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Update in the diagnosis and management of preeclampsia and hypertensive disorders of pregnancy

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INTRODUCTION

Preeclampsia, a disease unique to human pregnancy, affects 2-8% of pregnancies and is one of the leading causes of maternal and neonatal morbidity and mortality[1]. Maternal risks include eclampsia, placental abruption, pulmonary edema, renal failure, stroke and death. Fetal risk includes growth restriction, oligohydramnios, intrauterine death and prematurity. It remains unclear why some women develop preeclampsia. Most cases of preeclampsia occur in primiparous patients with no known risk factors.

MATERNAL MORTALITY

In the United States, 7.4% of maternal deaths from 2011-2013 were attributed to hypertensive disorders of pregnancy[2]. Maternal mortality ratio (MMR) is the number of maternal deaths per 100,000 live births from any cause related to or aggravated by pregnancy or its' management for any given year. This includes death during pregnancy, childbirth or within 42 days of termination of pregnancy, regardless of the duration and site of the pregnancy[2]. With the exception of California, the U.S. has seen an increase in mortality in the last 2 decades when compared to other developed nations. The MMR varies widely by location. The following are World Health Organization (WHO) data on maternal mortality from 2015: Canada 7, U.S. 14, Chile 22, Costa Rica 25, Mexico 38, Brazil 44, Argentina 52, El Salvador 54, Columbia 64, Ecuador 64, Peru 68, Guatemala 88, Dominican Republic 92, Panama 94, Venezuela 95, Honduras 129, Paraguay 132, Nicaragua 150, Bolivia 206, Guyana 229[3]. The most common cause of death related to preeclampsia is hemorrhagic stroke. Implementation of maternal early warning tools reduces morbidity compared to hospitals without such tools[4]. Additionally, timely treatment of severe hypertension in preeclamptic patients has been shown to reduce severe maternal morbidity[5]. Given morbidity and mortality related to preeclampsia is frequently preventable, it is important that health care providers understand the latest management recommendations for patients with this disease.

DIAGNOSTIC CRITERIA AND DISEASE CLASSIFICATION

The American College of Obstetricians and Gynecologists (ACOG) released an update on hypertensive disorders in pregnancy in 2013, revising diagnostic criteria for preeclampsia, as well as disease classification[6]. Proteinuria is no longer required for diagnosis, as it does not correlate with maternal and fetal outcomes and delay in diagnosis due to lack of proteinuria may result in adverse outcomes. The presence of hypertension (BP > 140/90 mmHg on two separate occasions four hours apart) and proteinuria (> 300 mg/24 hours or urine protein: urine creatine ≥ 0.3) after 20 weeks gestation is diagnostic for preeclampsia[6]. If BP is > 160/110 mmHg, a shorter interval (30-60 minutes) is used to confirm measurement so as not to delay treatment. In the absence of proteinuria, the diagnosis can be made when a patient has hypertension and at least one the following severe features: headache, blurry vision, seizures, elevated liver enzymes (twice normal), persistent right upper quadrant or epigastric pain, elevated creatinine > 1.1 mg/dL, platelets < 100,000/µL or pulmonary edema[5]. The presence of elevated liver enzymes and low platelets is consistent with HEELP syndrome (hemolysis elevated liver enzymes and low platelets).

Disease classification also changed with the 2013 ACOG update. The disease is termed «preeclampsia without severe features» or «preeclampsia with severe features»[6]. This change was made to emphasize that preeclampsia is a dynamic and progressive disease, and providers should remain vigilant to detect when a patient develops severe features and escalate care to prevent maternal morbidity.

Gestational hypertension (GHTN) is hypertension (> 140/90 mmHg) after 20 weeks gestation without other organ system involvement. Up to 50% of patients who develop this diagnosis before 30 weeks gestation will progress to preeclampsia[7]. Patients with GHTH are managed the same as preeclampsia without SF. Patients with gestational hypertension presenting with blood pressure ≥ 160/110 mmHg should be diagnosed with preeclampsia, and antihypertensive medications given[1]. Patients who have hypertension before 20 weeks gestation are diagnosed with **chronic hypertension**. These patients are also at risk for developing preeclapmsia. Chronic hypertension with superimposed preeclampsia is diagnosed when a patient has worsening hypertension that is not responsive to medication, or when signs of end organ dysfunction develop, such as elevated liver enzymes.

ECLAMPSIA

Eclampsia is new onset seizures in a pregnant or postpartum patient without other etiologies for seizure activity. Immediate management of eclampsia consists of supportive care including preventing maternal injury, oxygen administration, assist ventilation when needed and seizure termination. Patients should be loaded with magnesium sulfate 4-6 grams and continued on an infusion (1-2 grams/hour) until 24 hours after delivery to prevent recurrent seizures. Magnesium sulfate reduces maternal mortality by 50% in eclamptic patients. Eclampsia is an indication for delivery, but does not necessitate emergent intervention. Maternal stabilization and *in-utero* fetal resuscitation is the priority[1,8]. Intubation is indicated only for persistent hypoxia, aspiration or non-terminating seizure. Vaginal delivery is reasonable in multiparous patients or those with advanced cervical dilation.

