

Anesthetic Management of the Preeclamptic Patient

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Introduction

Preeclampsia remains one of the three leading causes of maternal mortality in the United States, with the specific cause of death usually stroke. In contrast to other causes of maternal mortality such as hemorrhage and anesthesia that are decreasing in incidence, deaths due to preeclampsia have remained constant for at least 30 years. Preeclampsia occurs in 6-8% of pregnancies with 75% of cases being mild and 25% being severe. Anesthesiologists are involved in the delivery of these high risk parturients and should consider themselves an important part of the team when caring for these critically ill patients.

Definitions

In 2000 the American College of Obstetricians and Gynecologists (ACOG) developed a new classification system for hypertensive diseases of pregnancy. (1) Besides new terminology, the definitions provide an estimate of risk for the mother and fetus.

- Preeclampsia / Eclampsia presents after 20 weeks gestation with hypertension > 140/90, proteinuria, and a spectrum of multi-system dysfunction such as thrombocytopenia. HELLP syndrome is a subset of severe preeclampsia defined by hemolysis (H), elevated liver enzymes (EL) and low platelets (LP).
- 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. This diagnosis carries a substantial risk for the mother and fetus.
- Transient or gestational hypertension is hypertension in late pregnancy, without other evidence of preeclampsia, which resolves postpartum. The diagnosis carries no increased risk.
- The terms "PIH" or "pregnancy-induced hypertension" are no longer used.

Etiology / Pathogenesis

Despite years of research, the etiology of preeclampsia remains unknown. Theories include placental origin, immunologic origin and genetic predisposition. No theory has stood the test of time, and no preventive measure has proven useful. Preventive measures that have been tested include supplementation with magnesium, zinc, fish oil, anti-oxidant vitamins (C and E) and calcium, protein or salt restriction, antihypertensive medications in women with chronic hypertension, heparin or LMWH treatment, and exercise. (2) None have reduced the incidence of preeclampsia. Low-dose aspirin therapy provided a small decrease in preeclampsia and fetal/neonatal deaths, and may be used in high-risk pregnancies. In contrast, the risk factors for developing preeclampsia are well known: nulliparity, extremes of age (< 18 and > 35), a family or personal history of preeclampsia, barrier contraception and donor egg or sperm, black race, obesity, multiple gestations (twins, triplets), thrombophilias, and vascular diseases such as diabetes, collagen vascular disorders, and chronic hypertension.

The pathophysiology of preeclampsia develops in early and late stages. The early stage involves abnormal placentation. The spiral arteries fail to become dilated, flaccid vessels seen in normal pregnancies, and may even show signs of atherosclerosis. This reduces placental perfusion and leads to release of vasoactive substances. The later stage is a maternal systemic disorder with increased sensitivity of the vasculature to any pressor agent, activation of the coagulation cascade, microthrombi and intravascular fluid loss. Vasospasm, hemoconcentration, and ischemic changes in the placenta, kidney, liver and brain are seen.

Prediction / Diagnostic Tools

A gene encoding a protein (sFlt1) is overactive in preeclamptic placentas. This protein is known to thwart blood vessel growth; i.e., it is anti-angiogenic. There is growing evidence that the measurement of certain antiangiogenic proteins can predict preeclampsia months before its clinical onset. Recent work suggests a key role for altered expression of placental antiangiogenic factors, soluble Flt1 and soluble endoglin. They are secreted by the placenta and increase in the maternal circulation weeks before the onset of preeclampsia, producing systemic endothelial dysfunction such as hypertension, proteinuria and the other manifestations of preeclampsia. A systematic review of the literature on the use of elevated sFlt-1 and reduced placental growth factor (PlGF) in predicting preeclampsia concluded that third-trimester increases in sFlt-1 combined with decreases in placental growth factor levels are

associated with severe preeclampsia. Whether they can be used for screening is unclear, but prospective studies needed to determine their clinical usefulness are starting to appear. A comparison of soluble sFlt-1 and soluble endoglin levels in gestational hypertension, chronic hypertension, preeclampsia and normal pregnancies demonstrated a high sensitivity and specificity in differentiating women with preeclampsia from those with other hypertensive diseases during pregnancy. (3)

