

MANAGEMENT OF PREECLAMPSIA AND ECLAMPSIA

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MATERNAL MORTALITY

Causes of maternal mortality in the United States:

Embolism	20%
Hemorrhage	18%
Preeclampsia	16%
Infection	13%
Cardiomyopathy	8%
CVA	5%
Anesthesia	2%

Obstet Gynecol 2003;101:289

DEFINITIONS

The ACOG classification system puts all hypertension during pregnancy into one of four categories:

- **Preeclampsia / Eclampsia** presents after 20 weeks gestation with hypertension $>140/90$, proteinuria and a spectrum of multi-system disorders such as thrombocytopenia.

DEFINITIONS

- **Chronic hypertension** is unrelated to pregnancy and presents before 20 weeks gestation (or before conception).
- **Preeclampsia superimposed on chronic hypertension** presents with new onset thrombocytopenia or proteinuria. Carries ↑↑↑ risk for mother and fetus.

DEFINITIONS

- **Transient or gestational hypertension** is hypertension in late pregnancy without other evidence of preeclampsia that resolves postpartum. Carries no increased risk.

The terms “PIH” or “pregnancy-induced hypertension” are no longer used.

Am J Obstet Gynecol 2000;183:S1-23

ETIOLOGY

?????????

No theory has stood the test of time.

Likewise, no preventive measure has
proven useful.

PREVENTION

The use of 60mg aspirin daily did not prevent development of preeclampsia in 2 large multicenter trials. There was no ↑ risk of complications with aspirin use.

NEJM 1993;329:1123

Lancet 1994;343:619

PATHOGENESIS

- Stage 1, **Abnormal Placentation**: the spiral arteries fail to become dilated, flaccid tubes \pm atherosclerosis \rightarrow reduced placental perfusion and release of vasoactive substances.
- Stage 2, **Maternal Systemic Disorder**: increased sensitivity of the vasculature to any pressor agent, activation of the coagulation cascade \rightarrow microthrombi, and intravascular fluid loss.

PATHOGENESIS

- A gene encoding a protein (sFlt1) is overactive in preeclamptic placentas. This protein is known to thwart blood vessel growth – i.e., antiangiogenic.
- Serum from preeclamptic women stifled development of human blood vessel cells in vitro, while serum from normal pregnant women stimulated cell growth.
- sFlt1 caused preeclampsia symptoms when injected into rats – finally, an animal model!

J Clin Investigation, March 2003

PATHOGENESIS

- High levels of sFlt-1 and low levels of placental growth factor (PlGF) predict development of preeclampsia in women.
- Urinary PlGF levels are reduced at 25-28 weeks in women who subsequently develop preeclampsia (32 pg/ml vs. 234 pg/ml in controls).
- Urine dip screening test for early intervention?

JAMA 2005;293:77

RISK FACTORS

Nulliparity

Age <18, >35

Family, personal hx

Black race

Barrier contraception

Donor egg or sperm

Obesity

Multiple gestations

Diabetes

Collagen vascular dz

Chronic HTN

Thrombophilias

RISK FACTORS

- Normal first pregnancies have increased levels of sFlt-1 (anti-angiogenesis) compared to subsequent pregnancies.
- This may explain the increased risk for preeclampsia in first pregnancies when other factors increase placental sFlt-1 levels or its anti-angiogenic effects.

Am J Obstet Gynecol 2005;193:16

CONTROVERSIAL AREAS

- When and how should delivery occur?
- What should we do if she has a seizure?
- When is invasive monitoring needed?
- How should we manage fluids?
- Platelet counts – how low can we go?
- Is spinal anesthesia for cesarean delivery safe and appropriate?
- Should α -agonists replace ephedrine as pressors?

**CURRENT OBSTETRIC
MANAGEMENT
STRATEGIES**

ANTEPARTUM ASSESSMENT

- Maternal assessment includes defining severity and end-organ involvement, eg. hematologic, renal, hepatic, neurologic.
- Fetal evaluation includes nonstress test, ultrasound for growth and gestational age, and biophysical profile.
- Then, delivery or expectant management?

