platelets 128,000
- Underwent induction for GHTN
- No $MgSO_4$
- NSVD without complication
- BP's decreased after delivery
- Platelets returned to normal
- Home ppd 2; home BP, visit in 1 week
- Internist for long-term f/u

CHTN in Pregnancy

- 2-6% prevalence
- Prevalence rising (age, obesity)
- <20% Severe ≥160/110
- >80% Mild 140-159/90-110

ACOG: *Obset Gynecol 2012*
Meis: *AJOG* 1998

Criteria for Diagnosis of CHTN in Pregnancy

- Blood pressure levels
  - **Mild**: Systolic ≥140 mmHg
    Diastolic ≥90 mmHg
  - **Severe**: Systolic ≥160 mmHg
    Diastolic ≥105 mmHg

New ACOG guidelines 2013 uses diastolic ≥105 mmHg
Note: severe 2002 systolic ≥170 or ≥180, 2012 ≥110 diastolic

- Antihypertensive Rx before pregnancy
- Onset of HTN <20th week of gestation
- Persistence of HTN beyond usual pp period

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CHTN in Pregnancy
Well-Established Complications

Outcome	Incidence	AOR
Preeclampsia	25.3%	X3-10
IUGR	11.1%	X2-3
Abruption	1.5%	X2-3
Preterm birth	38.0%	X3-4
PTB<35 week	18.1%	X4-5
Perinatal death	6.2%	X3-5

Bateman: *AJOG* 2012; Caritis: *NEJM* 1998; Gordon: JRM 2007

CHTN in Pregnancy
Rare Complications

Outcome	AOR
Maternal death	X3-5
Pulmonary edema/CHF	X6-12
Ventilator support	X5-8
Cerebrovascular accident	X4-7
Acute renal failure	X10-16
Stay >6 days	X6-7

Bateman: *AJOG* 2012; Gordon: JRM 2007

Suggested Evaluation for Women with Long Standing or Severe Hypertension

- Electrocardiogram
- Echocardiography
- Ophthalmologic examination
- Serum creatinine
- Urine protein/creatinine ratio
  or
- 24 hour urine for protein and creatinine clearance
- Renal sonogram

Box 2. Suggested Evaluation for Secondary Causes of Hypertension

- Pheochromocytoma
  - Plasma metanephrines
  - 24-hour urine assessment for metanephrines, unconjugated catecholamines
  - Magnetic resonance imaging or computed tomography of adrenal
- Primary aldosteronism
  - Serum potassium level assessment
  - Plasma renin activity, 24-hour urine aldosterone excretion assessment
- Cushing's syndrome
- Sleep apnea
- Methamphetamine or cocaine use
- Renal artery stenosis
  - Renal ultrasound
  - Doppler flow or magnetic resonance angiography

- Refer to physician with expertise in treating HTN

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Laboratory evaluation for CHTN

- Baseline for superimposed preeclampsia
  - Liver function tests
  - Hemoglobin/hematocrit
  - Platelet count
  - Creatinine
  - Urine protein: P/C ratio or 24 hour
- Repeat labs if preeclampsia suspected

Treatment of CHTN

- BP ≥160 systolic or ≥105 diastolic treat with Rx
- BP <160 systolic or <105 diastolic and no end organ disease no Rx
- Rx: maintain 120-160 systolic, 80-105 diastolic
- Antihypertensives: Labetalol, nifedipine or methyldopa
- No ACE, ARB, renin inhibitors, or mineralocorticoid receptor antagonists unless proteinuric renal disease
- End-organ disease or secondary HTN: keep BP in normal range

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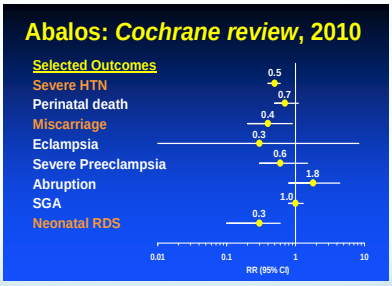
Antihypertensive therapy vs. no treatment or placebo for hypertensive disorders during pregnancy



- 46 trials (N = 4282)
- Point estimates suggest potential for beneficial impact of Rx

Does treating mild CHTN impact the fetus?

- Meta-analysis of 38 trials, von Dadelszen 2002
  - Decreased severe HTN
  - No improvement in perinatal outcomes
  - Increase in frequency of SGA infants
- Magee 2007 randomized pilot trial tight (diastolic 85) vs less tight (diastolic 100) BP control
  - Less tight control
    - More severe HTN
    - Larger infants with fewer complications

CHTN Management: Maternal

- Home BP monitoring (poorly controlled)
- Well controlled BP and exercise:

  continue moderate exercise
- Low dose ASA if prior Pre PTD <34 wks, Pre ≥2
- Follow guidelines for Antihypertensive Rx
- Delivery ≥ 38 0/7 – 39 weeks (no complications)

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CHTN Management: Fetal

- US to screen for IUGR
- Antenatal testing
  - On antihypertensive Rx
  - Underlying medical conditions
  - IUGR
  - Superimposed preeclampsia
- Umbilical artery Dopplers if IUGR

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How do you distinguish CHTN from superimposed preeclampsia?