PATHOPHYSIOLOGY OF THE DISEASE

Preeclampsia occurs when placental vessels fail to undergo remodeling or have incomplete vascular remodeling during 8-18 weeks of pregnancy. The result is inadequate placental blood supply resulting in placental ischemia. The ischemic placenta releases anti-angiogenic factors such as soluble endoglin and soluble fms-like tyrosine kinase 1, which have been implicated in maternal endothelial dysfunction particularly in the kidneys, liver and central nervous system. The clinical phase of preeclampsia occurs after 20 weeks when symptoms of endothelia dysfunction develop. It is possible that measurement of these angiogenic factors could have future diagnostic and/or therapeutic utility[1].

DISEASE PREVENTION

Many studies have been performed looking at the role of low dose aspirin (ASA) and low molecular weight heparin (LMWH) for prevention of preeclampsia in high-risk patients[9,10]. Several randomized controlled trials and meta-analyses have shown that low dose aspirin decreases the risk of preeclampsia, particularly among patients with a history of preeclampsia. Data regarding LMWH is less consistent and its use for this indication is controversial. According to ACOG, low dose aspirin should be initiated before 16 weeks gestation in high-risk patients, including those with a history of preeclampsia, diabetes, kidney disease, multifetal gestation, hypertension or autoimmune diseases such as lupus. Patients with at least two moderate risk factors should also receive aspirin. Moderate risk factors include obesity, history of preeclampsia in a mother or sister, nulliparity, age > 35, low socioeconomic status and African American race[1].

EARLY VS LATE ONSET

Patients who develop preeclampsia before 34 weeks gestation (early onset) have 6-fold higher risk of fetal death and 16-fold risk of perinatal death and serious neonatal morbidity compared to those presenting after 34 weeks (late onset). African American race, history of chronic hypertension and fetal anomalies are strongly associated with early onset disease. Diabetes, nulliparity and age < 18 are associated with late-onset preeclampsia[11]. Patient with late onset disease have higher cardiac output (CO) and lower total vascular resistance (TVR), where early-onset disease is characterized by low CO, high TVR and abnormal uterine artery doppler suggesting placental mediated disease[12]. These differences in hemodynamic profile likely reflect variable etiologies for disease development. Therefore, it is not surprising that fetal/neonatal outcomes are variable as well. Fortunately early-onset disease is much less common than late-onset disease[11].

OBSTETRIC MANAGEMENT

Hypertensive disorders of pregnancy represent a continuum rather than separate disease processes. However, classifying the disease is necessary to determine appropriate treatment including delivery timeline. Following diagnosis, the obstetric team must decide if immediate delivery is indicated, or if the patient may be expectantly managed under close observation to minimize fetal prematurity and allow for corticosteroid administration for fetal lung maturity. Patients with preeclampsia with severe features should be delivered at 34 weeks gestation, 48 hours after steroids. If there are unstable maternal or fetal conditions, such as uncontrolled HTN, eclampsia, pulmonary edema, placental abruption, DIC, non-reassuring fetal status or IUFD, delivery should not be delayed.

Patients with preeclampsia without severe features and gestational HTN should be delivered at 37 weeks gestation, or

earlier for unstable maternal or fetal conditions. Patients with chronic HTN are generally delivered ≥ 38 weeks gestation unless they develop superimposed preeclampsia[6]. Based on HYPITAT trials, induction of labor (IOL) between 38 and 39 weeks improves maternal outcomes with no change in neonatal outcomes, and no increased risk of cesarean delivery compared to expectant management. Recently, the ARRIVE trial, which randomized low-risk nulliparous women at 39 weeks to IOL or expectant management, showed no difference in risk of cesarean delivery while IOL resulted in a reduced incidence of preeclampsia and gestational hypertension. These trials indicate no benefit of expectant management for GHTN beyond 39 weeks[13-15].

The median duration of expectant management is 7-14 days. During this time, mother and fetus are monitored for disease progression, indicating the need for delivery. Surveillance includes serial laboratory assessment, BP evaluation, assessment of symptoms such as headache, and fetal testing to evaluate fetal well-being. BP should be monitored frequently and treated with IV hydralazine, IV labetolol or PO nifedipine with a goal of reducing blood pressure to 140-155/90-100 mmHg. Blood pressure > 160/110 mmHg should be treated within 30-60 minutes to reduce the risk of seizure and hemorrhagic stroke. In cases of refractory hypertension, invasive BP monitoring may be needed. Potent vasodilators, such as nicardipine, may be required to maintain target blood pressure.