ANTEPARTUM ASSESSMENT

- Hematologic: ↓ platelets, hemolysis
- Hepatic: epigastric pain, ↑ LFTs
- Neurologic: headache, visual changes
- Renal: oliguria, ↑ creatinine, proteinuria
- Pulmonary: pulmonary edema
- Placental: IUGR, oligohydramnios, abnormal umbilical artery Doppler studies

Severe Preeclampsia

- Admit to labor and delivery area
- Maternal and fetal evaluation x 24 hrs
- Parenteral $MgSO_4$ x 24 hrs.
- Antihypertensives if DBP ≥ 110 mmHg

Maternal distress
Severe IUGR
Fetal distress
Labor
>34 weeks gestation

Yes

Delivery

No

<28 weeks

Maternal counseling

≥ 24 weeks

Intensive maternal-fetal management

28-32 weeks

Steroids
Antihypertensive drugs
Daily evaluation of maternal & fetal conditions

≤ 23 weeks

Termination of pregnancy

33-34 weeks

Amniocentesis

Immature fluid

Steroids
Deliver 48 hrs later

Mature fluid

Delivery

TREATMENT OF HELLP

A comparison of outcomes in 474 patients with HELLP syndrome before / after adopting use of high dose dexamethasone (10mg q 12 hrs):

- Improved laboratory parameters (platelets)
- Less disease progression
- Lesser degree of HTN and need for therapy
- Reduced use of transfusion
- Fewer maternal morbidities
- Shortened postpartum recovery

Am J Obstet Gynecol 2003;189:830

TREATMENT OF HELLP

A retrospective analysis of 69 women with HELLP syndrome and platelets < 90K showed that those who received steroids were *more* likely to receive regional anesthesia for delivery (57% vs 0%) and *less* likely to receive general anesthesia (22% vs 100%), presumably due to higher platelet counts.

Am J Obstet Gynecol 2002;186:475

TREATMENT OF HELLP

132 women with HELLP syndrome were randomized to dexamethasone or placebo.

- No difference was found in time to recovery of platelet counts or LFTs.
- No difference in length of hospitalization.
- No difference in complication rates.
- Sickest patients (platelets < 50K) did show benefit.

Am J Obstet Gynecol 2005;193:1591

MODE OF DELIVERY

- Although eclampsia is an indication for *delivery*, it is not an indication for *cesarean* delivery.
- 93 women with severe preeclampsia had either a cesarean delivery or a trial of labor. 63% who attempted were able to deliver vaginally.
- Morbidity was *not* lower in the cesarean group, and pulmonary complications were actually *more* common in mother and neonate.

Am J Obstet Gynecol 2002;186:921

**MANAGEMENT OF
HYPERTENSION
AND USE OF INVASIVE
MONITORING**

MATERNAL MORTALITY

Maternal mortality from hypertensive disorders of pregnancy is either due to:

- Ischemia / hypoperfusion / vasospasm manifest as eclampsia, or
- Hyperperfusion / hypertension manifest as cerebrovascular accidents.

Obstet Gynecol 2003;101:289

ENDPOINTS OF THERAPY

- Prevent maternal morbidity from pulmonary edema or cerebral hemorrhage
- Decrease systolic pressure < 160 mmHg and diastolic pressure < 110 mmHg
- Watch for fetal compromise due to uteroplacental insufficiency as maternal pressure is lowered

ENDPOINTS OF THERAPY

Should there be more focus on *systolic* hypertension?

In a review of 28 patients who had a stroke associated with diagnosed severe preeclampsia:

- 93% were hemorrhagic events
- 54% died; all but 3 survivors had severe permanent disability
- 100% had systolic pressure > 155 mmHg, while only 12% had diastolic pressure > 110 mmHg
- Treat HTN to keep systolic pressures < 160 mmHg

Obstet Gynecol 2005;105:246

HEMODYNAMIC SUBSETS

Cardiac Index (CI)	HIGH	NORMAL	LOW
Afterload (SVR)	LOW	HIGH	HIGH
Volume (PCWP)	NORMAL	LOW	HIGH
Therapy	β -Blocker	Volume / Vasodilator	Vasodilator

INVASIVE MONITORING

Arterial lines are low risk and useful for:

- Blood pressures consistently $> 160/110$
- Use of vasodilator infusions
- Coagulopathy
- Hypoxia / pulmonary edema
- Obesity or marked edema (access for labs)

INVASIVE MONITORING

PA catheter monitoring is high risk and not proven to affect outcome. May be useful:

- Cardiac failure or pulmonary edema
- Large A-a O₂ gradient
- Oliguria despite volume and afterload reduction

Consider your nursing resources on L&D!