Another step forward occurred in 2008 with the publication of a study showing that a preeclampsia-like syndrome developed in mice injected with autoantibodies that activate the angiotensin II type 1a (AT1 receptor). (4) They also showed that the syndrome was prevented when the mice were also injected with losartan, an AT1 receptor antagonist. If confirmed in human studies, clinicians could monitor autoantibody levels and detect the disease weeks before symptoms of hypertension, proteinuria, glomerular endotheliosis, placental abnormalities and growth-restricted fetuses develop. Drugs could be developed to inhibit the activation of the AT1 receptor, since ACE inhibitors such as losartan are teratogenic in humans. (4)

Controversial Areas in the Clinical Management of the Patient with Preeclampsia

- When and how should delivery occur, especially when preeclampsia develops at an early gestational age?
- When is invasive monitoring needed?
- What are the benefits and risks of various anti-hypertensives?
- How should we manage an eclamptic seizure?
- Why administer magnesium versus other anti-seizure medications?
- How should we manage fluid intake?
- Platelet counts – how low can we go during neuraxial anesthetic management?
- Is spinal anesthesia for cesarean delivery safe and appropriate in severe preeclampsia?
- Should α -agonists replace ephedrine as our first-line pressor to treat hypotension?

Current Obstetric Management Strategies

The only cure for preeclampsia is delivery, but the benefit to the mother must be weighed against the risk of prematurity to the fetus. Women with gestational hypertension and mild preeclampsia may be managed expectantly at home with frequent maternal monitoring and fetal surveillance. Any patient with severe preeclampsia must be admitted to L&D for assessment and development of a delivery plan. Those with a favorable cervix may undergo induction, but elective cesarean delivery should be considered for patients in very early gestation who have an unfavorable cervix.

Maternal assessment is done to define the extent of end-organ involvement. Systems evaluated should include: hematologic (\downarrow platelets, hemolysis), hepatic (epigastric pain, \uparrow LFT), neurologic (headache, visual changes), renal (oliguria, proteinuria, \uparrow creatinine), pulmonary (pulmonary edema), and placental (growth restricted fetus, oligohydramnios, and abnormal umbilical artery Doppler studies). Fetal evaluation will include a non-stress test, ultrasound for growth and gestational age, and biophysical profile. Based on the results of the evaluations, a decision for immediate delivery or in-hospital expectant management will be made. If the pregnancy is < 34 weeks, there may be an attempt to delay delivery for 48 hours to administer steroids for fetal lung maturity, but this requires daily maternal and fetal monitoring, magnesium sulfate infusion and anti-hypertensive drugs as needed for systolic BP > 170 or diastolic BP > 110 mmHg. (5)

HELLP syndrome is a variant and the most severe form of preeclampsia. Use of high-dose glucocorticoids (dexamethasone 10mg BID for example) has been reported to improve maternal and fetal outcome, but without large multicenter trials to define the limits of benefit and any maternal or fetal risk. A review of the current literature on use of glucocorticoids for HELLP syndrome (including a management algorithm) concludes that the bulk of evidence to date is positive - improved platelet count, reduced stroke and death, and less hepatorenal morbidity. The authors conclude that glucocorticoids should remain the cornerstone of treatment for HELLP. (6)

Management of Hypertension and Use of Invasive Monitoring

The goal of anti-hypertensive therapy is to prevent maternal morbidity from pulmonary edema or cerebral hemorrhage by decreasing systolic blood pressure < 160 mmHg and diastolic < 110 mmHg. At the same time, treatment should not impair uteroplacental perfusion or cause fetal compromise. A recent review suggests systolic hypertension is more important for preventing stroke from severe preeclampsia. (7) They found that 93% of the

strokes they reviewed were hemorrhagic, 54% of women died, and all but 3 who lived had severe permanent disability. All had systolic pressure > 155 mmHg while only 12% had diastolic pressure > 110 mmHg.