Cerebral edema and hemorrhagic stroke are thought to result from endothelial dysfunction, disruption of the blood brain barrier and loss of cerebral autoregulation, resulting in hyperperfusion, vasogenic edema and possibly vessel rupture[16]. Mortality from hemorrhagic stroke is over 50%, with the majority of survivors having long-term neurologic deficits[17]. The importance of aggressive blood pressure control cannot be overstated, as it has been shown to reduce severe maternal morbidity[5].

Patients who have preeclampsia with severe features should receive magnesium (4-6 gram load followed by 1-2 grams per hour) for seizure prophylaxis. Risk benefit analysis does not favor using magnesium in patients without severe features, as the risk of seizure in these patients in only 1:200[1]. Deep tendon reflexes, mental status and urine output are monitored for toxicity. Renal insufficiency and oliguria may reduce clearance of magnesium. These patients should have serum magnesium levels checked every 4 hours, with a goal of 4-7 mEq/L. Toxicity is treated with 1 gram calcium gluconate[8].

POSTPARTUM HYPERTENSION/PREECLAMPSIA

Up to 50% of women who develop preeclampsia are diagnosed post-partum. The National Partnership for Maternal Safety consensus statement noted 75% of deaths secondary to hypertensive disorders of pregnancy occurred postpartum, with 41% occurring greater than 48 hours after delivery[18]. Maternal blood pressure may decline after delivery, followed by increasing blood pressures peaking three to six days postpartum. Therefore, patients with preeclampsia should have increased surveillance with frequent blood pressure assessment 1 to 2 weeks postpartum. Postpartum patients with severe range blood pressure should be admitted for treatment with anti-hypertensives and magnesium sulfate.

ANESTHETIC MANAGEMENT

Once the decision is made to proceed with delivery, planning includes mode and timing of delivery, safety of neuraxial anesthesia, blood product availability, venous access, invasive monitoring and neonatal resuscitation needs. Vaginal delivery is preferred, but there may be indications for cesarean delivery, such as malpresentation or prior cesarean delivery. Consideration should be given to early placement of a labor epidural. Advantages include management of blood pressure, improved placental perfusion, potential for development or worsening of thrombocytopenia, as well as preparation for possible operative procedure. The presence of a labor epidural does not increase the risk of cesarean delivery. Prior to neuraxial anesthesia, clinical history of bleeding and assessment of platelet count and function should be reviewed to rule out HELLP syndrome. Platelet trend is important given the propensity for rapid decline. While there is no firm cutoff for platelet count below which neuraxial is contraindicated, review of the literature supports use of ≥ 70,000/L in the obstetric patient with no other concerns for coagulopathy[19].

Neuraxial anesthesia is preferred for cesarean delivery. Spinal anesthesia is equally as safe as epidural anesthesia in preeclamptic patients and results in fewer block failures. While frequency of hypotension requiring vasopressor use is slightly higher in the spinal group, this is easily treated with small doses of medication[20,21]. The increased rate of failure with epidural anesthesia increases need for general anesthesia and potential for failed intubation and aspiration. A combined spinal epidural provides the benefit of a dense and reliable block, with the potential to extend surgical anesthesia if needed.

General anesthesia may be required in some circumstances such as recent anticoagulation administration, severe thrombocytopenia or urgency. Considerations include aspiration prophylaxis, an airway contingency plan and blood pressure monitoring and management. Intubation may be more difficult due to edema and tissue friability so difficult airway adjuncts should be immediately available. During laryngoscopy, as well as surgery and emergence, consideration of blood pressure is crucial not only because of the risk for hemorrhagic stroke, but preeclampsia is frequently complicated by cerebral edema and elevated intracranial pressure[22]. Attenuation of the hypertensive response to stimulation is paramount to mitigate

cerebrovascular and cardiovascular complications. Esmolol (1.5 mg/kg) and/or nitroglycerin (1-2 µg/kg) used along with propofol may achieve hemodynamic stability during intubation. Additional agents include nicardipine (15-30 µg/kg) or remifentanil (1 µg/kg). A neonatal resuscitation team should be present at delivery[23]. Intravenous fluids should be used with caution, as these patients are at risk for pulmonary edema. Due to increased sensitivity to endogenous and exogenous vasopressors, methylergonovine is relatively contraindicated in treatment of uterine atony.

FUTURE RISKS AND RESEARCH

Based on several large epidemiologic studies, women with a history of preeclampsia are at increased risk of cardiovascular disease later in life, equal to that associated with obesity and smoking. This risk is much higher if preeclampsia developed prior to 37 weeks' gestation or if the patient had recurrent preeclampsia. Risks include hypertension, stroke, myocardial infarction and heart failure[1,24]. A history of preeclampsia should be considered a cardiovascular risk.

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