INVASIVE MONITORING

Why not just a CVP?

- Risks of central access are very similar
- Correlation with PCWP is very poor for CVP values > 6
- Provides no measure of cardiac output or vascular resistance

INVASIVE MONITORING

“Critically ill obstetric patients differ from those usually encountered in medical-surgical intensive care units. They are likely to be younger, to have fewer major organ systems involved, to have fewer chronic illnesses, and to recover fully with supportive care.”

Chest 1992;101:1429

INVASIVE MONITORING

From the ASA Practice Guidelines on Pulmonary Artery Catheterization, 2003:

“PA catheterization has been recommended for severe preeclampsia, case reports have supported its value, and its use in critical illness seems common, but controlled clinical outcome studies have not been reported.”

Anesthesiology 2003;99:998

INVASIVE MONITORING

ASA Practice Guidelines on Obstetrical Anesthesia:

“...it is not necessary to routinely use central invasive hemodynamic monitoring for severe preeclamptic parturients. The decision to perform invasive hemodynamic monitoring should be individualized and based on clinical indications that include the patient’s medical history and cardiovascular risk factors.”

Anesthesiology 1999;90:600

MAGNESIUM SULFATE

There is no substantial long-term effect on BP, but Mg^{++} has other beneficial effects:

- Attenuates the vascular response to pressor substances (endogenous or exogenous)
- Dilates vascular beds by multiple effects:
 - ↑ prostacyclin release by endothelial cells,
 - ↓ plasma renin activity, ↓ ACE levels

HYDRALAZINE

Pros:

- Arteriolar vasodilator
- Increases uterine and renal blood flow

Cons:

- Unpredictable onset and duration
- Reflex tachycardia
- Ventricular dysrhythmias
- Neonatal hypotension

HYDRALAZINE

- A meta-analysis of 21 studies using hydralazine for treatment of hypertension in pregnancy does *not* support its use as first-line therapy.
- Hydralazine was less effective than other drugs and was associated with more adverse outcomes – hypotension, abruption, nonreassuring FHT, C/S, oliguria, and lower Apgar score at one minute.

BMJ 2003;327:955

LABETALOL

Pros:

- No change in heart rate or cardiac output
- Decreases SVR
- Preserves placental blood flow
- No sympathetic blockade in neonate

Cons:

- Variable dose requirements
- Variable duration

NITROPRUSSIDE

Pros:

- Fast onset
- Short duration
- Preserves uterine blood flow (UBF)

Cons:

- Cyanide toxicity
- Reflex tachycardia
- Cerebral vasodilator
- Potential hypoxia (↓ HPV)
- Inconvenient to use

CALCIUM CHANNEL BLOCKERS

Pros:

- Increased renal perfusion and urine output
- Rapid smooth ↓ in BP

Cons:

- Interaction with magnesium sulfate??
- Uterine relaxation / atony
- Headache

Does use of nifedipine with magnesium increase serious side effects?

- In a retrospective review of 377 women who received MgSO_4 alone, MgSO_4 + nifedipine, or MgSO_4 + another anti-hypertensive, there was *no* increase in neuromuscular weakness and actually *less* hypotension in the nifedipine group.
- Most women receiving MgSO_4 experienced some side effects: nausea and vomiting, drowsiness or confusion, dizziness or flushing.

Am J Obstet Gynecol 2005;193;153

NIMODIPINE

- Reverses vasospasm in small cerebral resistance vessels on trans-cranial Doppler exam.
- Produces a moderate decrease in maternal BP using 30mg PO q 4 hours.
- Well-tolerated by the fetus despite placental transfer.

Am J Obstet Gynecol 1994;171:417

VASODILATORS

- An in vitro study of the effect of vasodilators on isolated human umbilical arteries found:

NTG > hydralazine = nicardipine

- Fenoldopam actually caused *vasoconstriction* at high concentrations → mediated by α adrenergic receptors.