Use of invasive monitoring is rarely necessary in obstetric patients. To quote, "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." (8) However, arterial lines are low risk and can be useful in patients whose blood pressures are consistently > 160/110 mmHg as well as when vasodilator infusions are deemed necessary. They may also be useful for patients with coagulopathy needing frequent blood draws and when the patient is obese or has marked edema making venipuncture difficult. If pulmonary edema develops, the arterial line can be used to monitor arterial blood gases. In contrast, central venous monitoring is higher risk and not proven to affect outcome. A CVP or PA catheter may be useful if there is cardiac failure or pulmonary edema, a large A-a oxygen gradient, or oliguria despite fluid administration and afterload reduction. Consider your nursing resources on L&D before initiating invasive monitors; can they manage a CVP or pulmonary artery catheter on L&D, or will ICU admission be necessary?

Numerous agents are effective and safe to use as anti-hypertensives in severe preeclampsia:

1. Magnesium sulfate has no substantial long-term effect on blood pressure, but has other beneficial effects. It attenuates the vascular response to pressor substances (either endogenous or exogenous) and dilates vascular beds by increasing prostacyclin release from endothelial cells, decreasing plasma renin activity and decreasing ACE levels.
2. Hydralazine 5-20mg is a popular choice in obstetrics because it is an arteriolar vasodilator that increases uterine and renal blood flow. However it has an unpredictable onset and duration, causes reflex tachycardia and occasionally ventricular arrhythmias. It has also been reported to cause neonatal hypotension by crossing the placenta.
3. Labetalol decreases systemic vascular resistance without maternal tachycardia and while preserving placental blood flow. It does not cause sympathetic blockade in the neonate. It can be transitioned to an oral form after delivery. However its dosing and duration are quite variable.
4. Nitroprusside has a fast onset, short duration, and preserves uterine blood flow. However there is reflex tachycardia and the potential for cyanide toxicity. It causes cerebral vasodilation and potential hypoxia from decreased hypoxic pulmonary vasoconstriction. Finally, it is inconvenient to use and requires an arterial line, as does nitroglycerin.
5. Calcium channel blockers such as nifedipine and nimodipine cause a rapid smooth fall in blood pressure while increasing renal perfusion and urine output. Although there has been concern about combining magnesium and nifedipine, a study found there was no increase in muscle weakness over magnesium alone and there was less hypotension with nifedipine than with other anti-hypertensives. (9) Nimodipine reverses cerebral vasospasm measured by trans-cranial Doppler and is well-tolerated by mother and fetus. However, calcium channel blockers cause uterine relaxation, making induction of labor more difficult and causing atony after delivery.

Prevention and Management of Seizures / Eclampsia

Eclampsia has a maternal mortality rate of ~4% and a perinatal mortality rate of 13-30%. Seizures occur antepartum in 50% of patients, intrapartum in 25% and postpartum in 25%. Why do we use magnesium to prevent eclampsia in preeclamptic patients versus other anti-seizure medications? In large randomized clinical trials, magnesium has been proven superior to placebo (58% lower risk of seizures), phenytoin (no seizures in the magnesium group versus ~1% in the phenytoin group), diazepam (52% lower risk of recurrent convulsions), and nimodipine (risk of eclampsia was 3.2 times higher in the nimodipine group). No therapy has proven superior for the prevention of eclampsia. (10, 11)

Magnesium therapy can cause maternal morbidity and unpleasant side effects however. It has tocolytic properties that prolong labor and increase bleeding at delivery; it decreases fetal heart rate variability, depresses maternal and neonatal neuromuscular function, and can cause maternal respiratory depression and cardiac toxicity at high blood levels. Clearance is reduced with renal insufficiency, and signs of toxicity are only partially reversed with calcium. Since the major complications of preeclampsia occur in the 25% of patients with the severe form of the disease, should magnesium be used in mild preeclampsia? What is the risk/benefit ratio for the mother? A decision analytic model of magnesium therapy or no magnesium therapy found that 400 women with mild preeclampsia need to be treated to prevent 1 seizure. The number needed to treat to prevent a seizure (NNT) fell to 129 in severe

preeclampsia, and the NNT fell further to only 36 in severe preeclampsia with symptoms such as headache, visual disturbances or epigastric pain. (12) Not all women with mild preeclampsia will need to receive magnesium sulfate.