- Worsening BP: ? systolic >3o, ? diastolic >15 mm
- New onset proteinuria
- Acute worsening of preexisting proteinuria
- Labs can be helpful
- Without severe features: HTN and proteinuria
- With severe features: systemic involvement in addition to HTN and proteinuria

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CHTN with Superimposed Preeclampsia

- Without severe features
  - Delivery at 37 weeks
  - <34 weeks: administer steroids for FLM
- With severe features
  - <34 weeks: administer steroids
  - Expectant management only at center with ICU
  - Delivery ≤ 34 weeks
  - $MgSO_4$ recommended at delivery

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CHTN with Superimposed Preeclampsia

- Deliver immediately
  - Uncontrolled severe hypertension
  - Eclampsia
  - Pulmonary edema
  - Abruptio placentae
  - DIC
  - Nonreassuring fetal status
  - HELLP

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Case: MS

37 y/o G1 at 26 wks transported for CHTN with superimposed preeclampsia. BP 180-200/90-107, 4+ protein, 1+ edema, nausea/emesis and HA. She was started on $MgSO_4$, labetalol IV and increased po to 1200 mg BID, and po hydaralazine begun, betamethasone given.

Labs: 3.5 g protein/24 hr, uric acid 5.3, no HELLP

US: EFW 655 g, normal AFI, BPP 8/8 and nl UA Doppler

What do you do?

Case: MS

HD 2: BP decreased to 150-160/70-100, protein 3+ and $MgSO_4$ discontinued; NST TID, BPP QD.

HD 6: Systolic BP increased to 170-190

What should you do?

Methyldopa was added; the fetus had decreased EDF, BPP 8/8, FHR reassuring.

BP improved, fetus stable.

Case: MS

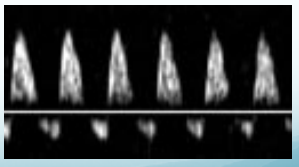
HD 13: Fetus had absent EDF with fair LTV, no decels, BPP 8/8

Do you change management?

Case: MS

HD 15: Maternal visual symptoms, worsening edema, 4+ protein but BP stable. NST poor LTV, reversed EDF.

What do you do?



Case: MS

- Decision for CS: infant 28 1/7 wk, 850 g Apgars 5/8, did well in NICU.
- Mother did well and was D/C'd on POD 3 on labetalol and diuretic.

Postpartum GHTN, Pre, Super Pre management

- Monitor BP at least 72 hrs after delivery
- NSAIDS increase BP and should be avoided
- BP check 7-10 days after delivery
- Maternal symptoms: see sooner for BP
- Universal D/C information on signs and symptoms of Preeclampsia

*https://www.**preeclampsia**.org*

PREECLAMPSIA foundation
6767 N. Wickham Road, Suite 400
Melbourne, FL USA 32940-2025
321.421.6957 office
800.665.9341 toll-free
321.821.0450 fax

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Postpartum HTN

- New onset HTN with HA or visual complaints: $MgSO_4$
- Preeclampsia with severe BP: $MgSO_4$
- BP $\geq$ 150 systolic or $\geq$100 diastolic x 2: Antihypertensive Rx
- Persistent BP $\geq$160 systolic or $\geq$110 diastolic: TREAT within 1 HOUR

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Case: GP

39 year old G1 P1 11 days pp from NSVD presented to the ER with unremitting headache for 4 days; today she began vomiting . BP 180/120. Her highest prenatal or intrapartum BP was 132/74.

- What is the differential diagnosis?
- What laboratory tests would you obtain?
- Would you obtain any imaging studies?

Case: GP

- She had a seizure in the radiology suite after her MRI.
  - Does this change your management?
- About 30 minutes later, she had another seizure.
  - Does this change your management?

Case: GP

- MRI suggests patchy, high signal changes, particularly in the posterior white matter
  - posterior reversible leukoencephalopathy (PRES)
    - eclampsia
    - hypertensive encephalopathy
- How should we treat her?
- What is her prognosis long-term?

Implications for Later Life CV Disease

- 2X increased risk with any preeclampsia
- 8X-9X increased risk with preeclampsia <34 wks
- American Heart Association
  - Pregnancy history part of CV risk evaluation
  - Pre and CV disease share common risk factors
- High risk women:
  - Lifestyle modification
  - Yearly evaluation of BP, lipids, fasting glucose, BMI

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JNC 8: Antihypertensive Therapy Non-pregnant

- Goal <60 y/o: BP <140/90
- DM, Renal: BP <140/90
- AA initial Rx: thiazide diuretic or CCB
- Nonblack: thiazide diuretic, CCB, ACE or ARB

JNC 8: *JAMA* 2014;311:507-520

Thank you !

Questions ?

Summary of main changes

- Be alert to progression of Pre
- Amount of proteinuria does not predict outcome
- IUGR no longer criteria for severe features
- Pre without severe features: do not del until 37 weeks, no bedrest, US for growth and antenatal testing
- Increased awareness of pp Pre
- NSAIDS increase BP; should be avoided

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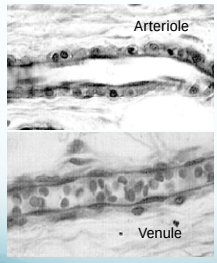
Preeclampsia/HELLP – Eclampsia System Dysfunction



- Endothelial damage
- Protein leakage
- Vasoconstriction
- Ischemia
- Infarction
- Microangiopathic hemolysis
- Lower platelets, ATIII
- Hemorrhagic lesions
- Glomerular endotheliosis
- Hepatoacellular necrosis