Anesth Analg 2003;96:539

ADVERSE EFFECTS

Esmolol	Decreased fetal pO ₂ Prolonged fetal β -blockade Decreases fetal tolerance of asphyxia
Clonidine	Fetal hypoxemia Increased uterine tone Decreased uterine blood flow
ACE inhibitors	Neonatal hypotension Neonatal renal failure Teratogenicity

THERAPEUTIC ANESTHETIC

20 severely preeclamptic patients were randomized to usual treatments \pm long term epidural analgesia. Positive findings in the epidural group:

- Lower blood pressures
- \uparrow platelet counts
- \downarrow umbilical artery resistance
- 36 vs 10 days from admission to delivery
- \uparrow birth weight (2240 vs 1590 grams)

J Human Hypertension 1999;13:167

THERAPEUTIC ANESTHETIC

A small pilot study of women with IUGR or preeclampsia at 22-32 weeks randomized them to “usual therapy” or chronic epidural local anesthetic infusion. The low-dose epidural group had improved uteroplacental perfusion and a longer time to delivery.

Anesthesiology 2004;100:SOAP A21

**PREVENTION AND
MANAGEMENT OF
SEIZURES / ECLAMPSIA**

MAGNESIUM

There is now international consensus that magnesium is the treatment of choice for preeclampsia and eclampsia, but the mechanism remains debatable.

NEJM 2003;348:275

MAGNESIUM

- Eclamptic seizures may be due to local ischemia produced by severe vasospasm.
- Magnesium promotes prostacyclin (PGI₂) production by endothelial cells.
- Prostacyclin is a vasodilator and platelet inhibitor.

MAGNESIUM vs PLACEBO

- In the MAGPIE Trial, 5071 women were randomized to receive magnesium and 5070 to receive placebo for treatment of preeclampsia.
- Benefits in the magnesium group:
 1. 58% lower risk of eclamptic seizures
 2. Relative risk of abruption was 0.67.
 3. Relative risk of maternal mortality was 0.55.

Lancet 2002;359:1877

MAGNESIUM vs PHENYTOIN

- 2138 severely hypertensive women were randomized to receive phenytoin or magnesium sulfate for seizure prophylaxis during labor and delivery.
 - Incidence of seizures:
 - 0/1040 in magnesium group
 - 10/1089 in phenytoin group (p=0.004)
- NEJM 1995;333:201

MAGNESIUM vs DIAZEPAM

- 905 women *with eclampsia* were randomized to received magnesium or diazepam (10mg loading plus an infusion titrated to consciousness) for prevention of recurrent seizures.
- The magnesium group had 52% lower risk of recurrent convulsions.

Lancet 1995;345:1455

MAGNESIUM vs NIMODIPINE

- 1650 women with severe preeclampsia were randomly assigned to receive oral nimodipine (60mg q 4 hours) or IV magnesium sulfate from admission through 24 hours postpartum.
- The risk of eclampsia was 3.2 times higher in the nimodipine group, especially postpartum.
- More women in the Mg group needed anti-hypertensive therapy.

NEJM 2003;348:304

MAGNESIUM THERAPY

- 4-6 gm loading dose over 20 minutes
- 2 gm/hr infusion is titrated against deep tendon reflexes and/or magnesium levels.
- Clearance is reduced with renal insufficiency → monitor creatinine.
- Signs of toxicity *may* be temporized with calcium, but be prepared for airway management.

MAGNESIUM TOXICITY

Loss of patellar reflex	• 10 mg/dl
Feelings of warmth	• 10 mg/dl
Somnolence, slurred speech	• 10 mg/dl
Muscular paralysis	• 15 mg/dl
Respiratory difficulty	• 15 mg/dl
Cardiac arrest	• 30 mg/dl

ADVERSE EFFECTS OF MAGNESIUM

- Tocolytic effects: prolonged labor and ↑ bleeding at delivery
- Decreased FHR variability
- Maternal and neonatal neuromuscular depression
- Low Apgar scores?
- Maternal cardiac toxicity at high doses
- Maternal respiratory depression

RISK-BENEFIT OF MAGNESIUM THERAPY

- Mild preeclampsia: 400 women need to be treated to prevent 1 seizure (assuming risk ↓ 60%).