When an eclamptic seizure occurs, the following steps should be taken:

- Administer high flow supplemental oxygen by mask and place a pulse oximeter.
- Turn her full left or right lateral decubitus and have suction immediately available.
- Give a small dose of propofol or thiopental to terminate the seizure if available. Avoid poly-pharmacy and long-lasting medications so that a neurologic exam can be done as soon as possible.
- Administer an additional 2 gram magnesium sulfate bolus.
- Monitor the fetus if possible, but recognize that heart rate abnormalities are common and usually resolve soon after the seizure is terminated. Do not intervene unless abruption or cord prolapse has occurred.
- Consider CT or MRI imaging to rule out a cerebral hemorrhage if seizures are recurrent or focal, if seizures occur despite therapeutic and repeated magnesium dosing, or if there is decreasing level of consciousness when not post-ictal.
- Although eclampsia is an indication for delivery, it is not an indication for cesarean delivery. Consider whether induction is feasible or whether labor is already progressing.

Anesthetic Management During Labor and Delivery

When the decision has been made to proceed to delivery, the anesthesiologist must have 3 potential scenarios in place: labor followed by a spontaneous or instrumented vaginal delivery, labor followed by an urgent or emergent cesarean for fetal or maternal reasons, and planned cesarean for the patient who is not a candidate to labor. All must take into account whether the use of neuraxial analgesia is appropriate based on platelet count or other measure of coagulopathy.

The advantages of neuraxial analgesia for labor are numerous. It provides the best quality of analgesia, attenuates hypertensive responses to pain, reduces circulating catecholamines, and does not require preloading with fluids when using dilute local anesthetic / opioid solutions. Two studies have compared the use of intravenous patient-controlled opioids (IV PCA) to epidural analgesia for women with severe preeclampsia. In the first, 738 women were randomized to IV PCA or epidural, and cesarean delivery rates were similar. (13) Neonates in the IV PCA group required more naloxone (12% versus 1%), but women in the epidural group had a longer second stage of labor, more forceps deliveries and required ephedrine more often (11% versus 0%). Not surprisingly, epidural pain relief was superior. (13) Results were similar in the second study. (14) There was no difference in cesarean delivery rates, neonates were more likely to receive naloxone in the opioid group (54% versus 9%), and epidural patients had significantly better pain relief but required more ephedrine (9% versus 0%). Perhaps most importantly, there were no differences in preeclampsia-related complications. (14) ACOG makes a strong statement supporting regional anesthesia in their Practice Bulletin "Diagnosis and Management of Preeclampsia and Eclampsia". "With improved techniques over the past two decades, regional anesthesia has become the preferred technique for women with severe preeclampsia and eclampsia – both for labor and delivery. A secondary analysis of women with severe preeclampsia 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." (15)

Fluid management has been a controversial topic between obstetricians who want to restrict fluids and anesthesiologists who want to administer fluids, however the obstetricians are probably correct. The vasculature has been described as "contracted and porous due to endothelial damage but not underfilled". In addition, the colloid osmotic pressure is low in pregnancy, and even lower in preeclamptic patients with proteinuria. Crystalloids and colloids readily leak out, increasing the risk of pulmonary edema postpartum. Typical obstetric management is to "run dry" at 80-100 ml per hour total fluids including magnesium and oxytocin infusions. Our anesthetic management should complement theirs, using conservative preload for surgical regional anesthesia and no preload for labor analgesia. A number of studies including a systematic review have shown weak if any benefit of crystalloid preloading in preventing hypotension during obstetric regional anesthesia. (16)