Risk > Benefit

- Severe preeclampsia: NNT = 129 women.

Risk = Benefit

- Severe preeclampsia with symptoms (HA, blurred vision, epigastric pain): NNT = 36.

Benefit > Risk

Am J Obstet Gynecol 2004;190:1520

MANAGEMENT OF SEIZURES

- Oxygen supplementation by mask
- Airway support vs. intubation
- Left or right lateral position
- Thiopental 50-100mg IV will terminate seizure.
- Administer an additional 2gm magnesium bolus.
- Avoid polypharmacy!
- Ignore the fetus unless abruption or cord prolapse has occurred. In-utero resuscitation is best.

Obstet Gynecol 2005;105:402

CRITERIA FOR CT/MRI

- Recurrent seizures
- Focal seizures
- Seizures despite therapeutic and repeated magnesium dose
- Decreasing level of consciousness
- Differential diagnosis: aneurysm or AVM, cerebral venous thrombosis, metabolics...

**ANESTHETIC MANAGEMENT
DURING LABOR AND
DELIVERY**

LABOR ANALGESIA

Advantages of regional analgesia:

- Best quality of analgesia.
- Attenuates hypertensive responses to pain.
- Circulating catecholamines are reduced.
- Using dilute solutions does not require much (any?) fluid preloading.

FLUID MANAGEMENT

- The vasculature has been described as “contracted and porous but not underfilled”.
- Crystalloids and colloids readily leak out → pulmonary edema postpartum.
- Typical obstetric management = run “dry” at 80-100 mL total per hour.
- Careful and conservative preload for regional *anesthesia*, ?? none for *analgesia*.

LABOR ANALGESIA

- 738 women with preeclampsia were randomized to epidural or IV PCA meperidine for labor analgesia.
- Cesarean delivery rates were similar.
- Neonates in the IV PCA group required more naloxone (12% vs 1%).
- Epidural patients had a longer second stage of labor, ↑ forceps deliveries, and required ephedrine more often (11 vs 0%).
- Epidural pain relief was superior.

Am J Obstet Gynecol 2001;185:970

LABOR ANALGESIA

- A comparison of PCA opioid vs. epidural analgesia for women with severe preeclampsia:
- No difference in cesarean delivery rates.
- Neonates in the opioid group required *more* naloxone (54% vs 9%).
- Epidural patients required ephedrine more often (9% vs 0%) *but* had significantly better pain relief.
- There were no difference in preeclampsia-related complications.

Obstet Gynecol 2002;99:452

ACOG PRACTICE BULLETIN #33

January 2002

“With improved techniques over the past two decades, regional anesthesia has become the preferred technique for women with severe preeclampsia and eclampsia....A secondary analysis in the NICHD trial of low-dose aspirin reported that epidural anesthesia was not associated with an increased rate of cesarean delivery, pulmonary edema or renal failure.”

PLATELET COUNTS

- There is no test and no specific result that predicts bleeding into the epidural space.
- Most obstetric anesthesiologists are comfortable with >75K if stable, no clinical signs of bleeding.
- TEG adds information, but there is still no magic cut-off. Pregnancy → hypercoagulable state.

Br J Anaesth 1996;77:157

PLATELET COUNTS – HOW LOW CAN YOU GO?

Balance the risk-benefit ratio for each case:

- **Pro regional:** worrisome airway exam, lengthy induction, rarity of epidural hematoma (~1:100,000; 8 OB cases in the world literature)
- **Pro parenteral or general:** clinical signs of bleeding, rapidly worsening coagulation tests, need for urgent cesarean and a good airway
- The use of regional with borderline labs requires frequent intra and postpartum neuro checks.

NEUROLOGIC INJURY

A 10-year review of severe complications following 1.7 million spinal or epidural blocks found:

- More complications after epidurals than spinal
- More injuries in surgical than obstetric patients (incidence after obstetric epidural was 1:25,000 vs 1:3600 after surgical epidurals in females)
- Neuraxial hematoma = 1:200,000 in obstetric patients - one each after spinal or epidural catheter removal – **both patients had HELLP syndrome.**

Anesthesiology 2004;101:950

INTRAVENOUS FENTANYL PCA

- Fentanyl bolus loading dose 2-3 μ g/kg
- Initial parameters: Bolus: 50 μ g
Lockout: 10 minutes
Basal: none
- As labor progresses and titration is needed, decrease lockout from 10 \rightarrow 5 minutes, then increase bolus from 50 \rightarrow 75 μ g.