Despite years of concern and study, there is still no platelet function test and no specific platelet count that predicts bleeding into the neuraxis after regional anesthetic techniques. Many obstetric anesthesiologists are comfortable with platelet counts as low as 75,000 provided the count is stable and not falling and that there are no signs of clinical bleeding at venipuncture sites, gums, etc. Thromboelastography can add information if the test is available,

but there is still no cut-off value of any variable that is predictive of complications. Since pregnancy is a thrombophilic state, parturients have tremendous reserve before becoming coagulopathic. A review of 1.7 million spinal or epidural blocks found that complications were more common after epidural than spinal anesthetics and that obstetric patients were less likely than surgical patients to have an injury (1:25,000 in obstetric patients versus 1:3600 after surgical epidurals in females). (17) There were 2 obstetric patients in their series that developed a neuraxial hematoma, for an incidence of 1:200,000. One occurred after a spinal and the other after epidural catheter removal, and both patients had HELLP syndrome. This low incidence is reassuring, but you must balance the risk-benefit ratio for each case and each patient. Factors that would support a regional anesthetic with borderline labs would be a worrisome airway exam, the prospect of a lengthy induction, and the rarity of epidural hematoma. Factors that would support use of IV opioids or general anesthesia would be clinical signs of bleeding, a rapidly worsening platelet count, the need for an urgent cesarean and a good airway. If you feel that a neuraxial anesthetic is not appropriate, remember that we are the consultants in pain management. Our obstetric colleagues will appreciate help with an IV regimen for the patient's analgesia. For example, fentanyl can be used in an IV PCA as follows: give a bolus loading dose of 2-3 $\mu\text{g}/\text{kg}$ to get the patient comfortable. Set the PCA pump with a 50 μg incremental bolus, 10 minute lockout interval and no basal rate. As labor progresses and titration is needed, decrease the lockout from 10 to 5 minutes, then increase the bolus dose from 50 to 75 μg . (18)

The choices for cesarean anesthesia are epidural, spinal (or combined spinal-epidural) and general. In the past, spinal anesthesia was avoided because of concerns that hypotension would be more severe and less treatable than that seen after the sympathectomy from an epidural anesthetic. However, a comparison of women with severe preeclampsia to healthy women having a cesarean delivery with spinal anesthesia found that the preeclamptic women actually had less hypotension (17% versus 53%) despite receiving less fluid preload and (by chance), a larger dose of bupivacaine in their spinal. (19) A randomized comparison of spinal or epidural anesthesia for cesarean delivery in women with severe preeclampsia found that although hypotension was more frequent after spinal and required slightly more ephedrine, the duration of hypotension was short and the neonatal outcomes were similar in both groups. (20) Regardless of the choice of neuraxial anesthesia, pressors must be immediately available to treat even mild hypotension since these fetuses may not tolerate any decrease in uteroplacental perfusion. Clinical studies in humans have consistently shown that use of α -agonists such as phenylephrine produce better umbilical pH values in the newborn. (21) A study randomizing women with severe preeclampsia to spinal or general anesthesia for cesarean delivery for non-reassuring fetal heart tones found that spinal anesthesia was associated with more acidotic fetal pH values and higher base deficits. (22) Maternal hemodynamics were similar, but the patients receiving spinal anesthesia received more ephedrine (14 mg versus 3 mg) and phenylephrine was not used. Did the use of ephedrine affect acidosis? If maternal heart rate is above 70, choose phenylephrine as your first-line pressor agent.

If general anesthesia is chosen, the areas of concern are attenuating hypertensive responses during laryngoscopy and intubation, managing a difficult airway due to edema, and treating complications related to magnesium such as uterine atony and maternal weakness. A number of adjuncts to rapid sequence induction agents have been described and used successfully: esmolol, labetalol, lidocaine, remifentanyl and nitroglycerin. Include at least one as part of your rapid sequence induction or have them immediately available to treat hypertension if it occurs. Use of the laryngeal mask airway (LMA) has been described in the setting of HELLP syndrome and inability to intubate or ventilate. (22) This patient was even ventilated for 8 hours in the ICU using the LMA! Remember that magnesium is a uterine relaxant and other oxytocics such as Cytotec® or Hemabate® should be available to treat uterine atony after delivery in addition to the oxytocin infusion. If the mother has a high level of magnesium and exhibits muscle weakness prior to induction (i.e., can she do a 5-second head lift before her anesthetic?), it may be best to discontinue the magnesium sulfate infusion during the case to let her magnesium level decrease. Non-depolarizing muscle relaxants should be avoided during the case. If she cannot meet criteria for safe extubation at the end of the cesarean, she may require brief ventilation until she is strong enough to protect her airway.