Clin Obstet Gynecol 2003;46:616

CESAREAN ANESTHESIA

Several small studies have shown no difference in the incidence of hypotension or maternal or fetal outcome when comparing spinal to epidural anesthesia.

Obstet Gynecol 1995;86:193

Anesthesiology 1999;90:1276

IJOA 1999;8:85

CESAREAN ANESTHESIA

Women with severe preeclampsia ($\geq 160/110$) had *less* hypotension after spinal anesthesia for cesarean than healthy women (17% vs 53%), despite receiving less fluid preload and a larger dose of bupivacaine in their spinal.

Anesth Analg 2003;97:867

CESAREAN ANESTHESIA

Is the decrease in hypotension due to preeclamptic factors or a smaller uterus?

- During spinal anesthesia for cesarean, preeclamptic patients had less hypotension (RR 0.6) and required less ephedrine (10mg vs 16mg) than parturients with preterm pregnancies.

Anesth Analg 2005;101:869

CESAREAN ANESTHESIA

In a randomized trial, spinal and epidural anesthesia were compared in severely preeclamptic patients.

- Hypotension was more frequent with spinal.
- More ephedrine use with spinal (6 vs 0mg).
- Duration of hypotension was short (≤ 1 min).
- Neonatal outcomes were similar in both groups.

Anesth Analg 2005;101:862

CESAREAN ANESTHESIA

Can a lower dose of spinal anesthetic be used?

- 46 women received a combined spinal-epidural anesthetic for cesarean using 7.5mg bupivacaine and 25 μ g fentanyl. Four needed additional epidural 2% lidocaine to attain a T4 level.
- There were modest hemodynamic changes and no adverse neonatal effects.

Reg Anesth Pain Med 2001;26:46-51

CHOICE OF PRESSOR

Consistently, clinical studies in humans have shown that use of α -agonists versus ephedrine produces better umbilical pH values and less maternal nausea. Ephedrine may \uparrow fetal oxygen consumption, thereby \downarrow overall oxygen delivery.

Anesth Analg 2002;94:920

Anesthesiology 2002;97:1582

Br J Anaesth 2004;92:459

CHOICE OF PRESSOR

- Patients with severe preeclampsia were randomized to *spinal or general* anesthesia for cesarean delivery for NRFHT.
- Spinal anesthesia was associated with more acidotic fetal pH values and higher base deficits.
- Maternal hemodynamics were similar, but *patients receiving spinal anesthesia received more ephedrine (14 vs 3mg)*. Did this affect acidosis?

Anesthesiology 2003;99:561

AIRWAY ISSUES: LMA?

During cesarean delivery for HELLP syndrome, a patient could not be intubated or ventilated. A ProSeal™ LMA was inserted and the stomach drained of 300ml. Postoperatively she was ventilated for 8 hours until stabilized, using the LMA.

Anesth Analg 2004;98:1467

POSTPARTUM ISSUES

- Acute and long term blood pressure control.
- Fluid mobilization → monitor urine output, lung fields and pulse oximetry.
- Continue magnesium for 24 hours.
- Thrombocytopenia may not resolve for several days. Epidural catheter removal?
- 33% of eclampsia occurs postpartum.

ECLAMPSIA

In a review of 89 cases of eclampsia:

- 33% had seizures postpartum.
- 79% of those presented > 48 hours postpartum.
- Most did *not* have an antepartum diagnosis of preeclampsia.
- Most *had* prodromal symptoms (headache, visual changes).

Am J Obstet Gynecol 2002;186:1174

CONCLUSIONS

- Be conservative with fluid preloading.
- Normalize low blood pressure with phenylephrine in preference to ephedrine.
- Use platelet count trends; there is no absolute value to use as a cut-off.
- Spinal anesthesia for cesarean delivery is safe. Use the smallest dose advisable and treat hypotension with α -agonists.