Postpartum issues will require intense monitoring on L&D. The mother may need both acute and long term blood pressure control with anti-hypertensives. Fluid mobilization will begin to occur during the first 24 hours postpartum, and this is when she is most at risk for pulmonary edema. Monitor urine output, lung fields and pulse oximetry. Thrombocytopenia may not resolve for several days. If she has an epidural catheter in place, decide when removal is appropriate based on her platelet count and coagulation studies. About a third of eclamptic seizures occur postpartum. A review of 89 cases of eclampsia found that 33% of seizures occurred postpartum and 79% of those presented > 48 hours postpartum. Most did not have an antepartum diagnosis of preeclampsia, but most did

have prodromal symptoms such as headache and visual changes. (23) If the anesthesia team is called to evaluate a headache, be vigilant and consider late presenting preeclampsia in your differential diagnosis.

Future Follow-up After Preeclampsia

Does development of preeclampsia provide a marker for maternal disease risks later in life? A growing literature indicates that pregnancy is a form of “stress test” that may predict later health issues in the mother. For example, post-menopausal women who had preeclampsia decades earlier were 57% more likely to have coronary calcification on CT. (24) Women with increased pre-pregnancy BMI were more likely to develop hypertension during pregnancy (OR 5.5 for BMI > 30), and those women had higher mortality rates 30 years later (OR 2.9 for obese women who had hypertension during pregnancy versus obese women who had not been hypertensive). (25) At 21 years after delivery, women who had hypertension during pregnancy were twice as likely to have diabetes as those who had not been hypertensive. (26) These studies all recommend better long term follow-up of these women; the implications of this disease do not end at delivery.

In conclusion:

1. Be conservative with your fluid preloading before neuraxial procedures.
2. Normalize low blood pressure with phenylephrine in preference to ephedrine.
3. The blood pressure goal is to keep maternal pressure close to her baseline to sustain uteroplacental perfusion, but < 160 mmHg systolic to prevent maternal cerebrovascular complications.
4. Use platelet count trends and your clinical judgment. There is no absolute value to use as a cut-off.
5. Spinal anesthesia for cesarean delivery is safe. Limit fluid preload and treat hypotension aggressively with α -agonists.
6. Be part of the team when caring for these high risk obstetric patients.

References

1. Am J Obstet Gynecol 2000;183:S1-23
2. Lancet 2005;365:785
3. NEJM 2006;355:992
4. Nature Med 2008;14:810, 855
5. Am J Obstet Gynecol 2007;196:514
6. Am J Obstet Gynecol 2006;195:914
7. Obstet Gynecol 2005;105:246
8. Chest 1992;101:1429
9. Am J Obstet Gynecol 2005;193:153
10. Lancet 2002;359:1877
11. NEJM 2003;348:304
12. Am J Obstet Gynecol 2004;190:1520
13. Am J Obstet Gynecol 2001;185:970
14. Obstet Gynecol 2002;99:452
15. Obstet Gynecol 2002;99:159
16. Anesth Analg 2001;92:997
17. Anesthesiology 2004;101:950
18. Clin Obstet Gynecol 2003;46:616
19. Anesth Analg 2003;97:867
20. Anesth Analg 2005;101:862
21. Br J Anesth 2004;92:459
22. Anesth Analg 2004;98:1467
23. Am J Obstet Gynecol 2002;186:1174
24. Hypertension 2007;49:1
25. Am J Obstet Gynecol 2007;197:490
26. Am J Obstet Gynecol 2007;197:492